HEMOBLAST™ Bellows

Hemostatic Agent

Caution: Federal law restricts this device to sale on or by the order of a physician.

Note: A glossary of symbols used in the device labels is provided in Section 10.

Manufacturer

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1. Device Description

The HEMOBLAST™ Bellows consists of a powder composed of collagen, chondroitin sulfate, and thrombin. The powder is dry, sterilized, biocompatible, and non-pyrogenic. It is resorbed within 4 weeks. No preparation, mixing or heating is required.

HEMOBLAST™ Bellows is composed predominantly of highly purified porcine collagen with smaller amounts of bovine chondroitin sulfate and human pooled plasma derived thrombin. Each device contains a maximum of 1500 IU of thrombin. Plasma donations are from US plasma centers only. All individual donations of the plasma were tested for HBsAg, anti-HIV1/-HIV2 and anti-HCV, and found to be negative. The plasma pools were tested and found to be non-reactive for HCV RNA, HBV DNA, and HIV1 RNA as determined by PCR (NAT). The product complies with the specifications of the manufacturer and World Health Organization (WHO).

The manufacturing procedures for the HEMOBLAST™ Bellows include processing steps designed to reduce the risk of viral transmission.

The HEMOBLAST™ Bellows is MR Safe.

2. Indications for Use

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 ophthalmic procedures.

3. Contraindications

- HEMOBLAST™ Bellows is not intended for intradural or cranial neurosurgical use.
- 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.

4. Warnings and precautions

Warnings:

- The safety and effectiveness of HEMOBLAST™ Bellows has not been evaluated in ophthalmic and urologic procedures.
- Because HEMOBLAST™ Bellows is made from human blood, it may carry a risk of transmitting infectious agents, e.g., viruses, and theoretically, the Creutzfeldt- Jakob disease (CJD) agent. This also applies to any unknown or emerging viruses or other types of infections. The physician should discuss the risks and benefits of this product with the patient.
- HEMOBLAST™ Bellows contains chondroitin sulfate from bovine origin which is associated with a remote risk for Transmissible Spongiform Encephalopathies (TSE), which has been minimized in accordance with regulatory guidelines by a manufacturing process with demonstrated TSE inactivation capacity.
- The use of HEMOBLAST™ Bellows in robotic assisted surgery procedures has not been studied and should not be used for acquiring hemostasis.
- HEMOBLAST™ Bellows is not intended as a substitute for meticulous surgical technique and the proper application of ligatures or other conventional procedures for hemostasis.
- When applied to a bleeding site, HEMOBLAST™ Bellows swells up to 60% within about 5 minutes. Caution should be used when applying HEMOBLAST™ Bellows in any cavities or closed spaces due to the swelling of the device.
- Do not attempt to trim the applicator tip.
- HEMOBLAST™ Bellows should not be used at the site of a valve replacement or repair as valvular dysfunction could occur.
- HEMOBLAST™ Bellows should not be applied at the site of a synthetic graft or patch implant due to potential for decreased effectiveness.
- The product should not be in contact with circulating cerebrospinal fluid (CSF).
- Do not implant in an infected or necrotic site or one that is likely to develop an infection.
- The safety and effectiveness of the combined use of the hemostatic agent with other devices has not been evaluated in controlled clinical trials.
- The material has not been tested on children and pregnant or lactating women.
- HEMOBLAST™ Bellows during neurosurgical procedures is only intended for use in open spine surgery.
- HEMOBLAST™ Bellows should not be applied at sites where the dura is open.
- HEMOBLAST™ Bellows should not be used during transperitoneal laparoscopic or transthoracic thoracoscopic approaches to the anterior spine.

Precautions:

- For single use only.
- Avoid direct contact between the nozzle or cannula tip and irrigation or bodily fluids during use to minimize the potential for clogging the tip during HEMOBLAST™ Bellows application.
- Do not re-sterilize. Consequences of re-sterilizing and/or re-using the hemostatic powder were not evaluated during the design. Therefore, the efficacy of the product may be reduced.
- Do not use HEMOBLAST™ Bellows in circumstances that result in negative peripheral venous pressure, e.g. patient positioning with head up may create negative pressure in venous structures above the diaphragm, as it may draw material into the vascular system, potentially resulting in life- threatening thromboembolic events.
- Exposure to solutions containing alcohol, iodine, or heavy metals may cause the thrombin in hemostatic agent to be inactivated.
- Do not allow powder to enter into cell saver equipment, extracorporeal cardiopulmonary bypass circuits, or autologous blood salvage circuits.

- Do not use on bone surfaces where adhesives, such as methylmethacrylate or other acrylic adhesives, will be required to attach a prosthetic device.
- Avoid applying the HEMOBLAST™ Bellows device to open venous channels or sinuses of the liver parenchyma.
- HEMOBLAST™ Bellows should not be used for the primary treatment of coagulation disorders.
- Potential risk of thrombosis if absorbed systemically.
- Do not disrupt the HEMOBLAST™ Bellows clot complex by physical manipulation. This may cause clot disruption and subsequent bleeding.
- Do not use after the expiration date indicated on the package.
- Ensure that the packaging of each product is intact before use.
- Do not use if the package or the product is damaged.
- Do not use if the product has been exposed to extreme heat.
- The product must be manipulated by qualified personnel according to the general principles of sterility and pre-medication.
- The bellows should be handled with sterile powder-less gloves.
- There is a risk of human parvovirus B19 transmission. Human parvovirus B19 most seriously affects pregnant women, or immune-compromised individuals. Symptoms of human parvovirus B19 include fever, drowsiness, chills, and runny nose followed about two weeks later by a rash and joint pain. Patients should report such symptoms to their physician if they appear.
- Long-term animal studies to evaluate the carcinogenic potential of HEMOBLAST™ Bellows or studies to determine the effect of HEMOBLAST™ Bellows on fertility have not been performed.
- It is not known whether HEMOBLAST™ Bellows can cause fetal harm when administered to pregnant women or can affect reproduction capacity.
- HEMOBLAST™ Bellows should not be used in patients who have religious or other objections to the use of porcine or bovine components.
- In urological procedures HEMOBLAST™ Bellows should not be placed in the renal pelvis, renal calyces, bladder, urethra or ureters to reduce the potential foci for calculus formation.
- Erectile dysfunction has been reported when hemostatic agents are used in surgical procedures involving cavernous nerves occasionally exposed during radical prostatectomy procedures.

5. Directions for use

Inspect the integrity of the product packaging prior to use. If damaged, do not use. The instructions must be read before use.

1. Peel open the trays/blisters to remove contents with attention to sterile procedures.
2. Remove cap using a twisting motion.
3. Attach the 10 cm nozzle extension to the nozzle when additional nozzle length is needed.
4. Blot excess blood from the target bleeding site with gauze/pad or suction so the hemostatic implant material may be applied directly to the source of bleeding. The wound surface should be as dry as possible just before application.
5. Apply hemostatic implant material to the source of bleeding by compressing the bellows. Enough implant material should be applied to cover the entire source of bleeding.
6. Immediately use a wet laparotomy pad to hold the hemostatic material at the target bleeding site against the bleeding surface using wound appropriate pressure to conform the powder to the source of bleeding.
7. Maintain the hemostatic material at the target bleeding site for approximately three minutes.
8. Gently lift the laparotomy pad and inspect the area.
9. If hemostasis has not been achieved, repeat steps 4-7 or use an alternate method of hemostasis treatment.
10. Discard any unused product after opening.

Notes:

- Multiple layers of the hemostatic agent may be applied onto the wound to cover the bleeding surface.
- When applied with the nozzle tip 2-3 cm from the target bleeding site, HEMOBLAST™ Bellows can treat a surface area up to 50 cm2.
- Do not disrupt the HEMOBLAST™ Bellows clot complex by physical manipulation.
- Once bleeding has ceased, excess HEMOBLAST™ Bellows powder not incorporated in the hemostatic clot should be removed by gentle irrigation.
- Once hemostasis is achieved, excess HEMOBLAST™ Bellows should be removed from the site of application by irrigation and aspiration particularly when used in and around the posterior fossa, foramina of bone, areas of bony confine, the spinal cord, and/or the optic nerve and chiasm.
- HEMOBLAST™ Bellows should not be used for controlling post-partum bleeding or menorrhagia.

6. How Supplied

HEMOBLAST™ Bellows is supplied as a bellows pre-loaded with hemostatic powder. The bellows contains 1.65g of implant material. A 10 cm nozzle extension is included to assist with the application of the powder to active bleeding sites where a slightly longer tip is desired by the surgeon. The product is sterilized using gamma-sterilization and provided in double-packaging.

7. Storage

- The product is sterile unless the package has been opened, damaged, or otherwise contaminated.
- The product must be stored between 2°C and 25°C (36-77°F) in a dry environment.
- The product can be used throughout the duration of the operation without any known or reported hazards.
- The product must be discarded after use.

8. 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 ophthalmic and urological procedures in the US under IDE # G150037, G160063, and G200210. Data from these clinical studies were the basis for the PMA approval decisions. 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 study was a single arm study which included patients undergoing only orthopedic and abdominal surgeries with associated bleeding sites; the was no cardiothoracic arm.

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

Table 1: 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 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

A subject must have met all the following preoperative inclusion criteria to be enrolled into the investigation:
- 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.

A subject had to meet all of the following intraoperative inclusion criteria to be enrolled into the investigation:
- 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 or conventional means for hemostasis are ineffective or impractical; and
- Subject has a TBS with SBSS score of 1, 2, or 3.

A subject had to meet all of the following preoperative exclusion criteria to be enrolled into the investigation:
- 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 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. <u>Accountability</u>

A total of 31 subjects met preoperative eligibility criteria, including roll-in subjects. Four 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 efficacy analysis. Therefore, 24 subjects enrolled in the study are considered the efficacy analysis population. The exploratory analysis population includes 25 subjects total (the efficacy analysis population plus one subject who met pre-operative eligibility requirements but failed intra-operative eligibility criteria). Enrollment was fairly balanced across all 3 sites, with 9 subjects being enrolled at Site 2 and 8 and 10 subjects enrolled at Site 6 and Site 8, respectively. Site 2 had 3 subjects that were excluded intraoperatively, Site ~~0~~8 had 1 subject that was excluded intraoperatively, while no subjects were excluded intraoperatively at Site 6.

Table 2: 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 3: 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 4: 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%)

Table 5: 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) for categorical measures.

Table 6: 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%)
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%)
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 ± SD (N)/ median for continuous measures, and n/N (percent) for categorical measures.

D. Safety and Effectiveness Results

The mean paired kappa across all sites was 0.9301 indicative 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 minor 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™ Bellows applied to the liver parenchymal edge of resection and resolved with anticoagulation.

Table 7: 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*						
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%,5 4.7%)	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 8: Thromboembolic Events

	Total Thromboembolic Events	Pulmonary Embolism	Deep Venous Thrombosis	Stroke	Thrombosed AV Fistula	Other (portal vein thrombosis)
HEMOBLAST™ Bellows 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™ Bellows induced hemostasis at 3 minutes for half of all subjects in the efficacy 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 9: 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.

Pivotal Study:

A. <u>Study Design</u>

This was a prospective, randomized, controlled, multicenter pivotal study to evaluate the safety and efficacy of the HEMOBLAST™ Bellows 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 ™ Bellows or the control treatment, an absorbable gelatin sponge, USP and recombinant thrombin ("G+T"). The study also included a lead-in phase, to ensure correct device application procedures, wherein subjects were not randomized. Lead-in subjects received HEMOBLAST™ Bellows and were followed for safety only.

The specific objective of the study was to evaluate the safety and efficacy of HEMOBLAST™ Bellows compared to G+T. The primary hypothesis in this study was that HEMOBLAST™ Bellows 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 efficacy data, respectively.

1. Clinical Inclusion and Exclusion Criteria

A subject must have met all the following preoperative inclusion criteria to be enrolled into the investigation:
- 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.

A subject must have met all the following intraoperative inclusion criteria to be enrolled into the investigation:
- 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 excluded 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™ Bellows, 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.
For cardiothoracic procedures, the TBS was identified after heparin reversal. Additionally, the TBS was not at the site of a valve implant or at the site of a synthetic graft or patch implant. Bleeding severity and hemostasis were assessed using the SBSS.

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
The primary efficacy endpoint of this clinical investigation was non-inferiority of HEMOBLAST™ Bellows relative to G+T for success at achieving hemostasis within 6 minutes.

The secondary efficacy endpoints of this clinical investigation were:
- Superiority of HEMOBLAST™ Bellows relative to G+T in mean preparation time from the opening of package to product being ready to use;
- Non-inferiority of HEMOBLAST™ Bellows relative to G+T for success at achieving hemostasis within 3 minutes;
- Superiority of HEMOBLAST™ Bellows relative to G+T for success at achieving hemostasis within 6 minutes; and
- Superiority of HEMOBLAST™ Bellows 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™ Bellows 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 efficacy data would be available on a maximum of 400 treated subjects (approximately 267 patients treated with HEMOBLAST™ Bellows 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.

B. Accountability of PMA Cohort

The study was stopped early for efficacy, 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 minutes hemostasis primary endpoint and superiority at the 10-30% superiority at all the secondary endpoints including hemostasis at 6minutes, 3 minutes and 10 minutes as well as superiority on time to preparation for use. Furthermore, the pivotal study demonstrated non inferiority of HEMOBLAST™ Bellows for hemostasis at 10 minutes.

Table 10 represents the enrollment for each treatment group and **Table 11** represents the enrollment for each surgical arm. Randomization was stratified by surgical arm.

Table 10: Enrollment Details for Each Treatment Group

Population	All	HEMOBLAST™ Bellows	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 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.

Table 11: 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 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

Table 12 presents physical measurement for height, weight, BMI, and blood pressure, which were similar between treatment arms.

Table 12: Physical Measurements by Treatment Group

Measure	All (n=258)	HEMOBLAST™ Bellows (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 13 and **Table 14** present the baseline SBSS score for the TBS by treatment group and surgical arm, respectively.

Table 13: Baseline SBSS Score for Each Treatment Group

Measure	All (N=242)	HEMOBLAST™ Bellows (N=159)	G+T (N=83)
Investigator SBSS Score			
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	158 (65.3%)	100 (62.9%)	58 (69.9%)

Numbers are n/N (percent).

Table 14: 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%)
SBSS score ≥2	158/242 (65.3%)	44/58 (75.9%)	82/90 (91.1%)	32/94 (34.0%)

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™ Bellows 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™ Bellows vs. 13.3% for G+T, p=0.5415). The two groups were found to have a similar number of subjects experiencing an adverse event related to the device.

There were 3 possible device-related adverse events reported in 3 subjects receiving HEMOBLAST™ Bellows:

- Subject reported symptoms indicating possible systemic inflammatory response syndrome. This event was classified as possibly related to HEMOBLAST™ Bellows; 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™ Bellows 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™ Bellows, but probably related to the investigational procedure.

There were 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 sum, there was a single event identified as a SADE (subject who experienced skin reaction, described above).

Table 15: Serious Adverse Events

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.

Adverse Event Type*	All	HEMOBLAST™ Bellows	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™ Bellows: Pancolitis, diarrhea positive for clostridium difficile, dental abscess; G+T: tricuspid valve vegetation

[2]HEMOBLAST™ Bellows: 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

Non-serious adverse events

Table 16 lists non-serious AEs occurring in 5% or more of all patients, or in one of the treatment arms.

Table 16: Number of Subjects Experiencing Each Type of Non-serious Adverse Event

Adverse Event Type*	All	HEMOBLAST™ Bellows	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™ Bellows: 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.

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 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.

2. Effectiveness Results

Primary endpoint

The primary efficacy endpoint of non-inferiority of HEMOBLAST™ Bellows relative to G+T for success at achieving hemostasis within 6 minutes was met, with 93.1% of the HEMOBLAST™ Bellows 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 17**. 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 17: Primary Efficacy Endpoint with Full Efficacy Population

Time	HEMOBLAST™ Bellows	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 18. The HEMOBLAST™ Bellows group showed a higher proportion of patients achieving hemostasis at each time point assessed.

Table 18: Proportion of Each Treatment Group Achieving Hemostasis at 3, 6, and 10 Minutes

Time	All	HEMOBLAST™ Bellows	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 19, 20** and **21**. The HEMOBLAST™ Bellows 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 19: Proportion Achieving Hemostasis for Cardiothoracic Surgical Arm

Time	All	HEMOBLAST™ Bellows	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 20: Proportion Achieving Hemostasis for Abdominal Surgical Arm

Time	All	HEMOBLAST™ Bellows	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 21: Proportion Achieving Hemostasis for Orthopedic Lower Extremity Surgical Arm

Time	All	HEMOBLAST™ Bellows	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

Secondary endpoints are reported for the overall population.

Mean preparation time

The preparation time for the HEMOBLAST™ Bellows group was found to be significantly shorter than the G+T group, with a mean of 0.37 minutes (22 seconds) for the HEMOBLAST™ Bellows 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 minutes

The HEMOBLAST™ Bellows group met the secondary endpoint of non-inferiority in success achieving hemostasis at the 3 minutes time point, with 71.1% of HEMOBLAST™ Bellows 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™ Bellows in achieving hemostasis at 6 minutes was met in the overall population. As described in the Primary Endpoint section, the proportion of HEMOBLAST™ Bellows 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™ Bellows in achieving hemostasis at 3 minutes was met in the overall population. As described in the Primary Endpoint section, the proportion of HEMOBLAST™ Bellows 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 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 cm2 in the HEMOBLAST™ Bellows group and 5.8 cm2 in the G+T group.

Spine Clinical Study:

A. Study Design

This was a prospective, randomized, controlled, multicenter pivotal study to evaluate the safety of the HEMOBLAST™ Bellows in Spine Surgery. A total of 60 subjects were enrolled and randomized in a 2:1 ratio to HEMOBLAST ™ Bellows or the control treatment, an absorbable gelatin sponge, USP and recombinant thrombin (Gelfoam+Thrombin [G+T]). The study also included a lead-in phase, to ensure correct device application procedures, wherein subjects were not randomized. Lead-in subjects received HEMOBLAST™ Bellows and were followed for safety. The specific objective of the study was to assess the safety of HEMOBLAST™ Bellows for use in spine surgery compared to G+T, although efficacy information was also captured and reported.

1. Clinical Inclusion and Exclusion Criteria

A subject needed to meet all of the following preoperative inclusion criteria to be enrolled into the investigation:
- Subject is undergoing an open, elective, spine surgery;
- Subject or an authorized legal representative is willing and able to give prior written informed consents for investigation participation; and
- Subject is 22 years of age or older.

A subject needed to meet all of the following intraoperative inclusion criteria to be enrolled into the investigation:
- Subject does not have an active or suspected infection at the surgical site;
- 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. (see Table 1)

A subject needed to not meet any of the following preoperative exclusion criteria to be enrolled into the investigation:
- Subject is undergoing an emergency surgical procedure;
- Subject is undergoing a laparoscopic approach;
- Subject is undergoing a cervical spine surgery (added for Stage 2 at FDA request);
- Subject is pregnant, planning on becoming pregnant during the follow-up period, or actively breast-feeding;
- Subject has 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 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 a known sensitivity or allergy to Gadolinium;
- The subject has a contra-indication for MRI or gadolinium contrast agent according to clinical guidelines, local regulations or manufacturer's recommendations;
- Subject suffers from claustrophobia or fear of MRI, or has any contraindication to MRI (e.g., metal implants, spinal cord stimulator, etc. not suited to MRI) (added for Stage 2 at FDA request);
- Subject has ASA classification of ≥ 5;
- Subject has a life expectancy of less than 3 months;
- Subject has a documented severe congenital or acquired immunodeficiency;
- Subject has religious or other objections to porcine, bovine, or human components;
- 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
- Per investigator opinion subject is unable to fully cooperate with the study protocol.

A subject needed to not meet any of the following preoperative exclusion criteria to be enrolled into the investigation:
- The product will be at a site where the dura is open; and
- The product will be placed in the intradural or cranial space.

2. Patient Follow-up Schedule

Table 22 details the clinical investigation visits, corresponding timing, and evaluations performed at each visit.

Table 22. Investigational Evaluation Schedule

Visit	Timing	Evaluations
Visit 1	Within 4 weeks before surgery	Informed consent, preoperative eligibility criteria confirmation, preoperative evaluations
Visit 2	Day of surgery; day 0	Intraoperative inclusion criteria confirmation, safety assessments
Visit 3	Discharge	Safety assessments, conditional MRI with Gd if indicated
Visit 4	6 weeks (± 2 weeks) postoperatively	Safety assessments, conditional MRI with Gd if indicated
Visit 5	12 weeks (± 2 weeks) postoperatively	Safety assessments, mandatory or conditional MRI with Gd, study discontinuation

3. Clinical Endpoints

The primary safety endpoint of this clinical investigation was:
The primary endpoint of this clinical investigation was designed to assess safety, defined as the incidence of Unanticipated Adverse Device Effect (UADE), including epidural fibrosis and arachnoiditis, for subjects treated with HEMOBLAST™ Bellows, as determined by the Independent Data Monitoring Committee (IDMC).

MRI with Gd:
To conduct the adjudication for the presence of epidural fibrosis and arachnoiditis, the Independent Adjudication Committee (IAC) reviewed MRI + Gd scans on an individual patient basis. Throughout the clinical investigation, MRI + Gd data and corresponding subject's data was collected from study sites according to IAC procedures.
The MRI + Gd scans and the corresponding subject's data collected from the study sites, were provided to the IAC as part of any individual event Data Package. The content of the Data Packages as well as the adjudication process were summarized in the IAC Charter.

The secondary safety endpoint of this clinical investigation was:
The secondary endpoint of this clinical investigation was defined as the proportion of AEs for subjects treated with HEMOBLAST™ Bellows compared to subjects treated with G+T.

B. <u>Accountability</u>

A total of 71 subjects were screened for the study and 60 met the pre-operative eligibility criteria. No subjects withdrew prior to intraoperative randomization and 0 were considered as intraoperative ineligible leaving to 60 subjects to be enrolled intraoperatively. 59 subjects were randomized and 1 subject was not due to failure of the randomization process with the subject then nonrandomized to the HEMOBLAST™ Bellows group arbitrarily and as a lead-in (one of first two HEMOBLAST™ Bellows subjects at that site). The 60 subjects included 8 lead-in subjects (the first two HEMOBLAST™ Bellows subjects at each of 4 sites (a 5th site enrolled only one subject that was randomized to receive G+T and thus, had no lead-in subjects)). Table 23 represents the enrollment for each treatment group.

The safety analyses were conducted on the full analysis safety population, defined as all subjects enrolled in the study, which includes lead-in subjects. A total of 60 subjects were enrolled in the study and included in the safety analysis population as in Table 23; 40 in the HEMOBLAST™ Bellows group and 20 in the G+T group.

The efficacy analyses were conducted on the TTH efficacy population, defined as all subjects who were randomized, received study intervention, and had a TTH assessment recorded regardless of whether the measurement was censored. Lead-in subjects are not part of the TTH Population. A total of 52 subjects were included in the TTH population as in **Table 23**; 32 subjects in the HEMOBLAST™ Bellows group and 20 subjects in the G+T group.

Table 23. Enrollment Details for Each Treatment Group

Population	All	HEMOBLAST™ Bellows	G+T
TOTAL: Preoperative eligible + lead-in subjects	60	40	20
Intraoperative ineligible subjects	0	0	0
SAFETY ANALYSIS POPULATION (Full Analysis): Preoperative AND Intraoperative eligible (ENROLLED and includes lead-in subjects)	60	40	20
Lead-in subjects	8	8	0
EFFICACY ANALYSIS POPULATION (TTH Analysis): Preoperative AND Intraoperative eligible (ENROLLED and EXCLUDES lead-in subjects)	52	32	20

The first 25 subjects were part of Stage 1 with mandatory MRIs with Gd as per the protocol and the next 35 subjects were part of Stage 2 with conditional MRIs with Gd and no cervical procedures permitted to maximize the extent of epidural fibrosis as per the FDA suggested protocol revisions. Two subjects in Stage 1 failed to undergo MRIs with Gd and 4 subjects in Stage 2 underwent clinically necessary MRIs with Gd not indicated by the protocol.

C. Study Population Demographics and Baseline Parameters

Table 24 presents baseline demographic characteristics by treatment group for all enrolled subjects. Age, gender, ethnicity, race, and smoking data were collected and found to be similar between treatment groups and representative of the target intended use population.

The average age for all subjects was 55.8 years old with the average age of the HEMOBLAST™ Bellows group (52.8) observed to be approximately 10 years younger than the G+T group (61.8). For gender, the distribution in the HEMOBLAST™ Bellows group was 65% female and 35% male, while in the G+T group it was 50% for females and 50% males.

With respect to ethnicity, Hispanics were identified in the HEMOBLAST™ Bellows group 5.0%, but not in the G+T group (0.0%) and unknown was the second most frequent ethnicity (6.7%). The majority of subjects (86.7%) self-identified as Caucasian, while African Americans (5.0%) and subjects identifying race as unknown (5.0%) were the second most frequent race designation.

With respect to smoking histories, the incidence of current smoking for the HEMOBLAST™ Bellows group (22.5%) and the G+T group (15.0%) were observed to be comparable.

Table 24. Baseline Demographics for Each Treatment Group in All Enrolled Subjects.

	All (N=60)	HEMOBLAST™ Bellows (N=40)	G+T (N=20)
Age (Years)	55.8 ± 13.57 (60) 57.0 [24, 78]	52.8 ± 14.01 (40) 54.5 [24, 78]	61.8 ± 10.58 (20) 63.5 [37, 76]
Gender			
Female	36/60 (60.0%)	26/40 (65.0%)	10/20 (50.0%)
Male	24/60 (40.0%)	14/40 (35.0%)	10/20 (50.0%)
Ethnicity			
Hispanic or Latino	2/60 (3.3%)	2/40 (5.0%)	0/20 (0.0%)
Not Hispanic or Latino	54/60 (90.0%)	35/40 (87.5%)	19/20 (95.0%)
Unknown	4/60 (6.7%)	3/40 (7.5%)	1/20 (5.0%)
Race			
Caucasian	52/60 (86.7%)	33/40 (82.5%)	19/20 (95.0%)
Black or African American	3/60 (5.0%)	2/40 (5.0%)	1/20 (5.0%)
Asian	2/60 (3.3%)	2/40 (5.0%)	0/20 (0.0%)
American Indian or Alaska Native	0/60 (0.0%)	0/40 (0.0%)	0/20 (0.0%)
Native Hawaiian or Other Pacific Islander	0/60 (0.0%)	0/40 (0.0%)	0/20 (0.0%)
Other	0/60 (0.0%)	0/40 (0.0%)	0/20 (0.0%)
Unknown	3/60 (5.0%)	3/40 (7.5%)	0/20 (0.0%)
Smoking History			
Current smoker	12/60 (20.0%)	9/40 (22.5%)	3/20 (15.0%)
Ex-smoker	20/60 (33.3%)	11/40 (27.5%)	9/20 (45.0%)
Has never smoked	28/60 (46.7%)	20/40 (50.0%)	8/20 (40.0%)

Table 25 presents baseline demographic characteristics by treatment group for the TTH analysis population. The subjects' population, age, gender, ethnicity, race, and smoking data were observed to be similar between treatment groups and representative of the target intended use population.

The average age for the TTH population was 55.3 years old with the average age of the HEMOBLAST™ Bellows group (51.3) observed to be approximately 10 years younger than the G+T group (61.8). For gender, the distribution in the HEMOBLAST™ Bellows group was 62.5% female and 37.5% male, while in the G+T group it was 50% for females and 50% males.

With respect to ethnicity, Hispanics were identified in the HEMOBLAST™ Bellows group 6.3%, but not in the G+T group (0.0%) and unknown was the second most frequent ethnicity (7.7%). The majority of subjects (90.4%) self-identified as Caucasian, with subjects identifying race as unknown were the second most frequent race designation (5.8%).

With respect to smoking histories, the incidence of current smoking for the HEMOBLAST™ Bellows group (21.9%) and the G+T group (15.0%) were observed to be comparable.

Table 25. Demographics and Baseline Characteristics in the TTH Analysis Population

	All (N=52)	HEMOBLAST™ Bellows (N=32)	G+T (N=20)
Age (Years)	55.3 ± 13.32 (52) 56.5 [24, 76]	51.3 ± 13.40 (32) 54.0 [24, 75]	61.8 ± 10.58 (20) 63.5 [37, 76]
Gender			
Female	30/52 (57.7%)	20/32 (62.5%)	10/20 (50.0%)
Male	22/52 (42.3%)	12/32 (37.5%)	10/20 (50.0%)
Ethnicity			
Hispanic or Latino	2/52 (3.8%)	2/32 (6.3%)	0/20 (0.0%)
Not Hispanic or Latino	46/52 (88.5%)	27/32 (84.4%)	19/20 (95.0%)
Unknown	4/52 (7.7%)	3/32 (9.4%)	1/20 (5.0%)
Race			
Caucasian	47/52 (90.4%)	28/32 (87.5%)	19/20 (95.0%)
Black or African American	2/52 (3.8%)	1/32 (3.1%)	1/20 (5.0%)
Asian	0/52 (0.0%)	0/32 (0.0%)	0/20 (0.0%)
American Indian or Alaska Native	0/52 (0.0%)	0/32 (0.0%)	0/20 (0.0%)
Native Hawaiian or Other Pacific Islander	0/52 (0.0%)	0/32 (0.0%)	0/20 (0.0%)
Other	0/52 (0.0%)	0/32 (0.0%)	0/20 (0.0%)
Unknown	3/52 (5.8%)	3/32 (9.4%)	0/20 (0.0%)
Smoking History			
Current smoker	10/52 (19.2%)	7/32 (21.9%)	3/20 (15.0%)
Ex-smoker	18/52 (34.6%)	9/32 (28.1%)	9/20 (45.0%)
Has never smoked	24/52 (46.2%)	16/32 (50.0%)	8/20 (40.0%)

Numbers are mean ± SD (n)/ median [min, max] for continuous measures, and n/N (percent) for categorical measures.

Subject physical characteristics were observed to be relatively well matched between the two treatment groups in all enrolled subjects, see **Table 26**. As the physical characteristics were similar between treatment groups, these differences would not be expected to have a material impact on the study conclusions.

Table 26. Physical Measurements by Treatment Group in All Enrolled Subjects

Measure	All (N=60)	HEMOBLAST™ Bellows (N=40)	G+T (N=20)
Height (cm)	168.28 ± 11.568 (60) 166.35 [137.6, 195.5]	166.14 ± 11.031 (40) 165.10 [137.6, 190.5]	172.56 ± 11.698 (20) 170.10 [154.9, 195.5]
Weight (kg)	93.79 ± 22.391 (60) 90.70 [51.9, 147.2]	90.75 ± 23.320 (40) 83.90 [51.9, 147.2]	99.87 ± 19.551 (20) 97.30 [72.6, 146.4]
BMI (kg/m^2)	32.98 ± 6.429 (60) 31.85 [19.0, 48.1]	32.78 ± 7.200 (40) 31.60 [19.0, 48.1]	33.38 ± 4.656 (20) 32.90 [25.5, 47.6]
Systolic Blood pressure (mmHg)	137.8 ± 19.82 (60) 134.0 [99, 192]	137.2 ± 21.38 (40) 134.0 [99, 192]	139.0 ± 16.71 (20) 135.0 [105, 174]
Diastolic Blood pressure (mmHg)	79.0 ± 9.59 (60) 79.0 [58, 109]	78.8 ± 10.77 (40) 79.0 [58, 109]	79.3 ± 6.88 (20) 80.5 [67, 92]
Pulse Rate (beats/min)	76.7 ± 13.98 (60) 78.0 [48, 102]	77.8 ± 15.02 (40) 80.0 [48, 102]	74.3 ± 11.59 (20) 72.5 [48, 98]

Numbers are mean ± SD (n)/ median [min, max].

D. Safety and Effectiveness Results

1. Safety Results

Primary Endpoint:

The number of subjects reporting any UADEs was 0% in both treatment groups, as shown in **Table 27** below.

Table 27. Summary of Unanticipated Adverse Device Effects by System Organ Class and Preferred Term

	All (N=60)		HEMOBLAST™ Bellows (N=40)		G+T (N=20)	
Event Type	**Events**	**Subjects n/N (%)**	**Events**	**Subjects n/N (%)**	**Events**	**Subjects n/N (%,)**
Unanticipated adverse device effects (UADEs)	0	0/60 (0.0%)	0	0/40 (0.0%)	0	0/20 (0.0%)

Epidural Fibrosis:

The amount of epidural fibrosis was graded on a scale of 0-4 for each quadrant at each MR imaging slice of the operative level: 0 = no epidural fibrosis present/trace scar; 1 > 0% and ≤ 25% of quadrant filled with scar; 2 > 25% and ≤ 50% of quadrant filled with scar; 3 > 50% and ≤ 75% of quadrant filled with scar; 4 > 75% and ≤ 100% of quadrant filled with scar[3].

Epidural fibrosis was absent in 12/27 subjects. For the remaining subjects, the number of quadrants scored for HEMOBLAST™ Bellows subjects ranged from 60 to 108, and G+T subjects ranged from 48 to 108. Most quadrants scored for both HEMOBLAST™ Bellows and G+T subjects were given a score of 0, indicating epidural fibrosis was not present.

The summary of stage 1 epidural fibrosis scores is shown in **Table 28**. Almost all participants (13/15) in the HEMOBLAST™ Bellows group were categorized as either a score of 0 (6/15, 40.0%) or a score of 4 (7/15, 46.7%) with the average epidural fibrosis score being 2.2 ±1.93. Similarly, in the G+T group, all participants (8/8) were either a score of 0 (5/8, 62.5%) or a score of 4 (3/8, 37.5%), with an average score of 1.5 ± 2.07. Overall, the rate of developing epidural fibrosis in stage 1 was similar between treatment groups and is reflective of the incidence of epidural fibrosis reported to be as high as 64%[4].

Table 28. Summary of Stage 1 Epidural Fibrosis Scores.

	All (N=23)	HEMOBLAST™ Bellows (N=15)	G+T (N=8)
Epidural Fibrosis Score (Categorical)			
0	11/23 (47.8%)	6/15 (40.0%)	5/8 (62.5%)
1	0/23 (0.0%)	0/15 (0.0%)	0/8 (0.0%)
2	1/23 (4.3%)	1/15 (6.7%)	0/8 (0.0%)
3	1/23 (4.3%)	1/15 (6.7%)	0/8 (0.0%)
4	10/23 (43.5%)	7/15 (46.7%)	3/8 (37.5%)
Epidural Fibrosis Score (Continuous)	2.0 ± 1.97 (23) 2.0 [0, 4]	2.2 ± 1.93 (15) 3.0 [0, 4]	1.5 ± 2.07 (8) 0.0 [0, 4]

Numbers are mean ± SD (n)/ median [min, max] for continuous measures, and n/N (percent) for categorical measures.

In Stage 1 of the study, 23 subjects had mandatory MRI + Gd studies at 12 +/- 2weeks.

3. Jeffrey S. Ross, M.D., James T. Robertson, M.D., Robert C. A. Frederickson, Ph.D., Jonathan L. Petrie, M.D., Nancy Obuchowski, Ph.D., Michael T. Modic, M.D., Nicolas deTribolet, M.D., Association Between Peridural Scar and Recurrent Radicular Pain After Lumbar Discectomy: Magnetic Resonance Evaluation, Neurosurgery, Volume 38, Issue 4, April 1996, Pages 855–863, https://doi.org/10.1227/00006123-199604000-00053

4. Mohi Eldin MM, Abdel Razek NM. Epidural Fibrosis after Lumbar Disc Surgery: Prevention and Outcome Evaluation. Asian Spine J. 2015 Jun;9(3):370-85. doi: 10.4184/asj.2015.9.3.370. Epub 2015 Jun 8. PMID: 26097652; PMCID: PMC4472585.

Stage 2 epidural fibrosis scores are summarized in **Table 29**. All participants (3/3) in the HEMOBLAST™ Bellows group were categorized as either a score of 0 (1/3, 33.3%) or a score of 4 (2/3, 66.7%) with the average epidural fibrosis score being 2.7 ± 2.31. In the G+T group, one participant had a score of 4 (1/1, 100.0%%), with an average score of 4.0 ±. Overall, the rate of developing epidural fibrosis in stage 2 was similar between treatment groups.

Table 29. Summary of Stage 2 Epidural Fibrosis Scores.

	All (N=4)	HEMOBLAST™ Bellows (N=3)	G+T (N=1)
Epidural Fibrosis Score (Categorical)			
0	1/4 (25.0%)	1/3 (33.3%)	0/1 (0.0%)
1	0/4 (0.0%)	0/3 (0.0%)	0/1 (0.0%)
2	0/4 (0.0%)	0/3 (0.0%)	0/1 (0.0%)
3	0/4 (0.0%)	0/3 (0.0%)	0/1 (0.0%)
4	3/4 (75.0%)	2/3 (66.7%)	1/1 (100.0%)
Epidural Fibrosis Score (Continuous)	3.0 ± 2.00 (4) 4.0 [0, 4]	2.7 ± 2.31 (3) 4.0 [0, 4]	4.0 ± 0.00 (1) 4.0 [4, 4]

Numbers are mean ± SD (n)/ median [min, max] for continuous measures, and n/N (percent) for categorical measures.
Four subjects had MRI + Gd studies in Stage 2 of the study as determined to be clinically necessary by the investigator.

Arachnoiditis:
Arachnoiditis was not observed by the IAC in any subjects using methods established in the literature[5-7].

Secondary Endpoint:
Adverse Events:
There were 80 reported adverse events in the HEMOBLAST™ Bellows group, occurring in 27/40 (67.5%) of the subjects. In the G+T group, there were 41 reported adverse events, occurring in 13/20 (65.0%) of the subjects. The difference between groups was 2.50%. Mild adverse events occurred in 17.5% (7/40) of HEMOBLAST™ Bellows subjects and 15.0% (3/20) of G+T subjects. The difference between groups was 2.5%. Moderate adverse events occurred in 45.0% (18/40) of HEMOBLAST™ Bellows subjects and 45.0% (9/20) of G+T subjects. The difference between groups was 0.0%. Severe adverse events occurred in 5.0% (2/40) of HEMOBLAST™ Bellows subjects and 5.0% (1/20) of G+T subjects. Again, the difference between groups was 0.0%. There were no reports of device related adverse events or subjects with device related adverse events. Adverse events related to the investigational procedure occurred in 62.5% (25/40) of HEMOBLAST™ Bellows subjects and 50.0% (10/20) of G+T subjects. The difference between groups was 12.5%.

2. Efficacy Results

Efficacy was assessed as the proportion of subjects achieving hemostasis in each treatment group. Time-to-hemostasis was defined as the interval from the application of study intervention until investigator identified hemostasis at the pre-specified assessment time points of 3, 6, or 10 minutes after hemostat application. Hemostasis was assessed via the SBSS, with a score of 0 representing hemostasis.

An overview of the proportion of each treatment group that achieved hemostasis at 3, 6, and 10 minutes can be found in **Table 30**. Achievement of hemostasis at 3 minutes occurred in 84.4% (27/32) of HEMOBLAST™ Bellows subjects and 55.0% (11/20) of G+T subjects. The difference in achievement of hemostasis at 3 minutes between HEMOBLAST™ Bellows subjects and G+T subjects was 29.4%.

5.Ross JS, Masaryk TJ, Modic MT, Delamater R, Bohlman H, Wilbur G, Kaufman B. MR imaging of lumbar arachnoiditis. AJR Am J Roentgenol. 1987 Nov;149(5):1025-32. doi: 10.2214/ajr.149.5.1025. PMID: 3499773.
6.Delamarter RB, Ross JS, Masaryk TJ, Modic MT, Bohlman HH. Diagnosis of lumbar arachnoiditis by magnetic resonance imaging. Spine (Phila Pa 1976). 1990 Apr;15(4):304-10. doi: 10.1097/00007632-199004000-00011. PMID: 2353276.
7.Wright MH, Denney LC. A comprehensive review of spinal arachnoiditis. Orthop Nurs. 2003 May-Jun;22(3):215-9; quiz 220-1. doi: 10.1097/00006416-200305000-00010. PMID: 12803151.

Table 30. Proportion of Each Treatment Group Achieving Hemostasis at 3, 6, and 10 Minutes

	HEMOBLAST™ Bellows (N=32)	G+T (N=20)	Difference
3 minutes	27/32 (84.4%)	11/20 (55.0%)	29.4%
6 minutes	30/32 (93.8%)	16/20 (80.0%)	13.8%
10 minutes	31/32 (96.9%)	18/20 (90.0%)	6.9%

Numbers are n/N (percent).

9. Potential Adverse Events

Risks possibly related to the use of hemostats similar to HEMOBLAST™ Bellows 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 efficacy;
- Nerve deficit;
- Thrombosis or thromboembolism;
- Transmissible Spongiform Encephalopathies (TSE); and
- Viral disease transmission.

Hypersensitivity or allergic/anaphylactoid reactions may occur with HEMOBLAST™ Bellows. Symptoms associated with allergic anaphylactic reactions include: flush, urticaria, pruritus, nausea, drop in blood pressure, tachycardia or bradycardia, dyspnea, severe hypotension, and anaphylactic shock.

These reactions may occur in patients receiving HEMOBLAST™ Bellows for the first time or may increase with repetitive applications of HEMOBLAST™ Bellows. In the event of hypersensitivity reactions, discontinue administration of HEMOBLAST™ Bellows. Mild reactions can be managed with antihistamines. Severe hypotensive reactions require immediate intervention using current principles of shock therapy.

8. Symbols Glossary

Symbol	Standard	Reference #	Title	Definition
	ISO 15223-1	5.1.5	Batch code	Indicates the manufacturer's batch code so that the batch or lot can be identified.
	ISO 15223-1	5.1.6	Catalogue number	Indicates the manufacturer's catalogue number so that the medical device can be identified.
	ISO 15223-1	5.1.4	Use-by date	Indicates the date after which the medical device is not to be used.
	ISO 15223-1	5.3.7	Temperature Limit. Store between 2°C and 25°C (36-77°F).	Indicates the temperature limits to which the medical device can be safely exposed.
	ISO 15223-1	5.2.6	Do not re-sterilize	Indicates a medical device that is not to be resterilized.
	ISO 15223-1	5.2.8	Do not use if package is damaged and consult instructions for use	Indicates a medical device that should not be used if the package has been damaged or opened and that the user should consult the instructions for use for additional information.
	ISO 15223-1	5.4.2	Do not re-use	Indicates a medical device that is intended for one single use only.
	ISO 15223-1	5.4.3	Consult the instructions for use	Indicates the need for the user to consult the instructions for use.
	ISO 15223-1	5.2.4	Sterilized using irradiation	Indicates a medical device that has been sterilized using irradiation.
	ISO 15223-1	5.2.12	Double sterile barrier system	Indicates two sterile barrier system.
	ISO 15223-1	5.6.3	Non-Pyrogenic	Indicates a medical device that is non-pyrogenic.
	FDA Guidance "Alternative to Certain Prescription Device Labeling Requirements", issued 1/21/2000	N/A	Caution : Federal law restricts this device to sale on or by the order of a physician	Requires prescription in the United States.
	ISO 15223-1	5.1.1	Manufacturer	Indicates the medical device manufacturer.
	N/A	N/A	Contents	Numeral represents quantity of units inside the packaging.