PROSPECTIVE, RANDOMIZED, CONTROLLED, MULTICENTER, PIVOTAL, CLINICAL INVESTIGATION EVALUATING THE SAFETY AND EFFICACY OF HEMOBLAST™ BELLOWS IN CARDIOTHORACIC, ABDOMINAL, AND ORTHOPEDIC LOWER EXTREMITY SURGERIES

CLINICAL INVESTIGATIONAL PLAN

CIP Number	ETC 2015-002
CIP Version (Date)	Version 4.0 (20 June 2016)

Sponsor Address	Biom'Up SA 8, allée Irène Joliot Curie 69800 Saint-Priest France US Representative of Company: Elaine Whitmore, PhD Biom'Up Medical Expert: William Spotnitz, MD Chief Medical Officer, Biom'Up
Sponsor Contacts	Valérie Centis, Chief Scientific Officer Phone: +33 (0) 4 86 57 36 10 Fax: +33 (0) 4 37 69 00 84 E-mail: valerie.centis@biomup.com Elaine Whitmore, US Representative of Company Phone: +1 941 524 2546 E-mail: ejwhitmore@verizon.net
Monitor / Sponsor Representative	NAMSA 4050 Olson Memorial Hwy, Suite 450 Minneapolis, MN 55422 USA Phone: +1 (763) 287-3830 +1 (877) 814-7529 Fax: +1 (763) 287-3836

Table of Contents

Appendices

Clinical Investigational Plan

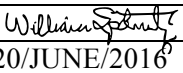
Approval Page

PROSPECTIVE, RANDOMIZED, CONTROLLED, MULTICENTER, PIVOTAL, CLINICAL INVESTIGATION EVALUATING THE SAFETY AND EFFICACY OF HEMOBLAST™ BELLOWS IN CARDIOTHORACIC, ABDOMINAL, AND ORTHOPEDIC LOWER EXTREMITY SURGERIES

This Clinical Investigational Plan has been read and approved by:

Sponsor

Name	Valérie Centis, PhD
Title, Institution	Chief Scientific Officer, Biom'Up
Signature	
Date (DD/MMM/YYYY)	

Name	William Spotnitz, MD
Title, Institution	Chief Medical Officer, Biom'Up
Signature	
Date (DD/MMM/YYYY)	20/JUNE/2016

Sponsor Representative

Name	Rachel Hoffman
Title, Institution	Principal Medical Research Manager, NAMSA
Signature	
Date (DD/MMM/YYYY)	20/JUNE/2016

Coordinating Investigator – United States

Name	William C Chapman, MD, FACS
Title, Institution	Professor of Surgery, Washington University in St. Louis
Signature	
Date (DD/MMM/YYYY)	

Clinical Investigational Plan

Principal Investigator Approval Page

PROSPECTIVE, RANDOMIZED, CONTROLLED, MULTICENTER, PIVOTAL, CLINICAL INVESTIGATION EVALUATING THE SAFETY AND EFFICACY OF HEMOBLAST™ BELLOWS IN CARDIOTHORACIC, ABDOMINAL, AND ORTHOPEDIC LOWER EXTREMITY SURGERIES

I, the undersigned, have read and understood the Clinical Investigational Plan specified above, and agree on the contents. The Clinical Investigational Plan and the Clinical Investigation Agreement will serve as a basis for cooperation in the clinical investigation.

Further, I agree to conduct the clinical investigation in accordance with the ethical principles that have their origin in the Declaration of Helsinki, guidelines of the International Conference on Harmonization (ICH) E6 Good Clinical Practice (GCP), United States (US) Code of Federal Regulations (CFR) [45 CFR Part 46; 21 CFR Parts 11, 50, 54, 56, and 812], and any other applicable national requirements.

I am aware of my responsibilities as a Principal Investigator. I agree to conduct the study according to these guidelines and to appropriately direct and assist the study staff.

Principal Investigator Name	
Institution	

Principal Investigator Signature	
Date (DD/MMM/YYYY)	

Clinical Investigational Plan

Revision History

Version Number (Date)	Summary of Revision(s)	Justification for Revision(s)
Version 1.0 (09 Feb 2015)	None – new document	Not applicable
Version 2.0 (16 Mar 2016)	• Remove spinal surgical arm • Change control device • Revise sample size and statistical section • Revise secondary efficacy endpoints • Revise inclusion/exclusion criteria	• Take FDA recommendations into account • Select control that is widely used hemostat with similar components as investigational device • Statistical updates to be consistent with anticipated performance of control device • Add superiority as secondary efficacy endpoints • Ensure inclusion/exclusion criteria are consistent with previous communications with FDA and cardiothoracic surgical arm, and removal of a spinal surgical arm
Version 3.0 (20 Apr 2016)	• Addition of preoperative exclusion criterion regarding application of investigational or control device at site of synthetic graft or patch	• Based on conference call with FDA on 20 April 2016
Version 4.0 (20 June 2016)	• Revise inclusion/exclusion criteria • Revise investigational device labeling information • Include antibody testing • Include additional details on control • Revise statistical section • Removal of Germany	• Based on additional modifications for consideration in the FDA approval letter for G160063 dated April 22, 2016

1 SYNOPSIS

Title	Prospective, Randomized, Controlled, Multicenter, Pivotal, Clinical Investigation Evaluating the Safety and Efficacy of HEMOBLAST™ Bellows in Cardiothoracic, Abdominal, and Orthopedic Lower Extremity Surgeries
Investigational Plan Number	ETC 2015-002
Purpose/Objectives	To evaluate the safety and efficacy of a new hemostatic device (HEMOBLAST™ Bellows) compared to a control device, absorbable gelatin sponge USP with thrombin.
Indication	HEMOBLAST™ Bellows is intended for use in surgical procedures as an adjunct to hemostasis when control of bleeding by conventional procedures is ineffective or impractical, except in neurosurgical, ophthalmic, and urological procedures.
Study Design	Prospective, randomized, controlled
Number of Subjects/Sites	A maximum of 450 subjects enrolled across a maximum of 25 investigational sites. A maximum of 50 lead-in subjects will be enrolled, with 400 subjects randomized, enrolled, and included in the primary analysis for efficacy; all subjects will be evaluated for safety.
Preoperative Inclusion Criteria	A subject must meet all of 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 consent for investigation participation; • Subject undergoing cardiothoracic surgery is not allergic to protamine; and • Subject is 21 years of age or older.
Preoperative Exclusion Criteria	A subject must not meet any 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 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.
Intraoperative Inclusion Criteria	A subject must 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 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.
Length of Investigation	The estimated duration of the study is approximately 10 months from the time of first subject enrollment to the last study protocol-required follow-up visit.
Follow-Up Schedule	6 ± 2 weeks postoperatively
Investigational Device	HEMOBLAST™ Bellows (Biom'Up, France), hereinafter referred to as HEMOBLAST™
Comparator Device	Surgifoam® (Ethicon™; Somerville, New Jersey) with Recothrom® (Zymogenetics, Inc.; Seattle, Washington); absorbable gelatin sponge USP and thrombin, hereinafter referred to as G+T

Primary Endpoint	The primary efficacy endpoint of this clinical investigation is non-inferiority of HEMOBLAST™ relative to G+T for success at achieving hemostasis within 6 minutes.
Secondary Endpoints	The secondary efficacy endpoints of this clinical investigation are: • 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.

2 INTRODUCTION

2.1 Purpose

The purpose of this study is to evaluate the safety and efficacy of HEMOBLAST™ Bellows, a hemostatic device.

2.2 Device Name

HEMOBLAST™ Bellows (hereinafter referred to as HEMOBLAST™) will be used in this study.

2.3 Intended Use

HEMOBLAST™ is intended for use in surgical procedures as an adjunct to hemostasis when control of bleeding by conventional procedures is ineffective or impractical, except in neurosurgical, ophthalmic, and urological procedures.

2.4 Study Overview

2.4.1 Duration of the Study

The estimated duration of the study is approximately 10 months from the time of first subject enrollment to the last study protocol-required follow-up visit. Each subject will be followed for 6 ± 2 weeks.

2.4.2 Number of Subjects and Investigational Sites

A maximum of 450 subjects will be enrolled across a maximum of 25 investigational sites in the United States. Four hundred patients will be randomized, enrolled, and evaluated for efficacy (Time to Hemostasis [TTH] Population). There will be a maximum of 50 lead-in subjects (one per enrolling investigator).

On average, approximately 18 subjects will be enrolled per site, with no more than 15% of the total TTH Population (60 subjects) being enrolled at any single site.

2.5 Sponsor Contact Information

Biom'Up SA
8, allée Irène Joliot Curie
69800 Saint-Priest
France

Valérie Centis, Chief Scientific Officer
Phone: +33 (0) 4 86 57 36 10
Fax: +33 (0) 4 37 69 00 84

Elaine Whitmore, US Representative of Company
Phone: +1 941 524 2546
E-mail: ejwhitmore@verizon.net

3 INVESTIGATIONAL DEVICE DESCRIPTION

3.1 Investigational Device Description and Intended Use

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

HEMOBLAST™ is composed predominantly of highly purified porcine collagen with smaller amounts of bovine chondroitin sulfate and human derived thrombin. Each device contains a maximum of 1500 IU of thrombin in 1.65 g of powder. 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 WHO.

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

HEMOBLAST™ Bellows is intended for use in surgical procedures as an adjunct to hemostasis when control of bleeding by conventional procedures is ineffective or impractical, except in neurosurgical, ophthalmic, and urological procedures.

The Instructions for Use are included as Appendix A.

3.2 Investigational Device Manufacturer Details

The manufacturer of the HEMOBLAST™ investigational device is Biom'Up, which is located in Saint Priest, France. Biom'Up is ISO 13485 certified.

3.3 Control Device

The control device for this clinical investigation is absorbable gelatin sponge USP with thrombin (hereinafter referred to as G+T). Specifically, the absorbable gelatin sponge USP will be Surgifoam®

(Ethicon™; Somerville, New Jersey). The thrombin will be Recothrom® 5mL kit (Zymogenetics, Inc.; Seattle, Washington).

Recothrom® labeling also states "RECOTHROM may be used in conjunction with an absorbable gelatin sponge, USP."

G+T was selected as the control because:

1. G+T is one of the most frequently used hemostats in the US;[1]
2. G+T components are similar to those in HEMOBLAST™;
    a. Surgifoam® is composed of porcine gelatin,
    b. Recothrom® is topical recombinant human thrombin and contains 5,000 IU of thrombin in the 5mL kit with a concentration of 1,000 IU/mL of thrombin,
    c. The risk profile of G+T is similar to that of HEMOBLAST™, due to the similarity of components and type of thrombin (recombinant human thrombin).
3. FDA has recognized G+T as an appropriate control in other hemostatic agent studies, as summarized in Table 1 below. These studies include use in all three of the surgical applications that will be included in this pivotal clinical investigation (cardiothoracic, abdominal, and orthopedic). The use of G+T has been approved for each of these types of surgery and its safety and efficacy is supported with clinical data.[1, 2, 3, 4, 5]

Table 1. Hemostatic Product Clinical Trials

Biologic			
Hemostatic Product	**Surgical Arms**	**Control Hemostat**	**Source**
Raplixa	Cardiovascular, Spine, General (liver, soft tissue)	Gelatin sponge	U.S. Food and Drug Administration, Center for Biologics Evaluation and Research. FDA approves Raplixa to help control bleeding during surgery; FDA News Release, April 30, 2015. http://www.fda.gov/newsevents/newsroom/pressannouncements/ucm445247.htm U.S. Food and Drug Administration, Center for Biologics Evaluation and Research. Summary Basis for Regulatory Action: Raplixa Fibrin Sealant, April 3, 2015. http://www.fda.gov/downloads/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/LicensedProductsBLAs/FractionatedPlasmaProducts/UCM447129.pdf
Recothrom	Cardiovascular, Spine, Abdominal	Bovine thrombin + Gelfoam	U.S. Food and Drug Administration, Center for Biologics Evaluation and Research. Chairman's Summary—RECOTHROM, January 11, 2008. http://www.fda.gov/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/LicensedProductsBLAs/FractionatedPlasmaProducts/ucm120565.htm
Medical Device			
Floseal	Cardiac, Vascular, Spine	Gelfoam + Thrombin	U.S. Food and Drug Administration, Center for Devices and Radiological Health. Summary of Safety and Effectiveness; FloSeal™ Matrix P990009, December 8, 1999. http://www.accessdata.fda.gov/cdrh_docs/pdf/P990009b.pdf
Surgifoam	Cardiovascular, Orthopedic,	Gelfoam	U.S. Food and Drug Administration, Center for Devices and Radiological Health. Summary of Safety and Effectiveness; Surgifoam Absorbable Gelatin Sponge USP, P990004, September

[1] DNA Ink Study. US hemostat sales. (*IMS MIDAS 2013, Evaluate Pharma 2013, Frost & Sullivan 2006 & 2008*); market research report retained at Sponsor

	General		30, 1999. http://www.accessdata.fda.gov/cdrh_docs/pdf/P990004b.pdf

3.4 Device Storage and Accountability

Following the execution of all applicable contracts, receipt of essential documents from the investigational site, and approval by the applicable Regulatory Authorities (FDA) and applicable Institutional Review Boards (IRBs), investigational product will be shipped to the investigational site. The Sponsor is responsible for the traceability and accountability for the investigational product being used in this study.

Investigational product will be traced using lot numbers. The Sponsor or designated Sponsor representative will verify that the investigational device is being properly stored and accounted for during the conduct of the clinical investigation. Each investigational site will identify a designee who will be held responsible for controlling the investigational device and ensuring that it is dispensed only for the purposes of this investigation. This designee will be expected to retain all unopened, unused, investigational product supplied until the completion of the investigation or until the Sponsor or designated Sponsor representative has made arrangements for the return or proper destruction of unused investigational product.

3.5 Investigational Device Packaging and Labeling

HEMOBLAST™, the investigational device, is supplied as bellows pre-loaded with hemostatic powder. The bellows contains 1.65g of implant material. The product is sterilized using gamma irradiation and is provided in double-packaging.

HEMOBLAST™ will be specifically labeled for this investigation as "Investigational Product" per applicable laws and regulations. Use of the device outside of this clinical investigational plan is strictly prohibited; further, the instructions for use will be strictly followed.

4 BACKGROUND AND RATIONALE

4.1 Definition of Hemostasis

Despite advances in surgical techniques, excessive bleeding remains a major complication associated with surgery and contributes to poor clinical outcomes.[6] There is no universally accepted definition of hemostasis. The most current definition is the "cessation of bleeding."[7] The term comes from the Greek roots *heme* (blood) and *stasis* (halt). Hemostasis can be considered as control of bleeding within the finely tuned balance of procoagulant, anticoagulant, fibrinolytic, and anti-fibrinolytic activities.[8]

Hemostasis refers to the process of causing blood to form a clot (the opposite of hemostasis is hemorrhage). Most of the time, this process includes the changing of blood from a fluid to a solid state. Intact blood vessels are central to moderating blood's tendency to clot. The endothelial cells of intact vessels prevent blood coagulation by secretion of heparin-like molecules and thrombomodulin and prevent platelet aggregation by the secretion of nitric oxide and prostacyclin. When endothelial injury occurs, the endothelial cells cease secretion of coagulation and aggregation inhibitors and instead secret von Willebrand factor and tissue thromboplastin which initiate the maintenance of hemostasis after injury. Hemostasis has three major steps: vasoconstriction, formation of a platelet plug, and blood coagulation.

4.2 Current Hemostatic Therapeutic Strategies

Hemorrhage control is vital for successful clinical outcomes after surgery. It is essential to decrease postoperative morbidity and operative time, leading to potential cost savings.[9, 10, 11] During surgical operations, it is important to maintain a fine balance between bleeding and clotting so that blood continues to flow to the tissues at the surgical site without excessive blood loss. There are many tools used for hemorrhage control; these include preventive measures, transfusion of blood products, and traditional methods.[6]

A variety of manual, mechanical, and thermal techniques are available for maintaining hemostasis in surgery. Application of direct pressure or compression at a bleeding site is often the Investigator's first choice to assist in the control of bleeding. The placement of direct pressure over the injury site serves to compress vascular structures and promote localized clotting. Direct pressure, while widely accepted as standard of care for the control of all levels of bleeding severity, has limited discourse in the surgical literature. Other mechanical methods, including sutures, staples, and ligating clips, are useful if the source of bleeding is easily identifiable and able to be sealed.[11]

Compression and other mechanical methods may not be appropriate during all surgical procedures; this method of controlling bleeding may not be sufficient when the source of bleeding is hard to identify, as for diffuse venous bleeding.[12] Moreover, the mechanical methods are not applicable in some surgical procedures because of localization and the inaccessibility of structures.

To summarize, these techniques show their limits in terms of bleeding control efficacy.[11, 12, 13, 14, 15] Furthermore, they may be associated with the occurrence of complications.[14]

Since ancient times, hemostasis has also been facilitated by application of local agents.[16] One of the earliest local hemostatic agents was cotton, in the form of gauze sponges. Absorbable local hemostatic agents have since been developed and they currently provide useful adjunctive therapy when conventional methods of hemostasis are ineffective or impractical. Local agents can be applied directly to the bleeding site and may prevent continuous bleeding throughout the entire surgical procedure and during the post-operative recovery period.

4.3 Assessment of Bleeding

A method for the consistent assessment of bleeding that is applicable to any surgical procedure is important for use in a clinical investigation assessing the performance of a hemostatic agent.

The goal is to ensure that the hemostat is applied when control of bleeding by conventional procedures is ineffective or impractical, but not applied to severe bleeding for which hemostatic agent is not designed to control. It is also important to ensure consistency of bleeding severity assessments across investigators and that similar bleeding severities are enrolled during the trial.

An estimate of total intraoperative blood loss is an integral part of any surgical procedure and is considered routine care. The wide variety of surgical specialties and operations make quantitative standardization of total blood loss difficult, yet estimates may still be provided. Estimating total blood loss during a surgical procedure, supplemented with other variables such as blood pressure, are data helpful for the ongoing evaluation of a subject's condition and the assessment/modification of intra- and post-operative management.

A tool to assess the severity of intraoperative bleeding at a target bleeding site (TBS) has been developed and validated by the Sponsor. This Surface Bleeding Severity Scale (SBSS) will be used to evaluate bleeding, as well as hemostasis, for the purposes of this clinical investigation.

The SBSS was developed by Biom'Up in cooperation with the FDA. This method of bleeding severity assessment was validated in preclinical and clinical studies and will be used in this clinical investigation. The utility of the SBSS was confirmed in a clinical setting during the pilot clinical investigation, also providing initial data on the safety and efficacy of HEMOBLAST™. The agreement between Investigators utilizing the SBSS in the pilot clinical study met all pre-defined criteria. Satisfactory assessment with respect to agreement of bleeding severity, hemostasis, and eligibility using the SBSS was demonstrated in the pilot clinical investigation, substantiating its use in this pivotal clinical investigation.

Severity of bleeding of the TBS for each subject in the clinical investigation will be assessed by assignment of an SBSS score, as defined in Table 2 below.

Table 2. Surface Bleeding Severity Scale (SBSS)

SBSS 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[2] Shock Risk Class	1	1	1	2	3	4

[1] 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 – involves 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.

The SBSS will be used to determine the intraoperative eligibility (described further in Section 5.5.1.3) as well as hemostatic success (described further in Section 6.4.3). Use of the SBSS will ensure consistent enrollment of TBSs of similar bleeding severities and help ensure subject safety by excluding those who have severe bleeding.

Investigators will be trained and tested on the SBSS prior to their enrollment of any subjects into the clinical investigation, as described further in Appendix D.

4.4 Rationale

Although the properties of the ideal local hemostatic agent may vary according to the surgical specialty, some properties are universally valued including: rapid and effective control/cessation of bleeding; ability to make effective contact with the bleeding surface; acceptable safety profile; and ease of preparation and use.

According to Spotnitz *et al,* the ideal hemostat, sealant or adhesive must have certain performance characteristics (safety, efficacy, usability, cost, and approvability) that enable it to be used by Investigators.[17] No single product can yet be used for all potential applications. The challenge is to develop a local agent that may combine all those characteristics.

Biom'Up (France) has developed and manufactured a new medical device, HEMOBLAST™, which is intended for use in surgical procedures as an adjunct to hemostasis when control of bleeding by

conventional procedures is ineffective or impractical. A clinical investigation is warranted to assess the safety and efficacy of this hemostat.

5 METHODOLOGY

5.1 Overall Study Design

This is a prospective, randomized, controlled, multicenter, clinical investigation.

5.1.1 Objectives

The objective of this pivotal clinical investigation is to evaluate the safety and efficacy of a new hemostatic device (HEMOBLAST™) compared to G+T.

5.2 Primary Efficacy Endpoint

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

5.3 Secondary Efficacy Endpoints

The secondary efficacy endpoints of this clinical investigation are:

- 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.

5.4 Additional Exploratory Outcomes

The additional exploratory outcomes of this clinical investigation that will be described and quantified are:

- Operative time for HEMOBLAST™ subjects compared to G+T subjects;
- Duration of hospitalization for HEMOBLAST™ subjects compared to G+T subjects; and
- Number of units of blood transfused intraoperatively for HEMOBLAST™ subjects compared to G+T subjects.

5.5 Subject Selection Criteria

A maximum of 450 (400 efficacy, maximum of 50 lead-in) subjects undergoing elective open cardiothoracic, abdominal, and orthopedic lower extremity surgeries will be enrolled into the clinical investigation. Subjects will need to meet all eligibility criteria to be enrolled into the investigation, as detailed below.

5.5.1.1 Preoperative Inclusion Criteria

A subject must meet all of 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.

5.5.1.2 Preoperative Exclusion Criteria

A subject must not meet any 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 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[3];
- 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;

[3] ASA Classification: 1 – normal health patient; 2 – patient with mild systemic disease; 3 – patient with severe systemic disease; 4 – patient with severe systemic disease that is constant threat to life; 5 – moribund patient who is not expected to survive with the operation; 6 – a declared brain-dead patient whose organs are being removed for donor purposes

- 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.

5.5.1.3 Intraoperative Inclusion Criteria

A subject must 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 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.

Table 3. Enrollment Based on SBSS Score

SBSS 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
Eligible for Enrollment	**No**	**Yes**	**Yes**	**Yes**	**No**	**No**

5.6 Point of Enrollment

All patients presenting to the Investigator for elective (non-emergent) open cardiothoracic, abdominal, or orthopedic lower extremity surgical procedures are potential study subjects and should be screened for eligibility. Subjects will need to meet all eligibility in order to be enrolled into the investigation.

A subject is enrolled when he/she meets all preoperative inclusion/exclusion criteria, signs the informed consent forms, and meets the intraoperative inclusion criteria. The point of enrollment into the clinical investigation will occur intraoperatively.

5.7 Withdrawal Criteria

Subjects may withdraw from the clinical investigation at any time without providing a reason. Subjects will not be penalized nor lose any benefits to which they are otherwise entitled if they should choose to withdraw. The Investigator may also choose to withdraw the subject if he or she feels that this is in the subject's best interest.

The possible situations for subject withdrawal will be managed as such:

- Subjects who withdraw from the study after receiving investigational device will be followed for safety through the end of the study if they agree. Efforts will be made to collect any final data and information regarding the reason for withdrawal. Data collected prior to withdrawal from the study may be used in in study analyses; or
- Subjects who withdraw from the study before receiving investigational device receive routine care. No study-specific safety or efficacy assessments will be conducted.

5.8 Subject Compliance

Every reasonable effort will be made to maintain subject compliance and participation in the clinical investigation until final follow-up is completed.

Subject loss to follow-up is not expected to impact the efficacy analysis, as the efficacy endpoints are collected intraoperatively. However, it is still important for subjects to complete the 6 ± 2 week follow-up to assess safety. The investigational site will make all reasonable efforts to contact those subjects who do not return for the 6 ± 2 week follow-up visit to collect as much follow-up information as possible to assess investigational device safety.

6 INVESTIGATIONAL PROCEDURES

6.1 Schedule Overview

Table 3 details the clinical investigation visits, corresponding timing, and evaluations to be performed at the visit. Table 4 lists the CRFs that need to be completed at each visit. Figure 1 represents the subjects' participation in the clinical investigation.

Table 4. Investigational Evaluation Schedule

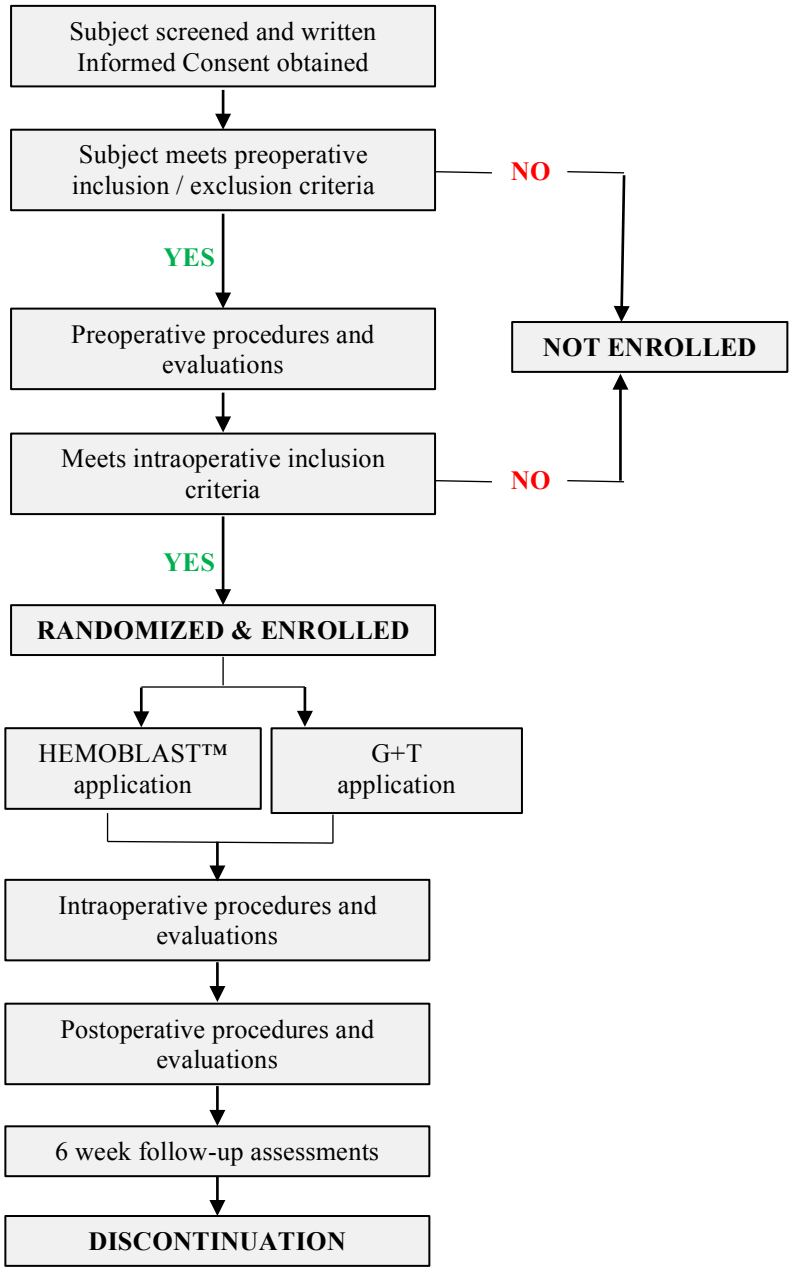
Visit	Timing	Evaluations
Preoperative	Within 4 weeks before surgery	Informed consent, preoperative eligibility criteria confirmation, preoperative evaluations, and blood draw for antibody evaluation
Intraoperative	Day of surgery; day 0	Intraoperative inclusion criteria confirmation, efficacy assessments, and safety assessments
Postoperative	Postoperative day 1	Safety assessments
6 Week Follow-Up	6 weeks (± 2 weeks) postoperatively	Safety assessments, blood draw for antibody evaluation, and study discontinuation

Table 5. CRF Completion Schedule

CRF	Screening	Preoperative	Intraoperative	Postoperative	Follow-Up	Discontinuation
Preoperative Eligibility CRF	**X**					
Preoperative CRF		**X**				
Intraoperative CRF			**X**			
Concomitant Medication CRF		**O**	**O**	**O**	**O**	
Laboratory CRF		**X**		**X**		
Postoperative CRF				**X**		
Follow-Up CRF					**X**	
Discontinuation CRF						**X**
Adverse Event CRF			**O**	**O**	**O**	
Device Deficiency CRF			**O**			
Reoperation CRF				**O**	**O**	

X	Mandatory
O	As applicable

Figure 1. Subject Participation in the Clinical Investigation



6.2 Screening Evaluations

*6.2.1 **Informed Consent***

Prior to performing any study specific procedures, a detailed explanation of the study procedures, potential discomforts, risks and benefits of participation, and alternatives will be reviewed with potential study subjects by a qualified member of the study team. The informed consent process will follow applicable institutional and regulatory guidelines. Subjects will be provided adequate

time to review the informed consent document and all questions will be answered to the satisfaction of the subject prior to signing the informed consent.

If the subject is willing to participate in the clinical investigation, he/she or an authorized legal representative must sign the informed consent form indicating that they have read and understand the information provided. Each site will follow their local IRB and applicable regulatory guidelines for obtaining informed consent. Documentation of the informed consent process for each subject and the original signed informed consent will be retained at the site and as required by applicable regulations.

6.2.2 Preoperative Eligibility

Once written informed consent has been obtained, the Preoperative Eligibility CRF will be completed to document adherence to the preoperative inclusion and exclusion criteria from Section 5.5.

Where a subject fails to fulfill any element of the preoperative eligibility criteria, this will be documented and any signed consent form and completed preoperative inclusion/exclusion criteria retained by the Principal Investigator. The subject will not be advanced any further into this clinical investigation.

6.2.3 Subject Identification

After a subject has signed informed consent and/or met the preoperative inclusion and exclusion criteria, the subject will be allocated to the next available investigation number (subject ID number).

The subject ID number will consist of the site number and the subject number. The subject number will be 01 for the first subject, 02 for the second subject and so on. This subject ID number will be the unique identifier of the subject and included on each CRF page and all other investigational documentation relating to that subject.

6.3 Preoperative Procedures and Evaluations

The following data will be collected and recorded at the preoperative visit on the Preoperative CRF:

- Demographic data;
  - Age,
  - Gender,
  - Race and ethnicity,
- Physical exam and laboratory tests;
  - Height,
  - Weight,
  - Diastolic and systolic blood pressure,
  - CBC (Laboratory CRF),
  - Coagulation status (Laboratory CRF),
  - Chemistry panel (Laboratory CRF),
  - Pregnancy test for females of child-bearing age (Laboratory CRF),
  - Blood draw for antibody testing,
- Medical history; and
  - Coagulation disorder(s),

- History of bleeding requiring hospitalization in the last five years,
- Disease process / indication for surgery,
- Concomitant illnesses,
- Surgical history related to the surgical area,
- Diabetes,
- Smoking history,
- Malignancies and prior therapies,
- Hepatic disease,
- Concomitant medications potentially impacting coagulation status (Concomitant Medication CRF).

The Laboratory CRF will be completed and applicable concomitant medications will be recorded on the Concomitant Medication CRF. A blood draw for antibody testing will be performed and handled per specified procedures agreed upon with the investigational site and core laboratory.

6.4 Intraoperative Procedures and Evaluations

All subjects will undergo the same intraoperative investigational evaluations. Intraoperative is defined as the time interval from when the subject enters the surgical suite until the subject exits the surgical suite.

Subjects undergoing the open elective cardiothoracic, abdominal, and orthopedic lower extremity surgeries are eligible for enrollment into the clinical investigation. The Investigator will perform the surgery per his or her standard procedures, including conventional methods of hemostasis (pressure, ligature, cautery, etc.).

6.4.1 Intraoperative Inclusion Criteria

A subject must then meet all of 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 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.

If all of these intraoperative eligibility criteria are met, then the subject is formally randomized and enrolled into the clinical investigation (unless the subject is a lead-in subject; all lead-in subjects will receive HEMOBLAST™).

6.4.2 Randomization and Hemostat Application

At the start of each surgical procedure, a single HEMOBLAST™ device and a single G+T device will both be prepared per the respective Instructions for Use (unless the subject is a lead-in subject; all lead-in subjects will have a single HEMOBLAST™ device prepared). The preparation time for both devices will be recorded for the TTH Population subjects.

Randomization will be performed through sequentially numbered sealed envelopes. Four-hundred subjects (TTH Population) will be randomized to receive HEMOBLAST™ or G+T in a 2:1 ratio:

- 267 subjects will be randomized to receive HEMOBLAST™; and
- 133 subjects will be randomized to receive G+T.

There will be a maximum of 50 lead-in subjects; these subjects will not be randomized. The first subject for each investigator will be treated as a lead-in subject. These subjects will receive HEMOBLAST™ and will be followed for safety only (maximum Full Analysis Population of 450); lead-in subjects will not count towards the TTH Population. Please see Section 12 below for additional detail on subject populations.

Randomization will be stratified by surgical indication and will incorporate blocking; additional details of randomization and blocking will be included in a separate Randomization Plan.

After randomization and enrollment, the assigned hemostat will be used in the investigational subject; the other hemostat will be discarded following institutional procedures.

A study-specific stopwatch will be used to track hemostat application and the times of hemostasis evaluation. The time of initial hemostat application will be considered time 0; at this time, the stopwatch will be started by the study coordinator. The stopwatch will run continuously without stopping.

Hemostasis will be evaluated by the investigator at the following time points until hemostasis has been achieved:

- 3 minutes;
- 6 minutes; and
- 10 minutes.

Reapplication of the randomized hemostat will be performed at the 3 minute and 6 minute evaluation time points, as described below.

For cardiothoracic procedures, the TBS will be identified after heparin reversal. Additionally, the TBS will not be at the site of a valve implant or at the site of a synthetic graft or patch implant.

HEMOBLAST™ will be applied according to its instructions for use.

1. Peel open the pouches to remove contents with attention to sterile procedures.
2. Remove cap using a twisting motion.
3. 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 before application.
4. Apply hemostatic implant material to the source of bleeding by squeezing the bellows. Enough implant material should be applied to cover the entire source of bleeding.
5. Immediately use a wet laparotomy pad to hold the hemostatic material at the target bleeding site using wound appropriate pressure to conform the powder to the source of bleeding.
6. Maintain the hemostatic material at the target bleeding for approximately three minutes. Gently lift the laparotomy pad and inspect the area.
7. If hemostasis has not been achieved, repeat steps 3-6 or use an alternate method of hemostasis treatment.
8. Discard any unused product after opening.

HEMOBLAST™ contraindications include:

- Do not inject directly into the blood vessels.
- 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 HEMOBLAST™ Bellows for treatment of severe or brisk bleeding.
- Do not administer to patients with known allergies or hypersensitivity to materials of porcine or bovine origin.
- To avoid risk of allergic-anaphylactoid reaction and/or thromboembolic events, which may be life-threatening, do not inject HEMOBLAST™ Bellows into a vessel or tissue.
- 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.

After randomization, G+T will be applied to the TBS per the Instructions for Use for subjects assigned to this treatment group.

6.4.3 Bleeding Severity and Hemostasis Evaluations

Bleeding severity and hemostasis will be assessed using the SBSS.

An SBSS score will be assigned at the following time points until hemostasis is achieved:

- Baseline – when evaluating intraoperative eligibility;
- 3 minutes;
- 6 minutes; and
- 10 minutes.

An SBSS score of 0 is equivalent to hemostasis. All other SBSS scores are considered failure of hemostasis. See below in Table 6.

Table 6. Bleeding Severity and Hemostasis

SBSS 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
Hemostasis	**Yes**	**No**	**No**	**No**	**No**	**No**

In cases where the target bleeding site is still bleeding at the 3 minute or 6 minute assessment time points, repeat application of the randomized hemostat will be performed.

In cases where hemostasis is not achieved by 10 minutes, the Investigator may use whatever means necessary in order to control bleeding, except for any hemostatic products containing thrombin or aprotinin (Thrombin-JMI, Evithrom, Floseal, Tisseel, Evicel, Tachosil, Evarrest). Recothrom should not be used in subjects randomized to receive HEMOBLAST™, but may be used in subjects randomized to the G+T arm.

In any case where hemostasis is initially achieved but bleeding recurs prior to subject closure, the event will be documented and treated as an adverse event, and the time of observation of the re-bleed will be recorded.

6.4.4 Other Bleeding Sites

For bleeding sites other than the TBS, the Investigator may use any means necessary to control bleeding, except for any hemostatic products containing thrombin or aprotinin (Thrombin-JMI, Evithrom, Floseal, Tisseel, Evicel, Tachosil, Evarrest). Recothrom should not be used in subjects randomized to receive HEMOBLAST™, but may be used in subjects randomized to the G+T arm.

The Investigator may also use any of the remaining randomized hemostat on these bleeding sites.

6.4.5 Intraoperative Data Collection

The following data will be recorded on the Intraoperative CRF:

- Surgical procedure(s);
- Preparation times for each device;
- Description of TBS;
    - Location,
    - Tissue type,
    - Conventional means for hemostasis (pressure, suture, cautery, etc.),
- Confirmation of intraoperative eligibility criteria;
- Approximate dimensions of target bleeding site;
- SBSS score at baseline and each evaluation time point (3, 6, and/or 10 minutes) until hemostasis is achieved;
- Randomization;
    - Randomization envelope number,
    - Time of randomization,
    - Treatment arm and device lot/batch number data,
- Hemostat application;
    - Application amount
    - HEMOBLAST™ application amount will be approximated by indicating the amount of powder left in the bellows after application
    - G+T application amount will be documented by approximating the dimensions of Surgifoam sponge applied
- Rescue treatment(s), if any;
- Use of other hemostatic agent(s), if any;
- Skin open and skin closure times;
- Intraoperative administration of blood products;
- Total intraoperative estimated blood loss;
- Incidence of any device deficiencies; and

- Incidence of any complications or adverse events.

The Concomitant Medication, Adverse Event, and Device Deficiency CRFs will be completed as applicable.

Table 7 below shows a timeline of intraoperative procedures.

Table 7. Timeline for Intraoperative Procedures*

Time Point (Minutes:Seconds)	Study Procedures or Assessments
Prior to 00:00	• Prepare both hemostatic devices and record time of preparation • Identify Target Bleeding Site (TBS) • Assign SBSS score • Perform randomization (unless lead-in subject)
00:00	• Start stop-watch • Apply HEMOBLAST™ or G+T
03:00	• Assign SBSS score ***If SBSS = 0*** • Intraoperative efficacy evaluation completed ***If SBSS is NOT 0*** • Re-apply HEMOBLAST™ or G+T
06:00	• Assign SBSS score ***If SBSS = 0*** • Intraoperative efficacy evaluation completed ***If SBSS is NOT 0*** • Re-apply HEMOBLAST™ or G+T
10:00	• Assign SBSS score ***If SBSS = 0*** • Intraoperative efficacy evaluation completed ***If SBSS is NOT 0*** • Rescue treatment

* Assuming subject meets all intraoperative eligibility criteria

The Concomitant Medication, Reoperation, and Adverse Event CRFs will be completed as applicable.

6.5 Postoperative Procedures and Evaluations

All subjects will undergo the following assessments within 24 hours postoperatively, which will be recorded on the Postoperative CRF:

- CBC (Laboratory CRF);
- Postoperative visit date;
- Coagulation status (Laboratory CRF);
- Chemistry panel (Laboratory CRF);
- Clinical signs or symptoms of bleeding;

- Any administration of blood products;
- Incidence of reoperation for bleeding; and
- Incidence of any complications or adverse events.

The Laboratory CRF will be completed and the Concomitant Medication, Reoperation, and Adverse Event CRFs will be completed as applicable.

6.6 Follow-Up Procedures and Evaluations

All subjects will undergo the following assessments 6 weeks ± 2 weeks postoperatively, which will be recorded on the Follow-Up CRF:

- Date of hospital discharge;
- Signs or symptoms of bleeding;
- Blood draw for antibody testing;
- Incidence of reoperation for bleeding; and
- Incidence of any complications or adverse events.

The Concomitant Medication, Reoperation, and Adverse Event CRFs will be completed as applicable. A blood draw for antibody testing will be performed and handled per specified procedures agreed upon with the investigational site and core laboratory.

6.7 Discontinuation Procedures and Documentation

The Discontinuation CRF should be completed in the following cases:

- Subject has completed the 6 week follow up;
- Subject withdrawal;
- Subject death; or
- Subject loss to follow-up.

The reason for discontinuation and the date of discontinuation will be noted on the Discontinuation CRF.

6.8 Reoperation Documentation

In cases of reoperation, the following evaluations will be recorded on the Reoperation CRF:

- Date of reoperation;
- Description of surgical procedure;
- Reason for reoperation; and
    - If for bleeding, an Adverse Event CRF will need to be completed
- Previous target bleeding site assessments, if able; and
    - If hemostat (HEMOBLAST™ or G+T) is visually present,
    - If the site is still bleeding,
    - Any other significant findings (e.g., infection, adhesion, etc.).

7 ADVERSE EVENTS

7.1 General

An adverse event (AE) is defined according to the European Standard EN ISO 14155 as 'any untoward medical occurrence in a subject'. An adverse event related to a device is defined as an 'adverse device effect' (ADE) and is defined as 'any untoward and unintended response to an investigational medical device'.

An adverse event or an adverse device effect may be mild, moderate or severe and are usually unexpected.

A device deficiency is defined as the inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance, which may include device malfunctions, use errors and inadequate labeling.

All adverse events, adverse device effects, and or device deficiencies, either observed by the Principal Investigator or reported by the subject, must be reported to the Sponsor/Sponsor representative. To report an adverse event or adverse device effect or device deficiency, the Principal Investigator will complete an adverse event report form or relevant form located in the Case Report Form. The report will include the following information: nature, severity, date of onset, duration, course and history of the adverse event/adverse device effect and causality. The subject will be questioned about any adverse event(s) and adverse device effect(s) at each visit.

Expected adverse events and anticipated adverse device effects are included in Section 13.

7.2 Adverse Event Documentation

Adverse events will be documented by the Principal Investigator on the appropriate source document(s) at the investigational site and also on the Adverse Event CRF. Adverse events are to be recorded and dated according to when they are first observed. The subsequent treatment(s) should also be documented. The following will be recorded on the Adverse Event CRF:

- Accepted medical term for the event;
- Description of the event;
- Date of onset;
- Date of resolution, if applicable;
- Outcome;
- Treatment(s)/action(s) taken;
- Severity;
- Relationship to the investigational device; and
- Determination of reportability (see Reporting Section below).

The severity of the event will be determined by the Principal Investigator using the following definitions:

- Mild: the symptoms are transient, barely perceptible by the subject and do not hinder normal activity; no treatment is usually prescribed to reduce these symptoms;
- Moderate: the symptoms are sufficiently severe to provoke discomfort in the subject and sufficiently uncomfortable to prevent normal activity; a treatment may be required; or
- Severe: the symptoms considerably modify the normal course of the subject's activities or are disabling or are life-threatening; the treatment studied should be suspended; a treatment for the symptoms is prescribed.

The relationship to the investigational device will be determined by the Principal Investigator using the following definitions:

- Not related: the adverse event is due to the underlying disease state or is due to concomitant medications or therapy not related to the use of the device;
- Possibly related: the adverse event has a reasonable temporal relationship to the use of the device but alternative etiology is equally or more likely compared to the potential relationship to the use of the device;
- Probably related: the adverse event has a strong temporal relationship to the use of the device and alternative etiology is less likely compared to the potential relationship to the use of the device; or
- Definitely related: the adverse event has a strong temporal relationship to the use of the device, follows a known response pattern and cannot reasonably be explained by known characteristics of the subject's clinical state or other therapies.

The expectedness of the adverse event will be determined by the Principal Investigator as:

- Anticipated; or
- Unanticipated.

7.3 Reporting

A serious adverse event (SAE) is defined as an adverse event that:

- Led to death;
- Led to a serious deterioration in the health of the subject, that either resulted in a life-threatening illness or injury, or a permanent impairment of a body structure or a body function, or in-patient hospitalization or prolongation of existing hospitalization, or resulted in medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function; or

A serious adverse device effect (SADE) is defined as an adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event or that might have led to any of these consequences if suitable action had not been taken or intervention had not been made or if circumstances had been less opportune.

An unanticipated [serious] adverse device effect (UADE/USADE) is any serious adverse effect on health or safety, any life-threatening problem or death caused by, or associated with a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the protocol; or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

All SAEs, SADEs, and UADEs must be reported to the Sponsor representative within 24 hours of the Principal Investigator becoming aware of it.

There are two methods of reporting. The first is to complete and save the Serious Adverse Event eCRF within 24 hours of the Principal Investigator becoming aware of the SAE, SADE, or UADE.

The second method of reporting is to contact the Sponsor representative for event reporting:

Contact Name: Rachel Hoffman

Telephone Number: +1 404 702 9253 (24 hour availability)
E-Mail: rhoffman@namsa.com

The Principal Investigator should institute appropriate therapeutic and follow-up measures in accordance with good medical practice and record them in the subject's source documentation and on the Adverse Event CRF. It is the responsibility of the Principal Investigator to inform the appropriate personnel as required by IRB policy.

For SAEs that are unresolved, the Principal Investigator will continue to follow the event to resolution per standard medical care. Serious adverse event follow-up information regarding resolution will be provided to the Sponsor representative until the subject completes the 6 week follow-up and is discontinued from the clinical investigation. If the subject is discontinued prior to resolution of the event, the Principal Investigator will continue to follow the event until the event is deemed medically stable or resolved. Follow-up information after subject discontinuation will not need to be provided to the Sponsor representative.

For SADEs and UADEs, the event will be followed until resolution and follow-up information will be provided to the Sponsor representative.

7.4 Regulatory Authority and Institutional Review Board Notifications

The Sponsor shall report results of their evaluations of UADEs to the FDA, all reviewing IRBs, and all participating Investigators within 10 business days after the Sponsor/Sponsor representative first receives notice of the event.

Further, the Sponsor shall report results of their evaluations of UADEs to the Regulatory Authority and all applicable reviewing IRBs, and all participating Investigators within 10 business days after the Sponsor/Sponsor representative first receives notice of the event.

Please see Tables 10 and 11 below for reporting requirements and associated timelines.

8 INDEPENDENT DATA MONITORING COMMITTEE

An Independent Data Monitoring Committee (IDMC) will be formed to review data from the clinical investigation to evaluate the safety and efficacy of the investigational device. The IDMC will be formed prior to subject enrollment and the names, affiliations, and academic backgrounds of all members will be provided to the Regulatory/Competent Authority.

The members of the IDMC are responsible for safeguarding the interests of study participants, assessing the safety and efficacy of study procedures, and reviewing the overall conduct of the clinical investigation. The IDMC will review clinical investigation data to evaluate study conduct, investigational device safety, and scientific validity and integrity of the investigation.

The IDMC will provide recommendations regarding the implementation and progress of clinical investigation, including continuation, suspension and/or termination of the clinical investigation. A separate charter for the IDMC will define and describe:

- Roles and responsibilities;
- Membership;

- Frequency of meetings; and
- Documentation and reporting.

A separate CEC (Clinical Events Committee) will be formed to review all SAEs and corresponding data for each SAE. The CEC will be formed prior to subject enrollment and the names, affiliations, and academic backgrounds of all members will be provided to the Regulatory Authority.

The members of the CEC will be responsible for reviewing and adjudicating SAEs for relatedness to the hemostatic device and expectedness. A separate charter for the CEC will define and describe:

- Roles and responsibilities;
- Membership;
- Frequency of meetings;
- Adjudication process; and
- Documentation and reporting.

9 DATA COLLECTION

9.1 Completion of Case Report Forms

Prior to the start of the clinical investigation, the Sponsor representative will provide the Principal Investigator and designated investigational site staff with training on electronic CRF completion procedures. The Principal Investigator will be responsible for the timing, accuracy, and completeness of CRFs for each individual subject. The personal data recorded on all paper and electronic documents will be regarded as confidential.

The Principal Investigator will maintain a separate list of all subjects entered into the clinical investigation showing each subject's name, date of birth, and assigned subject number (for identification purposes). A Subject Identification Log will also be provided in the Investigation Site File to record the subject's initials and assigned subject number.

9.2 Source Documentation

Source documents are where clinical investigation information for subjects are first recorded. Data collected for the clinical investigation must be supported by source documents, and may include, but is not limited to, subject medical records, hospital charts, operative reports, laboratory and diagnostic test reports, and study worksheets.

9.3 Retention of Clinical Investigation Documentation

Clinical investigation records will be stored in a confidential manner so as to protect the confidentiality of subject information. All records related to this clinical investigation will be retained in appropriate investigation files.

The Principal Investigator is responsible for retaining all copies of the records for a period of no less than 5 years from the latter of the two dates: the date on which the clinical investigation is completed/terminated or the date that records are no longer required for the purposes of supporting a marketing application. In all cases, the Principal Investigator must contact the Sponsor prior to disposing of any records related to the clinical investigation. Included in records to be maintained are the signed Clinical Investigational Plan, copies of the Case Report Forms, signed consent forms, IRB approval

letters, product accountability records, correspondence concerning the clinical, and any other documents to identify the subjects.

The Sponsor must approve the destruction of any investigational records.

In addition, if the Principal Investigator moves/retires, etc., he/she should provide the Sponsor with the name and address of the person who will look after and be responsible for the clinical investigation related records.

9.4 Training

Principal Investigators and investigational site staff will be trained on the clinical investigation and the specific tasks to which they are delegated. Investigational site staff will also have documented training on applicable regulations and guidances, including Good Clinical Practice.

Further, investigators (Principal Investigators and sub-investigators responsible for enrolling study subjects and applying the investigational and control devices) will have training on use of the investigational device, control device, and the SBSS. Investigator training procedures and requirements are detailed within the Investigator Training Plan (Appendix D).

10 TERMINATION OF THE CLINICAL INVESTIGATION

10.1 Subject Withdrawals and Discontinuation

During the course of this clinical investigation, subjects will be or may elect to withdraw from investigation participation for any of the following reasons:

- Subject's withdrawal of consent;
- Any unexpected adverse device effect which is, in the opinion of the Principal Investigator, related to the device and will endanger the well-being of the subject if the treatment is continued;
- The development of any undercurrent illness(es), infection(s) or condition(s) that might interfere with the Clinical Investigational Plan; or
- Any problem deemed by the Principal Investigator and/or Sponsor to be sufficient to cause discontinuation.

All subjects discontinued from the clinical investigation due to an UADE, directly related to the clinical investigation, will be treated until the effect resolves. The Principal Investigator will clearly document the date and reason(s) for subject withdrawal in Discontinuation CRF.

Subjects who are withdrawn will not be replaced if they have received the investigational or control device. If possible, any procedures or assessments planned for the subject on withdrawal from the clinical investigation should be performed when intention to withdraw the subject is announced.

Subjects who are withdrawn prior to receiving investigational or control device will be replaced.

10.2 Early Termination of the Clinical Investigation

Both the Sponsor and Principal Investigator reserve the right to terminate the clinical investigation at any time. Should this be necessary, the procedures will be arranged on an individual site basis after review

and consultation by both parties. In terminating the clinical investigation, the Sponsor and the Principal Investigator will assure that adequate consideration is given to the protection of the subjects' interests.

11 DATA MANAGEMENT

All data will be housed in a validated database program. All data queries will be resolved with the assistance of monitoring and investigational site staff.

On resolution of all data queries, the database will be closed and data listings, summary tables, graphical output and descriptive statistics produced. All data listings, except SAEs (the final report will include the CEC adjudications for all SAEs), for inclusion into the final report, will be subject to sample quality control checks against the Case Report Forms.

Once all the subject data has been collected, the analysis and reporting will be conducted. Any data existing for subjects who have not received treatment, will not be used in the analysis. Details of these subjects will, however, be referenced in the final report.

Any data existing for subjects who have received the investigational or control device, who withdraw voluntarily or who are withdrawn from the clinical investigation, will be used in the final analysis. The inclusion of partial data will be documented in the final report. The final report will be the responsibility of Biom'Up.

12 STATISTICS

12.1 Overview

12.1.1 Primary Efficacy Endpoint

The primary efficacy endpoint of this clinical investigation is non-inferiority of HEMOBLAST™ relative to G+T for success at achieving hemostasis within 6 minutes. The definition of the primary endpoint is provided in Table 7.

12.1.2 Secondary Efficacy Endpoints

Pre-defined secondary efficacy endpoints and hypotheses that will be assessed at study completion will be:

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

The definitions of each secondary endpoint are listed in Table 8.

Table 8: Primary and secondary endpoints and hypotheses

Endpoint and Hypothesis	Definition of Endpoint
Primary Efficacy Endpoint and Hypothesis	
Non-inferiority for TTH within 6 minutes	Binary indicator of patient achieving hemostasis within 6 minutes. Time-to-hemostasis is defined as the interval from the application of study intervention until investigator deemed hemostasis. Hemostasis will be assessed via the SBSS. For the primary endpoint, a subject will be considered a success if complete hemostasis (SBSS of 0) is achieved and maintained within 6 minutes without the use of an additional hemostatic product or surgical rescue.
Secondary Endpoints and Hypotheses	
Superiority for Preparation Time	Mean preparation time, defined as the average time from the opening of package to product being ready to use (measured in minutes and seconds).
Non-inferiority for TTH within 3 minutes	Binary indicator of subject achieving hemostasis within 3 minutes. Time-to-hemostasis is defined as the interval from the application of study intervention until investigator deemed hemostasis. For this secondary endpoint, a subject will be considered a success if complete hemostasis (SBSS of 0) is achieved and maintained within 3 minutes without the use of an additional hemostatic product or surgical rescue.
Superiority for TTH within 6 minutes	Binary indicator of subject achieving hemostasis within 6 minutes. Time-to-hemostasis is defined as the interval from the application of study intervention until investigator deemed hemostasis. For this secondary endpoint, a subject will be considered a success if complete hemostasis (SBSS of 0) is achieved and maintained within 6 minutes without the use of an additional hemostatic product or surgical rescue.
Superiority for TTH within 3 minutes	Binary indicator of subject achieving hemostasis within 3 minutes. Time-to-hemostasis is defined as the interval from the application of study intervention until investigator deemed hemostasis. For this secondary endpoint, a subject will be considered a success if complete hemostasis (SBSS of 0) is achieved and maintained within 3 minutes without the use of an additional hemostatic product or surgical rescue.

12.1.3 Safety Outcomes

Endpoints 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.

12.1.4 Individual Subject and Overall Study Success

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.

12.2 General Analysis Considerations

All statistical analyses will be performed using SAS® and R. Unless otherwise specified, all continuous endpoints will be summarized using descriptive statistics, which will include the number of subjects (n), mean, standard deviation, median, minimum, and maximum. All categorical endpoints will be summarized using frequencies and percentages.

12.2.1 Analysis Populations

Safety analyses will be performed on the Full Analysis Population, defined as all subjects who were randomized into the study and received study intervention and all lead-in subjects. Efficacy analyses will be conducted on the time to hemostasis (TTH) Analysis 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). Data summaries will be based on the intervention received, regardless of which intervention was randomly assigned.

12.2.2 Handling of Missing Data

In primary analyses, missing TTH values will not be imputed. All values right censored prior to 6 minutes will be considered treatment failures for the purpose of the primary analysis. Further sensitivity analyses for the impact of potential missing data will be defined in the Statistical Analysis Plan (SAP).

12.2.3 Subgroup Analyses

Descriptive analyses of safety and efficacy data will be presented by surgery type. The primary efficacy endpoint, as well as all secondary efficacy endpoints and safety outcomes will be presented by surgery type. Estimates of the distribution of TTH over a maximum follow-up of 10 minutes will be computed using the Kaplan-Meier method, stratified by surgery type. Kaplan-Meier estimates for the probability of continued bleeding at all scheduled assessment times (3 minutes, 6 minutes, and 10 minutes) will be displayed on each plot along with corresponding 95% confidence intervals. Additionally, the primary efficacy endpoint, as well as all secondary efficacy endpoints and safety outcomes will be presented stratified by:

- The number of interventions (separate applications of randomized hemostat);
- Baseline SBSS score; and
- Abnormal versus normal coagulation values.

The study will recruit patients undergoing elective surgery. Based upon this and the inclusion/exclusion criteria to be implemented, it is assumed that patients with abnormal coagulation studies will not be randomized and treated. In the unlikely event that patients with abnormal coagulation studies are present, a secondary analysis of the primary endpoint considering only those subjects with normal coagulation studies will also be conducted. Further, to assess the robustness of the primary endpoint with respect to possible imbalances in the frequency of patients with abnormal studies by treatment arm, a "worst-case" sensitivity analysis assuming all randomized and treated subjects in the HEMOBLAST™ arm with abnormal studies are treatment failures for the primary endpoint (TTH greater than 6 min) while all randomized and treated subjects in the G+T arm with abnormal studies are treatment successes (TTH less than 6 min). These subgroup and sensitivity analyses will be presented along with the primary results conducted on the TTH Population defined in Section 12.2.1.

12.2.4 Accounting for Multiple Comparisons

The primary analysis comparing the probability of TTH within 6 minutes in subjects receiving HEMOBLAST™ to those receiving G+T will be conducted to maintain an overall 0.025 (one-sided) significance level accounting for one interim analysis and one final analysis (see Sections 12.4.1 and

12.4.2). The exclusion of a >10% difference in the probability of TTH at 6 minutes will be indicated by the lower limit of a 95% confidence interval for the adjusted difference in binomial proportions (HEMOBLAST™ – G+T). All reported inference (confidence intervals and p-values) will account for the planned interim analysis.

Adjustment for multiple comparisons when assessing secondary endpoints will be performed using a fixed sequence closed testing procedure. The experiment-wise Type I error rate will be controlled in the strong sense at a (two-sided) 5% significance level. In a fixed sequence testing procedure, the formal inferential testing can proceed to the next step only when statistical significance is declared in the current step. If the testing sequence is stopped, the remaining endpoints in the testing sequence will be considered exploratory. Furthermore, any comparisons that are not presented in the a priori specified testing procedure will also be considered exploratory. The fixed sequence testing procedure will be employed among the primary and secondary endpoints in the order presented below:

1) Primary endpoint: Success at achieving hemostasis within 6 minutes for the first treated bleeding site (comparable efficacy of HEMOBLAST™ relative to G+T, evaluated using a 10% non-inferiority margin);
2) Secondary endpoint: The difference between arms in mean preparation time, defined as the time from the opening of package to product being ready to use (measured in minutes and seconds);
3) Secondary endpoint: Success at achieving hemostasis within 3 minutes for the first treated bleeding site (comparable efficacy evaluated using a 10% non-inferiority margin);
4) Secondary endpoint: Success at achieving hemostasis within 6 minutes for the first treated bleeding site (superiority of HEMOBLAST™ relative to G+T); and
5) Secondary endpoint: Success at achieving hemostasis within 3 minutes for the first treated bleeding site (superiority of HEMOBLAST™ relative to G+T).

12.2.5 Data Transformations

No transformations of data are planned.

12.2.6 Subject Disposition and Characteristics

The number of subjects randomized to each treatment arm will be tabulated and a flow diagram describing the disposition of subjects will be constructed. Demographic variables will include age (continuous and by age category [categorized by decade of life]), sex, race, ethnicity, height, and weight. Baseline disease characteristics will include reason for surgery and related co-morbidities. All continuous endpoints will be summarized using descriptive statistics, that will include the number of subjects (n), mean, standard deviation, median, minimum, and maximum. All categorical endpoints will be summarized using frequencies and percentages.

12.2.7 Subject Compliance

Because the study device will be applied by the study investigator during a single surgery, subject compliance with completing the efficacy evaluation is not an issue and will not be reported. Subject compliance with completing the follow-up visit will be reported.

12.2.8 Protocol Deviations

Eligibility criteria that were not met will be listed along with whether or not an exception was granted. Important protocol deviations will be summarized by treatment group. Important protocol deviations are defined as:

- Any unauthorized protocol deviations that result in a significant added risk to the study subject;
- Non-adherence to eligibility criteria without prior Sponsor approval;
- Non-adherence to good clinical practices, FDA regulations, and/or ICH guidelines (e.g., failure to obtain proper informed consent or failure to report SAEs);
- A high frequency of unauthorized non-adherence to study procedures or schedules that do not involve eligibility;
- Development of withdrawal criteria during the study without corresponding subject withdrawal;
- Receipt of a prohibited concomitant medication by a subject; and
- Protocol deviations will be summarized in tables produced by the Medical Monitor or Clinical Research Associate.

12.3 Analytic Methods

12.3.1 Analysis of Primary and Secondary Efficacy Endpoints

12.3.1.1 Analysis Population

Efficacy analyses will be conducted on the 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. Lead-in subjects are *not* part of the TTH Population.

12.3.1.2 Methods of Analysis

The primary efficacy endpoint is the difference in the probability of TTH within 6 minutes comparing HEMOBLAST™ to G+T. The lower bound of the 95% confidence interval for the difference in binomial probabilities will be used to assess comparable efficacy. The primary efficacy analysis will be conducted on data from the first identified bleeding site for each subject. The estimated difference in the probability of TTH at 6 minutes between treatment arms will be adjusted for surgical indication by weighting the stratum-specific differences in observed proportions using Cochran-Mantel-Haenszel weighting.[18] The trial seeks to establish comparable efficacy based upon a non-inferiority margin of 10% for the difference in the probability of TTH within 6 minutes comparing HEMOBLAST™ to G+T (HEMOBLAST™–G+T). Letting θ denote the true difference in the probability of hemostasis at 6 minutes between HEMOBLAST™ to G+T, the trial will test the null hypothesis H_0: $\theta \leq -0.10$ vs. the alternative hypothesis H_A : $\theta > -0.10$ using a one-sided level 0.025 test. The null hypothesis of inferiority will be rejected and comparable efficacy will be established if the resulting lower bound of the 95% confidence interval for θ is greater than -0.10. Comparable efficacy will be evaluated using a group sequential testing design as described in Section 12.4 with stopping boundaries defined to ensure a maximum overall 1-sided significance level of 0.025. Following the completion of the trial, a confidence interval for the estimated difference in the probability of hemostasis at 6 minutes will be computed using the Cochran-Mantel-Haenszel estimator and asymptotic variance estimate in combination with the repeated confidence interval method.[19] Estimates of the distribution of TTH over a maximum follow-up of 10 minutes will be computed based on all available assessment times (3 minutes, 6 minutes, and 10 minutes) using the Kaplan-Meier method.

Analyses of the secondary efficacy endpoints will be evaluated only once, at the end of the study, using a family-wise 2-sided significance level of 0.05. Adjustment for multiple comparisons when assessing

secondary endpoints will be performed using a fixed sequence closed testing procedure to control the family-wise type I error rate at 0.05, as described in Section 12.2.4. The difference in mean preparation time will be tested using a linear regression model with stratified adjustment for surgery type. The difference in the probability of TTH within 3 minutes will be tested using a general linear model with stratified adjustment for surgery type as described above. Wald-based 95% confidence intervals for the difference in probability of TTH will be computed.

12.3.2 Analysis of Safety Outcomes

12.3.2.1 Analysis Population

Safety analyses will be 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.

12.3.2.2 Methods of Analysis

Summaries of the number and percent of subjects with at least one SAE will be provided. Comparisons of the proportion of subjects experiencing SAEs will be made between treatment arms. Summaries of the number of percent of AEs will be provided for each treatment arm.

Differences in mean overall blood loss, mean volume of intra-operative transfusions, mean total operative time, and mean duration of hospitalization will be estimated using linear regression models with stratified adjustment for surgery type and separated by surgery type. In all cases, the robust variance estimator will be used and a 95% Wald-based interval will be computed. Comparisons of the incidence of re-operation (total and reoperation due to bleeding) and the incidence post-surgery bleeding complications will be made using a general linear model to estimate the difference in the probability of each outcome after stratified adjustment for surgery type. Comparisons of the incidence of re-operation and the incidence post-surgery bleeding complications within each surgery type will be made using a two sample binomial test of proportions.

12.4 Interim Analyses

12.4.1 Interim Efficacy/Futility Analysis

A single interim analysis will be performed on the primary efficacy endpoint (difference in the probability of TTH within 6 minutes) using data on the 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.

The study will be monitored by an Independent Data Monitoring Committee (IDMC). The IDMC will be provided with blinded efficacy data at the time of the interim analysis. Detail of the activities associated with the IDMC will be provided in an IDMC Charter. In the following, we provide the description of the *a priori* defined interim analysis plan that will be used in the trial.

In making a decision to recommend early termination of the study, the IDMC shall be guided by a formal stopping rule based on the primary efficacy endpoint. The test statistic shall be the estimated difference in the probability of TTH within 6 minutes between the HEMOBLAST™ and G+T arms as described in Section 12.3.1.2. The clinical trial may only be stopped early either for reasons of futility (the observed difference in the probability of TTH within 6 minutes comparing HEMOBLAST™ to G+T is not sufficiently high enough to warrant continuation of the trial) or efficacy (the observed difference in the

probability of TTH within 6 minutes comparing HEMOBLAST™ to G+T is sufficiently high enough to conclude non-inferiority).

The formal stopping boundaries will be determined by futility and efficacy boundaries defined within the unified family of group sequential stopping rules.[20] In the notation of the latter paper, the stopping rule will be based on a one-sided group sequential design testing an upper alternative hypothesis at a level of significance α =0.025 with a lower (futility) stopping boundary relationship specified by P_a =0.8 and a upper (efficacy) stopping boundary relationship specified by P_d =0.8 (a boundary with conservatism in between the Pocock type boundary and an O'Brien-Fleming type boundary).[21, 22]

The trial will utilize a 2:1 randomization scheme (HEMOBLAST™ : G+T). Randomization will be stratified by surgery indication and it is anticipated that accrual to each surgical indication will be roughly equal. It is envisioned that one interim analysis will be performed during the monitoring of the study, occurring after outcomes have been observed for 240 randomized and treated subjects belonging to the TTH Population (approximately 160 subjects treated with HEMOBLAST™ under 2:1 randomization), and may continue to a maximal sample size of 400 subjects (approximately 267 subjects treated with HEMOBLAST™ under 2:1 randomization). Although the above interim analysis is pre-defined, final inference for comparable efficacy will treat the futility boundary as non-binding (implying that the type I error rate for the trial will be bounded at or below .025 even if the futility boundary is crossed at the interim analysis but the trial continues on).

Under such a monitoring schedule and assuming a probability of TTH within 6 minutes of 88% in both the HEMOBLAST™ arm and the G+T arm, a maximal sample size of 400 treated subjects (267 in the HEMOBLAST™ arm and 133 in the G+T arm) will provide approximately 80.1% power to determine comparable efficacy based upon a 10% non-inferiority margin of absolute difference in the probability of TTH within 6 minutes. Of particular note, if the study were to stop in favor of comparable efficacy at the interim analysis after 60% of the maximal sample size were accrued, data would be available on approximately 160 patients in the TTH Population treated with HEMOBLAST™ plus up to an additional 50 lead-in subjects. Assuming equal accrual to each surgical indication this would provide safety data on roughly 70 subjects treated with HEMOBLAST™ for each surgery type.

Enrollment will continue in parallel with the interim analysis. Thus, if the interim analysis supports early termination of the clinical investigation, the number of subjects included may be higher than the number available at the time of the interim analysis. All available data for the analysis populations defined above will be included in the final analysis and report.

Under the planned schedule of one interim analysis at 240 treated subjects and a assumed 6 min TTH success rate of 88% in the G+T arm, Table 9 presents the stopping boundaries at the interim and final analysis for the specified stopping rule expressed as the normalized fixed sample z-statistic for testing non-inferiority and the corresponding fixed sample p-value.

Table 9: Stopping boundaries for a level 0.025 one-sided design with a single interim analysis (NON-BINDING FUTILITY (P_a =0.8) AND EFFICACY (P_d =0.8) occurring at 240 patients, and a maximal sample size of 400 patients (2:1 randomization). The boundaries assume a 88% probability of TTH within 6 minutes on the G+T arm and a 10% non-inferiority margin. Stopping boundaries are expressed as the difference in the probability of TTH within 6 minutes (HEMOBLAST™ – G+T).

Analysis	Total Sample Size (H, G+T)*	Futility (lower) Stopping Boundary		Comparable Efficacy (upper) Stopping Boundary	
		Z-statistic	P-value	Z-statistic	P-value
1	240 (160, 80)	0.788	0.215	2.373	0.009

2	400 (267, 133)	2.036	0.021	2.036	0.021

* H : HEMOBLAST™

Thus, according to the above table, if the observed Z-statistic for testing non-inferiority (Cochran-Mantel-Haenszel estimate minus the non-inferiority margin, divided by the estimated standard error) is 0.788 *or lower* when 240 subjects have been treated and observed for TTH on the study, the stopping rule would suggest that the study be terminated early with a decision that it was futile to continue the trial because there was not sufficient evidence that HEMOBLAST™ would be determined to be comparably efficacious if the study were to continue. Alternatively, if the observed Z-statistic for testing non-inferiority is 2.373 *or higher* when 240 subjects have been treated and observed for TTH on the study, the stopping rule would suggest that the study be terminated early with a decision in favor of comparable efficacy between the two products. A repeated 95% confidence interval for the stratum-weighted difference in proportions, corrected for the stopping rule, will be computed at the completion of the trial. In the event that true probability of TTH within 6 minutes for G+T arm is observed to be different from 88% or the timing of the interim analysis differs, the stopping boundaries will be adjusted to maintain a one-sided type one error rate of 0.025 as described in Section 12.4.3.

12.4.2 Sample Size Justification

The sample size for the proposed study is based on a level 0.025 (one-sided) test to exclude a probability of TTH within 6 minutes that is 10% less among subjects treated with HEMOBLAST™ compared to those treated with G+T. The maximum number of subjects enrolled will be computed as to provide approximately 80.1% power to declare comparable efficacy when the two treatments have the same probability of TTH within 6 minutes. The variance estimate in the sample size calculation assumes an 88% 6 minute hemostasis success rate in both the HEMOBLAST™ and G+T arms. The planned stopping rule will implement a single interim analysis after outcome data have been observed on 240 treated subjects. If the study were to continue to the final analysis with a decision in favor of comparable efficacy, it is anticipated that efficacy data would be available on 400 treated (approximately 267 patients treated with HEMOBLAST™ under a 2:1 randomization scheme). Assuming equal accrual to each surgical indication this would provide efficacy data on roughly 89 subjects treated with HEMOBLAST™ for each surgery type.

The variance of a proportion is dependent on the proportion itself. Hence, power for the study will be partially determined by the probability of TTH within 6 minutes on each of the treatment arms. Under the design assumption that the probability of TTH within 6 minutes on the G+T arm is 88%, the study will require a maximum of 400 treated subjects to attain approximately 80.1% power to declare comparable efficacy based upon a 10% non-inferiority margin. As discussed in Section 12.4.3, in order to maintain approximately 80.1% power should a larger variance be observed, a flexible sample size based on statistical information from pooled trial data will be used.[23]

12.4.3 Implementation of the Stopping Boundary

Modifications of the stopping rule to account for changes in the schedule of the interim analysis and estimates of variability will be made by using the parametric form of the stopping rule as specified above, a blinded sample size recalculation will be performed prior to the interim analysis. An independent statistical reporting group preparing reports for the IDMC will use the constrained boundaries method as implemented in S+SeqTrial® to recalculate the maximal sample size based on the marginal response rate observed in the study at the time of the pre-planned interim analysis (marginalized over treatment arms).[23] The one-sided type I error rate for the study will be maintained at 0.025, and the maximal sample size will

be adjusted up to maintain 80.1% power provided that the recalculated maximal sample size is 460 treated subjects or less within the TTH Population as defined in 12.3.1.1. Further details of the implementation of the stopping boundary will be provided in the Statistical Analysis Plan.

13 RISK/BENEFIT ANALYSIS

13.1 Anticipated Clinical Benefits

It is anticipated that application of the investigational device to a bleeding site will result in a reduced time to hemostasis compared to conventional methods of hemostasis (pressure, suture, or cautery). Individual subjects may not directly benefit from participation in this investigation. However, conducting this research could contribute to the overall advancement of medical and scientific knowledge and may benefit future patients.

13.2 Risks Associated with Participation in the Clinical Investigation

There are possible risks, complications, and discomforts associated with undergoing a surgical procedure. There are also additional risks specifically associated with the surgical arm (cardiothoracic, abdominal, orthopedic lower extremity). The Investigator will be responsible for discussing these risks, complications and discomforts with subjects along with the risks associated with anesthesia.

Adverse events observed during and after the application of a hemostatic agent other than HEMOBLAST™ in a large pivotal clinical trial of 309 patients at a greater than 1% frequency included:

- Anemia;
- Arrhythmia;
- Atelectasis;
- Confusion;
- Dural tear;
- Edema;
- Fever;
- Fibrillation Atrial;
- Fibrillation Ventricular;
- Heart Failure Right;
- Hemorrhage;
- Hypotension;
- Infection;
- Pleural Effusion
- Pneumonia;
- Rash;
- Respiratory distress;
- Thrombosis Arterial; and
- Urinary Tract Infection.

None of the adverse events that occurred were judged by the surgeon to be “Probably Related” to the use of the hemostatic agent.

Adverse events observed during and after the application of a hemostatic agent other than HEMOBLAST™ in a large pivotal clinical trial of 309 patients at a less than 1% frequency included:

- Abscess;
- Acute kidney failure;
- Back pain;
- Bradycardia;
- Cellulitis;
- Cerebrovascular accident;
- Dehiscence;
- Diarrhea;
- Dyspnea;
- Gastritis;
- Hallucination;
- Heart arrest;
- Heel ulcer;
- Hyperglycemia;
- Kidney tubule necrosis;
- Lung edema;
- Myocardial Infarction;
- Nausea;
- Nausea and vomiting;
- Neuropathy;
- Pain;
- Paraesthesia;
- Pneumothorax;
- Rash;
- Skin ulcer;
- Transfusion reaction;
- Urinary Retention; and
- Ventricular Tachycardia.

None of the adverse events that occurred were judged by the surgeon to be "Probably Related" to the use of the hemostatic agent.

Risks possibly related to the use of hemostats similar to HEMOBLAST™ include:

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

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

Subjects randomized to receive the control are exposed to risks associated with G+T, as described in the current device labeling.

Participation in this clinical investigation also presents additional risks or inconveniences. These may include, but are not limited to:

- An additional blood draw preoperatively and an additional blood draw at 6-week follow-up for antibody evaluation;
- Urine or serum pregnancy test (females of child bearing age) performed preoperatively;
- Additional intraoperative assessments of bleeding severity at 3, 6, and 10 minutes after hemostat application; and
- Follow-up visit at 6 ± 2 weeks postoperatively.

There may also be other unforeseen risks.

13.3 Risk/Benefit Analysis

Individual patients may experience no direct benefit from participation in the study. However, potential benefits of HEMOBLAST to be investigated in the study include shorter preparation time, in addition to the other endpoints that will be tested for potential superiority as discussed above. Risk mitigation steps have been taken through investigational device specifications and the performance of non-clinical testing and a clinical study. Risk mitigation steps are also implemented in the manufacture and shipment of the investigational device.

The Sponsor, Medical Expert, and co-ordinating Investigator have determined that this clinical investigation is justified because the potential benefits outweigh the potential risks. Additionally, an IDMC is being put in place to perform continual reviews on the study, including making recommendations based on risk/benefit.

13.4 Conduct of Clinical Investigation to Reduce Risk

Further efforts to minimize risk in this clinical investigation will involve selecting investigators who are experienced and skilled in their respective areas of surgery, have clinical investigation experience, and who are adequately trained on the use of the investigational device and study procedures.

Risks and benefits of this clinical investigation are included in the sample Subject Informed Consent Form, included as Appendix B. Potential risks and benefits will be discussed with potential subjects during the informed consent process.

14 REPORTS AND PUBLICATIONS

14.1 Interim Reports

Interim reports will not be issued during the conduct of this clinical investigation. Thus, if the interim analysis support early termination of the clinical investigation, the number of subjects included may be higher than the number available at the time of the interim analysis. All available data for the analysis populations defined above will be included in the final analysis and report.

14.2 Final Report

The final report will be compiled by the Sponsor or designated Sponsor representative and reviewed, approved and signed off by the co-ordinating investigator.

14.3 Publications

The conduct and results of this clinical investigation will be documented in the final report, as mentioned above. Because this investigation is a multicenter investigation, it is intended that the combined clinical data from all participating sites will be presented and/or published. Individual investigators will not publish or present results prior to publication of the combined multicenter results without prior written consent from the Sponsor. All publications must include the name of the Sponsor (Biom'Up, France).

Detailed publication policies will be included within the Investigator Agreement.

15 ETHICAL CONSIDERATIONS

15.1 Institutional Review Board Approval

Prior to the initiation of this clinical investigation, the Principal Investigator must submit the Clinical Investigational Plan, patient consent form and any other documents as may be required to the appropriate IRB for review and approval. The Principal Investigator, and any other member of the investigational team, must not participate in the decision-making. A signed and dated letter granting IRB approval must be provided to the Sponsor prior to the initiation of the clinical investigation. A list of the members of the IRB reviewing this Clinical Investigational Plan will be requested.

15.2 Informed Consent and Patient Information

The Principal Investigator or designee must explain to each subject the nature of the clinical investigation, including any risks and benefits, its purpose and procedures, and expected duration of involvement in the clinical investigation. Each subject must be informed that participation in the clinical investigation is voluntary and non-participation will not affect his/her right to the most appropriate surgical treatment or affect the doctor/clinician-patient relationship. Subjects have the full right to withdraw from the clinical investigation at any time, irrespective of their initial consent.

Each subject must also give their permission for representatives of the Sponsor, auditor and regulatory authorities to review their hospital records for purposes of source data verification.

15.3 Subject Confidentiality

Confidentiality of subject data will be maintained at all times. Subject anonymity will be guaranteed and all documentation relating to a subject will be kept in a secure location.

15.4 Declaration of Helsinki and IDE Regulations

Outside the United States, this clinical investigation will be conducted in accordance with the relevant articles of the Declaration of Helsinki as adopted by the 18th World Medical Assembly in 1064 and as revised in Tokyo (1975), Venice (1983), Hong Kong (1989), South Africa (1996), Edinburgh (2000), Washington (2002), Tokyo (2004) and Seoul (2008). In the United States, the investigation will be conducted in accordance with applicable FDA regulations and guidance, including 21 CFR Parts 50, 56, and 812.

15.5 Indemnity

The Sponsor recognizes its liability in law to compensate for any injury sustained by a subject participating in this clinical investigation in accordance with applicable laws and guidelines and as agreed upon in the Clinical Trial Agreement which each investigational site.

15.6 Insurance

The Sponsor is responsible for obtaining and maintaining clinical investigation insurance.

16 COMPLIANCE

16.1 Overview

This clinical investigation will be conducted in accordance with Note for Guidance of Good Clinical Practice: CPMP/ICH/135/95.

The following Federal Regulations will also be followed: 21 CFR Parts 11, 50, 56, and 812 and 45 CFR Part 46.

16.2 Clinical Investigation Personnel Responsibilities

Prior to the initiation of this clinical investigation, each Principal Investigator will approve this Clinical Investigational Plan by signing the signature page. This signature confirms that the clinical investigation will be performed in compliance with the Clinical Investigational Plan.

Investigator reporting responsibilities and timelines are included in

Table 11 below. Applicable IRB procedures and any conditions set forth in the Investigator Agreement must also be followed.

Table 11. Investigator Reporting Responsibilities

Responsibility	Report To	Timeline	Details
SAEs, SADEs	Sponsor / Sponsor Representative	24 hours	The Investigator must notify the Sponsor of any SAEs, including those that are potentially device-related, within 24 hours of awareness.
Unanticipated [Serious] Adverse Device Effects (UADEs/USADEs)	Local IRB/EC	10 business days or less and as required by local IRB/EC policy	The Investigator must submit evaluation of any UADE within 10 business days after Investigator awareness and as required by local IRB/EC policy.
	Sponsor / Sponsor Representative	24 hours	The Investigator must notify the Sponsor of any UADE within 24 hours after Investigator awareness.
Withdrawal of IRB/EC approval	Sponsor / Sponsor Representative	5 business days	The Investigator must report a withdrawal of the reviewing IRB approval within 5 business days.
Progress Report	Sponsor and Local IRB/EC	Yearly	Progress reports on the investigation will be submitted to the Sponsor, monitor, and reviewing IRB/EC at regular intervals, but in no event less often than yearly, or as required by local IRB/EC policy.
Deviation from clinical investigational plan in emergency	Sponsor / Sponsor Representative	24 hours	Deviations from the clinical investigational plan that are made to protect the life or physical well-being of a patient in an emergency situation must be reported within 24 hours after the emergency occurred.
	Local IRB/EC	5 business days or less as required by applicable IRB/EC policy	Deviations from the clinical investigational plan that are made to protect the life or physical well-being of a patient in an emergency situation must be reported within 5 business days after the emergency occurred.
Deviation from protocol that affects the scientific soundness of the study plan or the rights, safety, or welfare of human subjects	Sponsor / Sponsor Representative	Prior approval	Prior approval by the Sponsor is required when a deviation of this nature is anticipated.
Failure to obtain informed consent	Sponsor / Sponsor Representative	5 business days	If the investigational device was used without obtaining informed consent, the Investigator must notify the Sponsor within 5 business days of the use of the device.
	Local IRB	5 business days	If the investigational device was used without obtaining informed consent, the Investigator must notify the IRB within 5 business days of the use of the device.
Final report	Sponsor and Local IRB/EC	3 months	The investigators will submit a final report to the Sponsor and local IRB/EC within 3 months after termination or completion of the investigation, or as required by local IRB/EC policy.

The Sponsor shall also provide accurate, complete, and current information about any aspect of the clinical investigation as requested by FDA or reviewing IRB(s).

The Investigator is also responsible for the retention of the clinical investigation records per 21 CFR Parts 812.2(b) and 812.140.

The Sponsor reporting responsibilities and timelines are included in

Table 12 below.

Table 12. Sponsor Reporting Responsibilities

Responsibility	Report To	Timeline	Details
Unanticipated [Serious] Adverse Device Effects (UADEs/USADEs)	FDA, all reviewing IRBs, and Investigators	10 business days	The Sponsor must report the results of an evaluation of a UADE to FDA and all reviewing IRBs and Investigators within 10 business days after Sponsor notification.
Withdrawal of IRB/EC approval	FDA, all reviewing IRBs, and Investigators	5 business days	The Sponsor must notify FDA and all reviewing IRBs and participating Investigators of the withdrawal of IRB/EC approval of an investigation (or any part of an investigation) within 5 business days of receipt of the withdrawal of approval, or as required by applicable national regulations.
Current investigator list	FDA	6 month intervals	The Sponsor will be a current list of the names and addresses of all investigators participating in the investigation 6 months after FDA approval, and at 6 month intervals.
Progress report	Reviewing IRBs	Annually	At regular intervals and at least yearly, the Sponsor must provide progress reports to all reviewing IRBs.
Recall and device disposition	FDA and all reviewing IRBs	30 business days	The Sponsor must notify FDA and all reviewing IRBs of any request that an Investigator return, repair, or dispose of any investigational device. The notice must be made within 30 business days after the request is made and must state why the request was made.
Final report	Reviewing IRBs, and FDA	6 months / 12 months	The Sponsor will submit a final report to FDA and all reviewing IRBs within 6 months after clinical investigation completion or termination.
Informed consent	FDA	5 business days	The Sponsor shall submit to FDA a copy of any report by an investigator of use of a device without obtaining informed consent within 5 business days of receipt of notice of such use.
Significant risk device determination	FDA	5 business days	If an IRB determines that the device is a significant risk device and not a non-significant risk device as the Sponsor had propose to the IRB, a report must be submitted to FDA within 5 business days after the Sponsor learns of the IRB determination.

The Sponsor shall also provide accurate, complete, and current information about any aspect of the clinical investigation as requested by FDA or reviewing IRB(s). Current applicable national regulations shall be followed.

The Sponsor is also responsible for the retention of clinical investigation documentation per 21 CFR Parts 812.2(b) and 812.140 and as required by applicable national regulations.

16.3 Monitoring

The monitor will be responsible for securing the compliance of the Principal Investigators to the signed agreement, the Clinical Investigational Plan, GCP, applicable laws and regulations, and conditions of approval imposed by the reviewing IRBs or regulatory authorities.

The Principal Investigator will permit the Sponsor or designated representative of the Sponsor to inspect all CRFs and corresponding portions of the subject's clinic records and/or original hospital medical records, at regulatory intervals throughout the clinical investigation. These inspections are for the purpose of verifying adherence to the Clinical Investigational Plan and the completeness and accuracy of the data being entered on the CRFs.

The planned extent of source data verification is detailed within the monitoring plan.

A Principal Investigator found not to be in compliance will receive telephone and/or written notification of the deficiency, which will include a request that deviation be corrected immediately. If the corrective actions are not taken, shipment of investigational devices to the institution will be suspended. A request will be made to the Principal Investigator that any investigational devices still in his/her possession are returned to the Sponsor.

16.4 Audits

During the conduct of the clinical investigation, the Sponsor may appoint Quality Assurance (QA) personnel to provide audit of the administration and conduct of the clinical investigation, at the investigational site(s), Sponsor, and/or Sponsor representative(s).

The relevant Regulatory Authority also has the right to conduct an audit of the clinical investigation, that the clinical investigations were, in fact, performed at stated investigational sites and that the data reported to the authority accurately reflects the data in the records of the Principal Investigator. The authority also inspects such studies to verify that the clinical investigations were conducted in accordance with applicable laws and regulations. It is the joint responsibility of the Sponsor and the Principal Investigator to ensure that the clinical investigation has been conducted in accordance with all government regulations.

In the event that the regulatory authority desires to inspect this clinical investigation, the Principal Investigator will permit authorized inspectors to inspect all facilities and records relating to the clinical investigation and aid the Inspector to perform the audit in a timely fashion.

16.5 Modifications to the Clinical Investigational Plan

Except in emergency situations, prior approval by the Sponsor is required for changes in or deviations from this Clinical Investigational Plan. This provision does not apply to those changes made to reduce discomfort or overt risks to the subject. In the event of an emergency situation, the Principal Investigator must institute any and all medical procedures he/she deems to be medically sound. All such events and procedures must be documented in the subjects Case Report Form and reported within the timelines specified in Section 16.2 above.

17 ABBREVIATIONS AND DEFINITIONS

Abbreviation / Term	Definition
ACS-ATLS	American College of Investigators – Advanced Trauma Life Support® Shock Risk Class: 1 – involves up to 15% of blood volume; typically no charge 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.
ADE	Adverse Device Effect - any untoward and unintended response to an investigational medical device
AE	Adverse Event - any untoward medical occurrence in a subject
Antiplatelet Medications	• Abciximab • Anagrelide • Dipyridamole • Cilostazol • Clopidogrel • Eptifibatide • Prasugrel • Terutoban • Ticagrelor • Ticlopidine • Tirofiban • Vorapaxar
ASA Classification	American Society of Anesthesiologists Classification: 1 – normal health patient; 2 – patient with mild systemic disease; 3 – patient with severe systemic disease; 4 – patient with severe systemic disease that is constant threat to life; 5 – moribund patient who is not expected to survive with the operation; 6 – a declared brain-dead patient whose organs are being removed for donor purposes
CEC	Clinical Events Committee
CFR	Code of Federal Regulations
CRF	Case Report Form
Device deficiency	Inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance, which may include device malfunctions, use errors and inadequate labelling
Enrollment	For this investigation, the point of enrollment is intraoperatively, when the subject meets all intraoperative inclusion criteria
FDA	Food and Drug Administration

ICF	Informed Consent Form
IDMC	Independent Data Monitoring Committee
INR	International Normalized Ratio
Intraoperative Time	Time from skin open to skin closure
IRB	Institutional Review Board
QA	Quality Assurance
Relationship (of an adverse event to the investigational device)	• Not related: the adverse event is due to the underlying disease state or is due to concomitant medications or therapy not related to the use of the device • Possibly related: the adverse event has a reasonable temporal relationship to the use of the device but alternative etiology is equally or more likely compared to the potential relationship to the use of the device • Probably related: the adverse event has a strong temporal relationship to the use of the device and alternative etiology is less likely compared to the potential relationship to the use of the device • Definitely related: the adverse event has a strong temporal relationship to the use of the device, follows a known response pattern and cannot reasonably be explained by known characteristics of the subject's clinical state or other therapies
SADE	Serious Adverse Device Effect – an adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event or that might have led to any of these consequences if suitable action had not been taken or intervention had not been made or if circumstances had been less opportune
SAE	Serious Adverse Event – an adverse event that: • Led to death • Led to a serious deterioration in the health of the subject, that either resulted in a life-threatening illness or injury, or a permanent impairment of a body structure or a body function, or in-patient hospitalization or prolongation of existing hospitalization, or resulted in medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function •
SBSS	Surface Bleeding Severity Scale
Severity (of an adverse event)	• Mild: the symptoms are transient, barely perceptible by the subject and do not hinder normal activity; no treatment is usually prescribed to reduce these symptoms • Moderate: the symptoms are sufficiently severe to provoke discomfort in the subject and sufficiently uncomfortable to prevent normal activity; a treatment may be required • Severe: the symptoms considerably modify the normal course of the subject's activities or are disabling or are life-threatening; the treatment studied should be suspended; a treatment for the symptoms is prescribed
Significant coagulation	For this investigation, a significant coagulation disorder is a platelet

disorder	count < 100,000 per microliter or International Normalized Ratio > 1.5
TBS	Target Bleeding Site
TTH	Time to hemostasis
UADE (also USADE)	Unanticipated [Serious] Adverse Device Effect – any serious adverse effect on health or safety, any life-threatening problem or death caused by, or associated with a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the application; or any other unanticipated serious problem associated with a device that relates to the rights, safety or welfare of subjects
WHO	World Health Organization

18 REFERENCES

[1] Oz MC, *et al.* Controlled clinical trial of a novel hemostatic agent in cardiac surgery. The Fusion Matrix Study Group. *Ann Thorac Surg* 2000;69(5):1376-1382.
[2] Doria C, *et al.* Phase 3, randomized, double-blind study of plasma-derived human thrombin versus bovine thrombin in achieving hemostasis in patients undergoing surgery. *Curr Med Res Opin* 2008;24(3):785-794.
[3] Jackson MR, *et al.* Hemostatic efficacy of fibrin sealant (human) on expanded polytetrafluoroethylene carotid patch angioplasty: a randomized clinical trial. *J Vasc Surg* 1999;30(3):461-467.
[4] Nasso G, *et al.* Prospective, randomized clinical trial of the Floseal matrix sealant in cardiac surgery. *Ann Thorac Surg* 2009;88:1520-1526.
[5] Weaver FA, *et al.* Gelatin-thrombin-based hemostatic sealant for intraoperative bleeding in vascular surgery. *Ann Vasc Surg* 2002;16:286-293.
[6] Boucher BA, *et al.* Achieving hemostasis in the surgical field. *Pharamacotherapy* 2009;29:2S-7S.
[7] Levy JH, *et al.* Multidisciplinary approach to the challenge of hemostasis. *Anesth Analg* 2010;110:354-364.
[8] Adams GL, *et al.* The balance of thrombosis and hemorrhage in surgery. *Hematol Oncol Clin North AM* 2007;21(1):13-24.
[9] Renkens KL, *et al.* A multicenter, prospective, randomized trial evaluating a new hemostatic agent for spinal surgery. *Spine* 2001;26(15):1645-1650.
[10] Tomizawa Y, *et al.* Clinical benefits and risk analysis of topical hemostats: a review. *J Artif Organs* 2005;8(3):137-142.
[11] Samudrala S. Topical hemostatic agents in surgery: a surgeon's perspective. *AORN J* 2008;99(3):S2-S11.
[12] Oz MC, *et al.* Floseal® Matrix: new generation topical hemostatic sealant. *J Card Surg* 2003;18:486-493.
[13] Mangano DT, *et al.* Mortality associated with aprotinin during 5 years following coronary artery bypass graft surgery. *JAMA* 2007;297(5):471-479.
[14] Fergusson DA, *et al.* A comparison of aprotinin and lysine analogues in high-risk cardiac surgery. *N Eng J Med* 2008;358:2319-2331.
[15] Mangano DT, Tudor IC, Dietzel C, for the Multicenter Study of Perioperative Ischemia (McSPI) Research Group and the Ischemia Research and Education Foundation. The risk associated with aprotinin in cardiac surgery. *N Engl J Med* 2006;354-365.
[16] Achneck HE, *et al.* A comprehensive review of topical hemostatic agents: efficacy and recommendations for use. *Ann Surg* 2010;25(2):217-228.
[17] Spotnitz WD. Hemostats, sealants, and adhesives: components of the surgical toolbox. *Transfusion* 2008;1502-1516.
[18] Ge M, Durham LK, Meyer RD, Xie W and Thomas N. Covariate-Adjusted Difference in Proportions from Clinical Trials Using Logistic Regression and Weighted Risk Differences. Drug Information Journal. 2011; 45: 481 - 493

[19] Jennison C and Turnbull B. Interim Analyses: The Repeated Confidence Interval Approach. *Journal of the Royal Statistical Society. Series B (Methodological)* Vol. 51, No. 3 (1989), pp. 305-361.
[20] Kittelson JM and Emerson SS. (1990). A unifying family of group sequential test designs. Biometrics 55, 874-923.
[21] Pocock SJ. (1977). Group sequential methods in the design and analysis of clinical trials. Biometrika 64, 191-199.
[22] O'Brien PC and Fleming TR. (1979). A multiple testing procedure for clinical trials. Biometrics 35, 549-556.
[23] Burington BE and Emerson SS. (2003). Flexible implementations of group sequential stopping rules using constrained boundaries. Biometrics 59, 770-777.