3584-001 CLINICAL INVESTIGATION PLAN

CELSTAT

A Prospective, Randomized, Controlled Study to Evaluate the Effectiveness and Safety of CELSTAT as an Adjunct to Hemostasis for Tissue Bleeding in Cardiothoracic, General and Vascular Surgery

STUDY 3584-001

Amendment 2: 2015 NOV 09

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Study Sponsor: **Baxter Healthcare Corporation**
One Baxter Parkway
Deerfield, IL 60015 USA

Contract Research Organization: [redacted]
[redacted]
[redacted] SWITZERLAND

[redacted]

1. STUDY PERSONNEL

1.1 Authorized Representative (Signatory)/Responsible Party

Sponsor's Medical Expert	Sponsor's Clinical Study Team Leader
[redacted], MD, PhD [redacted] Life Sciences & Operations Baxter Healthcare Corporation Tel [redacted]	[redacted], PhD Global Therapeutic Area [redacted] Life Sciences & Operations Baxter Healthcare Corporation Tel [redacted]
[redacted], MD [redacted] 875 First Avenue King of Prussia, PA, USA 19406 Main Office Phone: [redacted]	[redacted], MSc [redacted] Lochhamer Str. 13, 82152 Martinsried/Planegg, Germany Tel [redacted]

1.2 Study Organization

In this fully outsourced study, the contract research organization (CRO) [redacted] takes on all types of contact with the study sites for the sponsor (Baxter Healthcare Corporation). The name and contact information of the individuals involved with the study (eg, investigator(s), sponsor's medical expert and study monitor, the CRO's representative(s), laboratories, steering committees, and oversight committees [including institutional review boards (IRBs), independent ethics committees (IECs), research ethics boards (REBs), as applicable]) will be maintained by the CRO and provided to the investigator. Details on investigators (including curricula vitae), sub-investigators and other relevant study personnel, and IRBs/IECs/REBs are maintained in the study's trial master file.

An independent data safety monitoring board (DSMB) will be established to review and analyze all safety data on a regular basis. Further information on the DSMB is presented in Section 16.4.

[redacted]

2. SERIOUS ADVERSE EVENT/SERIOUS INJURY/SERIOUS ADVERSE DEVICE EFFECT/DEVICE DEFICIENCY REPORTING

For reporting of serious adverse events (SAEs)/serious injuries (SI), serious adverse device effects (SADEs), and device deficiencies that could have led to an SADE to the IRBs/IECs/REBs, the investigator will comply with applicable national regulations and requirements as laid down in this clinical investigation plan (CIP) or mandated by the IRB/IEC/REB and the regulatory authorities.

For information on the definition and assessment of adverse events (AEs), device deficiencies, and SADEs, refer to Section 12.3.2.

ALL SAEs/SIs, SADEs, AND DEVICE DEFICIENCIES THAT COULD HAVE LED TO AN SADE ARE TO BE REPORTED ON THE SERIOUS ADVERSE EVENT REPORT (SAER) FORM AND FAXED/E-MAILED TO THE CRO WITHIN 24 HOURS AFTER BECOMING AWARE OF THE EVENT.

REPORTS ON NEW FINDINGS/UPDATES IN RELATION TO ALREADY REPORTED EVENTS WILL ALSO BE FAXED/E-MAILED TO THE CRO WITHIN 24 HOURS AFTER BECOMING AWARE OF THEIR OCCURRENCE.

See relevant report form for contact information.
Further details are also available in the study team roster.

[redacted]

3. UNANTICIPATED ADVERSE DEVICE EFFECT REPORTING

The investigator will comply with applicable requirements for reporting unanticipated adverse device effects (UADEs) to the reviewing IRB/IEC/REB. For sites in the United States, Food and Drug Administration regulations [21 CFR 812.150(a)(1)] for a device require investigators to report any UADEs to their IRB no later than 10 working days after the investigator first learns of the effect. For the definition of UADEs, refer to Section 12.3.2.1.7.

ALL UADEs ARE TO BE REPORTED ON A SAER FORM AND FAXED/E-MAILED TO THE CRO WITHIN 24 HOURS AFTER BECOMING AWARE OF THE EVENT.

See relevant report form for contact information.

Further details are also available in the study team roster.

[redacted]

4. SYNOPSIS

INVESTIGATIONAL DEVICE	
Name of Investigational Device	CELSTAT Absorbable Hemostat
Name(s) of Active Ingredient(s)	Oxidized cellulose
CLINICAL CONDITION(S)/INDICATION(S)	
Intended for use adjunctively in surgical procedures to assist in the control of capillary, venous and small arterial hemorrhage when ligation or other conventional methods of control are impractical or ineffective	
STUDY ID	3584-001
CLINICAL INVESTIGATION PLAN TITLE	A prospective randomized, controlled, study to evaluate the effectiveness and safety of CELSTAT as an adjunct to hemostasis for tissue bleeding in cardiothoracic, general and vascular surgery.
Short Title	Effectiveness and safety of CELSTAT for hemostasis in intraoperative tissue bleeding
PLANNED STUDY PERIOD	
Initiation	First subject's enrollment: Q1 2016
Primary Completion	Last subject's primary outcome assessed: Q1 2017
Study Completion	Last subject's last visit: Q2 2017
Duration	14 months
STUDY OBJECTIVES AND PURPOSE	
Study Purpose	
To evaluate the effectiveness and safety of CELSTAT as an adjunct to hemostasis in subjects undergoing cardiothoracic, general and vascular surgery as compared to Surgicel Original.	
Primary Objective	
To assess the hemostatic effectiveness of CELSTAT in comparison to Surgicel based on the proportion of subjects in which hemostasis is achieved at 5 minutes after the start of study treatment application	
Secondary Objectives	
1. To evaluate additional hemostatic effectiveness parameters of CELSTAT in comparison to Surgicel 2. To evaluate the safety of CELSTAT	
STUDY DESIGN	
Study Type	Effectiveness, Safety
Control Type	Concurrent (Active)

[redacted]

Study Indication Type	Treatment
Intervention Model	2-group, parallel
Blinding/Masking	Subject-blinded
Study Design	This study is a prospective, controlled, randomized, multicenter study to compare effectiveness and safety of CELSTAT versus Surgicel in a total of 258 randomized subjects (1:1 randomization) undergoing cardiothoracic, general or vascular surgery.
Planned Duration of Subject Participation	The subject participation period is approximately 15 weeks from enrollment to subject completion.

Primary Endpoints

Effectiveness

Proportion of subjects with hemostasis achieved at the target bleeding site (TBS) at 5 minutes after the start of application of the study device

Safety

Postoperative rebleeding from the TBS requiring surgical re-exploration during the subject's study participation

Secondary Endpoints

Effectiveness

- Time to hemostasis (TTH) at the TBS within the 10-minute assessment period
- Proportions of subjects with intraoperative hemostasis at the TBS at 3, 7 and 10 minutes after start of the application of the study device
- Intraoperative rebleeding from the TBS after occurrence of hemostasis

Safety

- Occurrence of adverse events (AEs)/adverse device effects (ADEs) during the subject's study participation
- Clinical laboratory parameters
- Vital signs

INVESTIGATIONAL DEVICE(S), DOSE AND MODE OF ADMINISTRATION	
Investigational Device	**Dosage form**: Oxidized cellulose strip (CELSTAT) **Dosage frequency**: Single-use treatment **Mode of Administration:** Intraoperative, direct application to the TBS
Comparator	**Dosage form**: Oxidized regenerated cellulose strip (Surgicel Original) **Dosage frequency**: Single-use treatment **Mode of Administration:** Intraoperative, direct application to the TBS
SUBJECT SELECTION	
Targeted Number of Subjects	258 randomized subjects at approximately 26 sites in the United States (20) and Europe (6)
Number of Arms	2 arms

[redacted]

Inclusion Criteria

Preoperative

1. Male or female subjects, 18 years or older at the time of signing the informed consent form (female subjects of childbearing potential must present with a negative serum pregnancy test, and must agree to employ adequate birth control measures [restricted to abstinence, barrier contraceptives, intrauterine contraceptive devices or licensed hormonal products] for the duration of their participation in the study)
2. Subject is undergoing planned (non-emergency) cardiothoracic, general or vascular surgery
3. Subject is willing and able to comply with the requirements of the clinical investigation plan

Intraoperative

Bleeding scale Grade 1 or 2 (mild or moderate) soft tissue, vascular or parenchymal bleeding present at the TBS after standard conventional surgical hemostatic methods (eg, ligature, suture, compression, cautery) prove to be ineffective or impractical.

Exclusion Criteria

Preoperative

1. Subject needs emergency surgery
2. Subject will undergo renal transplantation, or minimally invasive/laparoscopic surgery
3. Subject will undergo neurological or ophthalmological surgery
4. Subject will undergo urological or gynecological surgery (except for gynecological surgery in a postmenopausal subject or that results in removal of childbearing potential [eg, hysterectomy or other permanent sterilization procedure])
5. Subject has congenital coagulation disorder (eg, hemophilia)
6. Subject has known hypersensitivity to components of the investigational device
7. Subject has a clinically significant medical condition (eg, concomitant illness, psychiatric disorder, drug/ alcohol abuse), that, in the investigator's opinion, could adversely affect the safety of the subject and/ or compliance with the study procedures
8. Subject has participated in another clinical study involving an investigational product within 30 days prior to enrollment, or is scheduled to participate in another clinical study involving an investigational product during their participation in this study
9. Subject is a family member or employee of the investigator
10. Subject is pregnant or lactating at the time of enrollment, or becomes pregnant prior to the planned surgery

Intraoperative:

1. Occurrence of any surgical complication that requires resuscitation or deviation from the planned surgical procedure prior to identification of a TBS
2. Disseminated intravascular coagulopathy
3. Application of any topical hemostatic product to the TBS prior to application of the study treatment
4. TBS is within an inflamed or actively infected field
5. TBS is in, around, or in close proximity to foramina in bone, area of bony confinement or the spinal cord
6. Bleeding scale Grade 3 or 4 (severe or life-threatening) bleeding at the TBS
7. TBS is a non-treated hemorrhage from a visible capillary, vein or small artery, where ligation or other conventional means are likely to be effective

STATISTICAL ANALYSIS

Sample Size Calculation

In this non-inferiority study, the proportions of subjects meeting the primary endpoint are assumed to be [redacted]% for CELSTAT and [redacted]% for Surgicel; the non-inferiority margin is defined as 10%, the 1-sided Type 1 error rate (α) is 2.5%; and the statistical power (1-β) is 80%. This results in a sample size of 121 evaluable subjects per treatment group. To reach this number, 129 subjects are to be randomized per treatment group.

Planned Statistical Analysis

Primary Endpoints

The primary effectiveness endpoint, achievement of hemostasis within 5 minutes, will be investigated by a 2-sided test for non-inferiority using logistic regression, taking into account the following covariates: study center, surgery type (cardiothoracic, general or vascular), and initial bleeding severity (mild or moderate). Non-inferiority of CELSTAT to Surgicel will be assessed using the confidence-interval approach and a non-inferiority margin of 10%.

The difference in the proportion of subjects having postoperative rebleeding during study participation will be performed using the same logistic regression model described for the primary efficacy endpoint.

Secondary Endpoints

The logistic regression model used for the primary endpoint will also be performed on the proportions of subjects with hemostasis achieved at 3, 7, and 10 minutes after treatment application, and on the proportion of subjects with intraoperative rebleeding from the TBS after achievement of hemostasis.

The TTH will be presented by Kaplan-Meier curves. In addition, a log-rank test will be performed to assess the difference between the distributions of TTH for CELSTAT and Surgicel.

Descriptive statistics will be generated for the secondary safety endpoints (AEs, clinical laboratory parameters and vital signs). Shift tables will be generated for laboratory parameters.

5. TABLE OF CONTENTS

[redacted]

LIST OF TABLES

6. LIST OF ABBREVIATIONS

Abbreviation	Definition
ADE	adverse device effect
AE	adverse event
CI	confidence interval
CFR	Code of Federal Regulations
CIP	clinical investigation plan
CRO	contract research organization
DSMB	data safety monitoring board
eCRF	electronic case report form
FAS	full analysis set
GCP	Good Clinical Practice
IB	Investigator's Brochure
ICF	Informed consent form
IEC	independent ethics committee
IRB	institutional review board
ISO	International Organization for Standardization
IWRS	interactive Web-response system
MedDRA	Medical Dictionary for Regulatory Activities
NMC	non-medical complaint
OC	oxidized cellulose
PPS	per-protocol analysis set
REB	research ethics board
SADE	serious adverse device effect
SAE	serious adverse event
SAER	serious adverse event report
SI	serious injury
SIC	subject identification code
SSRI	selective serotonin re-uptake inhibitor
TBS	target bleeding site
TTH	time to hemostasis
UADE	unanticipated adverse device effect

7. BACKGROUND INFORMATION

7.1 Identification and Description of Investigational Device

CELSTAT is a medical device intended for use adjunctively in surgical procedures to assist in the control of capillary, venous and small arterial hemorrhage when ligation or other conventional methods of control are impractical or ineffective. It is a gamma sterilized, absorbable hemostat in a flat form with textile structure of high flexibility. It consists entirely of oxidized cellulose (OC) and does not contain any excipients. The hemostatic effect is immediate and total hemostasis is usually obtained within several minutes after application. CELSTAT is currently marketed in several European countries as Traumastem (distributed by Baxter Healthcare Corporation), Traumastem TAF Light (distributed by [redacted] or Traumacel TAF Light (distributed by [redacted]. in the Czech Republic). Hereafter in this CIP, the product will be referred to as CELSTAT.

Once applied, CELSTAT absorbs blood, turns brown, and adheres to the wound, thereby preventing thrombocytes from being washed out and accelerating hemostasis.[1] CELSTAT is 100% absorbable by the body and generally can, but does not have to be, left in situ. Results from International Organization for Standardization (ISO) 10993 testing documented that it causes no adverse immune or inflammatory reactions, is accepted by the organism, and does not affect any biological healing processes.

In this study, CELSTAT will be compared to Surgicel Original (marketed as Tabotamp in some European countries [see Section 9.8.1.2], referred to as Surgicel for the remainder of this document), a commercially available hemostatic agent based on oxidized regenerated cellulose, manufactured by Johnson and Johnson's Ethicon subsidiary. For study purposes the investigational devices will be traced by means of lot numbers.

7.2 Clinical Condition/Indication

Absorbable hemostats like CELSTAT or Surgicel are used in situations where ligature or conventional procedures are either ineffective or impractical. The devices play an important role in controlling bleeding during surgery and in minimizing rebleeding in the postoperative period, and can have a significant impact on surgical outcomes and postoperative complications.

Both CELSTAT and Surgicel are suitable for use in general and digestive surgery, plastic surgery, vascular and thoracic surgery, gynecology, stomatology, and other related fields.

In this study, CELSTAT will be compared to Surgicel as hemostatic adjunct during open field cardiothoracic, general and vascular surgery. Target bleeding sites (TBSs) include

mild to moderate parenchymal (organ tissue), vascular (small arteries or veins or surgical reconnections) and soft tissue (muscle, fat, ligament, connective tissue) bleeding. Examples of cardiothoracic, general and vascular surgery and the associated possible tissue types are provided in Table 1 (however, this list is not exclusive). Excluded from this study are neurological, ophthalmological, urological, and gynecological surgery (except in postmenopausal women or for gynecological surgery that results in removal of childbearing potential).

Table 1. Examples of Cardiothoracic, General and Vascular Surgery Types and Associated Possible Tissue Types

Broad Surgery Types Included in Study	Defined Surgery Type (examples, not exclusive)	Associated Tissue Types (examples, not exclusive)
Cardiothoracic	Vascular anastomosis	Vascular
	CABG (coronary artery bypass graft)	Vascular, soft tissue
	Valvular operations	Vascular
	Aneurysm resection or repair	Vascular, soft tissue
General (including intraabdominal and retroperitoneal)	Colectomy	Soft tissue
	Retroperitoneal tumor resection	Parenchymal, vascular, soft tissue
	Abdominoperineal resection	Vascular, soft tissue
	Hepatic resection	Parenchymal, vascular, soft tissue
	Lymphadenectomy	Vascular, soft tissue
Vascular	Open repair of aneurysm of aorta abdominalis	Vascular
	Creation of arteriovenous fistula	Vascular
	Aortobifemoral bypass	Vascular
	Carotid endarterectomy	Vascular
	Femoropopliteal, femorocrural bypass	Vascular

Subjects 18 years and older with planned cardiothoracic, general or vascular surgery will be recruited.

Subjects eligible for randomization will present with an intraoperative TBS suitable for treatment with a hemostatic adjunct, after conventional surgical hemostasis has been completed. Male or female subjects of any ethnic group and race may be recruited.

7.3 Justification for the Design of the Clinical Investigation

The design of this clinical investigation is based on the experience from a previous clinical study with CELSTAT, clinical studies with other absorbable hemostatic devices, and on preclinical study results with CELSTAT.

Surgicel was chosen as comparator, as it is considered standard among comparable marketed devices. CELSTAT or Surgicel will only be applied after primary/conventional hemostatic procedures (eg, ligature, suture, compression, cautery) prove to be either ineffective or impractical. Treatment of Grade 3 or 4 (severe or life-threatening; see Table 2) bleeding is prohibited and subjects with such a bleeding at the TBS will be excluded from this study.

According to the anticipated clinical use, this study intends to demonstrate the hemostatic effectiveness and safety of CELSTAT in a broad range of open surgical procedures including cardiothoracic, general and vascular surgeries.

7.3.1 CELSTAT Preclinical Studies

Nonclinical data were obtained in 22 nonclinical studies investigating the safety and efficacy of CELSTAT. In 2 studies on swelling properties and the effects on pH of CELSTAT when exposed to neutral buffered media, the swelling and chemical properties of CELSTAT were similar to those of Surgicel OriginaI. In 14 biocompatibility and toxicology studies, no potential for CELSTAT to cause sensitization, irritation, toxicity, or systemic coagulation activation was detected; CELSTAT was determined to be biocompatible; and no toxicologic risk resulting from exposure to extractable materials identified in CELSTAT was found.

Effectiveness of CELSTAT was assessed in 6 nonclinical studies. Three of these studies examined the time to hemostasis after CELSTAT application in comparison to commercially available hemostatic products (BloodSTOP or Surgicel Original). These studies used either a porcine liver square model or a porcine gastrointestinal punch biopsy model. In all 3 studies, CELSTAT showed a statistically significantly shorter time to hemostasis than the comparator products. CELSTAT was also more successful than BloodSTOP in controlling and maintaining hemostasis over time. One study examined hemostatic success (bleeding, yes or no) following application of CELSTAT or Surgicel Original in a rabbit femoral vein bleeding model. Statistical superiority of CELSTAT to Surgicel Original was demonstrated at 30, 60, and 90 seconds after application. Another study compared the hemostyptic properties of CELSTAT and Surgicel Original in a pig split skin hemostasis model. Bleeding scores were statistically significantly reduced with

CELSTAT compared to Surgicel. An additional study on hemostatic effectiveness, local tissue response and absorption of CELSTAT versus Surgicel in a rabbit femoral vessel bleeding model showed comparability of the 2 devices in effectiveness, local tissue response and absorption.

These studies are summarized in the Investigator's Brochure (IB) for CELSTAT.

7.3.2 Prior CELSTAT Clinical Investigation

The sponsor conducted a pilot clinical study (Study 621101) to evaluate the safety and effectiveness of CELSTAT (brand name Traumastem in the study report) as an adjunct to hemostasis for tissue bleeding in subjects undergoing open cardiac, intraabdominal (including retroperitoneal) or pelvic surgery as compared to Surgicel. This was a prospective, randomized, positive-controlled, subject-blinded, multicenter study.

In eligible subjects, the study treatment was applied at the TBS after conventional surgical hemostasis was completed. The number and size of layers of device used was at the discretion of the surgeon. The investigational device did not need to be removed and could be left in situ.

All 82 subjects enrolled achieved hemostasis at the primary TBS within 10 minutes. At 5 minutes after the start of device application hemostasis was achieved in 51 of 55 subjects (93%) in the CELSTAT group and in 24 of 27 subjects (89%) in the Surgicel group. Median time to hemostasis (TTH) in the CELSTAT group was 117 seconds, compared with 158 seconds in the Surgicel group.

The proportion of subjects with any adverse event (AE)/adverse device effect (ADE) was similar for the CELSTAT and Surgicel groups, with 74.5% (41/55 subjects) and 74.1% (20/27 subjects), respectively. Only 3 AEs/ADEs (postprocedural hematoma, postprocedural complication, and liver abscess) in the Surgicel group, all occurring in 1 subject, were considered by the investigator to be related to study treatment.

The pilot study defined AEs/ADEs of special interest as any of the following:

- Postoperative rebleeding
- Infection: signs included fever >100°F or >37.8°C after the first 48 hours with malaise and or lethargy
- Hematoma at the surgical site

- Change in coagulation parameters (as noted by change from normal or abnormal without clinical significance, respectively, at baseline to abnormal or abnormal with clinical significance at Day 7 (±1)/Discharge (Visit 3): prothrombin time, activated partial thromboplastin time, platelet count
- Increased wound healing time (more than 2 weeks) or wound dehiscence
- Foreign body reactions and allergic reactions (to device and material); signs of inflammation or encapsulation
- Embolization (especially vascular surgeries) and associated complications

The Surgicel group had a higher proportion of treatment-emergent AEs/ADEs of special interest (22.2%, 6/27 subjects, 6 events), compared with the CELSTAT group (7.3%, 4/55 subjects, 4 events). In the Surgicel group, the 6 events of special interest were wound infections (2 events), postprocedural hematoma (2 events), postprocedural hemorrhage, and wound dehiscence; in the CELSTAT group, the 4 events of special interest were abdominal abscess, wound infections, postprocedural hemorrhage, and wound dehiscence.

The proportions of SAEs/SADEs were similar between treatment groups, with 12.7% of subjects in the CELSTAT group reporting SAEs/SADEs and 11.1% of subjects in the Surgicel group reporting SAEs/SADEs. The Surgicel group had 1 SAE/SADE (liver abscess, moderate intensity) considered by the investigator to be related to study treatment. No related SAEs/SADEs were reported in the CELSTAT group. In each group, 1 fatal AE/ADE occurred, neither of which was related to study treatment.

The results of the pilot study demonstrated the safety and effectiveness of CELSTAT as a treatment option to achieve hemostasis in subjects undergoing intraabdominal, pelvic, or open cardiac surgery. The present study (3584-001) will test CELSTAT versus Surgicel in a larger population of 258 subjects scheduled for cardiothoracic, general and vascular surgery.

7.3.3 Choice of Surgicel as Comparator

Surgicel was chosen as comparator, as it is the standard among comparable marketed devices. Surgicel has been an approved medical device since 1960 (N12159, approval date 14 Oct 1960) in the United States. It has a long history of safety and effectiveness. The study device will only be used after primary surgical hemostasis has been achieved. Only bleeding sites appropriate for use of an OC device will be chosen. Therefore, no additional comparators are necessary.

[redacted]

7.3.4 Types of Surgery

Feasibility data show that OC/Surgicel is frequently used during general, vascular, gynecological, and oncological surgeries. A pilot clinical study of CELSTAT (Study 621101), conducted to provide sound relevant experience for planning the current study, supported cardiothoracic and general surgery. Therefore, general and vascular surgeries were chosen for this protocol. Excluded from this study are neurological, ophthalmological, urological, and gynecological surgery (except for gynecological surgery in postmenopausal women or surgery that results in removal of childbearing potential).

Minimally invasive surgery, as a distinct technique within each of the surgery types featured in this protocol, will not be allowed due to a potential significant bias resulting from, among others, differences in subject profile, technical demands, pre-and postoperative conduct, level of trauma and hemostasis achievement compared to the open surgery.

7.3.5 Primary Effectiveness Endpoint

TTH is the most meaningful criterion to assess the effectiveness of a hemostatic device. Timepoints were selected based on adequacy of demonstrating effectiveness of CELSTAT. In 3 nonclinical studies (Studies 53075, 52483, and 54201, summarized in the CELSTAT IB), the TTH after CELSTAT application was compared to commercially available hemostatic strip products (BloodSTOP or Surgicel Original); in all 3 studies, CELSTAT showed a statistically significantly shorter TTH than the comparator products. Other clinical studies use TTH between 3 minutes and 10 minutes after application of the device. A TTH of 5 minutes, which is supported by the pilot study, is a good compromise and applicable for all surgery types.

7.3.6 Statistical Considerations

Subgroup analyses in the pilot study showed that the surgery type seems to have high potential to influence the effectiveness results. Randomization will be stratified by surgery type in this study to control this effect. The sample size estimation is based on the assumption that the proportion of achieved hemostasis for the primary endpoint is [redacted]% for CELSTAT and [redacted]% for Surgicel.

The non-inferiority margin is defined as 10%. While the pilot study identified different rates of hemostasis at 5 minutes across surgery types, and surgery type had a high potential to influence effectiveness, a non-inferiority margin of 10% is still regarded as

appropriate, as the small-scaled pilot study may not provide adequate information allowing for a consistent judgement.

7.3.7 Relevant Literature and Data

Absorbable hemostatic adjuncts based on OC were first introduced into the market in the 1940s[2,3] and devices based on oxidized regenerated cellulose were launched in 1960.[4] OC offers superior handling characteristics when compared with gelatin foams. The knitted tissue strips can be cut to fit any size. The device does not stick to instruments and can easily be held firmly against the bleeding tissue until hemostasis is achieved.[5] The device forms a lattice-like structure that traps platelets and contributes to clot formation by expanding and absorbing up to several times its own weight.[6] Although the time to absorption of OC is thought to range from 2 to 6 weeks, depending on the amount used,[7] there are reports describing histologic evidence of OC fibers several years after cardiac surgery.[8,9,10]

Complications like allergic reactions, infections, granulomas and interference with bone healing have been noticed only rarely after the application of topical hemostatics.[11] Complications with the use of OC devices may arise from local swelling or possible inflammatory reactions.[12] Swelling of Surgicel in the proximity of the spinal cord or optic nerve has been linked to paralysis or nerve damage[13,14] and it is therefore recommended to remove Surgicel after use in confined areas. Additionally, foreign body reactions have been reported after the use of OC devices.[15]

7.4 Anticipated Benefits and Risks of the Investigational Device and Clinical Investigation

Benefits

The use of CELSTAT as an adjunct to hemostasis offers the following benefits:

- CELSTAT is intended to serve as an adjunctive treatment to hemostasis similar to other OC devices. It offers a wide application range within the surgical area with currently only brisk (major) arterial bleeding as contraindication
- CELSTAT is a biodegradable material that can be left in situ, if used in accordance with instructions and general site practice, thus reducing the risk of recurrent bleeding, traumatization of the subject and disruption of the healing process

- Based on former and current animal data, CELSTAT is expected to be well tolerated. To date, no undesirable effects such as allergic reactions at the application site have been reported for CELSTAT
- CELSTAT is easy to use and requires no specific preparations before application. Based on its ease of use, effective hemostasis, and comparably low costs, CELSTAT may reduce the overall costs for therapy

Risks

Potential risks associated with the use of either CELSTAT or Surgicel include the following:

- Foreign body reaction
- Inflammatory reaction (including adhesive disease)
- Infection
- Rebleeding at the treated site (with or without removal of the device after acheivement of hemostasis
- Hematoma/seroma
- Thromboembolic hazards (blood clots)
- Compression-related problems (eg, stenosis, nerve damage, or sequelae related to decreased blood flow)

The study inclusion and exclusion criteria (see Section 10), and the study-specified device application procedures (see Section 9.8.1.3), have been developed to minimize the magnitude of these risks, while still allowing the study objectives to be met.

Conclusions

Considering that it is not planned to include surgery types with the highest of the associated risks and that the study device application procedures are designed to further mitigate these risks, and the previously noted potential benefits, the study is considered to be medically justified.

7.5 Compliance Statement

This study will be conducted in accordance with this CIP, the Declaration of Helsinki (as currently amended), Title 21 of the United States Code of Federal Regulations Parts 50, 54, 56, and 812, the International Conference on Harmonisation Guideline for Good

Clinical Practice (GCP) E6 (Apr 1996), GCP as laid down in ISO Norm 14155:2011, the European Union Medical Devices Directive 93/42/EEC as amended by Directive 2007/47/EC, MEDDEV 2.7/3 and MEDDEV 2.7/4 Guidelines on Medical Devices, and applicable national and local regulatory requirements.

8. OBJECTIVES OF THE CLINICAL INVESTIGATION

8.1 Primary Objective

The primary objective of the study is to assess the hemostatic effectiveness of CELSTAT in comparison to Surgicel, based on the achievement of hemostasis within 5 minutes after the start of treatment application (for a detailed definition see Section 9.4.1.1).

8.2 Secondary Objectives

The secondary objectives of the study are:

- To evaluate additional hemostatic effectiveness parameters of CELSTAT in comparison to Surgicel (for detailed definition, see Section 9.4.2.1)
- To evaluate the safety of CELSTAT (see Section 9.4.2.2)

9. STUDY DESIGN

9.1 Brief Summary

This is a prospective, randomized, controlled, single-blind pivotal trial of CELSTAT as an adjunct to hemostasis for the treatment of mild to moderate bleeding in subjects undergoing cardiothoracic, general and vascular surgery. The study is to evaluate the effectiveness and safety of CELSTAT vs active control in 258 subjects. It will be conducted at approximately 26 sites in the United States (20) and Europe (6).

9.2 Overall Study Design

This is a prospective, randomized, positive-controlled, subject-blinded, multicenter study.

Surgicel was chosen as comparator, as it is the standard among comparable marketed devices.

A total of 258 subjects scheduled for cardiothoracic, general and vascular surgery are planned to be randomized, at a 1:1 ratio to CELSTAT or Surgicel, in the study. Patients will be evaluated for eligibility at screening (Visit 1; in- or outpatient setting) within 14 days prior to the planned surgery. Final inclusion of subjects depends on the fulfillment of the intraoperative eligibility criterion. On the day of surgery (Visit 2;

Day 1), inclusion and exclusion criteria will be verified pre- and intraoperatively. The surgeon will be kept blinded to treatment assignment until after the TBS is selected.

The bleeding scale developed for use in the study in determining TBS inclusion suitability and response to study treatment is presented in the following table (Table 2).

Table 2. Bleeding Severity Scale

Grade	Visual Presentation	Anatomical Appearance	Qualitative Description	Visually Estimated Rate of Blood Loss (mL/min)
0	No bleeding	No bleeding	No bleeding	≤1.0
1	Ooze or intermittent flow	Capillary-like bleeding	Mild	>1.0-5.0
2	Continuous flow	Venule- and arteriolar-like bleeding	Moderate	>5.0-10.0
3	Controllable spurting and/or overwhelming flow	Non-central venous- or non-arterial-like bleeding	Severe	>10.0-50.0
4	Unidentified or inaccessible spurting or gush	Central arterial- or venous-like bleeding	Life threatening[a]	>50.0

[a] Systemic resuscitation is required (eg, volume expanders, vasopressors, blood products).

Administration of the device is detailed in Section 9.8.1.3. Effectiveness and safety of the device will be assessed as described in Section 12.

Postoperative follow-up visits are scheduled for hospital discharge (or at Day 8 [±1] if the subject remains hospitalized for more than 1 week postsurgically; Visit 3); Day 31 (±5) (Visit 4); Day 61 (±10) (Visit 5); and Day 91 (±10) (Visit 6; end of study).

AEs and device related complications will be recorded from enrollment (time of signing of the informed consent form [ICF]) until the subject has completed participation in the study. Concomitant medication will be recorded from enrollment through the end of study participation. Safety laboratory assessments including coagulation parameters will be assessed at specified time points and the subject's vital signs will be monitored. Intraoperative complications and intra- as well as postoperative rebleeding events will be documented.

An overview of the study design is presented in Supplement 21.1.

[redacted]

9.3 Duration of Study Period(s) and Subject Participation

The planned overall duration of the study is approximately 14 months from study initiation (ie, first subject's enrollment) to study completion (ie, last subject's last visit). The recruitment period is expected to be approximately 10 months.

The subject participation period is approximately 15 weeks from screening to subject completion (ie, last study visit), unless prematurely discontinued.

9.4 Outcome Measures

9.4.1 Primary Outcome Measures

9.4.1.1 Effectiveness

The primary effectiveness outcome measure is the proportion of subjects with hemostasis achieved at the TBS at 5 minutes after the start of application of the study device.

Hemostasis is defined as Grade 0 bleeding (no bleeding; see Table 2 in Section 9.2) at the TBS after application of the randomized treatment, with no subsequent rebleeding at the TBS through surgical closure and no additional hemostatic treatment of another type after application of the randomized treatment.

9.4.1.2 Safety

The primary safety outcome measure is postoperative rebleeding from the TBS requiring surgical re-exploration during the subject's study participation.

9.4.2 Secondary Outcome Measures

9.4.2.1 Effectiveness

- TTH at the TBS within the 10-minute assessment period
- Proportions of subjects with hemostasis achieved at the TBS at 3, 7 and 10 minutes after the start of application of the study device
- Intraoperative rebleeding from the TBS after occurrence of hemostasis

9.4.2.2 Safety

- Occurrence of AEs/ADEs during the subject's study participation
- Clinical laboratory parameters
- Vital signs

9.5 Factors Influencing the Outcome

Surgery type (cardiothoracic, general and vascular) and bleeding severity (mild, moderate) may potentially influence hemostatic effectiveness. Therefore, these factors will be considered in the analysis.

9.6 Randomization and Blinding

9.6.1 Randomization

Subjects will be randomly assigned to CELSTAT or Surgicel at a ratio of 1:1. Randomization will be stratified by study center and surgery types (cardiothoracic, general, vascular surgery). It is aimed to achieve a similar distribution of the 3 surgery types in the randomized study population. This will be controlled via an interactive Web-response system (IWRS), [redacted] USA), using dynamic allocation. Within [redacted], a capping strategy will be used to ensure equal allocation of randomized subjects across surgical types. On the day of surgery, upon confirmation of preoperative eligibility criteria, a member of the site study staff other than the surgeon will obtain a treatment assignment (CELSTAT or Surgicel) from the IWRS. To keep the surgeon blinded until an eligible TBS has been identified for study treatment, adequate amounts of each study product (CELSTAT and Surgicel) will be taken into the operating room for potential use of one of them as the study treatment.

Immediately after the subject's intraoperative eligibility for study treatment has been confirmed (ie, an eligible TBS with Grade 1 or 2 bleeding has been identified), the assigned treatment will be revealed to the surgeon and the assigned device will be applied to the TBS. Following surgery, the treatment assignment and the actual treatment applied will be entered in the electronic case report form (eCRF) for the subject.

If the subject's eligibility is not confirmed pre- or intraoperatively, the subject's operation will be performed according to hospital standards. The study site designee will enter the date and reason(s) for the subject's exclusion in the eCRF.

9.6.2 Blinding

This will be a single-blinded study. The subjects undergoing scheduled surgery will be blinded. In addition, the surgeon performing the surgery will remain blinded until an eligible TBS has been identified for study treatment (see Section 9.6.1). Otherwise, investigators, surgery personnel, site study personnel, CRO personnel and sponsor personnel will not be blinded.

[redacted]

9.7 Suspension or Premature Termination of the Clinical Investigation

This study will be terminated if 1 or more of the following criteria are met:

- The incidence of device-related AEs/ADEs signals a potential health hazard
- New scientific data on the investigational device do not justify a continuation of the clinical study
- Serious or persistent non-adherence to the protocol, GCP, and/or applicable regulatory requirements by an investigator site may lead to a stop of recruitment and closure at this specific site
- The study is stopped by the sponsor for any reason

The clinical investigation may be terminated at an individual study site if no subjects are recruited within 6 months after site initiation, as well as in case of GCP non-compliance.

Subject follow-up after premature termination of the clinical investigation will include all procedures scheduled for the post-operation follow-up visits on Day 8 (±1)/discharge, Day 31 (±5), Day 61 (±10), and Day 91 (±10)/End of Study (Supplement 21.2).

9.8 Investigational Device(s) and Comparator(s)

9.8.1 Description and Administration of Treatment

9.8.1.1 Description of the Investigational Device - CELSTAT

CELSTAT is a medical device intended for use adjunctively in surgical procedures to assist in the control of capillary, venous and small arterial hemorrhage when ligation or other conventional methods of control are impractical or ineffective. It is a gamma-sterilized absorbable hemostat in a flat (matrix/OC) form based on OC. It has a textile structure and the raw material for manufacturing of CELSTAT is natural cotton. The cotton is oxidized in the gaseous phase by nitrogen dioxide. This reaction results primarily in the conversion of hydroxyl groups to carboxylic acid groups, making the material soluble at physiological conditions. Cellulosic acid within the device causes localized denaturation of blood proteins. The device does not contain substances derived from natural rubber latex, and is both polyvinyl chloride-free and diethylhexyl phthalate-free.

The manufacturer and supplier of CELSTAT is [redacted], Czech Republic. The manufacturer takes all necessary measures to ensure that the investigational device corresponds to the manufacturing and sterilization documentation.

[redacted]

CELSTAT is provided sterilized (gamma irradiated), endotoxin-free with the following physical properties:

- Composition: OC (100%)
- Weight: 90 to 120 g/m2
- Nitrogen content: ≤0.5%
- Quantity of carboxyl groups: 16% - 24%
- Loss on drying: ≤15%

For this study, CELSTAT sheets with the dimension 5×7.5 cm will be provided. Each sheet will be packed in a sterile pouch. Ten sterile pouches (each containing 1 CELSTAT sheet) will be included in each box of CELSTAT.

CELSTAT should be stored in a dry area protected from light between 2ºC and 30ºC. CELSTAT's shelf-life is 3 years after sterilization in original packaging.

9.8.1.2 Description of Comparator Device – Surgicel

Surgicel is a commercially available hemostatic device manufactured by Johnson and Johnson's Ethicon subsidiary. Surgicel is an absorbable knitted fabric prepared by the controlled oxidation of regenerated cellulose (polyanhydroglucuronic acid).

Surgicel is used adjunctively in a variety of surgical procedures to assist in the control of capillary, venous, and small arterial bleeding when conventional methods of control are impractical or ineffective.

Surgicel is white with a pale yellow cast and has a faint, caramel-like aroma. It is strong and can be sutured or cut without fraying. After Surgicel has been saturated with blood, it swells into a brownish or black gelatinous mass.

For this study, Surgicel Original will be supplied to the investigator sites in the configuration as prepared for final use by the manufacturer: knitted fabric sheets of 5.1×7.6 cm Surgicel Original (for United States investigator sites) or 5.0×7.5 cm Tabotamp (for European investigator sites). Each sheet will be packed in a sterile pouch containing an inner sterile envelope that houses the sheet. Twelve or 24 sheets and 1 Instructions for Use insert will be included in each box of the product.

Surgicel should be stored at controlled room temperature (Surgicel at 15° to 30°C / Tabotamp at 15° to 25°C). Surgicel's shelf life is 3 years.

[redacted]

9.8.1.3 Administration of the Study Device

In case more than 1 bleeding site is identified after conventional hemostasis, the first site appearing adequate according to the study eligibility criteria will be considered the TBS for hemostatic effectiveness and safety assessments. Additional bleeding sites are to be treated according to the hospital's standard of care, but not using either the CELSTAT or Surgicel that was supplied for study use, or any CELSTAT or Surgicel product otherwise available at the site. These bleeding sites will not be assessed for efficacy as part of the study.

Sterile technique should be observed in removing the study device from its sterile container. Once removed, the device is applied directly to the dried TBS. The nuber and size of layers required depends on the nature and intensity of the bleeding to be stopped. No upper limit is stipulated. The surgeon may obtain different sheet sizes by cutting the provided sheets with dry scissors. Only as much (length/width/numbers of layers) CELSTAT or Surgicel is to be used as is necessary to achieve hemostasis. The study device should not be wrapped too tightly when used as a wrap during vascular surgery.

The device is to be laid on the TBS and held firmly in place against the TBS for at least 30 seconds. The way the product is held in place is at the discretion of the surgeon depending on the nature of the TBS and should be similar for both products. The device should not be used for packing or wadding, unless it is to be removed after hemostasis is achieved.

The achievement or lack of hemostasis following treatment application to the TBS will be recorded at different time points during the first 10 minutes after the start of device application, as described in Section 12.2. If hemostasis appears to be achieved early, but rebleeding occurs during the 10-minute assessment period, more of the randomized product may be applied and the hemostasis assessment will continue.

During the 10-minute observation period all efforts should be made to achieve hemostasis at the TBS only by using the randomized study treatment.

Prior to surgical closure, any parts of the device not soaked with blood are to be carefully cut off to promote absorption and minimize the possibility of foreign body reaction.

Both CELSTAT and Surgicel are considered absorbable hemostats (based on preclinical data, absorption of CELSTAT is expected to take no more than 30 days). For study safety assesment purposes, both devices should be left in situ after hemostasis has been achieved, unless the investigator believes that the subject's safety would be jeopardized,

or if the product is ineffective. However, **no more than 5 CELSTAT sheets or 14 Surgicel sheets are to remain in situ at surgical closure in a given subject** (see Section 9.8.2). If some or all of the applied sheets are removed, the removal of the device(s) must be recorded on the eCRF, along with the rationale for removal.

Any rebleeding from the TBS after the 10-minute assessment period following treatment application is to be recorded as an AE, and is to be treated according to standard of care as determined by the surgeon. Should the investigator think that only OC is indicated, the randomized study device should be used if possible. However, **no more than 5 CELSTAT sheets or 14 Surgicel sheets are to remain in situ at surgical closure in a given subject.**

9.8.2 Number of Investigational Devices and Justification

No more than 5 CELSTAT sheets are to remain in situ at surgical closure in a given subject. The results of a toxicological evaluation of CELSTAT demonstrated that no risk of adverse effects caused by extractable substances is anticipated when up to 5 of the 5.0 x 7.5 cm sheets are applied per adult patient (ie, approximately 1 sheet per 14 kg [31 lb] body weight). This corresponds to an amount of 43 mg of CELSTAT per kg body weight (eg, 5 sheets for a 70 kg [154 lb] adult).

In order to allow an adequate safety comparison between the test and control products, no more than **14 Surgicel sheets are to remain in situ at surgical closure in a given subject.** This provides an approximately equivalent maximum mass of Surgicel, which has a lower density than CELSTAT, that can be allowed to be left in situ.

9.8.3 Justification for Use of Comparator(s)

Surgicel was chosen as active comparator, as it is considered standard among comparable marketed devices.

9.9 Investigational Device Accountability

The investigator will ensure that the investigational device and the comparator are stored as specified in the CIP and that the storage area is secured, with access limited to authorized study personnel, as described in the Clinical Study Agreement. A temperature log will be completed on a daily basis, in order to ensure maintenance of the correct storage temperature. In addition, the investigator will maintain records that the investigational device and comparator were received, including the date received, device identity code, date of manufacture or expiration date, number of devices received and their disposition. The investigational device and comparator must be dispensed only at

the study site. Records will be maintained that include the subject identification code (SIC) (see Section 11.2), application date, and number of devices used. All unused boxes and pouches of investigational device will be disposed of in accordance with the sponsor's instructions and all applicable laws and regulations after study completion/termination.

9.10 Source Data

Source data are defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial that are necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies), which may be in paper and/or electronic format. Source data for this study comprise the following:

- Paper or electronic hospital records
- Paper or electronic medical records
- Hospital discharge summaries
- Study-specific source document templates, if used
- Treatment care records
- Nursing care records
- Anesthesia reports
- Signed and dated central laboratory reports indicating clinical relevancy
- Clinical and office charts
- Laboratory notes, memoranda
- Pharmacy dispensing records
- Copies or transcriptions certified after verification as being accurate copies
- Subject files and records kept at the pharmacy/ at the laboratories involved in the clinical study.

For additional information on study documentation and eCRFs refer to Section 17.2.

10. SUBJECTS

A total of 258 subjects (129 subjects per treatment group) will be randomized (see sample size calculation in Section 13.1). This is expected to be achieved in an enrollment period

of 10 months. The number of subjects should be approximately equally distributed among the 26 planned sites.

The following inclusion and exclusion criteria define the population.

10.1 Inclusion Criteria

Subjects who meet **ALL** of the following criteria are eligible for this study:

Preoperative

1. Male or female subjects, 18 years or older at the time of signing the ICF (female subjects of childbearing potential must present with a negative serum pregnancy test, and must agree to employ adequate birth control measures [restricted to abstinence, barrier contraceptives, intrauterine contraceptive devices or licensed hormonal products] for the duration of their participation in the study)
2. Subject is undergoing planned (non-emergency) cardiothoracic, general or vascular surgery
3. Subject is willing and able to comply with the requirements of the CIP

Intraoperative

Bleeding scale Grade 1 or 2 (mild or moderate; see Table 2) soft tissue, vascular or parenchymal bleeding present at the TBS after standard conventional surgical hemostatic methods (eg, ligature, suture, compression, cautery) prove to be ineffective or impractical

10.2 Exclusion Criteria

Subjects who meet ANY of the following criteria are not eligible for this study:

Preoperative

1. Subject needs emergency surgery
2. Subject will undergo renal transplantation, or minimally invasive/laparoscopic surgery
3. Subject will undergo neurological or ophthalmological surgery
4. Subject will undergo urological or gynecological surgery (except for gynecological surgery in a postmenopausal subject or that results in removal of childbearing potential [eg, hysterectomy or other permanent sterilization procedure])

5. Subject has known congenital coagulation disorder (eg, hemophilia)
6. Subject has known hypersensitivity to any ingredient of the investigational device
7. Subject has a clinically significant medical condition (eg, concomitant illness, psychiatric disorder, drug/alcohol abuse), that, in the investigator's opinion, could adversely affect the safety of the subject and/or compliance with the study procedures
8. Subject has participated in another clinical study involving an investigational product within 30 days prior to enrollment, or is scheduled to participate in another clinical study involving an investigational product during their participation in this study
9. Subject is a family member or employee of the investigator
10. Subject is pregnant or lactating at the time of enrollment, or becomes pregnant prior to the planned surgery

Intraoperative:

1. Occurrence of any surgical complication that requires resuscitation or deviation from the planned surgical procedure prior to identification of a TBS
2. Disseminated intravascular coagulopathy
3. Application of any topical hemostatic product to the TBS prior to application of the study treatment
4. TBS is within an inflamed or actively infected field
5. TBS is in, around, or in close proximity to foramina in bone, area of bony confinement or the spinal cord
6. Bleeding scale Grade 3 or 4 (severe or life-threatening; see Table 2) bleeding at the TBS
7. TBS is a non-treated hemorrhage from a visible capillary, vein or small artery, where ligation or other conventional means are likely to be effective

10.3 Criteria and Procedures for Subject Withdrawal or Discontinuation

Any subject may voluntarily withdraw (ie, reduce the degree of participation in the study) consent for continued participation and data collection. The reason for withdrawal will be

recorded on the end-of-study eCRF. The data collected on withdrawn subjects will be used in the analysis and included in the clinical investigation report.

Discontinuation (ie, complete withdrawal from study participation) may be due to dropout (ie, active discontinuation by subject) or loss to follow-up (ie, discontinuation by subject without notice or action). Additionally, the investigator and the sponsor have the discretion to discontinue any subject from the study if, in their judgment, continued participation would pose an unacceptable risk for the subject.

For subjects who terminate the clinical investigation prematurely after treatment exposure, a final examination including all Day 8 (±1)/discharge, Day 31 (±5), or Day 61 (±10)/end-of-study follow-up assessments, depending on the time of withdrawal, should be performed, if possible. If a subject cannot come to a final examination, the investigator should try to clarify the reason and timepoint for discontinuation/drop out and document this in the source document used at the site. In case of drop out due to an SAE/SADE/UADE/AE of special interest, the event has to be documented sufficiently in the SAER form and the investigator has to report the SAE/SADE/UADE/AE of special interest to the CRO within 24 hours (see Section 12.3.2.4).

11. PROCEDURES

11.1 Informed Consent and Enrollment

Any subject who provides informed consent (ie, signs and dates the ICF, see Section 16.3) is considered enrolled in the study. Any subject who meets the inclusion criteria (including the intraoperative inclusion criterion) and does not fulfill the exclusion criteria is considered eligible for randomization. Screening failures are subjects who provide informed consent, but do not meet the eligibility criteria for treatment.

11.2 Subject Identification Code

The following series of numbers will comprise the SIC: 3584-001-SSS-EEEE

- 3584-001: CIP identifier
- SSS: 3-digit study site number
- EEEE: 4-digit enrolment number, reflecting the order of signing the ICF

For example, the third subject who signs an ICF at study site 02 will be identified as Subject 3584-001-002-0003.

All subject-related study documents (eg, eCRFs, clinical documentation, sample containers, device accountability logs) will be identified with the SIC.

11.3 Screening and Study Visits

All screening data will be collected and reported in eCRFs, regardless of screening outcome. In case a subject provided informed consent, was assigned an SIC, was screened and is eligible, but the operation could not be performed within 14 days, the End-of-Study eCRF will be completed indicating that the subject was not randomized and treated. In such a case, re-screening is allowed. If the subject is re-screened, a new ICF, new SIC, and new eCRF are required for the subject. The eCRF for the original SIC will be retained.

The study flow chart is illustrated in Supplement 21.1. An overview on the procedures to be performed at each study visit, including screening, can be found in Supplement 21.2.

11.4 Medications and Non-Drug Therapies

The following medications may be discontinued prior to the surgery according to the local standard of care:

- Anti-platelet agents
- Anti-coagulant therapy (oral or intravenous) and thrombolytic agents
- Non-steroidal anti-inflammatory drugs

Selective serotonin re-uptake inhibitors (SSRIs) may increase the risk of bleeding events.[16] Discontinuing an SSRI prior to the scheduled surgery should, therefore, be considered.

However, if antiplatelet agents or anticoagulant therapy cannot be discontinued prior to surgery due to medical reasons, these drugs must be documented as concomitant medication.

Homeopathic medications should generally be avoided because of the lack of information on safety and efficacy or possible effects on coagulation.

11.5 Subject Completion/Discontinuation

A subject is considered to have completed the study when he/she ceases active participation in the study because the subject has completed all study visits in accordance with the CIP (with or without deviations).

Reasons for discontinuation will be reported on the end-of-study eCRF, including: screen failure, completion, premature discontinuation, and, if applicable, the reason for premature discontinuation (AE, discontinuation by subject [eg, lost to follow-up, defined

as 3 documented unsuccessful attempts to contact the subject, or dropout), physician decision, study terminated by sponsor, or other reason [to be specified by the investigator]). Regardless of the reason, all data available for the subject up to the time of discontinuation will be recorded on the appropriate eCRF and will be used in the analysis and included in the clinical study report. Refer to Section 10.3 for reasons for premature discontinuation or withdrawal.

Every effort will be made to have prematurely discontinuing subjects complete the procedures/assessments scheduled for the end-of-study visit (Visit 6). The assessment results shall be recorded on the end-of-study (Visit 6) eCRF, and not as an unscheduled visit. If a subject prematurely terminates participation in the study during or immediately after a scheduled visit and does not return for an additional premature termination visit, the data from their last scheduled visit will remain as recorded (ie, no data from that visit will be repeated on or transferred to the Visit 6 eCRF).

In the event of subject discontinuation due to an AE/ADE, clinical and/or laboratory investigations that are beyond the scope of the required study observations/assessments may be performed as part of the evaluation of the event. These investigations will take place under the direction of the investigator in consultation with the CRO, and the details of the outcome may be reported to the appropriate regulatory authorities by the CRO.

11.6 Procedures for Monitoring Subject Compliance

All study procedures are to be performed under the direct supervision of the investigator/a licensed healthcare professional at the study site, and thus, no separate procedures are needed to monitor subject compliance.

12. ASSESSMENT OF OUTCOMES

12.1 Medical, Medication and Non-Drug Therapy History

At screening, the subject's medical history (including surgery; disease or condition severity [mild, moderate, or severe as defined in Section 12.3.2.2]; and start and end dates) will be described for the following body systems, if known: eyes, ears, nose, and throat; respiratory; cardiovascular; gastrointestinal; musculoskeletal; neurological; endocrine; hematopoietic/lymphatic; dermatological; and genitourinary. Subject demographics will also be entered in the eCRF.

All medications taken and non-drug therapies received from enrollment through the end of study participation will be recorded on the concomitant medications and non-drug therapies eCRFs.

For the purpose of this study, standard routine perioperative medication/treatment and anesthesia in relation to the surgical intervention (*except* anticoagulation and reversal) do not have to be recorded as concomitant medication.

12.2 Assessment of Effectiveness

For statistical analysis, the observation period includes the 10 minutes after start of application of the study device to the TBS.

The surgeon (who will be trained on the Bleeding Severity Scale [see Table 2] prior to study participation) will perform all intraoperative hemostasis assessments of the TBS, including identifying the TBS.

The severity of bleeding (Grade 1 or 2; see Table 2) at the TBS at the time of its identification (and prior to start of study device application) will be recorded.

A stop watch will be started at the start of device application. After application, the device is to be held firmly in place for at least 30 seconds. The occurrence and time of occurrence (or absence) of hemostasis (ie, Grade 0 bleeding; see Table 2) at the TBS will be recorded after the start of device application. Recurrence of bleeding, time of recurrence, and subsequent time of hemostasis will also be recorded, if applicable.

If hemostasis appears to be achieved early, but rebleeding occurs during the 10-minute assessment period, more of the randomized product may be applied and the hemostasis assessment will continue. TTH is defined as the time from the start of application of the study device until the first timepoint at which hemostasis at the TBS was observed and after which no rebleeding from the TBS occurred during the 10-minute observation period (subsequent intraoperative rebleeding will be considered a treatment failure).

In addition, any intraoperative rebleeding from the TBS after the initial 10-minute assessment period and prior to surgical closure will be recorded.

Treatment failure is defined as any of the following:

- Hemostasis not being achieved within 10 minutes
- Occurrence of bleeding complications during the 10-minute hemostasis assessment period requiring hemostatic measures other than application of the randomized study treatment
- Intraoperative rebleeding after the 10-minute hemostasis assessment period that is treated with the randomized study treatment or with any other hemostatic measures

The responsible study personnel will also record the following surgical, TBS, device administration, and hemostasis/rebleeding information during the peri- and intraoperative periods:

- Date of surgery
- Time of start and end of surgery (first skin incision/last skin suture)
- Surgery type (cardiothoracic, general, vascular)
- Indication for surgery and surgical procedure performed
- Anatomical location of TBS
- Tissue type (soft tissue, parenchymal or vascular)
- Type of conventional hemostatic measures at the TBS before randomization
- Time of completion of conventional hemostatic methods at TBS
- Identity (CELSTAT or Surgicel) and lot number of the applied study product
- Number of sheets of the study product applied to the TBS
- Number of sheets of the study product left in situ at surgical closure
- Reason, if study product removed prior to surgical closure
- Use of additional hemostatic treatment (yes/no) other than the study product at the TBS (ie, if hemostasis was not obtained during the 10-minute observation period, or if hemostasis was achieved but intraoperative rebleeding occurred); time of use (ie, number of minutes after clock start or after the 10 minute observation period), and type of additional hemostatic treatment

- Use of anticoagulation and reversal during surgery, including:
  - Whether any anticoagulation was used (yes/no)
  - Anticoagulant used, start and end times of administration and dose administered for each dose administered
  - Reversal agent used (if any), start and end times of administration and dose administered for each dose administered
  - Whether cardiopulmonary bypass was used (yes/no) and, if yes, start and end times of bypass
- Timepoint(s) of intraoperative rebleeding, if any, at the TBS after the 10-minute observation period (to also be documented as an AE [see Section 12.3.2.4])
- Intraoperative complications including death (to be documented as AEs)

12.3 Assessment of Safety

12.3.1 Postoperative Rebleeding

The occurrence of any postoperative rebleeding from the TBS requiring surgical re-exploration during the remainder of the subject's participation in the study will be recorded in the eCRF and will also be documented as an AE.

12.3.2 Adverse Events, Adverse Device Effects and Device Deficiencies

12.3.2.1 Definitions

12.3.2.1.1 Adverse Event

An AE (also refers to adverse experience) is defined as any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device. This definition includes events related to the investigational medical device or the comparator, as well as events related to the procedures involved. However, for users or other persons, this definition is restricted to events related to investigational medical devices.

AEs occurring after application of the study device are to be specified as treatment-emergent AEs.

Certain events that do not necessarily meet the definition of AEs, regardless of causal association with the investigational device(s), will still be recorded because they may be

reportable to regulatory authorities according to AE reporting regulations. These include the following:

- Exposure to a device during pregnancy
- Inadvertent or accidental exposure
- Unexpected therapeutic or clinical benefit from the medical device
- Application errors (ie, incorrect use of product)

12.3.2.1.2 Serious Adverse Event/ Serious Injury

An SAE/SI is an AE that:

- Leads to death
- Leads to serious deterioration in the health of the subject, that either results in:
  - A life-threatening illness or injury (NOTE: "Life-threatening" in the definition of "serious" refers to an AE in which the subject was at risk of death at the time of the event or reaction; it does not refer to an event or reaction which hypothetically might have caused death had it been more severe), or
  - A permanent impairment of a body structure or a body function, or
  - In-patient or prolonged hospitalization (NOTE: Planned hospitalization for a pre-existing condition, or a procedure required by the CIP without serious deterioration in health, is not considered an SAE), or
  - Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function
- Leads to fetal distress, fetal death or a congenital abnormality or birth defect
- Is a medically important event that may not be immediately life-threatening or require hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the definitions above. Examples of such events are:
  - Rebleeding requiring surgical revision
  - Wound infection requiring surgical re-exploration

- Intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization

12.3.2.1.3 Nonserious Adverse Event

A nonserious AE is an AE that does not meet the criteria of an SAE.

12.3.2.1.4 Unexpected Adverse Event

An unexpected AE is an AE whose nature, severity, specificity, or outcome is not consistent with the term, representation, or description used in the reference safety information (eg, IB, Instructions for Use). "Unexpected" also refers to the AEs that are mentioned in the IB as occurring with a class of devices or as anticipated from the properties of the device, but are not specifically mentioned as occurring with the particular device under investigation.

For the purposes of this investigation, each unexpected AE experienced by a subject treated with the study device will be recorded on the AE eCRF.

12.3.2.1.5 Adverse Device Effect

An ADE is an AE related to the use of an investigational medical device. ADEs include AEs resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device. ADEs also include any event resulting from use error or from intentional misuse of the investigational medical device.

12.3.2.1.6 Serious Adverse Device Effect

A SADE is an ADE that has resulted in any of the consequences characteristic of an SAE.

12.3.2.1.7 Unanticipated (Unexpected) Serious Adverse Device Effect

An unanticipated SADE is any SADE on health or safety or 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 investigational plan/application/instructions for use, or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

An anticipated serious ADE is an effect which by its nature, incidence, severity, or outcome has been identified in the IB, risk analysis report, or Instructions for Use.

In case an ADE or AE has been reported with other products of the same class but not with the investigational device, this ADE or AE shall be considered unanticipated/ unexpected for the investigational device.

12.3.2.1.8 Adverse Events of Special Interest

In this study, AEs of special interest are defined as any of the following events (Medical Dictionary for Regulatory Activities [MedDRA] preferred terms shown in parentheses):

- Postoperative rebleeding (post procedural hemorrhage) from the TBS during the subject's participation in the study
- Signs of local inflammation, adhesions or encapsulation (post procedural inflammation, postoperative adhesion, encapsulation reaction) at the device application site
- Local infection (post procedural infection, postoperative abscess) at the TBS
- Hematoma (post procedural hematoma) at the TBS
- Foreign body reactions (foreign body reaction), and allergic reactions (hypersensitivity) to the device, both systemic or local
- Thromboembolic events (postoperative thrombosis, deep vein thrombosis postoperative), especially in a vascular surgery case

AEs of special interest will be reported to the CRO's Safety Department on the SAER form (see Section 2). However, AEs of special interest should not be considered serious unless they meet SAE criteria (see Section 12.3.2.1.2). Nonserious AEs of special interest are to be reported to the authorities or committees concerned according to the procedures and timelines applicable for nonserious AEs. Serious AEs of special interest are to be reported according to the procedures and timelines applicable for SAEs (see Section 2).

12.3.2.1.9 Device Deficiency

A device deficiency is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance.

All device deficiencies related to the identity, quality, durability, reliability, safety, or performance of an investigational medical device shall be documented on the appropriate forms throughout the clinical investigation (see also Section 12.3.2.10 for documentation and reporting of device deficiencies that did not lead to an AE, ie, non-medical complaints).

Device deficiencies that did not lead to an AE but might have led to a SADE if either suitable action had not been taken, intervention had not been made, or circumstances had been less fortunate, must be reported as specified in Section 2.

12.3.2.2 Severity

The investigator will assess the severity of each AE using his/her clinical expertise and judgment based on the most appropriate description as follows:

- Mild
  - The AE is a transient discomfort and does not interfere in a significant manner with the subject's normal functioning level
  - The AE resolves spontaneously or may require minimal therapeutic intervention
- Moderate
  - The AE produces limited impairment of function and may require therapeutic intervention
  - The AE produces no sequelae
- Severe
  - The AE results in a marked impairment of function and may lead to temporary inability to resume usual life pattern
  - The AE produces sequelae, which require (prolonged) therapeutic intervention

12.3.2.3 Causality

Causality is a determination of whether there is a reasonable possibility that the investigational device is etiologically related to/associated with the AE. Causality assessment includes, eg, assessment of temporal relationships, dechallenge/rechallenge information, association (or lack of association) with underlying disease, presence (or absence) of a more likely cause, and physiological plausibility. For each AE assessed as not related or unlikely related, the investigator shall provide an alternative etiology. For each AE, the investigator will assess the causal relationship between the investigational device and the AE, using his/her clinical expertise and judgment according to the following most appropriate algorithm for the circumstances of the AE:

- Not related (both circumstances must be met)

  - Is due to underlying or concurrent illness, complications, concurrent treatments, or effects of concurrent drugs
  - Is not associated with the investigational device (ie, does not follow a reasonable temporal relationship to the administration of investigational device or has a much more likely alternative etiology)
- Unlikely related (either one or both circumstances are met)
  - Has little or no temporal relationship to the investigational device
  - A more likely alternative etiology exists
- Possibly related (both circumstances must be met)
  - Follows a reasonable temporal relationship to the administration of the investigational device
  - An alternative etiology is equally or less likely compared to the potential relationship to the investigational device
- Probably related (both circumstances must be met)
  - Follows a strong temporal relationship to the administration of an investigational device, which may include but is not limited to the following:
    - Reappearance of a similar reaction upon re-administration (positive rechallenge)
    - Positive results in a sensitivity test (eg, skin test)
    - Toxic level of one or more components of the investigational device, as evidenced by measurement of concentration in the blood or other bodily fluid
  - Another etiology is unlikely or significantly less likely

12.3.2.4 Assessment of Adverse Events

Each AE occurring after the subject signs the ICF until study completion or premature discontinuation from the study (except for specified forseeable events; see Section 12.3.2.7) will be described on the AE eCRF (ie, 1 AE per form) using the medical diagnosis (preferred), or, if no diagnosis could be established at the time of reporting the AE, a symptom or sign, in standard medical terminology in order to avoid the use of vague, ambiguous, or colloquial expressions (see definition in Section 12.3.2.1.1). Each AE will be evaluated by the investigator for:

- Seriousness as defined in Section 12.3.2.1.2
- Severity as defined in Section 12.3.2.2

- Causal relationship to investigational device exposure as defined in Section 12.3.2.3

For each AE, the outcome (ie, recovering/resolving, recovered/resolved, recovered/resolved with sequelae, not recovered/not resolved, fatal) and action taken (ie, dose increased, dose not changed, dose reduced, device interrupted, device withdrawn, not applicable, or unknown) will also be recorded on the AE eCRF. Recovering/resolving AEs will be followed until resolution, until medically stabilized, or for 30 days after the subject's study completion/termination visit, whichever comes first. Only outcome-related follow-up information received after the subject's study completion/termination visit will be recorded in the AE eCRF.

If an investigator becomes aware of an SAE occurring in a subject after study completion, the SAE must be reported on the SAER form within 24 hours after becoming aware of the SAE (see Section 12.3.2.4).

AE and laboratory safety data will be monitored by an independent DSMB on a regular basis. Further information on the DSMB is presented in Section 16.4.

12.3.2.5 Expedited Adverse Event Reporting

All SAEs/SADEs/UADEs occurring during the course of the study will be reported to the CRO within 24 hours of becoming aware of the event.

AEs of special interest (see Section 12.3.2.1.8) will also be captured on the SAER form and reported to the CRO; however, they will only be considered serious if they meet the SAE criteria (see Section 12.3.2.1.2). Within 24 hours of becoming aware of the event, the study site will send the completed SAER form to the CRO by e-mail or fax.

As required, the CRO will report SAEs, SADEs, and UADEs to the competent authorities, manufacturers, central reviewing IRBs/IECs/REBs, and investigative sites according to country-specific reporting timelines. Reporting to the competent authorities will be performed by the sponsor (Baxter) for CELSTAT.

Nonserious AEs of special interest are to be reported to the authorities or IRBs/IECs/REBs concerned according to the procedures and timelines applicable for nonserious AEs. Serious AEs of special interest are to be reported according to the procedures and timelines applicable for SAEs (see Section 2).

[redacted]

12.3.2.6 Pre-existing Diseases

Pre-existing diseases that are present before entry into the study as described in the medical history, and that manifest with the same severity, frequency, or duration after investigational device exposure, will not be recorded as AEs. However, when there is an increase in the severity, duration, or frequency of a pre-existing disease, the event must be described on the AE eCRF.

12.3.2.7 Foreseeable Adverse Events

A foreseeable AE is defined as an AE inherent to the surgical procedure that is expected to occur in all subjects. Each of the following events experienced after device exposure will not be considered an AE, will *not* be captured in the eCRF and thus, will not be included in the analysis of AEs (*unless* their severity and/or duration exceeds the clinically expected range):

- Postoperative nausea
- Postoperative vomiting
- Postoperative sleep disturbances
- Postoperative tiredness/fatigue
- Postoperative pain at the surgery site
- Back/neck/shoulder pain related to lying on the operating table
- Postoperative constipation

12.3.2.8 Urgent Safety Measures

The investigator is to take appropriate urgent safety measures in order to protect subjects against any immediate hazard to their health or safety. This does not need prior authorization from the sponsor. In the event(s) of an apparent immediate hazard to the subject, the investigator will notify the CRO immediately by phone and confirm notification to the CRO in writing as soon as possible, but within 1 calendar day after the change is implemented. The CRO will also ensure the responsible ethics committee and competent authorities are notified of the urgent measures taken in such cases according to local regulations.

12.3.2.9 Untoward Medical Occurrences Not Considered Adverse Events

Each **serious** untoward medical occurrence experienced before the first investigational device exposure (eg, from the time of signed informed consent up to, but not including, the first investigational device exposure) will be described on the SAER form and will be

entered into the eCRF. However, these events will not be considered as SAEs and will not be included in the analysis of SAEs.

Each nonserious untoward medical occurrence experienced by a subject before the first investigational device exposure will be recorded on the AE eCRF; these events will not be considered as AEs and will not be included in the analysis of AEs.

For the purposes of this study, *preplanned elective procedures* and hospitalizations for such procedures, before and after device exposure will not be considered AEs (unless the condition for which the procedure was planned has worsened since baseline) and thus, not included in the analysis of AEs. Such preplanned procedures must be recorded at screening.

12.3.2.10 Non-Medical Complaints

A non-medical complaint (NMC) is any alleged product deficiency that relates to identity, quality, durability, reliability, safety, and performance of the product but did not result in an AE. NMCs include but are not limited to the following:

- Device malfunctions, which are defined as failure of the device to meet its performance specifications or otherwise to perform as intended
- Missing components
- Damage to the product or unit carton
- A mislabeled product (potential counterfeiting/tampering)
- A bacteriological, chemical, or physical change or deterioration of the product causing it to malfunction or to present a hazard or fail to meet label claims

Any NMCs will be documented on an NMC form. If an investigational device fails to perform in the expected manner, the CRO will be notified within one (1) business day. If requested, defective devices will be returned to the sponsor for inspection and analysis according to specified procedures.

For reporting of device deficiencies that did not lead to an AE, but could have led to an SADE, refer to Section 12.3.2.1.8 and Section 2.

12.3.3 Physical Examinations

At screening and each of the postsurgical study visits, a physical examination will be performed on the following body systems (being described as normal or abnormal): general appearance, head and neck, eyes and ears, nose and throat, chest, lungs, heart,

abdomen, extremities and joints, lymph nodes, skin, and neurological system. At screening, if an abnormal condition is detected, the condition will be described on the medical history eCRF. At subsequent study visits, if a new abnormality or a worsened pre-existing abnormality is detected, the condition will be reported as an AE on the AE eCRF. If the abnormality was not deemed an AE because it was due to a preexisting disease (described in Section 12.3.2.6), is not clinically significant, is a symptom of a new/worsened condition already recorded as an AE, or due to another issue, the investigator will record the justification on the source record.

12.3.4 Clinical Laboratory Parameters

12.3.4.1 Hematology, Clinical Chemistry and Coagulation

The hematology panel will consist of complete blood count [hemoglobin, hematocrit, erythrocytes (ie, red blood cell count), and leukocytes (ie, white blood cell count)] with differential (ie, basophils, eosinophils, lymphocytes, monocytes, neutrophils) and platelet counts.

The clinical chemistry panel will consist of sodium, potassium, calcium, chloride, bicarbonate, protein, albumin, alanine aminotransferase, bilirubin, alkaline phosphatase, blood urea nitrogen, creatinine, and glucose.

The coagulation panel will consist of prothrombin time, activated partial thromboplastin time and, where applicable, international normalized ratio.

Blood samples will be drawn for assessment of hematology and clinical chemistry parameters at screening (Visit 1) and at each of the postsurgical study visits (Visits 3 through 6). A central laboratory will be used. Blood samples will be handled and stored according to the instructions provided by the central laboratory. The laboratory reports provided by the central laboratory will be reviewed, signed and dated by the investigator and attached to the source documents.

Screening laboratory samples (for hematology, clinical chemistry, coagulation and serum pregnancy test) must be taken *within 7 days prior to surgery*.

12.3.4.2 Other Laboratory Tests

A serum pregnancy test for females of childbearing potential will be performed at screening to confirm that the subject is not pregnant (preoperative exclusion criterion 9; see Section 10.2). The serum pregnancy test will be performed by the central laboratory. An additional urine pregnancy test will be performed preoperatively on the day of

surgery if the serum pregnancy test was performed >7 days prior to the planned surgery. The urine pregnancy test will be performed by the investigator site.

12.3.4.3 Assessment of Laboratory Values

The investigator's assessment of each abnormal laboratory value is to be recorded on the eCRF. For each abnormal laboratory value, the investigator will determine whether the value is considered clinically significant. For clinically significant values, the investigator will consider whether or not to report an AE (see definition in Section 12.3.2.1.1). If yes, the sign, symptom, or medical diagnosis will be recorded on the AE eCRF. If the abnormal value was not deemed clinically significant, the investigator will indicate on the eCRF the reason (ie, lab error, due to pre-existing disease [described in Section 12.3.2.6]), symptom of a new/worsened condition already recorded as an AE, or due to another issue that will be specified). Additional tests and other evaluations required to establish the significance or etiology of an abnormal result, or to monitor the course of an AE should be obtained when clinically indicated. Any abnormal value that persists should be followed at the discretion of the investigator.

Clinically significant abnormal deviations of laboratory parameters (ie, values suggesting an unknown disease and requiring further clinical evaluation) revealed at the screening visit are not considered to be AEs.

12.3.5 Vital Signs

Vital signs will include body temperature (°C or °F; otic, oral or axillary method), respiratory rate (breaths/min), pulse rate (beats/min), and systolic and diastolic blood pressure (mmHg). Height (in or cm) and weight (lb or kg) will also be collected.

Vital signs will be measured at screening and at all postsurgical study follow-up visits (height will only be collected at screening).

Vital sign values are to be recorded on the eCRF. For each vital sign value recorded postoperatively, the investigator will determine whether the value is considered an AE (see definition in Section 12.3.2.1.1). If assessed as an AE, the medical diagnosis (preferably), symptom, or sign, will be recorded on the AE eCRF. If the abnormal value was not deemed an AE, the investigator will indicate the reason on the source record (ie, error, due to a pre-existing disease [described in Section 12.3.2.6], not clinically significant, a symptom of a new/worsened condition already recorded as an AE, or due to another issue that will be specified). Additional tests and other evaluations required to establish the significance or etiology of an abnormal result, or to monitor the course of an

AE should be obtained when clinically indicated. Any abnormal value that persists should be followed at the discretion of the investigator.

13. STATISTICAL CONSIDERATIONS

13.1 Sample Size and Power Calculations

The study is designed to show non-inferiority of CELSTAT compared to Surgicel based on the primary effectiveness endpoint, ie, the proportion of subjects achieving hemostasis within 5 minutes of the start of application of study treatment, which is maintained until surgical closure. These proportions are assumed to be [redacted]% for CELSTAT and [redacted]% for Surgicel (based on the experience from the pilot study, Study 621101 [see Section 7.3.2] and considering some buffer in the proportions). Using a non-inferiority margin of 10% (the largest clinically acceptable difference), a 1-sided Type 1 error rate (α) of 2.5%, and a statistical power (1-β) of 80%, the sample size estimation results in 121 evaluable subjects per treatment group. The estimation of the sample size was performed using [redacted] ([redacted], NC).

The primary analysis will be performed on the per-protocol analysis set (PPS). Assuming that the PPS is 5% less than the total number of randomized subjects and adjusting slightly upward to allow for equal numbers of subjects of the 3 surgery types, 129 subjects per treatment group have to be randomized.

13.2 Datasets and Analysis Cohorts

Two types of analyses of effectiveness are planned: analysis of the full analysis set (FAS) and of the PPS. Assessment of safety will be carried out on all subjects treated (safety analysis set).

Full analysis set: The FAS will consist of all subjects who are randomized. Subjects will be analyzed as randomized.

Per-protocol analysis set: The PPS is defined as a subset of the FAS. Subjects will be excluded from the PPS if they:

- Do not meet all inclusion/exclusion criteria
- Are randomized but not treated according to the randomization scheme
- Violate other major study procedures that may influence the study results

Safety analysis set: The safety analysis set will consist of all subjects who are treated with CELSTAT or Surgicel. Subjects will be analyzed as treated.

13.3 Handling of Missing, Unused, and Spurious Data

Only subjects for whom data are available will be included in the statistical analysis. Missing values will be neither replaced nor estimated in the primary analysis. A sensitivity analysis, in which all missing data will be considered as treatment failures will be performed for the FAS to assess the influence of missing data on the primary efficacy results. In addition, a worst-case analysis will also be performed, in which any subjects in the CELSTAT treatment group with missing primary efficacy data will be categorized as treatment failures, and any subjects in the Surgicel treatment group with missing primary efficacy data will be categorized as treatment successes.

13.4 Methods of Analysis

13.4.1 Primary Outcome Measures

The primary efficacy analysis will be carried out on the PPS. The analysis using the FAS will be used as a supportive analysis.

The primary efficacy parameter is defined as follows: The primary endpoint is set to success if hemostasis is achieved at 5 minutes after the treatment application and is maintained until surgical closure. If hemostasis is not achieved at 5 minutes, if additional hemostatic treatment other than study device is required, or if intraoperative rebleeding occurs, the primary endpoint will be set to “treatment failure”.

The primary effectiveness endpoint will be investigated by a 2-sided test for non-inferiority using the confidence-interval (CI) approach to compare the CELSTAT group to the Surgicel group. A non-inferiority margin of 10% (the largest clinically acceptable difference) will be used; thus, if the lower bound of the 2-sided 95% CI (based on normal approximation) around the difference in proportions (CELSTAT group - Surgicel group) is greater than -10% in the final analysis, CELSTAT will be declared non-inferior to Surgicel.

The specific hypotheses of the risk difference to be tested are as follows:

H_0: $P_{CELSTAT} - P_{Surgicel} \leq -\delta$

H_1: $P_{CELSTAT} - P_{Surgicel} > -\delta$

where

$P_{CELSTAT}$ = the proportion (%) of subjects achieving hemostasis by 5 minutes in the CELSTAT group,

$P_{Surgicel}$ = the proportion (%) of subjects achieving hemostasis by 5 minutes in the Surgicel group, and

δ = the non-inferiority margin of 10%.

Additionally, if the lower bound of the 2-sided 95% CI is larger than zero, superiority of CELSTAT versus Surgicel will be claimed.

The null hypothesis will be tested against the alternative using logistic regression, taking into account the following covariates: study center, surgery type (cardiothoracic, general or vascular) and initial bleeding severity (mild or moderate).

The primary safety analysis, of the difference in proportion of subjects rebleeding from the TBS requiring surgical re-exploration during the subject's study participation, will be performed using the same logistic regression model described for the primary efficacy endpoint.

13.4.2 Secondary Outcome Measures

The logistic regression model used for the primary analysis will also be performed for the following secondary endpoints:

- The difference in proportion of subjects having achieved hemostasis at 3 minutes and which is maintained until surgical closure
- The difference in proportion of subjects having achieved hemostasis at 7 minutes and which is maintained until surgical closure
- The difference in proportion of subjects having achieved hemostasis at 10 minutes and which is maintained until surgical closure

[redacted]

- The difference in proportion of subjects with intraoperative rebleeding from the TBS after achievement of hemostasis

The TTH will be presented by Kaplan-Meier curves. In addition, a log-rank test will be performed to assess the difference between the distributions of TTH for CELSTAT and Surgicel.

AEs that occurred during or after treatment application will be presented in summary tables. Summary tables shall indicate the number of subjects who experienced AEs. In addition, tables will be prepared to list each AE, the number of subjects in each treatment group who experienced an AE at least once, and the rate of subjects with AEs. AEs grouped by MedDRA system organ class and preferred term will be presented by severity grade (mild, moderate, severe) and relatedness to treatment ("possibly related" or "probably related" AEs will be considered "related"; "unlikely related" or "not related" AEs will be considered "not related").

All AEs for each subject, including the same event on several occasions, will be listed, giving both MedDRA preferred term and the original term used by the investigator, system organ class, severity grade, seriousness, relation to the treatment, onset date, and stop date.

AEs that occurred before the start of treatment application will be listed separately.

Clinical laboratory parameters and vital signs will be summarized by visit and treatment group. Shift tables will be generated for laboratory parameters.

13.5 Interim Analysis

No interim analysis is planned for the study.

14. ACCESS TO SOURCE DATA

The investigator/study site will cooperate and provide direct access to study documents and data, including source documentation for monitoring by the study monitor, audits by the CRO and sponsor, review by the IRBs/IECs/REBs, and inspections by applicable regulatory authorities, as described in the Clinical Study Agreement. If contacted by an applicable regulatory authority, the investigator will notify the CRO of this contact, cooperate with the authority, provide the CRO with copies of all documents received from the authority, and allow the CRO to comment on any responses, as described in the Clinical Study Agreement.

15. QUALITY CONTROL AND QUALITY ASSURANCE

15.1 Investigator's Responsibility

The investigator will comply with the CIP (which has been approved/given favorable opinion by the IRBs/IECs/REBs), GCP, and applicable regulatory requirements as described in the Clinical Study Agreement. The investigator is ultimately responsible for the conduct of all aspects of the study at the study site and verifies by signature the integrity of all data transmitted to the CRO. The term "investigator" as used in this CIP as well as in other study documents, refers to the investigator or authorized study personnel that the investigator has designated to perform certain duties. Sub-investigators or other authorized study personnel are eligible to sign for the investigator, except where the investigator's signature is specifically required.

Where required by national regulations and/or the responsible IRB/IEC/REB, the investigator will submit written progress reports of the study's status to the CRO and/or the reviewing IRB/IEC/REB and/or a final report to the CRO and/or the reviewing IRB/IEC/REB.

15.2 Training

The study monitor will ensure that the investigator and study site personnel understand all requirements of the CIP, the investigational status of the investigational device, and his/her regulatory responsibilities as an investigator. Training may be provided at an investigator's meeting, at the study site, and/or by instruction manuals. In addition, the study monitor will be available for consultation with the investigator and will serve as the liaison between the study site and the CRO.

15.3 Monitoring

The study monitor is responsible for ensuring and verifying that each study site conducts the study according to the CIP, standard operating procedures, other written instructions/agreements, GCP, and applicable regulatory guidelines/requirements. The investigator will permit the study monitor to visit the study site at appropriate intervals. Monitoring processes specific to the study will be described in the clinical monitoring plan.

15.4 Auditing

The CRO and sponsor may conduct audits to evaluate study conduct and compliance with the CIP, standard operating procedures, other written instructions/agreements, GCP, and applicable regulatory guidelines/requirements. The investigator will permit auditors to

visit the study site, as described in the Clinical Study Agreement. Auditing processes specific to the clinical investigation will be described in the auditing plan.

15.5 Noncompliance with the Clinical Investigation Plan

The investigator may deviate from the CIP to eliminate an apparent immediate hazard to the subject. In the event(s) of an apparent immediate hazard to the subject, the investigator will notify the CRO immediately by phone and confirm notification to the CRO in writing as soon as possible, but within one (1) calendar day after the change is implemented. The investigator will also notify the responsible IRB/IEC/REB of the urgent measures taken in such cases according to local regulations (see also Section 12.3.2.8).

If monitoring and/or auditing identify serious and/or persistent non-compliance with the CIP, the CRO may terminate the investigator's participation. The CRO will notify the IRB/IEC/REB and applicable regulatory authorities of any investigator termination.

15.6 Laboratory Standardization

Not applicable; a central laboratory will be used for all clinical laboratory tests.

16. ETHICS

16.1 Subject Privacy

The investigator will comply with applicable subject privacy regulations/guidance as described in the Clinical Study Agreement.

16.2 Ethics Committee and Regulatory Authorities

Before enrollment of subjects into this study, the CIP, ICF, any promotional material/advertisements, and any other written information to be provided to the subjects will be reviewed and approved/given favorable opinion by the IRB/IEC/REB and applicable regulatory authorities. The IB will be provided for review. The IRB/IEC/REB's composition or a statement that the IRB/IEC/REB's composition meets applicable regulatory criteria will be documented. The study will commence only upon the CRO's receipt of approval/favorable opinion from the IRB/IEC/REB and, if required, upon the CRO's notification of applicable regulatory authority(ies) approval, as described in the Clinical Study Agreement.

If the CIP or any other information given to the subject is amended, the revised documents will be reviewed and approved/given favorable opinion by the IRB/IEC/REB and applicable regulatory authorities, where applicable. The CIP amendment will only be

implemented upon the CRO's receipt of approval and, if required, upon the CRO's notification of applicable regulatory authority(ies) approval.

16.3 Informed Consent

Investigators will choose subjects for enrollment considering the study eligibility criteria. The investigator will exercise no selectivity so that no bias is introduced from this source.

All subjects and/or their legally authorized representative must sign an ICF before entering into the study according to applicable regulatory requirements and GCP. Before use, the ICF will be approved by the IRB/IEC/REB and regulatory authority(ies), where applicable. The ICF will include a comprehensive explanation of the proposed treatment without any exculpatory statements, in accordance with the elements required by GCP and applicable regulatory requirements. Subjects or their legally authorized representative(s) will be allowed sufficient time to consider participation in the study. By signing the ICF, subjects or their legally authorized representative(s) agree that they will complete all evaluations required by the study, unless they withdraw voluntarily or are terminated from the study for any reason.

The CRO will provide to the investigator in written form any new information that significantly bears on the subjects' risks associated with investigational device exposure. The informed consent will be updated, if necessary. This new information and/or revised ICF, that have been approved by the applicable IRB/IEC/REB and regulatory authorities, where applicable, will be provided by the investigator to the subjects who consented to participate in the study.

16.4 Data Safety Monitoring Board

This study will be monitored by an independent unblinded DSMB. The DSMB will be composed of 4 members, 3 of whom are recognized experts in the field of surgery, clinical care and research, and the fourth of whom is a biostatistician. The DSMB surgeons will have expertise in the areas of cardiothoracic, general and vascular surgeries, and will not be involved in enrolling or treating study subjects.

The DSMB will review the safety data (AEs and laboratory test results) from the study after approximately one-third and two-thirds of the subjects have been treated, and will have the discretion to recommend stopping the trial due to safety concerns. The DSMB will monitor ongoing safety data for evidence of postsurgical adhesion formation, wound infection, fistula formation, and persistent bleeding at the TBS.

Details of the composition of and procedures used by the DSMB will be presented in a formal DSMB charter issued prior to the start of study enrollment.

17. DATA HANDLING AND RECORD KEEPING

17.1 Confidentiality Policy

The investigator will comply with the confidentiality policy as described in the Clinical Study Agreement.

17.2 Study Documentation and Case Report Forms

The investigator will maintain complete and accurate paper format study documentation in a separate file. Study documentation may include medical records, records detailing the progress of the study for each subject, signed ICFs, device/drug disposition records, correspondence with the IRB/IEC/REB and the study monitor/CRO, enrollment and screening information, eCRFs, SAERs, laboratory reports, and data clarifications requested by the CRO.

The investigator will comply with the procedures for data recording and reporting. Any corrections to study documentation must be performed as follows: 1) the first entry will be crossed out entirely, remaining legible; and 2) each correction must be dated and initialed by the person correcting the entry; the use of correction fluid and erasing are prohibited.

The investigator is responsible for the procurement of data and for the quality of data.

Only authorized study site personnel will record or change data on the eCRFs. Changes to an eCRF will require documentation of the reason for each change. An identical (electronic/paper) version of the complete set of eCRFs for each subject will remain in the investigator file at the study site in accordance with the data retention policy (see Section 17.4).

The handling of data by the CRO, including data quality assurance, will comply with regulatory guidelines (eg, ISO 14155, GCP) and the standard operating procedures of the CRO. Data management and control processes specific to the study will be described in the data management plan.

17.3 Extent of Source Data Verification

Site monitors will follow the instructions given in the monitoring plan for source data verification. In this study, 100% source data verification will be performed for all

enrolled subjects. The investigator will ensure that the site monitor has access to all source documents for the enrolled subjects.

17.4 Document and Data Retention

The investigator will retain study documentation and data (paper and electronic forms) in accordance with applicable regulatory requirements, site requirements, and the document and data retention policy as described in the Clinical Study Agreement.

18. FINANCING AND INSURANCE

The investigator will comply with investigator financing, investigator/sponsor insurance, and subject compensation policies, if applicable, as described in the Clinical Study Agreement.

The insurance will be provided for each subject in the clinical investigation. Clinical trials insurance is product liability coverage designed to respond to claims brought by study subjects, or their families, for bodily injury.

19. AMENDMENTS TO THE CLINICAL INVESTIGATION PLAN

The investigator or CRO should not implement any deviation from, or changes of, the CIP without mutual agreement, prior review and documented approval from the IRB/IEC/REB of a respective amendment. The only exceptions are where necessary to eliminate an immediate hazard to study subjects, or when the changes involve only logistical or administrative aspects of the study (eg, change in monitor(s), change of telephone number(s)).

The party initiating an amendment must confirm it clearly in writing and it must be signed and dated by the same persons who have signed the original CIP. CIP amendments will be submitted to the appropriate IRBs/IEC/REBs and competent authorities as required.

20. PUBLICATION POLICY

The investigator will comply with the publication policy as described in the Clinical Study Agreement.

21. SUPPLEMENTS

21.1 Study Flow Chart

Visit Number (Study Day)	Visit Type/Assessments
Visit 1 (Day-14 to -1)	Screening visit
	Assessment of inclusion and exclusion criteria
Visit 2 (Day 1)	Randomization and treatment visit (day of surgery)
	Preoperative: Confirmation of preoperative inclusion/randomization criteria; randomization
	Intraoperative: Identification of eligible target bleeding site; treatment application; assessment of hemostatic effectiveness and safety
Visit 3 (hospital discharge or Day 8 [±1] if hospitalized longer than 1 week)	Hospital discharge visit
	Assessment of postoperative rebleeding and safety
Visit 4 (Day 31 [±5])	Follow-up visit
	Assessment of postoperative rebleeding and safety
Visit 5 (Day 61 [±10])	Follow-up visit
	Assessment of postoperative rebleeding and safety
Visit 6 (Day 91 [±10] or at premature discontinuation)	End-of-study visit
	Assessment of postoperative rebleeding and safety

[redacted]

21.2 Schedule of Study Procedures and Assessments

	Visit 1 Screening Day -14 to -1	Visit 2 Randomization/Surgery Day 1	Visit 3 Discharge ≤ Day 8 (±1)[a]	Visit 4 Follow-up Day 31 (±5)	Visit 5 Follow-up Day 61 (±10)	Visit 6 End of Study Day 91 (±10)
Informed consent	X					
Inclusion/exclusion	X	X[b]				
Demographic characteristics	X					
Medical history	X					
Concomitant medication	X[c]	X	X	X	X	X
Physical examination	X		X	X	X	X
Vital signs	X		X	X	X	X
Hematology and clinical chemistry tests[d]	X[e]		X	X	X	X
Pregnancy test[f]	X	X				
Randomization		X				
Study device application		X				
Hemostasis assessments[g]		X				
Additional intraoperative assessments[g]		X				
Postoperative rebleeding		X	X	X	X	X
Adverse events	X	X	X	X	X	X

[a]To be performed on the day of discharge from the hospital; or on Day 8 (±1) should the subject remain in the hospital for more than a week postsurgically.
[b]Review of preoperative and assessment of intraoperative eligibility criteria.
[c]Medication will be recorded from enrollment (signing of informed consnet form) through the end of study participation.
[d]Hematology: prothrombin time, activated partial thromboplastin time, international normalized ratio (when applicable), hemoglobin, hematocrit, erythrocytes, leukocytes with differential (ie, basophils, eosinophils, lymphocytes, monocytes, neutrophils) and platelet counts. Clinical chemistry: sodium, potassium, calcium, chloride, bicarbonate, protein, albumin, alanine aminotransferase, bilirubin, alkaline phosphatase, blood urea nitrogen, creatinine and glucose.
[e]Screening samples (for hematology, clinical chemistry and serum pregnancy test) to be taken within 7 days prior to surgery.
[f]Serum pregnancy test at screening; urine pregnancy test at Day 1 (prior to surgery) if serum pregnancy test >7 days prior to Day 1.
[g]See Section 12.2 for details.

[redacted]

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CELSTAT

A Prospective, Randomized, Controlled Study to Evaluate the Effectiveness and Safety of CELSTAT as an Adjunct to Hemostasis for Tissue Bleeding in Cardiothoracic, General and Vascular Surgery

INVESTIGATION PLAN IDENTIFIER: 3584-001

By signing below, the investigator acknowledges that he/she has read, understands and agrees to this clinical investigation plan. He/she will comply with the requirements for obtaining informed consent from all study subjects prior to initiating any investigation-specific procedures, obtaining written initial and ongoing IRB/IEC/REB (s) investigation plan review and approval, understands and abides by the requirements for maintenance of source documentation, and provides assurance that this study will be conducted according to all requirements as defined in this clinical investigation plan, Clinical Study Agreement, GCP guidelines, and all applicable regulatory requirements.

Signature of Principal Investigator Date

Print Name of Principal Investigator

[redacted]