Statistical Analysis Plan: 3584-001

Study 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
Study Number:	3584-001
Study Phase:	N/A
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.
Product Name:	CELSTAT Absorbable Hemostat
Formulation	Oxidized cellulose
Indication:	For use adjunctively in surgical procedures in the control of hemorrhage
Statistician:	[redacted], MS [redacted] Baxter Healthcare One Baxter Parkway Deerfield, IL 60015, USA
Sponsor:	Baxter Healthcare Corporation One Baxter Parkway Deerfield, IL 60015 USA
Responsible Medical Officer:	[redacted], MD, PhD, [redacted]
Version	1.6
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Confidentiality Statement

[redacted]

Table of Contents

List of Appendices

No table of figures entries found.

1. SIGNATURE PAGE

Study 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
Study Number:	3584-001
Statisticians:	[redacted], MS

I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study.

Prepared by:_____ Date:_____
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2. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ADE	adverse device effect
AE	adverse event
ATC	Anatomical Therapeutic Chemical
CFR	Code of Federal Regulations
CI	confidence interval
CIP	clinical investigation plan
CRO	contract research organization
DSMB	data safety monitoring board
eCRF	electronic case report form
FAS	full analysis set
ICF	informed consent form
IWRS	interactive web-response system
IRB	Institutional Review Board
MedDRA	Medical Dictionary for Regulatory Activities
NMC	non-medical complaint
OC	oxidized cellulose
PPS	per-protocol analysis set
SADE	serious adverse device event
SAE	serious adverse event
SAER	serious adverse event report
SI	serious injury
SD	standard deviation
SE	standard error
TBS	target bleeding site
TTH	time to hemostasis
UADE	unanticipated adverse device effect
WHO	World Health Organization

3. INTRODUCTION

This Statistical Analysis Plan is intended to describe the planned statistical analysis of project 3584-001. 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. Once applied, CELSTAT absorbs blood, turns brown, and adheres to the wound, thereby preventing thrombocytes from being washed out and accelerating hemostasis.

In this study, CELSTAT will be compared to Surgicel Original, referred to as Surgicel for the remainder of this document. 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 re-bleeding 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.

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.

4. TRIAL OBJECTIVES

The objective of this trial is 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.

4.1 Primary Objectives

The primary objective is to show non-inferiority in 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. Time to hemostasis (TTH) is the most meaningful criterion to assess the effectiveness of a hemostatic device.

4.2 Secondary Objectives

The secondary objectives are to evaluate the following:

- Additional hemostatic effectiveness parameters of CELSTAT in comparison to Surgicel.
- Safety of CELSTAT

4.3 Exploratory Objectives

Not applicable.

5. STUDY DESIGN AND CONDUCT CONSIDERATIONS

5.1 Study Design

This is a prospective, randomized, controlled, single-blind pivotal multicenter study to compare effectiveness and safety of CELSTAT versus Surgicel in a total of 258 randomized subjects (1:1 randomization) undergoing cardiothoracic, general and vascular surgery. The study will be conducted at approximately 26 sites in the United States (20) and Europe (6).

5.2 Baseline definition

Baseline values are not applicable for effectiveness measures. Safety measures of clinical laboratory parameters and vital signs will be evaluated with respect to initial values taken during the screening visit.

5.3 Sample Size

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. 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 SAS 9.2 software ([redacted]).

The primary analysis will be performed on the per-protocol analysis set (PP). Assuming that the PP 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.

5.4 Randomization Procedure

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). 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.

Details of the IWRS and its use will be described in a separate IWRS instruction manual that will be maintained in the trial master file and in each center's investigator trial file.

5.5 Schedule of Visits and Procedures

	Visit 1 Screening Day -14 to -1	Visit 2 Randomization/Surgery Day 1	Visit 3 Discharge ≤ Day 8 (±1)[a]	Visit 4 Safety Follow-up Day 31 (±5)	Visit 5 End of Study Day 61 (±10)
Informed consent	X				
Inclusion/exclusion	X	X[b]			
Demographic characteristics	X				
Medical history	X				
Concomitant medication	X[c]	X	X	X	X
Physical examination	X		X	X	X
Vital signs	X		X	X	X
Hematology and clinical chemistry tests[d]	X[e]		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
Adverse events	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 Clinical Investigation Plan for details.

5.6 Efficacy Measures

The primary efficacy parameter is the proportion of subjects with hemostasis achieved at the TBS at 5 minutes after the application of the study device, and is further 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. The primary endpoint will be set to "treatment failure" should any of the following occur:

- Hemostasis is not achieved within 5 minutes and maintained until surgical closure
- Bleeding complications occur requiring hemostatic measures other than application of the randomized study treatment
- Intraoperative re-bleeding occurs

Secondary efficacy parameters include the following:

- The proportion of subjects with hemostasis achieved at the TBS at 3, 7 and 10 minutes after the application of the study device
- Out of subjects who achieved hemostasis, the proportion of subjects with intraoperative re-bleeding from the TBS after occurrence of hemostasis
- TTH at the TBS within the 10-minute observation period

A stop watch will be started at the start of device application. The occurrence and time of occurrence (or absence) of hemostasis at the TBS will be recorded after the start of device application. If hemostasis appears to be achieved early, but re-bleeding 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 time point at which hemostasis at the TBS was observed and after which no re-bleeding from the TBS occurred during the 10-minute observation period. Observations which have not achieved hemostasis at the end of the 10-minute observation period will be censored.

5.7 Safety Measures

The primary safety outcome measure is postoperative re-bleeding from the TBS requiring surgical re-exploration during the subject's study participation. Safety will also be assessed by means of adverse events, clinical laboratory parameters and vital signs.

5.8 Completion and Discontinuation

Any subject may voluntarily withdraw 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 Visit 3 Discharge ≤ Day 8 (±1), or Visit 4 Safety Follow up Day 31 (±5), or Visit 5 End of Study Day 61 (±10) 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 time point for discontinuation/drop out and document this in the source document used at the site.

6. STUDY POPULATIONS

6.1 Subject Disposition

The number of subjects who signed informed consent (enrolled), met the pre- and intra-operative inclusion and exclusion criteria (eligible), were randomized, and withdrew early will be displayed. Early withdrawals will be summarized according to reason for withdrawal. Subjects who have been assigned a treatment based on pre-operative criteria, but were found not eligible intraoperatively are not considered to be randomized (for more detail on randomization see section 5.4).

6.2 Analysis Populations

Two types of analyses of effectiveness are planned: analysis of the full analysis set (FAS) and of the per-protocol analysis set (PPS). The primary efficacy analysis will be carried out on the PPS. The analysis using the FAS will be used as a supportive analysis. 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 with any major deviation that may impact the primary efficacy parameter will be excluded from the per-protocol analysis set (see section 6.3 for more detail on protocol deviations leading to exclusion).

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.

6.3 Protocol Deviations

Protocol deviations will be classified as minor or major deviations and reviewed at a data review meeting. Subjects with any major deviation that may impact the primary efficacy parameter will be excluded from the per-protocol analysis set, including the following:

- Violations inclusion and/or exclusion criteria (pre and/or intra-operative assessment)
- Use of prohibited medication known to influence hemostasis
- Randomization or treatment errors
- Improper administration of study product
- Improper assessment of hemostasis

7. STATISTICAL ANALYSIS

7.1 General

The analyses described in this SAP refer to Amendment 2 of the Clinical Investigation Plan (dated 2015 Nov 09). Unless otherwise noted, all analyses will be performed using SAS/GRAPH® 9.4 software, SAS/STAT® 14.1 software and Base SAS® 9.4. Copyright© 2002-2012, [redacted]. SAS and all other [redacted] Inc. product or service names are registered trademarks or trademarks of [redacted] Inc., Cary, NC, USA. All Rights Reserved. If not specified otherwise, data will be presented by planned treatment group and overall. Safety data will be summarized by actual treatment and overall. Continuous variables will be summarized by the following sample statistics: number of non-missing observations, mean, standard deviation (SD), median, minimum and maximum. Categorical variables will be presented by their absolute frequency and percentage (based on the number of subjects in the respective group).

7.2 Handling of Missing 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. For the primary efficacy endpoint, a sensitivity analysis as described in section 11.2 will be performed.

7.3 Data Safety Monitoring Board

AE and laboratory safety data will be monitored by an independent DSMB 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.

7.4 Interim Analysis

No interim analysis is planned for this study.

7.5 Pooling Strategy for Study Sites

Generally, the data of all study sites will be analyzed together. The logistic regression model for the efficacy analysis will use study site as a factor. In the case of study sites with fewer than 5 subjects, those study sites may be combined into entities of similar size for the purpose of including in the logistic regression model as a factor.

7.6 Visit Windows/Unscheduled Visits

For tabulation, values will be summarized according to the planned time point as recorded in the eCRF. Data recorded at unscheduled visits will only be listed.

7.7 Other Issues

Not applicable.

7.8 Changes to Planned Analyses Described in the Clinical Investigation Plan

Not applicable.

8. DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Demographic and baseline variables as collected in the eCRF will be summarized according to the general principles as detailed above. Demographics will include sex, race, ethnicity, age (years), height (cm), weight (kg) and BMI (kg/m^2). Medical history will be coded using MedDRA and incidences will be tabulated by System Organ Class and Preferred Term. Previous medication (stopped before the surgery) and concomitant medication and non-drug therapies (ongoing at the time of surgery or started between surgery and end of study participation) will be coded using WHO Drug Dictionary

(medications) and MedDRA (non-drug therapies) and tabulated by ATC Term and Preferred Term.

9. SURGERY DETAILS AND EXPOSURE

The number and percentage of subjects treated will be presented. The following information on the surgery will be tabulated and/or provided in a listing.

9.1 Planned Surgery Details

- Hospitalization admission/discharge dates (listing only)
- Indication for surgery (free text, listing only)
- Surgical procedure name (free text, listing only)
- Duration of surgery [min] (date/time of last skin suture – date/time of first skin incision)
- Surgery type (cardiothoracic, general, vascular)
- Bleeding severity (Grade 1 or Grade 2)
- Anatomical location of TBS (free text, listing only)
- Bleeding tissue type present at TBS (soft tissue, parenchymal or vascular)
- Type of conventional hemostatic methods applied at TBS before IP administration (listing only)
    - Time of completion of conventional hemostatic methods at the TBS:
    - Reason, if no conventional hemostatic methods were applied (free text)
- Cardiopulmonary bypass used during surgery (yes/no)
    - Time of bypass start/discontinuation (listing only)
    - Put back on bypass (yes/no) (listing only)
        - Time of bypass start/discontinuation (listing only)

- Any intraoperative complications occur, excluding intraoperative re-bleeding from TBS (yes/no)
- Additional intraoperative assessments (yes/no, listing only)
    - Description of additional intraoperative assessments (listing only)

9.2 Intraoperative Anticoagulation Therapy and Reversal (listing only)

- Reversal therapy applied (yes/no)
- Anticoagulation therapy applied (yes/no)
- Medication (free text, listing only)
- Start/End time (listing only)
- Timepoint in regards to study device application (before device application, after device application, not applicable) (listing only)
- Timepoint after device application (before hemostasis was achieved within the 10-minute observation period, after hemostasis was achieved within the 10-minute assessment period, after the 10-minute assessment period) (listing only)
- Dose (free text, listing only)
- Unit (listing only)
- Route (listing only)

9.3 Study Treatment Administration

- Actual treatment applied (listing only)
- Time of start of study treatment application (start of stopwatch) (listing only)
- Number of sheets of the study product applied to the TBS (listed, and summarized as a continuous variable)
- Number of sheets of the study product left in situ at surgical closure (listed, and summarized as a continuous variable)
    - Reason if no study product left in situ (listing only)

9.4 Intraoperative Assessment of Primary Hemostasis and Rebleeding Assessment at TBS (after 10 min Observation Period)

- Primary hemostasis achieved during 10 minute assessment period after study device application (yes/no)
- Elapsed time after start of stopwatch when hemostasis achieved
- Re-bleeding occurred (no/yes, within 10 min observation period/yes, after 10 minute observation period)
    - Elapsed time(s) after start of stopwatch of rebleeding (listing only)
    - Elapsed time after start of stopwatch hemostasis achieved (listing only)
    - Actions performed to achieve hemostasis (listing only)

10. EFFICACY

10.1 Primary Analysis

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

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 (grade 1/mild or grade 2/moderate). The method described in ref. 1 will be used: The parameters of the fitted logistic regression model will be used to predict the success rate of all subjects for both CELSTAT and Surgicel treatment. The average response rate per group will be calculated as well as the difference between the two rates. The standard error of the difference will be derived using the delta method in order to construct a 95% confidence interval.

10.2 Sensitivity Analysis

A sensitivity analysis, in which all missing data on the primary efficacy endpoint 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.

10.3 Secondary Analysis

The approach as described in section 11.1 will be applied to the dichotomous secondary endpoints as listed in section 5.5 (achievement of hemostasis at 3, 7 and 10 minutes, and among subjects who achieve hemostasis the proportion who experience intraoperative re-bleeding from the target bleeding site after achievement of hemostasis).

Time to hemostasis (TTH) at the TBS within the 10-minute assessment period is defined as the time between the (first) application of the study device to the TBS and the achievement of hemostasis up to ten minutes after application, if no bleeding is recorded afterwards during the 10-minute observation period. Otherwise, TTH will be considered as censored at 10 minutes, or at the time of the last assessment, if this is before the 10 minutes time point. TTH will be summarized using 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.

10.4 Exploratory Analysis and Subgroups

Exploratory subgroup analysis to investigate treatment effect on the primary efficacy parameter within each surgical group and within each bleeding severity (grade 1 or 2) will be conducted. A logistic regression model investigating the treatment effect within each surgical group will take into account the following covariates: study center and bleeding scale; a logistic regression model investigating the treatment effect within each bleeding severity will take into account the following covariates: study center and surgical group.

Additionally, logistic regression models investigating the effects of using anticoagulant therapy (one model will investigate anticoagulant effects regardless of reversal therapy [1], and a second will incorporate reversal therapy [2]) and antiplatelet therapy [3] on the primary efficacy parameter will be run. Models [1] and [3] will include terms for treatment, anticoagulant {antiplatelet} use (yes/no) and an interaction term for treatment by anticoagulant {antiplatelet} use, and model [2] incorporating reversal therapy will have the following terms: treatment, anticoagulant/reversal therapy (no anticoagulant therapy, anticoagulant therapy without reversal therapy, anticoagulant therapy with reversal therapy prior to and after study treatment application, anticoagulant therapy with reversal therapy prior to study treatment application, and anticoagulant therapy with reversal therapy after study product application), and an interaction term for treatment by anticoagulant/reversal therapy used. In addition to the full model, a model containing treatment only will be run for each subgroup (used anticoagulant {antiplatelet} therapy or did not use anticoagulant {antiplatelet} therapy, anticoagulant therapy without reversal therapy, anticoagulant therapy with reversal therapy prior to and after study treatment application, anticoagulant therapy with reversal therapy prior to study treatment application, and anticoagulant therapy with reversal therapy after study product application).

11. SAFETY

Adverse Events will be coded using MedDRA. AEs that occurred after the start of study treatment application (treatment-emergent AEs) will be presented in summary tables. In case of incomplete information on study treatment or AE onset, events will be classified as treatment-emergent unless there is sufficient data to rule out the possibility that the event started after the start of study treatment application.

Summary tables shall indicate, by treatment group, the number and percentage of subjects who experienced any AEs, AEs leading to withdrawal of device, AEs leading to discontinuation of the study, serious AEs, AEs leading to death and AEs of special interest. AEs of special interest in this study will include the following:

- Postoperative re-bleeding (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

In addition, tables will be prepared to list each AE (grouped by MedDRA System Organ Class and Preferred Term) and the number and percentage of subjects in each treatment group who experienced each AE at least once. The same type of summary will be prepared for Serious Adverse Events, Adverse Events of Special Interest, Adverse Device Effects (possibly or probably related to the device applied) and Serious Adverse Device Effects. 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 and AEs with missing information on relatedness 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 time, and stop date and time. Similar listings of AEs leading to withdrawal of device, AEs leading to discontinuation of the study, AEs leading to death and AEs of special interest will be prepared.

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. Absolute values and changes from baseline will be presented. Shift tables for baseline vs. worst post baseline assessment (normal, abnormal/not clinically significant, abnormal/clinically significant) will be generated for laboratory parameters.

12. OTHER RELEVANT DATA ANALYSES/SUMMARIES

See section 10.4 for description of planned exploratory subgroups analyses.

13. REFERENCES

1. Covariate-Adjusted Difference in Proportions from Clinical Trials Using Logistic Regression and Weighted Risk Differences, Miaomiao Ge, L. Kathryn Durham, R. Daniel Meyer, Wangang Xie, Neal Thomas, Drug Information Journal vol. 45, no. 4, pp. 481-493, 2011

14. LIST OF TABLES, FIGURES AND LISTINGS

14.1 List of Tables

Applicable Analysis Populations	Table Number	Table Name
NA	14.1.1	Subject Disposition
PPS	14.1.2.1	Demographic and Baseline Characteristics
FAS	14.1.2.2	Demographic and Baseline Characteristics
Safety	14.1.2.3	Demographic and Baseline Characteristics
PPS	14.1.3.1	Vital Signs
FAS	14.1.3.2	Vital Signs
Safety	14.1.3.3	Vital Signs
PPS	14.2.1.1.1	Primary Outcome Variable - Hemostasis Achieved 5 Minutes Post Study Treatment Application Model Results
FAS	14.2.1.1.2	Primary Outcome Variable - Hemostasis Achieved 5 Minutes Post Study Treatment Application Model Results
PPS	14.2.1.2.1	Primary Outcome Variable - Hemostasis Achieved 5 Minutes Post Study Treatment Application
FAS	14.2.1.2.2	Primary Outcome Variable - Hemostasis Achieved 5 Minutes Post Study Treatment Application
PPS	14.2.1.3.1	Primary Outcome Variable - Subgroup Analysis Model Results
FAS	14.2.1.3.2	Primary Outcome Variable - Subgroup Analysis Model Results
PPS	14.2.1.4.1	Primary Outcome Variable - Subgroup Analysis
FAS	14.2.1.4.2	Primary Outcome Variable - Subgroup Analysis
PPS	14.2.1.5.1	Primary Outcome Variable - Exploratory Analysis Anticoagulant or Antiplatelet Model Results
FAS	14.2.1.5.2	Primary Outcome Variable - Exploratory Analysis Anticoagulant or Antiplatelet Model Results
PPS	14.2.1.6.1	Primary Outcome Variable - Exploratory Analysis Anticoagulant or Antiplatelet Use
FAS	14.2.1.6.2	Primary Outcome Variable - Exploratory Analysis Anticoagulant or Antiplatelet Use
FAS	14.2.1.7	Primary Outcome Variable - Sensitivity Analysis Model Results
FAS	14.2.1.8	Primary Outcome Variable - Sensitivity Analysis
PPS	14.2.2.1.1	Secondary Outcome Variables - Hemostasis Measurements at 3, 7 and 10 minutes Model Results
FAS	14.2.2.1.2	Secondary Outcome Variables - Hemostasis Measurements at 3, 7 and 10 minutes Model Results
PPS	14.2.2.2.1	Secondary Outcome Variables - Hemostasis Measurements at 3, 7 and 10 minutes
FAS	14.2.2.2.2	Secondary Outcome Variables - Hemostasis Measurements at 3, 7 and 10 minutes

PPS	14.2.2.3.1	Secondary Outcome Variables - Time to Hemostasis Model Results
FAS	14.2.2.3.2	Secondary Outcome Variables - Time to Hemostasis Model Results
PPS	14.2.2.4.1	Secondary Outcome Variables - Time to Hemostasis
FAS	14.2.2.4.2	Secondary Outcome Variables - Time to Hemostasis
PPS	14.2.2.5.1	Secondary Outcome Variables - Proportion of Subject who Experienced Re-bleeding After Achieving Hemostasis Model Results
FAS	14.2.2.5.2	Secondary Outcome Variables - Proportion of Subject who Experienced Re-bleeding After Achieving Hemostasis Model Results
PPS	14.2.2.6.1	Secondary Outcome Variables - Proportion of Subject who Experienced Re-bleeding After Achieving Hemostasis
FAS	14.2.2.6.2	Secondary Outcome Variables - Proportion of Subject who Experienced Re-bleeding After Achieving Hemostasis
PPS	14.2.3.1	Summary of Planned Surgery Details
FAS	14.2.3.2	Summary of Planned Surgery Details
Safety	14.3.1.1	Summary of Adverse Events
Safety	14.3.1.2	Summary of Adverse Events (Serious and Non-Serious) by System Organ Class and Preferred Term
Safety	14.3.1.3	Summary of Serious Adverse Events by System Organ Class and Preferred Term
Safety	14.3.1.4	Summary of Adverse Events (Serious and Non-Serious) by System Organ Class, Preferred Term and Severity
Safety	14.3.1.5	Summary of Serious Adverse Events by System Organ Class, Preferred Term and Severity
Safety	14.3.1.6	Summary of Adverse Events (Serious and Non-Serious) by System Organ Class, Preferred Term and Relation to Study Product
Safety	14.3.1.7	Summary of Serious Adverse Events by System Organ Class, Preferred Term and Relation to Study Product
Safety	14.3.1.8	Summary of Adverse Events (Serious and Non-Serious) by System Organ Class, Preferred Term and Relation to Study Procedure
Safety	14.3.1.9	Summary of Serious Adverse Events by System Organ Class, Preferred Term and Relation to Study Procedure
Safety	14.3.1.10	Summary of Adverse Events of Special Interest (Serious and Non-Serious) by System Organ Class and Preferred Term
Safety	14.3.1.11	Summary of Serious Adverse Events of Special Interest by System Organ Class and Preferred Term
Safety	14.3.1.12	Summary of Adverse Events of Special Interest (Serious and Non-Serious) by System Organ Class, Preferred Term and Severity
Safety	14.3.1.13	Summary of Serious Adverse Events of Special Interest by System Organ Class, Preferred Term and Severity
Safety	14.3.2.1	Listing of Serious Adverse Events
Safety	14.3.2.2	Listing of Adverse Events of Special Interest
Safety	14.3.2.3	Listing of Adverse Events Leading to Discontinuation from the Study
Safety	14.3.2.4	Device Deficiencies

Safety	14.3.4.1.1	Shift Table of Hematology Laboratory Parameters
Safety	14.3.4.1.2	Hematology Laboratory Summary
Safety	14.3.4.1.3	Listing of Abnormal Hematology Laboratory Values
Safety	14.3.4.2.1	Shift Table of Chemistry Laboratory Parameters
Safety	14.3.4.2.2	Chemistry Laboratory Summary
Safety	14.3.4.2.3	Listing of Abnormal Chemistry Laboratory Values
Safety	14.3.4.3.1	Shift Table of Coagulation Parameters
Safety	14.3.4.3.2	Coagulation Laboratory Summary
Safety	14.3.4.3.3	Listing of Abnormal Coagulation Laboratory Values

14.2 List of Figures

Applicable Analysis Populations	Figure Number	Figure Name
PPS	14.2.2.4.1	Time to Hemostasis (TTH) Kaplan-Meier Curves
FAS	14.2.2.4.2	Time to Hemostasis (TTH) Kaplan-Meier Curves

14.3 List of Listings

Listing Number	Listing Name
16.2.1	Subject Disposition
16.2.2	Protocol Deviations
16.2.3	Patients excluded from PP
16.2.4.1	Subject Demographics
16.2.4.2	Subject Vital Signs
16.2.4.3	Medical History
16.2.4.4	Concomitant Medications and Non Drug Therapies by Coded Drug Term
16.2.5.1	Planned Surgery Details
16.2.5.2	Intraoperative Anticoagulation Therapy and Reversal
16.2.5.3	Study Treatment Administration
16.2.5.4	Device Deficiencies
16.2.6.1	Intraoperative Assessment of Primary Hemostasis and Re-bleeding Assessment at TBS
16.2.6.2	Clinical Assessment of Post-Operative Rebleeding
16.2.7	Adverse Events
16.2.8.1	Subject Laboratory Chemistry Results
16.2.8.2	Subject Laboratory Hematology Results
16.2.8.3	Subject Laboratory Coagulation Results