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

STATISTICAL ANALYSIS PLAN

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1 PURPOSE

This statistical analysis plan (SAP) describes the statistical methods to be used during the reporting and analysis of data collected under the Biom'Up HEMOBLAST Pivotal IDE Study titled, "Prospective, randomized, controlled, multicenter, pivotal, clinical investigation evaluating the safety and efficacy of HEMOBLAST™ bellows in cardiothoracic, abdominal, and orthopedic lower extremity surgeries."

2 SCOPE

This SAP should be read in conjunction with the study protocol and electronic case report forms (eCRFs). This version of the plan has been developed with respect to the HEMOBLAST Pivotal IDE Study protocol version 4, dated 19-May-2016. Any further changes to the protocol or eCRF may necessitate updates to the SAP.

3 APPLICABLE DOCUMENTS

Document Number	Document Title
ETC-2015-002	PROSPECTIVE, RANDOMIZED, CONTROLLED, MULTICENTER, PIVOTAL, CLINICAL INVESTIGATION EVALUATING THE SAFETY AND EFFICACY OF HEMOBLAST™ BELLOWS IN CARDIOTHORACIC, ABDOMINAL, AND ORTHOPEDIC LOWER EXTREMITY SURGERIES (Version 4.0)
STATSOP-002	Statistics Standard Operating Procedure – Statistical Analysis Plan
	ETC-2015-002 Case Report Forms

4 SOFTWARE

All tables, listings and figures will be primarily produced using SAS Version 9.2 (SAS Institute, Cary, NC) or a later version of SAS and R.

5 ABBREVIATIONS AND DEFINITIONS

Abbreviation / Term	Definition
ADE	Adverse Device Effect - any untoward and unintended response to an investigational medical device
AE	Adverse Event - any untoward medical occurrence in a subject
CRF	Case Report Form
eCRF	Electronic Case Report Form
Enrolled	A subject is enrolled when he/she meets all preoperative inclusion/exclusion criteria, signs the informed consent form, and meets the intraoperative eligibility criteria.
IDE	Investigation Device Exemption
IDMC	Independent Data Monitoring Committee
IFU	Instructions for Use
SADE	Serious Adverse Device Effect – an adverse device effect that has resulted in any of the consequences characteristic of a serious adverse

	event or that might have led to any of these consequences if suitable action had not been taken or intervention had not been made or if circumstances had been less opportune
SAE	Serious Adverse Event – an adverse event that: • Led to death • Led to a serious deterioration in the health of the subject, that either resulted in a life-threatening illness or injury, or a permanent impairment of a body structure or a body function, or in-patient hospitalization or prolongation of existing hospitalization, or resulted in medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function • Led to fetal distress, fetal death or a congenital abnormality or birth defect
SAP	Statistical Analysis Plan
SBSS	Surface Bleeding Severity Scale
TBS	Target Bleeding Site
UADE	Unanticipated Adverse Device Effect – any serious adverse effect on health or safety, any life-threatening problem or death cause 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 study protocol; or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects

6 STUDY OBJECTIVES

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

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

7 STUDY ENDPOINTS

7.1 Primary Endpoint

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

7.2 Secondary Endpoints

The secondary efficacy endpoints of this clinical investigation are:

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

- Superiority of HEMOBLAST™ relative to G+T for success at achieving hemostasis within 6 minutes; and
- Superiority of HEMOBLAST™ relative to G+T for success at achieving hemostasis within 3 minutes

8 STUDY DESIGN

8.1 Overview

The ETC-2015-002 study is a prospective, randomized, multicenter, pivotal clinical investigation. A total of 450 subjects will be enrolled across a maximum of 25 investigational sites. Fifty subjects (one per enrolling investigator) will be treated as roll-in patients; data from the roll-in subjects will only be considered for the safety analyses.

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

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

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

Table 1 details the clinical investigation visits, corresponding timing, and evaluations to be performed at the visit. Table 2 lists the CRFs that need to be completed at each visit. Figure 1 represents the subjects' participation in the clinical investigation.

Table 1. Investigational Evaluation Schedule

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

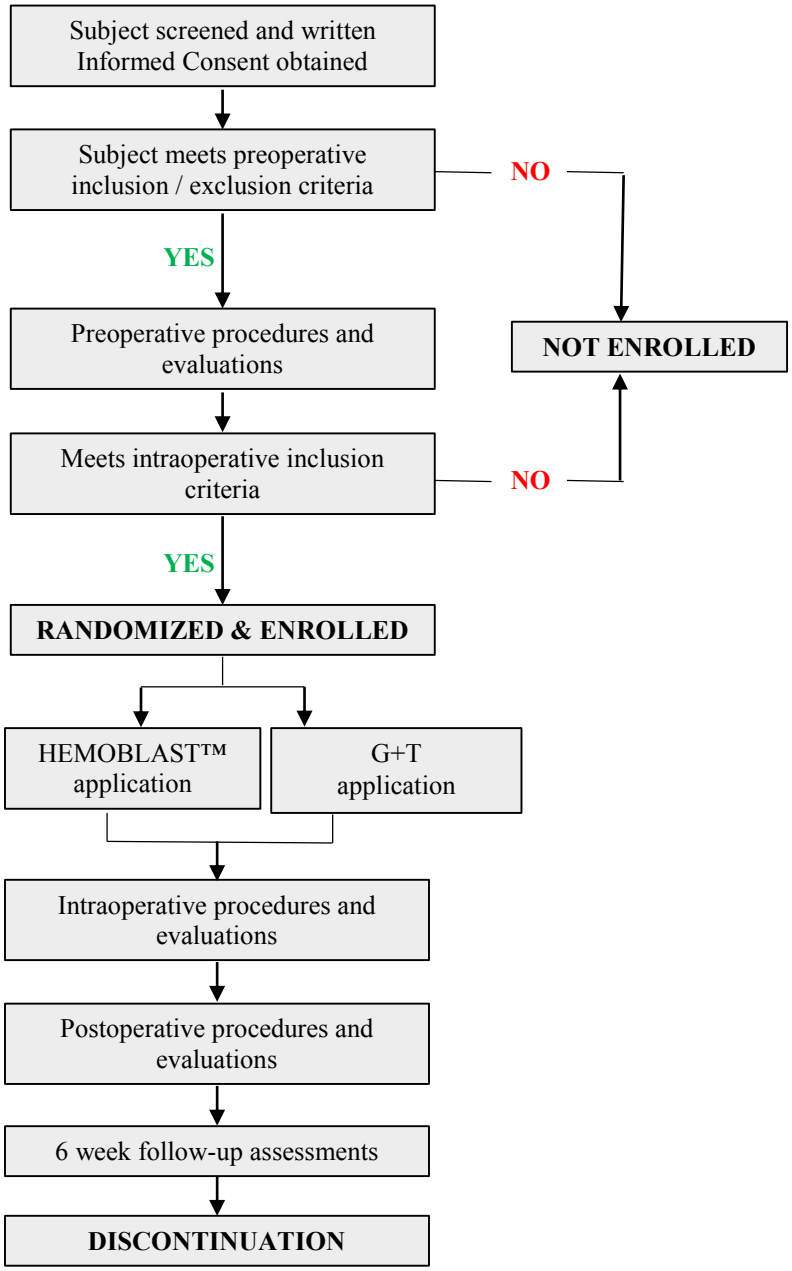
Table 2. CRF Completion Schedule

CRF	Screening	Preoperative	Intraoperative	Postoperative	Follow-Up	Discontinuation
Preoperative Eligibility CRF	**X**					
Preoperative CRF		**X**				
Intraoperative CRF			**X**			
Concomitant Medication CRF		**O**	**O**	**O**	**O**	

Laboratory CRF		**X**		**X**		
Postoperative CRF				**X**		
Follow-Up CRF					**X**	
Discontinuation CRF						**X**
Adverse Event CRF			**O**	**O**	**O**	
Device Deficiency CRF			**O**			
Reoperation CRF				**O**	**O**	

X	Mandatory
O	As applicable

Figure 1. Subject Participation in the Clinical Investigation



Bleeding severity and hemostasis will be assessed using the SBSS.

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

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

An SBSS score of 0 is equivalent to hemostasis. All other SBSS scores are considered failure of hemostasis.

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

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

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

8.2 Randomization

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

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

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

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

Randomization will be stratified by site and will incorporate random permuted blocking; additional details of randomization and blocking will be included in a separate Randomization Plan.

8.3 Blinding

8.4 Subjects will be blinded to treatment assignment. Sample Size Considerations

The sample size for the proposed study is based on a level 0.025 (one-sided) test to exclude a probability of TTH within 6 minutes that is 10% less among subjects treated with HEMOBLAST™ compared to those

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

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

9 DATA STRUCTURE AND HANDLING

9.1 Data Handling and Transfer

Data management will be undertaken by NAMSA Data Management. NAMSA Biostatistics will either be provided access to download SAS datasets or NAMSA Data Management will provide them upon request.

Programming of analysis datasets, tables, figures and listings will be conducted during the data management phase of the study. Tables, figures, and listings may be reviewed prior to final data lock for data review. Any data values requiring investigation or correction will be identified, and protocol deviations will be reviewed. The final run of outputs will take place after the data is deemed final.

9.2 Missing Data

In primary analyses, missing TTH values will not be imputed. All values right censored prior to 6 minutes will be considered treatment failures for the purpose of the primary analysis. Due to the fact that all primary endpoint data is recorded within minutes after enrollment into the study, enrolled patients are not expected to be lost to follow-up or withdraw consent before this data is recorded. Thus the effect of missing data on this endpoint is expected to be minimal. As a supplement to the primary analyses, a 'worst-case' sensitivity analyses will also be conducted. "Worst-case" sensitivity analysis will assume all randomized and treated subjects in the HEMOBLAST™ arm with missing data are treatment failures for the primary endpoint (TTH greater than 6 min) while all randomized and treated subjects in the G+T arm with missing data are treatment successes (TTH less than 6 min).

9.3 Visit Windows

All data attributed to a time point per the CRF will be included in the analysis of that time point, regardless of whether it is out of window. Since all primary efficacy endpoint analysis data is recorded immediately during the procedure, no out of window data will pertain to these endpoints and will not influence their calculation. Unscheduled visit data will be included in adverse event and other summaries that are not specific to a time point.

9.4 Pooling Data Across Sites

The pooling of outcome data from different clinical sites will be first evaluated by examining the homogeneity of the primary effectiveness endpoints across sites using logistic regression. If homogeneity is demonstrated across sites, then outcome results will be combined across study sites.

If significant heterogeneity is found across sites (treatment by site interaction with an associated p-value of 0.15 or less), then:

- The univariable association between select baseline factors and outcome will be examined with chi-square and Student's t-tests

- The effect of any differences in baseline factors across sites on outcome (considering those baseline factors previously found to be associated with outcome (p-values ≤ 0.20)), will be examined with multivariable logistic regressions to determine whether they explain observed site differences.

If significant differences across sites remain after adjustment for baseline factors, then results for the primary effectiveness outcomes, from multivariable analyses that incorporate both site differences and site-by-treatment interactions, will be reported. If necessary, sites with less than 9 enrolled subjects will be combined into one group for purposes of the above analyses. Also, smaller sites will be pooled together for the analysis to allow for at least one failure and one success in each arm.

10 STATISTICAL ANALYSES

10.1 General Considerations

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

10.2 Analysis Populations

Safety analyses will be performed on the Full Analysis Population, defined as all subjects who were randomized into the study and received study intervention and all lead-in subjects. Efficacy analyses will be conducted on the time to hemostasis (TTH) Analysis Population, defined as all subjects who were randomized, received study intervention, and had a TTH assessment recorded regardless of whether the measurement was censored (defined as the use of an additional hemostatic product or surgical rescue prior to the end of observation time, or failing to achieve and maintain complete hemostasis prior to the end of observation time). Data summaries will be based on the intervention received, regardless of which intervention was randomly assigned.

10.3 Subject Disposition and Characteristics

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

10.4 Subject Compliance

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

10.5 Analytic Methods

10.5.1 Analysis Population

Efficacy analyses will be conducted on the TTH Population, defined as all subjects who were randomized, received study intervention, and had a TTH assessment recorded regardless of whether the measurement was censored. Lead-in subjects are *not* part of the TTH Population.

10.5.2 Methods of Analysis

The primary efficacy endpoint is the difference in the probability of TTH within 6 minutes comparing HEMOBLAST™ to G+T. The lower bound of the 95% confidence interval for the difference in binomial probabilities will be used to assess comparable efficacy. The primary efficacy analysis will be conducted on data from the first identified bleeding site for each subject. The estimated difference in the probability of TTH at 6 minutes between treatment arms will be adjusted for surgical indication by weighting the stratum-specific differences in observed proportions using Cochran-Mantel-Haenszel weighting.[ii] The trial seeks to establish comparable efficacy based upon a non-inferiority margin of 10% for the difference in the probability of TTH within 6 minutes comparing HEMOBLAST™ to G+T (HEMOBLAST™– G+T). Letting θ denote the true difference in the probability of hemostasis at 6 minutes between HEMOBLAST™ to G+T, the trial will test the null hypothesis H_0: $\theta \leq -0.10$ vs. the alternative hypothesis H_A : $\theta > -0.10$ using a one-sided level 0.025 test. The null hypothesis of inferiority will be rejected and comparable efficacy will be established if the resulting lower bound of the 95% confidence interval for θ is greater than -0.10. Comparable efficacy will be evaluated using a group sequential testing design as described in Section 10.7 with stopping boundaries defined to ensure a maximum overall 1-sided significance level of 0.025. Following the completion of the trial, a confidence interval for the estimated difference in the probability of hemostasis at 6 minutes will be computed using the Cochran-Mantel-Haenszel estimator and asymptotic variance estimate in combination with the repeated confidence interval method.[iii] Estimates of the distribution of TTH over a maximum follow-up of 10 minutes will be computed based on all available assessment times (3 minutes, 6 minutes, and 10 minutes) using the Kaplan-Meier method.

Analyses of the secondary efficacy endpoints will be evaluated only once, at the end of the study, using a family-wise 2-sided significance level of 0.05. Adjustment for multiple comparisons when assessing secondary endpoints will be performed using a fixed sequence closed testing procedure to control the family-wise type I error rate at 0.05, as described in Section 10.10. The difference in mean preparation time will be tested using a linear regression model with stratified adjustment for surgery type. The difference in the probability of TTH within 3 minutes will be tested using a general linear model with stratified adjustment for surgery type as described above. Wald-based 95% confidence intervals for the difference in probability of TTH will be computed.

10.6 Analysis of Safety

10.6.1 Analysis Population

Safety analyses will be conducted on the Full Analysis Population, defined as all subjects who were randomized into the study and received study intervention and all lead-in subjects.

10.6.2 Analytic Methods

Endpoints used to characterize the safety profile include the rate of occurrence of all AEs and SAEs, reoperation rate due to bleeding, mean volume of intraoperative transfusions, total operative time, mean

duration of hospitalization, intraoperative blood product administration, and post-operative blood product administration.

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

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

For binary endpoints, the proportion and corresponding 95% scored-based confidence interval will be computed. The proportion of UADEs or SADEs will also be computed and a 95% scored-based confidence interval will be computed for the true UADE or SADE rate. In the event that no UADEs or SADEs are observed, the upper bound of the 95% confidence interval will be based upon the exact binomial distribution.

10.7 Interim Analyses

10.7.1 Interim Efficacy/Futility Analysis

A single interim analysis will be performed on the primary efficacy endpoint (difference in the probability of TTH within 6 minutes) using data on the TTH Population, defined as all subjects who were randomized, received study intervention, and had a TTH assessment recorded regardless of whether the measurement was censored.

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

In making a decision to recommend early termination of the study, the IDMC shall be guided by a formal stopping rule based on the primary efficacy endpoint. The test statistic shall be the estimated difference in the probability of TTH within 6 minutes between the HEMOBLAST™ and G+T arms as described in Section 12.5.2. The clinical trial may only be stopped early either for reasons of futility (the observed difference in the probability of TTH within 6 minutes comparing HEMOBLAST™ to G+T is not sufficiently high enough to warrant continuation of the trial) or efficacy (the observed difference in the probability of TTH within 6 minutes comparing HEMOBLAST™ to G+T is sufficiently high enough to conclude non-inferiority).

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

upper (efficacy) stopping boundary relationship specified by P_d =0.8 (a boundary with conservatism in between the Pocock type boundary and an O'Brien-Fleming type boundary).[v, vi]

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

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

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

Under the planned schedule of one interim analysis at 240 treated subjects and a assumed 6 min TTH success rate of 88% in the G+T arm, Table 3 presents the stopping boundaries at the interim and final analysis for the specified stopping rule expressed as the normalized fixed sample z-statistic for testing non-inferiority and the corresponding fixed sample p-value.

Table 3: Stopping boundaries for a level 0.025 one-sided design with a single interim analysis (NON-BINDING FUTILITY (P_a =0.8) AND EFFICACY (P_d =0.8) occurring at 240 patients, and a maximal sample size of 400 patients (2:1 randomization). The boundaries assume an 88% probability of TTH within 6 minutes on the G+T arm and a 10% non-inferiority margin. Stopping boundaries are expressed as the difference in the probability of TTH within 6 minutes (HEMOBLAST™ – G+T).

Analysis	Total Sample Size (H, G+T)*	Futility (lower) Stopping Boundary		Comparable Efficacy (upper) Stopping Boundary	
		Z-statistic	P-value	Z-statistic	P-value
Interim	240 (160, 80)	0.788	0.215	2.373	0.009
Final	400 (267, 133)	2.036	0.021	2.036	0.021

* H: HEMOBLAST™; G+T: absorbable gelatin sponge USP and thrombin

Thus, according to the above table, if the observed Z-statistic for testing non-inferiority (Cochran-Mantel-Haenszel estimate minus the non-inferiority margin, divided by the estimated standard error) is 0.788 *or lower* when 240 subjects have been treated and observed for TTH on the study, the stopping rule would

suggest that the study be terminated early with a decision that it was futile to continue the trial because there was not sufficient evidence that HEMOBLAST™ would be determined to be comparably efficacious if the study were to continue. Alternatively, if the observed Z-statistic for testing non-inferiority is 2.373 *or higher* when 240 subjects have been treated and observed for TTH on the study, the stopping rule would suggest that the study be terminated early with a decision in favor of comparable efficacy between the two products. A repeated 95% confidence interval for the stratum-weighted difference in proportions computed via the Cochran-Mantel-Haenszel method and using the asymptotic variance of this estimator, corrected for the stopping rule, will be computed at the completion of the trial.[iii] The actual critical values used at the time of stopping, adjusted for any departures in the implemented timing of analyses will be used in formulating the repeated confidence interval. In the event that true probability of TTH within 6 minutes for G+T arm is observed to be different from 88% or the timing of the interim analysis differs, the stopping boundaries will be adjusted to maintain a one-sided type one error rate of 0.025 as described in Section 12.4.3.

10.7.2 Implementation of the Stopping Boundary

Modifications of the stopping rule to account for changes in the schedule of the interim analysis and estimates of variability will be made by using the parametric form of the stopping rule as specified above, a blinded sample size recalculation will be performed prior to the interim analysis. An independent statistical reporting group preparing reports for the IDMC will use the constrained boundaries method as implemented in S+SeqTrial® to recalculate the maximal sample size based on the marginal response rate observed in the study at the time of the pre-planned interim analysis (marginalized over treatment arms).[23] The one-sided type I error rate for the study will be maintained at 0.025, and the maximal sample size will be adjusted up to maintain 80.1% power provided that the recalculated maximal sample size is 460 treated subjects or less within the TTH Population as defined in 10.5.1.

10.8 Exploratory Analyses

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

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

Additional, ad hoc exploratory analyses may also be conducted.

10.9 Subgroup Analyses

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

- The number of interventions (separate applications of randomized hemostat);
- Baseline SBSS score; and

- Abnormal versus normal coagulation values.

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

10.10 Accounting for Multiple Comparisons

The primary analysis comparing the probability of TTH within 6 minutes in subjects receiving HEMOBLAST™ to those receiving G+T will be conducted to maintain an overall 0.025 (one-sided) significance level accounting for one interim analysis and one final analysis (see Sections 12.4.1 and 12.4.2). The exclusion of a >10% difference in the probability of TTH at 6 minutes will be indicated by the lower limit of a 95% confidence interval for the adjusted difference in binomial proportions (HEMOBLAST™ – G+T). All reported inference (confidence intervals and p-values) will account for the planned interim analysis.

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

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

10.11 Other Data

10.11.1 Protocol Deviations

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

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

11 VERSION HISTORY

Version	Date	Changes
1.0	01July2016	

[i] Burington BE and Emerson SS. (2003). Flexible implementations of group sequential stopping rules using constrained boundaries. Biometrics 59, 770-777.
[ii] Ge M, Durham LK, Meyer RD, Xie W and Thomas N. Covariate-Adjusted Difference in Proportions from Clinical Trials Using Logistic Regression and Weighted Risk Differences. Drug Information Journal. 2011; 45: 481 - 493
[iii] Jennison C and Turnbull B. Interim Analyses: The Repeated Confidence Interval Approach. *Journal of the Royal Statistical Society. Series B (Methodological)* Vol. 51, No. 3 (1989), pp. 305-361.
[iv] Kittelson JM and Emerson SS. (1990). A unifying family of group sequential test designs. Biometrics 55, 874-923.
[v] Pocock SJ. (1977). Group sequential methods in the design and analysis of clinical trials. Biometrika 64, 191-199.
[vi] O'Brien PC and Fleming TR. (1979). A multiple testing procedure for clinical trials. Biometrics 35, 549-556.