Official Title: A Prospective, Randomized, Active-Controlled, Single-blind, Parallel Group Clinical Trial to Evaluate the Safety and Efficacy of Fibrin Sealant Grifols (FS Grifols) as an Adjunct to Haemostasis during Surgery in Paediatric Subjects

NCT Number: NCT03461406

Document Date: SAP Version 1.0: 02 November 2020

STATISTICAL ANALYSIS PLAN

Protocol Number: IG1405

A Prospective, Randomized, Active-Controlled, Single-blind, Parallel Group Clinical Trial to Evaluate the Safety and Efficacy of Fibrin Sealant Grifols (FS Grifols) as an Adjunct to Haemostasis during Surgery in Paediatric Subjects

Protocol Version: Version 3.0/ 06Nov2019

Author's Name and Address: [redacted] MS
Grifols Therapeutics, LLC.
79 TW Alexander Drive
Research Triangle Park, NC 27709

Version: V1.0

Approved by: [redacted] Firmado digitalmente por [redacted] Fecha: 2020.11.02 12:13:53 +01'00' Date: _____

Name: [redacted], MD

Title: - [redacted]

Approved by: [redacted] Digitally signed by [redacted] Reason: Document signed remotely due to the COVID-19 pandemic Date: 2020.11.02 09:49:52 -05'00' Date: November 2, 2020

Name: [redacted], PhD

Title: [redacted] Biostatistics and Data Management

Approved by: [redacted] Firmado digitalmente por [redacted] Fecha: 2020.10.30 15:30:26 +01'00' Date: 30 October 2020

Name: [redacted], MSc

Title: [redacted]

ABBREVIATIONS

ADR	adverse drug reaction
AE	adverse event
AR	adverse reaction
ATC	Anatomical Therapeutic Chemical
CBC	complete blood count
CSR	clinical study report
eCRF	electronic case report form
FS Grifols	Fibrin Sealant Grifols
ITT	Intent-to-treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
mL	milliliter
PT	preferred term
PP	per-protocol
SAE	serious adverse event
SAP	statistical analysis plan
SOC	system organ class
TStart	time of start of initial study treatment application
T_{Start2}	time of start of study treatment reapplication after T_{End} and before T_4, if applicable
T_4	hemostatic assessment at 4 minutes following TStart
T_7	hemostatic assessment at 7 minutes following TStart
T_{10}	hemostatic assessment at 10 minutes following TStart
TClosure	time of completion of the surgical closure by layers of the exposed surgical field containing the TBS
TCompletion	time of completion of the surgical incision closure – when the last skin closure stitch is put in – of the last exposed field, regardless of whether it was the field containing the TBS
TBS	target bleeding site
TEAE	treatment emergent adverse event
T_{End}	time of end/completion of initial study treatment application
T_{End2}	time of end/completion of study treatment reapplication, if applicable

TABLE OF CONTENTS

1 INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to outline the planned analyses to support the completion of the clinical study report (CSR) for protocol IG1405. Exploratory analyses not identified or defined in this SAP may be performed to support the clinical development program or manuscript. Any post-hoc or unplanned analyses performed and not identified in this SAP will be documented in the respective CSR.

2 STUDY DESIGN AND OBJECTIVES

2.1 Study Design

This is a prospective, randomized, active-controlled, single-blind, parallel group clinical trial to evaluate the efficacy and safety of Fibrin Sealant Grifols (FS Grifols) as an adjunct to hemostasis during surgery in pediatric subjects.

Pediatric subjects (<18 years of age) requiring an elective (non-emergent), open (non-laparoscopic), pelvic, abdominal, or thoracic (non-cardiac) surgical procedure, wherein a target bleeding site (TBS) is identified and a topical hemostatic agent is indicated, will be eligible to participate in the clinical trial.

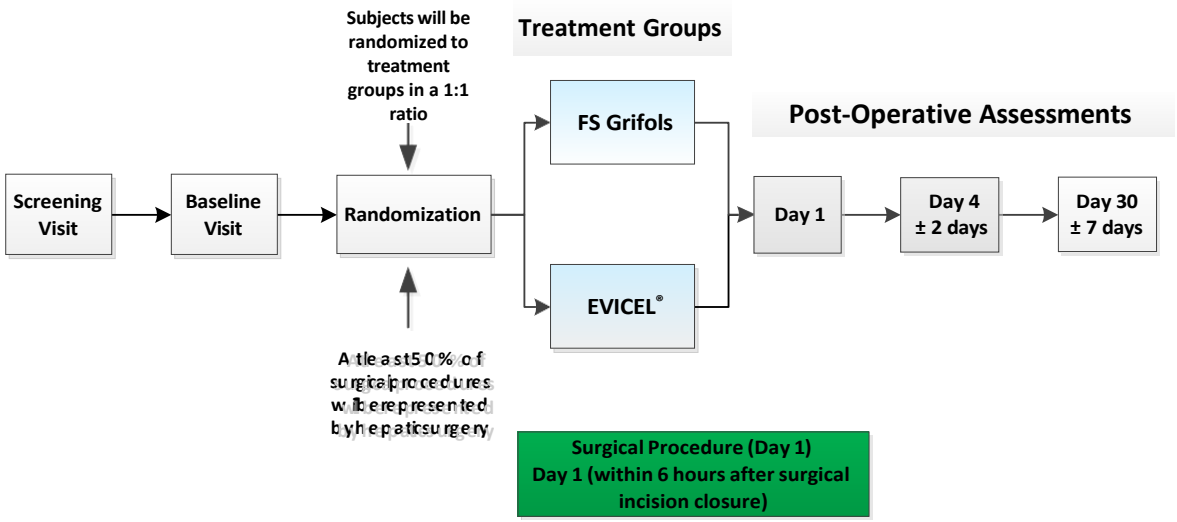
The study treatments will be applied on the cut parenchymous surface of a solid organ (i.e., liver) and in soft tissue (i.e., fat, muscle, or connective tissue).

A specific bleeding site will be defined as the TBS when it is determined by the investigator (the surgeon) that control of bleeding by conventional surgical techniques (including suture, ligature, and cautery) is ineffective or impractical and requires an adjunct treatment to achieve hemostasis.

When the TBS is identified, the investigator will record the precise anatomical location of the TBS, rate the intensity of the bleeding at the TBS (Grade 1-4 according to the 5-point validated bleeding severity scale [see Section 3 for the scale]) and record the size of the approximate bleeding surface (small, medium, large). For soft tissue surgery only, the investigator will also record the type of soft tissue (i.e., fat, muscle, or connective tissue). In this clinical trial, only subjects with a TBS with bleeding intensity of Grade 1 (mild) or Grade 2 (moderate) will be enrolled.

Subjects will be randomly allocated in a 1:1 ratio into 1 of 2 treatment groups: FS Grifols or EVICEL. The first 24 subjects to be enrolled in the study will be adolescents (age range 12 to 17 years). The term “enrolled” implies that the subject was actually randomized to and treated with either the FS Grifols or EVICEL. Enrollment will be monitored by surgery type to ensure at least 50% of the surgical procedures are hepatic. Subjects who are randomized and treated with any amount of study drug and withdrawn from the study will not be replaced.

The overall study schema is presented in the figure below:



2.2 Study Objectives

The purposes of this clinical trial are to evaluate the efficacy and safety of FS Grifols as an adjunct to achieve hemostasis during surgery in pediatric subjects.

2.2.1 Efficacy Objectives

2.2.1.1 Primary Efficacy Objective

- To evaluate if FS Grifols is non-inferior to EVICEL in terms of the proportion of subjects achieving hemostasis at the TBS by 4 minutes (T_4) from the start of treatment application (T_{Start}) with no occurrence of rebleeding until the completion of the surgical closure by layers of the exposed surgical field containing the TBS ($T_{Closure}$)

2.2.1.2 Secondary Efficacy Objectives

- To determine the cumulative proportion of subjects achieving hemostasis at the TBS by the defined observation time points of T_7 and T_{10}
- To determine prevalence of treatment failures

2.2.1.3 Exploratory Efficacy Objectives

- To determine the proportion of subjects achieving at least 1 point decrease in bleeding intensity according to the 5-point validated bleeding severity scale at the defined observation time points of T_4, T_7, and T_{10}
- To determine the mean change from baseline in bleeding intensity according to the 5-point validated bleeding severity scale at the defined observation time points of T_4, T_7, and T_{10}

2.2.2 Safety Objective

- To evaluate the safety and tolerability of FS Grifols in pediatric subjects undergoing surgery

3 STUDY VARIABLES

3.1 Efficacy Measures

For surgical procedures in both treatment groups, the following data will be collected and recorded to assess the efficacy of hemostasis by the investigator (surgeon):

T_{Start}	time of start of initial study treatment application to TBS
T_{End}	time of end/completion of initial study treatment application to TBS
T_{Start2}	time of start of study treatment reapplication after T_{End} and before $T_{4,}$ if applicable
T_{End2}	time of end/completion of study treatment reapplication, if applicable
T_4	hemostatic assessment at 4 minutes following T_{Start}
T_7	hemostatic assessment at 7 minutes following T_{Start}
T_{10}	hemostatic assessment at 10 minutes following T_{Start}
$T_{Closure}$	time of completion of the surgical closure by layers of the exposed surgical field containing the TBS
$T_{Completion}$	time of completion of the surgical incision closure – when the last skin closure stitch is put in – of the last exposed field, regardless of whether it was the field containing the TBS

Unless otherwise noted, if an observation is missing at a specific scheduled visit/time point, the value at that visit should not be imputed and should be reported as "missing". Hemostasis assessment is an exception. A missing hemostasis assessment at any scheduled time point will be deemed not to have achieved hemostasis at that specific time point only.

The 5-point validated bleeding severity scale is used to assess the hemostasis and shown below:

Table 3-1 Validated Bleeding Severity Scale

Grade	Visual Presentation	Anatomic 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

Table 3-1 Validated Bleeding Severity Scale

Grade	Visual Presentation	Anatomic Appearance	Qualitative Description	Visually Estimated rate of Blood Loss (mL/min)
2	Continuous flow	Venule and arteriolar-like bleeding	Moderate	>5.0-10.0
3	Controllable spurting and/or overwhelming flow	Noncentral venous- and 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, etc).

3.1.1 Primary Efficacy Variable

The primary efficacy variable is the proportion of subjects achieving hemostasis (binary decision: hemostatic response, Grade 0 = Yes/Grade ≥1 = No) at the TBS by T_4 without occurrence of rebleeding or reapplication of study treatment after T_4 and until $T_{Closure}$, and without Grade 3 or Grade 4 bleeding, or use of alternative hemostatic treatment after T_{Start} and until $T_{Closure}$. Hemostasis is defined as Grade 0 bleeding at the TBS according to the investigator's (surgeon's) judgment, so that the surgical closure of the exposed field could begin. Rebleeding is defined as Grade ≥1 bleeding from the TBS requiring further hemostatic intervention (eg, manual pressure) after hemostasis was previously achieved at the TBS.

The primary efficacy endpoint of hemostasis by T_4 is shown below.

	Hemostasis achieved?[a]			Was study treatment re-applied at TBS after T_4 and before $T_{Closure}$?[b]	Did the TBS re-bleed after the 10 minute observation period and before $T_{Closure}$, or was alternative hemostatic treatment used at the TBS, or was there Grade 3 or Grade 4 bleeding at TBS during the 10-minute observational period and until $T_{Closure}$?[b]	**Primary Efficacy Endpoint: Hemostasis by T_4?**
Scenario	T_4	T_7	T_{10}			

1	Yes	Yes	Yes	No	No	**Yes**
2	**No**	Either Yes or No at any time point		Either Yes or No	Either Yes or No	**No**
3	Either Yes or No	**No at any time point**		Either Yes or No	Either Yes or No	**No**
4	Either Yes or No			**Yes**	Either Yes or No	**No**
5	Either Yes or No			Either Yes or No	**Yes**	**No**

[a] Any missing to the question will be deemed "No".

[b] Any missing to the question will be deemed "Yes".

3.1.2 Secondary Efficacy Variables

3.1.2.1 Cumulative Proportion of Subjects Achieving Hemostasis at the Target Bleeding Site by the Time Points of T_7 and T_{10}

The cumulative proportion of subjects achieving hemostasis at the TBS by the time points of T_7 and T_{10} defined as an absence/cessation of bleeding (Grade 0) at the TBS by that time point without occurrence of rebleeding, Grade 3 or Grade 4 bleeding, use of alternative hemostatic treatment, and reapplication of study treatment after T_4 and until $T_{Closure}$.

3.1.2.2 Prevalence of Treatment Failures

The following cases will be considered treatment failures:

- Persistent bleeding at the TBS beyond T_4
- Grade 3 or Grade 4 breakthrough bleeding from the TBS that jeopardizes subject safety according to the investigator's judgment at any moment during the 10-minute observational period and until $T_{Closure}$
- Use of alternative hemostatic treatments or maneuvers (other than the study treatment) at the TBS during the 10-minute observational period and until $T_{Closure}$, or use of study treatment at the TBS beyond T_4 and until $T_{Closure}$
- Rebleeding (Grade $\geq$1) at the TBS after the assessment of the primary efficacy endpoint at T_4 and until $T_{Closure}$

In the event of Grade 3 or Grade 4 breakthrough bleeding that jeopardizes subject safety according to the investigator's judgment at the TBS at any moment during the 10-minute observational period and until the completion of the surgical closure by layers of the exposed

surgical field, the surgeon may use any other hemostatic measures at his/her discretion if deemed necessary (use of FS Grifols, EVICEL, or other plasma-derived hemostatic agents are not allowed in this case). In such a case, the subject will be considered a treatment failure. The alternative treatment used will be recorded in the subject's source documents and electronic case report forms (eCRFs).

3.1.3 Exploratory Efficacy Variables

- The proportion of subjects achieving at least 1 point decrease in bleeding intensity according to the 5-point validated bleeding severity scale by the defined observation time points of T_4, T_7, and T_{10}
- The mean change from baseline in bleeding intensity according to the 5-point validated bleeding severity scale at the defined observation time points of T_4, T_7, and T_{10}

3.2 Safety Variables

- Adverse events (AEs) including serious adverse events (SAEs), suspected adverse drug reactions (ADRs)/adverse reactions (ARs), and discontinuations due to AEs
- Clinical laboratory panels (i.e., coagulation panel, hematology, serum clinical chemistry)
- Physical examination
- Vital signs

4 GENERAL STATISTICAL CONSIDERATIONS

Statistical analyses and data presentations will be generated using SAS version 9.4 or higher.

Unless otherwise noted, for continuous variables, descriptive statistics will include the number of non-missing values, mean, standard deviation, median, minimum and maximum. For categorical variables, descriptive statistics will include counts and percentages per category. All statistical inference will be tested at 2-sided with α=0.05.

Unless otherwise noted, all data collected in the eCRFs or electronically transferred (such as central laboratory data) will be presented in data listings. Subjects will be identified in the data listings by subject number (which includes site number) and grouped by different treatment groups.

For table summaries, the data will be presented at the scheduled visits according to protocol. Any data collected at the unscheduled visits will be listed.

4.1 Data Handling

Unless otherwise noted, if an observation is missing at a specific scheduled visit/timepoint, the value at that visit will not be imputed and will be set to missing except for the hemostasis assessment that a missing hemostasis assessment at a time point would be deemed not to have achieved hemostasis at that specific time point only.

Unless otherwise noted, baseline will be defined as the last non-missing measurement prior to the start of the study treatment application

This is a single-blind study. Treatment assignment for subjects participating in the study will be blinded from the sponsor, except for personnel from study drug supply groups. Treatment allocation will only be unblinded as necessary within Grifols Global Pharmacovigilance group for subjects that experience a serious and unexpected ADR, as defined in protocol Section 8.3.7, and reported according to the procedure described in protocol Section 8.3.9.1.

4.2 Analysis Populations

Intent-to-treat (ITT) population

ITT population includes all subjects who are randomized, regardless of meeting intra-operative enrollment criteria and regardless of whether the investigational product (IP) was administered to the subject.

Modified ITT (mITT) population

mITT population includes all subjects in the ITT population who meet intra-operative enrollment criteria, and thus treated with any amount of IP.

Per Protocol (PP) population

PP population includes all subjects in the mITT population who do not have any major protocol deviations (to be determined at a data review meeting prior to unblinding) which could impact the analysis of primary efficacy endpoint.

Safety population

Safety population includes all subjects who receive any amount of IP.

4.3 Sample Size Considerations

The sample size of the study was estimated to provide sufficient power (at least 80%) to demonstrate the hemostatic efficacy of FS Grifols in parenchymous and soft tissue surgery.

Assuming that the true response rate is 80% for the FS Grifols group and 80% for the EVICEL group, it can be shown that a sample size of 172 subjects (86 subjects in the FS Grifols treatment group and 86 subjects in the EVICEL treatment group, with a 1:1 assignment ratio) would give a power of at least 80% to establish non-inferiority, with lower 95% CI for the ratio of the proportion of subjects with hemostasis success by 4 minutes in the 2 treatment groups (FS Grifols relative to EVICEL) above 0.80.

The approximate number of subjects planned to be randomized according to age range will be as follows:

- Adolescents (12 to 17 years): approximately 100
- Children (2 to 11 years): approximately 50
- Infants and toddlers (28 days to 23 months): approximately 16
- Preterm (up to gestational age <37 weeks) and term newborn infants (0 to 27 days): approximately 6

4.4 Interim Analysis

No interim analysis is planned to be performed.

5 SUBJECT DISPOSITION

Subject disposition will include the number of subjects screened, number of subjects randomized, number and percentage of subjects in each analysis population, and number and percentage of subjects completing the study by treatment groups.

The number and percentage of subjects discontinuing early from the study after the study treatment will be summarized for primary reasons of discontinuation. Also, the number and percentage of pre-operative screen failures and intra-operative screen failures will be summarized for primary reasons of ineligibility.

Disposition status will be listed for all subjects.

6 PROTOCOL DEVIATIONS

Protocol deviations will be identified and evaluated during the study and finalized before the database lock. The type of protocol deviations and severity (e.g., minor, major, and critical) will be summarized by treatment groups. The type and severity of protocol deviations, subject specific or general site protocol deviations will also be listed.

7 DEMOGRAPHY AND MEDICAL HISTORY

7.1 Demographic and Baseline Characteristics

Demographic and baseline characteristics including sex, race, ethnicity, age at randomization (years) derived based on the number of years and the number of months collected in eCRF, age categories (<=27 days, 28 days - <=23 months, 2-11 years, 12-17 years), baseline pregnancy test (if applicable), height, weight and body mass index will be summarized by treatment groups. All subjects will be summarized and listed for type of intervention (i.e., parenchymous surface of liver or soft tissue), intensity of the bleeding at TBS (i.e., Grade 1 = mild or Grade 2 = moderate) and size of the approximate bleeding surface at TBS (small; medium; and large). The date/time of induction of anesthesia, skin incision, and recovery from anesthesia for all surgery types will also be listed.

7.2 Medical and Surgical History

Medical and surgical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and summarized/listed by treatment groups.

8 CONCOMITANT MEDICATION AND TREATMENT

8.1 Prior and Concomitant Medication

All medications including topical hemostats and blood products will be coded using ATC classification codes via the World Health Organization Drug classification Dictionary. All medications will be summarized by treatment groups and sorted alphabetically by medication class (i.e., ATC level 2) and medication sub-class (i.e., ATC level 4). If the ATC level 4 term is missing, the ATC level 3 term will be used in the medication summary table and data listing.

The following convention will be used for missing or partial end date information in order to determine whether a medication is prior or concomitant:

The unknown portions of a medication end date will be assumed to be as late as possible. If a medication end date is incomplete but the month/year of medication end date is prior to the month/year of the start of study treatment, then the medication will be considered a prior medication. If a medication end date is incomplete but the month/year of medication end date is the same as the month/year of the start of study treatment, then the medication will be considered a concomitant medication. All other incomplete medication end dates and all medications with missing end dates will be assumed to be concomitant medications. The unknown portions of a medication end time will be assumed to be as late as possible. Start/end dates and time reported in the eCRFs will be presented in the listings.

Prior medications are defined as any medication ended prior to the start of study treatment (i.e., application of FS Grifols or EVICEL).

Concomitant medications are defined as any medication started on or after the start of study treatment, or any medication taken prior to the start of study treatment and continued after the start of study treatment during the study.

All medications including topical hemostats and blood products will be listed.

8.2 Extent of Study Treatment Exposure

The extent of study treatment exposure in mL to TBS will be summarized for FS Grifols and EVICEL treatment groups.

The estimated total quantity in mL (i.e., Kit #1 volume in mL x estimated percentage volume applied to TBS + Kit #2 volume in mL x estimated percentage volume applied to TBS) of FS Grifols and EVICEL will be summarized.

The volume of each kit and estimated percentage volume applied to TBS will be listed.

The mode of application (i.e., drip or spray) will be listed and summarized.

9 EFFICACY ANALYSIS

The efficacy analyses will be performed using the mITT population. Additionally, the primary efficacy endpoint of the proportion of subjects achieving hemostasis by 4 minutes at TBS will be analyzed using the PP population (if different from mITT population). As sensitivity analysis, the primary efficacy endpoint will be analyzed using ITT population. For subjects in both treatments in the ITT population who do not meet the intra-operative criteria and do not receive the study treatment, they will be deemed not achieving hemostasis for the primary efficacy endpoint.

9.1 Primary Efficacy Analysis

The primary efficacy variable is the proportion of subjects achieving hemostasis by T_4 based on its nominal scheduled time point at TBS.

Assuming that T is the response rate for the FS Grifols treatment group, C is the response rate for the EVICEL group (control group), M is the pre-specified non-inferiority margin.

The null hypothesis (H_0) is: Risk Ratio (T/C) < 1-M
and
the alternative hypothesis (H_1) is: Risk Ratio (T/C) >= 1-M,

where 1-M is 0.8.

The primary efficacy endpoint will be analyzed using Cochran-Mantel-Haenszel (CMH) test stratified by type of surgery (i.e., parenchymous surface of liver versus soft tissue surgery). The ratio of proportion (RR_{pooled}) of subjects meeting the primary efficacy endpoint in the two treatment groups (FS Grifols relative to EVICEL) and its two-sided asymptotic 95% confidence interval (CI) will be provided:

$$RR_{pooled} = \frac{\sum_i a_i * m_{0i} / N_i}{\sum_i b_i * m_{1i} / N_i}$$

The asymptotic 95% confidence interval of RR_{pooled} is calculated as:

$$Lower\ limit = \exp\{\ln(RR_{pooled}) - Z_{\alpha/2} * SE\}$$

$$Upper\ limit = \exp\{\ln(RR_{pooled}) + Z_{\alpha/2} * SE\}$$

Where the standard error (SE) is calculated as:

$$SE = \sqrt{\frac{\sum_i (n_{1i} * m_{1i} * m_{0i} - a_i * b_i * N_i) / N_i^2}{(\sum_i a_i * m_{0i} / N_i)(\sum_i b_i * m_{1i} / N_i)}}$$

where a_i, b_i, c_i, d_i, n_{1i}, n_{0i}, m_{1i}, m_{0i}, and N_i are the number of subjects defined in following table; i = 1 or 2 according to different types of surgeries (i.e., parenchymous surface of liver or soft tissue surgery).

		FS Grifols	EVICEL	Total
Hemostasis achieved?	Yes	a_i	b_i	n_{1i}
	No	c_i	d_i	n_{0i}
Total		m_{1i}	m_{0i}	N_i

The non-inferiority will be deemed to have been demonstrated if the lower limit of the 95% CI exceeds 0.8. After the non-inferiority of FS Grifols to EVICEL is established, its superiority may be additionally claimed if the 95% CI for the ratio is entirely above 1.

In this study, 2 types of applicator devices are used to apply FS Grifols (Fibrijet® device up to 30 November 2019, VistaSeal™ Dual Applicator thereafter). A sensitivity analysis for the primary efficacy endpoint using mITT will be performed for the subgroups based on the use of different applicators, to compare FS Grifols-treated subjects with either type of applicator device vs the Evicel treatment group. A subgroup analysis by surgery type will also be provided for this by applicator type analysis.

If any missing hemostatic assessment at TBS at T_4 for a randomized subject occurs, it will be treated as non-hemostasis at TBS at T_4 for the subject in the primary efficacy analysis. A sensitivity analysis with non-missing observational hemostatic assessment at TBS at T_4 will be performed.

Considering that the hemostasis assessment may not be performed exactly at the scheduled time point, as supportive analyses, the primary efficacy variable based on the time window below will also be analyzed using the CMH test. The hemostasis assessment data at each time point will be classified into the appropriate category based on the time window in the table below, according to the elapsed time of hemostasis assessment from the start of initial treatment application (T_{Start}) to T_4, T_7 and T_{10} time points in eCRF.

Scheduled Event	Time Window (MM:SS)
T_4 (4 minutes from start of application)	<=4:10
T_7 (7 minutes from start of application)	>=4:11 to <=7:10
T_{10} (10 minutes from start of application)	>=7:11 to <=10:10

If multiple hemostasis assessments fall within the same time window, for purpose of the supportive analyses, the following two scenarios will be considered:

(a) the first hemostasis assessment will be selected;

(b) the last hemostasis assessment will be selected.

If there is no hemostasis assessment within a specific time window, the last hemostasis assessment within the previous time window will be carried forward. If there is no hemostasis assessment within the first time window (<=4:10), the hemostasis assessment will be deemed non-hemostasis success at T_4. The hemostasis assessment with the elapsed time from T_{Start} greater than 10 minutes and 10 seconds will be classified into the period that is after the 10-minute observational period and before the $T_{Closure}$.

For primary efficacy endpoint, subgroup analyses will be provided for surgery type, age group, gender, race, baseline TBS bleeding intensity, and TBS size category.

9.2 Secondary Efficacy Analyses

Analyses relating to secondary efficacy variables, the cumulative proportions of subjects achieving hemostasis by other individual assessment times (i.e., 7 minutes and 10 minutes), will be similarly analyzed using CMH test.

The proportion of subjects with treatment failures will be summarized and analyzed using CMH test.

9.3 Exploratory Efficacy Analyses

Exploratory efficacy endpoints will be descriptively summarized by treatment group. The proportion of subjects achieving at least 1 point decrease in bleeding intensity according to the 5-point validated bleeding severity scale by each of the defined observation time points (i.e., T4, T7 and T10) will be analyzed using CMH test stratified by type of surgery (i.e., hepatic versus soft tissue surgery).

Also, an ordered categorical analysis of the hemostatic status at each of the assessment time points (i.e., T4, T7 and T10) will be presented. For this, the subjects will be assigned to 1 of 4 categories on the basis of their time to hemostasis (0 to ≤4 minutes; >4 to ≤7 minutes; >7 to ≤10 minutes; >10 minutes). The comparison between treatment groups will be done using an ordinal logistic model assuming proportional odds.

Change from baseline in bleeding intensity according to the 5-point validated bleeding severity scale at the defined observation time points (i.e., T4, T7 and T10) will be summarized. The 5 grades (i.e., 0, 1, 2, 3, and 4) will be considered continuous values in this analysis.

10 SAFETY ANALYSIS

Safety analyses are based on the Safety Population.

10.1 Adverse Events

All reported AEs will be coded and summarized by system organ class (SOC) and preferred term (PT) according to MedDRA.

When an AE is classified, assessing causal relationship by the investigator, as definitively or possibly related, the event will be defined as a suspected ADR. A suspected ADR with a causal relationship of "definitively" will be defined as an AR. When the causal relationship is labeled "Unrelated", then it will be considered that the AE is not imputable to the investigational medicinal product and it is not a suspected ADR. The sponsor will consider the investigator's causality assessment and also provide its own assessment. If there is any disagreement in causality assessment between the investigator and the sponsor, separate summary of suspected ADRs/ARs will be provided.

For summary purposes, AEs will be classified as treatment emergent AEs (TEAEs) or non-treatment emergent AEs (non-TEAEs) depending on the comparison of AE onset date/time with the start date/time of study treatment. A TEAE will be defined as an AE which occurred between the start of study treatment and the final visit of the clinical trial. Non-TEAEs and TEAEs will be summarized separately.

The incidence of TEAEs, suspected ADRs, ARs, and SAEs will be summarized by treatment group, SOC, and PT. Also, the incidence of TEAEs by causal-relationship, intensity (severity), and seriousness (serious vs non-serious) will be descriptively summarized. At each level of summarization, a subject will only be counted once per SOC or PT using the most severe AE, or the AE with the strongest causal relationship to study treatment.

Subjects with SAEs, AEs leading to death, and TEAEs leading to the discontinuation from the study will also be separately listed.

The TEAEs/suspected ADRs reported due to clinically relevant abnormal laboratory results, vital signs or physical assessments will be collected.

All AEs/suspected ADRs will be presented in a data listing.

10.2 Laboratory Assessments

Complete blood count (CBC) (red blood cells count, Hgb, hematocrit, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, mean corpuscular volume, white blood cells count and differential, and platelet count), serum clinical chemistry (creatinine, blood urea nitrogen, total bilirubin, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, lactate dehydrogenase, glucose, sodium, potassium, chloride and calcium), and coagulation panel (prothrombin time and activated partial thromboplastin time) data will

be collected at the assigned visits according to protocol. All laboratory panels above will be performed by central laboratory.

The CBC panel, clinical chemistry panel, and coagulation parameters will be summarized with number of subjects, mean, standard deviation, median, minimum, and maximum values at each visit. Change from baseline will be descriptively summarized. Shift tables, based on the high/normal/low flags, will also be summarized by parameter and visit.

All laboratory data will be presented in data listings.

10.3 Vital Signs

Vital sign data (heart rate, respiration rate, systolic and diastolic blood pressure and temperature) and their changes from baseline will be summarized with the number of subjects, mean, standard deviation, median, minimum, and maximum values. The vital sign data collected at the Baseline Visit will be defined as the baseline values. The counts and percentages of abnormal values will be summarized by visit and for all post-baseline visits. Subjects with invasive measurement and subjects on mechanical ventilation will be summarized by visit and for all post-baseline visits with counts and percentages.

All vital sign data will be listed.

10.4 Physical Assessments

Physical assessment findings will be summarized with numbers and percentages by body system. Entries for 'Other' body systems will be grouped together; a subject with 2 or more 'Other' entries will be counted only once. All physical assessment data will be listed.