CONFIDENTIAL STATISTICAL ANALYSIS PLAN

A Prospective, Randomised, Controlled, Study Evaluating the Safety and Effectiveness of EVARREST® Sealant Matrix in Controlling Mild or Moderate Hepatic Parenchyma or Soft Tissue Bleeding During Open Abdominal, Retroperitoneal, Pelvic and Thoracic (non-cardiac) Surgery in Paediatric Patients

Version: Amendment 1 **Date: June 15, 2020**

Protocol Number: 400-12-004 (Admin Change 5, dated April 29, 2020)

AUTHENTICATION

The contents of this statistical analysis plan (SAP) adhere to current regulatory guidelines[1,2]. We the undersigned declare that to the best of our knowledge this study will be reported and analysed in accordance with the following SAP.

[redacted]

[redacted]

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CHANGES MADE FROM FINAL VERSION

-For clarity, in section 5, in the definition of the Full Analysis Set, the text "Subjects who do not complete the procedure after randomisation will be included in the FAS analysis" was changed to: "Subjects who do not complete the procedure with the use of EVARREST or SURGICEL after randomization will be included in the FAS analysis."

-In section 5, the definition of Per-Protocol set was changed from "The Per-Protocol (PP) analysis set (Evaluable set) consists of all FAS subjects who have no major protocol deviations and have data available for primary effectiveness endpoint" to "The Per-Protocol (PP) analysis set (Evaluable set) consists of all FAS subjects who have no major protocol deviations affecting the primary effectiveness endpoint and have data available for this endpoint." In addition, the text "Major protocol deviations are deviations that have an impact on the primary endpoint, or that have an impact on the randomization assignment. These will be determined prior to database lock" was changed to: "Major protocol deviations will be determined prior to database lock." The PP set should only exclude ITT subjects with major protocol deviations affecting the primary effectiveness endpoint, instead of all subjects with major protocol deviations. This change is consistent with the manner in which the major protocol deviations for this study have been assessed – there are major deviations that do NOT affect the primary endpoint and do NOT exclude the subjects from the PP set.

1. STUDY OBJECTIVES

The objective of this study is to evaluate the safety and hemostatic effectiveness of EVARREST Sealant Matrix (EVARREST Fibrin Sealant Patch) (EVARREST) in controlling mild or moderate soft tissue and parenchymal bleeding during open hepatic, abdominal, pelvic, retroperitoneal, and thoracic (non-cardiac) surgery in pediatric patients.

2. STUDY DESIGN

This is an open label, prospective, randomized, multicentre, controlled, clinical study comparing EVARREST to SURGICEL [oxidized regenerated cellulose (ORC)] (Control) as an adjunct to hemostasis when conventional methods of controlling mild or moderate bleeding are ineffective or impractical during surgery in pediatric patients.

At least 40 qualified pediatric subjects with an appropriate mild or moderate bleeding Target Bleeding Site (TBS) will be randomized in a 1:1 allocation ratio to either EVARREST or SURGICEL. Absolute time to hemostasis at the target bleeding site will be assessed as well as hemostasis at 4 and 10 minutes from randomization.

Enrollment will be staggered by age, as required by the European Medicines Agency (EMA) Paediatric Committee. The first 36 subjects enrolled will be aged ≥1 years to <18 years of age. Enrollment of a subsequent group including 4 subjects from 1 month (≥ 28 days from birth) to <1 year of age will follow. Ongoing safety assessment will ensure adequate safety monitoring occur during the staged enrollment.

The Target Bleeding Site (TBS) will be defined as the first accessible mild or moderate bleeding site identified in the hepatic parenchyma or soft tissue, where conventional methods of controlling bleeding are ineffective or impractical, and is amenable to manual compression. Once the TBS is identified, the surgeon will immediately randomize the subject into the study. The randomly assigned treatment (EVARREST or SURGICEL) will be applied immediately at the actively bleeding TBS.

EVARREST can only be used on a single TBS to be evaluated. If additional soft tissue or hepatic parenchymal bleeding sites are identified, the surgeon should treat according to their standard of care.

Randomization will be used to avoid bias in the assignment of treatment to each subject, to increase the likelihood that attributes of the subject are balanced across treatment groups, and to enhance the validity of statistical comparisons across treatment groups.

ETHICON will provide each site with computer-generated randomization envelopes, each bearing the subject randomization number, and containing the treatment allocation. Treatment, either EVARREST or SURGICEL, will be assigned randomly to each subject on a 1:1 basis. In the event that a potential subject fails intraoperative criteria (i.e. no TBS identified, or an intraoperative exclusion), and is not randomized to the study, the unused randomization envelope should be returned to the series, and used for the next subject. Given the difference between the two treatment groups, it will not be possible for the surgeon to be blinded to the treatment. However, to avoid any bias in the conduct of the surgical procedure, randomization should only take place after completion of the following steps:

1. EVARREST and SURGICEL will be prepared and available in the sterile field in the operating room, ready for administration for each patient.

2. The investigator must perform the surgical procedure according to his/her standard of care.

3. Once the investigator encounters an appropriate hepatic parenchyma or soft tissue TBS related to the primary operative procedure, randomization should immediately take place. The randomization envelope will be opened simultaneously with starting the stopwatch.

Subjects will be followed post-operatively through hospital discharge and at 30 days (±14 days) post-surgery.

3. STUDY ENDPOINTS

The primary effectiveness endpoint is absolute time to hemostasis, defined as the absolute time elapsed from randomization to the last moment in time at which detectable bleeding at the TBS is observed.

The following secondary effectiveness endpoints will be included in this study:

- Proportion of subjects achieving hemostatic success at 4 minutes following randomization and no bleeding requiring treatment at the TBS occurs any time prior to final fascial closure;

- Proportion of subjects achieving hemostatic success at 10 minutes following randomization and no bleeding requiring treatment at the TBS occurs any time prior to final fascial closure;

- Proportion of subjects with no re-bleeding at the TBS.

In addition, the following safety endpoints will be included in this study:

- Proportion of subjects with adverse events that are potentially related to bleeding at the TBS;

- Proportion of subjects with adverse events that are potentially related to thrombotic events;

- Proportion of subjects with re-treatment at the TBS;

- Incidence of adverse events;

- Hemoglobin, Hematocrit, Platelets, Volume of blood loss, Volume of blood and blood products transfusions.

4. CHANGES IN THE CONDUCT OF THE STUDY OR PLANNED ANALYSIS

Not applicable.

5. ANALYSIS SETS

The following three analysis sets defined:

- The Full Analysis Set (FAS) consists of all randomized subjects (equivalent to the Intent-to-Treat [ITT] set). Subjects who do not complete the procedure with the use of EVARREST or SURGICEL after randomization will be included in the FAS analysis;

- The Per-Protocol (PP) analysis set (Evaluable set) consists of all FAS subjects who have no major protocol deviations affecting the primary effectiveness endpoint and have data available for this endpoint;

- The Safety analysis set consists of all subjects who received treatment.

Major protocol deviations will be determined prior to database lock.

The primary effectiveness endpoint will be analyzed using the FAS and the PP set. However, the primary analysis will be based on the FAS. The PP analysis will be considered supportive.

All secondary effectiveness endpoints (listed in section 8.3) will be analyzed using the FAS set, while safety endpoints (listed in section 9) will be analyzed using the Safety set.

If any patients are mis-randomized (randomized to one treatment, but received the other), then data for the FAS will be summarized 'as randomized', and data for the safety set will be summarized 'as treated'.

If more than 2 patients are mis-randomized, then additional analyses for the FAS will be performed, with patients allocated to treatment groups 'as treated'. Patients who are mis-randomized will be considered major protocol deviations.

6. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

6.1 Demographic and other baseline characteristics

Demographic and other baseline data will be summarized descriptively for subjects in each treatment group in the FAS set. The categorical data will be summarized descriptively by frequencies along with the associated percentages. The continuous data will be presented using summary statistics such as number of subjects, mean, standard deviation, minimum, median and maximum.

The following demographic variables will be summarized:

- Age;
- Gender;

- Race/ethnicity;
- Height;
- Weight;
- Body mass index;
- Indication of subject being of child bearing age.

In addition, the following screening and baseline data will be collected:

- Physical examination, including documentation of relevant medical and surgical history;
- Full blood count (FBC) with white blood cell differential, and coagulation parameters;
- Documentation of medical history and all concomitant medications during 24 hours prior to surgery;
- Review of inclusion / exclusion criteria to confirm subject eligibility.

7. PROCEDURE DATA

Procedure data will be summarized descriptively for subjects in each treatment group in the FAS set. The categorical data will be summarized descriptively by frequencies along with the associated percentages. The continuous data will be presented using summary statistics such as number of subjects, mean, standard deviation, minimum, median and maximum.

The following procedure variables will be analyzed:

- Primary operative procedure;
- Operating room (OR) time;
- Procedure duration (from first incision to last suture/staple);
- Procedure duration from first incision to initiation of final fascial closure (when applicable);
- For liver resections patients: time from start of liver resection to last suture/staple and time from start of liver resection to initiation of final fascial closure (when applicable);
- Specification of treatment to which subject is randomized;
- Estimated intraoperative blood loss, blood or blood product transfusions from surgery through hospital discharge, and cell saver usage data;
- Primary method used to obtain hemostasis at the TBS;
- TBS length, width, area, and location, type of bleeding, and TBS tissue type;
- For liver only TBS: estimated total transected plane area, estimated portion of total transected plan area which is treated, reason for liver resection, type and location of resection at TBS, hepatic parenchyma classification/type and specification (if abnormal), predominant source of bleeding, type of arterial bleeding, type of venous bleeding, area of bleeding and specification (if "diffuse");
- Approximate length and width of product applied at the TBS, TBS area, and size of EVARREST implanted (in cm^2 per kilogram of body weight);
- For patients treated with EVARREST: total number of EVARREST units used at TBS, indication of appropriate identification of TBS, presence of adequate access to TBS, indication of sufficient coverage of TBS, indication of EVARREST pads overlap at TBS, including number of overlap locations and presence of sufficient overlap, surgeon's ability to properly apply EVARREST at its first application to TBS, and reasons for incorrect EVARREST application;
- For patients treated with SURGICEL: number of kits used at TBS and indication of SURGICEL use according to IFU;
- Hemostasis assessment data, such as time from randomization to initial application of the hemostatic product with manual compression, TBS hemostasis presence at 4 and 10 minutes from

randomization, absolute time to hemostasis (from randomization), and presence of any bleeding at TBS between 4 minutes following randomization and final fascial closure;
- For patients with bleeding at TBS between 4 minutes following randomization and final fascial closure: type of bleeding, indication of additional treatment required to assure durability of hemostasis, indication of any re-treatment due to application error, reason for any additional treatment used at the TBS, time from randomization to re-bleed, and treatments applied; for patients re-treated with EVARREST, approximate length and width of EVARREST used;
- Length of subject hospital stay (from hospital admission to hospital discharge, as well as from procedure to hospital discharge);
- Time from screening visit to hospital admission, time from baseline visit to hospital admission, time from screening visit to surgery, time from baseline visit to surgery, and time from surgery to 30-day visit.

8. EFFECTIVENESS

8.1 General methods of analysis

The Clinical Data Management and Biostatistics groups within Clinical Development at ETHICON will be responsible for the overall analysis of data from this protocol. All analyses/summaries will be produced using SAS® Studio.

Data will be summarized descriptively for subjects in each treatment group in the FAS set. The categorical data will be summarized descriptively by frequencies along with the associated percentages. The continuous data will be presented using summary statistics such as number of subjects, mean, standard deviation, minimum, median and maximum.

8.2 Primary effectiveness analysis

The primary effectiveness endpoint is absolute time to hemostasis, defined as the absolute time elapsed from randomization to the last moment in time at which detectable bleeding at the TBS is observed.

The primary effectiveness endpoint will be summarized descriptively by treatment group. The primary endpoint will also be summarized descriptively by treatment group and pediatric group [1 month ($\geq$28 days from birth) to <1 year and 1<18 years], as well as treatment group and age group [Infants and toddlers (28 days to 23 months), Children (2 to 11 years), and Adolescent (12 to <18 years)]. In addition, 95% distribution-free confidence intervals (CIs) for median absolute time to hemostasis will be reported separately for EVARREST and Control groups.

Absolute time to hemostasis will also be analyzed descriptively separately for subjects who achieved hemostasis with and without additional randomized treatments being required.

8.2.1 Sample size justification

No formal sample size calculation has been performed for this study. The sample size required for the trial is at least 40 randomized paediatrics subjects recruited from sites within the European Union and Canada. This sample size is considered adequate to achieve the study objectives and provide sufficient information to evaluate data descriptively.

8.3 Secondary effectiveness analysis

The following secondary effectiveness endpoints will be summarized descriptively by treatment group for the FAS:

- Proportion of subjects achieving hemostatic success at 4 minutes following randomization and no bleeding requiring treatment at the TBS occurs any time prior to final fascial closure;
- Proportion of subjects achieving hemostatic success at 10 minutes following randomization and no bleeding requiring treatment at the TBS occurs any time prior to final fascial closure;
- Proportion of subjects with no re-bleeding at the TBS.

Two-sided 95% CIs for the proportions of subjects with hemostasis at 4 minutes and 10 minutes will be constructed for each treatment group separately (P_E for EVARREST and P_C for Control), using the Clopper-Pearson method. In addition, for each time point, a two-sided 95% CI will be reported for the ratio proportion of successes (hemostasis achieved) in the EVARREST group/proportion of successes in Control group (P_E/P_C), using the Farrington-Manning score method.

8.4 Analysis of follow-up data

The following follow-up data will be summarized descriptively for post-surgery to hospital discharge (within 72 hours prior to discharge) and for 30-day (±14 days) visit:

- Re-hospitalizations, surgical procedures, and transfusions since hospital discharge [for 30-day (±14 days) visit only];
- Relevant changes in medical history since screening;
- Presence of clinically significant changes to subject since baseline;
- Presence and duration of subject presence in elevated care unit (ICU, step-down unit, etc.);
- Presence and duration of subject being on ventilator post-operatively;
- Laboratory data (full blood count with white blood cell differential, and coagulation parameters) (only for post-surgery to hospital discharge - within 72 hours prior to discharge).

8.5 Statistical/analytical issues

8.5.1 Handling of dropouts or missing data

It is not anticipated that there will be any data missing for treated subjects for the primary endpoint, but if there is, missing data will not be imputed for the primary effectiveness analysis.

Analyses of binary secondary endpoints will consider missing data as failures; missing data for other secondary endpoints will not be imputed.

If there are incomplete dates and calculations (e.g. time since procedure) are needed, the following rules are used (no rules will be applied for missing years; this data would normally be expected to be queried):

- Missing date which includes the procedure data: the rules below are followed unless the derived date is pre-procedure, when the derived date will be 1 day after the procedure.
- Missing day: 15th used

8.5.2 Interim analyses and data monitoring

No interim analysis will be performed for this study.

8.5.3 Multiple comparison / multiplicity

Not applicable.

9. SAFETY EVALUATION

9.1 Adverse events

The following safety/secondary endpoints will be descriptively summarized using the Safety set:

- Proportion of subjects with adverse events that are potentially related to bleeding at the TBS;
- Proportion of subjects with adverse events that are potentially related to thrombotic events;
- Proportion of subjects with re-treatment at the TBS;
- Incidence of adverse events;
- Hemoglobin, Hematocrit, and Platelets, at screening, baseline, and post-surgery to hospital discharge (within 72 hours prior to discharge);
- Estimated intra-operative blood loss;
- Volume of blood and blood products transfusions (red blood cells, whole blood. fresh frozen plasma, platelets, and cryoprecipitates), intra-operatively, prior to hospital discharge, and after discharge.

9.2 Clinical laboratory evaluation

Blood samples will be taken for full blood count with white blood cell differential, and coagulation parameters, at screening, baseline, and post-surgery to hospital discharge (within 72 hours prior to discharge).

9.3 Vital signs, physical findings and other observations related to safety

Vital signs will not be collected in this study. A physical exam will be performed and medical/surgical history data will be collected at screening. In addition, a physical exam will be performed post-surgery to hospital discharge (within 72 hours prior to discharge).

9.4 Methods of analysis

All safety variables will be summarized descriptively only, for Safety analysis set. No inferential statistical analysis will be carried out.

Adverse events will be summarized descriptively by the treatment received, using Medical Dictionary for Regulatory Activities (MedDRA) terminology, in SI units. Values and changes from baseline will be listed, but not summarized.

10. DATA PRESENTATION

The report forms part of an integrated clinical study report. The actual numbering of tables, listings and other outputs may change. Numbering is in accordance with ICH guideline E3[2].

10.1 Procedure or treatment labels

The following labels will be used for all output: **EVARREST** and **SURGICEL**.

10.2 Tables and figures

Data will be tabulated by treatment group and, if appropriate, by visit. Continuous data summaries will present (unless stated otherwise) number of observations, number of missing observations (if there are any), mean, standard deviation, minimum, median and maximum. Categorical data summaries will present the number of observations and the corresponding percentage. The following tables will be produced:

10.2.1 In-text tables and figures

These will be produced for the main report in conjunction with the medical writer. These will include, but will not be limited to:

No	Title of table/figure	Notes
F1	Subject disposition	Based on Table 14.1.1.4
T1	Demographic characteristics – FAS analysis set	Summary of Table 14.1.2.1
T2	Surgical procedure – FAS analysis set	Summary of key items from Tables 14.1.3.1-14.1.3.7
T3	Statistical summary for primary effectiveness endpoint – Per-Protocol and FAS analysis sets (including sensitivity analysis summary)	Summary of Tables 14.2.1.1 and 14.2.1.2
T4	Summary of AEs occurring in >5% of subjects– Safety analysis set	Summary of 14.3.1.3

T=Table F=Figure

10.2.2 Section 14 tables

Shell tables shown in Appendix 1, according to the code in the 'Shell' column. All table numbers will be prefixed with 14.

No	Title of table/figure	Notes	Shell[1]
1.1	Disposition of subjects, analysis sets and protocol deviations		
1.1.1	Disposition of subjects by centre – FAS	Includes number withdrawn – by center	DS

[1] Shell: Example table from Appendix 1 (Shell tables). Letters refer to standard output, numbers to project specific output.

No	Title of table/figure	Notes	Shell[1]
1.1.2	Enrollment by center – FAS	By center	E
1.1.3	Summary of protocol deviations – FAS	Includes both minor and major protocol deviations	PD
1.1.4	Analysis sets – FAS		ST
1.2	Baseline data	Excludes baseline data that is also measured post procedure and/or safety data	
1.2.1	Demographics – FAS	Age, height, weight, BMI – continuous data (c); gender, race, ethnicity, and indication of subject being of child bearing age – all discrete data (d)	DG
1.2.2	Baseline characteristics – FAS	Presence of relevant history of prior surgery, indication of any relevant changes in medical history between screening and 24 hours before procedure, and confirmation of subject eligibility - all (d)	G1[2]
1.2.3	Physical exam / medical / surgical history – FAS	Includes frequencies	HX
1.3	Operative data		
1.3.1	Operative data: Surgery details, transfusions, and randomization – FAS	Primary operative procedure, treatment to which subject is randomized (both d), estimated intraoperative blood loss (mL) (c), indication of subject receiving blood or blood product transfusions from surgery through hospital discharge (d), indication of cell saver usage (d), and cell saver volume (mL) collected and returned (c)	G2
1.3.2	Operative data: Target Bleeding Site (TBS) identification – FAS	Primary method to obtain hemostasis at the TBS (d), TBS length (cm), width (cm), area (cm2) (all c), and location (d), type of bleeding (d), TBS tissue type (d); for liver only TBS: estimated total transected plane area (cm^2) (c), estimated portion of total transected plan area which is treated, reason for liver resection, type and location of resection at TBS, hepatic parenchyma classification/type and specification (if abnormal), predominant source of bleeding, type of arterial bleeding, type of venous bleeding, area of bleeding and specification (if "diffuse") (all d)	G2
1.3.3	Operative data: Treatment application – FAS	Approximate length and width of product applied at the TBS (cm), TBS area (cm^2), and size of EVARREST implanted (cm^2 per kilogram of body weight) (all c); For patients treated with EVARREST: total number of EVARREST units used at TBS (both c and d), indication of appropriate identification of TBS, presence of adequate access to TBS, indication of sufficient coverage of TBS, indication of EVARREST pads overlap at TBS, including number of overlap locations and presence of sufficient overlap, surgeon's ability to properly apply EVARREST at its first application to TBS, and reasons for incorrect EVARREST application (all d); For patients treated with SURGICEL: number of kits used at TBS (both c and d) and indication of SURGICEL use according to IFU (d)	G2

[2] For Tables G1, G2, G3 notes will indicate if data is continuous or discrete.

No	Title of table/figure	Notes	Shell[1]
1.3.4	Operative data: Hemostasis assessments – FAS	Time from randomization to initial application of hemostatic product with manual compression (sec) (c), TBS hemostasis presence at 4 and 10 minutes from randomization (both d), absolute time to hemostasis (from randomization) (sec) (c), and presence of any bleeding at TBS between 4 minutes from randomization and final fascial closure (d)	G2
1.3.5	Operative data: Bleeding/durability details – FAS	For patients with bleeding at TBS between 4 minutes following randomization and final fascial closure: type of bleeding, indication of additional treatment required to assure durability of hemostasis, and indication of any re-treatment due to application error (all d)	G2
1.3.6	Operative data: Additional treatments – FAS	Reason for any additional treatment used at the TBS (d), time from randomization to re-bleed (c), and treatments applied (d); for patients re-treated with EVARREST, approximate length and width of EVARREST used (cm) (both c)	G2
1.3.7	Operative data timings and other durations – FAS	Time in operating room (min), length of procedure (from first incision to last suture/staple) (min), length of procedure measured as time from first incision to initiation of fascial closure (when applicable) (min), time from screening visit to hospital admission (days), time from baseline visit to hospital admission (days), time from screening visit to surgery (days), time from baseline visit to surgery, and time from surgery to 30-day visit (days) (all c); For liver resections patients: time from start of liver resection to last suture/staple (min) and time from start of liver resection to initiation of final fascial closure (when applicable) (min) (both c)	G2
2	Effectiveness data		
2.1	Primary endpoint: Absolute time to hemostasis, elapsed from randomization	Includes analysis by treatment group and pediatric group, as well as by treatment group and age group; Includes analysis separately for subjects who achieved hemostasis with and without additional randomized treatments being required; Includes 95% CIs for median absolute time to hemostasis, reported separately for EVARREST and Control groups	
2.1.1	Primary effectiveness analysis: Absolute time to hemostasis, elapsed from randomization – FAS	Continuous data	G2
2.1.2	Primary effectiveness analysis: Absolute time to hemostasis, elapsed from randomization – PP set (supportive analysis)	Continuous data	G2
2.2	Secondary effectiveness endpoints		

No	Title of table/figure	Notes	Shell[1]
2.2.1	Hemostasis at 4 minutes following randomization and no bleeding requiring treatment at the TBS occurs any time prior to final fascial closure – FAS	Discrete data Includes 95% CI for proportion of subjects with hemostasis at 4 minutes separately for each group, as well as 95% CI for the ratio of proportions	G2
2.2.2	Hemostasis at 10 minutes following randomization and no bleeding requiring treatment at the TBS occurs any time prior to final fascial closure – FAS	Discrete data Includes 95% CI for proportion of subjects with hemostasis at 10 minutes separately for each group, as well as 95% CI for the ratio of proportions	G2
2.2.3	Proportion of subjects with no re-bleeding at the TBS – FAS	Discrete data	G2
2.3	Follow-up assessments		
2.4	Post-surgery to hospital discharge (within 72 hours prior to discharge) and 30-day (±14 days) follow-up assessments – FAS	Indication of re-hospitalizations since hospital discharge, indication of surgical procedures since hospital discharge, indication of transfusions since hospital discharge [all for 30-day (±14 days) visit only] (all d), indication of relevant changes in medical history since screening (d), presence of clinically significant changes to subject since baseline (d), subject presence in elevated care unit (ICU, step-down unit, etc.) (d), duration of subject presence in elevated care unit (ICU, step-down unit, etc.) (c), subject presence on ventilator post-operatively (d), duration of subject being on ventilator post-operatively (c), length of subject hospital stay from admission to discharge (days) (c), and length of subject hospital stay from procedure to hospital discharge (days) (c)	G2
3	Safety data		
3.1	Adverse Events		
3.1.1	Number of subjects experiencing any during/post treatment AE by category – Safety analysis set		AS
3.1.2	Adverse events (during/post treatment) by subject, MedDRA preferred term and system organ class – Safety analysis set		AM
3.1.3	Summary of during/post treatment adverse events by subject and coded terms, preferred terms occurring in >=5% of subjects – Safety analysis set		AM

No	Title of table/figure	Notes	Shell[1]
3.1.4	Summary of during/post treatment serious adverse events by subject and coded terms – Safety analysis set	Includes adverse events for which the answer for CRF question "Serious?" in the CRF is "Yes"	AM
3.1.5	Summary of during/post treatment surgical procedure related (possibly, definitely) adverse events by subject and coded terms – Safety analysis set	Includes adverse events for which the answer for CRF item "Relationship to surgical procedure" is "Possibly related" or "Related".	AM
3.1.6	Summary of during/post treatment study treatment related (possibly, definitely) adverse events by patient and coded terms – Safety analysis set	Includes adverse events for which the answer for CRF item "Relationship to study treatment" is "Possibly related" or "Related".	AM
3.2	Laboratory data	Reported in SI units	
3.2.1	Laboratory data: Full Blood Count - Safety analysis set	At screening, at baseline, and post-surgery to hospital discharge - within 72 hours prior to discharge)	L
3.2.2	Laboratory data: White Blood Cell Differential - Safety analysis set	At screening, at baseline, and post-surgery to hospital discharge - within 72 hours prior to discharge)	L
3.2.3	Laboratory data: Coagulation Parameters - Safety analysis set	At screening, at baseline, and post-surgery to hospital discharge - within 72 hours prior to discharge)	L
3.3	Other safety data		
3.3	Safety/secondary endpoints – Safety analysis set	Proportion of subjects with adverse events that are potentially related to bleeding at the TBS, proportion of subjects with adverse events that are potentially related to thrombotic events, proportion of subjects with re-treatment at the TBS (all d), estimated intra-operative blood loss (mL) (c), and volume of blood and blood products transfusions (red blood cells, whole blood, fresh frozen plasma, platelets, and cryoprecipitates), intra-operatively, prior to hospital discharge, and after discharge (all c)	G2

Note: '–' indicates a new line in the title.

10.3 Listings

Listings will be presented in centre, subject and visit order. The listings will be produced using the data from all subjects.

The columns indicate the listings that will be included in the report. All data available on the database, with the exception of fields used for administration, e.g. signature fields, will be included in the listing for the report.

Missing data will be shown by a space.

10.3.1 Appendix 16.2 listings:

All listings will be prefixed with 16.2.

No	Title of listing	Notes	CRF Page
1	Disposition of subjects		
1.1	Disposition of subjects	Includes reason for withdrawal and time to withdrawal	47
1.2	Visit dates	Includes informed consent and discharge details Includes derived data: -Nights in hospital -Days from procedure	Various
2	Protocol deviations		
2	Protocol deviations		45 and 46
3	Subjects excluded from the analysis		
3	Definition of analysis sets	As defined in Section 5 of this SAP	
4	Baseline characteristics		
4.1	Demographics, pregnancy test, and subject eligibility		3, 7, 11, and 13
4.2	Physical exam / medical / surgical history		8, 9, 10, 26, and 27
4.3	Inclusion and exclusion criteria		2, 5, and 6
4.4	Concomitant medications	Derived data: -Days from procedure to start -Duration of Con Med	37 and 38
5	Surgical details		
5.1	Surgical procedure – timings	Includes derived data: time in operating room, length of procedure (from first incision to last suture/staple), length of procedure measured as time from first incision to initiation of fascial closure (when applicable), time from screening visit to hospital admission, time from baseline visit to hospital admission, time from screening visit to surgery, time from baseline visit to surgery, and time from surgery to 30-day visit; for liver resections patients: time from start of liver resection to last suture/staple and time from start of liver resection to initiation of final fascial closure (when applicable)	3, 4, 11, 12, 13, 14, 17, 28, and 30
5.2	Operative data - Surgery details, transfusions, and randomization		17, 18, and 22
5.3	Operative data - Target Bleeding Site (TBS) identification		19, 20, and 21
5.4	Operative data - Treatment application		22 and 23

No	Title of listing	Notes	CRF Page
5.5	Operative data - Hemostasis assessments		24
5.6	Operative data - Bleeding/durability details		24
5.7	Operative data - Additional treatments		25
6	Effectiveness data		
6.1	Effectiveness - primary effectiveness endpoint		
6.1	Primary effectiveness endpoint - absolute time to hemostasis, elapsed from randomization - FAS and PP set		
6.2	Effectiveness – secondary endpoints		
6.2	Secondary endpoints - hemostasis at 4 and 10 minutes following randomization and no bleeding requiring treatment at the TBS occurs any time prior to final fascial closure, and indication of no re-bleeding at the TBS		
6.3	Follow-up assessments		
6.3.1	Length of hospital stay	Includes derived data: -Days from admission to discharge -Days from procedure to discharge	3
6.3.2	Post-surgery to hospital discharge (within 72 hours prior to discharge) and 30-day (±14 days) follow-up assessments		3, 4, 11, 12, 13, 14, 28, 29, 30, and 31
7	Safety data		
7.1	Adverse event listings (each subject)		
7.1.1	Adverse events	Includes derived data: -Days from procedure to start -Duration of AE	34, 35, and 36
7.1.2	Adverse event comments		35
7.1.3	Adverse events (MedDRA codes)		34, 35, and 36
7.1.4	Serious adverse events		34, 35, and 36
7.2	Laboratory data		
7.2.1	Laboratory data - Full Blood Count	At screening, at baseline, and post-surgery to hospital discharge - within 72 hours prior to discharge)	32
7.2.2	Laboratory data - White Blood Cell Differential	At screening, at baseline, and post-surgery to hospital discharge - within 72 hours prior to discharge)	32

No	Title of listing	Notes	CRF Page
7.2.3	Laboratory data – Coagulation Parameters	At screening, at baseline, and post-surgery to hospital discharge - within 72 hours prior to discharge)	33
7.3	Other safety data		
7.3	Safety/secondary endpoints	Includes derived data: -Proportion of subjects with adverse events that are potentially related to bleeding at the TBS -Proportion of subjects with adverse events that are potentially related to thrombotic events -Proportion of subjects with re-treatment at the TBS -Estimated intra-operative blood loss -Volume of blood and blood products transfusions (red blood cells, whole blood, fresh frozen plasma, platelets, and cryoprecipitates), intra-operatively, prior to hospital discharge, and after discharge	17, 18, 25, 29, 31, 35, 36, 41, and 42

10.3.2 Data review

Listings will be available for regular listing reviews to be organized by Data Management.

11. REFERENCES

1 ICH harmonised tripartite guideline - Statistical principles for clinical trials (E9) – Step 4, 05 Feb 1998.

2 ICH harmonised tripartite guideline - Structure and contents of clinical study reports (E3) – Step 4, 30 Nov 1995.

APPENDIX 1: TABLE TEMPLATES (SEE ATTACHED DOCUMENT)