CONFIDENTIAL STATISTICAL ANALYSIS PLAN

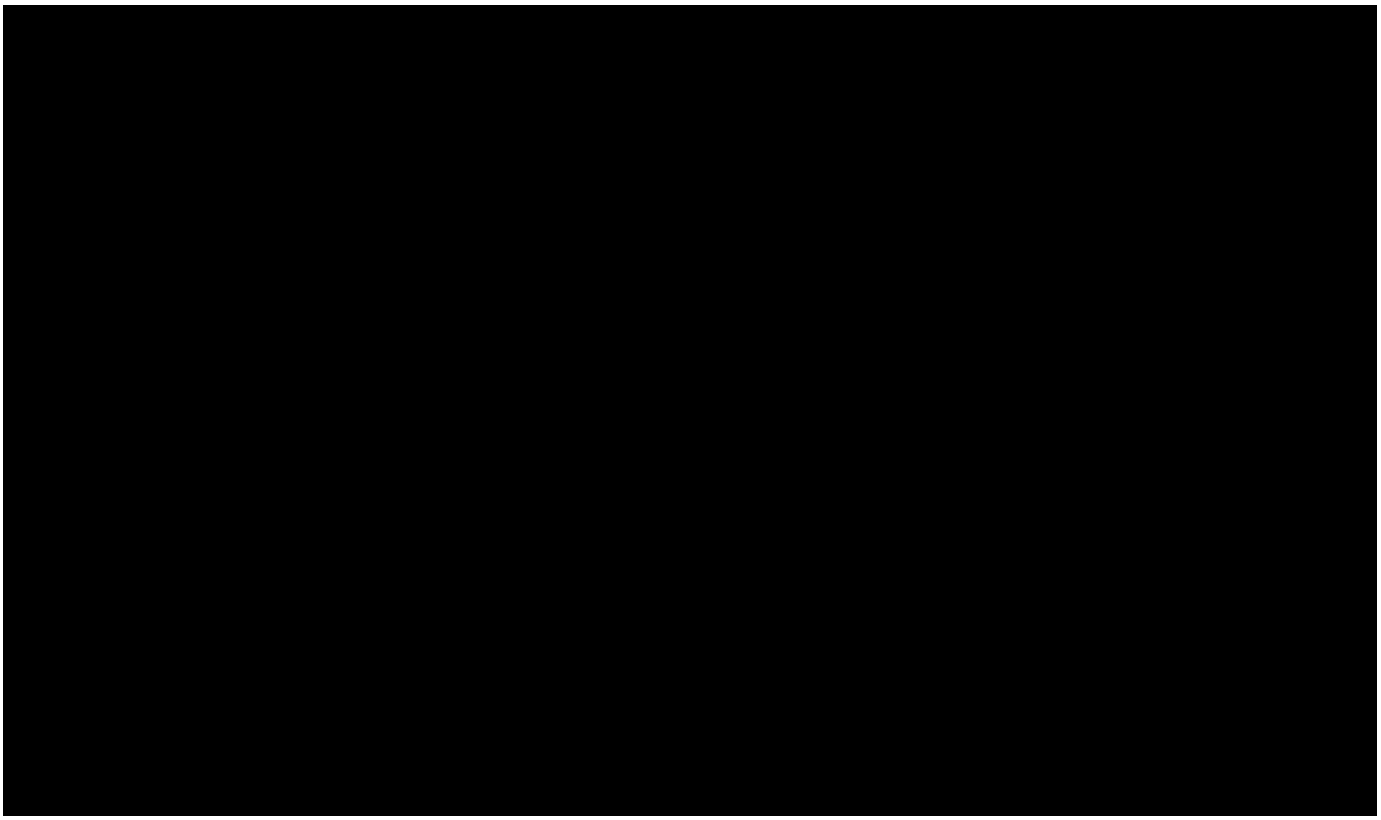
A Prospective, Randomized, Controlled Study Evaluating EVICEL® Fibrin Sealant as an Adjunct to Hemostasis During Abdominal, Retroperitoneal, Pelvic or Thoracic (Non-Cardiac) Surgery in Pediatric Patients

Version: AMENDMENT 1 Date: July 1, 2019

Protocol Number: 400-12-006 (Amendment 4, dated January 8, 2018)

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.



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CHANGES MADE FROM FINAL VERSION

In section 2, Study Design, the following text was removed: "Enrolment will be staggered by age. The first group enrolled will include subjects ≥1 years to <18 years of age and the subsequent group will include subjects from birth (including pre-term neonates born ≤37 weeks gestation) to <1 years of age. Ongoing safety assessment will ensure adequate safety monitoring occur during the staged enrolment". The change was made because study protocol (Amendment 4) removed the staged enrolment requirement.

1. STUDY OBJECTIVES

The objective of this study is to evaluate the safety and effectiveness of the EVICEL® (EVICEL) Fibrin Sealant (Human) as an adjunct to achieve hemostasis during surgery in pediatric patients.

2. STUDY DESIGN

This is a multi-centre, prospective, randomized, controlled, study in paediatric patients evaluating the safety and hemostatic effectiveness of EVICEL compared with SURGICEL® (SURGICEL) to control mild or moderate soft tissue bleeding or parenchymal organ bleeding during abdominal, pelvic, retroperitoneal or thoracic (non-cardiac) surgery for which standard methods of achieving haemostasis are ineffective or impractical.

At least 40 eligible pediatric subjects with an appropriate Target Bleeding Site (TBS), recruited from study centers within The European Union and Canada, will be randomized in a 1:1 allocation ratio to either EVICEL or SURGICEL treatment. Hemostasis will be assessed at 4, 7 and 10 minutes from randomization.

For this study, the TBS will be defined as the first actively bleeding site identified during the soft tissue or parenchymal organ dissection related to the primary operative procedure with challenging mild to moderate bleeding, where conventional methods of control (i.e. suture, ligature, cautery) have been deemed ineffective or impractical, and require an alternative method to achieve hemostasis. The randomly assigned treatment (EVICEL or SURGICEL) will be applied immediately at the actively bleeding TBS.

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 EVICEL 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. EVICEL 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 soft tissue or parenchymal organ TBS related to the primary operative procedure, randomization should immediately take place.

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

3. STUDY ENDPOINTS

The primary effectiveness endpoint is the absolute time to hemostasis (elapsed from randomization), defined as the absolute time when there is no detectable bleeding at the Target Bleeding Site (TBS).

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

- Haemostasis at 4, 7 and 10 minutes following randomization;
- Incidence of treatment failures (defined as haemostasis not achieved within 10 minutes or bleeding at the TBS during the ten-minute observational period that requires further hemostatic measures, other than re-application of the assigned hemostatic adjunct);
- Incidence of adverse events (including thrombotic events and events associated with TBS re-bleeding);
- Proportion of subjects with no re-bleeding;
- Haemoglobin, Haematocrit, 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);
- The Per-Protocol (PP) analysis set (Evaluable set) consists of all FAS subjects who have no major protocol deviations;
- The Safety analysis set consists of all subjects who received treatment.

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.

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 confirmatory.

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 closure completion);
- Procedure duration from first incision to initiation of final fascial closure (when applicable);
- Specification of treatment to which subject is randomized;
- TBS length, width, area, and location, type of bleeding, and TBS tissue or parenchymal organ type;

- 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;
- Surgical approach;
- For patients treated with EVICEL, approximate amount of EVICEL used (up to 10 minutes following randomization), number of EVICEL kits used, quantity per kit; in addition, for all EVICEL kit used - type of tip, method of application, and size of kit;
- For patients treated with SURGICEL, number of kits used, indication of SURGICEL use according to IFU, approximated SURGICEL length and width used at the TBS, and SURGICEL area applied;
- Hemostasis assessment data, such as time from randomization to initial application of randomized hemostatic product, TBS hemostasis presence at 4, 7, and 10 minutes from randomization, absolute time to hemostasis (from randomization), and presence of any bleeding at TBS between 4 and 10 minutes following randomization;
- Bleeding/durability data, such as indication of any additional treatment use at the TBS, indication of any rebleeding, and, for all rebleeds - treatment used for rebleed;
- 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, and time from baseline visit to surgery.

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® (Version 9.1 (EG) or later).

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 the absolute time to hemostasis (elapsed from randomization), defined as the absolute time when there is no detectable bleeding at the Target Bleeding Site (TBS).

The primary effectiveness endpoint will be summarized descriptively by treatment group. The primary endpoint will also be summarized descriptively by treatment group and age group [Neonates (birth to 30 days), Infants and toddlers (31 days to <24 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 EVICEL and control groups.

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:

- Haemostasis at 4 minutes following randomization;
- Haemostasis at 7 minutes following randomization;
- Haemostasis at 10 minutes following randomization;
- Incidence of treatment failures (defined as haemostasis not achieved within 10 minutes or bleeding at the TBS during the ten-minute observational period that requires further hemostatic measures, other than re-application of the assigned hemostatic adjunct).

Two-sided 95% CIs for the proportions of subjects with hemostasis at 4 minutes, 7 minutes, and 10 minutes, will be constructed for each treatment group separately (P_E for EVICEL 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 EVICEL 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 and surgical procedures 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:

- Incidence of treatment failures (defined as haemostasis not achieved within 10 minutes or bleeding at the TBS during the ten-minute observational period that requires further hemostatic measures, other than re-application of the assigned hemostatic adjunct);
- Incidence of subjects with adverse events;
- Incidence of subjects with thrombotic events;
- Incidence of subjects with events associated with TBS re-bleeding;
- Proportion of subjects with no re-bleeding;
- Haemoglobin, Haematocrit, 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, 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/secondary 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: **EVICEL** 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 14.1.3.1-14.1.3.9
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
1.1.2	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 and randomization – FAS	Primary operative procedure, primary method to obtain hemostasis at the TBS (prior to randomization), surgical approach, treatment to which subject is randomized (all d)	G2
1.3.2	Operative data: Target Bleeding Site (TBS) identification – FAS	TBS length (cm), width (cm), area (cm^2) (all c), and location (d), type of bleeding (d), TBS tissue or parenchymal organ type (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
1.3.3	Operative data: EVICEL application – FAS	For patients treated with EVICEL: approximate amount of EVICEL used (up to 10 minutes following randomization) (mL) (c), total number of EVICEL kits used (both c and d), and quantity per kit (mL) (c)	G2
1.3.4	Operative data: SURGICEL application – FAS	For patients treated with SURGICEL: number of kits used (both c and d), indication of SURGICEL use according to IFU (d), approximated SURGICEL length and width (cm) used at the TBS (c), and SURGICEL area applied (cm^2) (c)	G2
1.3.5	Operative data: EVICEL application summary – FAS	For all EVICEL kits used: type of tip, method of application, and size of kit used (all d)	G2

[1] Shell: Example table from Appendix 1 (Shell tables). Letters refer to standard output, numbers to project specific output.
[2] For Tables G1, G2, G3 notes will indicate if data is continuous or discrete.

No	Title of table/figure	Notes	Shell[1]
1.3.6	Operative data: Hemostasis assessments – FAS	Time from randomization to initial application of randomized hemostatic product (sec) (c), TBS hemostasis presence at 4, 7, and 10 minutes from randomization (d), absolute time to hemostasis (from randomization) (sec) (c), and presence of any bleeding at TBS between 4 and 10 minutes following randomization (d)	G2
1.3.7	Operative data: Bleeding/durability details – FAS	Indication of any additional treatment use at the TBS (d) and indication of any rebleeding (d)	G2
1.3.8	Operative data: Treatments for re-bleeding – FAS	For all rebleeds - treatment used for re-bleeding (d)	G2
1.3.9	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), and time from baseline visit to surgery (days) (all c)	G2
2	Effectiveness data		
2.1	Primary endpoint: Absolute time to hemostasis, elapsed from randomization	Includes analysis by age group; Includes 95% CIs for median absolute time to hemostasis, reported separately for EVICEL 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 (confirmatory analysis)	Continuous data	G2
2.2	Secondary effectiveness endpoints		
2.2.1	Haemostasis at 4 minutes following randomization – 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	Haemostasis at 7 minutes following randomization – FAS	Discrete data Includes 95% CI for proportion of subjects with hemostasis at 7 minutes separately for each group, as well as 95% CI for the ratio of proportions	G2
2.2.3	Haemostasis at 10 minutes following randomization – 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

No	Title of table/figure	Notes	Shell[1]
2.2.4	Incidence of treatment failures (defined as haemostasis not achieved within 10 minutes or bleeding at the TBS during the ten-minute observational period that requires further hemostatic measures, other than re-application of the assigned hemostatic adjunct) – FAS	Discrete data	G2
2.3	Follow-up assessments		
2.3	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 (d), indication of surgical procedures since hospital discharge [both for 30-day (±14 days) visit only] (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
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

No	Title of table/figure	Notes	Shell[1]
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	Incidence of treatment failures (defined as haemostasis not achieved within 10 minutes or bleeding at the TBS during the ten-minute observational period that requires further hemostatic measures, other than re-application of the assigned hemostatic adjunct), incidence of subjects with thrombotic events, incidence of subjects with events associated with TBS re-bleeding, proportion of subjects with no re-bleeding (all d), estimated intra-operative blood loss (mL) (c), and volume of blood and blood products transfusions (red blood cells, 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	55
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		51 and 53
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		1 and 6
4.2	Physical exam / medical / surgical history		8, 10, and 12
4.3	Inclusion and exclusion criteria		4
4.4	Concomitant medications	Derived data: -Days from procedure to start -Duration of Con Med	47 and 49
5	Surgical details		
5.1	Surgical procedure – timings, including operation room, procedure duration (from first incision to closure completion), procedure duration from first incision to initiation of final fascial closure, time from screening visit to hospital admission, time from baseline visit to hospital admission, time from screening visit to surgery, and time from baseline visit to surgery, and primary operative procedure	Includes derived data (timings)	1 and 14
5.2	Operative data - Target Bleeding Site (TBS) identification, blood and blood product use, hemostasis method, surgical approach, and randomization data		16 and 19
5.3	Operative data - EVICEL application		19
5.4	Operative data - SURGICEL application		19
5.5	Operative data - EVICEL application summary		19 and 20

No	Title of listing	Notes	CRF Page
5.6	Operative data - Hemostasis assessments		23
5.7	Operative data - Bleeding/durability details		25
5.8	Operative data - Treatments for re-bleeding		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 - haemostasis at 4, 7, and 10 minutes following randomization, and incidence of treatment failures (defined as haemostasis not achieved within 10 minutes or bleeding at the TBS during the ten-minute observational period that requires further hemostatic measures, other than re-application of the assigned hemostatic adjunct)		
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	1
6.3.2	Post-surgery to hospital discharge (within 72 hours prior to discharge) and 30-day (±14 days) follow-up assessments		1, 27, 29, 35, and 37
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	41, 43 and 44
7.1.2	Adverse event comments		43
7.1.3	Adverse events (MedDRA codes)		41, 43 and 44
7.1.4	Serious adverse events		41, 43 and 44
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)	39

No	Title of listing	Notes	CRF Page
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)	39
7.2.3	Laboratory data – Coagulation Parameters	At screening, at baseline, and post-surgery to hospital discharge - within 72 hours prior to discharge)	39
7.3	Other safety data		
7.3	Safety/secondary endpoints	Includes derived data: -Incidence of treatment failures (defined as haemostasis not achieved within 10 minutes or bleeding at the TBS during the ten-minute observational period that requires further hemostatic measures, other than re-application of the assigned hemostatic adjunct) -Incidence of subjects with thrombotic events -Incidence of subjects with events associated with TBS re-bleeding -Proportion of subjects with no re-bleeding -Estimated intra-operative blood loss -Volume of blood and blood products transfusions (red blood cells, fresh frozen plasma, platelets, and cryoprecipitates), intra-operatively, prior to hospital discharge, and after discharge	16, 19, 20, 23, 25, 31, 33, 43, and 44

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)