Study Title:

A Phase I/II, randomized, prospective, controlled, multi-center, open-label, two-arm study evaluating the safety and preliminary efficacy of sFilm-FS in controlling liver bleeding during elective surgery

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INDEX

1 ABBREVIATIONS

AE	Adverse Event
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
BIL	Bilirubin
BUN	Blood Urea Nitrogen
CRA	Clinical Research Associate
CRO	Contract Research Organization
CRP	C-reactive Protein
(N)CS	(Not) Clinically significant
DSMB	Data Safety Monitoring Board
eCRF	Electronic Case Report Form
ESR	Erythrocyte Sedimentation Rate
FAS	Full-analysis set
GCP	Good Clinical Practice
Hb	Hemoglobin
HC	Hematocrit
HD	Hospital Discharge
ICH	International Conference on Harmonization
ICU	Intensive Care Unit
IEC	Independent Ethics Committee
IMP	Investigational medicinal Product
INR	International Normalized Ratio
IRB	Institutional Review Board
ITT	Intention-to-treat
ICU	Intensive Care Unit
LDH	Lactate Dehydrogenase

LOS	Length of Stay
MCH	Mean Cell Hemoglobin
MCHC	Mean Cell Hemoglobin Concentration
MCV	Mean Corpuscular Volume
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
OR	Operating Room
PD	Protocol Deviation
PLT	Platelets
PM	Project Manager
PPS	Per-Protocol Set
PT	Preferred Term
RBC	Red Blood Cells
SAE	Serious Adverse Event
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase
SOC	System Organ Class
TBS	Target Bleeding Site
TEAE	Treatment-emergent Adverse Event
TEG	Thrombelastography
TTHP	Time to Hemostasis from First Product Application
TTHR	Time to Hemostasis from Patient Randomization
WBC	White Blood Cells
WHO	World Health Organization

2 GENERAL

This statistical analysis plan (SAP) describes the statistical methods to be used during the analysis and reporting of data collected under Sealantiun Medical Ltd Study Protocol HEM-01-17 version 5.0 dated 8th July 2021. This SAP should be read together with the Study Protocol, *annotated eCRF* (V 5.0), *Data Management Plan* (V 3.1) and *Data Monitoring Plan* (V 3.0).

This Statistical Analysis Plan will be finalized after the blind data review meeting before locking the study database.

In the Appendix 1 and Appendix 2 are reported shells for Listing and Tables, respectively.

3 STUDY DETAILS (AS PER STUDY PROTOCOL)

3.1 Study Design

This is a Phase I/II randomized, prospective, controlled, multi-center, open-label, two-arms study evaluating the safety and preliminary efficacy of sFilm-FS in controlling liver bleeding during elective surgery, when conventional methods of control are ineffective or impractical.

The surgical procedure was performed as per standard of care at the investigational site. A target bleeding site (TBS) was to be identified intra-operatively by the Investigator following transection of the hepatic parenchyma.

Target Bleeding Site (TBS) was defined as the first bleeding site in which conventional methods of bleeding control (i.e., suture, ligature, cautery) are ineffective or impractical. The TBS had to be a site where occlusion of the injured surface blood vessels is required to achieve hemostasis. It had to be possible to cover the TBS adequately, with an appropriate overlap, using a single unit of product (sFilm-FS or TACHOSIL®). This excluded bleeding from large defects in large arteries or veins requiring repair.

The TBS was the only site or region to be evaluated for hemostasis in this clinical study. If additional bleeding sites/regions requiring a topical hemostatic product was identified after the treatment of the initial target bleeding site, these bleeding sites were to be treated with the same study medication according to the patient's randomization assignment, if clinically appropriate. These areas were not to be assessed for hemostasis, but information was collected.

Once the TBS was identified (intra-operatively), the Investigator had to immediately enroll and randomize the patient into one of the following treatment arms (according to Inclusion/exclusion criteria reported in the paragraphs 8.2 and 8.3 of the study protocol):

- **Group A** (investigational product): sFilm-FS was applied at the target bleeding site immediately after conventional methods of control were exhausted. The sFilm-FS had to adequately cover the entire target bleeding site. After application of sFilm-FS, the Investigator immediately applied manual compression continuously for at least 2 minutes. A surgical sponge had to be used to assist in providing adequate pressure. Hemostasis was assessed after carefully releasing the compression at the site. sFilm-FS was not to be removed once bleeding has stopped. A maximum of 4 units of sFilm-FS were to be used per patient.
- **Group B** (active comparator): TACHOSIL® was applied at the target bleeding site immediately after conventional methods of control have been exhausted. TACHOSIL® had to be applied as per the approved prescribing information, with a manual compression of at least 3 minutes. A maximum of 4 units of TACHOSIL® were to be used per patient.

Patients were randomized with a 1:1 allocation ratio to either sFilm-FS (investigational product) or TACHOSIL® (active-comparator).

Patients were then monitored for a total period of 6 months following surgery. Patients were evaluated at study site at Screening Visit (Visit 1, between Day -21 and Day -1), Visit 2 (1 day before surgery), Visit 3 (Day 0, the day of surgery), Visit 4 (daily assessments post-surgery until the day before hospital discharge), Visit 5 (assessments post-surgery, at the day of hospital discharge), Visit 6 (follow-up visit 1; at 30 ± 3 days post-surgery), Visit 7 (follow-up visit 2; at 60 ± 7 days post-surgery), Visit 8 (follow-up visit 3; at 120 ± 14 days post-surgery), and Visit 9 (follow-up visit 4; at 180 ± 14 days post-surgery). Monitoring of patients included a list of evaluations, including vital signs, physical examination, blood, and urine sampling, MRI assessment, evaluation of antibodies for Human Fibrinogen and Human Thrombin, recording of adverse events, transfusion requirements and concomitant medications, as indicated in the Schedule of Assessments (Table 1). Efficacy assessment were to be evaluated intra-operatively by evaluation of hemostasis before patient's surgical closure.

The study was monitored by an independent Data Safety Monitoring Board (DSMB – paragraph 7.4 of Study protocol). The DSMB had the responsibility for the review of data and identification of any potential safety issues throughout the study. If necessary, the DSMB suggested recommendations regarding protocol revisions, and recommended whether the study had to proceed on the basis of safety data considering established stopping rules (refer to paragraph 7.3.2 of Study Protocol).

Visit Type	**Screening**	**Baseline**	**Surgery**	**Post-Surgery to Hospital Discharge (HD)**	**Hospital Discharge (HD)**	**Follow-Up #1**	**Follow-Up #2**	**Follow-Up #3**	**Follow-Up #4**
Visit N.**	**1**	**2***	**3**	**4**	**5**	**6**	**7**	**8**	**9**
Study Day	**D-21 to D-1**	**D-1**	**D0**	**Daily from D1 to D-HD**	**D-HD**	**D30 (±3)**	**D60 (±7)**	**D120 (±14)**	**D180 (±14)**
Informed Consent collection	x								
Inclusion/Exclusion Criteria evaluation	x	x	x						
Demographics/Medical History	x								
Physical Examination	x	x			x	x	x	x	x
Vital signs[1]	x	x	x	x[11]	x	x	x	x	x
Pregnancy test[2]	x	x							
Blood hematology & biochemistry[3]	x	x	x	x[11]	x	x	x	x	x
Urine analysis[4]	x	x	x		x	x			x
Coagulation (PT, PTT, INR)	x	x	x		x	x			x
Serum sample collection[5]	x								
Antibodies testing[6]	x					x			x
MRI assessment[7]	x								x
Randomization			x						
Product application			x						
Operative/Surgical information collection[8]			x						
Intra-operative details collection[9]			x						
Determination of hemostasis at TBS[10]			x						
Use of other hemostatic measures			x						
Adverse Events			x	x	x	x	x	x	x
Transfusion requirements			x	x	x	x	x	x	x
Bleeding, thrombotic, and transfusion-related complications			x	x	x	x	x	x	x
Concomitant medications	x	x	x	x	x	x	x	x	x

Table 1: Study flow chart

[*] V2 to be skipped in case V1 is performed one day before surgery (D-1).

[**] All patients can request or be requested to be evaluated in an additional visit (i.e., in case of suspected adverse events).

[1] Vital signs will include blood pressure, heart rate, temperature, and respiratory rate.

[2] β-HCG urine pregnancy tests will be conducted in case of patients with childbearing potential.

[3] Blood hematology and biochemistry tests include: Hb, HC, MCH, MCHC, MCV, RBC, WBC, PLT, Fibrinogen, lactate, D-Dimer, AT, ESR, CRP, BUN, creatinine, uric acid, BIL, LDH, AST (SGOT), ALT (SGPT), Gamma-GT, Na, Ca, P, glucose, albumin, total protein.

[4] Urine analysis tests include: specific gravity, pH, glucose, protein, blood, ketones, microscopic examination.

[5] A serum sample will be collected and stored at -70°C for possible future viral safety testing.

[6] Measurement of levels of antibodies against Human Fibrinogen and Human Thrombin. For this purpose, a serum sample will be collected and stored at -70°C for testing at the end of the study.

[7]Additional MRI will be performed throughout the study if the investigator identifies signs and symptoms of unanticipated or unexpected persistent inflammatory response, or unexplained abdominal pain or other symptoms (for instance signs of adhesions, bowel obstruction, etc.).

[8]Operative/surgical information include OR time, procedure time, time from liver resection/incision to initiation of fascial closure, drain usage, estimated blood loss, cell salvage use, transfusion information (if applicable), length of stay (ICU and overall LOS).

[9] Intra-operative details include hepatic parenchyma classification type (normal or abnormal, steatotic, cirrhotic or other), Investigator description of the TBS (area, density, arterial/venous/mixed, intensity of flow), alternative methods used to achieve hemostasis (if applicable), estimated TBS treated area and total resected area, number of product units applied at the TBS and at other areas rather than the TBS, incidence of post-operative bile leaks requiring intervention, hepatic segment information (anatomic resection/non-anatomic resection).

[10]Patients will be monitored for absence of bleeding at 2, 3, 5, 7, and 10 minutes after product application and thereafter, before closing the site.

[11] Assessments to be taken daily from one day after surgery (D1) until hospital discharge (D-HD).

3.2 Study Objectives

The primary objective of this study is to evaluate the safety of sFilm-FS versus inactive comparator (TACHOSIL®) when used as adjunct to conventional hemostatic techniques during elective surgery in which liver bleeding is encountered.

The secondary objective of this study is to preliminarily evaluate the hemostatic efficacy of sFilm-FS in controlling liver bleeding during elective surgery.

3.3 Study Endpoints

3.3.1 Primary Endpoint

The primary endpoint of the study consists of multiple safety variables as a composite marker for the safety. Variables of the composite marker were assessed during all study periods: from randomization to end of follow-up. It includes evaluation of treatment emergent adverse events (TEAEs), particularly TEAEs related to bleeding at TBS, thrombotic events, transfusion-related complications, post-operative adhesions (MRI assessment). It also includes evaluation of vital signs, physical examination, urine analysis, blood/coagulation parameters profiles, antibodies against fibrinogen and thrombin, and signs of systemic inflammation.

Primary endpoint is considered as a composite endpoint, because it includes multiple explanatory variables that support safety and tolerability of study treatment on the efficacy claim.

3.3.2 Secondary Endpoints

The secondary endpoints of the study are:

- The proportion of patients achieving hemostasis at TBS: at 2 (for sFilm-FS product only) 3, 5, 7 or 10 minutes following first product application, without the occurrence of re-bleeding, starting from 10 minutes after product application and until the completion of surgical closure. Hemostasis at TBS is defined as: absence of bleeding without the occurrence of re-bleeding.
- The incidence of re-treatment (defined as one or more additional patch of sFilm-FS or TACHOSIL®) at the TBS at the different time points (2 for sFilm-FS only, 3, 5, 7, 10 minutes from first product application).
- The Time to Hemostasis from first product application (TTHP).
- The proportion of all patients that have achieved hemostasis 10 minutes after first product application and therefore did not need to convert to standard of care treatment at the end of these 10 minutes. This includes all patients that achieved hemostasis with a single patch application and patients that required additional patches.
- The incidence of treatment failure. Treatment failure is defined as follows:

1. in case the bleeding at TBS (or re-bleeding) is still observed after 10 minutes following first application of product
2. if hemostasis at TBS is achieved, but the Investigator decides that and additional treatment is required to ensure the durability of hemostasis
3. if there is a breakthrough bleeding requiring treatment other than the product, at any time

From treatment failures definition are excluded those re-bleeding arising from the target bleeding site after hemostasis has been reached, and that are caused by movement of patch from the wound (caused by the surgeon or any other possible external factor) or other external factors. These cases should be regarded as Adverse Events rather than treatment failures. See Sponsor MEMO "*Clarification on treatment failure vs AE*" (AE=adverse event) dated 12th April 2022.

- The incidence of transfusion requirements in the 6 months follow-up period.

3.3.3 Supportive/ additional Endpoint

- Time to Hemostasis from patient randomization (TTHR).

3.4 Sample Size Calculation

A sample size of 15 patients per arm was considered as sufficient for the planned descriptive analyses and 95% confidence intervals of efficacy. Dropped patients during the course of the study will be replaced.

3.5 Randomization

A master randomization has been prepared for an excess of patients respect to sample size (patients has been randomized) using the software R.

Considering that in the study are involved three (3) centers in a competitive enrolment, a dynamically assignment of one or more blocks per time at each centre will be performed.

4 STATISTICAL ANALYSIS SETS

4.1 Definition of Sets for Statistical Analysis

Safety Analysis Set (SAF)
The Safety Analysis Set will consist of all patients who received at least one dose of any study medication.
Full-Analysis Set (FAS1)
FAS is defined as all randomized patients who underwent surgery, received at least one dose of study treatment and having no major violations of inclusion and exclusion criteria. Patients will be analyzed according to the treatment randomized regardless of which treatment was actually received.
Full-Analysis Set (FAS2)
FAS2 is an extension of the FAS1 and is defined as all randomized patients who underwent surgery, received at least one dose of study treatment.
Per-protocol set (PPS)
All patients according to the FAS definition without important/ major protocol deviations as specified in sec. 4.2.

For application of the different analysis sets to the analyses to be performed see sec. 6.3.

4.2 Violations and Deviations

Protocol violations or deviations (PD) are any non-adherences to the procedures outlined in the study protocol and its referenced manuals and include, but are not limited to, late evidence of exclusion criteria, missed evaluations, incorrect timing of evaluations or dosing and intake of prohibited medication.

Important/ major protocol deviations or violations (IPD) are a subset of protocol deviations that may significantly impact the completeness, accuracy, and/or reliability of the study data or that may significantly affect a subject's rights, safety, or well-being. The study team (contract research associate (CRA) and project manager (PM)) in collaboration with the Sponsor will classify every PD as minor or major according to the classification provided in Monitoring Plan. The final Protocol Deviation Tracking Log will be available in the study archive. Additional PDs emerging from the edit checks and data cleaning process will be processed and evaluated in the same way.

During training and study monitoring, the Investigators and center personnel will be informed that no deviations from, or changes of, the protocol should be initiated without prior written IRB/IEC approval/favorable opinion of an appropriate amendment, except when necessary to eliminate immediate hazards to the subjects or when the change(s)

involves only logistical or administrative aspects of the trial (e.g., change of monitor(s), telephone number(s)).

Protocol Deviations will be classified (PD/IPD) by PM and Sponsor (in collaboration) and tracked in a Protocol Deviation Register.

Prior to the statistical analysis, all protocol deviations will be listed and assessed as major (or serious) or minor during a blind data review meeting (BDRM) prior to database lock. Each deviation will be discussed case by case with the Sponsor. A major violation may also be a combination of minor deviations.

5 DATA REVIEW

5.1 Data Handling and Transfer

The data from this study will be verified and cleaned by the Data Management group at CRO in accordance with the study handling manual and data clarification policies. The data will be provided to the statistician as SAS datasets. The preferred term and system organ classification (SOC) from the version of MedDRA dictionary used will be provided for all Adverse Events collected. The ATC (Anatomical Therapeutic Chemical) group and sub-group from the relevant version of the WHO-DRUG dictionary will be provided for all prior and concomitant medications.

5.2 Data Review Meeting

When the database will be considered clean by data management, a set of blinded listing will be produced and distributed to the study team for the final review. A meeting will be held to review any data values requiring investigation or correction and to confirm the doubt protocol deviations reported during the study monitoring. The target of this revision is to consolidate the population used for all analyses.

After data review meeting will be also decided exploratory analyses on sub-groups (single patch and more patches) because these analyses are conditioned, even though are only descriptive, by the size of sub-groups.

All actions and changes defined during data review meeting will be consolidated in a written report supporting any implementations or changes in the analyses as defined in the protocol.

Once all data issue has been resolved, study database will be locked and data listing will be produced.

6 STATISTICAL ANALYSIS METHOD

6.1 General Principles

In general, categorical data will be presented using counts and percentages, whilst

continuous variables will be presented using the mean, standard deviation, standard error of mean, median, minimum, maximum and number of patients. Minima and maxima will usually be reported to the same level of accuracy as the raw data; means, medians, will be presented to one further decimal place; standard deviations and standard errors will be presented to 2 decimal places more than the raw data. Percentages will be rounded to the nearest integer or with one decimal. In tabulations, denominators for calculation of percentages will be taken as the number of non-missing responses in the specified analysis population and treatment group unless otherwise stated. 95% Clopper-Pearson Confidence Intervals for the means or the percentages will be produced if appropriate to explain the results [1].

Table will display data for each treatment group and overall (=Total column).

All data recorded in the CRF will be listed and sorted by treatment groups, subject number and visits [See Appendix 1].

Considering that the study is designed as phase I/II, in which phase I concerns to the primary endpoint (Safety) and phase II concerns to the preliminary data on effectiveness of sFilm-FS, data will not be presented in the two distinct frames, phase I and phase II.

The probability level for all analyses will be set at 5% and appropriate 95% Confidence Intervals will be produced according to the nature of the variables and will be based on a valid case approach, if so [e.g. percentages will be based on the number of observations available at the specific time point and not based on the number of patients at the visit.

6.2 Software used for Statistical Analysis

Statistical calculations will be performed using the statistical package SAS® (Statistical Analysis System) version 9.4.

6.3 Study Population considered in the Statistical Analysis

The primary endpoint of the study and all safety endpoints will use the Safety Set SAF while efficacy endpoints will use the Full-Analysis Sets FAS1, FAS2 and PPS. As Disposition and baseline characteristics will be displayed for all patients (disposition table), SAF, FAS and PPS for further tables on baseline characteristics. Analyses populations will be determined in a (blinded) data review meeting.

6.4 Subpopulations considered in the Statistical Analysis

A stratified analyses using patients with one patch and patients using more patches may be done following recommendations from the BDRM.

6.5 Handling of Missing Values

In accordance with the Study Protocol, no substitution or specific approach for missing data will be applied.

6.6 Multiple Comparison/ Multiplicity

No correction for multiplicity will be implemented due to the explorative nature of the study. All results must be seen as fully explorative.

6.7 Multicentre Studies

Subgroup analyses or adjustments by center are not reasonable because of too few patients per site.

6.8 Baseline Values

Baseline values are the ones measured short before application of the Investigational medicinal product (IMP).

6.9 Patients Disposition

The number and percentage of patients screened, randomized and treated in the study will be presented, together with the patients who withdrew from the study prematurely prior to Month 6 (Visit 9). Number and percentage of patients included in each of the analysis populations will also be tabulated.

Table will also display this information for each center.

Reasons for early withdrawal will be tabulated with counts and percentages.

Data on informed consent and randomization, analysis set assignments as well as patients with major or minor protocol deviations will be listed. All data relating to study completion or withdrawal will also be listed.

6.10 Demographic and Baseline Characteristics

Summaries of screening data will be produced using SAF, FAS and PPS populations and will be presented by treatment groups and overall.

Data for parameters measured at screening that are also measured at subsequent time points (e.g. physical examination, concomitant medications, clinical-chemical tests) will not presented in this section. All screening and baseline data will be listed.

6.10.1 Demographic data

Summary statistics for age (years), height (cm), weight (kg) and BMI (kg/m²) at screening will be presented, together with frequency counts and percentages for race and gender.

6.10.2 Significant Medical History

The total number and percentage of patients reporting any significant medical history and the total number and percentage of patients reporting significant occurrences ongoing at screening will be presented. In addition as medical history will be coded along MedDRA version 25.1, the number of medical histories, number and percentage of patients

reporting an item of significant medical history will also be presented by System Organ Class (SOC) and Preferred term (PT).

6.11 Surgery, Hepatic Parenchyma Characteristics and Target Bleeding Site (TBS)

Summary of surgery technique and timing, as reported in the eCRF, will be listed and summarized by treatment group. Surgery duration (minutes), time of stay in operating room (minutes), time from liver resection/ incision to fascial closure (minutes), drain usage, estimated blood loss, whether patient is transfused or not, number and blood volume of transfusions used (mL) during surgery, cell salvage used, type of cell salvage, time in Intensive Care Unit (ICU) (hours) and overall length of ICU stay (days) will be presented with the appropriate descriptive statistics.

Concerning Hepatic Parenchyma, summary of data related to the clinical characteristics (hepatic parenchyma classification type) will be tabulated by treatment group.

Data related to TBS (description of TBS via area, density, type and intensity of flow, estimated and total resected TBS treated area (cm^2), number of product units applied at the TBS and at other areas, post-operative bile leaks requiring intervention (and if yes how many leaks), hepatic segment) will be presented with the appropriate descriptive statistics and 95% confidence limits of the treatment difference will be calculated where appropriate.

6.12 Safety Evaluation

As previously stated, Safety is the primary endpoint.

Safety could be a composite endpoint because include more than one variable:

- ✓ Adverse Events
- ✓ Thrombotic Events
- ✓ Transfusion-Related Complications
- ✓ MRI Assessment (post-operative adhesions)
- ✓ Signs of Systemic Inflammations
- ✓ Antibodies against Fibrinogen and Thrombin
- ✓ Physical Examination
- ✓ Vital Signs
- ✓ Blood and Coagulation Parameters
- ✓ Urine Analyses

All Safety data will be listed by patients and treatment groups at each collected time and tabulated with the appropriate descriptive statistics by treatment groups at each collected

time.

Considering that no hypothesis testing for difference between treatments groups concerning AEs related to bleeding at TBS and the other safety data was planned in the protocol, only 95% confidence limits on differences between treatments will be done.

Concerning safety data, an independent data review will be done by a medical reviewer before data review meeting and database lock. The medical reviewer will identify and classify all safety endpoints with respect to e.g. thrombotic events, transfusion complications, etc. and will check correctness of MeDDRA classification (PT, SOC). At the end of this review, medical reviewer will be produced a detailed report.

6.12.1 Transfusion requirements and transfusion related complications for patients transfused

Concerning transfusions, summary statistics for the number of patients received transfusion at each visit. The number of patients who received transfusions will be used as denominator for percentages calculations. Total number of transfusions and total number of units transfused over the whole study period (as a sum from surgery until EoS) will be produced by treatment. Reasons for transfusions (based on number of transfusion) will be presented by counts and percentages.

Number and percentage of patients with transfusion related complications will be summarized by treatment. Number and percentage of related complications by SOC and PT following the layout of adverse event tables (cf. next section) will be produced, too. Related complications are depicted from the adverse event page.

6.12.2 Adverse events and Serious Adverse events

All AE will be coded according to MeDDRA version 25.1.

Concerning Adverse Events (AE) a summary of treatment-emergent adverse events (TEAE), including the total number of events reported, the number and percentage of patients reporting at least one adverse event, the number and percentage of IMP-related adverse events, the number and percentage of patients withdrawing prematurely due to an adverse event, the number and percentage of patients with at least one serious adverse event (SAE), the number of non-fatal serious adverse events and the number and percentage of deaths, will be presented by treatment.

A further tabulation of TEAEs by SOC and PT, and TEAEs by SOC and PT broken down by relationship to study drug will be presented. Relationship to study drug is categorized as none, unlikely, possible, probable and highly probable as recorded on the CRF. A summary of TEAEs reported by SOC and PT, broken down by severity (mild, moderate, severe, life threatening), will also be provided. In addition IMP related adverse events, deaths and non-fatal serious adverse events will be tabulated.

A summary of TEAEs leading to premature withdrawal will be provided, grouped by body

system and preferred term.

All tabulations by SOC and PT will be replicated for all serious TEAEs.

All adverse events recorded on the CRF will be listed.

6.12.3 Thrombotic and TBS related Bleeding Events

Summary statistics of thrombotic events and TBS related bleeding events/ complications will be presented separately by SOC and PT according to adverse event table layout by treatment.

6.12.4 Post-operative Adhesions - MRI assessment

MRI will be evaluated at screening visit and after 180 days after surgery (visit 9). Moreover, additional MRIs will be performed if the Investigator identifies signs and symptoms of unanticipated or unexpected persistent inflammatory response that can cause in the post-surgery risks for intra-abdominal adhesion or bowel obstruction.

Number and percentage of patients showing signs and symptoms and number of patients having shown signs at least once over the study period will be summarized by visit.

Specification of signs and symptoms are documented in the adverse event page and analyzed in this section.

6.12.5 Vital Signs and Physical Examination

6.12.5.1 Vital Signs

Vital signs, including systolic (mmHg), diastolic blood pressure (mm Hg), heart rate (beats/min), respiratory rate (breath/min) and body temperature (°C), are measured at Screening, Baseline, Surgery, Post- Surgery, Hospital Discharge and Follow-up (after 30, 60, 120 and 180 days from Surgery). Summary statistics for each of these parameters will be presented by treatment group at each time point.

6.12.5.2 Physical Examination

Physical Examination (Eyes; Ears, Nose and Throat; Head and Neck; Cardiovascular; Lungs; Abdomen; Musculoskeletal; Lymph nodes; Skin; Urogenital System; mental State; Other) is measured at Screening, Baseline, Hospital Discharge and Follow-up (after 30, 60, 120 and 180 days from Surgery). For each body system counts and percentages for the clinically abnormality will be presented by treatment group at each time point. Shift tables will present changes in frequency of normal and abnormal values for each post-baseline value to baseline. Shift tables will differ between body systems.

6.12.6 Clinical Laboratory Data

Results for each parameter at each time point and treatment will be presented as listing, low (L) and high (H) values will be flagged in listings; in the listing will be reported the normal range of each parameter processed, too. The following table will be used for all laboratory parameters:

1. Summary statistics in terms of number and percentages for categorized parameters will be generated by time point and treatment.
2. In case of continuous measurements descriptive statistics will be presented by time point.
3. Normal, abnormal Not Clinically Significant (NCS) and abnormal Clinically Significant (CS) counts and frequency classifications will be tabulated for all parameters having recorded data about.
4. Shift tables will show changes in frequency of normal, abnormal NCS and abnormal CS values for any post-baseline value compared to Baseline.
5. All continuous parameters will show tables with absolute change from Baseline.

6.12.6.1 Hematology

Hematological data will be recorded at Screening, Baseline, Surgery, Hospital Discharge and Follow-up (after 30, 60, 120 and 180 days from Surgery): Red Blood Cells (RBC), Hematocrit, Hemoglobin, White Blood Cells (WBC), Mean Cellular Hemoglobin (MCH), Mean Cellular Hemoglobin Concentration (MCHC), Mean Cellular Volume (MCV), Erythrocyte Sedimentation Rate (ESR), Fibrinogen, Platelet Count.

Summary statistics as denoted under 2.-4. will be presented.

6.12.6.2 Biochemistry

Biochemistry data will be recorded at Screening, Baseline, Surgery, Hospital Discharge and Follow-up ((after 30, 60, 120 and 180 days from Surgery): Blood Urea Nitrogen (BUN), Creatinine, Glucose, Lactate Dehydrogenase (LDH), Total Proteins, Albumin, Total Bilirubin, Uric acid, Aspartate Transaminase (AST), Alanine Amino Transferase (ALT), Gamma Glutamyl Transferase (GGT), D-Dimer, C-Reactive Protein (CRP), Anti-thrombin and Lactate, Sodium, Calcium, Phosphorus.

Summary statistics as denoted under 2.-4. will be presented.

6.12.6.3 Coagulation

Coagulation data will be recorded at Screening, Baseline, Surgery, Hospital Discharge and Follow-up ((after 30 and 180 days from Surgery): Prothrombin Time (PT), Partial Prothrombin Time (PTT) and International Normalized Ratio (INR).

Summary statistics as denoted under 2.-4. will be presented.

6.12.6.4 Urine

Urine analysis data will be recorded at Screening, Baseline, Surgery, Hospital Discharge and Follow-up ((after 30 and 180 days from Surgery): pH, Specific Gravity, Glucose, Protein, Blood and Ketones.

Summary statistics as denoted under 1.-4. will be presented.

6.12.6.5 Pregnancy Test

Pregnancy test data will be listed.

6.12.6.6 Thrombelastography (TEG) Reaction Time

Date of TEG, reaction time (min) and maximum amplitude (mm) of TEG, will be summarized with descriptive statistics for patients having data available. Note that TEG was removed in protocol 5.0 of 08JUL2021.

6.12.6.7 Immunogenicity - Antibodies against Human Fibrinogen and Thrombin

Values below lower limit of quantitation will be left missing for analysis. As antibody tests can undergo a second testing in case of positive tests the reconfirmed value will be taken for analysis in case of discrepancies.

Number and percentage of patients having positive/ negative results at each visit and over all visits will be tabulated.

Data on Human Antibodies against Fibrinogen and Thrombin levels will be summarized by time point with descriptive statistics for positive results.

6.13 Efficacy Evaluation

As described in sec. 3.3 of the SAP, efficacy evaluation will be a secondary endpoint and refers to Phase II of the study.

Note: Considering that no hypothesis testing for difference between treatments groups was planned in the protocol, only 95% confidence intervals on differences between treatments will be presented and no p-values.

All secondary and the additional endpoint variables will be listed and summarized by treatment groups and at each time will be collected.

6.13.1 Proportion of Patients achieving Hemostasis at TBS

For each patients achievement of hemostasis at TBS (absence of bleeding) at 2 (for sFilm-FS product only), 3, 5, 7 or 10 minutes following first product application will be derived. No occurrence of re-bleeding starting from 10 minutes after product application and until the completion of surgical closure must happen.

This variable, as being a time-profile in the efficacy response, will be considered to suggest a superiority in the efficacy of study drug versus control treatment. Since this is an exploratory proof of concept study and no hypothesis of extent in the difference between treatment groups a priori has been defined, we estimate the differences in the proportion of patients achieving at each time points hemostasis at TBS by the calculation of the exact 95% confidence interval (Clopper-Pearson exact method, considering the sample size) at each time point. This measure gives also a precision of the difference between treatments observed.

Beside Clopper-Pearson confidence intervals number and percentage of patients achievement of hemostasis at TBS will be tabulated by time point. The tabulation will also differ between first application and re-applications.

6.13.2 Incidence of Re-Treatment

Incidence of re-treatment (defined as one or more additional patch of sFilm-FS or TACHOSIL®) at the TBS at the different time points (2 for sFilm-FS, 3, 5, 7, 10 minutes from first product application) will be tabulated with counts and percentages. Differences in incidences between treatment groups will be estimated by Clopper-Pearson 95% confidence intervals for each time point.

6.13.3 Time to Hemostasis from first Product Application (TTHP)

Time to Hemostasis from first product application (TTHP) (minutes) is defined as the difference between time point of first product application during surgery until time point of reaching hemostasis. Descriptive statistics for TTHP will be shown.

For time-to-event analysis of TTHP, an event is defined as reaching hemostasis. In case no hemostasis has been reached the patient will be censored at 10 minutes. That means that in case that further patches have to be applied the clock for determination of TTHP is

prolonged. Kaplan-Meier curves for TTHP for each treatment will be generated. Tabulations will include number and percentage of patients failed and censored, median time to hemostasis with 95% confidence limits, first and third percentile, minimum and maximum time, estimates for 2-minute, 3-minute, 5- minute, 7 minute and 10 minute TTHP hemostasis incidence. Hazard ratio including confidence interval for sFilm-FS versus Tachosil® will be tabulated. Note that to connect correct estimation of hemostasis incidences to the estimations delivered by the survival model, a survival probability denotes the non-occurrence probability of hemostasis.

6.13.4 Time to Hemostasis from Patient Randomization (TTHR)

Time to Hemostasis from patient randomization (TTHR) (minutes) will be collected and displayed with descriptive statistics. TTHR is defined as time from randomization until hemostasis (in case of event) or 10 minutes observation end in case of censoring. Kaplan-Meier curve will be used to estimate the median TTHR in each treatment group. KM parameters and analyses will be tabulated in an analogue manner like in sec. 6.13.3.

6.13.5 Percentage of all Patients who achieved Hemostasis at 10 Minutes after first Product Application

Number and percentage of all patients (patients that achieved hemostasis with a single patch application and patients that required additional patches) that have achieved hemostasis 10 minutes after first product application and therefore did not need to convert to standard of care treatment at the end of these 10 minutes will be tabulated.

Data will be presented with descriptive statistics and 95% confidence intervals of the difference between treatments.

A stratified analyses by one-patch applicants and more than one patch users may be done depending on the results of the BDRM using strata single patch users and additional patch users. In case it is decided to perform a stratified analysis a table will be added to show number/ percentages of patients with one patch and with >1 patches.

6.13.6 Incidence of Treatment Failure

Incidence of treatment failure is defined on treatment failure criteria according to section 11.1.3 of the protocol:

- in case the bleeding at TBS (or re-bleeding) is still observed after 10 minutes following first application of study product;
- if hemostasis at TBS is achieved, but the Investigator decides that an additional treatment is required to ensure the durability of hemostasis;
- if there is a breakthrough bleeding requiring treatment other than the study product, at any time

Data will be presented only with the appropriate descriptive statistics and exact Clopper Pearson 95% confidence interval of the difference between treatments

6.13.7 Incidence of Transfusion Requirements

The number of patients requiring transfusion during the 6 months follow up period will be determined.

Data will be presented only with the appropriate descriptive statistics and exact 95% Clopper-Pearson confidence interval of the difference between treatments.

6.14 Previous and Concomitant Medication

Tables will distinguish between previous and concomitant medication with respect to start of medication compared to time point of surgery/ patch insertion. All medication starting before reference time point (first product application) are previous, all starting at or after reference time point will be concomitant.

All medications reported in the CRF, categorized by medication group according to WHO DRUG Dictionary DDE enhanced [version 2022 DDE+HD], ATC1 and ATC4 level will be summarized displaying number of medications in the specific ATC1 and ATC4 class, as well as number and percentage of patients taking it within each ATC1 and ATC4 class.

The number and percentage of patients using at least one medication within each medication group will be presented by time point (previous/ concomitant) and treatment.

7 Extent of Exposure

A frequency table showing counts and percentages of patients having applied one patch, two patches, three patches etc. will be shown.

8 INTERIM STATISTICAL ANALYSIS

Not applicable.

9 Changes to the Analyses/ Endpoints

9.1 Changes to the Analyses

The definition of the analyses populations in the protocol was extended:

The ITT population was renamed to Full-analysis Set (FAS) to be in concordance to the ICH GCP E9 Statistical Guideline [2].

In the same Guideline it is explained that a Per-Protocol Set (PPS) is the one without major violations. A PPS was added.

As the efficacy results are fully explorative, all three analyses sets FAS1, FAS2 and PPS will be used without further distinguishing on which main conclusions will be drawn.

9.2 Changes to the Endpoints

Originally the endpoint TTHR was not planned to be analyzed according to protocol. However the sponsor still wants to see data about it and the analysis of this endpoint was added.

10 STATISTICAL REFERENCES

[1.]C.J.Clopper and E.S. Pearson (1934): *The use of confidence or fiducial limits illustrated in the case of the binomial*, Biometrika, vol. 26, pp. 404-413.

[2.]ICH Topic E 9 Statistical Principles for Clinical Trials NOTE FOR GUIDANCE ON STATISTICAL PRINCIPLES FOR CLINICAL TRIALS (September 1998) (CPMP/ICH/363/96), Step 5. https://www.ema.europa.eu/en/ich-e9-statistical-principles-clinical-trials

11 Appendices

11.1 Appendix 1: Mock listings

see separate document

11.2 Appendix 2: Mock tables

see separate document