"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."

Study Protocol No:	HEM-01-17
EudraCT No:	2018-000434-34
Clinical Phase:	Phase I / II
Protocol Version and Date:	5.0 dated 8th July, 2021
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Sponsor:	Sealantium Medical Ltd. Ha'Amal 11 St. Rosh Ha'Ayin, Israel

This clinical study will be conducted in accordance with the Sponsor's and Sintesi Research's Standard Operating Procedures (SOPs), current Good Clinical Practice (GCP), the provisions of ICH (International Conference on Harmonization), EU Directives (for sites based in the European Community) and Code of Federal Regulation (for sites based in the U.S.A.).

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Revision History & Summary of changes		
Version	**Description of change**	**Reason for change**
1.0 of 18/09/18	First issue	---
2.0 of 10/04/19	Various updates, clarifications, and alignments with regulatory requirements	IND Immediate Requests from FDA
3.0 of 19/05/21	Various updates & clarifications, modification of sample size, inclusion of U.S. site	Sponsor's Decision
5.0 of 08/07/21	Removal of TEG testing and related exclusion criteria Varius updated, clarifications, and alignments with regulatory requirements	Sponsor's Decision IND Immediate Requests from FDA

PROTOCOL SIGNATURE PAGE

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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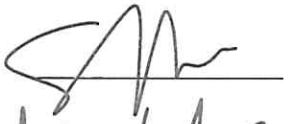
Signature: 

Date: 17/10/21

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INVESTIGATOR'S STATEMENT

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"**

1. Obtain Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approval of study protocol, Patient Informed Consent Form, any amendment(s) to the study protocol and yearly re-approval as required.
2. Obtain written informed consent from each participant or his/her legal representative, prior of the enrolment of the patient in the study, using the approved patient Informed Consent Form.
3. Conduct the study in strict accordance with this protocol, the Declaration of Helsinki, the current GCP guidelines, the laws and regulations of the countries involved in the Study, insurance requirements and will attempt to complete the study within the designated time.
4. Report any Serious Adverse Events to the Sponsor within 24 hours.
5. Keep the IRB/IEC informed of adverse events and report status of the study as required.
6. Keep records on all patients' information (eCRF, IP shipment and return forms and all other information collected throughout the study) according to the requirements specified in the Study agreement.
7. Assure access to patients' medical records to the Sponsor or to its designated representative(s).
8. Maintain confidentiality of all information received or developed in connection with this protocol.
9. Comply with EU Directives (for sites based in the European Community) and Code of Federal Regulation (for sites based in the U.S.A.) regarding the conduct of the trial, as applicable.

I have received and read the Investigator's Brochure for sFilm-FS, I have read the HEM-01-17 protocol and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

Principal Investigator's Name: _____

Signature: _____

Date: _____

Institution: _____

1. STUDY SYNOPSIS

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
Study Code	HEM-01-17
EudraCT N.	2018-000434-34
Clinical Phase	Phase I / II
Study Objectives	The primary objective of this study is to evaluate the safety of sFilm-FS versus an active-comparator (TACHOSIL®) when used as adjunct to conventional hemostatic techniques during elective liver surgery. The secondary objective of this study is to preliminarily evaluate the hemostatic efficacy of sFilm-FS in controlling liver bleeding during elective surgery.
Study Design	This is a 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. Patients will be randomized with a 1:1 allocation ratio to either sFilm-FS (investigational product) or TACHOSIL® (active-comparator). All patients will be followed post-operatively through discharge and up to 6 months post-surgery, following the Schedule of Assessments provided below. A Data Safety Monitoring Board (DSMB) will be established and have responsibility for the review of data and identification of any potential safety issues throughout the study. If necessary, the DSMB will make recommendations regarding protocol revisions and will recommend whether the study should proceed based on the safety data considering established stopping rules.
Study Procedure	The surgical procedure will be performed as per standard of care at the investigational site. A target bleeding site (TBS) will be identified intra-operatively by the Investigator when liver bleeding is encountered during surgery and conventional methods of bleeding control are ineffective. Target Bleeding Site (TBS) is defined as the first bleeding site in which conventional methods of bleeding control (i.e., suture, ligature, cautery) are ineffective or impractical. The TBS must be a site where occlusion of the injured surface blood vessels is required to achieve hemostasis. It must be possible to cover the TBS adequately, with an appropriate overlap, using a single unit of product (sFilm-FS or TACHOSIL®). This excludes bleeding from large defects in large arteries or veins requiring repair. Once the TBS has been identified, the Investigator will immediately enroll and randomize the patient into one of the following treatment arms, according to a pre-determined randomization scheme:

	• **Group A** (investigational product): sFilm-FS will be applied at the target bleeding site immediately after conventional methods of control have been exhausted. The sFilm-FS should cover adequately the entire TBS. Following application of sFilm-FS, the Investigator will immediately apply manual compression continuously for at least 2 minutes. A surgical sponge may be used to assist in providing adequate pressure. Hemostasis will be assessed after carefully releasing the compression at the site. sFilm-FS should not be removed once bleeding has stopped. A maximum of 4 units of sFilm-FS may be used per patient. • **Group B** (active comparator): TACHOSIL® will be applied at the target bleeding site immediately after conventional methods of control have been exhausted. TACHOSIL® should be applied as per the approved prescribing information, with manual compression for at least 3 minutes. A maximum of 4 units of TACHOSIL® may be used per patient. If additional bleeding sites/regions requiring a topical hemostatic product are identified after the treatment of the initial target bleeding site, these bleeding sites should be treated with the same study treatment according to the patient's randomization assignment, if clinically appropriate. These areas will not be assessed for hemostasis, but information will be recorded.
Investigational Product	sFilm-FS is a sterile bio-compatible bio-absorbable patch which consists of a polymeric film composed of a tri-block polymer (device component) containing Polyethylene Glycol (PEG) Poly-Caprolactone (PCL) and Poly-Lactide Acid (PLA), embedded with lyophilized powders of Human Fibrinogen, Human Thrombin (biological components) and calcium chloride. sFilm-FS is supplied ready to use in the patch size of 5 x 5 cm (~ 2 x 2 inch).
Comparator Product	TACHOSIL® is a fibrin sealant patch composed of an equine collagen patch coated with Human Fibrinogen and Human Thrombin. The product is ready for use and for the study it will be supplied in patch size of 4.8 x 4.8 cm (1.9 x 1.9 inch).
Study Population	Patients undergoing elective, open abdominal surgery in which liver bleeding is expected, with presence of an appropriate target bleeding site (TBS) identified intra-operatively by the Investigator. 30 completed patients are to be enrolled in this study.

Inclusion Criteria	1. Patients (males or females) aged ≥ 18 years old. 2. Patients requiring elective surgery in which liver bleeding will be encountered. 3. Hemoglobin ≥ 8.0 g/dL within 24 hours prior to surgical procedure. 4. Patients understanding the nature of the study and providing their informed consent prior to participation. 5. Patients willing to participate in the study and able to attend the visits and procedures foreseen by study protocol. <u>Intra-operative inclusion criteria</u>: 6. Patients with a target bleeding site (TBS) identified by the Investigator during surgery in which liver bleeding will be encountered.
Exclusion Criteria	1. Patients having undergone a therapeutic surgical procedure within 30 days from the study enrolment. 2. Patients with a severe coagulopathy defined as INR > 2.0. 3. Patients with platelet count <50,000 x109 PLT/L at the screening (ref. 11). 4. Patients admitted to trauma surgery. 5. Transplant patients due to fulminant hepatic failure. 6. Patients with known or suspected allergy or hypersensitivity to blood products or to one of the components of sFilm-FS or the active-comparator. 7. Patients with anesthesia risk judged to be higher than ASA3 by the Investigator. 8. Patients with at least one of the following concomitant conditions: severe co-morbid conditions known to pose a high risk for surgery and adequate recovery (i.e., liver cirrhosis with Child-Pugh score B or C, cholestasis, heart diseases), immunodeficiency diseases, blood clotting disorders, any conditions known to effect wound healing (i.e., collagen vascular disease), known or current alcohol or drug abusers. 9. Patients suffering from claustrophobia. 10. Patients with implanted or embedded metal objects, prostheses, pacemaker, or fragments in the head or body that would present a risk during the MRI scanning procedure or have worked with ferrous metals either as a vocation or hobby or following trauma (i.e., sheet metal workers, welders, or machinists) in such a way that might have led to unknown, indwelling metal fragments that could cause injury if they moved in response to placement in the magnetic field. 11. Patients being treated with at least one of the following treatments: antibiotic therapy for active infection, fibrin sealants, systemic steroids, or immunosuppressive agents. 12. Patients who are participating or have participated in other clinical studies within the 30 days before the study enrolment. 13. Female patients who are pregnant or breast-feeding or who wish to become pregnant during the period of the clinical study and for three months later. 14. Female patients of childbearing age (less than 24 months after the last menstrual cycle) who do not use adequate contraception. *

	Intra-operative exclusion criteria: 15. Patients identified with a TBS with major arterial bleeding requiring suture or mechanical ligation. 16. Patients identified by the Investigator to have intra-operative bleeding from large defects in large arteries or veins, requiring repair. 17. Patients identified by the Investigator to have intra-operative findings that may preclude conduct of study procedure. 18. Patients having an active local infection in the anatomic surgical area. 19. Patients with occurrence of major intra-operative complications that require resuscitation or deviation from the planned surgical procedure. 20. Patients with bleeding site in or near to foramina in bone. ** Adequate contraceptive methods may include any approved method of birth control such as combined estrogen and progestogen containing hormonal contraception, associated with inhibition of ovulation (oral, intravaginal, transdermal), progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable), intra-uterine devices, condoms, abstinence or vasectomized partner. Contraception should be maintained until study end.*
Primary Endpoint	The primary endpoint of the study is the evaluation of safety. Safety will be assessed from randomization of patients until the last follow-up visit and will include evaluation of treatment emergent adverse events. In particular, patients will be followed for AEs related to bleeding at TBS, thrombotic events, transfusion-related complications, post-operative adhesions (MRI assessment) as well as vital signs, physical examination, urine analysis, blood / coagulation parameters profiles, antibodies against fibrinogen and thrombin, and signs of systemic inflammation.
Secondary Endpoints	The secondary endpoints of the study are related to product hemostatic efficacy. For this purpose, hemostasis and treatment failure are defined. Hemostasis is defined as an absence/cessation of bleeding at the target bleeding site (TBS) according to the surgeon's judgement, so that the surgical closure of the field could be started. Treatment failure is defined as follows: - 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

Secondary Endpoints	Secondary endpoints include: • Proportion of patients achieving hemostasis at TBS at 2 (applicable only for sFilm-FS), 3, 5, 7 or 10 minutes following first product application, without the occurrence of re-bleeding, starting from10 minutes from first product application and until the completion of surgical closure. • Incidence of re-treatment (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). • Time to Hemostasis from first product application (TTHP). Time to Hemostasis from patient randomization (TTHR) will be collected as well but will not be used as endpoint. • Percentage of total 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. • Incidence of treatment failure based on pre-defined treatment failure criteria (see definition in Section 11.1.3 of the protocol). • Incidence of transfusion requirements in the 6 months follow up period.
Sample Size	The sample size will be of 30 patients completing the study. 15 patients will be included in the experimental treatment arm (Group A) and 15 patients in the active-comparator arm (Group B) to allow an adequate comparison between treatments. Dropped patients during the course of the study will be replaced.

Statistical Analysis	Data will be summarized with respect to demographic and baseline characteristics, efficacy and safety measurements. The statistical analysis will be performed on:
	• Patients' disposition;
	• Background and baseline characteristics;
	• Concomitant therapies;
	• Safety:
	  o adverse events
	  o vital signs
	  o physical examinations
	  o MRI assessment
	  o laboratory tests (including testing for antibodies)
	• Efficacy:
	  o hemostasis
	  o treatment failure
	  o re-treatment
	  o time to hemostasis

	Data will be summarized separately by treatment arm. Safety and efficacy analyses will be descriptive. Proportions of patients achieving hemostasis, experiencing treatment failure, and needing re-treatment will each be estimated along with 95% exact confidence intervals (CIs). Median time to hemostasis from first product application will be estimated using Kaplan-Meier methods.

2. SCHEDULE OF ASSESSMENTS

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

* 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. TABLE OF CONTENTS

4. ABBREVIATIONS

AE	Adverse Event
ALT	Alanine Aminotransferase
ASA	American Society of Anesthesiologists
AST	Aspartate Aminotransferase
AT	Anti-Thrombin
ATC	Anatomical Therapeutic Chemical
BIL	Bilirubin
BUN	Blood Urea Nitrogen
CA	Competent Authority
CRA	Clinical Research Associate
CRO	Contract Research Organization
CRP	C-reactive Protein
DSMB	Data Safety Monitoring Board
e-CRF	Electronic Case Report Form
ESR	Erythrocyte Sedimentation Rate
EU	European Union
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
Hb	Hemoglobin
HC	Hematocrit
HD	Hospital Discharge
ICH	International Conference on Harmonization
ICU	Intensive Care Unit
IEC	Independent Ethics Committee
INR	International Normalized Ratio
IP	Investigational Product
IRB	Institutional Review Board
ITT	Intention-to-treat
IU	International Unit
LDH	Lactate Dehydrogenase
LLT	Lowest Level Term
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
PCL	Poly-Caprolactone
PEG	Polyethylene Glycol
PhV	Pharmacovigilance

PLA	Poly-Lactide Acid
PLT	Platelets
QPPV	Qualified Person Responsible for Pharmacovigilance
RA	Regulatory Authority
RBC	Red Blood Cells
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase
SOP	Standard Operating Procedures
SUSAR	Suspected Unexpected Serious Adverse Reaction
TAH	Topical Absorbable Hemostats
TBS	Target Bleeding Site
TMF	Trial Master File
TTHP	Time to Hemostasis from First Product Application
TTHR	Time to Hemostasis from Patient Randomization
US	United States
U.S.A.	United States of America
WBC	White Blood Cells
WHO	World Health Organization

5. INTRODUCTION

The success of any surgical procedure is based on adequate hemostasis (ref. 1). Ineffective local hemostasis is the major cause of bleeding during surgery, but many other causes may be involved.

During surgery or in the surgical management of trauma, Investigators encounter bleeding from a variety of tissue types. The selection of appropriate methods or products for the control of bleeding is dependent upon many factors, which include but are not limited to bleeding severity, anatomical location of the source and the proximity of adjacent critical structures, whether the bleeding is from a discrete source or from a broader surface area, visibility and precise identification of the source and access to the source. Tissue type and fragility/friability, coagulation system status and patient stability are also factors for consideration.

Major bleeding can be controlled by standard surgical techniques, such as stitches, ligatures, or clips. Chemical, thermal, and mechanical procedures can be used during surgery to achieve hemostasis, especially when diffuse hemorrhages occur. Surgical tools such as electrocautery, argon beamer, or laser are often useful. However, sometimes these methods do not achieve satisfying results, generating medical consequences and related costs (ref. 2).

Many products have been developed as adjuncts to hemostasis in bleeding situations where traditional methods such as suture, clips or energy-based coagulation are ineffective or impractical (ref. 3). These products include topical absorbable hemostats (TAH) such as oxidized regenerated cellulose, gelatin in various forms with or without a topical thrombin solution, and collagen powder, as well as biologically active topical hemostatic products (topical thrombin solutions, fibrin sealants, fibrin patches, etc.) and a variety of synthetic topical sealants (ref. 4-7).

The products that can be used during surgery may be classified as topical hemostats, sealants, and adhesives (ref. 3). Hemostats can clot blood. Sealants can create sealing barriers. Adhesives bond tissue together. Collagen, gelatin, and cellulose are hemostatic agents.

The term “fibrin sealant” denotes a product containing coagulation factors, to be administered topically to produce a fibrin clot. Typical fibrin sealant products contain human fibrinogen, as a substrate of the clot and biologically active thrombin, which converts the fibrinogen to fibrin.

The intended benefit of the topical fibrin sealant application is to support local hemostasis, or “gluing” together of surfaces of injured tissues in order to obtain adaption or sealing of surfaces, to support sutures, or to improve repair and healing. Fibrin sealants have been used to support local hemostasis in surgical situations where tight tissue sealing is required, and the usage of other conventional surgical hemostatic means is not possible. Usage of this type of products is therefore particularly justified in surgical procedures involving parenchymal organs such as liver and lung, and/or where rapid reliable hemostasis is required.

Most TAH and fibrin sealant products are not as effective in the presence of active and/or brisk bleeding since the lack of sufficient adhesion strength allows forceful bleeding to simply “float” the products away from the bleeding tissue, prior to the achievement of full hemostasis. Fibrin sealants lack the mechanical strength needed to withstand the force of active hemorrhage and are not indicated for use in such settings. Investigators regularly encounter active and/or brisk bleeding for which traditional methods of control are ineffective or are impractical and for which currently available adjunctive products perform unsatisfactorily. In these instances, Investigators need to use a variety of methods and products, frequently sequentially, to control the bleeding. This can include prolonged surgical packing.

Fibrin patches are thought to be useful as hemostats in cases of active and/or brisk bleeding. The current approved fibrin patches include EVARREST® and TACHOSIL®. Both products are expensive. There is still a need for more cost- effective products or techniques to rapidly control active and/or brisk bleeding when treatment with conventional surgical techniques or conventional adjunctive hemostatic products is either ineffective or impractical.

Sealantium Medical Ltd. has developed a new product, sFilm-FS, aimed to help controlling of body fluid leakage in general surgery procedures, therefore proposing its use as an adjunct to hemostasis and/or sealing. sFilm-FS has been developed to help Investigators controlling hemorrhage and does not require a dry surgical surface for effective application. sFilm-FS is a cost-effective product as the quantities of fibrin sealant embedded into the product are minimal. sFilm is a transparent flexible product, therefore increasing its ease of use and allowing Investigators to see the target bleeding site through the application.

sFilm-FS is currently intended to be used as an adjunct to hemostasis in liver bleeding during elective surgery, when control of bleeding by standard surgical methods of hemostasis (such as suture, ligature, cautery) is ineffective or impractical.

5.1. Product Description

sFilm-FS is a sterile bio-compatible bio-absorbable patch which consists of a polymeric film composed of a tri-block polymer (device component) containing Polyethylene Glycol (PEG) Poly-Caprolactone (PCL) and Poly-Lactide Acid (PLA), embedded with lyophilized powders of Human Fibrinogen, Human Thrombin (biological components) and calcium chloride. The composition of sFilm-FS is presented in Table 1.

Table 1: sFilm-FS Composition

Component	Amount/Patch*	Function
Co-Polymer Film:		
Polyethylene Glycol (PEG) (mg)	66 ± 3.6	Backbone hydrophilic component
Poly-Caprolactone (PCL) (mg)	153.3 ± 8.4	Backbone hydrophobic component
Poly-Lactide acid (PLA) (mg)	5.7 ± 0.3	Backbone hydrophobic component
Indigo Blue (µg)	4.5 ± 2	Dye component
Coating:		
Human Fibrinogen (mg)	21.0 ± 0.5	Clotting component (substrate)
Human Thrombin (IU)	24.0 ± 0.5	Clotting component (enzyme)
$CaCl_2$ (mg)	1.2 ± 0.3	Cofactor

[1] Based on the weights of the components in the final patch; patch size 5 x 5 cm2

The polymeric film consists of a di-block polymer containing PEG and PLA, with the permutations to the polymer microstructure by addition of PCL to the synthesis mixture, which extends the degradation rate of the co-polymer. All the co-polymer components (PEG, PCL, and PLA) are used in approved implantable devices (CoSeal®, Monocryl®, Artelon®, Ligafix®, PREVADH®).

The lyophilized biological components (Human Fibrinogen and Human Thrombin) are licensed components (CSL Behring GmBH). The Human Fibrinogen is identical to the RiaSTAP product (STN # 125317/0, CSL Behring) used for treatment of acute bleeding in patients with congenital fibrinogen deficiency, afibrinogenemia and hypofibrinogenemia. The Human Thrombin component is approved for further manufacturing use (BLA FFMU STN #125357/0) and is being used in the manufacture of fibrin sealants. Human Fibrinogen and Human Thrombin components are equivalent to endogenous proteins, with well understood functional effect (ref. 8-10). These components are included in sFilm-FS in a relatively low amounts, compared to the amount of the same components used in EVARREST® or TACHOSIL® fibrin patches (see Table 2 below).

Table 2: Fibrin Sealants Components*

Product	Fibrinogen Amount* (mg/cm^2)	Thrombin Amount* (IU/cm^2)	App. Fib:Thr Ratio (mg : IU)
EVARREST®	8.6	37	1:4
TACHOSIL®	5.5	2.0	2:1
sFilm-FS	0.84	0.96	1:1

* Refers to nominal amounts

** In EU SmPC the nominal numbers are 8.1 mg/cm^2 for Fibrinogen and 40 IU/cm^2 for Thrombin

The polymeric film is durable, flexible, transparent, and non-permeable to body fluids. sFilm-FS is biodegradable. Within sFilm-FS manufacturing process, the lyophilized biological components are embedded onto the polymeric film using a unique printing method.

Preclinical safety and toxicological evaluations of sFilm-FS and its constituent components have uncovered no concern for risks of particular severity or seriousness and support the use of the product in the proposed clinical trial. See Investigator's Brochure for further details.

6. STUDY OBJECTIVES

The primary objective of this study is to evaluate the safety of sFilm-FS versus an active-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 in controlling liver bleeding during elective surgery.

7. STUDY DESIGN

7.1. Overview of 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 in controlling liver bleeding during elective surgery, when conventional methods of control are ineffective or impractical. Patients will be randomized with a 1:1 allocation ratio to either sFilm-FS (investigational product) or TACHOSIL® (active-comparator).

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

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

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

Once the TBS has been identified (intra-operatively), the Investigator will immediately enroll and randomize the Patient into one of the following treatment arms:

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

Patients will be then monitored for a total period of 6 months following surgery. Patients will be 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, the day of hospital discharge), Visit 6 (control visit 1; at 30 ± 3 days post-surgery) and Visit 7 (control visit 2; at 180 ± 14 days post-surgery). Monitoring of patients will include 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. Efficacy assessment will be evaluated intra-operatively by evaluation of hemostasis before patient's surgical closure.

The study will be monitored by an independent Data Safety Monitoring Board (DSMB). The DSMB will have responsibility for the review of data and identification of any potential safety issues throughout the study. If necessary, the DSMB will make recommendations regarding protocol revisions, and will recommend whether the study should proceed based on the safety data considering established stopping rules.

7.2. Number of Patients

The sample size will be of 30 patients completing the study. 15 patients will be included in the experimental treatment arm (Group A) and 15 patients in the active-comparator arm (Group B) to allow an adequate comparison between treatments. Dropped patients during the course of the study will be replaced.

7.3. Study Discontinuation

7.3.1. Patient Discontinuation Criteria

All randomized patients should be encouraged to remain in the study until they have completed the follow-up visits. Patients may discontinue participation in the study at any time and for any reason. However, if the patient decides to discontinue participation in the study, the reason must be documented when possible. Reasons for early withdrawal include, but are not limited to:

- Consent withdrawn by the patient;
- Patient refusal to complete study visits and/or procedures;
- Lost-to-follow-up: a certified letter will be sent to the patient at their last known address, after a minimum of three attempts to reach the patient by telephone have failed. If communication via certified letter is unsuccessful, the patient will be considered lost-to-follow-up.

Patients who discontinue from the study prematurely will be replaced.

Note: The eCRF should be completed as far as possible and all data relating to the patient prior to discontinuation will be made available to the Sponsor or its designee and DSMB.

7.3.2. Stopping Rules

If one of the following occurs during the enrollment period of patients receiving the test article (sFilm-FS) the study will be immediately suspended:

- Three or more patients developed a suspected unexpected serious adverse reaction (SUSAR) caused by a TBS post-operative re-bleeding (not requiring surgery re-intervention);
- Two or more patients had a TBS re-bleeding events following final observation period that required surgery re-intervention;
- Three or more patients developed other possible serious adverse reactions like thromboembolic events or severe allergic reactions.
- Three or more patients develop serious unanticipated or unexpected local reactions (serious adverse events) such as:
    - Signs of local reactions affecting the spleen and liver (persistent pain in the area of the application that is unanticipated or unexpected)
    - Persistent unanticipated and unexpected Systemic inflammatory response syndrome (SIRS), defined with at least two of these conditions: body temperature over 38 or under 36 degrees Celsius, heart rate greater than 90 beats/minute or respiratory rate greater than 20 breaths/minute or partial pressure of CO_2 less than

32 mmHg, leucocyte count greater than 12000 or less than 4000 /microliters or over 10% immature forms or bands

- Reactions on other local organs such as adhesions and reactions impacting the intestinal tract etc., assessed as being due to local reactivity. This would be diagnosed as a bowel obstruction that is unanticipated.

These stopping rules only apply to the investigational treatment group (Group A). The active-comparator group (Group B) patients should be followed according to the Investigator's standard practice as clinically appropriate.

After study suspension, the Data Safety Monitoring Board (DSMB), together with the Sponsor, will review the data and decide whether to continue or terminate the study.

7.3.3. Premature Termination of the Study

The Sponsor reserves the right to discontinue the study at any time. Premature termination of the study can be conducted voluntary by the Sponsor or by a regulatory agency at any time during the course of the study. Premature termination of the study can also be requested by the independent DSMB.

If the study is terminated for any reason, every attempt will be made to complete a follow-up visit, in which the patient will have a further blood sample taken for hematology and coagulation tests and a physical examination. In case of an adverse event, the patient will be followed-up until the event has been resolved or has been stabilized and no further change is expected.

7.4. Data Safety Monitoring Board (DSMB)

A DSMB will be convened for this study and will review the results of the trial at regular intervals, including safety reports, to protect patients participating in the study.

DSMB will make recommendations to the Sponsor regarding protocol revisions and will recommend whether the study should be closed prematurely based on safety concerns. For this, DSMB will receive timely all reports of patients with adverse events and patients discontinued from the study, with particular attention to patients who had intra-operative TBS re-bleeding events following final observation period that required re-intervention, patients with serious adverse event related to TBS post-operative re-bleeding, and patients who developed a suspected unexpected serious adverse reaction (SUSAR) following product application.

DSMB will operate based on a DSMB Charters. The charter will define the primary responsibilities of the DSMB, its relationship with other trial components, its membership, and the purpose and timing of its meetings. The charter will also provide the procedures for ensuring confidentiality and proper communication.

The DSMB will consist of at least three members, appointed by the Sponsor, who have agreed to serve. The DSMB includes experts in or representatives of the fields of relevant clinical expertise and clinical trial methodology.

At the first meeting of the DSMB, the individual members will vote to determine who will serve as the Chairperson. The Chairperson is responsible for overseeing the meetings and developing the agenda of DSMB meetings. The chairperson is the contact person for the DSMB. Periodic reports from the DSMB will be provided to the Sponsor. The Sponsor (or its designee), in turn, will submit these reports to the EC/IRB of each study investigational site in a timely manner.

HEM-01-17 Study is in compliance with the Guideline on Data Monitoring Committee, EMEA/CHMP/EWP/5872/03 Corr. of 27-7-2005.

8. STUDY POPULATION

8.1. Patient Screening Procedures

All patients requiring surgery in which liver bleeding will be encountered will be screened by each center for study inclusion. For each patient screened, all data will be registered in the eCRF, including the reason/s for exclusion for patients who are ineligible for enrollment.

Final enrollment of patients with be based on meeting all criteria, including intra-operative criteria observed at day of surgery (Day 0).

8.2. Inclusion Criteria

1. Patients aged ≥ 18 years old.
2. Patients requiring elective surgery in which liver bleeding will be encountered.
3. Hemoglobin ≥ 8.0 g/dL within 24 hours prior to surgical procedure.
4. Patients understanding the nature of the study and providing their informed consent prior to participation.
5. Patients willing to participate in the study and able to attend the visits and procedures foreseen by study protocol.

Intra-operative inclusion criteria:

6. Patients with a target bleeding site (TBS) identified by the Investigator during surgery in which liver bleeding will be encountered. TBS definition is provided in Section 7.1.

8.3. Exclusion Criteria

1. Patients having undergone a therapeutic surgical procedure within 30 days from the study enrolment.
2. Patients with a severe coagulopathy defined as INR > 2.0.
3. Patients with platelet count < 50,000 x10^9 PLT/L at the screening (ref. 11).
4. Patients admitted to trauma surgery.
5. Transplant patients due to fulminant hepatic failure.
6. Patients with known or suspected allergy or hypersensitivity to blood products or to one of the components of sFilm-FS or the active-comparator.
7. Patients with anesthesia risk judged to be higher than ASA3 by the Investigator.
8. Patients with at least one of the following concomitant conditions: severe co-morbid conditions known to pose a high risk for surgery and adequate recovery (i.e., liver cirrhosis Child-Pugh with score B or C, cholestasis, heart diseases), immunodeficiency diseases, blood clotting disorders, any conditions known to effect wound healing (i.e., collagen vascular disease), known or current alcohol or drug abusers.
9. Patients suffering from claustrophobia.
10. Patients with implanted or embedded metal objects, prostheses, pacemaker, or fragments in the head or body that would present a risk during the MRI scanning procedure or have worked with ferrous metals either as a vocation or hobby or following trauma (i.e., sheet metal workers, welders, or machinists) in such a way that might have led to unknown, indwelling metal fragments that could cause injury if they moved in response to placement in the magnetic field.
11. Patients being treated with at least one of the following treatments: antibiotic therapy for active infection, fibrin sealants, systemic steroids, or immunosuppressive agents.
12. Patients who are participating or have participated in other clinical studies within the 30 days before the study enrolment.
13. Female patients who are pregnant or breast-feeding or who wish to become pregnant during

the period of the clinical study and for three months later.
14. Female patients of childbearing age (less than 24 months after the last menstrual cycle) who do not use adequate contraception. *

Intra-operative exclusion criteria:

15. Patients with a TBS identified with major arterial bleeding requiring suture or mechanical ligation.
16. Patients identified by the Investigator to have intra-operative bleeding from large defects in large arteries or veins, requiring repair.
17. Patients identified by the Investigator to have intra-operative findings that may preclude conduct of study procedure.
18. Patients having an active local infection in the anatomic surgical area.
19. Patients with occurrence of major intra-operative complications that require resuscitation or deviation from the planned surgical procedure.
20. Patients with bleeding site in or near to foramina in bone.

** Adequate contraceptive methods may include any approved method of birth control such as combined estrogen and progestogen containing hormonal contraception, associated with inhibition of ovulation (oral, intravaginal, transdermal), progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable), intra-uterine devices, condoms, abstinence or vasectomized partner. Contraception should be maintained until study end.*

9. RANDOMIZATION

This is a randomized, open label, two-arm clinical trial. Patients enrolled will be randomized in a 1:1 ratio to receive the investigational product sFilm-FS or the active-comparator TACHOSIL®.

Each site will be provided by the CRO/Sponsor with a set of computer-generated randomization paper envelopes, each of them bearing the patient randomization number, and containing the treatment allocation.

The investigational sites will be provided with a dedicated "Instructions for Randomization" document to ensure consistency in the process.

Given the differences in appearance between treatment and control products, it will not be possible for the Investigator 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:

- Both study medications (investigational product and active-comparator) will be available in the operating room, ready for use;
- The Investigator will perform the surgical procedure according to his/her standard of care;
- Once the Investigator encounters an appropriate TBS, related to the primary operative procedure, randomization will immediately take place and the randomization envelope will be opened.

10. STUDY PRODUCTS INFORMATION

10.1. Formulation

The formulation of both the investigational product (sFilm-FS) and the active-comparator (TACHOSIL®) is summarized below:

- Investigational Product (Group A): sFilm-FS is a topical sterile bio-compatible bio-absorbable patch which consists of a polymeric film composed of a tri-block polymer (device component) containing Polyethylene Glycol (PEG), Poly-Caprolactone (PCL) and Poly-Lactide Acid (PLA), embedded with lyophilized powders of Human Fibrinogen, Human Thrombin (biological components) and calcium chloride. The lyophilized biological components of sFilm are purchased from an approved supplier (CSL Behring) and are well established components approved in US and in EU. sFilm-FS is manufactured at GMP facility at Nextar Ltd. ISRAEL, under the supervision of Sealantium Medical Ltd. – Ha'Amal 11 St. Rosh Ha'Ayin, ISRAEL. sFilm-FS is provided in patches of 5 x 5 cm (~2 x 2 inch) size. Upon opening of the sterile package, the product is ready for use.
- Active-comparator (Group B): TACHOSIL® is a licensed topical fibrin sealant patch consisting of Human Fibrinogen and Human Thrombin coated onto an equine collagen sponge. The product is manufactured by Takeda Austria GmbH. The product is ready for use. For this study, the product will be supplied in patch sizes of 4.8 x 4.8 cm (1.9 x 1.9 inch).

10.2. Labeling and Packaging

The labeling and packaging of both the investigational product (sFilm-FS) and the active comparator (TACHOSIL®) is summarized below:

- Investigational Product (Group A): each unit of sFilm-FS patch is packaged in a polyester tray and lid assembly, sealed with a Tyvek paper. The sealed product is included in an outer pouch composed of polyester laminated aluminum foil. The tray/lid assembly maintains product integrity during storage and transport and serve as barrier to microbial contamination. The outer aluminum pouch serves as a barrier to light, moisture, and microbial contamination. The outer pouch will be labeled according to the US and EU and/or local relevant guidance documents.
- Active comparator (Group B): each unit of TACHOSIL® patch is packaged in an appropriately sized blister pack of polystyrene formed foil and grid varnish coated medicinal paper and overwrapped with an aluminum laminated foil pack with a desiccant bag. The product is marketed with its own approved label. For the purpose of this clinical study an additional label will be added on the product package with specific details as required according to the US and EU relevant guidance documents.

10.3. Shipping, Handling and Storage Conditions

Both products (investigational and active-comparator) will be supplied free of charge by Sealantium Medical Ltd. – Ha'Amal 11 St. Rosh Ha'Ayin, Israel. Distribution to the clinical centers will be performed by a qualified person (QP) or appropriate distribution center with proper inventory and quality control capabilities.

- Investigational Product (Group A): sFilm-FS should be shipped under controlled refrigerated conditions (2 to 8 ºC). Unopened packages should be stored in a refrigerator at 2 to 8 ºC. Once opened, the product can remain in the sterile field for few hours throughout the surgical procedure but must be kept dry to avoid pre-activation. Unused,

open product should be appropriately discarded.

- Active-comparator (Group B): unopened packages of TACHOSIL® should be stored at 2-25 °C until use. See TACHOSIL® Prescribing Information for further information.

10.4. Preparation

Both the Investigational product (sFilm-FS) and the active comparator (TACHOSIL®) come ready to use in sterile packages and must be handled using sterile technique in aseptic conditions. Use only undamaged packages. Once the package is opened, re-sterilization is not possible. Both products do not require any preparation.

The following procedure for opening and applying the product should be followed, to ensure that the sterility of the products is maintained:

- Investigational Product (Group A): sFilm-FS should be brought into the operating room and the outer aluminum foil be cleansed before transition into the sterile field. Within the sterile field, the Tyvec should then be manually peeled, and the lid should be manually removed to discover the patch. The Tyvec and the lid should then be discarded. The tray contains the sFilm-FS with the active side facing downwards. The active side is powdery and white to off white in color and opaque. The non-active side is shiny white to off white with imprinted letters "SM1" in two opposite corners. sFilm-FS may be removed from the tray using forceps and handled taking care that active side is facing upwards and does not come in contact with any wet materials, to avoid any clotting reaction during handling. The opened sFilm-FS can remain in the sterile field to be available for use throughout the procedure but must be kept dry and should be discarded appropriately at the end of the procedure. sFilm-FS must be kept dry at all times before application to avoid pre-activation.
- Active comparator (Group B): TACHOSIL® should be brought into the operating room and the outer aluminum foil be cleansed before transition into the sterile field. Within the sterile field, both the outer aluminum foil pouch the inner sterile will be opened. TACHOSIL® should be prepared and handled in accordance with the approved Prescribing Information.

10.5. Dose and Route of Administration

Both the investigational product and the control active comparator are for topical (epilesional) use. Up to 4 patches may be applied per patient.

10.6. Study Products Accountability

Accountability for the study product at the investigational site is the responsibility of the Investigator. The Investigator will ensure that the study products are used only in accordance with this study protocol.

Study product accountability records indicating the product's delivery date to the site, inventory at the site, administered to each patient, and will be maintained by the clinical site. Accountability records will contain information on the date of products (both investigational and control products) administration, patient ID and quantity of study products dispensed including batch/serial numbers, expiration dates, details of any remaining product, and subsequent destruction. The study CRA will verify this log during the course of the study.

It is required that all study products, including empty packages, will be stored at the study investigational sites until the Sponsor or its designee has verified the study product accountability and made a reconciliation between delivered / used / unused product units at site. The unused product units will be returned to Sponsor before the study closure at the investigational sites.

10.7. Concomitant Medications

The use of any other topical hemostat, except fibrin sealants or topical thrombin, at the TBS will be permitted once the observational period is completed and hemostasis was not achieved or in the event of breakthrough bleeding requiring further treatment (as deemed necessary by the Investigator).

For additional bleeding sites, separate from the TBS, patients must be treated with the same study article according to the randomization assignment, when clinically appropriate. If other hemostatic products are needed the Investigator should revert to his/her standard of care (excluding fibrin sealants and topical thrombin).

Administration of all medications, including indication, dose, frequency, and route of administration will be recorded in the source documentation file and in the electronic Case Report Form (eCRF). All concomitant medications will be discussed and documented at each visit.

10.8. Treatment Compliance

All study products will be administered by study center personnel. Details of administration of study medication, including time of application and whether more than one dose was administered, will be recorded by the Investigator in the Case Report Form (eCRF).

11. STUDY EVALUATIONS

11.1. Study Procedures

The Schedule of Assessment included in the synopsis summarizes the frequency and timing of the study procedures. Data collected for the patient during the study will be recorded in the patient's medical records, and study worksheets/source documents, as appropriate, and will be transcribed into the eCRF.

11.1.1. Visit 1 (between Day -21 and Day -1 before Surgery) – Screening Visit

Prospective patients will be screened within 21 days prior to surgery. Prior to performing any study activities/evaluations, the patient must be thoroughly informed about all aspects of the study, including scheduled study visits and activities, and must sign the informed consent form. Signed

copies of the informed consent forms should be given to the patient. During this visit the patient will be assigned a screening number by the Investigator in sequential order.

During the visit, the Investigator will collect the following information, which will be recorded in the study eCRF and study file (when required):

- Informed Consent collection.
- Allocation of screening number.
- Demography / Medical history.
- Physical examination.
- Vital signs (blood pressure, heart rate, temperature, respiratory rate).
- Pregnancy test (β-HCG urine test) for female patients of childbearing potential.
- Blood hematology and biochemistry (see Schedule of Assessments for the list of tests).
- Measurement of coagulation parameters (PT, PTT, INR).
- Urine analysis (see Schedule of Assessment for the list of tests).
- 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.
- MRI assessment of the intervention site. 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.).
- An additional serum sample will be collected and stored at -70°C for possible future viral safety testing.
- Eligibility Criteria evaluation. In the event that a Patient is not eligible, the reason will be documented on the eCRF and screening log.
- Concomitant Medications.

11.1.2. Visit 2 (Day -1 before Surgery) – Baseline Visit

The following activities will be performed within 24 hours prior to the surgical procedure. Visit 2 will be skipped in case V1 is performed at Day -1.

Eligibility Criteria evaluation. In the event that a patient is not eligible, the reason will be documented on the eCRF and screening log.

- Physical examination and documentation of any changes in medical history from the screening visit.
- Eligibility Criteria verification. In the event that a Patient is not eligible, the reason will be documented on the eCRF and screening log.
- Vital signs (blood pressure, heart rate, temperature, respiratory rate).
- Pregnancy test (β-HCG urine test) for female patients of childbearing potential.
- Blood hematology and biochemistry (see Schedule of Assessments for the list of tests).
- Measurement of coagulation parameters (PT, PTT, INR).
- Urine analysis (see Schedule of Assessment for the list of tests).
- Concomitant medications documentation during 24 hours prior to surgery.

11.1.3. Visit 3 (Day 0) – Day of Surgery

During this visit the patient will undergo the surgical procedure. The Investigator will use his/her standard surgical techniques for the surgical procedure. Patients identified intra-operatively by the Investigator to have an appropriate target bleeding site and to be eligible to enter the study, will be enrolled and randomized to receive topical application of either sFilm-FS (investigational product)

or TACHOSIL® (active-comparator) at the target bleeding site. The TBS will be identified and will be the only specific site or region to be evaluated for efficacy in this clinical study.

The below activities will be performed, and information will be collected during the surgical procedure. All activities will be recorded in the eCRF and study file.

Before Randomization

The Investigator will perform the surgical intervention according to his/her standard of care. When the Investigator encounters the first appropriate TBS in the surgical area that requires an adjunct to achieve hemostasis because traditional methods have been determined to be ineffective or impractical, he/she will evaluate the patient for intra-operative eligibility and record all details related to the TBS.

Randomization

Once intra-operative eligibility is confirmed, and the TBS is defined, the patient will then be randomized immediately by opening the appropriate randomization paper envelope. The clock will then be started. This time point will be considered **TP-00**. The time and randomization/patient number will be recorded.

Following Randomization

Following randomization, the treatment medication assigned (either sFilm-FS or TACHOSIL®) will be applied.

Prior to application the patch can be cut to the correct size and shape if desired. The patch should cover the TBS and extend 1 to 2 cm beyond the margins of the wound. Only a single unit of product may be applied at a time at the identified TBS.

Prior to application, the area to be treated should be rinsed to remove disinfectants and other fluids. The fibrinogen and thrombin proteins can be denatured by alcohol, iodine or heavy metal ions. If any of these substances have been used to clean the wound area, thoroughly irrigate the area before the application.

The time of application will be considered **TP-01** and will be recorded as such. If the sFilm-FS is to be used, do not moisten the product prior to application, as the product will be activated immediately. TACHOSIL® should be used in accordance with the approved Prescribing Information.

Following product application, manual compression will be applied and will be maintained for at least 2 minutes for sFilm-FS and for at least 3 minutes for TACHOSIL®, until examination of TBS. The Investigator may use a surgical sponge (laparotomy pad or surgical gauze) to assist in providing adequate pressure to stem all bleeding over the entire treated surface area at the TBS. Hemostasis will then be assessed by carefully releasing manual compression and removing the surgical sponge (if used) without disturbing the hemostasis product. The product unit should be left in place once it adheres to organ tissue.

In case hemostasis is not achieved within 2 minutes (for sFilm-FS) or 3 minutes (for TACHOSIL®), the surgeon will wait 2 additional minutes applying additional pressure on the gauze before carefully releasing manual compression and checking again.

Hemostasis will be assessed at 2 (for sFilm-FS only), 3, 5, 7 and 10 minutes following product application. These time points will be recorded as **TP-02, TP03**, **TP-05**, **TP-07** and **TP-10** respectively.

Re-treatment: If the surgeon is not satisfied with the placement of the patch, or if hemostasis is not achieved, or if during the subsequent observation period bleeding requiring treatment recurs, the

Investigator may decide to apply an additional product unit as specified above. In this case, the already applied product unit should not be removed, unless it did not adhere to the TBS.

The time point of product re-application will be recorded as **TPR-01**. After re-treatment application, manual compression must be applied for at least 2 (for sFilm-FS) or 3 minutes (for TACHOSIL®, as described above. Hemostasis will then be assessed following product re-application at any time-points within the original 10 minutes observation period (**TPR-02, TPR-03** or other) and until site closure. A minimum of 5 minutes observation period at the TBS has to take place before site closure. The time followed by 5-minutes observation period to assess hemostasis will be recorded.

Hemostasis is defined as an absence/cessation of bleeding at the TBS according to the surgeon's judgement, so that the surgical closure of the field could be started. Time to hemostasis (TTH) is defined as time until hemostasis is achieved. **TTHP** will be considered as time from first product application and **TTHR** as time from randomization will be collected as well but will not be used as endpoint.

Treatment failure is defined as follows:

- in case the bleeding at TBS (or re-bleeding) is still observed after 10 minutes following first application of 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 product, at any time.

In case of treatment failure, the Investigator may revert the treatment to standard of care. If additional sites requiring a topical hemostasis product are identified after the treatment of the initial target bleeding site, these bleeding sites should be treated with the same treatment article according to the patient's randomization assignment, if clinically appropriate. If other hemostatic products are needed, the Investigator should revert to his/her standard of care (excluding fibrin sealants or topical thrombin).

The following information will be collected during surgery and recorded on the eCRF and in the study file:

- Determination of hemostasis at TBS.
- Use of other hemostatic measures.
- Collection of intra-operative details including 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).
- Collection of operative/surgical information, including 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).

Additional assessments will be taken at the end of surgery and will include the following:

- Vital signs (blood pressure, heart rate, temperature, respiratory rate).
- Blood hematology and biochemistry (see Schedule of Assessments for the list of tests).
- Measurement of coagulation parameters (PT, PTT, INR).
- Urine analysis (see Schedule of Assessment for the list of tests).

- Adverse events from surgery start (in particular related to post-operative adhesions, systemic inflammation, bleeding / thrombotic and transfusion-related complications).
- Transfusion requirements.
- Concomitant medications.

11.1.4. Visit 4 [Day 1 to Day of Hospital Discharge (D-HD)]

On Day 1 after surgery and until the day of hospital discharge, daily assessment will be conducted and will include:

- Vital signs (blood pressure, heart rate, temperature, respiratory rate).
- Blood hematology and biochemistry (see Schedule of Assessments for the list of tests).
- Adverse events (in particular related to post-operative adhesions, systemic inflammation, bleeding / thrombotic and transfusion-related complications).
- Transfusion requirements.
- Concomitant medications.

11.1.5. Visit 5 [Day of Hospital Discharge (D-HD)]

At the time of discharge the following assessment will be conducted and recorded on the eCRF and in the study file:

- Physical examination and documentation of any changes in medical history.
- Vital signs (blood pressure, heart rate, temperature, respiratory rate).
- Blood hematology and biochemistry (see Schedule of Assessments for the list of tests).
- Measurement of coagulation parameters (PT, PTT, INR).
- Urine analysis (see Schedule of Assessment for the list of tests).
- Adverse events (in particular related to post-operative adhesions, systemic inflammation, bleeding / thrombotic and transfusion-related complications).
- Transfusion requirements.
- Concomitant medications.

11.1.6. Visit 6 (Day 30±3 after surgery) – Follow up Visit #1

The following information will be recorded at the clinical follow-up visit approximately one month following surgery:

- Physical examination and documentation of any changes in medical history.
- Vital signs (blood pressure, heart rate, temperature, respiratory rate).
- Blood hematology and biochemistry (see Schedule of Assessments for the list of tests).
- Measurement of coagulation parameters (PT, PTT, INR).
- Urine analysis (see Schedule of Assessment for the list of tests).
- Testing of antibodies levels (against Human Fibrinogen and Human Thrombin).
- Adverse events (in particular related to post-operative adhesions, systemic inflammation, bleeding / thrombotic and transfusion-related complications).
- Transfusion requirements.
- Concomitant medications.

11.1.7. Visit 7 (Day 60±7 after surgery) – Follow up Visit #2

The following information will be recorded at the clinical follow-up visit approximately one month following surgery:

- Physical examination and documentation of any changes in medical history.

- Vital signs (blood pressure, heart rate, temperature, respiratory rate).
- Blood hematology and biochemistry (see Schedule of Assessments for the list of tests).
- Adverse events (in particular related to post-operative adhesions, systemic inflammation, bleeding / thrombotic and transfusion-related complications).
- Transfusion requirements.
- Concomitant medications.

11.1.8. Visit 8 (Day 120±14 after surgery) – Follow up Visit #3

The following information will be recorded at the clinical follow-up visit approximately one month following surgery:

- Physical examination and documentation of any changes in medical history.
- Vital signs (blood pressure, heart rate, temperature, respiratory rate).
- Blood hematology and biochemistry (see Schedule of Assessments for the list of tests).
- Adverse events (in particular related to post-operative adhesions, systemic inflammation, bleeding / thrombotic and transfusion-related complications).
- Transfusion requirements.
- Concomitant medications.

11.1.9. Visit 9 (Day 180±14 after surgery) – Follow up Visit #4

The following information will be recorded at the clinical follow-up visit approximately six months following surgery:

- Physical examination and documentation of any changes in medical history.
- Vital signs (blood pressure, heart rate, temperature, respiratory rate).
- Blood hematology and biochemistry (see Schedule of Assessments for the list of tests).
- Measurement of coagulation parameters (PT, PTT, INR).
- Urine analysis (see Schedule of Assessment for the list of tests).
- Testing of antibodies levels (against Human Fibrinogen and Human Thrombin).
- MRI assessment of the intervention site (mainly to exclude post-operative adhesions). This assessment can be done earlier in patients reporting abdominal symptomatology suspect for intra-abdominal adhesions or intestinal obstruction (ref. 12).
- Adverse events (in particular related to post-operative adhesions, systemic inflammation, bleeding / thrombotic and transfusion-related complications).
- Transfusion requirements.
- Concomitant medications.

All patients can request or be requested to be evaluated in an additional visit (i.e., in case of suspected adverse events). In such case will be examined as needed indicated at Section 13.5.

11.2. Procedures for Handling of Biological Samples

All laboratory investigations will be performed at the local hospital laboratory. The volume of blood to be taken will be determined according to the standard practices of each hospital. The normal reference ranges and laboratory accreditation certificates will be provided by the local site laboratory. Testing of antibodies (against Human Fibrinogen and Human Thrombin) will be performed at a central laboratory. In case of positive results for immunogenicity, an antibody retesting using a second separately drawn sample as confirmatory measurement will be performed.

12. EFFICACY AND SAFETY ASSESSMENTS

12.1. Primary Endpoint

The primary endpoint of the study is the evaluation of safety. Safety will be assessed from randomization of patients until the last follow-up visit and will include evaluation of treatment emergent adverse events. In particular, patients will be followed for AEs related to bleeding at TBS, thrombotic events, transfusion-related complications, post-operative adhesions (MRI assessment) as well as vital signs, physical examination, urine analysis, blood / coagulation parameters profiles, antibodies against fibrinogen and thrombin, and signs of systemic inflammation. For assessment of AEs please see Section 13.

12.2. Secondary Endpoints

The secondary endpoints of the study are:

- Proportion of patients achieving hemostasis at TBS (absence of bleeding) 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.
- Incidence of re-treatment (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).
- Time to Hemostasis from first product application (TTHP). Time to Hemostasis from patient randomization (TTHR) will be collected as well but will not be used as endpoint.
- Percentage of total 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.
- Incidence of treatment failure based on pre-defined treatment failure criteria (see definition in Section 11.1.3 of the protocol).
- Incidence of transfusion requirements in the 6 months follow-up period.

13. ASSESSMENT OF ADVERSE EVENTS

Safety will be assessed in all patients participating in the clinical study including monitoring of adverse events, as specified below.

13.1. Adverse Event (AE)

An adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical trial patient administered a medicinal product and which does not necessarily have a causal relationship with the treatment .In the study, any adverse event occurring after the clinical trial patient has signed the study Informed Consent should be recorded on the eCRF and reported as an AE. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medicinal product, whether or not considered related to the investigational medicinal product. A new condition or the worsening of a pre-existing condition will be considered an AE. Stable chronic conditions such as arthritis that is present prior to study entry and do not worsen during

the study will not be considered AE. Medical conditions/diseases present before starting study are only considered adverse events if they worsen after starting study treatment.

Abnormal results of diagnostic procedures, including abnormal laboratory findings, will be considered an AE if it:

- it is associated with significant clinical signs or symptoms;
- requires therapy.

Post-operative adhesions will be considered adverse events in this study. A MRI assessment will be performed at Visit 1 (Screening) and at Visit 7 (6 months post-surgery) for detection of intra-abdominal adhesions, or earlier in patients reporting abdominal symptomatology suspect for intra-abdominal adhesions or intestinal obstruction (ref. 12).

Systemic inflammation will be evaluated by the investigator, based on the following assessments:

- Body temperature, heart rate, respiratory rate, white blood cell count, CRP

The intensity or severity of the AE will be characterized as:

- Mild: AE which is easily tolerated.
- Moderate: AE sufficiently discomforting to interfere with daily activity.
- Severe: AE which prevents normal daily activities.

The relationship of an AE to the study product must be assessed by the Investigators using the following criteria and definitions:

Unrelated	This category applies to those adverse events which, after careful consideration, are clearly due to extraneous causes (disease, environment, etc.)	
Unlikely	In general, this category can be considered applicable to those adverse events, which after careful medical consideration at the time they are evaluated, are judged to be unrelated to the test drug.	An adverse experience may be considered unlikely related if or when (must have two): • It is an unknown reaction to the test drug • It does not follow a reasonable temporal sequence from the administration of the test drug. • It could have been produced by the patient's clinical state, environmental or toxic factors, or other treatments administered to the patient. It does not reappear or worsen when the drug is re-administered.

Possibly	This category applies to those adverse events for which, after careful medical consideration at the time they are evaluated, a connection with the test drug administration appears unlikely but cannot be ruled out with certainty.	An adverse experience may be considered possibly related if or when (at least two of the following): • It follows a reasonable temporal sequence from administration of the drug. • It could not be produced by the patient's clinical state, environmental or toxic factors, or other treatments administered to the Patient. • It is a known reaction to the test drug.
Probably	This category applies to those adverse events which, after careful medical consideration at the time they are evaluated, are felt with a high degree of certainty to be related to the test drug.	An adverse experience may be considered probably related if or when (at least three of the following): • It follows a reasonable temporal sequence from administration of the drug. • It could not be reasonably explained by the known characteristics of the patient's clinical state, environmental or toxic factors or other modes of therapy administered to the patient. • It disappears or decreases after discontinuation (de-challenge) of test drug or reduction of posology • It is a known reaction to the test drug.
Definitely	This category applies to those adverse events which, after careful medical consideration at the time they are evaluated, are considered to be related to the test drug.	An adverse experience may be considered certainly related if or when: • it follows a reasonable temporal sequence from administration to the clinical event - including laboratory test abnormalities - • which cannot be explained by a concomitant illness or by other medicinal products. • The reaction must have already been observed for the suspected medicinal product. • The reaction must improve with "de-challenge" and reappear with "re-challenge".

The date of onset, a description of the AE, severity, seriousness, action taken, relationship to the study drug, outcome of the event and date of resolution will be recorded.

13.2. Serious Adverse Event (SAE)

A Serious Adverse Event (SAE) is defined as an AE that results in any of the following:

- Death.
- Life-threatening.
- Requires hospitalization or prolongs existing in patients' hospitalization.
- Results in persistent or significant disability or incapacity.
- Results in a congenital abnormality or birth defect.
- An important medical event which requires medical intervention to prevent any of the above outcomes.

"Important medical events" are those which may not be immediately life-threatening but may jeopardize the patient and may require intervention to prevent one of the other serious outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; resulting in an adverse event will normally be considered serious by this criterion.

"In patient hospitalization or prolongation of existing hospitalization" means that hospital in patient admission and/or prolongation of hospital stay were required for treatment of AE, or that they occurred as a consequence of the event. It does not refer to pre-planned elective hospital admission for treatment of a pre-existing condition that has not significantly worsened, or to diagnostic procedure.

The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it was more severe.

Any new SAE that occurs after the study period and is considered to be related (possibly/probably) to the IP or study participation should be recorded and reported immediately. The study period for the purpose of SAE reporting is defined as the period from the patient's signature on the informed consent form until the end of the follow-up period.

Events NOT considered to be SAEs are hospitalizations which:

- Were planned before entry into the study.
- Are for elective treatment of a condition unrelated to the indication or its treatment.
- Occur on an emergency, outpatient basis and do not result in admission (unless fulfilling the criteria outlined above for a SAE).
- Are part of the normal treatment or monitoring of the indication and not associated with any deterioration in condition.

13.3. Suspected Unexpected Serious Adverse Drug Reaction (SUSAR):

An "Unexpected Adverse Drug Reaction" is any noxious and unintended response that is related to the administration of an investigational product that has not been reported as expected in the Summary of Product's Characteristics or in the Investigator's Brochure.

All SUSARs related to the investigational product will be subject to expedite reporting.

13.4. SAE Reporting

Any SAE, whether deemed study medication-related or not, must be reported to the Local Clinical Management (CRA and Sponsor Qualified Person Responsible for Pharmacovigilance (QPPV)) within 24 hours after the Investigator has become aware of its occurrence, using the SAE form. The SAE form completion and reporting must not be delayed even if all of the information is not

available at the time of the initial contact. The local Clinical Management will forward the report to the Sponsor's QPPV who will handle all the safety reports.

SAE originated in this study should be sent to:

seQure Life Sciences

PhV Officer

safety@sequrelifesciences.com

Fax: +39-0656561998

Additional information (follow-up) about any SAE unavailable at the initial reporting should be forwarded by the site within 24 hours of the information becoming available to the Local Clinical Management.

The following information should be provided on the SAE form to accurately and completely record the event:

- Investigator Name and Investigational site Number.
- Patient Number.
- Patient initials.
- Patient Demographics.
- Clinical Event:
    - ✓ Description.
    - ✓ Date of onset and end date.
    - ✓ Severity.
    - ✓ Treatment.
    - ✓ Relationship to study drug (causality).
    - ✓ Action taken regarding study drug (none / dose delayed / dose reduced / product withdrawn).
    - ✓ Outcome (completely recovery; sequelae; improvement; persistent; death; unknown).
- If the AE results in Death:
    - ✓ Cause of death (whether or not the death was related to study drug).
    - ✓ Autopsy findings (if available).
- Medical History case report form (copy).
- Concomitant Medication case report form (copy).
- Any relevant reports (laboratory, discharge, X-ray, etc).

SAE must be collected and reported regardless of the time elapsed from the last study. For both initial and follow-up SAE reports the Local Management forwards this information to PhV responsible within 48 hours.

13.5. Treatment and Follow-up of Adverse Events

Adverse events, especially those related to the study drug should be followed up until they have resolved (returned to baseline status) or stabilized. All AEs should be followed-up even after the Patient's participation in the study is completed, or in case of withdrawal of the Patient from the

clinical trial or of anticipated conclusion of the study. In particular, all SAE assessed by the Investigator as related to the study drug will continue to be followed-up until 30 days following last visit of the study or until SAE is resolved or stabilized.

If after follow-up, return to baseline status or stabilization cannot be established an explanation should be recorded on the eCRF. Any newly emergent SAE after treatment is discontinued or the Patient has completed the study and is considered to be related to the IP or study participation should be recorded and reported immediately.

13.6. Pregnancy Reports

A female Patient participating to the clinical study must be instructed to inform the Investigator immediately if she becomes pregnant during the study. Pregnancies occurring up to 90 days after the completion of the study drug must also be reported to the Investigator. The Investigator should report all pregnancies in female clinical trial Patients to PhV responsible (details above) within one working day of becoming aware of them using a clinical trial pregnancy reporting form. All pregnancy reports will be captured in the safety database. This includes normal pregnancies without an AE. Any Patient who becomes pregnant during the study period must not receive additional doses of investigational product and will be withdrawn from the study. If the Patient requests to know which treatment she received, this information will be provided to her. The pregnancy should be followed for outcome of the mother and the child, including any premature terminations, and should be reported to PhV responsible (details above) for any outcome.

13.7. Safety reporting to Investigators, IRB(s)/IEC(s) and RA(s)/CA(s)

The Sponsor, via QPPV, or its designee is responsible for reporting all applicable SUSAR via EVCTM, to EC that has issued the single opinion. The Sponsor, via QPPV, or its designee is responsible for reporting to all Investigators and to other ECs, as applicable, in accordance with national regulations in the countries where the study is conducted. The SUSARs will be submitted within 7 days for fatal and life-threatening events and within 15 days for other serious events.

14. STATISTICAL METHODS

Data will be summarized with respect to demographic and baseline characteristics, efficacy and safety measurements. It is planned that data from all investigational sites participating in the trial will be combined. Each analysis will show the results by treatment group and for entire sample.

14.1 Sample Size Determination

The sample size will be of 30 patients completing the study. 15 patients will be included in the experimental treatment arm (Group A) and 15 patients in the active-comparator arm (Group B) to allow an adequate comparison between treatments.

Dropped patients during the course of the study will be replaced.

The sample size of 15 patients per arm is sufficient for planned descriptive analyses and 95% confidence intervals of efficacy.

14.2 Study Population

The Intention-To-Treat (ITT) population will include all Patients registered, who underwent surgery and received the dose of study treatment and, with no major violations of the eligibility criteria. This population is considered as primary and will be used for all efficacy analyses.

The safety population will include all patients registered, who received one dose of study treatment. This population will be used for safety analysis.

14.3 Interim Analysis

No interim analysis is planned for this trial.

14.4 Handling of Missing Data

All efforts will be made to complete and report the observations in the study period and no particular approach for missing data after surgery visits will be applied. The primary reason for withdrawal from the study should be documented on the appropriate eCRF.

14.5 Level of Significance

Hypothesis testing is not specified for this study, rather estimation of efficacy endpoints will be accompanied by 95% exact confidence intervals.

14.6 Deviations from the Original Statistical Plan

Before database locking, when all data will be included and cleaned into the database, a complete and exhaustive Statistical Analysis Plan (SAP) will be redacted.

The SAP will contain a summary of the study protocol, the changes from original statistical plan, a detailed definition of the populations recruited, the description of protocol violators/deviators, the patient accountability and the detailed profile of the populations recruited, any other analysis concerning the endpoints of the study and the detailed description of safety.

14.7 Data Analysis

14.7.1 Overview of the Patient Disposition

Frequency by center, sample disposition, frequency and listing of major and minor protocol violators/deviations and composition of populations (ITT, safety) will be tabulated by treatment groups.

14.7.2 Background and Demographic Characteristics

Background and demographic characteristics such as age, gender, race, medical history will be summarized by treatment groups using appropriate descriptive statistics (mean, standard deviation, median and range for continuous variables, and frequencies and percentages for categorical variables). If treatment groups are not comparable in any of these variables, additional analyses may be performed to adjust for the influence of the variable on the efficacy outcome, if any.

14.7.3 Concomitant Therapies

Descriptive statistics such as frequency counts and percentages of Patients who use concomitant therapies will be provided by ATC therapy category, preferred term and also by treatment group.

14.8 Safety & Efficacy Evaluation

A descriptive analysis of safety and efficacy variables will be performed.

14.8.1 Primary Endpoint

The primary endpoint of the study is the evaluation of safety. Safety will be assessed from randomization of patients until the last follow-up visit and will include evaluation of treatment emergent adverse events. In particular, patients will be followed for AEs related to bleeding at TBS, thrombotic events, transfusion-related complications, post-operative adhesions (MRI assessment) as well as vital signs, physical examination, urine analysis, blood / coagulation

parameters profiles, antibodies against fibrinogen and thrombin, and signs of systemic inflammation. For assessment of AEs please see Section 13.

Descriptive safety analyses will be summarized separately by treatment arm.

14.8.2 Secondary Endpoints

The secondary endpoints of the study are:

- Proportion of patients achieving hemostasis at TBS (absence of bleeding) at 2 (for sFilm-FS product only), 3, 5, 7 or 10 minutes following first product application, without the occurrence of re-bleeding staring from 10 minutes after product application and until the completion of surgical closure.
- Incidence of re-treatment (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).
- Time to Hemostasis from first product application (TTHP). Time to Hemostasis from patient randomization (TTHR) will be collected as well but will not be used as endpoint.
- Percentage of total 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.
- Incidence of treatment failure, based on pre-defined treatment failure criteria (see definition in Section 11.1.3 of the protocol).
- Incidence of transfusion requirements in the 6 months follow up period.

Descriptive efficacy analyses will be summarized separately by treatment arm.

Primary analyses will calculate the proportion of patients achieving hemostasis at 3 minutes among the sFilm-SF treatment arm. With 15 patients randomized to sFilm-SF, reasonable confidence intervals (CI) can be estimated. For example, if 80% of the patients achieve hemostasis at 3 minutes (similar to a TACHOSIL® reported values of 81% for this endpoint), the accompanying 95% confidence interval (CI) is 52% to 96% (using exact confidence limits). This CI provides evidence that greater than 52% of patients with similar conditions will achieve hemostasis at 3 minutes. This will also be reported for the 15 patients randomized to the TACHOSIL® arm. There will be no formal comparison between the two-arms.

Similarly, proportions of patients and corresponding 95% CIs will be estimated for all of the following, separately by treatment arm:

- achieving hemostasis at TBS at each remaining time point,
- incidence of re-treatment (separately by time),
- incidence of treatment failure (as defined in Section 11.1.3), and
- incidence of transfusion requirements.

Median time to hemostasis from first product application will be estimated using Kaplan-Meier methods; minimum and maximum time will also be reported.

14.8.3 Adverse Events

The AEs will be described by System Organ Class, Preferred Term and Lowest Level Term (LLT) according to the MedDRA dictionary (Version 19.0).

The following Adverse events will be tabulated by Patient and preferred term, for each treatment group:

- any AE;
- any SAE;
- any related AE;
- any AE leading to discontinuation from study.

This listing, at minimum, will contain a description of AEs as to seriousness, severity, onset date and end date, duration, action taken (if any), outcome and relationship.

Deaths reportable as SAEs and non-fatal serious adverse events will be listed by Patient and tabulated by type of adverse event. Any other information collected will be listed as appropriate.

14.8.4 Vital Signs

Vital signs will be individually listed. Quantitative parameters will be summarised by using descriptive statistics, including the number of values within, lower and upper reference ranges (when appropriate).

14.8.5 Physical Examination

Patients with any change in physical examination from baseline to time points after dosing will be listed.

14.8.6 Clinical Laboratory Tests

All laboratory values recorded during the study will be individually listed. Quantitative parameters will be summarized by descriptive statistics, including the number of values within, lower and upper reference ranges (when appropriate) for blood and coagulation tests.

15. STUDY MONITORING

15.1 CRAs and Monitoring Visits

The CRA will be responsible for ensuring adherence to EU Directives, ICH guidelines and the Sponsor's or its designee Standard Operating Procedures. The Sponsor or its designee will provide study Monitors for this trial. The CRAs will operate according to the EU Directives and in compliance with ICH guidelines. Regular monitoring of study data at each site will be performed as defined by the study specific monitoring plan. Individual sites will be monitored to verify that enrollment rate, data recording, and protocol adherence are satisfactory.

The frequency of monitoring individual sites may fluctuate depending upon enrollment rate, quantity of data collected and the complexity of the study and will be described in the monitoring plan. These monitoring visits will be performed for the purposes of verifying adherence to the protocol and the completeness. The study CRA will verify eCRF entries by comparing them with the primary source documents (hospital/clinic/office records), which will be made available for this purpose, and accuracy of data entered on the eCRF. The CRA will review the maintenance of regulatory documentation and study product accountability. The monitor will review the progress of the study with the Investigator and other site personnel on a regular basis. eCRF sections may be collected during these visits. At the end of the study, a close-out monitoring visit will be performed. Monitoring visits will be arranged in advance with site personnel at a mutually acceptable time. Sufficient time must be allowed by the site personnel for the CRA to review eCRF and relevant source documents. The Investigator should be available to answer questions or resolve data clarifications. Adequate time and space for these visits will be made available by the Investigator.

15.2 Primary Source Documents

The Investigator must maintain primary source documents to support eCRF data entries. These documents, which are considered "source data", may include but are not limited to:

- Demographic information.
- Evidence supporting the diagnosis/condition for which the Patient is being studied.
- General information supporting the Patient's participation in the study.
- Medical history and physical findings.
- Hospitalization or Emergency Room records (if applicable).
- Each study visits by date, including any relevant findings/notes by the Investigator(s), occurrence (or lack) of adverse events, and changes in medication usage, including the date the study treatment was commenced and stopped.
- Any additional visits during the study.
- Any relevant telephone conversations with the Patient regarding the study or possible adverse events.
- Original, signed informed consent forms for study participation.

The Investigator must also retain all Patient specific printouts/reports of tests/procedures performed as a requirement of the study. During monitoring visits, the monitor will need to verify data in the eCRF against these source data.

16. QUALITY ASSURANCE AUDITS

The Sponsor or its designee will continuously assess the performance and deliverables as well as resource levels to ensure adequate cover. The Sponsor or its representative will maintain and guarantee the quality control of the Trial Master File (TMF) containing all essential documents relating to the clinical study which allow verification of the conduct of the study and the quality of the data generated.

The Sponsor or its designee may carry out an audit at any time.

Investigators will be given adequate notice before the audit occurs. The purpose of an audit is to confirm that the study is conducted as per study protocol, GCP, and applicable regulatory requirements, that the rights and well-being of the Patients enrolled have been protected, and that the data relevant for the evaluation of the investigational product have been captured, processed, and reported in compliance with the planned arrangements. The Investigator will permit direct access to all study documents, device accountability records, medical records, and source data.

Any steps taken at the investigational site or centrally to ensure the use of standard terminology and the collection of accurate, consistent, complete and reliable data, such as training sessions, monitoring of Investigators by Sponsor personnel, instruction manuals, data verification, cross-checking, or data audits should be described. It should be noted whether Investigator meetings or other steps will be taken to prepare Investigators and standardize performance.

Regulatory authorities may perform an inspection of the study, even up to several years after its completion. If an inspection is announced, the Sponsor or its designee must be informed immediately.

17. ETHICAL ASPECTS

The study will be conducted in accordance with the Declaration of Helsinki (1964), amended Japan (1975), Italy (1983), Hong Kong (1989), Republic of South Africa (1996), Scotland (2000), Brazil, (2013) and ICH Harmonized Tripartite Guidelines for Good Clinical Practice (1996).

The Investigator agrees, when signing the protocol, to adhere to the instructions and procedures described in it and thereby to adhere to the principles of Good Clinical Practice that it conforms to. A copy of the Declaration of Helsinki may be located on the internet at: http://www.wma.net.

17.1 Institutional Review Board (IRB) / Independent Ethics Committee (IEC)

Before implementing this study, the protocol, the proposed informed consent form and other information that will be provided to Patients must be reviewed by an IRB/IEC. A signed and dated statement that the protocol, informed consent has been approved by the IRB/IEC must be provided to the Sponsor or its representative before study initiation. Any amendment(s) to the protocol which need formal approval (such as sample size adjustment), as required by local law, will be approved by the IRB/IEC. The IRB/IEC should be notified in writing of all other amendment(s) (i.e., administrative changes).

17.2 Informed Consent

The principles of Informed Consent, according to the Declaration of Helsinki and its updates, ICH guidelines on GCP and EU Directives, will be followed. A Patient should not enter a clinical study until he/she has been properly informed, has been given time to contemplate participation, and has freely given his/her consent by signing and dating the IRB/IEC-approved Informed Consent Form.

This must be done prior to performing any study-related procedures. The proposed consent form and any other documents relevant to the consent process must be submitted to the IRB/IEC, together with the protocol, and must be approved prior to study start.

A copy of the fully signed and dated Informed Consent Form and any other documents relevant to the consent process will be given to the Patient and the original will be maintained at the site.

The Investigator must explain to each Patient (or legally authorized representative) the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved and any discomfort it may entail. Each Patient must be informed that participation in the study is voluntary and that he/she may withdraw from the study at any time and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician.

This informed consent should be given by means of a standard written statement, written in non-technical language. The Patient should read and consider the statement before signing and dating it and should be given a copy of the signed document. If the Patient cannot read or sign the documents, oral presentation may be made or signature given by the Patient's legally appointed representative, if witnessed by a person not involved in the study, mentioning that the Patient could not read or sign the documents.

No Patient can enter the study before his/her informed consent has been obtained. The informed consent form is considered to be part of the protocol and must be submitted by the Investigator with it for IRB/IEC approval.

17.3 Patient Confidentiality

All Patient data will be identified only by a Patient identification number and Patient initials or Patient dummy initials and date of birth in accordance with local regulations. After obtaining

Patient's consent, the Investigator will permit the study monitor, independent auditor or regulatory agency personnel to review that portion of the Patient's medical record that is directly related to the study. This shall include all study relevant documentation including Patient medical history to verify eligibility, laboratory tests results, admission/discharge summaries for hospital admissions occurring while the Patient is on study, and autopsy reports for deaths occurring during the study (if applicable).

18. DATA HANDLING AND RECORD KEEPING

18.1 Data Management Responsibilities

Data are entered in a validated database. The internal consistency and data integrity of the study database are defined by a validated set of checks defined and documented in the Study Validation Plan. A deviation from this set of pre-defined computerized checks creates a discrepancy which can be handled using the Clinical Data Management System application. Data queries will be generated and resolved. Adverse events will be coded with MedDRA version 19.0 and concomitant therapies with WHO-DD version of December 2011.

18.2 Electronic Data Capture Methods

Electronic CRF is used to record study data and it is an integral part of the study and subsequent reports. Therefore, the eCRF must be completed for each Patient included in the study. Each Patient will be given a specific Patient number. Patient data will be recorded in the eCRF using this number and will not be known in any other way to any person other than the parties involved in conducting and regulating the study.

18.3 Schedule and Content of Reports

A final Clinical Study Report will be prepared according to ICH E3 Guidelines.

18.4 Study Records Retention

The Investigator will maintain all study records according to ICH-GCP and applicable regulatory requirements. Records will be retained for at least two years after the last marketing application approval or two years after formal discontinuation of the clinical development of the investigational product or according to applicable regulatory requirements. If the Investigator withdraws from the responsibility of keeping the study records, custody must be transferred to a person willing to accept the responsibility.

18.5 Protocol Deviations

Any not purely formal, significant change of the approved protocol will be documented and explained. As soon as possible, the implemented deviation or change, the reasons for it, and, if appropriate the proposed protocol amendment(s) will be submitted:

- to the IRB/IEC for review and approval/favorable opinion,
- to the Sponsor for agreement, and
- to the regulatory authorities, if needed.

The Investigator will implement a deviation from or a change of the protocol to eliminate immediate hazards to the trial Patients without prior approval/favorable opinion of the IRB/IEC.

19. USE OF INFORMATION AND PUBLICATION

All information obtained during the course of this study will be regarded confidential and the property of the Sponsor. The Investigators agree not to disclose such information in any way without prior written permission from the Sponsor.

The information obtained from the clinical study will be disclosed to regulatory authorities, other Investigators, corporate partners, or consultants as required.

The clinical study is planned to be registered on clinicaltrials.gov public database within 1 month after study start and to be kept updated throughout the entire study period.

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