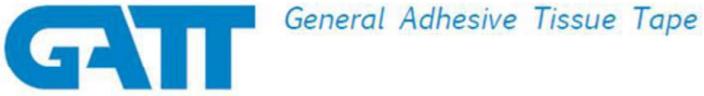
16.1.1 Clinical Investigation Plan

The latest version of the clinical investigation plan used during the trial is provided in this section. Previous versions of the clinical investigation plan are available on request.

Clinical Investigation Plan DHF-01-SFT-194 Version 8 dated 08-August-2023

CLINICAL INVESTIGATION PLAN



GATT Technologies BV

Clinical Investigation Plan Title: A Prospective, Multicenter, Randomized Clinical Investigation Evaluating the Safety and Efficacy of GATT-Patch versus TachoSil for Hemostasis during Open Liver Surgery

Clinical investigation plan Number: DHF-01-SFT-194

Short Title: GATT-Patch versus TachoSil in Liver Surgery

IDE Number:	G210325
EUDAMED Number:	CIV-22-06-039767
Name of Investigational Device:	GATT-Patch
UDI Number:	87202993601GATTPATCH49
Phase of Development:	Pivotal
Indication:	Hemostasis
Sponsor:	Stuart Head, MD, PhD Chief Medical Officer, GATT Technologies BV Novio Tech Campus Transistorweg 5 6534 AT Nijmegen The Netherlands Tel: +31 (0) 6 45306042 Email: s.head@gatt-tech.com
Clinical Investigation Plan Version:	8
Clinical Investigation Plan Date:	08-August-2023

CLINICAL INVESTIGATION PLAN APPROVAL SIGNATURES

Clinical Investigation Plan Title: A Prospective, Multicenter, Randomized Clinical Investigation Evaluating the Safety and Efficacy of GATT-Patch versus TachoSil for Hemostasis during Open Liver Surgery

Clinical Investigation Plan Number: DHF-01-SFT-194

This study will be conducted in compliance with the clinical study Clinical Investigation Plan (and amendments), ISO14155 (Clinical Investigation for Medical Devices for Human Subjects–Good Clinical Practice, and applicable regulatory requirements.

Sponsor Signatory

Stuart J. Head, MD, PhD
Chief Medical Officer, GATT Technologies BV

Stuart Head (Sep 18, 2023 16:23 GMT+2)

Signature

Sep 18, 2023

Date (DD-Mmm-YYYY)

Principal or Coordinating Investigator

Professor James V. Guarrera, MD, FACS
Rutgers New Jersey Medical School
New Jersey, United States of America

James V. Guarrera, MD, FACS (Sep 22, 2023 11:04 EDT)

Signature

Sep 22, 2023

Date (DD-Mmm-YYYY)

Professor dr. J. Hans W. de Wilt, MD, PhD
Radboud UMC
Nijmegen, The Netherlands

Hans de Wilt (Sep 18, 2023 17:21 GMT+2)

___ Signature

-

Sep 18, 2023

___ Date (DD-Mmm-YYYY)

Biostatistician and/or Medical Monitor

Alastair Smith, MD
Medical Monitor
Syneos Health

Alastair D. Smith

Signature

Sep 18, 2023

Date (DD-Mmm-YYYY)

INVESTIGATOR SIGNATURE PAGE

Clinical Investigation Plan Title: A Prospective, Multicenter, Randomized Clinical Investigation Evaluating the Safety and Efficacy of GATT-Patch versus TachoSil for Hemostasis during Open Liver Surgery

Clinical Investigation Plan Number: DHF-01-SFT-194

Confidentiality and Current Good Clinical Practice ISO14155 (ISO14155 Clinical Investigation of Medical Devices for Human Subjects–Good Clinical Practice)/ Compliance Statement ISO14155 for medical device studies

- I, the undersigned, have reviewed this Clinical Investigation Plan (and amendments<as applicable>), including appendices, and I will conduct the study as described in compliance with this Clinical Investigation Plan (and amendments), ISO14155 and relevant International Council for Harmonization (ICH) guidelines.
- I am thoroughly familiar with the appropriate use of the study device, as described in this Clinical Investigation Plan and any other information provided by GATT Technologies including, but not limited to, the current investigator's brochure.
- Once the Clinical Investigation Plan has been approved by the independent ethics committee (IEC)/institutional review board (IRB), I will not modify this Clinical Investigation Plan without obtaining prior approval of GATT Technologies and of the IEC/IRB. I will submit the Clinical Investigation Plan amendments and/or any informed consent form modifications to GATT Technologies and the IEC/IRB, and approval will be obtained before any amendments are implemented.
- I ensure that all persons or party assisting me with the study are adequately qualified and informed about the GATT Technologies investigational device GATT-Patch and of their delegated study-related duties and functions as described in the Clinical Investigation Plan.
- I ensure that source documents and trial records that include all pertinent observations on each of the site's trial subjects will be attributable, legible, contemporaneous, original, accurate, and complete.
- I understand that all information obtained during the conduct of the study with regard to the subjects' state of health will be regarded as confidential. No subjects' names will be disclosed. All subjects will be identified by assigned numbers on all case report forms, laboratory samples, or source documents forwarded to the Sponsor. Clinical information may be reviewed by the Sponsor or its agents or regulatory agencies. Agreement must be obtained from the subjects before disclosure of subject information to a third party.
- Information developed in this clinical study may be disclosed by GATT Technologies to other clinical investigators, regulatory agencies, or other health authority or government agencies as required.

<Name>

<Title>

Investigator Signature

Date (DD-Mmm-YYYY)

Institution

1. SYNOPSIS

Title of Study:	A Prospective, Multicenter, Randomized Clinical Investigation Evaluating the Safety and Efficacy of GATT-Patch versus TachoSil for Hemostasis during Open Liver Surgery
Clinical Investigation Plan Number:	DHF-01-SFT-194
Investigators/Study Sites:	A maximum of 12 sites in the United States and Europe, with a target number of sites of 4-7 in the US, 2-4 in The Netherlands, and 2-4 in Germany. The clinical investigation in the US will be limited to 2 US sites; expansion to further sites in the US will be covered in an IDE supplement, which will be submitted to FDA after enrollment of 10 US subjects. This report may also be provided to other local country authorities upon request.
Phase of Development:	Pivotal
Objectives:	The objective of this clinical investigation is to compare the safety and efficacy of GATT-Patch versus TachoSil in liver surgery
Study Endpoints:	Primary endpoint: The primary efficacy endpoint is defined as non-inferiority of GATT-Patch compared to TachoSil in the percentage of cases achieving hemostasis at 3 minutes without rebleeding at the 10-minute time point. Hemostasis will be defined by a grade of 0 (None/Dry) on the Surface Bleeding Severity Scale (SBSS). Secondary efficacy endpoints: • Median time to hemostasis (seconds); • Kaplan-Meier estimated distribution of time to hemostasis; • Treatment failure, defined as no hemostasis at 10 minutes; • Rebleeding after 10 minutes but before subject closure; and • Percentage of hemostasis at 30, 60, 90, 120, 150, 180, 210, 240, 270, 300, 360, 420, 480, 540, and 600 seconds. Safety endpoints: The safety of GATT-Patch will be assessed by the incidence, severity and relation to hemostatic device of all adverse events. The adverse events for the GATT-Patch group will be compared to those for the TachoSil group. Adverse events of special interest are bleeding-related events, thromboembolic events, biloma, and allergic reaction. Exploratory endpoints: • Procedure duration (minutes); • Estimated blood loss (mL) during surgery; • Number and type of blood transfusions during hospitalization; • Duration of Intensive Care Unit (ICU) stay; • Total hospitalization time; • Postoperative drainage volume, characteristics, and duration; • Need for and cause of reoperation; • Imaging of the liver resection at 6 weeks post-surgery to detect (1) fluid collection and its size (in mL) and aspect, (2) pseudo-aneurysm, (3) patch encapsulation, and (4) rolling up of the device on the resection plane; • Amount of hemostatic material needed versus bleeding surface; • User satisfaction (questionnaire) for GATT-Patch; • Physician treatment preference assessment (questionnaire); • Local recurrence of liver cancer at the resection; • Cancer-free survival; and • Overall survival.
Study Design:	This is a pre-market, prospective, randomized (2:1), multicenter, multi-national pivotal clinical investigation

Selection of Subjects:	Main Inclusion Criteria: A subject must meet all of the following pre-operative inclusion criteria to be enrolled into the clinical investigation: 1. Subject is scheduled to undergo elective open surgery on the liver; 2. Subject is willing and able to give written informed consent for the clinical investigation participation; 3. Subject is 22 years of age or older at the time of enrollment; and 4. Subject has been informed of the nature of the clinical investigation. A subject must meet all of the following intra-operative inclusion criteria to be enrolled into the clinical investigation: 1. Subject in whom the Investigator is able to identify a target bleeding site at the liver resection plane for which any applicable conventional means for hemostasis (e.g. suture, ligature or cautery) are ineffective or impractical, and the choice is made to use a hemostatic agent to stop the bleeding; and 2. Subject has a target bleeding site with a SBSS of 1, 2, or 3 (e.g. reflecting minimal, mild or moderate bleeding severities). Main Exclusion Criteria: A subject must not meet any of the following pre-operative exclusion criteria to be enrolled into the clinical investigation: 1. The target bleeding site is from a large defect in an artery or vein that requires vascular reconstruction with maintenance of vessel patency; 2. Subject is scheduled to undergo surgery on other organs than the liver and its associated biliary and vascular system; 3. Subject is scheduled to undergo a staged liver surgery procedure (e.g., Associating Liver Partition and Portal vein ligation for Staged hepatectomy [ALPPS]) 4. Subject is taking multiple antithrombotic therapies in therapeutic dosage up to the time of surgery, but allowing exclusive use of acetylsalicylic acid; 5. Subject has platelet count <100 x 109/L, an activated partial thrombin time of >100s, or international normalized ratio >2.5; 6. Subject has a total bilirubin level of ≥2.5 mg/dl; 7. Subject is pregnant, planning on becoming pregnant or actively breastfeeding during the 3-month follow-up period; 8. Subject has a known hypersensitivity to brilliant blue (FD&C Blue #1), porcine gelatin, or horse proteins; 9. Subject who has religious objections to receiving products with components of animal (porcine or equine) or human origin; 10. Subject has an active or suspected infection at the bleeding site; 11. Subject in whom the investigational device will be used at the site of a synthetic graft or patch implant; 12. Subject has a life expectancy of less than 3 months; 13. Subject has a documented severe congenital or acquired immunodeficiency; 14. Subject has had or has planned to receive any organ transplantation; 15. Subject is currently participating or has participated in another clinical investigation within the past 30 days that may affect the endpoints of the study, such as trials related to the surgical procedure, and on anti-coagulation; 16. Subject is not appropriate for inclusion in the clinical investigation, per the medical opinion of the Investigator; and 17. Subject has any incidental (pre- and peri-operative) findings deemed by the Investigator to potentially jeopardize the safety or welfare of the subject.
Withdrawal Criteria:	• Change in SBSS to ineligible (SBSS of 0, 4, or 5) between point of randomization and application of the hemostatic patch • Death of subject in the time between randomization and patch use
Planned Sample Size:	Sample size of 130 subjects of which a total of 87 subjects will undergo implantation of GATT-Patch.

Investigational Device:	GATT-Patch is a hemostatic patch with dimensions of 100x50 mm, which consists of a gelatin patch that is impregnated with a granulate of N-Hydroxysuccinimide (NHS) ester-functional poly(2-ethyl-2-oxazoline) polymer (NHS-POx) and a nucleophilic amine-functional poly(2-ethyl-2-oxazoline) polymer (NU-POx) particles also referred to as P(EtOx-NH2) polymer. GATT-Patch will be applied onto the wound site where the flexible and resorbable gelatin patch is activated by tissue contact and initiates the coagulation cascade, further enhanced by dehydrating the blood to concentrate the blood's solid elements leading to a matrix for platelet aggregation and release of coagulation factors enabling fibrin formation 'trapped' in the gelatin fibers. Once the patch is activated, via the combination of P(EtOx-OH-NHS), P(EtOx-NH2) and gelatin, a POx-hydrogel is formed. This POx-hydrogel has two effects: firstly, to adhere the patch to the tissue and secondly to form a seal across the damaged tissue. Both parts together help to ensure that high efficacy hemostasis can be achieved.
Reference Device:	TachoSil is a fibrin sealant patch indicated for use with manual compression in adult and pediatric patients as an adjunct to hemostasis in cardiovascular and hepatic surgery, when control of bleeding by standard surgical techniques (such as suture, ligature or cautery) is ineffective or impractical. TachoSil is a topical fibrin sealant patch consisting of human fibrinogen and human thrombin coated onto an equine collagen sponge.
Reduction of bias:	Due to the physical differences in the investigational and control devices, blinding of the surgeon is not possible. However, bias is minimized by using a validated bleeding scale to determine baseline bleeding severity prior to randomization, at which point in time the investigator is not aware of treatment assignment. Further, the training and testing required for all investigators to use a validated bleeding severity scale for assessment of successful hemostasis reduces subjectivity for the efficacy assessments. The following additional measures have been implemented to reduce potential bias in the assessment of safety and efficacy: • Blinding patients to the randomized and received treatment; • An independent adjudication committee will review all serious adverse events (SAEs) and adverse events of special interest (e.g., bleeding-related events, thromboembolic events, biloma, and allergic reaction) occurring during the 3-month follow-up after surgery for relatedness to the device and expectedness of the event based on the clinical scenario comprising of patient and procedural characteristics; and • A blinded independent data monitoring committee will review the overall safety and efficacy of the trial.
Treatment Duration:	The enrollment period is expected to take approximately 12 months, which includes an FDA review of data for the first 10 US subjects. This report will also be made available to other local country authorities for review upon request. The per subject duration of the clinical investigation from treatment to follow-up will be approximately 3 months. A full study report will be written based on the 3 month follow-up data and will be submitted to all relevant local country authorities, including a pre-market approval submission to FDA. The total expected duration of the clinical investigation until PMA submission is approximately 15 months. Five-year observational follow-up will furthermore be performed on all patients undergoing liver resection for liver malignancy or metastases. This observational follow-up will not be in direct contact with the patient, but through electronic health records and/or contact with the patient's treating physician.

Arms and Interventions:	This is a randomized clinical trial. GATT-Patch and TachoSil will be used to control bleeding during liver surgery. Each surgery will be performed according to the standard procedures of the hospital, with exception of the use of GATT-Patch versus TachoSil. Furthermore, during the week 6 follow-up, imaging as well as some laboratory test may be considered study specific assessments. Subjects who signed informed consent, who meet the preoperative eligibility criteria, and who have an appropriate bleeding site (SBSS 1, 2 or 3 and no contraindications) will be randomized between GATT-Patch and TachoSil in a ratio of 2:1. Randomization will be performed intra-operatively, after intra-operative eligibility criteria have been confirmed. GATT-Patch and TachoSil application will be according to their instructions for use, with 30 seconds of pressure for GATT-Patch and 3 minutes of pressure for TachoSil. If GATT-Patch or TachoSil does not result in hemostasis, rescue therapy with additional surgical techniques and/or hemostatic agents is allowed.
Statistical Methods and Planned Analyses:	• This study will include an FDA review of data for the first 10 US-based patients from 2 US-based sites. No formal statistical analyses will be performed on these data. The data will also be made available to other local country authorities for review upon request. After FDA approval to continue, the study utilizes an adaptive design with an interim analysis planned for the purposes of stopping the trial early for success and for sample size re-estimation. The interim analysis will be performed once 70% (n=91) of the planned evaluable subjects in total are treated. • Descriptive statistics will be presented for each variable. Continuous variables will be summarized by treatment group using number of subjects, mean, median, standard deviation, minimum, and maximum. Categorical variables will be summarized by treatment group using frequencies and percentages of subjects in each category. For time-to-event, a Kaplan-Meier plot will be presented, and 25%, 50%, and 75% percentiles and their 95% confidence intervals will be reported. • The primary analysis of the primary efficacy endpoint will be conducted using the Farrington-Manning test on the Per-Protocol (PP) population with available data. The primary efficacy endpoint will also be analyzed on the Intent-to-Treat (ITT) population as a secondary analysis. The key secondary endpoint of median time-to-hemostasis will be analyzed using a one-sided Wilcoxon-Mann-Whitney test. Other secondary endpoints, and exploratory and safety endpoints will be summarized descriptively.

2. TABLE OF CONTENTS

2.1. List of In-text Tables

2.2. List of In-text-Figures

3. LIST OF ABBREVIATIONS

Abbreviation	Definition
ADE	Adverse Device Effect
AE	Adverse Event
ASADE	Anticipated Serious Adverse Device Effect
CFR	Code of Federal Regulations
CIP	Clinical Investigation Plan
CTCAE	Common Terminology Criteria for Adverse Events
IDMC	Independent Data Monitoring Committee
(e)CRF	(electronic) Case Report Form
EDC	Electronic Data Capture
eGFR	estimated Glomerular Filtration Rate
EU	European Union
FAS	Full analysis set
FDA	Food and Drug Administration
FD&C	Federal Food, Drug, and Cosmetic Act
FSH	Follicle stimulating hormone
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
IAC	Independent Ajudication Committee
IB	Investigator's Brochure
ICF	Informed Consent Form
ICU / IC	Intensive Care Unit / Critical Care Unit
IDE	Investigational Device Exemption
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IFU	Instructions For Use
IRB	Institutional Review Board
ISO 14155	International Standard on the Clinical investigation of medical devices for human subjects — Good clinical practice
ITT	Intention-to-treat
MDR	Medical Device Regulation
MedDRA	Medical Dictionary for Regulatory Activities
NHS-POx	*N*-hydroxysuccinimide ester (NHS)-functional poly(2-oxazoline)s
NU-POx	Nucleophilically Activated Polyoxazoline
ORC	Oxidized Regenerated Cellulose
PI	Principal Investigator

PP	Per-protocol
PEG	Polyethylene glycol
P(EtOx-NH2)	nucleophilic amine-functional poly(2-ethyl-2-oxazoline) polymer (NU-POx) (polyoxazoline)
P(EtOx-OH-NHS)	N-Hydroxysuccinimide (NHS) Ester-Functionalized Poly(2-ethyl-2-oxazoline) Polymer (NHSPOx) (polyoxazoline)
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBSS	Surface Bleeding Severity Scale
SUSAR	Suspected Unexpected Serious Adverse Reactions
UADE	Unanticipated Adverse Device Effect
US	United States
USADE	Unanticipated Serious Adverse Device Effect
TBS	Target Bleeding Site
TEAE	Treatment-Emergent Adverse Event
TTH	Time To Hemostasis
TMF	Trial Master File

4. INTRODUCTION

4.1. Background on Liver Surgery

Hepatic surgery, such as liver resection, has been associated with considerable mortality and morbidity.[1] The postoperative mortality for major hepatectomy has been reported in a range from 0.7% to 2.6%.[2] The short-term and long-term outcomes of open liver surgery may be influenced by uncontrolled bleeding during the operation, and a need for blood transfusion.[1,2] A 2011 retrospective analysis of approximately 1.6 million surgeries, including cardiac, vascular, solid organ, and spinal surgeries, found that the rate of bleeding-related complications was 29.9%, with blood transfusions occurring in 21.2% of all patients. There are significant benefits to patients when hemostasis is addressed efficiently, and effective treatment of bleeding may reduce blood loss and peri-operative complications.[3]

During liver surgery, most luminal structures greater than 2 mm in diameter are controlled during parenchymal transection[4] temporary occlusion of inflow vessels (e.g., Pringle maneuver to control inflow of the portal triad), and control of bleeding from outflow vessels (lowering central venous pressure or anterior elevation of the liver to avoid back-bleeding).[4,5] After transection, small volume bleeding may occur from the cut surface of the future liver remnant. Ligation, or electrocautery techniques can be used to control bleeding from visible compromised vessels. Bleeding from generalized venous ooze is better controlled with topical hemostatic agents.

4.2. Background on Hemostatic Agents used during Liver Surgery

Previous European and US-based studies performed with hemostatic agents used during liver surgery have demonstrated that the patient population is anticipated to be an adult population with a mean age of 60-65 years, predominantly white/Caucasian and approximately 37-48% being female (Table 1). In terms of disease and liver characteristics, the main indication for liver resection surgery was metastasis and the presence of cirrhosis is typically 2-10% (with one outlier). Moreover, trials including US sites have similar characteristics as trials with purely non-US-based sites.

Included patients in the first-in-human clinical investigation (Section 4.7) were of a mean age of 59.7 years, 30% were female, and 91% being white/Caucasian. The indication for surgery was colorectal metastases in 66% of patients and 6% of patients had liver cirrhosis. The population as included in the first-in-human trial therefore represents a similar population as seen in other hemostatic trials in liver surgery, and the current pivotal trial is anticipated to include a similar patient population by including similar clinical sites.

Further details on the expected hemostatic performance of approved agents is summarized in Section 6.2.

Table 1. Summary of Hemostatic Trials in Liver Surgery

Reference	Study Design / Location(s)	Hemostatic Agents and Population	Age in years	Female sex (%)	Race	Liver Cirrhosis (%)	Main Surgical Indication
Bjelovic et al., 2018	RCT (1:1)	FS Grifols vs Surgicel (n=325)	Mean: 58	48%	Caucasian (91%)	4%	Unclear

Reference	Study Design / Location(s)	Hemostatic Agents and Population	Age in years	Female sex (%)	Race	Liver Cirrhosis (%)	Main Surgical Indication
	US, Europe, Russia						
Bochicchio et al, 2015	RCT (2:1) US and Europe	Fibrocaps vs Gelatin sponge (n=181)	Mean: 61	37%	White (95%)	Not reported	Not reported
Fisher et al., 2011	RCT (1:1) Denmark	TachoSil vs Argon Beam Coagulation (n=119)	Mean: 60	41%	Not reported	Excluded	Not reported
Genyk et al., 2016	RCT (1:1) US	TachoSil vs ORC (n=224)	Mean: 58	47%	Caucasian (79%)	10%	Malignant tumor (78%) with 49% metastatic
Koea et al., 2013	RCT (1:1) Europe	EVARREST vs Standard (n=88)	Median: 65	43%	Not reported	8%	Colorectal metastases (75%)
Koea et al., 2016	RCT (1:1) Europe	EVARREST vs Standard (n=102)	Median: 63-64	39%	Not reported	9%	Colorectal metastases (64%)
Moench et al., 2014	RCT (1:1) Germany	TachoSil vs Sangustop (n=127)	Mean: 62	42%	Not reported	Excluded	Liver metastasis (63%
Ollinger et al., 2013	RCT (2:1) Europe	Veriset vs TachoSil (n=50)	Mean: 62	40%	White (100%)	2%	“Neoplasms”
Rahbari et al., 2020	RCT (1:1) Germany	BioFoam vs Standard (n=101)	Mean: 63	40%	Not reported	32%	Metastatic malignancy (56%)

RCT = randomized controlled trial

4.3. Background on GATT-Patch

GATT-Patch (Figure 1) is a sterile, flexible and resorbable hemostatic patch. It presents as a blue, soft, flexible, porcine gelatin fiber-based carrier impregnated with an NHS-POx/NU-POx granulate. GATT-Patch measures 10 cm long by 5 cm wide. GATT Patch is active and can be applied on both sides. Blue color is an aid to visualize GATT Patch when applied onto a bleeding location.

GATT-Patch will be applied to the wound site where the fibrous gelatin patch presents as an adjunct to hemostasis by tamponade effect and formation of a mechanical barrier. The fibrous gelatin matrix supports the intrinsic coagulation process by dehydrating the blood to capture and concentrate the blood’s solid elements leading to a matrix for platelet aggregation and the release of coagulation factors enabling fibrin formation 'trapped' in the gelatin fibers. Once GATT-patch is in contact with an aqueous environment, a POx-hydrogel is formed. This POx-hydrogel has two effects: (1) to adhere the fibrous gelatin carrier to the tissue and (2) to form a seal across the damaged tissue. Together, these two effects help ensure that highly effective hemostasis can be achieved by a mechanical barrier function. The time to hemostasis (TTH) is expected to be 30 seconds based on the instructions for use, and as confirmed in the first-in-human clinical investigation.

GATT-Patch is a Class III medical device intended for application by trained physicians as an aid to hemostasis on internal organs during surgery after standard surgical hemostatic techniques have been applied. The effect is local and primarily mechanical and is not

dependent on the coagulation status of the patient. The product is not removed at the end of surgery but is resorbed in 4-6 weeks.[a]

Figure 1. GATT-Patch

4.4. Regulatory Classification

GATT-Patch is indicated for use as an adjunct to hemostasis in surgery for minimal, mild or moderate bleeding sites when control of bleeding by standard surgical techniques (such as suture, ligature or cautery) is ineffective or impractical. GATT-Patch is intended to be used for management of hemorrhage during surgeries on the liver. According to classification rule 8 of Annex VIII of the EU MDR 4 April 2017, the device is a long-term surgically invasive and implantable device. The device will be wholly absorbed and it will undergo a chemical change in the body.

According to classification rule 18 of Annex VIII of the EU MDR 4 April 2017, the device is manufactured utilizing derivatives of animal origin, which are non-viable or rendered non-viable.

Therefore, according to both classification rules, GATT-Patch is classified as a Class III medical device.

4.5. Materials

A listing of the raw materials used in the manufacturing of the final finished P(EtOx-OH-NHS) - P(EtOx-NH2) granulate-based hemostatic patches is provided in Table 2. GATT Patch is an implant, and all components are in direct contact with the human body.

Table 2. Raw Materials/Chemical Components GATT-Patch

Device Component	Raw Materials in Component	Supplier	CAS Number
Polymers	P(EtOx-OH-NHS) polymer	PolyVation	NA
	P(EtOx-NH2) polymer	PolyVation	NA
Blue Colorant FD&C Blue #1	FD&C Blue #1	Spectrum Chem. via VWR	3844-45-9

[a] The resorption time was estimated 4-6 weeks based on initial preclinical testing of prototypes. The outcomes of a recent GLP implantation study on the final design of GATT-Patch shows resorption in <4 weeks.

Granulate	P(EtOx-OH-NHS) and P(EtOx-NH2)	GATT Technologies	NA
Porous Gelatin carrier (porcine origin)	Gelatin	Gelita Medical	9000-70-8

4.6. Nonclinical Studies

GATT Technologies BV performed preclinical testing to assess residual risks associated with the device. In summary, a study on the use of GATT-Patch versus Surgifoam + Thrombin and Hemopatch in a porcine liver bleeding model was performed and demonstrated non-inferior time to hemostasis with GATT-Patch versus controls, a lower local tissue reactivity than controls, no device migration through the abdominal cavity, no more intra-abdominal adhesions than with the control products, device degradation within 28 days, and no adverse events (AEs) up to 8 weeks of follow-up. Design verification and validation was performed in accordance with national and international standards. The outcomes of the pre-clinical tests demonstrated that the device performs as intended.

A literature review was performed to establish clinical evidence referring to the clinical safety and performance, and associated risks and benefits of GATT-Patch (Literature Review Clinical Investigation Plan Version 01, 24 September 2020). The objective was to identify comprehensive and up-to-date information on established therapies, the safety and performance of state-of-the-art treatments and/or devices, methods to assess effectiveness, and known AEs that are related to the management of hemorrhage during liver surgery. Relevant outcomes included AEs, device deficiencies, study population (eligibility criteria), primary effectiveness/performance and safety outcome measures and secondary outcome measures. Overall, data obtained through the literature review was used to provide input to the assessment of acceptable benefit/risk profiles of GATT-Patch and to determine the performance goal for a proposed clinical investigation on GATT-Patch. A summary is provided below.

There are numerous hemostasis products approved for bleeding during surgery (Table 3). This includes both biological and synthetic products as well as patches and non-patches. These products have different modes of action based on their composition, but despite differences in composition and formation (patch vs non-patch), many of these products have a similar indication as adjunct to hemostasis. These products are thus relevant to consider as alternatives to GATT-Patch.

For the risk management activities, specific alternative patches that are approved for hemostasis in Europe, such as TachoSil, Veriset, and Hemopatch, and that have a similar mode of action and intended use as GATT-Patch, were used to provide input in the risk profile of GATT-Patch.

Table 3. Alternative Hemostatic Products

Category	Class
Mechanical	Porcine gelatin
	Bovine collagen
	Oxidized regenerated cellulose (ORC)
Active	Bovine thrombin

	Human-pooled plasma thrombin
	rhThrombin
Combined	Porcine gelatin + thrombin
	Bovine gelatin and human-pooled plasma thrombin
Fibrin sealants	Human plasma and human thrombin
	Human-pooled plasma and bovine thrombin
	Individual human plasma, bovine collagen and bovine thrombin
	Human-pooled plasma and equine collagen
Synthetic sealants, PEG-based	Two PEGs
	PEG, trilysine amine and FD&C Blue #1
	PEG and human serum albumin
Albumin and glutaraldehyde	Bovine serum albumin and 10% glutaraldehyde

In general, topical hemostatic agents have been found effective to control bleeding at bleeding sites that include raw diffuse bleedings and that are difficult to control using traditional hemostatic techniques.[1,2] GATT-Patch is intended to provide fast and persistent control of bleeding during surgeries on internal organs. When compared to other hemostatic agents that are considered standard of care or when compared to benchmark devices, it is expected that GATT-Patch will provide at least the same rate of hemostasis, but faster and with improved adhesion for a prolonged benefit. The flexibility and pliability of GATT-Patch allows it to be used in a variety of clinical situations where current standard of care patch products are impractical for use. Furthermore, the composition and mode of action of GATT Patch differentiates from currently approved products and thereby addresses the medical need of a combination of quick and persistent hemostasis and strong adhesion to the tissue.

The risks of GATT-Patch are considered similar to other hemostats used during liver surgery (patch and non-patch). There is low risk of AEs associated with topical hemostatic agents.[2] Device-related AEs that were identified for benchmark devices (devices with similar properties and the same intended use as GATT Patch) occurred with a low incidence rate: 0 to 18.2%, with 18.2% being a reported imbalance in treatment assignment to two investigators, who had a different interpretation of causal events than other investigators. If not taken into account, device-related AE occurred in a range of 0% to 6.7% and included the risk of bile leak, hematoma, anemia, diarrhea hypomagnesemia, localized intra-abdominal fluid collection, nausea, peritoneal abscess, pleural effusion, infectious peritonitis, liver abscess, postoperative abscess, postoperative adhesion and procedural hemorrhage. There is no risk of immunogenicity. One device-related event of increased C-reactive protein was identified (1.8%) but was considered non-serious.

4.7. Clinical Studies

In the Netherlands, a first-in-human, single-arm clinical investigation was conducted to confirm safety and efficacy of GATT-Patch. In patients undergoing open liver resection surgery, GATT-Patch was applied on the liver resection surface to initiate hemostasis for minimal, mild, or moderate bleeding in the case that standard surgical techniques were ineffective or impractical. After a preplanned initial safety enrollment cohort of 8 patients (Stage I), the Independent Data Monitoring Committee (IDMC) agreed to continue with an efficacy cohort (Stage II), on the basis of adequate safety. The success of GATT Patch was measured against a performance goal of 65.4%, which represents the lower bound of the 95%

confidence interval of a weighted mean number of patients who reach hemostasis within 3 minutes with already approved hemostatic products during liver surgery. The results of the trial showed that the percentage of Stage II subjects that achieved hemostasis at 3 minutes using GATT-Patch was 97.4%, and was higher than the literature-based performance goal of 65.4% ($P<0.001$). An additional analysis was performed on a per bleeding site basis, showing that the percentage of bleeding sites that achieved hemostasis at 3 minutes using GATT-Patch was 96.3% of the 54 bleeding sites treated during Stage II. In the trial, a total of 47 patients were treated with GATT-Patch on 63 target bleeding sites, and hemostasis at 3 minutes was achieved in 96.7% of the 63 bleeding sites.

Furthermore, the entire enrolled cohort was evaluated for safety of GATT-Patch. A total of 28 of the 47 subjects (59.6%) experienced AEs and 7 of the 47 subjects (14.9%) experienced serious AEs (SAEs). The incidence of device related AEs was 6.4% and the incidence of device related SAEs was 2.1%. Three of the 47 subjects experienced AEs that were related to both the device and procedure, all considered to be possibly related and there were no events with a probably or causal relationship with the device. These AEs involved one subject with biloma, one subject with a perihepatic abscess, and one subject with post-procedural hematoma. One of the 47 subjects experienced an SAE that was related to both the device and the procedure and involved a perihepatic abscess. The types and incidence of AEs seen for GATT-Patch are comparable to similar hemostatic products.

The present pivotal clinical investigation is intended to investigate whether the device is safe and performs as intended when compared to TachoSil.

This clinical investigation is intended to collect clinical safety and efficacy data to support marketing approvals in the United States and Europe.

Clinical data from competitor devices and standard of care treatment for open liver surgery were reviewed and were used to predict safety and performance outcomes of GATT-Patch and to create appropriate preventive measures for possible risks associated with the device. All residual risks for GATT-Patch have been assessed and reduced to an acceptable or tolerable level, as confirmed in the pilot clinical investigation. To date, there have been no comparative clinical investigation assessing the safety and efficacy of GATT-Patch. Therefore, this clinical investigation is warranted.

4.8. Clinical Risks/Benefits of the GATT-Patch

4.8.1. Risk associated with GATT-Patch

Possible risks for GATT-Patch were assessed and controlled using the EN-ISO 14971 "Medical devices – application of risk management to medical devices". The results of the risk management are recorded in the risk management report. In summary, according to the results of the use risk assessment, there were no risks identified as 'probable' or 'frequent' to occur, neither at a 'not acceptable' risk level. The following risks are judged as 'tolerable and improbable to occur', as 'tolerable and remote to occur', or 'tolerable and occasional to occur':

- Toxic response
- Thromboembolic event
- (Re)Bleeding
- Allergic reaction
- New surgery

- Infection (e.g., abscess)
- Blockage of artery or vein/ischemia of organs
- Damage of organs and vessels
- Adhesion to other organs
- (Pulsatile) hematoma
- Closing of intestinal track
- Biloma (e.g., bile leakage)

Note: these events can be considered procedure- or device-related events.

Furthermore, the risk for encapsulated or rolled-up device was identified during the risk management, at a lower risk level/incidence. This risk will be further investigated in this clinical investigation by means of the 6-weeks follow-up imaging.

In the first-in-human clinical investigation, the following adverse events occurred with a possible relationship to the device: hematoma (n=1/47, 2.1%), biloma (n=1/47, 2.1%) and perihepatic abscess (n=1/47, 2.1%). There were no adverse events with a probable or causal relationship to the device. While other adverse events occurred, these were considered not related to the device.

A full study report will be written based on the 3 month follow-up data and will be submitted to all relevant local country authorities, including a pre-market approval submission to FDA. Furthermore, 5 year observational follow-up will be performed to characterize long-term safety on all patients undergoing liver resection for liver malignancy or metastases, collecting data on local cancer recurrence, disease-free survival, and overall survival. This observational follow-up will not be in direct contact with patient, but through electronic health records and/or contact with the patient's treating physician.

4.8.2. Risks associated with participating in the clinical investigation

Participation in this clinical investigation may also present additional risks or inconveniences, including, but not limited to:

- Procedure-related adverse events during open liver surgery similar to the standard of care
- Inconvenience related to ultrasound imaging conducted at 6 weeks postoperatively
- Follow-up visits/assessments at 6 and 12 weeks postoperative
- Other unforeseen risks

Further, those patients randomized to receive TachoSil are subject to risks associated with use of that device, which could include:

- Anemia
- Nausea
- Vomiting
- Fever
- Abdominal pain
- Increase white blood cell count
- Ascites
- Itching
- Atrial fibrillation
- Pleural effusion

- Gastrointestinal hemorrhage
- Wound infection
- Hypophosphatemia
- Urinary tract infection
- Post-procedural bile leak

4.8.3. Risk control/migration

GATT Technologies BV performed risk analysis in accordance with EN ISO 14971:2019. All residual risks have been controlled and are mitigated to an acceptable level. Careful definitions of specific eligibility criteria, study procedures and instructions for use, appropriate selection, qualification and training of the investigators, and patient follow-up procedures have been designed as to further contribute to reduce risks as far as possible for the patient and residual risk acceptance.

Furthermore, potential risks associated with participation in this investigation will be minimized and managed in accordance with ISO 14155, and requirements of the approving IRBs and ECs.

4.8.4. Benefits

The intended clinical benefit of GATT-Patch is to provide fast and persistent hemostasis during surgeries on the liver. It is hypothesized that a high rate of fast and persistent hemostasis may result in less clinical risk of complications to patients undergoing these surgeries.

4.8.5. Potential benefits

It is anticipated that application of the investigational device to a target bleeding site will result in a reduced time to hemostasis compared to conventional methods of hemostasis, such as suture, ligature, or cautery. Individual patients may not benefit directly from participation in this clinical investigation, but conducting this research could contribute to the overall advancement of medical and scientific knowledge and may benefit future patients.

4.8.6. Benefit-risk rationale

GATT Technologies BV believes that any potential risk presented by this clinical investigation has been minimized and that adequate testing, safeguards, and safety monitoring have been incorporated into the clinical investigation to further minimize and mitigate the risks. GATT Technologies BV believes that the potential benefits of GATT-Patch outweigh the potential risks posed to participating subjects. This clinical investigation has been designed to involve as little pain, discomfort, fear and any other foreseeable risks as possible of the subjects. The risk threshold and degree of distress to subjects are defined in the risk analysis.

Further, oversight of the clinical investigation will be provided by:

- A blinded Independent Data Monitoring Committee (IDMC) will monitor the study to ensure safety of study participants and validity and integrity of the data.
- An Independent Adjudication Committee (IAC) will review all serious adverse events (SAEs) and adverse events of special interest (e.g., bleeding-related events, thromboembolic events, biloma, and allergic reaction) occurring during the 3-month

follow-up after surgery for relatedness to the device and expectedness of the event based on the clinical scenario comprising of patient and procedural characteristics.

Therefore, the Sponsor, Medical Expert, and coordinating investigator have determined that this clinical investigation is justified because its potential benefits outweigh potential risks.

4.9. Study Rationale

There is a wide variety of topical hemostatic devices, sealants and adhesives available on the market and these can generally be divided into products without active components, products that include active components that mimic natural coagulation and combined agents. Recently, there has been an increase in development of advanced hemostatic pads and patches that can provide hemostasis and sealant properties similar to fibrin sealants (e.g., TachoSil).[6] GATT Technologies BV developed a hemostatic patch that consists of a gelatin carrier and synthetic activated polymers (NHS-POx). GATT-Patch has been developed to provide a fast and robust control of bleeding during surgery.

In a pilot single-arm clinical trial of patients undergoing liver resection surgery in the Netherlands, the primary endpoint of successful hemostasis within 3 minutes was met with 97.4% versus a literature-derived performance goal of 65.4% ($P<0.001$), with adequate safety of GATT-Patch confirmed. The current clinical investigation will be a pivotal randomized clinical trial that will evaluate the safety and efficacy of GATT-Patch versus TachoSil in elective open liver surgery.

GATT-Patch is indicated for use as an adjunct to hemostasis in surgery for minimal, mild, or moderate bleeding sites when control of bleeding by standard surgical techniques (such as suture, ligature or cautery) is ineffective or impractical. GATT-Patch is intended to be used for management of hemorrhage during surgeries on the liver.

The hemostatic GATT-Patch will be intended for use in adult patients. The safety and performance of the device has not been yet established for use in specific populations as children, pregnant or lactating women.

It should not be used in patients with a known hypersensitivity to the component materials, including porcine proteins and brilliant blue (FD&C Blue #1).

5. STUDY OBJECTIVES AND ENDPOINTS

5.1. Objectives and Hypotheses of the Clinical Investigation

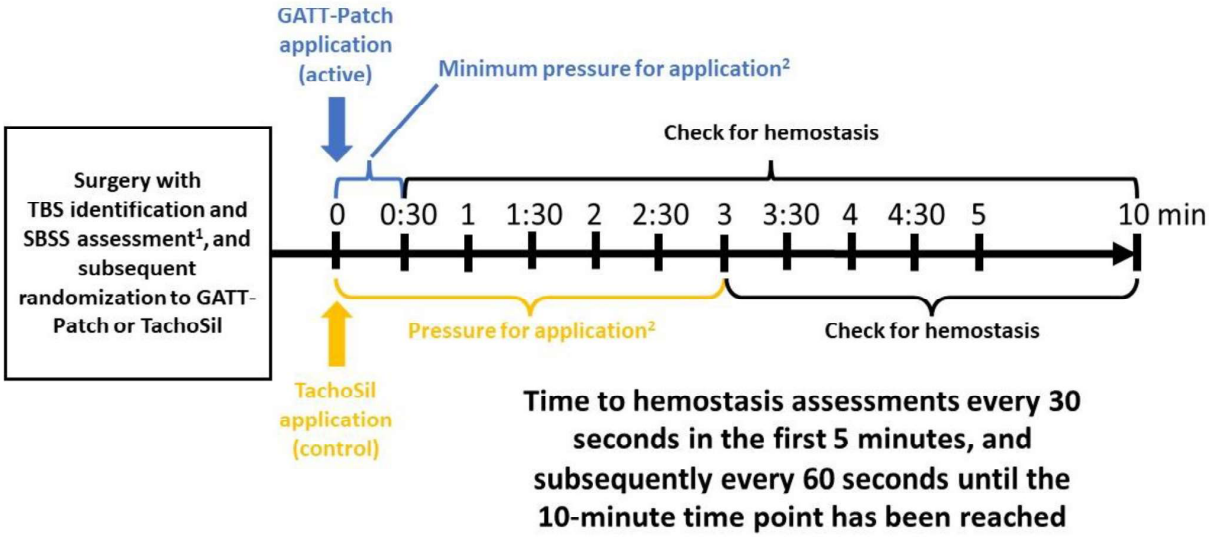
The objective of this clinical investigation is to compare the safety and efficacy of GATT Patch versus TachoSil in liver surgery.

5.2. Study Endpoints

5.2.1. Primary Efficacy Endpoint

The primary efficacy endpoint of this study is defined as non-inferiority of GATT-Patch compared to TachoSil in the percentage of cases achieving hemostasis at 3 minutes without rebleeding at the 10-minute time point. Figure 2 below represents the sequence of events for hemostatic assessments and pre-specified time points for assessment. Hemostasis will be defined by a grade of 0 (None/Dry) on the Surface Bleeding Severity Scale (SBSS), of the direct surface onto which GATT-Patch or TachoSil is applied. The SBSS provides a clinically validated score for assessment of bleeding at the target site, and consists of 6 scales (0 = none, 1 = minimal, 2 = mild, 3 = moderate, 4 = severe; not immediately life-threatening, 5 = extreme; immediately life-threatening).[7] Investigators will be trained and tested on the assessment scale prior to the clinical investigation to have consistent assessment of bleeding at the target site (Section 10.1).

Figure 2. Sequence of Events for Enrollment, Hemostatic Assessments and Time Points.



¹ Target bleeding site (TBS) can only be included with a Surface Bleeding Severity Scale (SBSS) of 1, 2, or 3.
² Time to hemostasis clock starts as soon as the application of GATT-Patch or TachoSil begins.

5.2.2. Secondary Endpoints

5.2.2.1. Efficacy Endpoints

The secondary endpoints for this clinical investigation as defined as:

- Median time to hemostasis in seconds (key secondary endpoint);
- Kaplan-Meier estimated distribution of time to hemostasis;
- Treatment failure, defined as no hemostasis at 10 minutes;
- Rebleeding after 10 minutes but before subject closure; and
- Percentage of hemostasis at 30, 60, 90, 120, 150, 240, 300, 360, 420, 480, 540 and 600 seconds.

Achievement of hemostasis will be verified every 30 seconds for the first 5 minutes and every 60 seconds between 5 and 10 minutes, starting from the time that the hemostatic patch is positioned and pressure is initiated. If hemostasis has not been achieved after 10 minutes of application (SBSS 1-5), then treatment is considered a failure and additional hemostatic agents or techniques may be used. If a subject is randomized to GATT Patch, rescue therapy cannot exist of products containing thrombin and/or fibrinogen.

5.2.2.2. Safety Endpoints

The safety of GATT-Patch will be assessed by the incidence, severity and relation to hemostatic device of all AEs. The AEs for the GATT-Patch group will be compared to those for the TachoSil group.

All AEs will be collected, with adverse events of special interest being:

- Bleeding-related events, including rebleeding of the bleeding site(s) treated with hemostatic patch at any point in time (within 10 minutes of application, prior to subject closure, and postoperative), and including hematoma;
- Thromboembolic events;
- Biloma; and
- Allergic reaction.

5.2.2.3. Exploratory Endpoints

The exploratory endpoints for this clinical investigation are defined as follows:

- Procedure duration (minutes);
- Estimated blood loss (mL) during surgery;
- Number and type of blood transfusion during hospitalization;
- Duration of Intensive Care Unit (ICU) stay;
- Total hospitalization time;
- Postoperative drainage volume, characteristics, and duration;
- Need for and cause of reoperation;
- Imaging of the liver resection at 6 weeks post-surgery to detect (1) fluid collection and its size (in mL) and aspect, (2) pseudo-aneurysm, (3) patch encapsulation, and (4) rolling up of the device on the resection plane;
- Amount of hemostatic material needed versus bleeding surface;
- User satisfaction (questionnaire) for GATT-Patch (Appendix 1, Section 15.1.1);
- Physician treatment preference assessment (questionnaire) (Appendix 2, Section 15.1.2);

- Local recurrence of liver cancer at the resection;
- Cancer-free survival; and
- Overall survival.

5.2.2.4. Five-year follow-up

A full study report will be written based on the 3 month follow-up data and will be submitted to all relevant local country authorities, including a pre-market approval submission to FDA. Furthermore, 5 year observational follow-up will be performed to characterize long-term safety on all patients undergoing liver resection for liver malignancy or metastases, collecting data on local cancer recurrence, disease-free survival, and overall survival. This observational follow-up will not be in direct contact with patient, but through electronic health records and/or contact with the patient's treating physician. Patients will give informed consent to have data up to 5-year follow-up collected. The 5 year observational review will be submitted to all relevant local country authorities through an annual progress report (i.e. FDA) or post-market clinical follow-up report (i.e., countries with EU MDR regulations).

Follow-up will be performed according to standard oncological follow-ups performed by the treating physician (e.g., oncologist or surgeon) and data will be collected at the following intervals: 3 months, 6 months, 9 months, 12 months, 18 months, 24 months, 30 months, 36 months, 42 months, 48 months, 54 months and 60 months (see also Table 7). During each follow-up, data on results of tumor marker analyses (if applicable), performed imaging, diagnostic biopsy or surgical procedures, or other diagnostics will be collected. Furthermore, data on performed additional therapies for cancer during follow-up will be collected: (i) adjuvant systemic chemotherapy, immunotherapy, or other, (ii) locoregional therapy such as ablation, or (iii) (re-)resection of the liver cancer, primary cancer (if applicable), or metastases.

6. INVESTIGATIONAL PLAN

6.1. Description of Overall Study Design and Plan

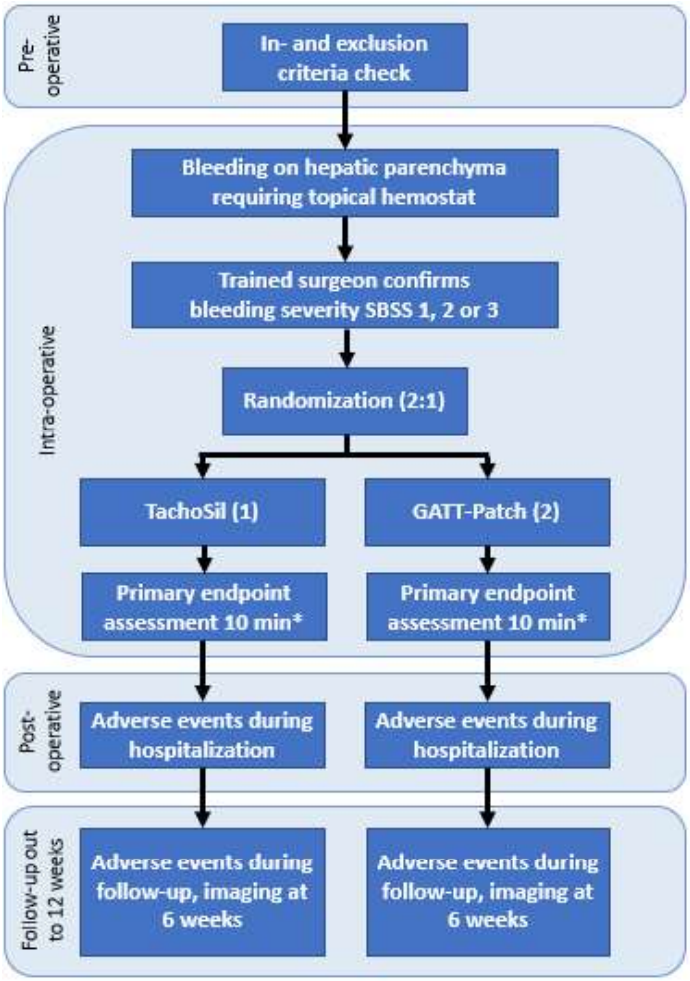
This is a pre-market, prospective, randomized (2:1), multicenter, multi-national pivotal clinical investigation.

Subjects meeting all eligibility criteria will be randomized (2:1) to receive the investigational device, GATT-Patch or the control, TachoSil, respectively. Patients will remain blinded for the randomized treatment and treatment given.

Each surgery will be performed according to the standard procedures of the hospital, with the exception of the use of GATT-Patch versus TachoSil. Subjects who signed informed consent, who meet the preoperative eligibility criteria, and who have an appropriate bleeding site (SBSS 1, 2, or 3 [e.g., reflecting minimal, mild, or moderate bleeding severity] and no contraindications) will be randomized to receive GATT-Patch and TachoSil. Randomization will be performed intraoperatively after intraoperative eligibility criteria have been confirmed. Surgeons cannot be blinded on the hemostatic patch use.

GATT-Patch will be used to control bleeding during open liver surgery. Each surgery will be performed according to the standard procedures of the hospital, with exception of the use of GATT-Patch or TachoSil. At the 6-week follow-up, imaging and some laboratory assessments may be considered study specific procedures, depending on standard-of-care follow-up assessments at sites. The study flow is shown below in Figure 3 and detailed further in the sections below.

Figure 3. Study Design



*Including secondary endpoints during surgery

6.2. Rationale for endpoint selection

Endpoints were selected based on outcomes reported for other topical hemostatic agents in the scientific literature. A meta-analysis identified 15 articles reporting on hemostatic techniques during open liver surgery, and this included 6 articles that specifically reported on the percentage of hemostasis at 3 minutes.[2,6,8,9,10,11,12] The percentage of hemostasis at 3 minutes was found to be a clinically relevant performance outcome for success of various hemostatic techniques during open liver surgery. Data from six different randomized trials that evaluated hemostatic products during liver surgery were pooled to establish an expected rate of successful hemostasis at 3 minutes (Table 4).

Table 4: Summary of Primary Endpoint Outcome reported in Scientific Literature and Used in Sample Size Calculation

Reference	Group	N	Time to hemostasis #[a]	Hemostasis at 3 min.

Bjelovic et al., 2018	Grifols	52	2.8 ± 0.1 min	85.6%
	Surgicel	49	3.8 ± 2.4 min	62.8%
Bochicchio et al., 2015	Fibrocaps	120	1.0 (median)	94.0%
	Gelfoam / Spongostan	61	2.0 min (median)	70.0%
Genyk et al., 2016	TachoSil	114	3.5 ± 1.3 min	80.7%
	ORC (Surgicel)	110	5.5 ± 4.6 min	50.0%
Moench et al., 2014	TachoSil	65	3.38 ± 0.9 min	80.0%
	Sangustop	62	2.2 ± 1.6 min	86.9%
Ollinger et al., 2013	Veriset	32	1.0 min (median)	94.0%
	TachoSil	18	3.0 min (median)	71.0%
Verhof et al., 2015	Fibrocaps	39 (NL) 47 (US)	1.9 min	76.9% (NL) 83.0% (US)
	Gelatin sponge (Gelfoam [US] or Spongostan [NL]	17 (NL) 23 (US)	4.8 min	52.9% (NL) 34.8% (US)
6 RCTs	TachoSil, ORC (Surgicel), Sangustop, Veriset, Grifols, Fibrocaps, Gelatin sponge (Gelfoam or Spongostan)	799	Range 1 min - 5.5 min	Weighted average: 74.8% (95% CI: 65.4% to 83.1%)

[a] # This is the mean time to hemostasis, if not otherwise reported.

The choice of TachoSil as the comparator has not been made to favor the test product, but to obtain the highest standards of clinical evidence in support of GATT-Patch by comparison with the standard-of-care hemostatic patch. Comparison with another hemostatic patch has the advantage of both products being ready-to-use, which limits blood loss during surgery and increases the comparability in safety and performance. The risk-benefit ratio for patches are similar because of comparable application methods and the position and structure of the patch on the target bleeding site in relation to the patient anatomy.

By using TachoSil, a fibrin sealant patch, as the comparator, the standard of care hemostatic agent for open liver surgery, supported by the largest body of evidence from multiple randomized clinical trials (see Table 4), is used in this clinical trial. TachoSil has been used in n=197 patients versus only N=32 for Veriset. Moreover, TachoSil demonstrated to have the highest success rate in up to moderate bleedings, whereas non-active products (Surgicel, Gelfoam, Spongostan, ORC, and Sangustop) had lower rates of hemostasis. In addition, a network meta-analysis including 20 randomized trials, 3267 patients and 7 different interventions found that fibrin sealant patch and fibrin glue were the most effective interventions for achieving hemostasis during liver resection.[1] Other hemostatic agents have been tested in the setting of open liver surgery with promising results, but the level of evidence is limited to only singular trials (i.e., Veriset). Moreover, other products are no longer available for clinical use (i.e., Fibrocaps).

In the PMA submission of TachoSil for an indication as an adjunct to hemostasis during liver surgery, the pooled results of three randomized clinical trials reported that 174 of 233 subjects (74.7%) in the TachoSil treatment group achieved hemostasis at 3 minutes compared with 117 of 231 subjects (50.6%) in the comparator treatment group (that was made up of non-actives) achieved this goal (P<0.0001). Nevertheless, because the rate of successful hemostasis at 3 minutes was 80.7% in the individual trial by Genyk et al[10], GATT chooses to use an estimate of 80% in the power calculation for the current Pivotal clinical investigation.[9]

6.3. Discussion of Study Design

This is a prospective, randomized clinical trial. The study was designed in this fashion in order to assess a balanced subject population undergoing liver surgery and the comparative efficacy and safety of GATT-Patch to another widely used hemostatic patch.

6.4. End of Study

A subject will have fulfilled the requirements for study completion if/when the subject has completed all study periods, including Week 12 follow-up visit/assessment. A full study report will be written based on this 3 month follow-up data and will be submitted to all relevant local country authorities, including a pre-market approval submission to FDA.

Furthermore, patients undergoing liver resection for liver malignancy or metastases will be observationally followed for 5 years to review local cancer recurrence, disease-free survival, and overall survival. This observational follow-up will not be in direct contact with the patient, but through electronic health records and/or contact with the patient's treating physician. The report will submitted to all relevant local country authorities through an annual progress report (e.g., for FDA) or post-market clinical follow-up report (e.g. for countries with EU MDR regulations).

The end of the study will be the last subject's last assessment as indicated in the Schedule of Assessments (Table 7) OR as requested by Sponsor.

7. SELECTION OF STUDY POPULATION

Section 12.2 provides information regarding number of subjects planned to be enrolled/randomized.

7.1. Inclusion Criteria

A subject must meet all of the following pre-operative inclusion criteria to be enrolled into the clinical investigation:

1 Subject is scheduled to undergo elective open surgery on the liver;
2 Subject is willing and able to give written informed consent for the clinical investigation participation;
3 Subject is 22 years of age or older at the time of enrollment; and
4 Subject has been informed of the nature of the clinical investigation.

A subject must meet all of the following intraoperative inclusion criteria to be enrolled into the clinical investigation:

1 Subject in whom the Investigator is able to identify a target bleeding site at the liver resection plane for which any applicable conventional means for hemostasis (e.g. suture, ligature or cautery) are ineffective or impractical, and the choice is made to use a hemostatic agent to stop the bleeding; and
2 Subject has a target bleeding site with a SBSS of 1, 2, or 3 (e.g. reflecting minimal, mild or moderate bleeding severities).

7.2. Exclusion Criteria

A subject must not meet any of the following pre-operative exclusion criteria to be enrolled into the clinical investigation:

1 The target bleeding site is from a large defect in an artery or vein that requires vascular reconstruction with maintenance of vessel patency;
2 Subject is scheduled to undergo surgery on other organs than the liver and its associated biliary and vascular system;
3 Subject is scheduled to undergo a staged liver surgery procedure (e.g., Associating Liver Partition and Portal vein ligation for Staged hepatectomy [ALPPS]);
4 Subject is taking multiple antithrombotic therapies in therapeutic dosage up to the time of surgery, but allowing exclusive use of acetylsalicylic acid;
5 Subject has platelet count <100 x 109/L, an activated partial thrombin time of >100s, or international normalized ratio >2.5;
6 Subject has a total bilirubin level of ≥2.5 mg/dl;
7 Subject is pregnant, planning on becoming pregnant or actively breastfeeding during the 3-month follow-up period;
8 Subject has a known hypersensitivity to brilliant blue (FD&C Blue #1), porcine gelatin, or horse proteins;
9 Subject who has religious objections to receiving products with components of animal (porcine or equine) or human origin;
10 Subject has an active or suspected infection at the bleeding site;
11 Subject in whom the investigational device will be used at the site of a synthetic graft or patch implant;

12 Subject has a life expectancy of less than 3 months;
13 Subject has a documented severe congenital or acquired immunodeficiency;
14 Subject has had or has planned to receive any organ transplantation;
15 Subject is currently participating or has participated in another clinical investigation within the past 30 days that may affect the endpoints of the study, such as trials related to the surgical procedure, and on anti-coagulation;
16 Subject is not appropriate for inclusion in the clinical investigation, per the medical opinion of the Investigator; and
17 Subject has any incidental (pre- and peri-operative) findings deemed by the Investigator to potentially jeopardize the safety or welfare of the subject.

7.3. Rescreening

Individuals who sign the informed consent form (ICF) to participate in the study but who do not subsequently meet all the requirements as outlined in the inclusion and exclusion criteria are considered screen failures. They will not be enrolled and may not be rescreened.

7.4. Study Withdrawal, Removal, and Replacement of Subjects

A sample size of 130 subjects of which a total of 87 subjects will undergo implantation of GATT Patch.

The enrollment period is expected to take approximately 12 months, which includes an FDA review of data for the first 10 US subjects. The per subject duration of the clinical investigation from treatment to follow-up will be approximately 3 months. The total expected duration of the clinical investigation is, therefore, approximately 15 months. Furthermore, 5 year observational follow-up will be performed to characterize long-term safety on all patients undergoing liver resection for liver malignancy or metastases, collecting data on local cancer recurrence, disease-free survival, and overall survival. This observational follow-up will not be in direct contact with the patient, but through electronic health records and/or contact with the patient's treating physician (see Section 5.8). A subject must meet all of the pre-operative and intra-operative inclusion criteria to be enrolled into the clinical investigation. It is expected that circa 80% of the subjects that pass pre-operative eligibility screening will pass intra-operative eligibility screening.

A subject may withdraw or discontinue participation at any time during the clinical investigation. There is no need to provide a reason for withdrawal or discontinuation. The investigator may also decide to stop a subject's participation in the clinical investigation, for example due to non-compliance to the Clinical Investigation Plan (CIP) or if the investigator feels it is in the subject's best interest to stop.

The Sponsor or its representative will be notified immediately when a subject is withdrawn or discontinued for any reason. Premature clinical investigation end date and reason (if known) will be documented on the electronic case report forms (eCRF). If a subject fails to return for a follow-up visit/assessment or cannot be contacted for a follow-up visit/assessment, the investigator will attempt to contact the subject to determine and document the reason for the subject failed to return and to encourage compliance with the study visit/assessment schedule. The investigator will ask for the subject's permission to follow his/her status/condition outside the study.

The data collected up to the time point the subject has withdrawn or discontinued will be included as part of the clinical investigation results. Additional safety information may be requested from a withdrawn or discontinued subject if it is considered clinically relevant. Subjects who withdrawn from the study will receive standard of care defined by applicable treatment Clinical Investigation Plan(s) for the disease at the investigational site. If any additional care is necessary because of the subjects' participation in the clinical investigation, this will be provided to the subject by the investigational site.

There will be no replacement of subjects who have been treated with the investigational or control product.

7.5. Investigational Sites

This clinical investigation will be conducted in the US, Netherlands, and Germany. The clinical investigation in the US will be limited to 2 US sites; expansion to further sites in the US will be covered in an IDE supplement, which will be submitted to FDA after enrollment of 10 US subjects. The report will also be made available to other local country authorities for review upon request. Upon approval of the FDA, additional US sites will be included in the study. A maximum of 12 sites will participate in this clinical investigation, with a distribution as outlined in the table below (Table 5).

Table 5. Number of Clinical Sites per Geography

	Minimum number of sites	Maximum number of sites
US	4	7
Netherlands	2	4
Germany	2	4

A single site may not enroll more than 20% of the total planned population, equivalent to no more than 26 subjects. Further, a minimum of 50% of the subjects will be enrolled in the United States to help ensure that the study subjects are representative of the US population for which this device will be indicated.

7.6. Suspension or Premature Termination of the Clinical Investigation

GATT Technologies BV reserves the right to terminate an investigator and/or investigational site for the following reasons:

- Failure to secure subject informed consent including protection of personal data prior to enrollment.
- Failure to report relevant safety events within 24 hours of discovery after learning of the event.
- Repeated investigational plan deviations.
- Repeated failure to appropriately complete case report forms.
- Failure to enroll an adequate number of subjects.
- Loss of or unaccounted for investigational product inventory.

In addition, GATT Technologies BV may choose to suspend or prematurely terminate the clinical investigation for the following reasons:

- Device deficiency or malfunction
- Production limitation
- Administrative decision

GATT Technologies BV will promptly notify the investigators, ethics committees and regulatory authorities in this event and provide for appropriate therapy and follow-up for the subjects.

- In case of study termination or suspension, the investigators must inform the subjects and may inform the personal physician of the subjects to ensure appropriate care and follow-up is provided. In the case of a study suspension, subject enrollment must stop until the suspension is lifted.

8. TREATMENTS

8.1. Details on the Investigational device

GATT-Patch will be used to control bleeding during open liver surgery as per EU and US GATT-Patch IFU. The differences between IFUs in EU and US related only to the indication for use and do not impact safety and efficacy assessments of GATT-Patch or the conduct of the trial. Please refer to Section 4 of this CIP.

8.1.1. Contraindications

GATT-Patch is not indicated for use on severe (e.g., pulsatile) bleedings with a Surface Bleeding Severity Scale of 4 or 5.

GATT-Patch is not intended for use on organs other than the liver.

GATT-Patch is not intended for intravascular use. Do not attempt to force GATT-Patch into blood vessels, and only apply GATT-Patch after standard surgical techniques have been used to close the vessel.

GATT-Patch should not be used in infected wounds.

GATT-Patch should not be used in patients with a known hypersensitivity to the component materials, including porcine proteins and FD&C Blue #1.

8.1.2. Warnings

GATT-Patch has not been studies in pregnant or lactating women.

GATT-Patch is not intended to be a substitute for standard surgical technique and/or the proper use of other conventional hemostatic techniques.

GATT-Patch should not be used when applying pressure on the entire surface of the patch would be difficult to achieve.

Care should be taken when using GATT-Patch in confined spaces.

Use the smallest number of patches required to cover and extend the margins of the entire bleeding area by at least 1 cm. Maximum dosage for GATT-Patch is 150 cm2, calculating to approximately 3 GATT-Patches, based on a 70 kg patient or 2.1 cm2 / kg. The safety of higher dosages has not been studied.

GATT-Patch should not be hydrated prior to application.

Do not replace, reposition, or peel off GATT-Patch after application with a wet gauze.

GATT-Patch should be wetted homogenously after application.

Degradation of GATT-Patch depends upon several factors including the amount used, degree of saturation with blood or other fluids (e.g., bile) and the tissue bed.

Contact with bile may impact the performance of GATT-Patch.

Prior to resorption, GATT-Patch may be present on imaging.

After application of GATT-Patch, manipulation of the bleeding site and the patch should be minimized.

Due to the properties of the product, it is expected that it can be combined with drugs. For information, please read the package insert of the respective medication.

8.1.3. Precautions

For single use only. Do not re-sterilize. Reuse of single-use devices creates a potential risk of patient infections.

Discard if packaging is damaged.

GATT-Patch should be used within 1 hour after the opening.

8.1.4. Administration

GATT-Patch is intended to be used by physicians trained in performing specific open surgical procedures when adequate pressure can be achieved upon application.

Dry gloves and surgical instruments (forceps, scissors) should be used to handle, cut and apply GATT-Patch. When applying GATT-Patch, minimize contact with wet or bloody surgical instruments or gloves as the adhesive may adhere to other surfaces.

GATT-Patch should not be hydrated prior to placement.

GATT-Patch may be cut to the desired size and shape. Select the appropriate size of GATT-Patch so that it overlaps the margins of the bleeding surface by at least 1 cm.

Multiple patches may be used for larger bleeding surfaces. GATT-Patch may be applied to, or (partly) overlap, a previously applied patch ("patch on patch").

It is recommended that dry parts of GATT-Patch after application are wetted.

Leave GATT-Patch in situ after hemostasis has been achieved. Do not try to forcefully remove the patch.

Do not remove GATT-Patch at the end of the surgery. Excess GATT-Patch material may be removed carefully, at the discretion of the surgeon.

Surgeons may use up to three patches, or multiple (cut) parts of patches, as long as total material used is no more than three full patches in total in the subject. Patch may be applied to or overlap a previously applied patch ("patch-on-patch").

If hemostasis has not been achieved after using three patches, other hemostatic agents/techniques may be used. If a subject is randomized to GATT-Patch, rescue therapy cannot exist of products containing thrombin and/or fibrinogen.

The following method of application is provided in the EU and US IFU of GATT-Patch:

- Apply GATT-Patch dry to the bleeding site with at least 1 cm margins and hold in place with a saline wetted gauze and uniform pressure over the entire patch surface for 30 seconds. Gently remove the wet gauze from the patch. If complete hemostasis has not been achieved in 30 seconds, re-apply pressure with a saline wetted gauze or surgical sponge for an additional 30 seconds;

- If hemostasis is not complete with a single patch and blood comes through the patch, apply a new (piece of) GATT-Patch on the bleeding site with a 1 cm overlap with tissue or previously placed GATT-Patch on all sides ("patch-on-patch"). Apply according to the steps above.
- If hemostasis is not complete because GATT-Patch is not adherent to the underlying tissue, with or without hematoma formation underneath, remove the non-adherent part and apply a new (piece of) GATT-Patch on the bleeding site with a 1 cm overlap with tissue or previously placed GATT-Patch on all sides ("patch-on-patch"). Apply according to the steps above.
- Repeat the above steps as necessary, with a maximum of 2.1 cm2/kg of subject body weight covered by GATT-Patch and remaining in-situ at the end of the operation (approximately 3 patches in an adult patient of 70 kg).

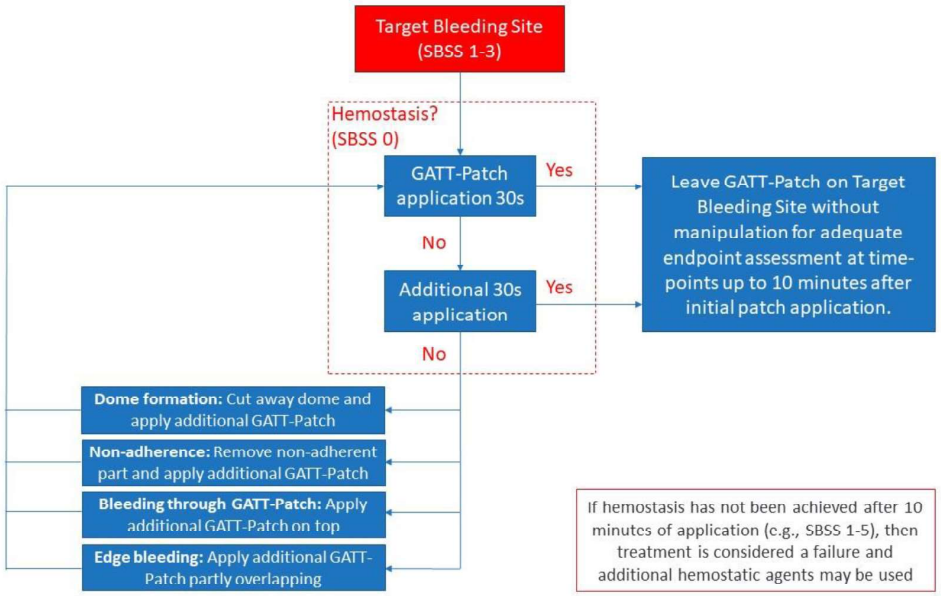
8.1.5. Handling in the Clinical Trial

To ensure adequate endpoint assessment in this clinical investigation, no manipulation of GATT-Patch and the Target Bleeding Site should be performed up to 10 minutes after GATT-Patch application, unless extra pressure or an additional patch is required per EU and US IFU and scenarios below.

As described in the EU and US IFU, certain situations can occur in which hemostasis is not achieved after an initial 30 seconds application time. The following description, and Figure 4, provides more details:

- Hemostasis is achieved (SBSS 0) but blood builds up underneath GATT-Patch as shown by a dome formation (e.g., caused by inadequate pressure) → re-apply 30 seconds of pressure. If after an additional 30 seconds of pressure a dome again arises, cut away the dome and apply a new (piece of) GATT-Patch on the bleeding site with a 1cm overlap with tissue or previously placed GATT-Patch on all sides. Apply pressure for 30 seconds. Repeat as necessary for up to 10 minutes. If hemostasis is achieved (SBSS 0) and GATT-Patch is adhesive to the tissue → leave GATT-Patch in place and do not manipulate until 10 minutes from the initial application have passed.
- Hemostasis is not achieved (SBSS ≥1) because GATT-Patch is not adherent to underlying tissue (e.g., caused by inadequate pressure) → re-apply 30 seconds of pressure. If after an additional 30 seconds of pressure (a part of) GATT-Patch is not adherent, cut away the non-adherent part and apply a new (piece of) GATT-Patch on the bleeding site with a 1 cm overlap with tissue or previously placed GATT-Patch on all sides. Apply pressure for 30 seconds. Repeat as necessary for up to 10 minutes. If hemostasis is achieved (SBSS 0) and GATT-Patch is adhesive to the tissue →leave GATT-Patch in place and do not manipulate until 10 minutes from the initial application have passed.
- Hemostasis is not achieved as blood is coming through GATT-Patch (SBSS ≥1) → re-apply 30 seconds of pressure. If after an additional 30 seconds of pressure, blood is still coming through the patch (e.g., potential cause is puncture of the patch), apply an additional (piece of) GATT-Patch on the bleeding site (e.g., “patch-on-patch”) with a 1 cm overlap on the previously placed GATT-Patch on all sides. Apply pressure for 30 seconds. Repeat as necessary for up to 10 minutes. If hemostasis is achieved (SBSS 0) and GATT-Patch is adhesive to the tissue → leave GATT-Patch in place and do not manipulate until 10 minutes from the initial application have passed.

Figure 4. GATT Application Flowchart



8.2. Details on the control product

The control device for this study is TACHOSIL® Fibrin Sealant Patch (Baxter Healthcare Corporation; Deerfield, IL, USA; hereinafter referred to as TachoSil). TachoSil is a fibrin sealant patch indicated for use with manual compression in adult and pediatric patients as an adjunct to hemostasis in cardiovascular and hepatic surgery, when control of bleeding by standard surgical techniques (such as suture, ligature or cautery) is ineffective or impractical.

TachoSil is a topical fibrin sealant patch consisting of human fibrinogen and human thrombin coated onto an equine collagen sponge. TachoSil usage in this clinical investigation will be in accordance with the product's Instructions for Use, with a minimum time of pressure during application of 3 minutes.

TachoSil was selected as the control device for this clinical investigation for the following reasons:

- One of the most commonly used hemostatic patches[b, c]
- Indication includes hepatic surgery
- Is also a patch and therefore has similarity in application method and presents similar risks
- Is a ready-to-use product allowing direct comparison without preparation time variation
- Is considered to be the standard-of-care hemostatic patch because of its high hemostatic performance of ~80% hemostasis at 3 minutes, as compared with ~60% with non-active products

[b] https://ec.europa.eu/commission/presscorner/detail/en%3E/ip_20_529
[c] https://ec.europa.eu/competition/mergers/cases1/202046/m9547_780_6.pdf

8.3. Surgical procedure

Each surgery will be performed according to the standard procedures at the hospital, with exception of the randomized use of GATT-Patch or TachoSil. GATT-Patch or TachoSil will be used if the subject has an appropriate bleeding site (SBSS 1, 2 or 3 as shown in Table 6 below).[7] Randomization to the use of GATT-Patch or TachoSil will only be considered during and/or after resection when control of bleeding by standard surgical techniques (such as suture, ligature or cautery) is ineffective or impractical, and the surgeon has made the decision to apply a topical hemostatic product. If there are multiple appropriate (SBSS 1-3) bleeding sites that require use of a topical hemostatic product, the first encountered bleeding site that requires topical hemostat application will be considered for the primary endpoint, but information on achieved hemostasis will also be collected for additional bleeding sites.

Table 6. Surface Bleeding Severity Scale

SBSS Score	**0**	**1**	**2**	**3**	**4**	**5**
Verbal Descriptor	None	Minimal	Mild	Moderate	Severe; not immediately life-threatening	Extreme; immediately life-threatening
Visual Descriptor	Dry	Oozing	Pooling	Flowing	Streaming	Gushing
Expected Intervention(s)	None	Manual pressure, cautery, adjuvant hemostat(s)	Manual pressure, cautery, suture, adjuvant hemostat(s)	Manual pressure, cautery, suture, adjuvant hemostat(s)	Manual pressure, cautery, suture, staples, tissue repair	Manual pressure, cautery, suture, staples, tissue repair
Maximum Expected ACS-ATLS Shock Risk Class	1	1	1	2	3	4

ACS-ATLS Shock Risk: American College of Surgeons - Advanced Trauma Life Support

Class1: involves up to 15% of blood volume; typically, no change in vital signs and fluid resuscitation is not usually necessary.

Class 2: involves 15%-30% of total blood volume; subject is often tachycardic with a narrowing of the difference between the systolic and diastolic blood pressures; the body attempts to compensate with peripheral vasoconstriction; skin may start to look pale and be cool to the touch; volume resuscitation with crystalloids is all that is typically required; blood transfusion is not typically required.

Class 3: involves loss of 30%-40% of circulating blood volume; subject's blood pressure drops; heart rate increases, peripheral hypoperfusion worsens; fluid resuscitation with crystalloid and blood transfusion are usually necessary.

Class 4: involves loss of > 40% of circulating blood volume; the limit of the body's compensation is reached, and aggressive resuscitation is required to prevent death.

Once intraoperative eligibility criteria are met, then the subject is formally randomized and enrolled into the clinical investigation. Randomization will be performed through Interactive Voice/Web Response System. Randomization to GATT-Patch and TachoSil will occur in a 2:1 ratio and stratified by site using random permuted block sizes of three or six for treatment assignment.

The handling instructions for GATT-Patch are provided in specific EU and US instructions for use (IFU) of the device. Select the appropriate size of the patch so that it overlaps the margins of the bleeding surface by at least 1 cm. The patch may be cut to the desired size and shape. Dry gloves and surgical instruments (forceps, scissors) should be used to handle and cut GATT-Patch. GATT-Patch can be placed on a wet gauze prior to placement, and after excess blood is removed from the bleeding site, directly applied on the bleeding site with continuous pressure for an initial 30-seconds application time. Application of TachoSil will follow the manufacturer's IFU, which requires a 3-minute application time. The primary endpoint of this investigation is hemostasis at 3 minutes, and therefore, is in line with the TachoSil IFU.

The choice for a different application time for GATT-Patch and TachoSil is supported by the specific design of GATT-Patch to achieve hemostasis quickly, as shown by the 82% rate of hemostasis after 30 seconds with GATT-Patch in the first-in-human trial (see Section 4.7). Therefore, the shorter compression times and assessment of hemostasis prior to the 3 minute time point for GATT-Patch is not anticipated to pose additional safety concerns for the patient. A shorter application time of TachoSil to align with GATT-Patch is inappropriate as it is assumed that the hemostatic performance of TachoSil will be less than the anticipated 75-80% at 3 minutes if handled under less optimal conditions than outlined in the IFU.

For calculation of the median time to hemostasis, achievement of hemostasis will be verified every 30 seconds starting after the initial 30 seconds of application for GATT-Patch, and every 30 seconds after the initial 3 minutes for TachoSil up to the 5-minute time point, and every 60 seconds between 5 and 10 minutes.

The primary performance endpoint is defined by the percentage of cases achieving hemostasis at 3 minutes without rebleeding within 10 minutes. Hemostasis will be defined by a grade of 0 (None/Dry) on the SBSS[d].

If hemostasis has not been achieved after 10 minutes of application (SBSS 1-5), then treatment is considered a failure and other additional hemostatic agents/techniques may be used. Subjects randomized to GATT-Patch may not undergo rescue with TachoSil and those subjects randomized to TachoSil may not undergo rescue with GATT-Patch. In the case 3 full GATT-Patches have been applied and a bleeding site other than a previously treated target bleeding site is identified, other additional hemostatic agents/techniques may be used that do not contain fibrinogen and/or thrombin components.

Placement of surgical drains will be left at the discretion of the treating surgeon on whether it is clinically indicated.

The investigators will complete a user questionnaire at the end of each procedure. At the end of the trial, each investigator will be asked to complete a physician preference questionnaire on GATT-Patch versus TachoSil.

The following procedural data will be collected:

- **Surgical procedure data:**

[d] The Surface Bleeding Severity Scale (SBSS) provides a validated score for assessment of bleeding at the target site, and consists of 6 scales (0=none, 1=minimal, 2=mild, 3=moderate, 4=severe; not immediately life-threatening, 5=extreme; immediately life threatening) (Spotnitz, 2017). Investigators will be trained and tested on the assessment scale prior to the clinical investigation to have consistent assessment of bleeding at the target site.

- Date of surgery
- Description of surgical procedure of the liver (e.g., anatomic or non-anatomic resection and extent of resection (e.g., left hemihepatectomy, right hemihepatectomy, extended left hemihepatectomy, extended right hemihepatectomy, segmentectomy [and which segment], bisegmentectomy [and which segments], trisegmentectomy [and which segments], non-anatomical wedge resection(s) and its location(s))
- Vascular reconstruction performed (yes/no)
- Biliary tree reconstruction performed (yes/no)
- Type of hepatic parenchyma (e.g., normal, cirrhotic, staetotic)
- Maneuvers to limit liver blood inflow (e.g., none, Pringle, total vascular exclusion, other) and duration
- Resection method (e.g., Cavitron Ultrasonic Surgical Aspirator [CUSA], harmonic scalpel, scalpel, other)
- Estimated size (cm x cm) of resection area(s)
- Description of target bleeding site(s) (location)
- Estimated size (cm x cm) of target bleeding site(s)
- Number and size (cm x cm) of devices used
- Amount of hemostatic material needed versus bleeding surface;
- Use of conventional means for hemostasis before topical hemostat use (e.g., cautery, sutures or staples)
- SBSS (0-5) of target bleeding site(s) at each pre-specified time point
- Time of SBSS classification
- Randomization to GATT-Patch or TachoSil
- Time of randomization
- Use of any (and which) rescue treatments after ineffective randomized treatment with GATT-Patch or TachoSil
- Number and type of intraoperative blood transfusions
- Incidence of any device deficiencies
- Incidence of any complications or AEs
- Estimated blood loss (mL)
- Procedure duration (from start incision to surgical site closure)
- Use of surgical drains
- User satisfaction per investigator per procedure (questionnaire)
- Macroscopic R0 resection for patients undergoing surgery for malignancy
- Microscopic R0/R1 resection for patients undergoing surgery for malignancy

- **Hospitalization:**
  - Duration of subject's time spent in the intensive care unit
  - Total hospitalization period
  - Postoperative drainage volume, characteristics, and duration;
  - Analysis of drainage fluid for bilirubin, if applicable;
  - Number and type of blood transfusions during post-operative hospitalization
  - Need for and cause of reoperation at the target bleeding site;
  - Incidence of any complications or AEs; and
  - Laboratory test data.

8.4. Measures to Minimize Bias

Due to the physical differences in the investigational and control devices, blinding of the surgeon is not possible. However, bias is minimized during this clinical investigation by performing a randomized trial and conducting this under the terms of an approved clinical investigation plan, use of specific inclusion and exclusion criteria, careful definitions for clinical investigation procedures and outcomes, and prospectively defined methods of data analysis. Moreover, a validated bleeding scale is used to assess the severity of bleeding before randomization and to evaluate hemostasis after patch use. The baseline bleeding severity will be assessed prior to randomization, at which point in time the investigator is not aware of the treatment assignment. Further, the training and testing required for all investigators to use a validated bleeding severity scale for the assessment of successful hemostasis reduces subjectivity for the efficacy assessments.

For the evaluation of safety events, bias is reduced by:

- Blinding patients to the randomized and received treatment;
- An independent adjudication committee will review all serious adverse events (SAEs) and adverse events of special interest (e.g., bleeding-related events, thromboembolic events, biloma, and allergic reaction) occurring during the 3-month follow-up after surgery for relatedness to the device and expectedness of the event based on the clinical scenario comprising of patient and procedural characteristics;
- A blinded independent data monitoring committee will review the overall safety and efficacy of the trial.

8.5. Device Accountability and Compliance

The principal investigator (PI) or other designated individual will maintain records of device delivered to the study site, the inventory at the study site, the distribution to and use by each subject, and the return of materials to the Sponsor for storage or disposal. These records should include dates, quantities, batch/serial numbers, expiration dates, and unique code numbers assigned to the device and study subject.

Administration of study device will be supervised by study site personnel to ensure compliance.

8.5.1. Device Accountability

Access to investigational devices will be controlled and the investigational devices will be used only in the clinical investigation and according to the CIP.

The Sponsor will keep records to document the location of all investigational devices from shipment of investigational devices to the investigational sites until return or disposal.

Investigational devices can be traced by a unique LOT number. The devices will be labelled with the text “CAUTION: Investigational Device Limited by Federal Law to investigational use” to avoid non approved use of the device.

The Sponsor will have instructions in place and make packaging materials available, if applicable, for the safe return or disposal of investigational devices, including potentially hazardous devices.

The PI or an authorized designee will keep records documenting the receipt, use, return and disposal of the investigational devices, which will include:

- name(s) of person(s) who received, used, returned or disposed the device,
- the date of the receipt,
- identification of each investigational device (batch number/serial number or unique code),
- quantity of investigational devices,
- the expiry date, if applicable,
- the date or dates of use,
- subject identification,
- the date of return of unused, expired or malfunctioning investigational devices, if applicable,
- the date and documentation of disposal of the investigational devices as per instructions of the Sponsor, if applicable.

Written procedures will be established for the entire process of device accountability.

8.6. Prior and Concomitant Therapy/Medication

Restricted prior therapies are provided in Section 7.2.

Medications taken by or administered to the subject at the time of screening will be recorded in the eCRF. After the baseline visit, any concomitant medication is acceptable. Medication or therapy that is taken by or administered to the subject during the course of the study must be recorded in the eCRF. Anesthetics used for the surgery are not required to be entered as concomitant medication. The entry must include the dose, regimen, route, indication, and dates of use.

9. STUDY PROCEDURES

Table 7 outlines the timing of procedures and assessments to be performed throughout the study. Section 11.3 specifies laboratory assessment samples to be obtained. See Sections 5 and 11 for additional details regarding efficacy assessments and safety assessments, respectively.

Table 7. Schedule of assessments

Assessments	Screening (<6 weeks before surgery)	Admission before surgery*	Treatment	Hospitalization after surgery	Week 6 (±2wks)	Week 12 (±2wks)	Up to 5 years follow-up****
Informed consent	X						
In- and exclusion criteria	X	X	X				
Baseline demographics and medical history (incl. allergies)	X						
Medication (incl. those impacting coagulation)	X	X		X	X	X	
Physical examination	X	X		X	X		
Laboratory tests	X**	X**		X	X		
Procedural data (incl. primary endpoint and device deficiency)			X				
User questionnaire			X				
Adverse events assessments (with specific attention to bleeding and thrombotic events)			X	X	X	X	
Imaging of resection					X***		
Cancer recurrence / progression						X	6 ± 1 months, 9 ± 1 months, 12 ± 2 months, 18 ± 3 months, 24 ± 3 months, 30 ± 3 months, 36 ± 3 months, 42 ± 3 months, 48 ± 3 months, 54 ± 3 months, 60 ± 3 months

*In situations where the patient is screened during the admission before surgery, this is considered to be the screening visit and no additional visit at admission before surgery is performed.

**At least once before surgery during one of the assessments, with the latest data being the final pre-surgical data used in analyses.

*** Ultrasound imaging is mandatory at the Week 6 (±2 weeks) follow-up point. If other imaging, for example Computed Tomography (CT), is performed in this follow-up window per standard of care for the evaluation of adverse events, these can replace the requirements of ultrasound imaging.

**** The last assessment with direct patient contact is at week 12 ± 2 regardless of indication for surgery. Patients undergoing liver resection for liver malignancy or metastases will be observationally followed for 5 years to review local cancer recurrence, disease-free survival, and overall survival. This observational follow-up will not be in direct contact with the patient, but through electronic health records and/or contact with the patient's treating physician.

A full study report will be written based on the 3 month follow-up data and will be submitted to all relevant local country authorities, including a pre-market approval submission to FDA.

Furthermore, patients undergoing liver resection for liver malignancy or metastases, will be observationally followed for 5 years to review local cancer recurrence, disease-free survival, and overall survival, and submitted to all relevant local country authorities through an annual progress report (e.g., for FDA) or post-market clinical follow-up report (e.g., for countries with EU MDR regulations).

9.1. Informed Consent

Prior to performing any study-specific procedures, a detailed explanation of the study procedures, potential discomforts, risks and benefits of participation, and alternatives will be reviewed with potential study subjects by a qualified and delegated member of the investigational site study team. Subjects will be provided adequate time to review the informed consent document and all questions will be answered to the satisfaction of the subject prior to signing the informed consent.

If the subject is willing to participate in the clinical investigation, he/she or an authorized legal representative must signed the ICF indicating that they have read and understand the information provided. Each investigational site will follow their local independent ethics committee (IEC)/institutional review board (IRB) and applicable regulatory guidelines for obtaining informed consent. Documentation of the informed consent process for each subject and the original signed consent will be retained at the investigational site.

9.2. Study Procedures

Assessments and their timing are to be performed as outlined in the Schedule of Assessments (Table 7). Section 11.3 specifies laboratory assessment samples to be obtained.

Assessments and procedures scheduled at a visit where study device is administered should be performed before treatment unless otherwise indicated in the Schedule of Assessments (Table 7). The expectation is that all assessments scheduled for this study are similar to a site's standard of care, with the exception of use of GATT-Patch, and week 6 follow-up imaging and additional laboratory assessments (which will differ between countries and sites).

Efficacy assessments are described in Section 5.

Safety assessments are described in Section 11.

The investigator may, at his/her discretion, arrange for a subject to have a medical assessment outside the study specified visits (Week 6 and Week 12), especially in the case of AEs that require follow-up, rehospitalization, or are considered by the investigator to be possibly related to the use of investigational device. The additional visit/assessment eCRF page must be completed for these medical assessments/visits. Follow-up of AEs, adverse device effects (ADEs), serious adverse events (SAEs), serious adverse device effects (SADEs), and unanticipated serious adverse device effect (USADEs) leading to study discontinuation is required (as further specified in Section 11.5Adverse Events).

10. CLINICAL PERFORMANCE ASSESSMENTS

The Schedule of Assessments (Table 7) outlines the efficacy assessments to be performed throughout the study and their timing.

On-site initiation visits will be organized, in which full training will be given to all appropriate staff members participating in the clinical investigation, including (principal) investigators, study coordinators and any other site personnel pivotal to the conduct of the clinical investigation. This training will include: instructions on the functions and use of the investigational device by the Sponsor, IFU on the control product, training on SBSS for assessment of bleeding at the target site, procedures outlined in the CIP, main principles of Good Clinical Practices for Medical Devices (ISO 14155), instructions on completion of the eCRFs, content of the investigator site file, and management of device deficiencies.

10.1. Surface Bleeding Severity Scale (SBSS)

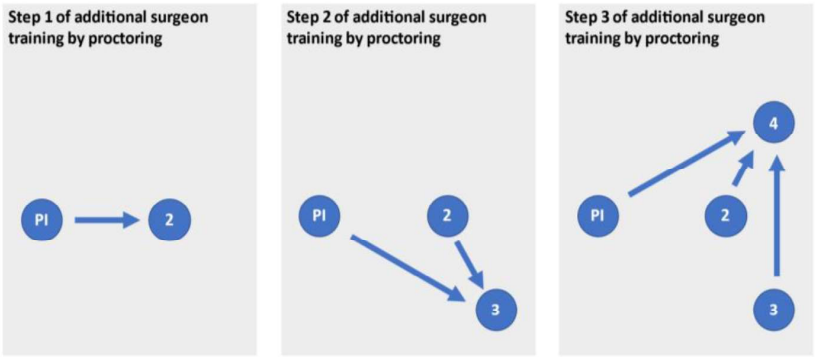
The investigators at each site will have training on the SBSS prior to the enrollment of any subjects. Training will be in conformity with GATT Technologies procedure as described in internal GATT document DHF-01-SR-107 (Appendix 3). In summary, investigators will be taught on the severity of bleeding via 36 instructional videos of different scenarios of blood flow and bleeding area size. Subsequently, investigators will undergo a test in which they are shown 108 videos in a random order, for which they have to indicate the bleeding severity on a scale of 0-5 on the SBSS. Training on the SBSS will be performed to reduce intra-rater variability in the assessment of bleeding at the target site, and adequate evaluation of hemostasis after application of the investigational or control product. A certificate will be provided when successfully completing the test and is subsequently filed in the Trial Master File (TMF). Only those surgeons trained and tested on the SBSS will be permitted to assess bleeding severity and hemostatic performance.

Clinical performance of GATT-Patch will be assessed using the SBSS. Hemostasis will be assessed at the pre-defined time points and is defined as an SBSS of 0 (none/dry). As this endpoint is assessed intraoperatively, study staff will undergo training on study-specific assessments and documentation processes.

10.2. Investigational Device and Procedure

All investigators will have training on the investigational device prior to the start to reduce a potential influence of a learning curve in using the device on outcome. A training record on the investigational device training will be signed on completion of the training and filed in the TMF. The PI will get acquainted with use of the device during implantation in animals, after which they can use GATT-Patch on trial subjects. Each additional surgeon that has not yet used GATT-Patch will be proctored by the PI or an experienced investigator that has previously used GATT-Patch at least once. The flow of training by proctoring is further explained in Figure 5. A training record for the proctoring session will be signed on completion of the training and filed in the TMF.

Figure 5. GATT-Patch Training Flow Chart



PI = principal investigator; numbers reflect additional surgeons performing surgery with GATT-Patch

11. SAFETY ASSESSMENTS

Safety assessments (vital signs, AEs, ADEs, SAEs, SADEs, clinical laboratory results (routine hematology and biochemistry) are to be performed at Clinical Investigation Plan-specified visits, as specified in the Schedule of Assessments (Table 7).

11.1. Medical History

Medical history will be recorded at screening. Investigators should document the occurrence, signs, and symptoms of the subject's preexisting conditions, including all prior significant illnesses, up to screening. Additional preexisting conditions present at the time when informed consent is given and up to the time of treatment are to be regarded as concomitant. Medical history will include the following:

- Allergies
- Smoking history (and current)
- Cardiac disorder(s)
- Systemic hypertension
- Renal dysfunction
- Diabetes
- Hereditary blood disorder(s)
- Blood transfusions in the last 3 months
- Previous abdominal surgery
- Liver disease
    - Child-Pugh classification
- Portal hypertension
- Malignancies and prior therapies
- Indication for surgery (e.g., hepatocellular carcinoma, colorectal metastases, non-colorectal metastases, cholangiocarcinoma, benign tumor, other)
- Other critical medical condition or previous surgery
- ASA classification

Illnesses first occurring or detected during the study and/or worsening of a concomitant illness during the study are to be documented as AEs on the eCRF in accordance with Section 11.5. All changes not present at baseline or described in the past medical history and identified as clinically noteworthy must be recorded as AEs.

Additionally, demographic data will be collected for all subjects and include:

- Age
- Sex
- Race and ethnicity

Race and ethnicity data is being collected for two primary reasons:

- The incidence of hepatic disease differs between racial backgrounds; and
- Per the Food and Drug Administration (FDA) guidance document "Collection of Race and Ethnicity Data in Clinical Trials" dated 26 October 2016.

11.2. Physical Examination

A physical examination (to include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal, and neurological systems) will be performed at time points according to Schedule of assessments (Table 7). Care should be taken to examine and assess any abnormalities that may be present, and add them to the patient's medical history if found at the screening visit or at admission before surgery.

Vital signs (heart rate, and systolic and diastolic blood pressure measurements, oxygen saturation) will be evaluated at the visits indicated in the Schedule of Assessments (Table 7). Blood pressure measurements are to be taken in the same arm for the duration of the study. Body weight (without shoes) will be recorded before surgery during the screening or admission assessment and after surgery when clinically indicated; height (without shoes) will be recorded at screening only.

Vital sign measurements will be repeated if clinically significant or machine/equipment errors occur. Out-of-range blood pressure, oxygen saturation or heart rate measurements will be repeated at the investigator's discretion. Any confirmed, clinically significant abnormal vital sign measurements must be recorded as AEs.

11.3. Laboratory Assessments

Laboratory tests will be collected prior to surgery, and through the postsurgical admission. The collection of laboratory tests is specified in Table 8. Tests that are indicated with an 'X' are required per this CIP. Tests that are indicated with an '**' are not dictated by this CIP: results will only be captured if these test data is collected per standard of care.

Table 8. Laboratory Testing Schedule

Laboratory Tests	Screening	Admission Before Surgery*	Through Admission**	Week 6 (±2 Weeks)
Hematology				
Complete blood count	X	*	X	X
Coagulation				
Prothrombin time (PT)	X	*	X	**
Activated partial thromboplastin time (aPTT)	X	*	X	**
International Normalized Ratio (INR)	X	*	X	**
Chemistry				
Bilirubin	X	*	X***	X
Calcium	X	*	**	**
Potassium	X	*	**	**
Sodium	X	*	**	**
Chloride	X	*	**	**
Albumin	X	*	X	X
Creatinine	X	*	X	**
Asparate transaminase (AST)	X	*	X	X
Alanine transaminase (ALT)	X	*	X	X
Gamma Glutamyl Transferase (gGT)	X	*	X	X

Laboratory Tests	Screening	Admission Before Surgery*	Through Admission**	Week 6 (±2 Weeks)
Other				
Pregnancy test (if applicable)	X	*	N/A	N/A

*Should be performed at least once before surgery during the screening visit or admission before surgery assessments, with the latest data being the final pre-surgical data used in analyses.

**Timing of collection of this data will be according to standard of care hospital procedures.

***And of the drainage fluid of a surgical drain, if applicable.

11.4. Equipment for Assessment

The following equipment will be required for assessment of endpoints:

- Imaging system for ultrasound of liver resection area, or other imaging modalities are allowed if performed per standard of care or evaluation of potential AEs; and
- Stopwatch.

Blood samples will be analyzed at local laboratories at each site. All laboratory reports must be reviewed, signed, and dated by the investigator. A legible copy of all reports must be filed with both the subject's eCRF and medical record (source document) for that visit. Any laboratory test result considered by the investigator to be clinically significant should be considered an AE (clinically significant AEs include those that require an intervention). Clinically significant abnormal values occurring during the study will be followed up until repeat test results return to normal, stabilize, or are no longer clinically significant.

11.5. Adverse Events

11.5.1. Adverse Events

An AE is any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device and whether anticipated or unanticipated.

This definition includes events related to the investigational medical device; events related to the procedures involved.

Subjects will be instructed to report AEs at each study visit. All AEs are to be followed up until resolution or a stable clinical endpoint is reached.

Each AE is to be documented on the eCRF with reference to date of onset, duration, frequency, severity, relationship to investigational device, action taken with study device, treatment of event, and outcome. Furthermore, each AE is to be classified as being serious or nonserious. Changes in AEs and resolution dates are to be documented on the eCRF.

For the purposes of this study, the period of observation for collection of AEs extends from the time the subject is enrolled and randomized until the last follow-up visit at 3 months. Follow-up of the AE is required if the AE persists until the event resolves or stabilizes at a level acceptable to the investigator.

When changes in the severity of an AE occur more frequently than once a day, the maximum severity for the event should be noted. If the severity category changes over a number of days, then those changes should be recorded separately (with distinct onset dates).

The severity of AEs will be graded according to the ISO14155:2020.

Specific guidelines for classifying AEs by severity and relationship to investigational device are given in Table 9 and Table 10.

Table 9. Classification of Adverse Events by Severity

MILD: Awareness of signs or symptoms, but easily tolerated and are of minor irritant type causing no loss of time from normal activities. Symptoms do not require therapy or a medical evaluation; signs and symptoms are transient.

MODERATE: Events introduce a low level of inconvenience or concern to the participant and may interfere with daily activities but are usually improved by simple therapeutic measures; moderate experiences may cause some interference with functioning.

SEVERE: Events interrupt the participant's normal daily activities and generally require systemic drug therapy or other treatment; they are usually incapacitating.

Table 10. Classification of Adverse Events by Relationship to Study Device

NOT RELATED: The relationship to the device, comparator or procedures can be excluded when:

- the event has no temporal relationship with the use of the investigational device or the procedures to application of the investigation device.
- the serious adverse event does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible.
- the discontinuation of medical device application or the reduction of the level of activation/exposure - when clinically feasible - and reintroduction of its use (or increase of the level of activation/exposure), do not impact on the serious adverse event.
- the event involves a body-site or an organ that cannot be affected; the serious adverse event can be attributed to another cause (e.g., an underlying or concurrent illness/ clinical condition, an effect of another device, drug, treatment or other risk factors).
- the event does not depend on a false result given by the investigational device used for diagnosis[e], when applicable.
- harms to the subject are not clearly due to use error.
- the event depends on a false result given by the investigational device used for diagnosis[f], when applicable.

In order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.

POSSIBLE: The relationship with the use of the investigational device or comparator, or the relationship with procedures, is weak but cannot be ruled out completely. Alternative causes are also possible (e.g., an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment). Cases where relatedness cannot be assessed or no information has been obtained should also be classified as possible.

PROBABLE: The relationship with the use of the investigational device or comparator, or the relationship with procedures, seems relevant and/or the event cannot reasonably be explained by another cause,

[e] If an investigational device gives an incorrect diagnosis, the subject might, for example, receive an unnecessary treatment and incur all the risks that accompany that treatment, or might be incorrectly diagnosed with a serious disease. In other cases, the subject might not receive an effective treatment (thereby
missing out on the benefits that treatment would confer), or might not be diagnosed with the correct disease
or condition.

[f] If an investigational device gives an incorrect diagnosis, the subject might, for example, receive an unnecessary treatment and incur all the risks that accompany that treatment, or might be incorrectly diagnosed with a serious disease. In other cases, the subject might not receive an effective treatment (thereby missing out on the benefits that treatment would confer),or might not be diagnosed with the correct disease or condition.

Causal relationship: The serious adverse event is associated with the investigational device, comparator, or with procedures beyond reasonable doubt when:

- the event is a known side effect of the product category the device belongs to or of similar devices and procedures;
- the event has a temporal relationship with investigational device use/application or procedures;
- the event involves a body-site or organ that:
    - the investigational device or procedures are applied to;
    - the investigational device or procedures have an effect on;
- the serious event follows a known response pattern to the medical device (if the response pattern is previously known);
- the discontinuation of medical device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of the level of activation/exposure), impact on the serious event (when clinically feasible);
- other possible causes (e.g., an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out;
- harm to the subject is due to error in use;
- the event depends on a false result given by the investigational device used for diagnosis[2], when applicable.

11.5.2. Adverse Device Effect

An ADE is an AE related to the use of an investigational medical device.

This definition includes AEs resulting from insufficient or inadequate IFU, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device. And this definition includes any event resulting from use error or from intentional misuse of the investigational medical device. And this definition includes 'comparator' if the comparator is a medical device.

11.5.3. Device Deficiency

Device deficiency is inadequacy of a medical device related to its identity, quality, durability, reliability, safety, or performance. Device deficiency includes malfunction, misuse or use errors, and inadequate labeling (ISO14155).

This includes device deficiencies that might have led to an SAE if:

- suitable action had not been taken,
- intervention had not been made, or
- if circumstances had been less fortunate (these are handled under the SAE reporting system).

11.5.4. Adverse Events of Special Interest

- Bleeding-related events, including rebleeding of the bleeding site(s) treated with hemostatic patch at any point in time (within 10 minutes of application, prior to subject closure, and postoperative), and including hematoma;
- Thromboembolic events
- Biloma; and
- Allergic reaction.

11.5.5. Foreseeable Adverse Events and Anticipated Adverse Device Effects

The following events were identified in the risk analysis for GATT-Patch and were found acceptable after mitigation steps:

- Toxic response
- Thromboembolic event
- (Re)Bleeding
- Allergic reaction
- New surgery
- Infection (i.e., abscess)
- Blockage of artery or vein/ischemia of organs
- Damage of organs and vessels
- Adhesion to other organs
- (Pulsatile) hematoma
- Closing of intestinal track
- Biloma

Furthermore, the risk for encapsulated or rolled-up device was identified during the risk management, at a lower risk level/incidence. This risk will be further investigated in this clinical investigation by means of the 6-weeks follow-up imaging.

In the first-in-human clinical investigation, the following adverse events occurred with a possible relationship to the device: hematoma (n=1/47, 2.1%), biloma (n=1/47, 2.1%) and perihepatic abscess (n=1/47, 2.1%). There were no adverse events with a probable or causal relationship to the device. While other adverse events occurred, these were considered not related to the device.

A full study report will be written based on the 3 month follow-up data and will be submitted to all relevant local country authorities, including a pre-market approval submission to FDA. Furthermore, 5 year observational follow-up will be performed to characterize long-term safety on all patients undergoing liver resection for liver malignancy or metastases, collecting data on local cancer recurrence, disease-free survival, and overall survival. This report will be submitted to all relevant local country authorities through an annual progress report (e.g., for FDA) or post-market clinical follow-up report (e.g., for countries with EU MDR regulations).

11.5.6. Serious Adverse Events

The relevant SAE definitions for this clinical investigation are aligned with MDCG 2020-10/1 and FDA serious criteria definitions.

An SAE is any adverse event that led to any of the following:

- Death
- Serious deterioration in the health of the subject, that resulted in any of the following:
    a. Life-threatening illness or injury, or
    b. Disability or permanent impairment of a body structure or a body function, or
    c. Hospitalization or prolongation of hospitalization, or

d. Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function, or
e. Chronic disease

- Foetal distress, foetal death, or a congenital physical or mental impairment or birth defect
- Other important medical event (applicable only for events in the US)

Planned hospitalization for a pre-existing condition, or a procedure required by the CIP, without serious deterioration in health, is not considered an SAE.

Other important medical events that may not be immediately life-threatening or result in death or hospitalization, based upon appropriate medical judgment, are considered serious AEs (SAEs) if they are thought to jeopardize the subject and/or require medical or surgical intervention to prevent one of the outcomes defining an SAE. SAEs are critically important for the identification of significant safety problems; therefore, it is important to take into account both the investigator's and the Sponsor's assessment. If either the Sponsor or the investigator believes that an event is serious, the event must be considered serious and evaluated by the Sponsor for expedited reporting.

11.5.7. Serious Adverse Event and Adverse Event Reporting

An SAE occurring from the time from which the patient is enrolled and randomized until discontinuation must be reported to the Syneos Health Safety and Device Vigilance group and will be communicated to the Sponsor. Any such SAE due to any cause, whether or not related to the investigational device, must be reported within 24 hours of occurrence or when the investigator becomes aware of the event. Device Deficiencies and Adverse Events of Special Interest also require reporting according to these timelines. Notification can be made using the dedicated fax line or email or by completing the adverse event CRF.

If the investigator contacts the Syneos Health Safety and Device Vigilance group by telephone, then a written report must follow within 24 hours and is to include a full description of the event and sequelae in the format detailed in the SAE reporting form.

The event must also be recorded on the standard AE eCRF. Preliminary reports of SAEs must be followed up by detailed descriptions later on, including clear and anonymized photocopies of hospital case reports, consultant reports, autopsy reports, and other documents when requested and applicable. SAE reports must be made whether or not the investigator considers the event to be related to the investigational device.

Appropriate remedial measures should be taken to treat the SAE, and the response should be recorded. Clinical, laboratory, and diagnostic measures should be employed as needed in order to determine the etiology of the problem. The investigator must report all additional follow-up evaluations to the Syneos Health Safety and Device Vigilance group within 24 hours of becoming aware of the additional information or as soon as is practicable. All SAEs will be followed up until the investigator and Sponsor agree the event is satisfactorily resolved.

Any SAE that is not resolved by the end of the study or upon discontinuation of the subject's participation in the study is to be followed up until it either resolves, stabilizes, returns to baseline values (if a baseline value is available), or is shown to not be attributable to the investigational device or procedures.

The reporting of any SAE to the Competent Authority and/or Ethical Committee has to be done by the Sponsor (or Syneos Health) immediately and not later than 2 calendar days after awareness. This includes all reportable events, which indicate an imminent risk of death, serious injury, or serious illness and that requires prompt remedial action for other subjects, users or other persons, or a new finding to it, or as required by the Competent Authority and/or Ethical Committee.

For any other reportable events or a new finding/update to it, the Sponsor (or Syneos Health) must report the event to the Competent Authorities and/or Ethical Committee immediately and not later than 7 calendar days following the date of awareness by the Sponsor (or Syneos Health) of the new reportable event or of new information in relation with an already reported event.

11.5.8. Serious Adverse Device Effect

A SADE is defined as an ADE that has resulted in any of the consequences characteristic of an SAE (ISO14155).

11.5.9. Unanticipated Serious Adverse Device Effects/ Unanticipated Adverse Device Effects

A USADE which by its nature, incidence, severity or outcome has not been identified in the current Risk Management section of the Investigator's Brochure (IB) and IFU.

Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with the GATT-Patch, that was not previously identified in nature, severity, or degree of incidence in the CIP, IB or IFU or any other unanticipated serious problem associated with the study device that relates to the rights, safety, or welfare of subjects.

An unanticipated event is one where the nature or severity is not consistent with the information in the current Risk Management section of the CIP, IB and IFU. Furthermore, reports which add significant information on specificity or severity of a known, already documented adverse effect constitute unanticipated events. For example, an event more specific or more severe than described in the IB would be considered 'unexpected'.

Unanticipation will be assessed by a Syneos Health Safety and Device Vigilance and reviewed by GATT Technologies.

The investigator will assess whether an event is causally related to investigational device. The Sponsor (or Syneos Health) will consider the investigator's assessment and determine whether the event meets the criteria for being reportable as a 7-day or 15-day safety report. USADEs that are fatal or life-threatening must be reported to the regulatory authorities and the IEC/IRBs (where required) within 7 days after the Sponsor (or Syneos Health) has first knowledge of them, with a follow-up report submitted within a further 8 calendar days. Other USADEs must be reported to the relevant regulatory authorities and the IEC/IRBs within 15 calendar days after the Sponsor (or Syneos Health) first has knowledge of them.

The Sponsor (or Syneos Health) is responsible for reporting USADEs and any other events required to be reported in an expedited manner to the regulatory authorities and for informing investigators of reportable events, in compliance with applicable regulatory requirements within specific timeframes. Investigators will notify the relevant IEC/IRBs of reportable events within the applicable timeframes.

11.5.10. Pregnancy

Women of childbearing potential must have a negative pregnancy test at screening.[13] Following administration of study device, any known cases of pregnancy occurring during the 3-month follow-up period after surgery in female subjects will be reported until the subject completes the 3-month study visit or withdraws from the study. The pregnancy will be reported immediately by faxing/emailing a completed pregnancy report to the Sponsor (or designee) within 24 hours of knowledge of the event. The pregnancy will not be processed as an SAE.

If pregnancy occurs within the 3-month follow-up period after surgery, the investigator will follow-up with the subject to provide any information on pregnancy outcomes that are available during follow-up in the trial (e.g., 3 months for patients undergoing liver surgery for other indications than liver malignancy or metastases, and until completion of the pregnancy in patients undergoing liver surgery for liver malignancy or metastases) by submitting a follow-up pregnancy report to the Sponsor (or designee), which includes information on spontaneous or therapeutic abortion (any congenital anomaly detected in an aborted fetus is to be documented), stillbirth, neonatal death, or congenital anomaly.

11.6. Independent Adjudication Committee

An Independent Adjudication Committee (IAC) will review all SAEs and AESIs occurring after surgery up to the 3-months study visit for the relatedness with the device and the expectedness of the event based on the clinical scenario comprising of patient and procedural characteristics. The IAC will meet to review events approximately every 3 months, but at least every 6 months; the Sponsor may also choose to schedule additional meetings as needed.

The IAC's composition, role, meeting schedule, functioning recommendations, and premature termination criteria will be described in a charter. This charter will be approved and signed by all parties before study start.

The IAC will be independent from the Sponsor, the investigators or anyone involved in the clinical care of the study subjects. Members will not have scientific, financial or other conflict of interest related to the Sponsor or investigators. Potential IAC members will sign a non-conflict-of-interest statement in this regard.

The IAC will function in accordance with applicable regulatory guidelines and the charter.

12. STATISTICAL ANALYSIS

A statistical analysis plan (SAP) will be prepared after the Clinical Investigation Plan is approved, or during the approval process, depending on the local country regulations. This document will provide further details regarding the definition of analysis variables and analysis methodology to address all study objectives.

The statistical evaluation will be performed using SAS® software version 9.4 or higher (SAS Institute, Cary, NC). All data will be listed, and summary tables will be provided. Summary statistics will be presented by the treatment group.

Descriptive statistics will be presented for each variable. Continuous variables will be summarized by treatment group using number of subjects, mean, median, standard deviation, minimum, and maximum. Categorical variables will be summarized by treatment group using frequencies and percentages of subjects in each category. For time-to-event, Kaplan-Meier plot will be presented, and 25%, 50% and 75% percentiles and their 95% confidence interval will be reported.

The primary analysis of the primary efficacy endpoint will be conducted on the PP population using the Farrington-Manning test with available data. The primary efficacy endpoint will also be analyzed on the ITT population as a secondary analysis. Key secondary endpoint will be analyzed in both the PP and ITT populations. Consistent results from the analysis of ITT and PP datasets are necessary to conclude the non-inferiority of GATT-Patch to TachoSil. Other secondary endpoints, and exploratory and safety endpoints will be summarized descriptively.

12.1. Study Hypothesis

The percentage of cases achieving hemostasis at 3 minutes using GATT-Patch is non-inferior to TachoSil. Based on the TachoSil FDA submission, the percentage of subjects achieving hemostasis at 3 minutes is 75% with TachoSil;[5] however, individual studies have reported that 80% of subjects achieve hemostasis at 3 minutes.[6,8] In the current trial, with an estimated 80% success and a 10% absolute non-inferiority margin, the statistical null (H0) and alternative (H1) hypotheses are the following:

H0: $PG - PT \leq -0.10$

H1: $PG - PT > -0.10$

Where PG is the true percentage of subjects achieving hemostasis at 3 minutes using GATT-Patch and PT is the true percentage of subjects achieving hemostasis at 3 minutes using TachoSil.

12.2. Determination of Sample Size

The sample size is powered to determine non-inferiority of GATT-Patch versus TachoSil on the primary endpoint of hemostasis at 3 minutes. Based on previous studies, it is assumed that 80% of subjects achieve hemostasis at 3 min after TachoSil application.[2,5,6] Patients will be randomized in a 2:1 fashion. Taking into consideration a non-inferiority margin of 10%, and assuming that hemostasis is achieved in 92% of patients treated with GATT-Patch. An interim analysis is planned when the primary endpoint is observed for 70% of patients and using the O'Brien-Fleming alpha-spending function for efficacy stopping boundary, we

currently estimate a total sample size of 130 subjects of which 87 patients will undergo implantation of GATT-Patch, to achieve 90% statistical power. The success percentage of 92% is based on the results from the Pilot trial, taking into account a ~5% absolute lower performance due to differences in patient population, use, or other factors. The sample size will take into account the result of the interim analysis of the primary performance endpoint to allow for possible early stopping for success or futility or sample size re-estimation.

12.3. Analysis Population

Per-Protocol Population (PP)

The Per-Protocol population will be the cohort for the primary endpoint analysis and includes all subjects in ITT population who receive the randomized treatment with GATT-Patch or TachoSil, and have an assessment of primary endpoint, and have no major protocol deviations.

Intent-to-Treat Population (ITT)

The ITT population will include all subjects who are randomized, irrespective of any deviation from the protocol or premature discontinuation. The treatment group assignment will be designated according to initial randomization. The ITT population will serve as the basis for the analysis of efficacy.

Safety Population

The safety population will include all randomized subjects who receive treatment with GATT-Patch or TachoSil. The treatment group assignment in this population will be defined by the treatment actually received. This population will be used for the analysis of safety.

Evaluable patients are patients that did not meet any of the following withdrawal criteria:

- Change in SBSS to ineligible (SBSS of 0, 4, or 5) between randomization and application of the hemostatic patch; or
- Death of subject in the time between patch application and patch use.

12.4. Efficacy Analysis

The primary endpoint is the percentage of cases (rate) achieving hemostasis at 3 minutes without rebleeding at the 10-minute time point, which will be analyzed using the Farrington-Manning test. The rate and the 95% exact (Clopper-Pearson) confidence interval for each group, and their difference in rate between the treatment group and the corresponding 95% Newcombe confidence interval will be reported. The noninferiority will be tested first based on these results, and then superiority will be tested.

A hierarchical testing procedure (alpha = 0.02275) will be applied. The order will be:

- Non-inferiority of GATT-Patch vs TachoSil for primary endpoint of hemostasis at 3 minutes without rebleeding at the 10- minutes time point,
- Superiority of GATT-Patch vs TachoSil for the key secondary endpoint of median time to hemostasis,
- Superiority of GATT-Patch vs TachoSil for the primary endpoint of hemostasis at 3 minutes without rebleeding at the 10- minutes time point.

For the key secondary endpoint, median time to hemostasis, group sample sizes of 87 and 43 achieve 91% power to reject the null hypothesis of equal group response distributions when the effect size is as low as 0.68 and the significance level is 0.02275 using a one-sided Wilcoxon-Mann-Whitney test. The effect size is the probability that an observation from GATT-Patch group is less than an observation from TachoSil group and was estimated to be 0.93, derived from Figure 2 in Öllinger et. al. (2015).[3]

The time to hemostasis will be censored at 10 minutes for the case which does not achieve hemostasis by 10 minutes. The uncensored time to hemostasis, as well as the censored time to hemostasis (with censored patients having a 10-minute time to hemostasis) will be summarized descriptively. The time to hemostasis will furthermore be analyzed using Log-rank test. Kaplan-Meier plot will also be presented, and 25%, 50% (median) and 75% percentiles and their 95% confidence interval will be reported. The Cox proportional hazard model may be used to include some prognostic variables and baseline characteristics as covariates.

The primary analysis for the primary endpoint and the key secondary endpoint will be performed in PP population. They will also be analyzed in ITT population as secondary analysis.

The other secondary endpoints and exploratory endpoints will be summarized descriptively by treatment groups.

12.5. Safety Analysis

All reported AEs will be coded using the most recent version of the Medical Dictionary for Regulatory Activities (MedDRA). The incidence of treatment-emergent AEs (TEAEs; events with onset dates on or after the study device) will be included in incidence tables. Events with missing onset dates will be included as treatment-emergent. If a subject experiences more than 1 occurrence of the same AE, the occurrence with the greatest severity and the closest association with the study device will be used in the summary tables. Serious adverse events, treatment-related AEs and AEs causing discontinuation will be tabulated. All AEs will be listed by subject, along with information regarding onset, duration, relationship and severity to study drug, action taken with study drug, treatment of event, and outcome.

Clinical laboratory data and vital signs will be summarized using descriptive statistics, including mean values and mean change from baseline values, as well as numbers of subjects with values outside limits of the normal range at each time point.

Summary tables will be provided for concomitant medications initiated during the study period.

The safety evaluation will report the cumulative incidence of all adverse events (AEs or SAEs) and by severity through 12 weeks post-treatment for each treatment group. The numbers and percentages of subjects with at least one adverse event, at least one serious adverse event, at least one treatment-related adverse event will be reported and compared between the groups. The results of the imaging at 6 weeks will also be compared between groups.

12.6. Other Analysis

The primary and key secondary endpoints may be analyzed based on all treated target bleeding sites.

12.6.1. Subgroup Analysis

For the primary endpoint, descriptive statistics of number and percent of patients meeting the primary endpoint in each randomized group will be presented separately for each investigational site. Homogeneity across sites in the primary endpoint will be checked based on deviance from logistic regression with achieving the primary endpoint (yes/no) as the dependent variable.

The following patient subgroups are defined for prespecified analyses:

- Age
- Sex (male/female)
- SBSS (1/2/3)
- Type of bleeding (venous/arterial/mixed)
- Type of hepatic parenchyma (normal/cirrhotic/staetotic)
- Portal hypertension (yes/no)
- Child Pugh classification (A/B/C/NA)
- MELD-Na Score (<17 / 17-20 / 21-22 / 23-26 / 27-31 / ≥ 32)
- Renal function (eGFR >90 / eGFR 60-90 / eGFR 30-60 / eGFR 15-30 / chronic dialysis)
- Antithrombotic medication use (yes/no)
- Concomitant chemotherapy (yes/no)
- Concomitant steroid therapy (yes/no)

A subgroup analysis for safety will be performed among groups with or without surgical drains on the presence of fluid collections, specifically biloma formation.

12.6.2. Interim Analysis

This study will include an FDA review of data after the enrolment of 10 US-based patients from 2 US-based sites, which will be made available to other relevant to other local country authorities for review upon request. No formal statistical analyses will be performed on these data.

After FDA approval to continue, the study utilizes an adaptive design with an interim analysis planned for the purposes of stopping the trial early for success or futility and for sample size re-estimation. The interim analysis will be performed once 70% (n=91) of the planned evaluable subjects in total are treated. To account for multiple testing and control the overall Type I error rate of the study at one-sided 0.025 level, a group-sequential design will be used based on the Lan-DeMets approach with an O'Brien-Fleming alpha-spending function. Based on this method, the efficacy goal of GATT-Patch with a 10% absolute non-inferiority margin compared to the standard of care, TachoSil, regarding the percentage of cases achieving hemostasis at 3 minutes, will be assessed at the interim review. A Farrington-Manning test of non-inferiority difference between two proportions at a one-sided 0.00738 significance level will be performed at the interim analysis. If the statistical analysis of the

primary efficacy endpoint at the interim review yields a one-sided p-value less than 0.00738: (1) a superiority analysis will subsequently be performed using two-sample t-test at a one-sided 0.00738 significance level, and (2) the IDMC may recommend stopping the trial for successful efficacy if non-inferiority is met. If the one-sided p-value is not less than 0.00738, then a sample size re-estimation (SSR) based on conditional power (probability of study success given the interim results) may be conducted to determine if the sample size will be increased. The interim decision rules will be:

- If the p-value is less than 0.00738, the IDMC may recommend stopping the trial for successful efficacy; otherwise
- If the conditional power is greater than 90%, the study will continue as planned;
- If the conditional power is between 50% and 90%, then the sample size will be re-estimated to achieve the 90% conditional power with the constraint of the maximum allowed sample size of 200;
- If the conditional power is less than 50%, the Sponsor may choose to continue the study as planned though it is less likely to be successful, or terminate the study.

When the conditional power is greater than 50%, a sample size increase will not require an additional penalty to the final significance (alpha) level according to Chen-Demets-Lan method. If the study is not stopped for successful efficacy, the study will continue to the sample size determined by the SSR and the final efficacy analysis will be evaluated according to the hierarchical testing procedure detailed in section 12.1.

Further details will be provided in the SAP.

12.6.3. Five-year follow-up

Data on five-year survival, cancer recurrence, and disease-free survival outcomes of all patients treated for liver malignancy or metastases will be provided in a tabulated manner with descriptive statistics. This observational follow-up will not be in direct contact with the patient, but through electronic health records and/or contact with the patient's treating physician. The review will be submitted to all relevant local country authorities through an annual progress report (i.e., for FDA) or post-market clinical follow-up report (i.e., for countries with EU MDR regulations).

12.7. Independent Data Monitoring Committee

Any safety concerns, serious adverse device effects (SADE), or death during the clinical investigation will be immediately referred, on a case-by-case basis, to the blinded Independent Data Monitoring Committee for safety review. The Medical Monitor, the unblinded team member, will monitor all emerging safety issues against pre-defined stopping rules of the clinical investigation. These stopping rules only apply to the investigational treatment group, (i.e., patients having received GATT-Patch).

The stopping rules are:

- One SADE classified as grade 5 on the Clavien-Dindo scale of surgical complications[14] (i.e., resulting in death and confirmed to be related to study device intraoperatively or post-operatively during the autopsy (if applicable)) OR
- Three SADEs classified on the Clavien-Dindo scale of surgical complications[14] as:

- Grade 3b (intervention under general anesthesia) requiring re-laparotomy for the treatment of the event, e.g. re-bleeding or abscess formation from the target bleeding site (TBS), or angiography for the detection and treatment of post-operative bleeding from the TBS
- Grade 4 (life-threatening complication requiring IC/ICU management), confirmed to be related to the study device

A further investigation by the sponsor will be conducted to determine if the study requires early termination.

The IDMC's composition, role, meeting schedule, functioning recommendations, and premature termination criteria will be described in a charter.

The IDMC will be independent from the Sponsor, the investigators or anyone involved in the clinical care of the study subjects. Members will not have scientific, financial or other conflict of interest related to the Sponsor or investigators. Potential IDMC members will sign a non-conflict-of-interest statement in this regard.

The IDMC will function in accordance with applicable regulatory guidelines and the charter.

13. STUDY MANAGEMENT

13.1. Approval and Consent

13.1.1. Regulatory Guidelines

This study will be conducted in accordance with the accepted version of the Declaration of Helsinki and/or all relevant regulations, as set forth in Parts 50, 56, 812, Subpart D, of Title 21 of the United States Code of Federal Regulations (CFR), ISO14155 (Clinical Investigation of Medical Devices for Human Subjects–Good Clinical Practice), and according to the appropriate regulatory requirements in the countries where the study was conducted.

13.1.2. Institutional Review Board/Independent Ethics Committee

Conduct of the study must be approved by an appropriately constituted IEC/IRB. Approval is required for the study Clinical Investigation Plan, Clinical Investigation Plan amendments (if applicable), IB or IFU, ICFs, recruitment material and subject information sheets and other subject-facing material. Additionally, the notification of changes to site personnel or any other relevant changes to the conduct of the study will follow local country regulatory requirements.

13.1.3. Informed Consent

The investigator is responsible for assuring that written informed consent is obtained from each subject prior to participation in the clinical investigation. Should the investigator delegate the responsibility of conducting the informed consent process to a designee, the investigator must ensure and document appropriate training of the authorized designee.

The investigator will use an approved ICF that was prepared in accordance with this CIP, ISO14155 and Regulatory Authority's requirements.

Subjects must be fully counselled and informed of their options, risks and benefits, and should have every opportunity to ask questions about participation in the clinical investigation. This process includes a thorough explanation of the subject information letter and ICF that the subject will be asked to sign, acknowledging that they understand and consent to participate in the clinical investigation.

While an investigator may discuss availability of the investigation with a prospective subject without first obtaining consent, informed consent must always be obtained from a subject prior to initiation of any clinical procedures dictated by the CIP that are performed solely for the purpose of determining eligibility to participate in the clinical investigation. A copy of the signed statement of informed consent will be provided to the subject.

If new information regarding the investigational device becomes available and/or the CIP changes and this information can significantly affect a subject's future health and medical care, subjects will be informed of the information and may be asked to sign a revised ICF. A subject may withdraw or discontinue participation at any time during the clinical investigation.

13.2. Data Handling

Data will be collected and recorded using a validated electronic data capture (EDC) system that meets all requirements as set forth in the FDA and ISO standards. An audit trail is available for tracking all information that the EDC user enters, modifies or deletes. One

electronic copy of the final database will be archived in the electronic database of Syneos Health and another copy will be stored at GATT Technologies BV.

The investigator or its designee will perform primary data collection drawn from original documents (printed, optical or electronic document containing source data), also referred to as source documents.

It is the responsibility of the investigator to ensure that the site files are maintained in accordance with ISO14155 - Good Clinical Practice for Medical Devices and applicable regulations.

Any data to be recorded directly on the eCRFs (to be considered as source data) will be identified at the start of the study. Data reported on the eCRF that are derived from source documents should be consistent with the source documents, or the discrepancies must be explained. See also Section 13.6

Clinical data will be entered by site personnel on eCRFs for transmission to the Sponsor. Data on eCRFs transmitted via the web-based data system must correspond to and be supported by source documentation maintained at the study site, unless the study site makes direct data entry to the databases for which no other original or source documentation is maintained. In such cases, the study site should document which eCRFs are subject to direct data entry and should have in place procedures to obtain and retain copies of the information submitted by direct data entry. All study forms and records transmitted to the Sponsor must only include coded identifiers such that directly identifying personal information is not transmitted. The primary method of data transmittal is via the secure, internet-based EDC system maintained by Syneos Health. Access to the EDC system is available to only authorized users via the study's internet web site, where a user unique assigned username and password are required for access.

Electronic CRFs will be considered complete when all missing and/or incorrect data have been resolved.

13.2.1. Source Documents

Source documents are considered to be all information in original records and certified copies of original records of clinical findings, observations, data, or other activities in a clinical study necessary for the reconstruction and evaluation of the study. The investigator will provide direct access to source documents and/or source data in the facilitation of trial-related monitoring, audits, review by IECs/IRBs, and regulatory inspections.

The investigator/institution should maintain adequate and accurate source documents and trial records that include all pertinent observations on each of the site's trial subjects. Source data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, not obscure the original entry, and be explained if necessary.

13.2.2. Record Retention

The investigator maintains all clinical investigation records for the minimum time required in the country in which the clinical investigation is conducted, which will be at least 15 years. Records to be retained may include: all correspondence, documentation of device receipt and disposition, each subject's case history and record of exposure to the device, the CIP and

amendments, Investigator Brochure, and dates and reasons for any deviations to the CIP or as otherwise specified by the applicable laws and regulations.

Furthermore, the documentation will be kept by GATT Technologies BV for a period of at least 15 years after the clinical investigation with the device in question has ended, or, in the event that the device is subsequently placed on the market, at least 10 years after the last device has been placed on the market.

For the United States only: The investigator agrees to comply with all applicable federal, state, and local laws and regulations relating to the privacy of subject health information, including, but not limited to, the Standards for Individually Identifiable Health Information, 45 CFR, Parts 160 and 164 (the Health Insurance Portability Accountability Act of 1996 [HIPAA] Privacy Regulation). The investigator shall ensure that study subjects authorize the use and disclosure of protected health information in accordance with HIPAA Privacy Regulation and in a form satisfactory to the Sponsor.

13.3. Monitoring

The study will be monitored according to Syneos Healths´ monitoring plan to ensure that it is conducted and documented properly according to the Clinical Investigation Plan, ISO14155, and all applicable regulatory requirements.

Monitoring visits, on-site and remote (telephone) and contacts will be made at appropriate times during the study. The PI will ensure he/she and adequate site personnel are available throughout the study to collaborate with clinical monitors. Clinical monitors must have direct access to source documentation in order to check the completeness, clarity, and consistency of the data recorded in the eCRFs for each subject.

The investigator will make available to the clinical monitor all source documents and medical records necessary to review Clinical Investigation Plan adherence and eCRFs. In addition, the investigator will work closely with the clinical monitor and as needed, provide them appropriate evidence that the study is being conducted in accordance with the Clinical Investigation Plan, applicable regulations, and ISO14155 guidelines.

13.4. Quality Control and Quality Assurance

The Sponsor or its designee will perform the quality assurance and quality control activities of this study; however, responsibility for the accuracy, completeness, security, and reliability of the study data presented to the Sponsor lies with the investigator generating the data.

13.5. Clinical Investigation Plan Amendment and Clinical Investigation Plan Deviation

13.5.1. Clinical Investigation Plan Amendment

Investigators may not modify (amend) this CIP without obtaining written concurrence of the Sponsor, involved ethics committee(s), and applicable regulatory authorities.

Amendments to the Clinical Investigation Plan that entail corrections of typographical errors, clarifications of confusing wording, changes in study personnel, and minor modifications that have no effect on the safety of subjects or the conduct of the study will be classed as administrative amendments and will be submitted to the IEC/IRB for information only. The Sponsor will ensure that acknowledgement is received and filed. Amendments that are classed as substantial amendments must be submitted to the appropriate regulatory authorities

and the IECs/IRBs for approval and will not be implemented at sites until such approvals are received other than in the case of an urgent safety measure.

13.5.2. Clinical Investigation Plan Deviations

Investigators may not deviate from this CIP without first receiving approval in writing from the Sponsor, involved ethics committee(s), and applicable regulatory authorities, except to protect the rights, safety and well-being of human subjects under emergency circumstances. Such deviations shall be documented and reported to the Sponsor and the ethics committee as soon as possible. All deviations will be documented on eCRFs. The use of waivers from the CIP is prohibited.

13.6. Ethical Considerations

This study will be conducted in accordance with this Clinical Investigation Plan, the accepted version of the Declaration of Helsinki and/or all relevant federal regulations, as set forth in Parts 50, 56, 812, Subpart D, of Title 21 of the CFR; EU 536/2014, Annex 1, D, 17 (a); and in compliance with ISO14155 (Clinical Investigation of Medical Devices for Human Subjects–Good Clinical Practice), the Medical Device Directive EC/93/42 guidelines.

IECs/IRBs will review and approve this Clinical Investigation Plan and the ICF. All subjects are required to give written informed consent before participation in the study.

13.7. Financing and Insurance

Before the study commences, the Sponsor (or its designee) and the investigator (or the institution, as applicable) will agree on costs necessary to perform the study. This agreement will be documented in a financial agreement (or as part of the clinical trial agreement) that will be signed by the investigator (or the institution signatory) and the Sponsor (or its designee).

The investigator is required to have adequate current insurance to cover claims for negligence and/or malpractice. The Sponsor will provide no-exclusion insurance coverage for the clinical study as required by national regulations.

13.8. Publication Policy/Disclosure of Data

After closure of the clinical investigation, the results will be summarized in a Clinical Investigation Report, which will be submitted to the investigators, ethics committee(s) and appropriate regulatory authorities. This Clinical Investigation Report will include a summary of the results based on a statistical evaluation and clinical assessment.

GATT Technologies BV may at any time publish the results of and information pertaining to the investigation subject only to compliance with regulatory requirements pertaining to patient protected health information. The conditions under which an investigator may publish results from this clinical investigation in any form are defined in detail in the clinical trial agreement.

Irrespective of the outcome of the clinical investigation, within one year of the end of the clinical investigation or within three months of the early termination or temporary halt, GATT Technologies BV will submit to the Member States in which a clinical investigation was conducted a Clinical Investigation Report.

The clinical study will be registered in a public database (clinicaltrials.gov) and a summary of the results will be posted in this database once they become available.

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15. APPENDICES

APPENDIX 1 User satisfaction questionnaire

APPENDIX 2 Physician Treatment Preference Assessment

APPENDIX 3 describes the training and testing requirements for the Surface Bleeding Severity Scale Report (SBSS)

APPENDIX 4 describes the safety reporting requirements for Germany.

APPENDIX 5 describes the safety reporting requirements for The Netherlands.

15.1.1. APPENDIX 1. User satisfaction questionnaire

System/device:	GATT-Patch
Date of use:	
Location (Hospital):	
Use environment:	Operating room
Name participant:	
Function participant:	
Name GATT Technologies* representative:	
Function GATT Technologies* representative:	

*If applicable

MATERIALS LIST:

- GATT-Patch
- Instructions for use (IFU)
- Implant card[g]
- Surgical gloves
- Gauzes
- Saline

[g] The manufacturer needs to provide an Implant Card for implantable medical devices, according to requirements of Regulation (EU) 2017/745 (MDR), article 18. The card can only be provided to patients after the final study assessment and should remain in possession at site until then.

A. SUS – System Usability Scale

		Strongly disagree				Strongly agree
1.	I think that I would like to use this device frequently	1	2	3	4	5
2.	I found the device unnecessarily complex	1	2	3	4	5
3.	I thought the device was easy to use	1	2	3	4	5
4.	I think that I would need the support of a technical person to be able to use this device.	1	2	3	4	5
5.	I found the various functions in this system were well integrated.	1	2	3	4	5
6.	I thought there was too much inconsistency in this system	1	2	3	4	5
7.	I would imagine that most people would learn to use this system very quickly.	1	2	3	4	5
8.	I found the system very cumbersome to use.					

1	2	3	4	5

9. I felt very confident using the system.

1	2	3	4	5

10. I needed to learn a lot of things before I could get going with this system

1	2	3	4	5

B. Medical Device specific questions

1. **On the non-sterile packaging of GATT-Patch, it is clear what the storage conditions need to be.**

Strongly disagree Strongly agree

1	2	3	4	5

2. **On the packaging of GATT-Patch, it is clear what the expiration date is.**

Strongly disagree Strongly agree

1	2	3	4	5

3. **It is clear how to safely open the packaging, without damaging GATT-Patch.**

Strongly disagree Strongly agree

1	2	3	4	5

4. **It is clear that GATT-Patch should be used within 1 hour after opening the blister.**

Strongly disagree Strongly agree

1	2	3	4	5

5. **It is clear on which organs GATT-Patch is allowed to be used.**

Strongly disagree Strongly agree

1	2	3	4	5

6. It is clear on which organs GATT-Patch is not allowed to be used.

Strongly disagree Strongly agree

1	2	3	4	5

7. It is clear for what severity of bleeding GATT-Patch can be used.

Strongly disagree Strongly agree

1	2	3	4	5

8. It is clear what contraindications of a patient prohibit use of GATT-Patch.

Strongly disagree Strongly agree

1	2	3	4	5

9. The information in the instructions for use is sufficient.

Strongly disagree Strongly agree

1	2	3	4	5

10. The packaging is easy to open without damaging GATT-Patch.

Strongly disagree Strongly agree

1	2	3	4	5

11. The size of GATT-Patch is adequate for its intended purpose.

Strongly disagree Strongly agree

1	2	3	4	5

12. A dry GATT-Patch does not stick to dry gloves and instruments (e.g. tweezers).

Strongly disagree Strongly agree

1	2	3	4	5

13. GATT-Patch is easy to cut with dry scissors.

Strongly disagree Strongly agree

1	2	3	4	5

14. GATT-Patch can be handled with dry tweezers without damaging/fragmentating.

Strongly disagree Strongly agree

1	2	3	4	5

15. It is clear that GATT-Patch should be applied with a wet gauze for an initial period of 30 seconds of pressure.

Strongly disagree Strongly agree

1	2	3	4	5

16. It is clear that GATT-Patch should be applied overlapping the margins of the bleeding surface by at least 1 cm.

Strongly disagree Strongly agree

1	2	3	4	5

17. GATT-Patch is pliable on irregular tissue when applied with a wet gauze.

Strongly disagree Strongly agree

1	2	3	4	5

18. After application, the wet gauze can be carefully and safely removed without damaging GATT-Patch.

Strongly disagree Strongly agree

1	2	3	4	5

19. GATT-Patch stays in place after application.

Strongly disagree Strongly agree

1	2	3	4	5

20. It is easy to ensure that GATT-Patch is fully hydrated after application.

Strongly disagree Strongly agree

1	2	3	4	5

21. It is clear how to apply a GATT-Patch (partly) on top of another GATT-Patch.

Strongly disagree Strongly agree

1	2	3	4	5

22. The maximum number of GATT-Patches used in a patient is clear.

Strongly disagree Strongly agree

1	2	3	4	5

23. The blue color helps to visualize GATT-Patch after application.

Strongly disagree Strongly agree

1	2	3	4	5

24. It is safe to remove excess non-adherent GATT-Patch without damaging adherent GATT-Patch.

Strongly disagree Strongly agree

1	2	3	4	5

25. GATT-Patch can be used intuitively.

Strongly disagree Strongly agree

1	2	3	4	5

26. I feel confident that GATT-Patch stops a bleeding.

Strongly disagree Strongly agree

1	2	3	4	5

27. I feel confident that GATT-Patch can be used safely.

Strongly disagree Strongly agree

1	2	3	4	5

28. GATT-Patch is easy to be used/handled.

Strongly disagree Strongly agree

1	2	3	4	5

29. It is clear what to do with the Implant Card.

Strongly disagree Strongly agree

1	2	3	4	5

Your comments to the design of the device or labelling are much appreciated:

_____

Signature of user

_____

Date and location of signature

15.1.2. Physician Treatment Preference Assessment

INTRODUCTION

While there are many approved hemostatic products on the market to be used as an adjunct to hemostasis, their use varies between surgeons, in part due to physician preference for certain products. Among hemostatic patches, TachoSil is the current global market leader and is often considered to be the standard of care for bleeding during liver surgery.

To evaluate the safety and efficacy of GATT-Patch for hemostasis during liver surgery, the current clinical investigation compares GATT-Patch to TachoSil in minimal, mild or moderate bleeding of the liver. In order to evaluate the use of GATT-Patch, a questionnaire has been developed to determine the preference of physicians and involved operating room staff towards TachoSil or GATT-Patch, on the basis of certain product characteristics.

Your answers to this questionnaire should be based on your experience in using TachoSil and GATT-Patch in this clinical investigation. For each topic, you need to indicate your (i) strong preference for TachoSil, (ii) slight preference for TachoSil, (iii) neutrality, (iv) slight preference for GATT-Patch, or (v) strong preference for GATT-Patch.

Preference questions

Indicate your preference for TachoSil or GATT-Patch for each of the below comments characteristics:

	Strong preference for **TachoSil**	**Slight** preference for **TachoSil**	**Neutral**	**Slight** preference for **GATT-Patch**	**Strong** preference for **GATT-Patch**
1. Opening the package without damaging product					
2. Opening package and present to sterile field					
3. Ability to use product straight out of the package					
4. Sticking to dry gloves and instruments					
5. Handling/cutting with dry instruments without damaging the patch					
6. Time of pressure when applied to tissue					
7. Conforming to irregular tissue					
8. Flexibility/pliability of the product					
9. Ease of wet gauze removal after application					
10. Product adhesion to tissue after application					
11. Staying in place after application					
12. Ease-of-use and intuitively to use product					
13. The hemostatic performance					
14. Time to hemostasis					
15. Severity of bleeding that the product can handle					
16. Hemostasis in patients with coagulopathic (hereditary or medication-related) conditions					
17. Hemostasis on a cirrhotic liver					
18. Level of assurance that no rebleed will occur					
19. The safety of the product					
20. My overall product preference					

Your remarks about the differences between products are much appreciated:

_____

Signature of user

_____

Date and location of signature

15.1.3. APPENDIX 3. Surface Bleeding Severity Scale (SBSS) Training and Testing

Report DHF-01-SR-107

15.1.4. APPENDIX 4. Safety Reporting Germany

Regulations:

The below definitions, for a clinical trial being subject to authorisation, are provided in the *European Regulation 2017/745 – Medical Device Regulation (MDR):*

"Serious Adverse Event" (SAE) means any adverse event that led to any of the following:
(a) death,
(b) serious deterioration in the health of the subject, that resulted in any of the following:
(i) life-threatening illness or injury,
(ii) permanent impairment of a body structure or a body function,
(iii) hospitalisation or prolongation of patient hospitalisation,
(iv) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,
(v) chronic disease,
(c) foetal distress, foetal death or a congenital physical or mental impairment or birth defect.

"Device Deficiency" (DD) means any inadequacy in the identity, quality, durability, reliability, safety or performance of an investigational device, including malfunction, use errors or inadequacy in information supplied by the manufacturer".

Section 11.5.6 of the CIP ("Serious Adverse Event (SAE)") provides further details on "Serious deterioration in the health"

Roles and Responsibilities:

Sponsor:

1. Trains all Investigators on the SAE and Device Deficiency reporting procedures in compliance with the CIP and in compliance with applicable regulations *(Germany follows European Regulation 2017/745 – MDR)*.

2. Reports without delay to BfArM *(European Regulation 2017/745 – Article 80 – Paragraph 2)*:

a) All SAEs that occurred at a German investigational site and that has a causal relationship with the investigational device, the comparator or the investigation procedure or where such causal relationship is reasonably possible
b) All Device Deficiency that occurred at a German investigational site and that might have led to a serious adverse event if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate
c) Any new findings in relation to any event referred to in points (a) and (b).

3. Reports without delay to BfArM *(European Regulation 2017/745 – Article 80 – Paragraph 3)* any events described in above paragraph 2 and that occurred in third countries in which a clinical investigation is performed under the same CIP.

4. Forwards without delay to BfArM any follow-up and final reports of events described in above paragraph 2 .

5. Reports without delay to the National Competent Authorities (NCAs) of all other Member States participating in the clinical trial, any events described in above paragraph 2 and that occurred at a German investigational site *(European Regulation 2017/745 – Article 80 – Paragraph 4)*.

6. Any events described in above paragraph 2 will be reported by the sponsor to BfArM as per the applicable reporting requirements specified on the BfArM webpage www.bfarm.de.

7. Sponsor will report to BfArM and relevant NCAs where the clinical study has commenced, all reportable events (occurred worldwide) by EUDAMED (once fully functional) or Clinical Investigation Summary Safety Report Form MDCG 2020-10-2.

8. Additionally, sponsor will report to BfArM quarterly summary of assessment of any events described in above paragraph 2 as per the applicable reporting requirements specified on the BfArM webpage www.bfarm.de.

Site/ Investigator:

1. Record all SAEs occurring in the trial within 24 hours on the appropriate Adverse Event pages in the eCRF and is classifying these AEs as "serious", in compliance with the CIP.

2. In addition, the investigator completes all relevant eCRF pages that provide further relevant detailed information regarding the event, e.g. concomitant medications and laboratory test results.

3. The entry of a serious AE in the eCRF by the investigator will trigger a notification to the CRO who will inform the sponsor of the SAE within one business day of receipt.

Timelines:

Reporting to BfArM of events described above *(European Regulation 2017/745 – Article 80 – Paragraph 2)* that occurred in Germany and in all other countries where the clinical trial is performed should be done according to the following timelines:

- Reportable event with imminent risk of death, serious injury, or serious illness and that require prompt remedial action for other patients/subjects, users or other persons or a new finding to it: immediately but not later than 2 calendar days after awareness by sponsor of a new reportable event or of new information in relation with an already reported event

- Any other reprotable event or a new finding / update to it: immediately but not later than not later than 7 calendar days after awareness by sponsor of a new reportable event or of new information in relation with an already reported event

Privacy Statement

The Sponsor (or its designee) and the investigator (or the institution, as applicable) shall treat all information as confidential and shall ensure the protection of the clinical trial subjects fundamental right to integrity and privacy through compliance with applicable data protection laws including but not limited to the Regulation (EU) 2016/679 on the protection of natural persons with regard to the processing of personal data and the free movement of such data (GDPR), the German Data Protection Act (BDSG) and the Data Protection Act of Baden-Württemberg (LDSG).

15.1.5. APPENDIX 5. Safety Reporting The Netherlands

Regulations:

The below definitions, for a clinical trial being subject to authorisation, are provided in the *European Regulation 2017/745 – Medical Device Regulation (MDR):*

"Serious Adverse Event" (SAE) means any adverse event that led to any of the following:
(a) death,
(b) serious deterioration in the health of the subject, that resulted in any of the following:
(i) life-threatening illness or injury,
(ii) permanent impairment of a body structure or a body function,
(iii) hospitalisation or prolongation of patient hospitalisation,
(iv) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,
(v) chronic disease,
(c) foetal distress, foetal death or a congenital physical or mental impairment or birth defect.

"Device Deficiency" (DD) means any inadequacy in the identity, quality, durability, reliability, safety or performance of an investigational device, including malfunction, use errors or inadequacy in information supplied by the manufacturer".

Section 11.5.6 of the CIP ("Serious Adverse Event (SAE)") provides further details on "Serious deterioration in the health"

Roles and Responsibilities:

Sponsor:

1. Trains all Investigators on the SAE and Device Deficiency reporting procedures in compliance with the CIP and in compliance with applicable regulations *(Germany follows European Regulation 2017/745 – MDR)*.

2. Reports without delay to CCMO *(European Regulation 2017/745 – Article 80 – Paragraph 2)*:

a) All SAEs that occurred at a Netherlands investigational site and that has a causal relationship with the investigational device, the comparator or the investigation procedure or where such causal relationship is reasonably possible
b) All Device Deficiency that occurred at a Netherlands investigational site and that might have led to a serious adverse event if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate
c) Any new findings in relation to any event referred to in points (a) and (b).

3. Reports without delay to CCMO *(European Regulation 2017/745 – Article 80 – Paragraph 3)* any events described in above paragraph 2 and that occurred in third countries in which a clinical investigation is performed under the same CIP.

4. Forwards without delay to CCMO any follow-up and final reports of events described in above paragraph 2 .

5. Reports without delay to the National Competent Authorities (NCAs) of all other Member States participating in the clinical trial, any events described in above paragraph 2 and that occurred at a Netherlands investigational site *(European Regulation 2017/745 – Article 80 – Paragraph 4)*.

6. Any events described in above paragraph 2 will be reported by the sponsor to CCMO as per the applicable reporting requirements specified on the CCMO webpage www.ccmo.nl.

7. Sponsor will report to CCMO and relevant NCAs where the clinical study has commenced, all reportable events (occurred worldwide) by EUDAMED (once fully functional) or Clinical Investigation Summary Safety Report Form MDCG 2020-10-2.

Site/ Investigator:

1. Record all SAEs occurring in the trial within 24 hours on the appropriate Adverse Event pages in the eCRF and is classifying these AEs as “serious”, in compliance with the CIP.

2. In addition, the investigator completes all relevant eCRF pages that provide further relevant detailed information regarding the event, e.g. concomitant medications and laboratory test results.

3. The entry of a serious AE in the eCRF by the investigator will trigger a notification to the CRO who will inform the sponsor of the SAE within one business day of receipt.

Timelines:

Reporting to CCMO of events described above *(European Regulation 2017/745 – Article 80 – Paragraph 2)* that occurred in Netherlands and in all other countries where the clinical trial is performed should be done according to the following timelines:

- Reportable event with imminent risk of death, serious injury, or serious illness and that require prompt remedial action for other patients/subjects, users or other persons or a new finding to it: immediately but not later than 2 calendar days after awareness by sponsor of a new reportable event or of new information in relation with an already reported event
- Any other reprotable event or a new finding / update to it: immediately but not later than not later than 7 calendar days after awareness by sponsor of a new reportable event or of new information in relation with an already reported event

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