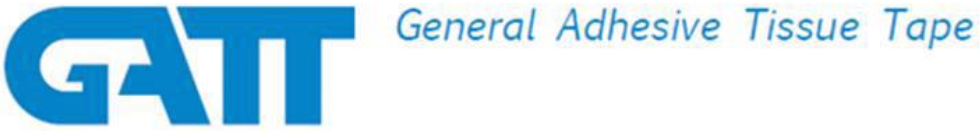

A Prospective, Multicenter, Single-arm, Clinical Investigation Evaluating the Safety and Performance of GATT-Patch for Hemostasis during Open Liver Surgery

Short title: Clinical Safety and Performance of GATT-Patch in Open Liver Surgery

Reference: DHF-01-QR-021

Version: Version 04

Date: 28 April 2021

GATT Technologies BV

Novio Tech Campus
Transistorweg 5
6534 AT Nijmegen
The Netherlands

Statement of Compliance

This clinical investigation will be conducted in compliance with ISO 14155:2020 guidelines and applicable regulatory requirements, including the Medical Device Regulation (MDR) 2017/745.

Confidentiality Statement

The information provided in this document is strictly confidential and may not be disclosed to parties other than clinical investigation staff, appropriate governmental and regulatory agencies and the Ethics Committee directly involved in this clinical investigation. All parties must understand that confidential information may not be disseminated further without prior written permission from GATT Technologies BV.

SPONSOR SIGNATURE PAGE

Clinical investigation: A Prospective, Multicenter, Single-arm, Clinical Investigation Evaluating the Safety and Performance of GATT-Patch for Hemostasis during Open Liver Surgery

Reference: DHF-01-QR-021

Sponsor's statement

I, the Sponsor, have reviewed this clinical investigation plan describing the design and specific provisions of the clinical investigation. I agree with the content of this document.

Dr Stuart Head, MD PhD	Chief Medical Officer
Sponsor representative name (print)	Title
	03/05/2021
Signature	Date

INVESTIGATOR SIGNATURE PAGE

Clinical investigation: A Prospective, Multicenter, Single-arm, Clinical Investigation Evaluating the Safety and Performance of GATT-Patch for Hemostasis during Open Liver Surgery

Reference: DHF-01-QR-021

Investigator's statement

I agree to conduct this clinical investigation in accordance with the design and specific provisions of this clinical investigation plan; modifications to the clinical investigation are only acceptable with a mutually agreed upon clinical investigation plan amendment as approved by the Sponsor and involved Ethics Committee(s).

I agree to await Ethics Committee approval of the clinical investigation plan and informed consent form before initiating the clinical investigation, to obtain consent from subjects prior to their enrollment, to collect and record data as required by the clinical investigation plan and associated case report forms, and to maintain documents related to the clinical investigation for the period of time required.

Confidential

This document contains confidential information belonging to GATT Technologies BV. Except as may be otherwise agreed to in writing, by accepting or reviewing these materials, I agree to hold such information in confidence and not to disclose it to others (except where required by applicable law), nor use it for unauthorized purposes.

Investigator name (print)

Signature Date

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SYNOPSIS

Clinical investigation plan	
Title	A Prospective, Multicenter, Single-arm, Clinical Investigation Evaluating the Safety and Performance of GATT-Patch for Hemostasis during Open Liver Surgery
Short title	Clinical Safety and Performance of GATT-Patch in Open Liver Surgery
Reference	DHF-01-QR-021
Investigational device	
Name	GATT-Patch
Description	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.
Indication for use	GATT-Patch is indicated for use as an adjunct to hemostasis and as a surgical sealant 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 internal organs, primarily parenchymatous organs such as liver, spleen or kidney; or in other abdominal surgeries. GATT-Patch is intended to be used by physicians trained in performing specific surgical and minimal invasive procedures.
Indication for use in the clinical investigation	GATT-Patch is intended to be used for management of hemorrhage during elective open liver surgery.
Sponsor	
Name	GATT Technologies BV
Contact details	Transistorweg 5 6534 AT Nijmegen The Netherlands info@gatt-tech.com
Investigation centers	
Number of centers	Up to 7 sites, with a maximum of 3 sites in Stage I
Location of centers	The Netherlands

Clinical investigation design	
Design	This is a pre-market, prospective, single arm, multicenter, first-in-human clinical investigation. The clinical investigation will be split into 2 stages: • **Stage I** of the clinical investigation will enroll a small cohort of subjects within which the initial safety of GATT-Patch will be evaluated. A maximum of 12 subjects (~25% of the overall population) will be treated[1] at a maximum of 3 sites, after which the enrollment into the clinical investigation will be paused. At minimum, 2 subjects shall be treated per site. • **Stage II** of the clinical investigation will enroll subjects until 39* Stage II subjects have been treated with the investigational device. (*Note: The number of Stage II subjects may increase to a maximum of 61 treated subjects [56 evaluable Stage II subjects, assuming 7.5% drop-out rate] if a sample size increase is deemed necessary based on the interim sample size re-estimation). Stage II will be used to evaluate safety and performance of GATT-Patch. In both Stage I and Stage II, subjects will follow the same clinical investigation pathway. Stage I subjects will be analyzed for safety only, whereas Stage II subjects will be analyzed for both safety and performance.
Objective	To evaluate the clinical safety and performance of GATT-Patch in open liver surgery.
Hypothesis	The percentage of cases achieving hemostasis at 3 minutes using GATT-Patch is significantly greater than the literature-based performance goal (PG) of 65.4% (i.e., whether GATT-Patch is non-inferior compared to the standard of care). Thus, the statistical null (H_0) and alternative (H_1) hypotheses are the following: H_0: $p_{GATT} \leq 65.4\%$ H_1: $p_{GATT} > 65.4\%$
Primary performance endpoint	The primary performance endpoint is defined as the percentage of cases achieving hemostasis at 3 minutes. Hemostasis will be defined by a grade of 0 (None/Dry) on the Surface Bleeding Severity Score (SBSS) [2]. Achievement of hemostasis will be verified every 30 seconds.

[1] Treated subjects include subjects that are actually implanted with the device, or had a treatment attempt with the device.

[2] The SBSS provides a validated score for assessment of bleeding at the target site, and consists of 6 subscales (0=none, 1=minimal, 2=mild, 3=moderate, 4=severe; not immediately life-threatening, 5=extreme; immediately life threatening) 1. Spotnitz, W.D., et al., *The SPOT GRADE: a new method for reproducibly quantifying surgical wound bleeding.* Spine, 2018. **43**(11): p. E664-E671.). Investigators will be trained on the assessment scale prior to the investigation to have consistent assessment of bleeding at the target site.

	If hemostasis has not been achieved after 5 minutes of application (SBSS 1-5), then treatment is considered a failure and additional hemostatic agents or techniques may be used.
Secondary performance endpoints	The following secondary endpoints are defined: • Mean time to hemostasis (seconds)[3] • Percentage of hemostasis at 30, 60, 90, 120 and 150 seconds. There will be no formal hypothesis testing on the secondary performance endpoints.
Safety endpoints	The safety of GATT-Patch will be assessed by the nature, severity and incidence of device related adverse events. The adverse events found for GATT-Patch will be compared to the current knowledge and state of the art for hemostatic methods in open liver surgery to assess whether the device is associated with acceptable safety outcomes.
Exploratory endpoints	In addition to the primary endpoint, the following exploratory endpoints will be recorded: • Surgery Time (minutes) • Blood loss (mL) during surgery • Blood Transfusion (mL) during hospitalization • SBSS (0-5) at the target bleeding site • Use of adjunct hemostatic agents/techniques (e.g. cautery, sutures or staples) • Amount of material needed versus bleeding surfaces • User satisfaction (questionnaire)
Arms and interventions	This is a single-arm clinical investigation. 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. Subjects who signed informed consent and meet the eligibility criteria will be treated with the device. GATT-Patch will be used if the subject has an appropriate bleeding site (SBSS 1, 2 or 3 and no contraindications).
Follow-up visits	1 Visit at 6 weeks follow-up (±2 weeks)[4]
Total duration	The enrollment period is expected to take approximately 6 months. The per subject duration of the clinical investigation from treatment to final follow-up will be approximately 6 weeks. With a 2-week temporary hold on enrollment for the safety evaluation, the total expected duration of the clinical investigation is, therefore, approximately 8 months.
Clinical investigation population	
Sample size	The plan is to enroll and treat the following number of subjects across two stages:

[3] Note that the mean time to hemostasis will be calculated based on time to hemostasis determined at 30 seconds intervals.

[4] Some subjects may have an additional phone consultation at 2-6 weeks post-procedure for the assessment of safety during Stage I of the clinical investigation. This visit will include assessment of adverse events and will only take place for subjects in Stage I of the clinical investigation who did not complete the 6 weeks follow-up visit.

	• Stage I: maximum of 12 subjects • Stage II: 39 subjects (36 evaluable subjects, assuming 7.5% drop-out rate)* *Note: The number of Stage II subjects may increase to a maximum of 61 treated subjects (56 evaluable subjects, assuming 7.5% drop-out rate) if a sample size increase is deemed necessary based on the interim sample size re-estimation Therefore, the current plan is to treat a total of up to 51 subjects. However, the total sample size may increase to a maximum of 73 (=61+12) treated subjects based on the interim sample size re-estimation. The sample size of Stage II is powered on the primary endpoint to allow for assessment of non-inferiority of GATT-Patch compared to the current knowledge (literature-based) of standard of care regarding the percentage of subjects achieving hemostasis at 3 minutes. Assuming the true percentage of subjects achieving hemostasis at 3 minutes using GATT-Patch is 89%, then an evaluable sample size of 36 evaluable subjects from Stage II achieves over 90% power to demonstrate non-inferiority of GATT-Patch compared to current (literature-based) knowledge of standard care (i.e., demonstrate that the percentage achieving hemostasis at 3 minutes for the population treated with GATT-Patch is significantly greater than the performance goal of 65.4%) using a one-sided continuity corrected Z-test of proportion. The sample size takes into account the interim analysis of the primary performance endpoint (performed when approximately 69% of the planned evaluable Stage II subjects are treated, i.e., n≈25 evaluable Stage II subjects) based on a group sequential design to allow for possible early stopping for overwhelming performance success. The Lan-DeMets approach[5] with an O'Brien-Fleming alpha-spending function is used to control the overall Type I error rate of the study at a one-sided 0.025 level. If the study does not stop for overwhelming performance success at the interim review, then an unblinded conditional power calculation and sample size re-estimation will also be conducted at the interim review. The sample size re-estimation analysis will be performed by an independent statistician according to the Mehta-Pocock Promising Zone[6] approach. The conditional power for demonstrating that the primary performance endpoint is significantly greater than performance goal of 65.4% will be calculated under the current protocol-specified evaluable sample size, under the assumption that the observed interim treatment effect (i.e., percentage achieving hemostasis at 3 minutes) is the true treatment effect size. If the conditional power under the protocol-specified evaluable sample size is between 39% to <90% (the promising zone), then the

[5] Lan KKG, DeMets DL. Discrete Sequential Boundaries for Clinical Trials. Biometrika. 1983; 70, 659–663.

[6] Mehta C, Pocock S. Adaptive increase in sample size when interim results are promising: a practical guide with examples. Stat Med. 2011;30:3267–84.

	evaluable sample size may increase to maintain conditional power of 90%. The sample size may increase to a maximum of 56 (i.e., up to 20 additional) evaluable subjects for Stage II. Such a sample size increase based on the Mehta-Pocock Promising Zone approach will not require an additional penalty to the final significance (alpha) level. The performance goal was established on a systematic literature review and meta-analysis, that found the lower 95% confidence interval of the random-effects meta-analytical estimate of the percentage achieving hemostasis at 3 min to be 65.4%, based on previous studies for hemostatic techniques used in open liver surgery. The assumption of the true rate of hemostasis at 3 minutes being 89% for GATT-Patch is based on the pre-clinical evidence and clinical judgement. Intraoperative eligibility after informed consent is estimated at 50%, where the other 50% of patients will have no bleeding requiring device use. In case this 50% is an underestimate of intraoperative inclusion, there is a limitation of replacement that is set at 153 patients, representing a rate of 25% of patients being able to be included intraoperatively.
Inclusion criteria	A subject must meet all of the following pre-operative inclusion criteria to be enrolled into the investigation: • Subject is scheduled to undergo an elective open surgery on the liver; • Subject is willing and able to give written informed consent for investigation participation; • Subject is 18 years of age or older at the time of enrollment; • Subject has been informed of the nature of the clinical investigation. A subject must meet all of the following intraoperative inclusion criteria to be treated with the investigational device: • 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 topical hemostat for control of hemostasis; • Subject has a target bleeding site with a SBSS of 1, 2, or 3.
Exclusion criteria	A subject must not meet any of the following pre-operative exclusion criteria to be enrolled into the clinical investigation: • Subject is scheduled to undergo surgery on other organs besides the liver (e.g. pancreas, colon, lungs); • Subject is taking multiple antithrombotic therapies in therapeutic dosage up to the time of surgery, allowing exclusive use of acetylsalicylic acid; • Subject has platelet count <100 x 10^9/L, an activates partial thrombin time of >100s, or international normalized ratio >2.5; • Subject is pregnant, planning on becoming pregnant or actively breast-feeding during the follow-up period; • Subject has a known hypersensitivity to brilliant blue (FD&C Blue #1);

	• Subject has an active or suspected infection at the surgical site; • Subject has a total bilirubin level of ≥ 2.5 mg/dl • Subject has had or has planned to receive any organ transplantation; • Subject has American Society of Anesthesiologists (ASA) classification of 4/5; • Subject has a life expectancy of less than 3 months; • Subject has a documented severe congenital or acquired immunodeficiency; • Subject in whom the investigational device will be used at the site of a synthetic graft or patch implant; • 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; • Subject is not appropriate for inclusion in the clinical investigation, per the medical opinion of the Investigator; • Subject has any incidental (pre- and peri-operative) findings deemed by the Investigator to potentially jeopardize the safety or welfare of the patient.
Statistical analysis	
Analysis sets	• Full Analysis Set (FAS): The FAS population will consist of all Stage II treated subjects. This population will be utilized as a primary analysis population for the primary and secondary performance endpoints and exploratory endpoints. • Per Protocol (PP): The PP population will consist of FAS subjects who do not have major protocol deviations with data analyzed according to treatment received. This population will be utilized as a secondary analysis population for the primary and secondary performance endpoints and exploratory endpoints. Major protocol deviations are defined in Section 9 of the protocol. • Safety Population: The Safety analysis population will consist of Stage I and Stage II treated subjects. This population will be utilized as the primary analysis population for the safety analyses. Summaries will be presented by study stage and overall.
Statistical design	Descriptive statistics will be presented for each variable. Continuous variables will be summarized using descriptive statistics (number of subjects, mean, median, quartiles, standard deviation, minimum, and maximum). Categorical variables will be summarized using frequencies and percentages of subjects in each category. This study utilizes an adaptive design with an interim analysis planned for the purposes of stopping the trial early for overwhelming performance success and for sample size re-estimation. The interim analysis will be performed once approximately 69% (n≈25) of the planned evaluable Stage II subjects 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 performance goal of 65.4% for the primary performance endpoint will be assessed at the interim review using the continuity corrected Z-test of proportion at a one-sided 0.0070 significance level. If the statistical analysis of the primary endpoint at the interim review yields a one-sided p-value less than 0.0070, then the DMC may recommend stopping the trial for overwhelming successful performance. If the one-sided p-value is not less than 0.0070, then the study will continue and the performance goal of 65.4% for the primary performance endpoint will be assessed using the continuity corrected Z-test of proportion at the one-sided 0.0229 significance level for the final analysis. A sample size increase based on the Mehta-Pocock Promising Zone approach will not require an additional penalty to the final significance (alpha) level. The primary analysis of the primary performance endpoint will be on the FAS with available data. The primary performance endpoint will also be analyzed on the PP population as a secondary analysis. Safety analyses will be descriptive and narrative in nature, including definitions of severity and relation for all adverse events, and focusing on serious adverse events.

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ABBREVIATIONS AND ACRONYMS

ADE	Adverse Device Effect
AE	Adverse Event
ASADE	Anticipated Adverse Device Effect
CI	Confidence Interval
CRF	Case Report Form
CRO	Contract Research Organization
DMC	Data Monitoring Committee
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
IFU	Instructions for Use
ISO14155	International Standard on the Clinical investigation of medical devices for human subjects — Good clinical practice
PI	Principal Investigator
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBSS	Surface Bleeding Severity Score
UADE	Unanticipated Adverse Device Effect
USADE	Unanticipated Serious Adverse Device Effect

REVISION HISTORY

Version	Date	Summary of Changes/Affected Sections
Version 01	14/DEC/2020	N/A – Initial Version
Version 02	21/JAN/2021	• Clarification on the statistical considerations • Clarification on the limitation of subject replacement • Addition of collecting photo and video material for training purposes
Version 03	09/MAR/2021	• Readdressing the use of Stage I data (safety analysis only) and associated analysis population definitions. • Limitation of number of sites in Stage I (max 3 sites), and minimum number of subjects per site in Stage I (min 2 subjects). • Removal of secondary endpoint for superiority of GATT-Patch in achieving hemostasis at 3 minutes. • Implementation of an adaptive design, i.e. an interim sample size re-estimation based on performance success. • Reference to Surface Bleeding Severity Score (SBSS) instead of SPOT GRADE. • Implementation of a maximum number of intraoperative screening failures. • Revision of several eligibility criteria. • Revision of the surgical procedure language, to align with revised Instructions for Use, and addition of detailed procedures in case hemostasis is not achieved after an initial 30 seconds application time. • Revision of the investigational device training requirements, including the option of proctoring by principal investigator or experienced investigators. • Revision of anticipated adverse device effects & residual risk language, to align with Risk Management Report. • Addition of overview of required laboratory testing, assessments at admission before surgery, and during hospitalization after surgery. • Minor formatting and language edits.
Version 04	28/APR/2021	• Revision and alignment of ASA score in exclusion criteria to 4/5 throughout protocol. • Clarification on Stage I safety analysis; to be performed when all 12 patients have at least 2 week FU data and not after completion of 6 week FU visit. • Defining treatment failure as ‘no hemostasis after 5 minutes’ instead of ‘prior to site closure’ to align with rest of protocol and DMC charter. • Addition of risk for encapsulated or rolled-up device at a lower risk level/incidence under foreseeable adverse events and anticipated adverse device effects • Minor formatting and language edits.

1. INTRODUCTION

1.1. Background

Hepatic surgery, such as liver resection, has been associated with considerable mortality and morbidity [2]. The postoperative mortality for major hepatectomy has been reported in a range from 0.7-2.6% [3]. 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 [2, 3]. 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 perioperative complications [4].

During liver surgery, most luminal structures greater than 2mm in diameter are controlled during parenchymal transection [5] by 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) [5, 6]. 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 are better controlled with topical hemostatic agents.

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) [7]. GATT Technologies BV developed a novel hemostatic patch that consists of a gelatin carrier and two synthetic activated polymers (NHS-POx). GATT-Patch has been developed to provide a fast and robust control of bleeding during surgery. The current investigation will be the first-in-human study that will evaluate the safety and the performance of GATT-Patch in elective open liver surgery.

1.2. Roles and responsibility

This clinical investigation is sponsored by GATT Technologies BV (Nijmegen, the Netherlands), the legal manufacturer of GATT-Patch.

GATT Technologies BV contracted Avania BV's services to assist in organization and the conduct of the clinical investigation. Avania is a full-service contract research organization (CRO) for medical devices and is responsible for statistics, data management, medical writing, monitoring, and study management.

Investigators at investigational sites will be responsible for patient screening, patient treatment and data collection as outlined in this clinical investigation plan (CIP). Each site will have a designated principal investigator (PI) and one or more study coordinators collectively responsible for the prospective data collection, inclusive of screening, enrollment, evaluation, and documentation, in accordance with the International Organization for Standardization (ISO) 14155: Clinical investigation of medical devices for human subjects — Good clinical practice guidelines. Per site, one physician will

be assigned as PI. Other involved physicians will be referred to as ‘sub-investigators’. Contact details of involved investigators will be kept on a separate file.

The CRO and investigational sites signed a confidentiality agreement to protect the commercial interests of the Sponsor. The agreements between the Sponsor and investigators will be outlined in a Clinical Trial Agreement. The investigators/investigational sites will receive a financial compensation for their participation in the clinical investigation. Financial compensation will be reimbursed through the Sponsor. The investigators will disclose other relevant financial compensation in a financial disclosure.

2. INVESTIGATIONAL DEVICE

2.1. Manufacturer

GATT Technologies BV (Nijmegen, the Netherlands) is the legal manufacturer of GATT-Patch.

2.2. GATT-Patch

GATT-Patch (Figure 2-1) is a resorbable hemostatic sealing patch, contained in a sterile blister pack within a pouch, for topical use in internal surgery. It does not require freezing or other special storage requirements. It presents as a blue, soft, flexible, gelatin fiber-based carrier impregnated with an NHS-POx / NU-POx granulate. The dimensions of GATT-Patch are 50x100mm. As GATT-Patch is a homogenously impregnated fibrous material, both sides are active and it is also suited to being torn into smaller pieces for application in irregularly shaped structures and areas that are difficult to access with a larger item.

FIGURE 2-1: GATT-PATCH

GATT-Patch will be applied onto the wound site where the flexible and resorbable gelatin patch via contact activation starts 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 high efficacy hemostasis can be achieved.

GATT-Patch is a Class III Medical Device intended for application by trained physicians as an aid to hemostasis and sealing in 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[7].

[7] 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.

2.2.1. Regulatory Classification

GATT-Patch is indicated for use as an adjunct to hemostasis and as a surgical sealant in surgery for minimal, mild or moderate bleeding sites. GATT-Patch is intended to be used for management of hemorrhage during surgeries on internal organs. GATT Patch will be totally introduced into the human body and intended to remain there after the procedure. It is fully degradable within 4-6 weeks.

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.

2.2.2. 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 1. GATT-Patch is an implant, and all components are in direct contact with the human body.

TABLE 1: 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 No. 1	FD&C Blue No.1	Spectrum Chem. via VWR	3844-45-9
Granulate	P(EtOx-OH-NHS) and P(EtOx-NH2)	GATT Technologies	NA
Porous Gelatin carrier (porcine origin)	Gelatin	Gelita Medical	9000-70-8

2.3. Intended populations and indications

2.3.1. Intended indications

GATT-Patch is indicated for use as an adjunct to hemostasis and as a surgical sealant 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 internal organs, primarily parenchymatous organs such as liver, spleen or kidney; or in other abdominal surgeries. GATT-Patch is intended to be used by physicians trained in performing specific surgical and minimal invasive procedures.

2.3.2. Intended populations

The hemostatic sealant GATT-Patch will be intended for use in adult, adolescent and pediatric patients.

The final recommendations will depend on pre-clinical and clinical data, as 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 No. 1).

2.4. Intended purpose in the clinical investigation

This clinical investigation focusses on the application of GATT-Patch in subjects that are candidate for elective open liver surgery.

2.5. Technical and functional features

GATT-Patch will be applied to the bleeding site where the flexible and resorbable gelatin patch starts the coagulation cascade via contact with tissue. This is further enhanced by dehydrating the blood to 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 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: (1) to adhere the patch to the tissue and (2) to form a seal across the damaged tissue. Together, these two effects help ensure highly effective hemostasis can be achieved independent of the patient's coagulation status, and that the tissue surface remains sealed, preventing leakage of fluids. The patch is resorbed within 4-6 weeks as tissue healing occurs.

The following technical and functional features are defined for GATT-Patch:

- GATT-Patch is a highly active, fibrous, flexible, blue-colored gelatin fiber-based patch that is homogeneously impregnated with an NHS-POx/NU-POx granulate for topical use during internal surgery.
- GATT-Patch can be stored at room temperature and can be used straight out of the package without preparation time.
- The results of preclinical tests have demonstrated that hemostasis could be obtained with 30 seconds of application time
- A flexible and pliable patch of 100 x 50mm size that can easily be cut to smaller size
- Active on both sides
- The patch is resorbed within 4-6 weeks as tissue healing occurs as demonstrated by a GLP implantation study

2.6. Medical/Surgical procedures

The severity of bleeding will be scored according to the Surface Bleeding Severity Scale (SBSS) [1].

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, cut and apply GATT-Patch.

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 patient. 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.

The following method of application is provided in the instructions for use of GATT-Patch (DHF-01-QR-008):

- Put GATT-Patch on a saline wetted gauze or surgical sponge and apply to the bleeding area, with at least 1 cm margins. Hold in place with 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 1cm 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 1cm 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 patient body weight, or approximately 3 patches in a normal adult patient, is covered by GATT-Patch and remains in-situ at the end of the operation.
- It is recommended that dry parts of GATT-Patch after application are wetted via a saline-soaked wet gauze or by irrigation.
- When applying GATT-Patch, minimize contact with wet or bloody surgical instruments or gloves as the adhesive may adhere to other surfaces.
- 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.
- Irrigate GATT-Patch after application and hemostasis, assess potential re-bleedings prior to closing the laparotomy.

It is recommended to use the product within 3 hours after opening (after 3 hours, the performance of the device may decrease). To ensure adequate endpoint assessment in this clinical investigation, no manipulation of GATT-Patch and the Target Bleeding Site should be performed up to 5 minutes after GATT-Patch application, unless extra pressure or an additional patch is required per instructions for use and scenarios below.

As described in the IFU, certain situations can occur in which hemostasis is not achieved after an initial 30 seconds application time. The following description, and Figure 2-2, provide 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 up to 5 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 5 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 1cm overlap with tissue or previously placed GATT-Patch on all sides. Apply pressure for 30 seconds. Repeat as necessary up to 5 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 5 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 1cm overlap on the previously placed GATT-Patch on all sides. Apply pressure for 30 seconds. Repeat as necessary up to 5 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 5 minutes from the initial application have passed.

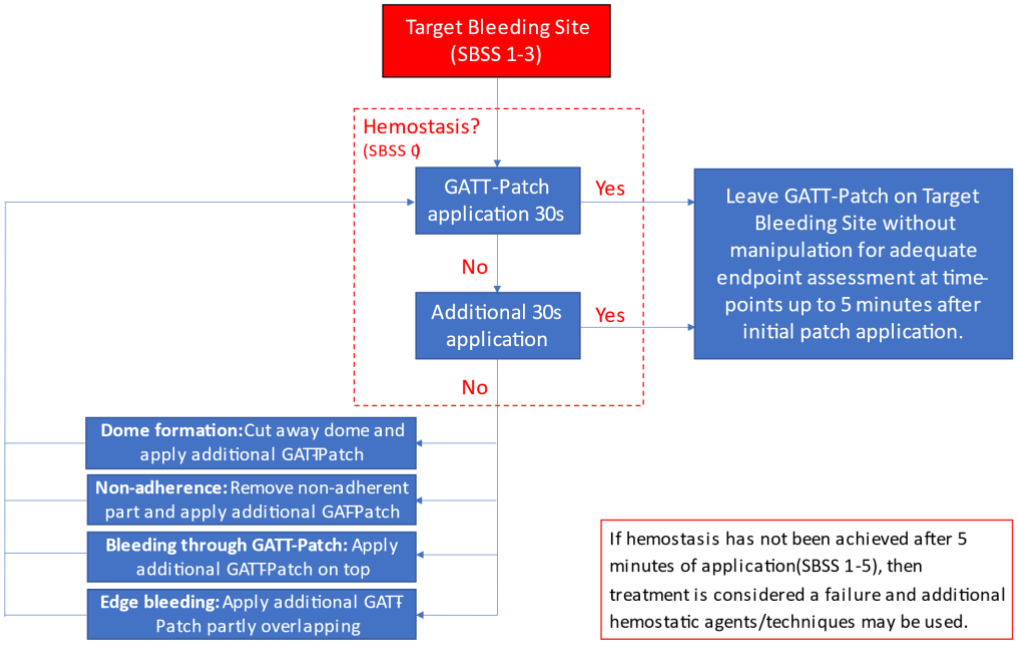

FIGURE 2-2: GATT APPLICATION FLOWCHART

2.7. Required training and experience

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 at least the following: instructions on the functions and use of the investigational device by the Sponsor, training on SBSS for assessment of bleeding at the target site, procedures outlined in the clinical investigation plan, main principles of Good Clinical Practices for Medical Devices (ISO 14155), instructions on completion of the case report forms, content of the investigator site file, and management of device deficiencies.

2.7.1. 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 the certified e-learning training set up by the SBSS developer and owner [1]. Training on the SBSS will be performed to reduce intra-rater variability in the assessment of bleeding at the target site. A training record will be signed on completion of the training and filed in the TMF.

2.7.2. Investigational Device and Procedure

All investigators will have extensive 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 principal investigator 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 principal investigator or an experienced investigator that has previously used GATT-Patch at least once. The flow of training by proctoring is further explained in Figure 2-3. A training record for the proctoring session will be signed on completion of the training and filed in the TMF.

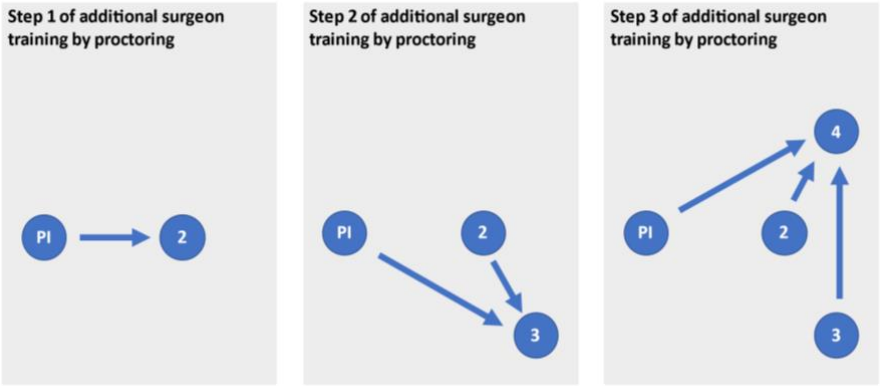

FIGURE 2-3: GATT-PATCH TRAINING FLOWCHART

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

2.7.3. Qualifications

The investigators will have adequate qualifications with regards to the following:

- trained on use of GATT-Patch;
- trained on the SBSS;
- trained in performing specific surgical procedures;
- experience and training in clinical studies, particularly clinical studies involving medical devices, and Good Clinical Practices for Medical Devices (ISO 14155);
- able to read and understand English.

2.8. Device traceability

Investigational devices used in this clinical investigation will be labelled with a unique LOT number. The unique LOT allows for identification and tracking of devices throughout the clinical investigation. The devices will be labelled with the text “Exclusively for Clinical Investigation” to avoid non approved use of the device. Further details are provided in Section 10. In addition, the patient card further ensures the identification of the device and continued traceability after study termination.

3. JUSTIFICATION FOR CLINICAL INVESTIGATION DESIGN

3.1. Pre-clinical testing

GATT Technologies BV performed pre-clinical testing to assess residual risks associated with the device. Details on pre-clinical testing are provided in the Investigator Brochure (DHF-01-SFT-164). 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 and is safe for use in humans.

3.2. State of the art

This first-in-human clinical investigation will generate the first clinical data for GATT-Patch. 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 Protocol 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 adverse events that are related to the management of hemorrhage during liver surgery. Relevant outcomes included adverse events, 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 the proposed clinical investigation on GATT-Patch. A summary is provided below. Detailed results are provided in a Literature Review Report (DHF-01-SFT-166, Version 01).

There are numerous hemostasis and sealing products approved for bleeding during surgery (Table 2). 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. The clinical evaluation will further elaborate on current alternative treatment options that have the same indication as GATT-Patch.

TABLE 2: ALTERNATIVE HEMOSTATIC (AND SEALING) AGENTS

Group	Category	Class
Hemostats	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
Hemostatic Sealants	Fibrin Sealants	Human plasma and human thrombin
		Human-pooled plasma and bovine thrombin

Group	Category	Class
		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 [2, 3]. GATT-Patch is intended to provide fast and persistent control of bleeding during surgeries on internal organs, as well as robust adhesion and sealing. 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 hemostasis, persistent hemostasis, and strong adhesion and tissue sealing.

The risks of GATT-Patch are considered similar to other hemostasis and sealing devices used during liver surgery (patch and non-patch). There is low risk of adverse events associated with topical hemostatic agents [3]. Device-related adverse events (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: 0-18.2%, 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 0-6.7% 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, post-operative 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 not considered non-serious.

The present clinical investigation is intended to investigate whether the device is safe and performs as intended when compared to the state of the art. It is hypothesized that (1) a high rate of hemostasis, (2) a short time to hemostasis, and (3) persistent hemostasis results in less intraoperative and postoperative risk to patients undergoing these surgeries.

3.3. Clinical development stage

This clinical investigation is intended to collect clinical safety and performance data for CE-mark of the device in Europe. In addition, the results will be used for the design of an investigational device exemption (IDE) trial and commercialization in the US.

3.4. Justification

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. The clinical investigation is performed to evaluate clinical safety and performance of the device for use in open liver surgery. The primary objective is to meet the general safety and performance requirements for GATT-Patch as intended for its CE marking in Europe as they relate to safety and performance and acceptability of the benefit-risk profile.

4. RISKS AND BENEFITS OF THE INVESTIGATIONAL DEVICE, CLINICAL PROCEDURE AND CLINICAL INVESTIGATION

4.1. Anticipated clinical benefits

The intended clinical benefit of GATT-Patch is to provide fast and persistent hemostasis during surgeries on internal organs, primarily parenchymatous organs such as liver, spleen or kidney; or in other abdominal surgeries. 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.

4.2. Anticipated adverse device effects & residual risks

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 (DHF-SFT-121). According to the results of the use risk assessment, 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
- Pain
- New surgery
- Infection
- Blockage of artery or vein / ischemia of organs
- Damage of organs and vessels
- 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.

There were no risks identified as ‘probable’ or ‘frequent’ to occur, neither at a ‘not acceptable’ risk level.

Note: these events can be considered procedure- or device-related events. Adjudication will be based on the definitions provided in Section 13.

4.3. Risks associated with participation in the clinical investigation

The risks that are anticipated for participation in the clinical investigation are:

- Anticipated adverse device effect for the use of GATT-Patch as provided in Section 4.2.
- Procedure-related adverse events during open liver surgery similar to the standard of care.

4.4. Risk control/mitigation

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 (DHF-01-QR-008), 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.

For the purpose of risk control and mitigation during the conduct of the study the clinical investigation will be split into 2 stages:

- **Stage I** of the clinical investigation will enroll a small cohort of subjects within which the initial safety of GATT-Patch will be evaluated. A maximum of 12 subjects (~25% of the overall population) will be treated[8] at a maximum of 3 sites, after which the enrollment into the clinical investigation will be paused. At minimum, 2 subjects shall be treated per site.
- **Stage II** of the clinical investigation will enroll subjects until 39* Stage II subjects have been treated with the investigational device. (*Note: The number of Stage II subjects may increase to a maximum of 61 treated subjects [56 evaluable Stage II subjects, assuming 7.5% drop-out rate] if a sample size increase is deemed necessary based on the interim sample size re-estimation). Stage II will be used to evaluate safety and performance of GATT-Patch.

Furthermore, potential risks associated with participation in this investigation will be minimized and managed in accordance with ISO 14155, and requirements of the approving Ethics Committee(s).

4.5. 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 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.

[8] Treated subjects include subjects that are actually implanted with the device, or had a treatment attempt with the device.

5. OBJECTIVES, HYPOTHESES AND ENDPOINTS

5.1. Primary objective & hypothesis

To primary objective is to evaluate the clinical safety and performance of GATT-Patch in open liver surgery.

It is expected that GATT-Patch will achieve hemostasis within a specified time frame in the majority of patients and having a good safety profile. Statistical criteria for acceptation or rejection of the hypothesis are provided in Section 7.1.

5.2. Primary endpoint

The primary performance endpoint is defined as non-inferiority of GATT-Patch compared to the standard of care regarding the percentage of cases achieving hemostasis at 3 minutes (i.e., demonstrate GATT-Patch is significantly greater than literature-based performance goal of 65.4%).

Hemostasis will be defined by a grade of 0 (None/Dry) on the Surface Bleeding Severity Score (SBSS). The SBSS provides a validated score for assessment of bleeding at the target site, and consists of 6 subscales (0=none, 1=minimal, 2=mild, 3=moderate, 4=severe; not immediately life-threatening, 5=extreme; immediately life threatening) [1]. Investigators will be trained on the assessment scale prior to the investigation to have consistent assessment of bleeding at the target site (Section 2.7).

Achievement of hemostasis will be verified every 30 seconds, starting from the time that GATT-Patch is positioned and pressure is initiated. If hemostasis has not been achieved after 5 minutes of application (SBSS 1-5), then treatment is considered a failure and additional hemostatic agents or techniques may be used.

5.3. Secondary objectives & hypotheses

The following secondary endpoints are defined:

- Mean time to hemostasis (seconds)
- Percentage of hemostasis at 30, 60, 90, 120 and 150 seconds

There will be no formal hypothesis testing on the secondary performance endpoints.

5.4. Safety objective and safety endpoints

The safety of GATT-Patch will be assessed by the nature, severity and incidence of device related adverse events. The adverse events found for GATT-Patch will be compared to the current knowledge and state of the art for hemostatic methods in open liver surgery to assess whether the device is associated with acceptable safety outcomes.

Adverse events may include:

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

- Blockage of artery or vein / ischemia of organs
- Damage of organs and vessels
- Pulsatile hematoma
- Closing of intestinal track
- Biloma
- Encapsulated or rolled-up device

No formal hypothesis testing will be performed for the safety objective and endpoint of this clinical investigation.

5.5. Exploratory endpoints

In addition to the primary endpoint, the following exploratory endpoints will be recorded:

- Surgery Time (minutes)
- Blood loss (mL) during surgery
- Blood Transfusion (mL) during hospitalization
- SBSS (0-5) at the target bleeding site
- Use of adjunct hemostatic agents/techniques (e.g. cautery, sutures or staples)
- Amount of material needed versus bleeding surfaces
- User satisfaction (questionnaire)

5.6. Rationale for endpoint selection

Endpoints were selected based on outcomes reported for other topical hemostatic agents in the scientific literature. The meta-analysis described in Section 3.2 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 [4, 8-12]. Percentage of hemostasis at 3 minutes was found a clinically relevant performance outcome for success of various hemostatic techniques during open liver surgery. Data from different studies and techniques were pooled to define a performance goal for GATT-Patch to be used in the sample size calculation (Table 3). Detailed results per article are provided in a Literature Review Report (DHF-01-SFT-166, Version 01). The performance goal of GATT-Patch is based on the lower bound of the pooled rate of hemostasis at 3 minutes.

TABLE 3: SUMMARY OF PRIMARY ENDPOINT OUTCOME REPORTED IN SCIENTIFIC LITERATURE AND USED IN SAMPLE SIZE CALCULATION

Reference	Group	N	Time to hemostasis #	Hemostasis at 3 min
6 RCTs	TachoSil, ORC (Surgicel), Sangustop, Veriset, Grifols, Fibrocaps, Gelatin sponge (Gelfoam or Spongostan)	799 patients	Range: 1 min-5.5 min	Weighted average: 74.8% (95% CI: 65.4% to 83.1%)

6. DESIGN OF THE CLINICAL INVESTIGATION

6.1. General

This is a pre-market, prospective, single arm, multicenter first-in-human clinical investigation.

The clinical investigation will be split into 2 stages:

- **Stage I** of the clinical investigation will enroll a small cohort of subjects within which the initial safety of GATT-Patch will be evaluated. A maximum of 12 subjects (~25% of the overall population) will be treated[9] at a maximum of 3 sites, after which the enrollment into the clinical investigation will be paused. At minimum, 2 subjects shall be treated per site. A DMC will review safety in this subset of subjects and decides whether the study may proceed (Section 13.8)
- **Stage II** of the clinical investigation will enroll subjects until 39* Stage II subjects have been treated with the investigational device. (*Note: The number of Stage II subjects may increase to a maximum of 61 treated subjects [56 evaluable Stage II subjects, assuming 7.5% drop-out rate] if a sample size increase is deemed necessary based on the interim sample size re-estimation). Stage II will be used to evaluate safety and performance of GATT-Patch.

In both Stage I and Stage II, subjects will follow the same clinical investigation pathway. Stage I subjects will be analyzed for safety only, whereas Stage II subjects will be analyzed for both safety and performance.

6.2. Investigational device and comparators

This is an uncontrolled clinical investigation. Subjects will be treated with GATT-Patch (5x10cm).

6.3. Subjects

The clinical investigation will enroll subjects that are candidate for elective open liver surgery.

6.3.1. Inclusion criteria

- Subject is scheduled to undergo an elective open surgery on the liver;
- Subject is willing and able to give written informed consent for investigation participation;
- Subject is 18 years of age or older at the time of enrollment;
- Subject has been informed of the nature of the clinical investigation.

A subject must meet all of the following intraoperative inclusion criteria to be treated with the investigational device:

- 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 topical hemostat for control of hemostasis;
- Subject has a target bleeding site with a SBSS of 1, 2, or 3.

[9] Treated subjects include subjects that are actually implanted with the device, or had a treatment attempt with the device.

6.3.2. Exclusion criteria

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

- Subject is scheduled to undergo surgery on other organs besides the liver (e.g. pancreas, colon, lungs);
- Subject is taking multiple antithrombotic therapies in therapeutic dosage up to the time of surgery, allowing exclusive use of acetylsalicylic acid;
- Subject has platelet count <100 x 10^9/L, an activates partial thrombin time of >100s, or international normalized ratio >2.5;
- Subject is pregnant, planning on becoming pregnant or actively breast-feeding during the follow-up period;
- Subject has a known hypersensitivity to brilliant blue (FD&C Blue #1);
- Subject has an active or suspected infection at the surgical site;
- Subject has a total bilirubin level of ≥ 2.5 mg/dl;
- Subject has had or has planned to receive any organ transplantation;
- Subject has American Society of Anesthesiologists (ASA) classification of 4/5;
- Subject has a life expectancy of less than 3 months;
- Subject has a documented severe congenital or acquired immunodeficiency;
- Subject in whom the investigational device will be used at the site of a synthetic graft or patch implant;
- 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;
- Subject is not appropriate for inclusion in the clinical investigation, per the medical opinion of the Investigator;
- Subject has any incidental (pre- and peri-operative) findings deemed by the Investigator to potentially jeopardize the safety or welfare of the patient.

6.3.3. Representativeness of included population

This clinical investigation will enroll subjects that are candidate for open liver surgery. Subjects with an appropriate bleeding site (SBSS of 1, 2, or 3) will be treated with GATT-Patch. Therefore, the included population is considered a representative sample for the intended use of GATT-Patch.

6.3.4. Definition of enrollment

A subject is considered enrolled in the clinical investigation after they have provided written informed consent, and if they meet the preoperative eligibility criteria (Section 6.3.1 and Section 6.3.2). The study will treat up to 73 subjects with the investigational device. Treated subjects include subjects that are actually implanted with the device, or had a treatment attempt with the device.

6.3.5. Randomization

N/A. This is a non-randomized clinical investigation.

6.3.6. Sample size

The current plan is to treat a total of up to 51 subjects with GATT-Patch, with a maximum of 153 replaceable subjects that may be enrolled (Section 6.3.9). However, the total sample size may increase to a maximum of 73 treated subjects based on the interim sample size re-estimation. The sample size calculation is provided in Section 7.2. It is expected that a comparable number of subjects is enrolled and treated at each investigational site.

In Stage I, there is a minimum of 2 subjects to be treated by each site (maximum of 3 sites). In Stage II, there is no minimum or maximum number of subjects to be enrolled or treated by each site, however distribution between participating sites is monitored during the enrolment period.

6.3.7. Study duration

The enrollment period is expected to take approximately 6 months. The per subject duration of the clinical investigation from treatment to final follow-up will be approximately 6 weeks. With a 2-week temporary hold on enrollment for the safety evaluation, the total expected duration of the clinical investigation is, therefore, approximately 8 months. GATT-Patch is expected to resorb within 4-6 weeks, and 6 weeks follow-up is therefore considered sufficient for the assessment of performance and safety of the device.

6.3.8. Subject withdrawal, discontinuation and study end

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 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 case report forms. If a subject fails to return for the follow-up visit, 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 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 protocol(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.

6.3.9. Subject replacement

The current plan is to treat a total of 51 subjects with the investigational device. However, the total sample size may increase to a maximum of 73 treated subjects based on the interim sample size re-estimation. There will be no replacement of subjects who have been treated with the investigational device. Intraoperative eligibility after informed consent is estimated at 50%, where the other 50% of patients will have no bleeding requiring device use. In case this 50% is an underestimate of intraoperative inclusion, there is a limitation of replacement that is set at 153 patients, representing

a rate of 25% of patients being able to be included intraoperatively. A re-evaluation of inclusion and exclusion criteria will be performed when a total of 51 treated subjects is not reached when the maximum of 153 subjects are replaced.

6.3.10. Investigational sites

This clinical investigation will be conducted in the Netherlands. Up to 7 sites will participate in this clinical investigation, with a maximum of 3 sites in Stage I. Any differences between site environment will be minimized through central training of the investigators and adherence to the same clinical investigation plan. Each site has a clinical environment that is representative of the normal conditions of use of the device in the target population.

Contact and site details of each participating site are listed in a separate document. Emergency contact details are provided the contact information sheet on page 4.

6.4. Procedures

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. GATT-Patch will be used if the subject has an appropriate bleeding site (SBSS 1, 2 or 3 and no contraindications).

6.4.1. Schedule of assessments

Table 4 provides a schedule of assessment for subjects screened and enrolled in the clinical investigation. All assessments are applicable for treated subjects, while only the assessments related to 'screening' and 'admission' are applicable for subjects that are enrolled but not treated.

TABLE 4: SCHEDULE OF ASSESSMENTS

Assessments	Screening	Admission before surgery	Treatment with investigational device	Hospitalization after surgery	Week 6 (±2 weeks) Post-procedure*
Informed consent	X				
Inclusion and Exclusion Criteria	X	X	X		
Baseline demographics	X				
Physical examination	X	X			
Relevant concomitant medication**	X	X			X
Medical history/Allergy	X				
Laboratory tests	X	X		X	
Procedural data			X		
Adverse events			X	X	X
User questionnaire			X		
Ultrasound imaging					X

* Some subjects may have an additional phone consultation at 2-6 weeks post-procedure for the assessment of safety during Stage I of the clinical investigation. This visit will include assessment of adverse events, and will only take place for subjects in stage I of the clinical investigation who did not complete the 6 weeks follow-up visit.

** Relevant concomitant medication will be captured from screening to study completion. Medication is considered relevant when related to any of the study eligibility criteria, or when it may affect any of the endpoints, at the discretion of the investigator. Relevant medication covers at a minimum the medication for the underlying medical condition for the surgical procedure, and medication for concomitant chronic pathologies.

6.4.1.1. Laboratory Tests

Laboratory tests will be collected prior to surgery, and through the postsurgical admission. The collection of laboratory tests is specified in Table 5. Tests that are indicated with an 'X' are required per this clinical investigation plan. Tests that are indicated with an '*' are not dictated by this clinical investigation plan: results will only be captured if these test data is collected per standard of care.

TABLE 5: LABORATORY TESTING SCHEDULE

Laboratory Tests	Screening	Admission before surgery	Through admission*
Hematology			
Hemoglobin (Hb)	X	*	X
Thrombocytes	X	*	*
Coagulation			
Prothrombin time (PT)	X	*	*
Activated partial thromboplastin time (aPTT)	X	*	*
International Normalized Ratio (INR)	X	*	*
Chemistry			
Bilirubin	X	*	*
Calcium	*	*	*
Potassium	*	*	*
Sodium	*	*	*
Chloride	*	*	*
Albumin	*	*	*
AST	*	*	*
ALT	*	*	*

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

6.4.2. Equipment for assessment

The following equipment will be required for assessment of endpoints:

- Ultrasound imaging system
- Stopwatch

6.4.3. Screening

During the Screening phase, the following assessments will be performed:

Informed consent

If the patient meets the criteria of the initial screening, informed consent will be obtained. Before performing any study-specific procedures, the potential subject must be thoroughly informed about all aspects of the clinical investigation, including scheduled study visits and activities, and must have signed the Ethics Committee-approved informed consent form. See also Section 12 for more details.

Baseline data

The following baseline demographics will be captured, if available:

- **Demographics:** Subject demographics (age, gender, race) will be recorded.
- **Physical examination**
- **Relevant concomitant medication**
- **Medical history:** The subject's relevant medical history will be recorded. Medical history is considered relevant when it is currently ongoing, when it is related to any of the study eligibility criteria, or when it may affect any of the endpoints. Relevant medical history covers at a minimum the underlying medical condition for the surgical procedure.
- **Laboratory test data**

6.4.4. Admission before surgery

The following baseline data will be captured during admission before surgery:

- **Confirmation of inclusion/exclusion criteria**
- **Physical examination**
- **Relevant concomitant medication**
- **Laboratory test data**

6.4.5. Treatment

GATT-Patch will be used to control bleeding during open liver surgery. Each surgery will be performed according to the standard procedures at the hospital, with exception of the use of GATT-Patch. GATT-Patch will be used if the subject has an appropriate bleeding site (SBSS 1, 2 or 3 and no contraindications). Use of GATT-Patch 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 bleeding sites, the first encountered bleeding site that requires topical hemostat application will be considered for the primary endpoint.

The handling instructions for GATT-Patch are provided in the Instructions for Use of the device (DHF-01-QR-008). 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, cut and apply 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. Failure is considered if after 5 minutes no hemostasis was obtained. Up to 3 full patches may be used. The patch may be applied to or overlap a previously applied patch ("patch on patch").

Achievement of hemostasis will be verified every 30 seconds. The primary performance endpoint is defined by the percentage of cases achieving hemostasis at 3 minutes. Hemostasis will be defined by a grade of 0 (None/Dry) on the SBSS[10]. If hemostasis has not been achieved after 5 minutes of

[10] The Surface Bleeding Severity Score (SBSS) provides a validated score for assessment of bleeding at the target site, and consists of 6 subscales (0=none, 1=minimal, 2=mild, 3=moderate, 4=severe; not immediately life-

application (SBSS 1-5), then treatment is considered a failure and other additional hemostatic agents/techniques may be used. This should not be 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.

The investigators will complete a user questionnaire at the end of each procedure. During surgery, photos and videos may be taken for documentation and/or training purposes. Patients will not be recognizable in these photos and videos.

The following procedural data will be collected:

- **Surgical procedure data:**
  - Date of surgery (month/year)
  - Procedure length (from start incision to surgical site closure)
  - Number of devices used
  - Blood loss (mL)
  - SBSS (0-5) of target bleeding site
  - Use of adjunct hemostatic agents/techniques (e.g., cautery, sutures or staples)
  - Amount of material needed versus bleeding surfaces
  - User satisfaction per investigator per procedure (questionnaire)
- **Hospitalization:**
  - Duration of patient's time spent in the intensive care unit
  - Total hospitalization period
  - Blood transfusion (mL)
- **Intraoperative device and/or procedure related adverse events**
- **Intraoperative device deficiencies**

6.4.6. Hospitalization after surgery

The following data will be captured the during hospitalization after surgery:

- **Laboratory test data**
- **Intraoperative device and/or procedure related adverse events**

6.4.7. Visit 1 (Week 6)

At follow-up Week 6 (±2 weeks), subjects will undergo ultrasound examination of the resection area to identify any encapsulation or rolled-up device, or evidence of a biloma or pseudo-aneurysm. In addition, relevant concomitant medications and adverse events will be assessed.

Optional: Some subjects may have an additional phone consultation at 2-6 weeks post-procedure for the assessment of safety during Stage I of the clinical investigation. This visit will include assessment of adverse events, and will only take place for subjects in stage I of the clinical investigation who did not yet complete the 6 weeks follow-up visit.

threatening, 5=extreme; immediately life threatening) (Spotniz, 2017). Investigators will be trained on the assessment scale prior to the investigation to have consistent assessment of bleeding at the target site.

6.4.8. Study completion

The study is completed when the 51 subjects were treated with the investigational device or when the number of subjects needed based on the planned interim analysis of the primary performance endpoint is treated with the investigational device, and the last treated subject completed the follow-up Visit 1, is lost to follow-up or pre-maturely ended the study for some other reason. Subjects are lost to follow-up when the following steps have been taken:

- Two phone calls should be made to the subject. Each attempt should be clearly documented in the source documents and the response or lack thereof should be captured.
- If there is no response to the phone calls, then certified letter should be written to the subject. A copy of the letter should be retained in the subject's source document.
- After a period of two (2) weeks following completion of the above actions, the subject will be considered Lost to Follow-up. The sponsor should be notified and appropriate eCRF should be completed.

6.4.9. Activities by Sponsor representatives

Procedures related to the clinical investigation will be performed by the principal investigator, study coordinators, and/or other authorized study staff, as applicable. A Sponsor representative may be present during investigational procedures for technical support. Photos and videos may be taken by the Sponsor representative for documentation and/or training purposes. Patients will not be recognizable in these photos and videos.

6.5. Minimization of bias

Potential for bias during this clinical investigation has been minimized by conduct 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 (see also Section 7.8).

6.6. Potential confounding factors

Investigators will be trained on the use of the device, and SBSS prior to initiation of the clinical investigation.

6.7. Scientific robustness

The clinical investigation design was based on the current knowledge/state of the art. Scientific robustness and validity is demonstrated by adequate sample size calculation prior to the study (Section 7.2). The data that is generated through this clinical investigation is therefore considered to reflect clinical safety and performance outcomes relevant for the intended use of GATT-Patch.

6.8. Monitoring plan

Monitoring will be conducted by Avania BV. Details of the monitoring activities are outlined in the Monitoring Plan.

7. STATISTICAL CONSIDERATIONS

7.1. Statistical design & methods

This study utilizes an adaptive design with an interim analysis planned when 69% (n≈25) of the planned evaluable Stage II subjects are treated. The interim analysis will be conducted for the purposes of 1) stopping the trial early for overwhelming performance success based on a group sequential design using the Lan-DeMets approach[11] with an O'Brien-Fleming alpha-spending function or 2) for increasing the sample size based on the Mehta-Pocock Promising Zone approach[12].

Descriptive statistics will be presented for each variable. Continuous variables will be summarized using descriptive statistics (number of subjects, mean, median, quartiles, standard deviation, minimum, and maximum). Categorical variables will be summarized using frequencies and percentages of subjects in each category.

7.1.1. Primary endpoint analysis

The primary performance endpoint is the percentage of patients achieving hemostasis at 3 minutes using GATT-Patch.

The statistical null (H_0) and alternative (H_1) hypotheses are the following:

$$H_0: p_{GATT} \leq 65.4\%$$

$$H_1: p_{GATT} > 65.4\%$$

where p_{GATT} is the percentage of patients achieving hemostasis at 3 minutes using GATT-Patch and 65.4% is the performance goal (PG) to demonstrate non-inferiority of GATT-Patch compared to current knowledge (literature-based) of standard of care.

The interim analysis of the primary performance endpoint will be performed once approximately 69% (n≈25) of the planned evaluable Stage II subjects 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, a test to demonstrate that the percentage of patients achieving hemostasis at 3 minutes using GATT-Patch is significantly greater than 65.4% will be performed at the interim review using the continuity corrected Z-test of proportion at a one-sided 0.0070 significance level. If the statistical analysis of the primary endpoint at the interim review yields a one-sided p-value less than 0.0070, then the DMC may recommend stopping the trial for overwhelming successful performance. If the one-sided p-value is not less than 0.0070, then the study will continue and a final analysis to demonstrate that the percentage of patients achieving hemostasis at 3 minutes using GATT-Patch is significantly greater than 65.4% will be performed using the continuity corrected Z-test of proportion at the one-sided 0.0229 significance level. A sample size increase based on the Mehta-Pocock Promising Zone approach will not require an additional penalty to the final significance (alpha) level. The primary analysis of the primary performance endpoint will be on the FAS with available data. The

[11] Lan KKG, DeMets DL. Discrete Sequential Boundaries for Clinical Trials. Biometrika. 1983; 70, 659–663.

[12] Mehta C, Pocock S. Adaptive increase in sample size when interim results are promising: a practical guide with examples. Stat Med. 2011;30:3267–84.

primary performance endpoint will also be analyzed on the PP population as a secondary analysis. The number and percentage of patients achieving hemostasis at 3 minutes using GATT-Patch will be reported, including the confidence interval (CI) of the percentage based on Wilson's method with continuity correction and the one-sided p-value from the continuity corrected Z-test of proportion. In order to correspond with the significance levels that will be used at the interim and final analyses, a two-sided 98.6% CI will be calculated for the interim analysis and 95.42% CI will be calculated for the final analysis.

7.1.2. Secondary endpoint analysis

The mean, standard deviation, median, quartiles, minimum, and maximum time to hemostasis (seconds) will be presented. The number and percentage of subjects achieving hemostasis at 30, 60, 90, 120, and 150 second will be presented.

There will be no formal hypothesis testing of these secondary endpoints.

7.1.3. Safety endpoints

Safety analyses will be performed for the Safety population and will be descriptive and narrative in nature, including definitions of severity and relation for all adverse events, and focusing on serious adverse events.

Adverse events may include:

- Toxic response
- Thromboembolic event
- (Re)Bleeding
- Allergic reaction
- Pain
- New surgery
- Infection
- Blockage of artery or vein / ischemia of organs
- Damage of organs and vessels
- Pulsatile hematoma
- Closing of intestinal track
- Biloma
- Encapsulated or rolled-up device

The number and percent of patients with any adverse event, any serious adverse event, any adverse event related to the study device, and any adverse event related to study procedure will be presented. No formal hypothesis testing will be performed.

7.1.4. Exploratory Endpoints

The following exploratory endpoints will be analyzed on the FAS and PP populations:

- Surgery time (minutes)
- Blood loss during surgery (mL)
- Blood transfusion during hospitalization (mL)
- SBSS (0-5)
- Use of adjunct hemostatic agents/techniques (e.g. cautery, sutures or staples)

- Amount of material needed versus bleeding surfaces
- User satisfaction (questionnaire) per investigator per procedure

Descriptive statistics will be presented for each endpoint. Continuous variables will be summarized using descriptive statistics (number of subjects, mean, median, quartiles, standard deviation, minimum, and maximum). Categorical variables will be summarized using frequencies and percentages of subjects in each category. No formal hypothesis testing will be performed for these exploratory endpoints. Exploratory endpoints will be analyzed on the FAS and PP populations.

7.2. Sample size

The plan is to enroll and treat the following number of subjects across two stages:

- Stage I: maximum of 12 subjects
- Stage II: 39 subjects (36 evaluable subjects, assuming 7.5% drop-out rate)*

*Note: The number of Stage II subjects may increase to a maximum of 61 treated subjects (56 evaluable subjects, assuming 7.5% drop-out rate) if a sample size increase is deemed necessary based on the interim sample size re-estimation

The sample size of Stage II is powered on the primary endpoint to allow for assessment of non-inferiority of GATT-Patch compared to the current knowledge (literature-based) of standard of care regarding the percentage of subjects achieving hemostasis at 3 minutes.

Assuming the true percentage of subjects achieving hemostasis at 3 minutes using GATT-Patch is 89%, then an evaluable sample size of 36 evaluable subjects from Stage II achieves over 90% power to demonstrate non-inferiority of GATT-Patch compared to current (literature-based) knowledge of standard care (i.e., demonstrate that the percentage achieving hemostasis at 3 minutes for the population treated with GATT-Patch is significantly greater than the performance goal of 65.4%) using a one-sided continuity corrected Z-test of proportion. The sample size takes into account the interim analysis of the primary performance endpoint (performed when approximately 69% of the planned evaluable Stage II subjects are treated, i.e., n≈25 evaluable Stage II subjects) based on a group sequential design to allow for possible early stopping for overwhelming performance success. The Lan-DeMets approach with an O'Brien-Fleming alpha-spending function is used to control the overall Type I error rate of the study at a one-sided 0.025 level.

If the study does not stop for overwhelming performance success at the interim review, then an unblinded conditional power calculation and sample size re-estimation will also be conducted at the interim review. The sample size re-estimation analysis will be performed by an independent statistician according to the Mehta-Pocock Promising Zone approach. The conditional power for demonstrating that the primary performance endpoint is significantly greater than performance goal of 65.4% will be calculated under the current protocol-specified evaluable sample size (n=36), under the assumption that the observed interim treatment effect (i.e., percentage achieving hemostasis at 3 minutes) is the true treatment effect size. If the conditional power under the protocol-specified evaluable sample size is between 39% to <90% (the promising zone), the evaluable sample size may increase to maintain conditional power of 90%. The sample size may increase to a maximum of 56 (i.e., 20 additional) evaluable subjects for Stage II. Such a sample size increase based on the Mehta-Pocock Promising Zone approach will not require an additional penalty to the final significance (alpha) level.

The performance goal was established on a systematic literature review and meta-analysis (see Section 5.6), that found the lower 95% confidence interval of the random-effects meta-analytical estimate of the percentage achieving hemostasis at 3 min to be 65.4%, based on previous studies for hemostatic techniques used in open liver surgery. The assumption of the true rate of hemostasis at 3 minutes being 89% for GATT-Patch is based on the pre-clinical evidence and clinical judgement.

7.3. Analysis populations

The following populations are defined for the analysis of the data:

- Full Analysis Set (FAS): The FAS population will consist of all Stage II treated subjects. This population will be utilized as a primary analysis population for the primary and secondary performance endpoints and exploratory endpoints.
- Per Protocol (PP): The PP population will consist of FAS subjects who do not have major protocol deviations with data analyzed according to treatment received. This population will be utilized as a secondary analysis population for the primary and secondary performance endpoints and exploratory endpoints. Major protocol deviations are defined in Section 9 of the protocol.
- Safety Population: The Safety analysis population will consist of Stage I and Stage II treated subjects. This population will be utilized as the primary analysis population for the safety analyses. Summaries will be presented by study stage and overall.

7.4. Missing data

The primary analysis of the primary performance endpoint will be on the FAS population with available data. Reasonable efforts will be made to obtain complete data for all subjects; however, missing observations may occur due to subjects lost to follow-up or noncompliance with required assessments. Any missing data on study endpoints will be described. For the primary performance endpoint regarding achieving hemostasis at 3 minutes, a “tipping point” sensitivity analysis will be used to assess the effect of missing data on the results of the hypothesis testing of the primary endpoint. I.e., for the primary endpoint, if the null hypothesis is rejected on the FAS population with available data, then FAS patients who are missing will be imputed as a failure (i.e., not achieving hemostasis at 3 min), one at a time cumulatively, and the null hypothesis will be tested after each cumulative imputation until the “tipping point” is reached (i.e., until the null hypothesis is no longer rejected). There will be no imputation of missing data for other endpoints.

7.5. Learning curve

The influence of learning curve on results is considered negligible. Investigators will have extensive training on the investigational device prior to the start.

7.6. Interim analysis

A data monitoring committee (DMC) will monitor all emerging safety issues against pre-defined stopping rules of the clinical investigation (Section 13.8). Any Serious Adverse Events or other safety concerns during Stage I of the clinical investigation will be immediately referred, on a case-by-case basis, to the DMC for review against the stopping rules. A formal review of safety against the stopping rules will be conducted by the DMC when all subjects of the initial cohort (Stage I) are treated and have at least 2 week FU data available. The re-opening of recruitment will only be triggered by

authorization from the DMC to proceed. The DMC may decide to temporarily halt the clinical investigation in case of safety concerns. The stopping rules are defined in the DMC Charter.

This study utilizes an adaptive design with an interim analysis of the primary performance endpoint planned for the purposes of 1) stopping the trial early for overwhelming performance success or 2) increasing the sample size if deemed necessary based on the interim sample size re-estimation. The interim analysis of the primary performance endpoint will be performed once approximately 69% (n=25) of the planned evaluable Stage II subjects 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, if the statistical analysis of the primary endpoint at the interim review yields a one-sided p-value less than 0.0070, then the DMC may recommend stopping the trial for overwhelming performance success. If the one-sided p-value is not less than 0.0070, then the study will continue. If the study does not stop for overwhelming performance success at the interim review, then an unblinded conditional power calculation and sample size re-estimation will also be conducted during the interim review. The sample size re-estimation analysis will be performed by independent statistician according to the Mehta-Pocock Promising Zone approach. The conditional power for demonstrating that the primary performance endpoint is significantly greater than performance goal of 65.4% will be calculated under the current protocol-specified evaluable sample size for the final analysis (n=36), under the assumption that the observed percentage achieving hemostasis at 3 minutes at the interim analysis is the true rate of hemostasis at 3 minutes for the population. If the conditional power under the protocol-specified evaluable sample size is between 39% to <90% (the promising zone), then the evaluable sample size may increase to maintain conditional power of 90%; otherwise, the study will continue as is without a sample size increase. The sample size may increase to a maximum of 56 (i.e., up to 20 additional) evaluable subjects for Stage II. The DMC will review the results of the interim analysis of the primary performance endpoint and provide the recommendation to the sponsor (e.g., “continue study as is”, “increase sample size to xx”, “stop study for overwhelming performance success”).

7.7. Statistical deviations

The statistical deviations and assessment will be defined in the statistical analysis plan (SAP). Statistical deviations from the study protocol and/or from the final SAP will be described in the clinical investigation report.

7.8. Management of bias

The following activities are intended to reduce the risk of bias:

- Prospective inclusion of study subjects from a consecutive cohort.
- Adhere to procedures that take into account all the data.
- Extensive training of investigators prior to the start of the clinical investigation to reduce the influence of a learning curve (Section 2.7).
- Centralized assessment of (serious) adverse events by a data monitoring committee (DMC) (Section 13.8).

7.9. Pooled data

In both Stage I and Stage II, subjects will follow the same clinical investigation pathway. The primary analysis of the performance and exploratory endpoints will only include Stage II subjects. However, a sensitivity analysis of the performance and exploratory endpoints may be conducted that includes both Stage I and Stage II subjects.

For the primary endpoint, descriptive statistics (i.e., number and percent of patients achieving hemostasis at 3 minutes) will be presented separately for each investigational site. Logistic regression, with achieving hemostasis at 3 min (yes/no) as the dependent variable and investigational site as the independent variable, will be used to assess homogeneity across sites in the primary endpoint. The association between “investigational site” and the primary performance outcome will be assessed at the 0.1 significance level.

8. DATA MANAGEMENT

8.1. Data entry and collection

An electronic data capture (EDC) system with electronic Case Report Forms (eCRFs) will be used for the purposes of this clinical investigation. Subjects are uniquely identified by a clinical investigation subject number, consisting of a site identifier (two digits) and unique subject identifier (three digits) in the following format: xx-xxx. All eCRFs will be completed in English and the investigator, or investigator's qualified designee, must review, electronically sign and date each completed eCRF where requested. The eCRFs will be completed in a timely manner after completion of the patient's visit.

The data reported on the eCRFs will be derived from source documents and be consistent with these source documents, and any discrepancies will be explained in writing. Any change or correction to data reported on an eCRF will be dated, initialed, and explained if necessary, and will not obscure the original entry (i.e., an audit trail will be maintained). This applies to both written and electronic changes or corrections.

8.2. Data review, database cleaning, and issuing and resolving data queries

The data entered into the EDC will be fully validated, using clinical investigation-specific range and consistency checks and database listings. Queries will be issued to the site via the EDC system, and are to be resolved by the investigator or his designee using the EDC system. Data validation will be completed on a regular basis. The entire database will be re-validated to ensure that there are no outstanding data discrepancies prior to database lock. Any changes to the database after that time will require written agreement by the Sponsor.

8.3. Procedures for verification, validation and securing of electronic clinical data systems

Data will be collected and recorded using a validated 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 Avania BV 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. Source documents will include, but are not limited to, progress notes, electronic data, screening logs, and recorded data from automated instruments. Data to be collected for purposes of the clinical investigation must not be entered directly into the eCRF before being recorded first in the source documents. All source documentation must be available for review by the study monitor during monitor visits. Source data is defined as all information in original records, certified copies of original records of clinical findings, observations, or other activities in a clinical investigation, necessary for the reconstruction and evaluation of the clinical investigation.

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.

8.4. Case report forms

The investigators will ensure the accuracy, completeness, legibility and timelines of the data reported in eCRF and in all required documentation. Data reported on the eCRF will be supported by the source documents with any discrepancies being explained. Any corrections made to documents will be done according to ISO 14155 guidelines. If an item is not available or is not applicable, this fact should be indicated. The investigator who has signed the clinical investigation plan signature page or his/her authorized designee is to personally sign the eCRFs to validate that the observations and findings are recorded on the eCRFs correctly and completely. The eCRFs are to be completed in a timely manner after the subject's visit. Failure to meet the documentation requirements may lead to the disqualification of an investigator.

8.5. Data 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 clinical investigation plan and amendments, Investigator Brochure, and dates and reasons for any deviations to the clinical investigation plan 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.

8.6. Subject confidentiality

Participant confidentiality will be maintained throughout the clinical investigation in a way that ensures the information can always be tracked back to the source data. For this purpose, a unique subject identification code will be used that allows identification of all data reported for each subject. Data relating to the clinical investigation might be made available to third parties (for example in case of an audit performed by regulatory authorities) provided the data are treated confidentially and that the subject's privacy is guaranteed.

8.7. Data protection

Data protection will be ensured in accordance with Regulation (EU) 2016/679 (General Data Protection Regulation, GDPR). This includes the following:

Personal data will be:

- processed lawfully, fairly and in a transparent manner in relation to the data subject ('lawfulness, fairness and transparency');
- collected for specified, explicit and legitimate purposes and not further processed in a manner that is incompatible with those purposes; further processing for archiving purposes in the public interest, scientific or historical research purposes or statistical purposes will, in accordance with Article 89(1), not be considered to be incompatible with the initial purposes ('purpose limitation');

- adequate, relevant and limited to what is necessary in relation to the purposes for which they are processed ('data minimization');
- accurate and, where necessary, kept up to date; every reasonable step must be taken to ensure that personal data that are inaccurate, having regard to the purposes for which they are processed, are erased or rectified without delay ('accuracy');
- kept in a form which permits identification of data subjects for no longer than is necessary for the purposes for which the personal data are processed; personal data may be stored for longer periods insofar as the personal data will be processed solely for archiving purposes in the public interest, scientific or historical research purposes or statistical purposes in accordance with Article 89(1) subject to implementation of the appropriate technical and organizational measures required by this Regulation in order to safeguard the rights and freedoms of the data subject ('storage limitation');
- processed in a manner that ensures appropriate security of the personal data, including protection against unauthorized or unlawful processing and against accidental loss, destruction or damage, using appropriate technical or organizational measures ('integrity and confidentiality').

8.8. Other aspects of clinical quality assurance

The clinical investigation will be conducted and monitored by Avania BV under the sponsorship of GATT Technologies BV. The Sponsor, or the Sponsor's representative, may conduct audits at the investigational sites. Audits may include, but are not limited to, device supply, presence of required documents, the informed consent process, and comparison of CRFs with source documents. The investigator agrees to participate with audits conducted at a reasonable time, in a reasonable manner.

8.8.1. Monitoring

A qualified monitor from Avania BV or a sponsor designee, will visit the site prior to the start of the clinical investigation and during the course of the clinical investigation, in accordance with the monitoring plan. Monitoring will be performed according to ISO14155. Data will be evaluated for compliance with the clinical investigation plan and accuracy in relation to source documents. Following written standard operating procedures, the monitors will verify that the clinical investigation is conducted and data are generated, documented and reported in compliance with the clinical investigation plan, ISO14155 and the applicable (national) regulatory requirements. Details of the monitoring requirements are provided in the Monitoring Plan.

8.9. Sample retention

All laboratory test samples collected at sites will be retained and/or destroyed per standard procedure at site.

9. AMENDMENTS, DEVIATIONS & WAIVERS

9.1. Amendments

Investigators may not modify (amend) this clinical investigation plan without obtaining written concurrence of the Sponsor, involved Ethics Committee(s), and applicable regulatory authorities.

9.2. Deviations and Waivers

Investigators may not deviate from this clinical investigation plan 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. All deviations will be documented on eCRFs. The use of waivers from the Clinical Investigation Plan is prohibited.

9.2.1. Reporting

Investigators will also adhere to procedures for reporting deviations to the involved Ethics Committee(s) in accordance with their specific reporting policies and procedures.

Under emergency circumstances, deviations from the clinical investigation plan to protect the rights, safety and wellbeing of human subjects may proceed without prior approval of the Sponsor and the EC. Such deviations will be documented and reported to the Sponsor and the EC as soon as possible, and will be in accordance with the national and local legislations.

Deviations from the clinical investigation plan to the in/exclusion criteria and deviations that affect the primary endpoints are considered major deviations. Deviations that may affect the secondary endpoints are considered minor deviations. All deviations will be reviewed by the medical monitor. The medical monitor is responsible for major/minor classification of the deviations.

9.2.2. Corrective and preventive actions

GATT Technologies BV or its representatives will evaluate deviations to the clinical investigation plan during monitoring visits. Individual event corrective and preventive actions may be recommended at that time. In addition, deviations occurring across investigational sites will be reviewed by GATT Technologies BV on a periodic basis to determine if more global preventive actions may be required.

9.2.3. Investigator disqualification criteria

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

- Failure to secure subject informed consent including protection of personal data prior to enrollment.
- Failure to report safety events within 24 hours of discovery after learning of the event.
- Failure to report serious adverse device effects within 24 hours of discovery.
- 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.

9.2.4. Follow-up management

Protocol deviations will be reported in the EDC. Subjects will receive standard of care in case a protocol deviation leads to the end, temporary halt or early termination of the investigation. The standard of care is defined by the applicable treatment protocol(s) for the disease at the investigational site. Each patient will receive a patient card describing the device and manufacturer, study investigator and site, and includes any important information on the device itself. The patient card further ensures the identification of the device and continued traceability after study termination (Section 2.8).

10. 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 clinical investigation plan. 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 (Section 2.8). 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 principal investigator or an authorized designee will keep records documenting the receipt, use, return and disposal of the investigational devices, which will include:

a) name(s) of person(s) who received, used, returned or disposed the device,
b) the date of the receipt,
c) identification of each investigational device (batch number/serial number or unique code),
d) quantity of investigational devices,
e) the expiry date, if applicable,
f) the date or dates of use,
g) subject identification,
h) the date of return of unused, expired or malfunctioning investigational devices, if applicable.
i) 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.

11. STATEMENTS OF COMPLIANCE

This clinical investigation will be conducted in compliance with the principles that have their origin in the latest version of the Declaration of Helsinki, this clinical investigation plan, requirements of the approving Ethics Committee(s) and Regulating Authorities, ISO 14155:2020, and other applicable national and regional regulatory requirements whichever provides the greater protection of the individual.

This clinical investigation will not be initiated until approval has been obtained from the Ethics Committee(s) and the Regulating Authorities. Any additional requirements imposed by the Ethics Committee(s) or Regulating Authorities will be followed, as appropriate. No deviation from the clinical investigation plan will be implemented without the prior review and approval of the Ethics Committee(s) except where it may be necessary to eliminate an immediate hazard to a subject. In such case, the deviation will be reported to the Ethics Committee and applicable regulatory authorities as soon as possible.

Clinical trial insurance will be secured prior to investigation initiation.

The Clinical Trial Agreement will outline the agreements made between the Sponsor and investigational sites.

12. INFORMED CONSENT PROCESS

The investigator is responsible for assuring that written informed consent is obtained from each patient 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 informed consent form that was prepared in accordance with this clinical investigation plan, ISO 14155 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 patient information letter and informed consent form 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 patient without first obtaining consent, informed consent must always be obtained from a patient prior to initiation of any clinical procedures dictated by the clinical investigation plan 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 patient.

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

13. ADVERSE EVENTS, ADVERSE DEVICE EFFECTS AND DEVICE DEFICIENCIES

13.1. Definitions

The definitions provided in this section are based on the ISO 14155:2020.

13.1.1. Adverse events

An adverse event 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. For users or other persons, this definition is restricted to events related to investigational medical devices.

13.1.2. Serious adverse event

The relevant serious adverse event (SAE) definitions for this clinical investigation include the following:

a) death,
b) serious deterioration in the health of the subject, users or other persons as defined by one or more of the following:
    a. a life-threatening illness or injury, or
    b. a permanent impairment of a body structure or a body function including chronic diseases, or
    c. In-patient or prolonged hospitalization, or
    d. in medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,

Planned hospitalization for a pre-existing condition, or a procedure required by the clinical investigation plan, without serious deterioration in health, is not considered a serious adverse event.

13.1.3. Device deficiency

A device deficiency is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, usability, safety or performance.

Device deficiencies include malfunctions, use errors, and inadequacy in the information supplied by the manufacturer including labelling. This definition includes device deficiencies related to the investigational medical device.

13.1.4. Adverse device effect

An adverse device effect (ADE) is an adverse event related to the use of an investigational medical device.

This definition includes adverse events resulting from insufficient or inadequate instructions for use, 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.

13.1.5. Serious adverse device effect

A serious adverse device effect (SADE) is an adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

13.1.6. Unanticipated serious adverse device effect

An unanticipated serious adverse device effect (USADE) is a serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current risk assessment.

13.1.7. Anticipated serious adverse device effect

Anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in the risk assessment.

13.2. Causality

This clinical investigation plan follows the MDCG 2020-10/1 with regards to the causality assessment. For the purpose of harmonizing reports, each SAE will be classified according to four different levels of causality:

- Not related
- Possible
- Probable
- Causal relationship

The Sponsor and the investigators will use the following definitions to assess the relationship of the serious adverse event to the investigational device, the comparator or the investigation procedure.

Not related: 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[13], when applicable;
- harms to the subject are not clearly due to use error;

[13] If an investigational device gives an incorrect diagnosis, the patient 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 patient 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.

- the event depends on a false result given by the investigational device used for diagnosis[14], 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 were 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 explained by another cause,

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[4], 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.

The Sponsor and the investigators will distinguish between the serious adverse events related to the investigational device and those related to the procedures (any procedure specific to the clinical investigation). An adverse event can be related both to procedures and the investigational device. Complications caused by concomitant treatments not imposed by the clinical investigation plan are considered not related. Similarly, several routine diagnostic or patient management procedures are

[14] If an investigational device gives an incorrect diagnosis, the patient 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 patient 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.

applied to patients regardless of the clinical investigation plan. If routine procedures are not imposed by the clinical investigation plan, complications caused by them are also considered not related.

In some particular cases the event may be not adequately assessed because information is insufficient or contradictory and/or the data cannot be verified or supplemented. The Sponsor and the investigators will make the maximum effort to define and categorize the event and avoid these situations. Where an investigator assessment is not available and/or the Sponsor remains uncertain about classifying the serious adverse event, the Sponsor should not exclude the relatedness; the event should be classified as “possible” and the reporting should not be delayed.

Particular attention will be given to the causality evaluation of unanticipated serious adverse events. The occurrence of unanticipated events related to the use of the device could suggest that the clinical investigation places subjects at increased risk of harm than was to be expected beforehand.

13.3. Severity

Each serious adverse event will be classified according to three (3) levels of severity. The Sponsor and the investigators will use the following definitions to assess the severity of the serious adverse event:

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.

13.4. Foreseeable adverse events and anticipated adverse device effects

Foreseeable adverse events and anticipated adverse devices effects as summarized in Section 4.2:

- Toxic response
- Thromboembolic event
- (Re)Bleeding
- Allergic reaction
- Pain
- New surgery
- Infection
- Blockage of artery or vein / ischemia of organs
- Damage of organs and vessels
- 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.

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

13.5. Non-reportable adverse events

N/A. This is a pre-market clinical investigation and all procedure- and device-related AEs will be reported for this clinical investigation.

13.6. Reporting requirements

13.6.1. Reporting adverse events

Adverse event reporting will start at the time of surgery and ends after the last subject completed the clinical investigation. Adverse events that occur between the signing of the informed consent and the initiation of the surgery will thus not be reported on the eCRFs. Underlying diseases are not reported as adverse events, but any deterioration in severity will be reported.

Adverse event information will be collected for all subjects. At every subject visit, the investigator will determine whether an adverse event has occurred since the last visit. All adverse events will be reported in the eCRF. The date of the initial event and the subsequent treatment will be documented.

Adverse events will be evaluated and differentiated by:

- Seriousness of the event
- Causality of the event (in relation to the device or procedure)
- Severity of the event

13.6.2. Reporting device deficiencies

All device deficiencies related to the identity, quality, durability, reliability, safety or performance of an investigational medical device will be documented throughout the clinical investigation and appropriately managed by the Sponsor.

13.6.3. Reporting serious adverse events and serious adverse device effects

Reporting requirements to the Sponsor and Regulatory authorities are summarized in the sections below.

13.6.3.1. Reporting to the Sponsor/CRO

The investigator will notify the Sponsor or its representative of any serious adverse events or serious adverse device effects, including device deficiencies that are declared as serious adverse events, immediately upon becoming aware of the event, by completing a “serious adverse event” form in the eCRF and immediately updating it once new information become available. In case the eCRF is not available when the investigator becomes aware of the event requiring immediate notification, the investigator will contact:

Avania B.V.
Prof. Bronkhorstlaan 10, Building 54
3723 MB Bilthoven
The Netherlands
+31 30 229 2727

The following timelines will apply for reporting by investigator to the Sponsor or its representative:

- Serious adverse events and serious adverse device effects within 24 hours;
- Any other reportable events within 7 days (initial reports) or 15 days (follow-up report).

13.6.3.2. Reporting to the Competent Authorities/Ethical Committees

The reporting of any serious adverse event as defined in Section 13.1 has to be done immediately and not later than 2 calendar days after awareness by the Sponsor, for all reportable events, which indicate an imminent risk of death, serious injury, or serious illness and that requires prompt remedial action for other patients/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 as defined in Section 13.1 or a new finding/update to it, the Sponsor 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 of the new reportable event or of new information in relation with an already reported event.

In the Netherlands serious adverse events will be reported by the Sponsor (or its representative Avania) to the accredited Ethics Committee that approved the clinical investigation plan and Competent Authorities.

Reporting Timelines to the Ethics Committee:

The Ethics committee requires that all SAEs occurring in all participating sites in the Netherlands and all foreign countries will be reported. The timelines and reporting requirements are as follows:

1. A serious adverse event which indicates an imminent risk of death, serious injury, or serious illness and that requires prompt remedial action for other patients/subjects, users or other persons or a new finding to it: immediately, but not later than 7 calendar days after awareness by the Sponsor of a new reportable event or of new information in relation with an already reported event.
2. All other serious adverse events will be reported within 15 calendar days.

Reporting to the Ethics Committee will occur by completing the Serious Adverse Event form in the ToetsingOnline portal (https://toetstingonline.ccmo.nl). These serious adverse events are automatically forwarded to the Ethics Committee.

Reporting Timelines to the Competent Authority in the Netherlands:

CCMO requires that all serious adverse events (device-related and not device-related) occurring in all participating sites in all participating countries are reported.

The reporting timelines are as follows:

1. A serious adverse event which indicates an imminent risk of death, serious injury, or serious illness and that requires prompt remedial action for other patients/subjects, users or other persons or a new finding to it: Immediately, within 2 working days, but not later than 4 calendar days after awareness by the Sponsor of a new reportable event or of new information in relation with an already reported event.
2. All other serious adverse events will be reported quarterly using serious adverse event line listing according to the reporting table of MEDDEV 2.7/3 SAE reporting guidelines.

Reporting to the Ethics Committee will occur by completing the Serious Adverse Event form in the ToetsingOnline portal (https://toetstingonline.ccmo.nl). These serious adverse events are automatically forwarded to the Competent Authority.

13.7. Medical monitor

A medical monitor, who is an independent physician not participating as a clinical investigator in the clinical investigation, will provide ongoing medical monitoring of incoming safety study data during the study conduct. Details of the medical monitor responsibilities are included in the Safety Data Handling Plan and include:

- Maintaining ongoing assessment of the safety profile of the investigational device during the investigation.
- Provide medical surveillance and evaluation of serious adverse events.

13.8. Data monitoring committee

A data monitoring committee (DMC) will monitor all emerging safety issues against pre-defined stopping rules of the clinical investigation. Any SAE or other safety concerns during the clinical investigation will be immediately referred, on a case-by-case basis, to the DMC for review against the stopping rules. A formal review of safety against the stopping rules will be conducted by the DMC during the enrolment pause when all subjects of the initial cohort (Stage I) are treated and have at least 2 week FU data available. The re-opening of recruitment will only be triggered by authorization from the DMC to proceed.

The DMC'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 DMC 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 DMC members will sign a non-conflict-of-interest statement in this regard.

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

14. VULNERABLE POPULATION

N/A. The subject population of this clinical investigation does not meet the criteria for a vulnerable population.

15. SUSPENSION OR PREMATURE TERMINATION OF THE CLINICAL INVESTIGATION

GATT Technologies BV reserves the right to terminate an investigator and/or investigational site for any of the reasons provided in Section 9.2. 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 patients and may inform the personal physician of the patients to ensure appropriate care and follow-up is provided. In the case of a study suspension, patient enrollment must stop until the suspension is lifted.

15.1. Stopping Rules

The DMC may decide to temporarily halt the clinical investigation in case of safety concerns. The stopping rules are defined in the DMC Charter.

16. PUBLICATION POLICY

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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Description

DHF-01-QR-021 - Clinical Safety and Performance of GATT-Patch in Open Liver

Justification

Update of document

Assigned To:	Initiated By:	Priority:	Impact:
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