

### **16.1.9 Documentation of Statistical Methods**

The document listed below is provided in this section.

[Statistical Analysis Plan \(DHF-01-SFT-194\) Version 1.0 dated 23-May-2023](#)

Statistical Analysis Plan for Interventional Studies

SAP Text Version Number: 1.0  
SAP Text Date: (DD-Mmm-YYYY): 23-May-2023

**Sponsor Name:** GATT Technologies BV

**Protocol Number:** DHF-01-SFT-194

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

**Protocol Version and Date: (DD-Mmm-YYYY):** 7.0 (22-Mar-2023)

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## Revision History

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I confirm that I have reviewed this document and agree with the content.

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## 1. Glossary of Abbreviations

Abbreviation	Description
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALPPS	Associating Liver Partition and Portal Vein Ligation for Staged Hepatectomy
ALT	Alanine Transaminase
APTT	Activated Partial Thromboplastin Time
AST	Aspartate Transaminase
ATC	Anatomical Therapeutic Chemical
BMI	Body Mass index
CI	Confidence Interval
COVID-19	Coronavirus disease 2019
DRL	Drug Reference List
DRM	Data Review Meeting
eCRF	electronic case report form
eGFR	estimated Glomerular Filtration Rate
FD&C	Federal Food, Drug, and Cosmetic Act
FDA	Food and Drug Administration
GATT	General Adhesive Tissue Tape
gGT	Gamma Glutamyl Transferase
ICU	Intensive Care Unit
IDE	Investigational Device Exemption
INR	International Normalized Ratio
ITT	Intention-to-treat
IVRS/IWRS	Interaction Voice/Web Response System
MedDRA	Medical Dictionary for Regulatory Activities
PP	Per-protocol
PT	Preferred Term
PT	Prothrombin Time

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Abbreviation	Description
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBSS	Surface Bleeding Severity Scale
SD	Standard Deviation
SI	Standard International System of Units
SOC	System Organ Class
TLF	Table, Listings and Figure
US	United States
WHO	World Health Organization

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## 2. Purpose

The purpose of this statistical analysis plan (SAP) is to ensure that the data listings, summary tables and figures which will be produced, and the statistical methodologies which will be used, are complete and appropriate to allow valid conclusions regarding the study objectives.

### 2.1. Responsibilities

Syneos Health will perform the statistical analyses and is responsible for the production and quality control of all tables, figures and listings.

### 2.2. Timings of Analyses

**Final Analysis:** The primary analysis of safety and efficacy is planned after all subjects complete the final study visit (week 12 +/- 2 weeks) or terminate early from the study.

**FDA Review:** This study will include an FDA review of data after the enrolment of 10 United States (US) based subjects from 2 US-based sites. No formal statistical analyses will be performed on these data.

**Interim Analysis:** The interim analysis will be performed once 70% (n=91) of the planned evaluable subjects in total are treated (for details on interim analysis see [Section 11](#)).

**Long-Term Follow-Up:** A 5-year observational follow-up will be performed to characterize long-term safety on all subjects undergoing liver resection for liver malignancy or metastases, collecting data on local cancer recurrence, disease-free survival, and overall survival. Results from these data will be tabulated using descriptive statistics. Subjects will give informed consent to have data up to 5-year follow-up collected.

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### **3. Study Objectives**

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

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## 4. Study Details/Design

### 4.1. Brief Description

This is a pre-market, prospective, randomized, multi-center, multi-national pivotal clinical investigation. The study was designed to assess a balanced subject population undergoing liver surgery and the comparative efficacy and safety of GATT-Patch to another widely used hemostatic patch.

130 subjects will be included in the study, and randomized in a ratio of 2:1, so that it is planned that 87 subjects will be given GATT-Patch and 43 will be given TachoSil. Randomization will continue until 87 patients have received GATT-Patch.

Surgery will be performed according to the standard procedures of the hospital, with the exception of the use of GATT-Patch versus TachoSil. Subjects who meet all preoperative eligibility criteria, who sign consent, and who meet all intraoperative eligibility criteria (e.g., have an appropriate bleeding site (Surface Bleeding Severity Scale [SBSS] score of 1, 2 or 3; reflecting minimal, mild, or moderate bleeding severity) at the liver resection) and no contraindications, will be randomized to receive the investigational device, GATT-Patch, or the control, TachoSil, in the ratio of 2:1, respectively, to control bleeding during open liver surgery.

Following surgery, subjects will be followed-up for 12 weeks +/- 2 weeks. A 5-year follow-up will be performed on all subjects undergoing liver resection for liver malignancy or metastases.

### 4.2. Subject Selection

Subjects who undergo open liver surgery, and who fulfil the eligibility criteria.

#### 4.2.1. Inclusion Criteria

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

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

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

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

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#### 4.2.2. Exclusion Criteria

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

1. The target bleeding site is from a large defect in an artery or vein that requires vascular reconstruction with maintenance of vessel patency;
2. Subject is scheduled to undergo surgery on other organs than the liver and its associated biliary and vascular system;
3. Subject is scheduled to undergo a staged liver surgery procedure (e.g., Associating Liver Partition and Portal vein ligation for Staged hepatectomy [ALPPS]);
4. Subject is taking multiple antithrombotic therapies in therapeutic dosage up to the time of surgery, but allowing exclusive use of acetylsalicylic acid;
5. Subject has platelet count  $<100 \times 10^9/L$ , an activated partial thrombin time of  $>100s$ , or international normalized ratio  $>2.5$ ;
6. Subject has a total bilirubin level of  $\geq 2.5 \text{ mg/dl}$ ;
7. Subject is pregnant, planning on becoming pregnant or actively breastfeeding during the 3-month follow-up period;
8. Subject has a known hypersensitivity to brilliant blue (FD&C Blue #1), porcine gelatin, or horse proteins;
9. Subject who has religious objections to receiving products with components of animal (porcine or equine) or human origin;
10. Subject has an active or suspected infection at the bleeding site;
11. Subject in whom the investigational device will be used at the site of a synthetic graft or patch implant;
12. Subject has a life expectancy of less than 3 months;
13. Subject has a documented severe congenital or acquired immunodeficiency;
14. Subject has had or has planned to receive any organ transplantation;
15. Subject undergoes surgery with the indication of being a living liver donor;
16. 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;
17. Subject is not appropriate for inclusion in the clinical investigation, per the medical opinion of the Investigator; and

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18. Subject has any incidental (pre- and peri-operative) findings deemed by the Investigator to potentially jeopardize the safety or welfare of the subject.

Subjects will be withdrawn from the trial for one of the following reasons:

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

#### **4.3. Determination of Sample Size**

The sample size is powered to determine non-inferiority of GATT-Patch versus TachoSil on the primary endpoint of in the percentage of cases achieving hemostasis at 3 minutes without rebleeding at the 10-minute time point.

Based on previous studies, it is assumed that 80% of subjects achieve hemostasis at 3 minutes after TachoSil application. Subjects will be randomized in a 2:1 fashion. Taking into consideration a non-inferiority margin of 10%, and assuming that hemostasis is achieved in 92% of subjects treated with GATT-Patch. An interim analysis is planned when the primary endpoint is observed for 70% of subjects and using the O'Brien-Fleming alpha-spending function for efficacy stopping boundary, a total sample size of 130 subjects is estimated, of which 87 subjects will undergo implantation of GATT-Patch, to achieve 90% statistical power. The success percentage of 92% is based on the results from the Pilot trial, taking into account a ~5% absolute lower performance due to differences in subject population, use, or other factors. The sample size will take into account the result of the interim analysis of the primary performance endpoint to allow for possible early stopping for success or futility or sample size re-estimation. Therefore, it is planned that, in total, 130 subjects will be randomized in a ratio of 2:1, so that it is planned that 87 subjects will be given GATT-Patch and 43 will be given TachoSil.

Missing data for the primary endpoint is expected to be minimal, since the primary endpoint will be assessed within 10-15 minutes after randomization, in the operating room during the same surgical session. Therefore, there is no risk of lost to follow-up, or data not being available. At the interim analysis at 70% of the enrollment, the occurrence of missing data will be reviewed and the sample size calculation could be adjusted to account for missing data.

For the key secondary endpoint, median time to hemostasis, group sample sizes of 87 and 43 achieve 91% power to reject the null hypothesis of equal group response distributions when the effect size is as low as 0.68 and the significance level is 0.02275 using a one-sided Wilcoxon-Mann-Whitney test. The effect size is the probability that an observation from GATT-Patch group is less than an observation from TachoSil group and was estimated to be 0.93, derived from a similar comparative analysis of Veriset, a polymer-based hemostatic patch, versus TachoSil (Figure 2 of Ollinger et. al. 2013).

Recruitment will take place in a maximum of 12 sites in the US and Europe, with a target number of sites of 4-7 in the US, 2-4 in The Netherlands, and 2-4 in Germany. The clinical investigation in the US will be limited to 2 US sites; expansion to further sites in the US will be covered in an Investigational Device Exemption (IDE) supplement, which will be submitted to the FDA after enrollment of 10 US subjects.

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#### 4.4. Treatment Assignment and Blinding

Surgery will be performed according to the standard procedures of the hospital, with the exception of the use of GATT-Patch versus TachoSil.

Randomization will be performed intra-operatively, after intra-operative eligibility criteria have been confirmed. Randomization will be performed using a Interaction Voice/Web Response System (IVRS/IWRS), in a 2:1 ratio, and stratified by site using random permuted block sizes of 3 or 6 for treatment assignment.

Due to the physical differences in the investigational and control devices, blinding of the surgeon is not possible. However, bias is minimized by using a validated bleeding scale to determine baseline bleeding severity prior to randomization, at which point in time the investigator is not aware of treatment assignment. Further, the training and testing required for all investigators to use a validated bleeding severity scale for assessment of successful hemostasis reduces subjectivity for the efficacy assessments. The following additional measures are also implemented to reduce potential bias in the assessment of safety and efficacy:

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

#### 4.5. Administration of Study Medication

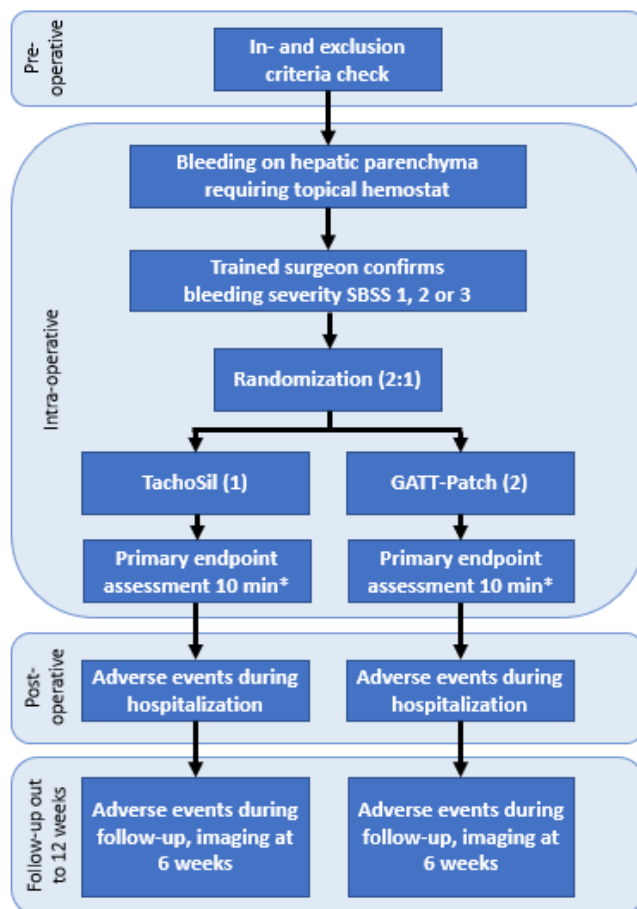
Each surgery will be performed according to the standard procedures at the hospital, with exception of the randomized use of GATT-Patch or TachoSil. GATT-Patch or TachoSil will be used if the subject has an appropriate bleeding site (SBSS 1, 2 or 3). Randomization to the use of GATT-Patch or TachoSil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

#### 4.6. Study Procedures and Flowchart

The study flow is show below in Table 1.

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**Table 1 Study Flow**



\*Including secondary endpoints during surgery

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The schedule of assessment is presented in Table 2, which outlines the timing of procedures and assessments to be performed throughout the study.

**Table 2 Schedule of Assessments**

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

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

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

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

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

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## 5. Endpoints

### 5.1. Primary Efficacy Endpoint

The primary efficacy endpoint is the percentages of cases achieving hemostasis at 3 minutes without rebleeding at the 10-minutes time point. Hemostasis will be defined by a grade 0 (None/Dry) on the SBSS.

### 5.2. Secondary Efficacy Endpoints

Secondary efficacy endpoints are:

- Median time to hemostasis (seconds);
- Kaplan-Meier estimated distribution of time to hemostasis;
- Treatment failure, defined as no hemostasis at 10 minutes;
- Rebleeding after 10 minutes but before subject closure;
- Percentage of hemostasis at 30, 60, 90, 120, 150, 180, 210, 240, 270, 300, 360, 420, 480, 540 and 600 seconds.

The key secondary endpoint is the median time to hemostasis.

### 5.3. Exploratory Endpoints

Exploratory endpoints:

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

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

#### **5.4. Safety Endpoints**

The safety of GATT-Patch will be assessed by the incidence, severity and relation to hemostatic device of all adverse events (AEs). The AEs for the GATT-Patch group will be compared to those for the TachoSil group. AESIs are bleeding-related events, thromboembolic events, biloma, and allergic reactions.

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## **6. Analysis Sets**

### **6.1. Intent-to-Treat (ITT) Population**

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

### **6.2. Per-Protocol (PP) Population**

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

### **6.3. Safety Population**

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

### **6.4. Evaluable Subjects**

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

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

### **6.5. Protocol Deviations**

Protocol Deviations and other non-compliances are identified, documented and reviewed during the conduct of the study. Protocol deviation management at Syneos Health is detailed in Protocol Deviation and Non-compliance Management Plan. Deviations to the in/exclusion criteria and deviations that affect the primary endpoints are considered major deviations.

Subjects with a major protocol deviation affecting efficacy analysis will be excluded from the PP population. The list of major protocol deviations potentially leading to PP population exclusion includes at least the following deviations:

- Violations of inclusion or exclusion criteria.
- Use of a patch in the instance of SBSS 0, 4, or 5.
- Use errors deeming the product ineffective.
- Use of disallowed medication (that may influence the interpretation of efficacy results).

The final list of subjects who are to be included in the PP population will be determined at the Data Review Meeting (DRM). The DRM will occur when all or nearly all queries have been resolved and the database is near to final. For the DRM meeting, a DRM Preparation Plan will be prepared. This plan will detail further the types of protocol deviation criteria and will include, as a minimum: 1) the exact criteria which will be used to determine if a subject will be excluded from the PP population; 2) the

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listings which will be prepared for sponsor review in order to determine which subjects to exclude from the PP population. Details of subject specific exclusions from the PP population will be detailed in the DRM Report.

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## 7. General Aspects for Statistical Analysis

### 7.1. General Methods

Unless otherwise specified, summaries will be presented by treatment group.

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

All subjects entered into the database will be included in subject data listings.

### 7.2. Key Definitions

For safety data, baseline is defined as the last non-missing value recorded prior to treatment.

### 7.3. Missing Data

Missing data are not expected for the primary endpoint for this study, as the measurement of the primary endpoint is completed within 10 minutes of patch application, within 10-15 minutes after randomization. However, should we observe more than 5% subjects with missing primary endpoint data, due to factors such as data collected not saved due to computer malfunction, data will be imputed as described in [Section 9.2](#).

### 7.4. Visit Windows

For visit windows see [Section 4.6](#): Table 2 Schedule of Assessments.

### 7.5. Pooling of Sites

No pooling of sites will be implemented for the primary analyses. Sites will be pooled for subgroup summaries in [section 7.6](#), with sites in same geographic area (US vs non-US) being pooled together.

### 7.6. Subgroups

The following subject subgroups are defined for pre-specified analyses:

- Site
- Geography (US / non-US)
- Age (22–47 / 48–63 /  $\geq 64$ )
- Sex (male/female)
- SBSS (1/2/3)
- Type of bleeding (venous/arterial/mixed)
- Type of hepatic parenchyma (normal/cirrhotic/steatotic)
- Portal hypertension (yes/no)
- Child Pugh classification (A/B/C/NA)
- MELD-Na Score ( $<17$  / 17-20 / 21-22 / 23-26 / 27-31 /  $\geq 32$ )
- Renal function (eGFR  $>90$  / eGFR 60-90 / eGFR 30-60 / eGFR 15-30 / chronic dialysis)
- Antithrombotic medication use (yes/no)
- Concomitant chemotherapy (yes/no)
- Concomitant steroid therapy (yes/no)
- Use of surgical drains (yes/no)

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

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## **8. Demographic, Other Baseline Characteristics and Medication**

### **8.1. Subject Disposition and Withdrawals**

Subject disposition and withdrawals will be summarized for all subjects who entered into the study.

The number and percentage of subjects screened, randomized, treated, completed, withdrew the study prematurely, together with the primary reason for withdrawal will be presented for each treatment.

Subjects in each population and reasons for exclusion from each of the analysis populations, will be presented for each treatment. Major protocol deviations will be tabulated, as well as Coronavirus disease 2019 (COVID-19) related protocol deviations.

### **8.2. Demographic and Baseline Characteristics**

Demographic and baseline characteristics, including age, sex, race and ethnicity will be summarized for the safety population and separately by site and by geography (US/non-US).

Age will be summarized using descriptive statistics for continuous data (n, mean, SD, median, minimum, and maximum).

Sex, race, and ethnicity will be summarized using frequencies and percentages.

In addition, summaries of the indication for surgery, Child-Pugh classification and ASA classification will be summarized for the safety population and separately by site and by geography (US/non-US).

### **8.3. Medical History and Concomitant Diseases**

Medical history includes collecting information in the following categories: allergies, smoking history (and current), cardiac disorders, systemic hypertension, renal dysfunction, diabetes, hereditary blood disorders, blood transfusions in the previous 3 months, previous abdominal surgery, liver disease, portal hypertension, malignancies and prior therapies, and other critical medical conditions or previous injury. The number of subjects who have each category of condition will be tabulated using frequencies and percentages.

### **8.4. Surgery Procedural Data**

Details about the surgery were collected and will be summarized using frequencies and percentages: whether the subject was taking acetyl-salicylic acid at the time of surgery, any other antiplatelet therapy, or anticoagulation medicine; the blood flow reduction method; resection method; type of hepatic parenchyma, and anatomic or non-anatomic resection; extent of resection; whether there was visible bile leakage that was surgically treated; whether vascular reconstruction was performed; whether biliary tree reconstruction was performed; if intravenous heparin was given within 12 hours before surgery; whether oral Coumadin was given with 2 days before surgery; if antiplatelet medications were given within 5 days before surgery; use of surgical drains, and occurrence of any surgical complications.

The duration of surgery (surgical site closure - start incision), blood inflow reduction, estimated total size of all resection area, estimated blood loss during procedure and type and units of transfusion will be summarized using summary statistics for continuous data.

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### **8.5. Bleeding Site Information**

Details about the bleeding site were collected and will be summarized using frequencies and percentages: Estimated total transected parenchyma area of current bleeding surface (max width x max length), description of target bleeding site, estimated size of target bleeding site (max width x max length), bleeding type, the SBSS score, and use of adjunct hemostatic techniques, and the proportion of patch used.

### **8.6. Medication**

All medications will be coded using the World Health Organization (WHO) Drug Reference List (WHO-DRL).

Concomitant medications will be summarized overall, by Anatomical Therapeutic Chemical (ATC) level 2 and ATC level 4 for each treatment arm and overall in the Safety population, presenting the number and percentage of subjects. A subject will be counted once at the ATC level 2 and once at each ATC level 4 within the ATC level 2. Medications will be sorted by descending frequency of ATC level 2 (overall, then by active treatment, then placebo) and then by descending frequency of ATC level 4. In case of identical frequency, sorting will be done alphabetically.

Separate summaries will be provided for prior and concomitant medications.

#### **8.6.1. Prior Medication**

Prior medications are those medications which stop before the surgery.

#### **8.6.2. Concomitant Medication**

Concomitant medications are medications which are taken at the same time as surgery, or afterwards. If a medication starts before surgery and continues after surgery, or starts after surgery, it will be considered to be concomitant.

Medications with missing/partial start and end dates, which cannot be determined to be a prior medication, will be considered to be concomitant.

### **8.7. Treatment Compliance**

Any Device deficiency that was reported will be tabulated to show the number of subjects who had a device deficiency, deficiency type and the specification device part.

This document is confidential.

## 9. Efficacy

The primary analysis for the primary endpoint and the key secondary endpoint will be performed for the PP population. They will also be analyzed using the ITT population, as secondary analysis. Consistent results from the analysis of ITT and PP datasets are necessary to conclude non-inferiority of GATT-Patch to TachoSil.

All other secondary endpoints, and exploratory analyses, will be summarized descriptively by treatment group, and no statistical analysis will be performed.

### 9.1. Hierarchical testing

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

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

### 9.2. Primary Efficacy Endpoint and Analysis

The primary efficacy endpoint is the percentages of cases achieving hemostasis at 3 minutes without rebleeding at the 10-minutes time point. Hemostasis will be defined by a grade 0 (None/Dry) on the SBSS.

Achievement of hemostasis will be verified every 30 seconds starting after the initial 30 seconds of application for GATT-Patch, and every 30 seconds after the initial 3 minutes for TachoSil up to the 5-minute time point, and every 60 seconds between 5 and 10 minutes, starting from the time that the hemostatic patch is positioned and pressure is initiated.

The analysis of the primary efficacy endpoint will be conducted using the Farrington-Manning test (Farrington, C. P. & Manning, G., 1990) on the PP population with available data. The rate and the 95% exact (Clopper-Pearson) confidence interval (CI) for each group, and their difference in rate between treatment group and the corresponding 95% Newcombe CIs will be reported. The non-inferiority will be tested first and, based on these results, superiority will be tested. If the study is not stopped for successful efficacy based on Interim Analysis, as detailed in [Section 11](#), the study will continue to the sample size determined by the sample size re-estimation, and the efficacy goal of non-inferiority of GATT-Patch compared to TachoSil will be assessed using the Farrington-Manning test of proportion at the one-sided 0.02275 significance level for the final analysis.

The primary efficacy endpoint will also be analyzed on the ITT population as a secondary analysis.

Hemostasis at 3 minutes without rebleeding at the 10-minute time point will also be analyzed based on target bleeding sites (and not subjects).

For the primary endpoint, descriptive statistics of number and percent of subjects meeting the primary endpoint in each randomized group will be presented separately for each investigational site. Homogeneity across sites in the primary endpoint will be checked based on deviance (McCullagh and Nelder, 1989) from logistic regression with achieving the primary endpoint (yes/no) as the dependent

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variable. Two logistic regression models will be used. One model includes treatment, investigational site (or pooled site), and treatment by site interaction as the independent variables, another model includes treatment and investigational site as independent variables. The difference in the deviances from the two models approximately follows a Chi-square distribution with a degree of the number of extra parameters. Thus the corresponding p-value can be used to check the homogeneity across sites. If  $p\text{-value} < 0.15$ , then the sites are not considered as homogenous, and a subgroup analysis based on sites will be reported. Homogeneity across geography in the primary endpoint will be analyzed similarly. The subject subgroups for pre-specified analysis are specified in [Section 7.6](#)

In case of missing data in more than 5% subjects a sensitivity analysis to assess the potential impact of missing data on the results of the primary efficacy analysis will be performed by conducting tipping point analysis and MI imputation in ITT population.

Prior to conducting tipping point analysis and MI imputation, subjects with data after the receipt of rescue therapy will be considered treatment failure i.e., non-responder for analysis.

Tipping point analysis and MI imputation will be performed for subjects with real missing data which is not induced by the receipt of rescue therapy. Tipping point analysis will be performed by imputing the missing response with different combinations of non-responders or responders for both treatment groups to assess the robustness of analysis. The number of imputed non-responder that overturns (i.e. non-significant) the primary results will represent the tipping point.

Missing data are not expected. However, in case it happens, such data will be imputed by multiple imputation using information from similar subjects of the same treatment group assuming 'missing at random' (MAR) mechanism. The MI will be carried out for the primary (binary) endpoint as follows. 50 imputed datasets will be created using SAS MI procedure based on the observed data (Markov-Chain-Monte-Carlo method, MCMC) in ITT population. The covariates used in the MI procedure will include baseline SBSS and type of bleeding (arterial, venous or mixed). The seed to be used is 7031981 (the study number).

The analysis will be conducted using each of the imputed complete datasets. Proportion of responders in each treatment arm, difference and CI will be calculated.

The results from the analysis of the multiple imputed datasets will be combined (Ratitch, Lipkovich and Q'Kelly, 2013) to produce pooled statistics and t-test based p-value using the MIANALYZE procedure in SAS.

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### 9.3. Secondary Efficacy Estimand(s) / Endpoint(s) and Analyses

Secondary efficacy endpoints are:

- Median time to hemostasis (seconds);
- Kaplan-Meier estimated distribution of time to hemostasis;
- Treatment failure, defined as no hemostasis at 10 minutes;
- Rebleeding after 10 minutes but before subject closure;
- Percentage of hemostasis at 30, 60, 90, 120, 150, 180, 210, 240, 270, 300, 360, 420, 480, 540, and 600 seconds.

#### 9.3.1. Time to Hemostasis

The key secondary endpoint is the time to hemostasis (seconds).

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

For the analysis, time to hemostasis will be censored at 10 minutes, in subjects who do not achieve hemostasis by 10 minutes.

The uncensored time to hemostasis, as well as the censored time to hemostasis (with censored subjects having a 10-minute time to hemostasis) will be summarized descriptively. Median time to hemostasis will be analyzed using a one-sided Wilcoxon-Mann-Whitney test with the significance level of 0.02275 to test superiority of GATT-Patch vs TachoSil as part of the hierarchical testing as described in [Section 9.1](#).

Time to hemostasis will furthermore be analyzed using Log-rank test. A Kaplan-Meier plot will be presented, and 25%, 50% (median), 75% percentiles, and their 95% CIs will be reported.

The Cox proportional hazard model may be used to include some prognostic variables and baseline characteristics (antithrombotic medication use [yes/no], type of hepatic parenchyma [normal/cirrhotic/steatotic], anatomic or non-anatomic resection [anatomic/non-anatomic], description of target bleeding site [flat surface/irregular surface/dimple or pit] as covariates.

#### 9.3.2. Treatment Failure

Treatment failure is defined as no hemostasis at 10 minutes.

The number and proportion of subjects who have treatment failure will be tabulated, by treatment.

The number of subjects who needed rescue treatment, and details of the other hemostatic product or technique used will be tabulated.

#### 9.3.3. Rebleeding after 10 Minutes but Before Subject Closure

The number and proportion of subjects who have rebleeding after 10 minutes but before subject closure will be tabulated, by treatment.

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9.3.4. **Percentage of Hemostasis at 30, 60, 90, 120, 150, 180, 210, 240, 270, 300, 360, 420, 480, 540, and 600 Seconds.**

The number and proportion of subjects who have hemostasis at 30 second intervals, from 30 seconds up to 10 minutes, will be tabulated, by treatment.

9.3.5. **Five Year Follow-Up**

Data on cancer follow-up, survival status, diagnostics, additional therapies, cure, local recurrence, newly developed liver metastases of all subjects treated, will be provided in a tabulated manner with descriptive statistics.

9.3.6. **Exploratory Endpoints**

The following endpoints will be tabulated using descriptive statistics.

9.3.6.1. **Procedure Duration**

Procedure duration will be measured in minutes and will be calculated as:

$$\text{Time of end of procedure} - \text{Time of start of procedure.}$$

Summary statistics for continuous data will be used to present procedure duration.

9.3.6.2. **Estimated Blood Loss during Surgery**

The estimated blood loss (mL) during surgery will be presented using summary statistics for continuous data.

9.3.6.3. **Blood Transfusions during Hospitalizations**

The number and type of blood transfusions during hospitalization will be tabulated using frequencies and percentages.

9.3.6.4. **Duration of ICU Stay**

The duration of ICU stay will be measured in days and will be calculated as:

$$\text{Date of discharge from ICU} - \text{Date of admission to ICU} + 1.$$

Summary statistics for continuous data will be used to present the duration.

9.3.6.5. **Total Hospitalization Stay**

The duration of total hospitalization stay will be measured in days and will be calculated as:

$$\text{Date of discharge from hospital} - \text{Date of start of admission to hospital} + 1.$$

Summary statistics for continuous data will be used to present the duration.

9.3.6.6. **Post-Operative Stay**

The duration of post-operative stay will be measured in days and calculated as:

$$\text{Date of discharge from hospital} - \text{Date of surgery} + 1.$$

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Summary statistics for continuous data will be used to present the duration.

**9.3.6.7. Post-Operative Drainage**

The duration of post-operative drainage will be measured in minutes and calculated as:

$$(\text{Time of end of drainage} - \text{Time of start of drainage}) / 60$$

Summary statistics for continuous data will be used to present the duration of drainage and the volume of drainage. The characteristics of drainage will be presented using frequencies and percentages.

**9.3.6.8. Re-Operation**

The need for and cause of re-operation will be presented using frequencies and percentages.

**9.3.6.9. Imaging of Liver Resection**

The Imaging of the liver resection at 6 weeks post-surgery was done to detect:

- (1) fluid collection and its size (mL) and aspect,
- (2) pseudo-aneurysm,
- (3) patch encapsulation, and
- (4) rolling up of the device on the resection plane.

The results from the imaging will be presented using summary statistics for continuous data, or frequencies and percentages, as appropriate.

**9.3.6.10. User Satisfaction**

A GATT-Patch Usability Scale was used to assess user satisfaction. The results of these questionnaires will be tabulated by question.

**9.3.6.11. Physician Treatment Preference**

In order to assess the Physician's treatment preference a questionnaire on GATT-Patch versus TachoSil was used. The results of this questionnaire will be tabulated by question.

**9.3.6.12. Local recurrence of Liver Cancer at Resection**

The number and percentage of subjects who have local recurrence of liver cancer at resection will be summarized.

**9.3.6.13. Cancer-Free and Overall Survival**

Cancer-free and overall survival will be based on data collected over the five year follow-up.

The duration of survival will be calculated (in days) as:

$$\text{Date of death} - \text{Date of treatment} + 1.$$

Subjects who have not died will be censored at the date they are last known to be alive. For the analysis of cancer-free survival, subjects who have died for a reason other than cancer, will be censored at their date of death.

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The duration of survival (time to death) and duration of cancer-free survival (time to death of cancer) will be presented using Kaplan-Meier estimates by treatment group: median, 25<sup>th</sup> and 75<sup>th</sup> percentiles and the corresponding CIs will be tabulated. The estimate of the survivor function in each treatment group will be displayed graphically using a Kaplan-Meier curve.

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## 10. Safety

The Safety population will be used for all safety presentations. The safety of GATT-Patch will be assessed by the incidence, severity and relation to hemostatic device of all AEs. The AEs for the GATT-Patch group will be compared descriptively to those for the TachoSil group. AESIs are bleeding-related events, thromboembolic events, biloma, and allergic reactions.

### 10.1. Adverse Events

For the purposes of this study, the period of observation for collection of AEs extends from the time the subject is enrolled and randomized until the last follow-up visit at 3 months (12 weeks).

A summary table will present the number and percentage of subjects reporting:

- Any AE,
- Any serious AE,
- Any device related (per investigator, sponsor, and IAC) AE,
- Any procedure of application of device related AE,
- Any study procedure related AE,
- Any device related (per investigator, sponsor, and IAC) serious AE,
- Any procedure of application of device related serious AE,
- Any study procedure related serious AE,
- Any AE leading to death,
- Any AESIs,
- Any Adverse Device Effect.

The number and percentage of subjects experiencing a AE in the following categories will also be summarized by the System Organ Class (SOC) and Preferred Term (PT):

- All AEs,
- Serious AEs,
- Device related (per investigator, sponsor, and IAC) AEs,
- Procedure of application of device related AEs,
- Study procedure related AEs,
- Device related (per investigator, sponsor, and IAC) serious AEs,
- Procedure of application of device related, serious AEs,
- Study procedure related serious AEs,
- AEs leading to death,
- AESIs.

A subject with more than one occurrence of the same AE in a particular SOC or PT, will only be counted once in the summary of that particular SOC or PT.

AEs will be considered to be related to procedure/device, unless the relationship is "Not Related". AEs with missing relationship (which is not expected with 100% SDV) will be considered to be related.

AEs with missing seriousness (which is not expected with 100% SDV) will be considered to be serious.

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AEs leading to death will be those AEs with outcome="Fatal".

The following AEs are categorised as AESIs:

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

#### **10.2. Biloma Formation**

Based on the presence of a peri-hepatic fluid collection, and the impression of the fluid being a biloma, biloma formation can be assessed at Week 6. In addition, biloma formation can be reported throughout the study as adverse event.

Summary statistics for continuous data will be used to present fluid collections and biloma formation at the Week 6 ultrasound by the presence or absence of surgical drains.

The number and percentage of subjects experiencing biloma formation at any time during the study will be summarized by the presence or absence of surgical drains.

#### **10.3. Laboratory Evaluations**

Blood samples for laboratory evaluations are taken at Screening (6 weeks before surgery, at admission before surgery, during hospitalization, and at the visit at Week 6.

The following laboratory parameters will be measured:

Hematology: hemoglobin, hematocrit, reticulocyte count, platelet count, white blood cell count, absolute neutrophils, absolute lymphocytes, absolute monocytes;

Chemistry: Bilirubin, Calcium, Potassium, Sodium, Chloride, Albumin, Creatinine, Aspartate Transaminase (AST), Alanine Transaminase (ALT), Gamma Glutamyl Transferase (gGT).

Coagulation: Prothrombin Time (PT), Activated Partial Thromboplastin Time (aPTT), International Normalized Ratio (INR).

Blood samples will be analyzed at local laboratories. To ensure that the data can be presented together, all data will be converted to standardized units (SI).

Baseline is defined as the last non-missing value recorded prior to treatment.

Summary statistics for continuous data will be presented for results by visit, and the change from baseline to each post-baseline visit (i.e. during hospitalization and Week 6 visit).

Shift tables with the number and percent of subjects with results above/below/within the normal reference range at each post-baseline visit, compared to baseline, will be presented.

Results for continuous data will be displayed graphically by visit per subject.

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#### 10.4. Vital Signs

Vital signs (heart rate, and systolic and diastolic blood pressure measurements, oxygen saturation) are reported at Screening (6 weeks before surgery, at admission before surgery, during hospitalization, and at the visit at Week 6).

If necessary, height will be converted to centimeters (cm) and weight will be converted to kilograms (kg), as follows:

$$\text{Height (in cm)} = \text{height (in inches)} * 2.54$$

[divide by 100 to convert to m]

$$\text{Weight (in kg)} = \text{weight (in lbs)} * 0.4536$$

BMI(kg/m<sup>2</sup>) will be calculated as:

$$\text{BMI (k/m}^2\text{)} = \text{weight (kg)} / [\text{height (m)}]^2.$$

Body temperature could be collected in degrees Centigrade (°C) and Fahrenheit (°F). All temperatures will be converted to °C using the formula:

$$\text{Temperature (in } ^\circ\text{C)} = 5/9 (\text{Temperature [in } ^\circ\text{F]} - 32).$$

Summary statistics for continuous data will be presented for results by visit, and the change from baseline to each post-baseline visit (i.e. during hospitalization and Week 6 visit).

#### 10.5. Physical Examination

A physical examination (to include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal, and neurological systems) will be performed at Screening (6 weeks before surgery, at admission before surgery, during hospitalization, and at the visit at Week 6).

Any anomalies will be reported either as Medical History or as an AE; therefore physical examination data will only be listed in the Subject Listings.

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## 11. Interim Analyses

This study will include an FDA review of data after the enrolment of 10 US-based subjects from 2 US-based sites. No formal statistical analyses will be performed on these data.

After FDA approval to continue, the study utilizes an adaptive design with an interim analysis planned for the purposes of stopping the trial early for success or futility and for sample size re-estimation. The interim analysis will be performed once 70% (n=91) of the planned evaluable subjects in total are treated. To account for multiple testing and control the overall Type I error rate of the study at one-sided 0.025 level, a group-sequential design will be used based on the Lan-DeMets (Lan, K.K.G. & DeMets D.L., 1983) approach with an O'Brien-Fleming alpha-spending function. Based on this method, the efficacy goal of GATT-Patch with a 10% absolute non-inferiority margin compared to the standard of care, TachoSil, regarding the percentage of cases achieving hemostasis at 3 minutes, will be assessed at the interim review. A Farrington-Manning test (Farrington, C. P. & Manning, G., 1990) of non-inferiority difference between two proportions at a one-sided 0.00738 significance level will be performed at the interim analysis. If the statistical analysis of the primary efficacy endpoint at the interim review yields a one-sided p-value less than 0.00738: (1) a superiority analysis will subsequently be performed using two-sample t-test at a one-sided 0.00738 significance level, and (2) the DMC may recommend stopping the trial for successful efficacy if non-inferiority is met. If the one-sided p-value is not less than 0.00738, then a sample size re-estimation (SSR) based on conditional power (probability of study success given the interim results) may be conducted to determine if the sample size will be increased. The interim decision rules will be:

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

When the conditional power is greater than 50%, a sample size increase will not require an additional penalty to the final significance (alpha) level according to Chen-Demets-Lan method (Chen, Y.H.J., DeMets D.L. & Lan, K.K.G., 2004). If the study is not stopped for successful efficacy, the study will continue to the sample size determined by the SSR, and final efficacy analysis will be evaluated according to the hierarchical testing procedure detailed in Section 9.1.

This document is confidential.

## 12. Changes from Analysis Planned in Protocol

Not applicable.

This document is confidential.

### **13. Reference List**

Chen, Y.H.J., DeMets D.L. and Lan, K.K.G. (2004). Increasing the Sample Size When the Unblinded Interim Result is Promising. *Statistics in Medicine* 23:1023-1038.

Farrington, C. P., and Manning, G. (1990). Test Statistics and Sample Size Formulae for Comparative Binomial Trials with Null Hypothesis of Non-zero Risk Difference or Non-unity Relative Risk. *Statistics in Medicine* 9:1447–1454.

Lan, K.K.G. and DeMets D.L. (1983). Discrete Sequential Boundaries for Clinical Trials. *Biometrika* 70: 659-663.

McCullagh, P., and Nelder, J.A. (1989). *Generalized Linear Models*. Chapman & Hall/CRC.

Öllinger, R., Mihaljevic, A. L., Schuhmacher, C., Bektas, H., Vondran, F., Kleine, M., Sainz-Barringa, M., Weiss, S., Knebel, P., Pratschke, J. & Troisi, R. I. (2013). A multicentre, randomized clinical trial comparing the Veriset™ haemostatic patch with fibrin sealant for the management of bleeding during hepatic surgery. *Hpb*, 15(7), 548-558.

Ratitch B., Lipkovich I. and Q'Kelly M. (2013). Combining Analysis Results from Multiply Imputed Categorical Data. <https://www.lexjansen.com/pharmasug/2013/SP/PharmaSUG-2013-SP03.pdf>

This document is confidential.

## 14. Programming Considerations

All Tables, Listings and Figures (TLFs), and statistical analyses will be generated using SAS Version 9.4 or a later version (SAS Institute Inc., Cary, NC, USA). Computer-generated TLF output will adhere to the following specifications.

### 14.1. General Considerations

- One SAS program can create several outputs, or a separate SAS program will be created for each output
- Each output will be stored in a separate file
- Output files will be delivered in Word format or portable document format pdf
- Numbering of TLFs will follow ICH E3 guidance

### 14.2. Table, Figure, and Listing Format

#### 14.2.1. General

- All TLFs will be produced in landscape format on American letter size, unless otherwise specified.
- All TLFs will be produced using Courier New font, size 8 which is the smallest acceptable point size for the Regulatory Authorities.
- The data displays for TLFs will have a minimum blank 1-inch margin on all 4 sides.
- Headers and footers for figures will be in Courier New font, size 8 which is the smallest acceptable point size for the Regulatory Authorities.
- Legends will be used for all figures with more than one variable, group, or item displayed.
- TLFs will be in black and white (no color).
- Specialized text styles, such as bolding, italics, borders, shading, superscripted and subscripted text, will not be used in the TLFs, unless otherwise specified. On some occasions, superscripts 1, 2, or 3 may be used (see below).
- Only standard keyboard characters will be used in the TLFs. Special characters, such as non-printable control characters, printer-specific, or font-specific characters, will not be used. Hexadecimal-derived characters will be used, where possible, if they are appropriate to help display math symbols (e.g.  $\mu$ ). Certain subscripts and superscripts (e.g.,  $\text{cm}^2$ ,  $C_{\text{max}}$ ) will be employed on a case-by-case basis.
- Mixed case will be used for all titles, footnotes, column headers, and programmer-supplied formats, as appropriate.
- All TLFs will be converted into Rich Text format, with the format/file extensions specified and collected into three separate complete documents. The combined documents will be in PDF format.

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#### 14.2.2. Headers

- All output will have the following header at the top left of each page:

*GATT Technologies BV: Protocol DHF-01-SFT-194 (Syneos Health study number: 7031981)*

- All output will specify the Draft/Final Run status at the top left of each page.
- All output will have Page n of N at the top or bottom right corner of each page. TLFs are internally paginated in relation to the total length (i.e., the page number will appear sequentially as page n of N, where N is the total number of pages in the table)
- The date the output was generated will appear along with the program name as a footer on each page

#### 14.2.3. Display Titles

- Each TLF will be identified by the designation and a numeral. (i.e. Table 14.1.1). A decimal system (x.y and x.y.z) are used to identify TLFs with related contents. The title will be centered. The analysis set will be identified on the line immediately following the title and will be enclosed in parenthesis. The title and table designation will be single spaced. A solid line spanning the margins will separate the display titles from the Column headers. There will be one blank line between the last title and the solid line.

Table x.y.z  
First Line of Title  
Second Line of Title if Needed  
(Analysis Population)

#### 14.2.4. Column Headers

- Column headings will be displayed immediately below the solid line described above in initial upper-case characters. *<Note: avoid the use of bold text since this requires more space>*
- In the case of efficacy tables, the variable (or characteristic) column is on the far left followed by the treatment group columns and total column (if applicable). P-values may be presented under the total column or in separate p-value column (if applicable). Within-treatment comparisons may have p-values presented in a row beneath the summary statistics for that treatment
- For numeric variables, include 'unit' in column or row heading when appropriate
- Analysis set sizes will be presented for each treatment group in the column heading as (N=xx) (or in the row headings, if applicable). This is distinct from the 'n' used for the descriptive statistics representing the number of subjects in the analysis set
- The order of treatments in the tables and listings will be Placebo first in the case of placebo controlled studies and Active comparators first in the case of active comparator trials, followed by a total column (if applicable)

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#### 14.2.5. Body of the Data Display

##### 14.2.5.1. General Conventions

Data in columns of a table or listing are formatted as follows:

- Alphanumeric values will be left-justified;
- Whole numbers (e.g., counts) will be right-justified; and
- Numbers containing fractional portions will be decimal aligned.

##### 14.2.5.2. Table Conventions

- Units will be included where available
- For categorical parameters the following conventions will be used, unless otherwise specified:
  - Categorical data will be presented as frequencies (n) and percentages (%).
  - All categories will be presented in the table, unless otherwise specified, so that if no subjects are included in a particular category, n would equal 0. For example, the frequency distribution for symptom severity would appear as:

Severity Rating	N
severe	0
moderate	8
mild	3

- Unless otherwise specified, percentages will be calculated out of the number of subjects in the analysis set, for the treatment group, who have an observation (denominator). Percentages will be presented to 1 decimal place, in parentheses with no spaces, one space after the count (e.g., 7 (12.8%), 13 (5.4%)). If the count is 0, no percent will be presented, ie. a count of 0 will be presented as 0, not 0 (0.0%). Percentages equating to 100% will be presented as 100%, without decimal places.
  - An Unknown or Missing category will be added to each parameter for which information is not available for 1 or more subjects.
  - If a subject can be included in more than one category, a footnote will be added for clarification.
- For continuous data summaries the following conventions will be used, unless otherwise specified:
  - Continuous data will be summarized using descriptive statistics: number of subjects (n), mean, standard deviation (SD), median, and range (minimum and maximum).
  - Unless otherwise specified, the mean and median for a set of values will be printed out to 1 more significant digit than the original values, and standard deviations will be printed out to 2 more significant digits than the original values. The minimum and maximum will report the same

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significant digits as the original values. For example, systolic blood pressure will be presented as follows:

n	XX
Mean	XXX.X
SD	X.XX
Median	XXX.X
Minimum	XXX
Maximum	XXX

- P-values will be presented to 3 decimal places, in the format: '0.xxx', where xxx is the value rounded to 3 decimal places. Every p-value less than 0.001 will be presented as <0.001. If the p-value are less than 0.0001, then present as <0.0001. If the p-value is returned as >0.999, then present as >0.999
- Tabular display of data for medical history, prior/concomitant medications, and all tabular displays of AE data will be presented by the body system, treatment class, or SOC with the highest occurrence in the active treatment group in decreasing order, assuming all terms are coded. Within the body system, drug class and SOC, medical history (by PT), drugs (by ATC1 code), and AEs (by PT) will be displayed in decreasing order. If incidence for more than 1 term is identical, they will then be sorted alphabetically. Missing descriptive statistics or p-values which cannot be estimated will be reported as '-'
- Where a category with a subheading (such as SOC) has to be split over more than one page, output the subheading followed by '(cont)' at the top of each subsequent page. The overall summary statistics for the subheading should only be output on the first relevant page

#### 14.2.5.3. Listing Conventions

- Listings will be sorted for presentation in order of treatment groups as above, subject number, visit/collection day, and visit/collection time
- Missing data will be represented on subject listings as either a hyphen ('-') with a corresponding footnote ('- = unknown or not evaluated'), or as 'N/A', with the footnote 'N/A = not applicable', whichever is appropriate
- Dates will be printed in SAS DATE9.format ('DD\_MMM\_YYYY': 01JUL2000). Missing portions of dates will be represented on subject listings as dashes (--JUL2000). Dates that are missing because they are not applicable for the subject will be output as 'N/A', unless otherwise specified
- All observed time values will be presented using a 24-hour clock HH:MM or HH:MM:SS format (e.g., 11:26:45, or 11:26). Time will only be reported if it was measured as part of the study
- Units will be included where available

#### 14.2.5.4. Figure Conventions

- Unless otherwise specified, for all figures, study visits will be displayed on the X-axis and endpoint (e.g., treatment mean change from Baseline) values will be displayed on the Y-axis

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#### 14.2.6. Footnotes

- A solid line spanning the margins will separate the body of the data display from the footnotes
  - All footnotes will be left justified with single-line spacing immediately below the solid line underneath the data display
  - Footnotes will always begin with 'Note:' if an informational footnote, or 1, 2, 3, etc. if a reference footnote. Each new footnote will start on a new line, where possible
  - Subject specific footnotes are avoided, where possible
  - Footnotes will be used sparingly and add value to the TLF. If more than six lines of footnotes are planned, then a cover page is strongly recommended to be used to display footnotes, and only those essential to comprehension of the data will be repeated on each page
  - The last line of the footnote section will be a standard source line that indicates the name of the program used to produce the data display, the date the program was run, and the listing source (i.e., 'Program : myprogram.sas Listing source: 16.x.y.z')
  - Sources and/or cross-references in footnotes will use the keyword prefix (in singular form) for each reference and will be separated by a comma when multiple cross-references are displayed
- Example  
Listing source: Listing 16.2.4.1.1, Listing 16.2.4.1.2, Listing 16.2.4.2.1

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## 15. Quality Control

Syneos Health End-to-End Process of the Production of Analysis Datasets (ADs) and Tables, Figures and Listings (TFLs) SOP (3922) and the SAS Programming and Validation Plan describe the quality control procedures that are performed for all SAS programs and output. Quality control is defined here as the operational techniques and activities undertaken to verify that the SAS programs produce the output by checking for their logic, efficiency and commenting and by review of the produced output.

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**Statistical Analysis Plan for Interventional Studies**

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## **19. Shells**

TLF shells will be provided as a separate document.

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## 20. Appendices

### Surface Bleeding Severity Scale (SBSS)

SBSS Score	0	1	2	3	4	5
<b>Verbal Descriptor</b>	None	Minimal	Mild	Moderate	Severe; not immediately life-threatening	Extreme; immediately life-threatening
<b>Visual Descriptor</b>	Dry	Oozing	Pooling	Flowing	Streaming	Gushing
<b>Expected Intervention(s)</b>	None	Manual pressure, cautery, adjuvant hemostat(s)	Manual pressure, cautery, suture, adjuvant hemostat(s)	Manual pressure, cautery, suture, adjuvant hemostat(s)	Manual pressure, cautery, suture, staples, tissue repair	Manual pressure, cautery, suture, staples, tissue repair
<b>Maximum Expected ACS-ATLS Shock Risk Class</b>	1	1	1	2	3	4
<p>ACS-ATLS Shock Risk: American College of Surgeons - Advanced Trauma Life Support</p> <p>Class 1: involves up to 15% of blood volume; typically, no change in vital signs and fluid resuscitation is not usually necessary.</p> <p>Class 2: involves 15%-30% of total blood volume; subject is often tachycardic with a narrowing of the difference between the systolic and diastolic blood pressures; the body attempts to compensate with peripheral vasoconstriction; skin may start to look pale and be cool to the touch; volume resuscitation with crystalloids is all that is typically required; blood transfusion is not typically required.</p> <p>Class 3: involves loss of 30%-40% of circulating blood volume; subject's blood pressure drops; heart rate increases, peripheral hypoperfusion worsens; fluid resuscitation with crystalloid and blood transfusion are usually necessary.</p> <p>Class 4: involves loss of &gt; 40% of circulating blood volume; the limit of the body's compensation is reached, and aggressive resuscitation is required to prevent death.</p>						

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Final Audit Report

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