General Adhesive Tissue Tape

Statistical Analysis Plan

for

DHF-01-QR-021 GATT-Patch

GATT Technologies

A Prospective, Multicenter, Single-arm, Clinical Investigation
Evaluating the Safety and Performance of GATT-Patch for Hemostasis during Open Liver Surgery
DHF-01-QR-021

Version 1.0 dated 17SEP2021

Author					
Name	**Function**	**Signature**	**Date**		
			dd	mmm	yy
Razieh Taghavi	**Biostatistician**		06	OCT	21

SIGNATURE PAGE

The undersigned hereby jointly declare that they have reviewed the Statistical Analysis Plan and agree to its form and content.

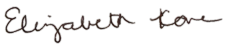
Approval by					
Name	**Function**	**Signature**	**Date**		
			dd	mmm	yy
Dr. Stuart Head	**GATT Technologies, Chief Medical Officer**		6	o c t	2 1
Timo van Laun	**Avania, Project Manager**		06	OCT	21
Elizabeth Kane	**Avania, Director, Analytical Services & Biostatistician**		0 6	O c t	2 1

TABLE OF CONTENTS

DOCUMENT HISTORY

Revision Date	Author	Version	Reason for Change
17SEP2021	Razieh Taghavi	1.0	NA – Initial Version

1 ABBREVIATIONS

Abbreviation	Definition
ADE	Adverse Device Effect
AE	Adverse Event
ALT	Alanine Aminotransferase
aPTT	Activated Partial Thromboplastin Time
AST	Aspartate Aminotransferase
BMI	Body Mass Index
CI	Confidence Interval
CIP	Clinical Investigation Plan
CRF	Case Report Forms
CRO	Contract Research Organization
CSR	Clinical Study Report
DMC	Data Monitoring Committee
eCRF	Electronic Case Report Form
FAS	Full Analysis Set
FU	Follow-Up
INR	International Normalized Ratio
PG	Performance Goal
PP	Per-Protocol Population
PT	Preferred Term
PTT	Prothrombin Time
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBSS	Surface Bleeding Severity Score
SOC	System Organ Class

2 SUMMARY

TITLE	A Prospective, Multicenter, Single-arm, Clinical Investigation Evaluating the Safety and Performance of GATT-Patch for Hemostasis during Open Liver Surgery
PREFACE	This Statistical Analysis Plan (SAP) describes the planned analysis and reporting for GATT Technologies protocol DHF-01-QR-021 (A Prospective, Multicenter, Single-arm, Clinical Investigation Evaluating the Safety and Performance of GATT-Patch for Hemostasis during Open Liver Surgery). This study is being completed to assess the safety and efficacy of GATT-Patch for the treatment of hemostasis among subjects 18 years of age and older undergoing surgery of the liver. The following documents were reviewed in preparation of this SAP: • Clinical Investigation Plan (CIP) DHF-01-QR-021, v4, issued 28APR2021 • Data Monitoring Committee (DMC) Charter, v3 issued 23MAR2021 • Case report forms (CRFs), v4, issued 21MAY2021 for Protocol DHF-01-QR-021
PURPOSE	The purpose of this SAP is to outline the planned analyses in support of the Clinical Study Report (CSR) for protocol DHF-01-QR-021. Exploratory analyses not necessarily identified in this SAP may be performed to support the clinical development program. Any post-hoc, or unplanned, analyses not identified in this SAP will be clearly identified in the respective CSR.
STUDY OBJECTIVE	To evaluate the clinical safety and performance of GATT-Patch in open liver surgery.
STUDY DESIGN	This is a pre-market, prospective, single arm, multicenter, first-in-human clinical investigation. The clinical investigation is split into 2 stages: • **Stage I** of the clinical investigation enrolled a small cohort of subjects within which the initial safety of GATT-Patch was evaluated. A maximum of 12 subjects (~25% of the overall population) was planned to be treated at a maximum of 3 sites, after which the enrollment into the clinical investigation would be paused. At minimum, 2 subjects were aimed to be treated per site. At the end of Stage I, 8 subjects were treated at 3 sites, after which the enrollment into the clinical investigation was paused for 2 weeks in order to perform an early safety assessment. • **Stage II** of the clinical investigation enrolls 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 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.

	The study will be interpreted as a success if the primary performance endpoint is met and the device is assessed to be safe according to Safety endpoints.
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). Achievement of hemostasis will be verified every 30 seconds. 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 performance 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.
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 ENPOINTS	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)
INTERIM ANALYSES	**Stage I:** Stage I of the clinical investigation enrolled a small cohort of subjects within which the initial safety of GATT-Patch was evaluated. A maximum of 12 subjects (~25% of the overall population) was planned to be treated at a maximum of 3 sites, after which the enrollment into the clinical investigation would be paused. At minimum, 2 subjects were aimed to be treated per site. At the end of Stage I, 8 subjects were treated at 3 sites, after which the enrollment into the clinical investigation was paused for 2 weeks in order to perform an early safety assessment. **Stage II:** 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.
FINAL ANALYSES	All final planned analyses identified in this SAP will be completed after the last subject has completed a 6-week follow-up.

3 STUDY OBJECTIVES AND ENDPOINTS

3.1 STUDY OBJECTIVE

3.1.1 PRIMARY OBJECTIVE

The 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.

3.2 STUDY ENDPOINTS

3.2.1 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). Investigators will be trained on the assessment scale prior to the investigation to have consistent assessment of bleeding at the target site (see CIP, 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.

If there are multiple appropriate bleeding sites for one patient, the first encountered bleeding site that requires topical hemostat application (primary bleeding site) will be considered for the analysis of the primary endpoint.

3.2.2 SECONDARY ENDPOINTS

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.

3.2.3 *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.

3.2.4 *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)

4 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),

Therefore, the current plan is to treat a total of up to 51 (=12+39) subjects with GATT-Patch. A maximum of 153 replaceable subjects may be enrolled.

Note that 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 total sample size may increase to a maximum of 73 (=12+61) 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 considers 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 CIP, 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.

5 Sequence of Planned Analyses

5.1 Interim Analyses

5.1.1 Stage I Analysis

Stage I of the clinical investigation enrolled a small cohort of subjects within which the initial safety of GATT-Patch was evaluated. A maximum of 12 subjects (~25% of the overall population) was planned to be treated at a maximum of 3 sites, after which the enrollment into the clinical investigation would be paused. At minimum, 2 subjects were aimed to be treated per site.

At the end of Stage I, 8 subjects were treated at 3 sites, after which the enrollment into the clinical investigation was paused for 2 weeks in order to perform an early safety assessment. At minimum, 2 subjects were treated per site and all 8 subjects had at least 2 week FU data available.

The data monitoring committee (DMC) monitored all emerging safety issues against pre-defined stopping rules of the clinical investigation, specified in the DMC charter of this study. The re-opening of recruitment was authorized from the DMC to proceed.

5.1.2 Interim Analysis for Design Adaptation

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").

5.1.3 Reports for DMC

Avania (CRO) provided DMC with any SAE or other safety concerns during Stage I of the investigation, which were reviewed by the DMC on a case-by-case basis against the stopping rules.

Avania may provide regular data summaries to the DMC members for review every 2 months during the course of the study. These documents will include a summary of adverse event data, as reported by the sites. These data summaries may include the following:

- Subject Accountability
- Site Enrollment
- Subject Demographics
- Primary and Secondary Safety Related Endpoints
- All serious adverse events (SAEs)
- Procedure/Device Observations resulting in adverse event
- All adverse device effects (ADEs)
- Protocol Deviations
- Efficacy Endpoints as appropriate

Modifications and/or additional tables/listings may be produced and distributed to the DMC per request of the committee, Avania, or Sponsor. In the event that no new safety events occur during a particular quarter, DMC members will be contacted accordingly and the update will not be distributed.

5.2 Final Analyses and Reporting

All final, planned, analyses identified in the protocol and in this SAP will be performed after the study completion.

The study is completed when the last treated subject completes the follow-up Visit 1, is lost to follow-up or pre-maturely ends the study for some other reason.

Key statistics and study results will be made available to the sponsor following database lock. Any post-hoc, exploratory analyses completed to support planned study analyses, which were not identified in this SAP, will be documented and reported as necessary. Any results from these unplanned analyses will also be clearly identified in the final study report as post-hoc analyses.

6 Analysis Populations

6.1 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.

6.2 Per-Protocol Population (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 violations are described in Section 7.4.

6.3 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 General Issues for Statistical Analysis

The study will use a frequentist approach to statistical analysis. Descriptive statistics (mean, standard deviation, frequencies, etc.) for baseline participant characteristics, patient disposition and other relevant study parameters will be reported.

7.1 Analysis Software

Analysis data sets, statistical analyses and associated output generated by Avania will be generated using SAS® Software version 9.4 or later.

7.2 Disposition of Subjects and Withdrawals

The data collected up to the time point the subject has withdrawn or discontinued will be included as part of the clinical investigation. The number and percent of subjects in each analysis population will be presented. All subjects who provide written informed consent will be accounted for.

The frequency and percent of subjects who completed each scheduled assessment will be presented in a table for the FAS population. The number and percentage of FAS patients prematurely withdrawing will be presented overall and by reason of discontinuation.

7.3 Methods for Withdrawals and Missing 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. Reasons for

missing visits and assessments will be captured in data collection forms as a protocol deviation or as a subject exit/termination. Any missing data on study endpoints will be described in the CSR.

The primary analysis of the primary performance endpoint will be on the FAS population with available data.

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, 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).

Data will be analyzed as available, with no imputation of missing data for other endpoints.

7.4 Protocol Deviations

Protocol deviations will be summarized in a summary table. This summary will include the number and percent of subjects (overall and by site) with each deviation type. A listing will be generated as well.

In this study, 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.

7.5 Multiple Comparisons and Multiplicity

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. The impact of the interim analysis on the type I error is in Section 9.1.

7.6 Assessment of Homogeneity

This clinical investigation will be conducted in the Netherlands and up to 7 sites will participate in this study. A test of homogeneity across sites will be done to determine if the study sites have reasonably homogeneous responses for the primary endpoint.

Logistic regression, with the primary endpoint, 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 on the FAS population.

It is expected that a comparable number of subjects is enrolled and treated at each investigational site. There is no minimum or maximum number of subjects to be enrolled or treated by each site, in stage II,

however distribution between participating sites is monitored during the enrolment period. Low enrolling sites will be pooled for the homogeneity analysis. Study sites with fewer than 5 subjects may be combined into pseudosites. All pseudosite categorizations will be determined before the database is locked.

The association between investigational site and the primary performance outcome will be assessed at the 0.15 significance level. If the responses are not homogenous, an appropriate regression analysis will be done to determine if the lack of homogeneity is due to the site or due to a possible imbalance in baseline characteristics of the subjects across study sites. If the site effect is no longer significant at a 0.15 level of significance after adding the potentially unbalanced baseline covariates, then site will not be considered a source of lack of homogeneity.

7.7 Timing of Assessments and Events for Analysis

Study day 0 is the date of the index procedure. Study days will be calculated as follows:

- Study Day = Event Date – Surgery Date

All the primary and secondary endpoints are collected at the treatment day. Safety endpoints are collected at the treatment, post-surgery, and 6 weeks (+/- 2 weeks) follow-up visit. 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.

8 Demographics and Other Baseline Characteristics

Safety and FAS populations will be utilized for the analyses discussed in this section. When summarizing data, continuous variables will be summarized with number of subjects, mean, standard deviation, median, quartiles, minimum, and maximum, while categorical variables will be summarized with frequency and percentage.

8.1 Demographics and Physical Exam

Subject's demographics and physical examination such as age, weight, heart rate and other continuous variables will be summarized by reporting number of observations, mean, standard deviation, median, quartiles, minimum, and maximum. Sex, race, and disease diagnosis will be summarized with frequency and percentage.

8.2 Prior and Concurrent Medications

All relevant prior and concurrent medications will be presented in a listing with medication name, route of administration, dose, and other data captured on the eCRF.

8.3 Baseline Medical History

The subject's relevant medical history and allergies will be recorded on the eCRF and presented in a summary table by frequency and percentage of subjects.

8.4 Baseline Labs

Tables presenting descriptive statistics (N, mean, standard deviation, median, quartiles, minimum, maximum) of laboratory values will be presented. The laboratory values include hematology tests (hemoglobin (Hb), thrombocytes), coagulation tests (prothrombin time (PTT), activated partial thromboplastin time (aPTT), international normalized ratio (INR)), chemistry tests (bilirubin level, calcium, potassium, sodium, chloride, albumin, AST, ALT). Whether or not laboratory values are normal or out of range of expected value will also be summarized by frequency and percentage.

9 Performance Analyses

9.1 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 null hypothesis (H_0) for this endpoint states that the true proportion of subjects treated with the GATT-Patch who achieve the primary performance endpoint is no higher than 65.4%. The alternative hypothesis the GATT-Patch trial aims to demonstrate is that the true proportion of subjects who achieve non-inferiority greater than 65.4%.

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 primary performance endpoint will also be analyzed on the PP population as a secondary analysis. If there are multiple appropriate bleeding sites for one patient, the first encountered bleeding site that requires topical hemostat application (primary bleeding site) will be considered for the analysis of the primary endpoint.

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.

9.2 Secondary Endpoint Analysis

The secondary performance endpoints will be determined using the FAS and PP population. The secondary endpoint analysis will be performed on the primary bleeding site. If there are multiple appropriate bleeding sites for one patient, this analysis will also be performed on all eligible bleeding sites that require topical hemostat application including the primary bleeding site.

The number of observations, mean, standard deviation, median, quartiles, minimum, and maximum time to hemostasis (seconds) will be presented, including the 95% CI of the mean. To account for the correlation within patient, when there are multiple bleeding sites available for one patient, the 95% CI will be estimated using a repeated measures linear regression model. An unstructured covariance matrix will be used. In the event that the model fails to converge, the compound symmetry covariance matrix will be used.

The number and percentage of bleeding sites achieving hemostasis at 30, 60, 90, 120, and 150 seconds, as well as the number and percentage of bleeding sites whichfail to reach hemostasis at 5 minutes will be presented. The 95% CI of the percentages based on Wilson's method with continuity correction will also be reported. To account for the correlation within patient, when there are multiple bleeding sites available for one patient, the 95% CI will be estimated using a repeated measures logistic regression model. An unstructured covariance matrix will be used. In the event that the model fails to converge, the compound symmetry covariance matrix will be used.

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

10 Safety Analyses

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.

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. Summaries will be presented by study stage and overall.

No formal hypothesis testing will be performed.

11 Adverse Events

All adverse events (AEs) collected between the index procedure and the 6 weeks (+/-2 weeks) follow-up visit will be recorded in the eCRFs and will be reported. All adverse events (AEs) will be coded using the standardized Medical Dictionary for Regulatory Activities (MedDRA) central coding dictionary, version 24.0 or later. The analysis is performed on the safety population.

11.1 All Adverse Events

Summaries of incidence rates of individual AEs by System Organ Class (SOC) and Preferred Term (PT) will be prepared. Because a subject may experience more than one AE, summaries will provide both the number of subjects experiencing at least one event and the number of events within a reporting period. Percentages provided will be the percent of subjects experiencing one or more adverse events. In addition, incidence of AEs will be presented by severity (mild, moderate, severe) and by relationship to investigational product. Subjects experiencing an event within a given PT and SOC more than once will be counted under the maximum severity/relationship experienced.

A listing of all adverse events will include the subject number, AE number, days since index procedure, the AE SOC and PT, the severity of AE, whether or not the AE is classified as serious (SAE), the relationship of the AE to the investigational device or procedure, the action taken, the outcome, and the adjudication status.

11.2 Adverse Events Leading to Withdrawal

A summary of incidence rates (frequencies and percentages) of AEs leading to study withdrawal, by SOC will be prepared for the Safety Population. A data listing of AEs leading to withdrawal will also be provided, displaying details of the event(s) captured on the eCRF.

11.3 Serious Adverse Events

Summaries of incidence rates and relationship to the investigational device/procedure of individual SAEs by SOC and PT will be prepared. Summaries will provide both the number of subjects and the number of events within a reporting period. Percentages provided will be the percent of subjects experiencing one or more serious adverse events. A data listing of SAEs will also be provided, displaying details of the event(s) captured on the eCRF.

11.4 Device Deficiency

Data listings of device deficiencies will also be provided, displaying deficiency type, specification of device part, description, and whether associated with any AEs or SAEs.

11.5 (Serious) Adverse Device Effects

Summaries of incidence rates of device and procedure related AEs by SOC and PT will be prepared. Summaries will provide both the number of subjects and the number of events within a reporting period. Percentages provided will be the percent of subjects experiencing one or more ADE events. Data listings of ADEs will also be provided, displaying details of the event(s) captured on the eCRF.

11.6 Deaths

Should any subjects die during the course of the GATT-Patch trial, relevant information will be supplied in a data listing.

12 Other Planned Analyses

12.1 Exploratory Endpoint Analyses

The exploratory endpoints will be analyzed on the FAS and PP populations. No formal hypothesis testing will be performed for these exploratory endpoints.

12.1.1 Surgery Time

Surgery time (minutes) will be presented as a summary table by reporting number of subjects, mean, standard deviation, median, quartiles, minimum, and maximum.

12.1.2 Blood Loss

Blood loss during surgery (mL) will be presented as a summary table by reporting number of subjects, mean, standard deviation, median, quartiles, minimum, and maximum.

12.1.3 Blood Transfusion

Blood transfusion during hospitalization (mL) will be presented as a summary table by reporting number of subjects, mean, standard deviation, median, quartiles, minimum, and maximum.

12.1.4 SBSS (0-5)

The Surface Bleeding Severity Score (SBSS) at the target bleeding site will be displayed on a 0-5 scale (0=none, 1=minimal, 2=mild, 3=moderate, 4=severe, 5=extreme). A summary table will be presented by reporting the frequencies and percentages of bleeding sites by each SBSS category (category 1, 2 and 3 are applicable for this study).

This exploratory analysis will be performed on the primary bleeding site. If there are multiple appropriate bleeding sites for one patient, this analysis will also be performed on all eligible bleeding sites that require topical hemostat application including the primary bleeding site.

12.1.5 Hemostatic Agents/Techniques

The use of adjunct hemostatic agents and/or techniques (e.g. cautery, sutures, or staples) will be presented as a summary table by reporting the frequencies and percentage.

This exploratory analysis will be performed on the primary bleeding site. If there are multiple appropriate bleeding sites for one patient, this analysis will also be performed on all eligible bleeding sites that require topical hemostat application including the primary bleeding site.

12.1.6 Amount of Material needed versus Bleeding Surfaces

Amount of material needed versus bleeding surfaces will be presented as a summary table by reporting number of bleeding sites, mean, standard deviation, median, quartiles, minimum, and maximum of the number of patches applied per cm^2 bleeding surface.

This exploratory analysis will be performed on the primary bleeding site. If there are multiple appropriate bleeding sites for one patient, this analysis will also be performed on all eligible bleeding sites that require topical hemostat application including the primary bleeding site.

12.1.7 User Satisfaction

User satisfaction is reported by the surgeons completing system usability scale (SUS) and medical device specific questionnaires with 5 response options from Strongly disagree to Strongly agree. Number and percentage of subjects in each response category will be reported for both questionnaires.

For the medical device specific questionnaire, the number and percentage of subjects with any neutral, agree or strongly agree responses will also be reported.

SUS includes 10 questions. The number and percentage of subjects with any neutral, agree or strongly agree responses will also be reported for the odd numbered questions. For the even numbered questions, the number and percentage of subjects with any neutral, disagree or strongly disagree responses will be reported. In addition, total SUS score will be presented by reporting number of subjects, mean, standard deviation, median, quartiles, minimum, and maximum.

12.2 Planned Subgroup Analyses

The number and percentage of bleeding sites achieving hemostasis at 30, 60 and 180 seconds will be summarized for the following variables. Difference of percentages between the groups will also be reported including 95% CIs based on Wilson's method with continuity correction.

- Gender (Male vs Female)
- Age (< median vs ≥ median)
- SBSS category (1/ 2/ 3)
- Antiplatelet/ anticoagulant use at baseline (Yes vs No)
- Transected parenchyma area (< median vs ≥ median)
- Bleeding surface area (< median vs ≥ median)
- Type of hepatic parenchyma (Normal/ Cirrhotic/ Staetotic)
- Type of bleeding (Venous/ Arterial/ Mixed)

Subgroup analyses will be performed on the primary bleeding site. If there are multiple appropriate bleeding sites for one patient, the analyses will also be performed on all eligible bleeding sites that require topical hemostat application including the primary bleeding site. In the case of multiple bleeding sites per patient, to account for the correlation within patient, the 95% CI will be estimated using a repeated measures logistic regression model. An unstructured covariance matrix will be used. In the event that the model fails to converge, the compound symmetry covariance matrix will be used.

12.3 Additional Analyses

12.3.1 Primary Performance Endpoint - Multiple Bleeding Sites

If there are multiple appropriate bleeding sites, the first encountered bleeding site that requires topical hemostat application will be considered for the primary analysis of the primary endpoint. An additional analysis on the primary endpoint will be performed on all eligible bleeding sites treated with GATT-Patch including the primary bleeding site. To account for the correlation within patient, the 95% CI will be estimated using a repeated measures logistic regression model. An unstructured covariance matrix will be used. In the event that the model fails to converge, the compound symmetry covariance matrix will be used.

12.3.2 Time To Hemostasis - Safety Population

The number of bleeding sites, mean, standard deviation, median, quartiles, minimum, and maximum time to hemostasis (seconds), including the 95% CI of the mean will be presented for Stage I and Stage II treated subjects (Safety population).

This analysis will be performed on the primary bleeding site. If there are multiple appropriate bleeding sites for one patient, the analysis will also be performed on all eligible bleeding sites that require topical hemostat application including the primary bleeding site. To account for the correlation within patient, the 95% CI will be estimated using a repeated measures linear regression model. An unstructured

covariance matrix will be used. In the event that the model fails to converge, the compound symmetry covariance matrix will be used.

12.3.3 Hemoglobin over Time

Hemoglobin (Hb) measure (mmol/l) will be reported at screening, pre-surgery admission and post-surgery hospitalization with number of observations, mean, standard deviation, median, quartiles, minimum, and maximum.

13 Reporting Conventions

All reporting will meet the standards of SOP-68 AS Data Analysis Reporting and SOP-83 AS Programming Standards.