Statistical Analysis Plan (SAP)

A Prospective, Single-Arm Multi-Center Study of the ENSEAL® X1 Curved Jaw Tissue Sealer and Generator G11 in Upper Gastrointestinal, Lower Gastrointestinal, and Gynecological Procedures

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The following individuals have reviewed this version of the Statistical Analysis Plan and are in agreement with the content. Signatures are collected digitally and can be found on the last page of this document.

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Revision History

Revision Number	Revision Date (DDMMMYYYY)	Reasons for Revision
0.1	09Mar2023	First draft
0.2	13Mar2023	Implemented trial team's comments
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0.4	17May2023	Implemented trial team's comments
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1.0	25May2023	First final version

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1 Introduction

This is the Statistical Analysis Plan (SAP) for the final analysis of data collected under Protocol ENG_2019_01. This SAP describes in detail the statistical methodology and statistical analyses for this protocol.

1.1 Study Objectives

The primary objective of this study is to demonstrate the acceptable performance and safety of the ENSEAL X1 and GEN11 devices when used per the instructions for use (IFU).

1.2 Study Design

This prospective, single-arm, multi-center study will collect clinical data in a post-market setting by procedure group (upper gastrointestinal (GI), lower GI, and gynecological). Investigators will perform each procedure using the device in compliance with their standard surgical approach and the ENSEAL X1 and GEN11 IFUs.

Subjects will be consented and screened anytime during a period of 8 weeks prior to the date of surgery. Subjects will be considered enrolled when the ENSEAL X1 device has been attempted to be used for a vessel transection during upper GI, lower GI, or gynecological procedures. All enrolled subjects will be followed post-operatively through discharge and again at 28 days (± 14 days) post-surgery; therefore, from the surgery date to study exit, the duration will be approximately 6 weeks.

A minimum of 133 subjects (maximum of 149 subjects) will be included in the study from up to 16 surgery centers in the United States and/or European Union and/or United Kingdom. The enrollment is planned with the following procedure targets:

- A minimum of 77 subjects enrolled to a maximum of 89 subjects enrolled for upper GI procedures to achieve 27 vessel transections in each of the four procedure subgroups. Subjects will be enrolled to the following procedure subgroups with corresponding enrollment restrictions:
    - A minimum of 14 subjects enrolled to a maximum of 17 subjects enrolled for fundoplication (Nissen, anterior or posterior [Toupet]) or hiatal hernia procedures);
    - A minimum of 27 subjects enrolled to a maximum of 30 subjects enrolled for gall bladder procedures;
    - A minimum of 10 subjects enrolled to a maximum of 13 subjects enrolled for sleeve gastrectomy procedures;
    - A minimum of 26 subjects enrolled to a maximum of 29 subjects enrolled for small intestine resection procedures (also includes Roux-en-Y gastric bypass [RYGB] and biliopancreatic diversion with duodenal switch [BPD/DS]);
- A minimum of 28 subjects enrolled to a maximum of 30 subjects enrolled for lower GI procedures (e.g., large intestine resections); and
- A minimum of 28 subjects enrolled to a maximum of 30 subjects enrolled for gynecological procedures (hysterectomies associated with oophorectomies).

2 Treatment Assignment

This is a single-arm study where all enrolled subjects will have the ENSEAL X1 device utilized for transection of at least one vessel.

3 Randomization and Blinding Procedures

As this is a single-arm study, no randomization will occur, and no blinding procedures are required.

4 Interval Windows

Interval windows for the purpose of analysis in this study will not be defined outside of those already specified in the protocol for visit scheduling as the collection of data for the primary and secondary performance endpoints occurs intra-operatively. The final visit occurs approximately 4 weeks after surgery, thus no interval windows need to be defined given the absence of long-term follow-up in this study. The Schedule of Events specifies a window of 14 days around the scheduling of the 4-week follow-up visit, and any information entered in the eCRFs at this visit will correspond to the 4-week visit. There will be no assigning of observations to time points outside of the visit to which they are recorded in the eCRFs.

5 Levels of Significance

The statistical hypothesis for the primary endpoint will be evaluated using a one-sided significance level of 0.025. A 95% confidence interval will be provided for the primary endpoint. Estimation of primary endpoint by procedure group and procedure subgroup will provide 95% confidence interval. Estimation of secondary and safety endpoints will be summarized by number and percentages only.

6 Analysis Sets

Full Analysis Set: Full Analysis Set (FAS) will include subjects for whom the ENSEAL X1 device is utilized during the surgical procedure and have assessment for the primary endpoint. The FAS includes subjects for whom the answer is “Yes” to at least one of the following questions from the “ENSEAL X1 Usage” form on eCRF: “Were adhesions removed or divided by ENSEAL X1”, “Were lymphatics bundles divided by ENSEAL X1”, “Were tissue bundles divided by ENSEAL X1”, “Was the ENSEAL X1 used for tissue grasping”, “Was the ENSEAL X1 used for tissue cutting”, “Was the ENSEAL X1 used for tissue dissection.” The summary of all primary and secondary performance endpoints will be performed using FAS by procedure group (upper GI, lower GI, and gynecological), procedure subgroup (fundoplication, gall bladder, sleeve gastrectomy, and small intestine resection) and on the entire pooled set of subjects.

Safety Analysis Set: The Safety Analysis Set (SAS) will include all subjects who signed informed consent and for whom the ENSEAL X1 device is utilized during the surgical procedure. The safety endpoints will be summarized using SAS by procedure group, procedure subgroup and in total.

All Enrolled Set: The All Enrolled Set (AES) contains all subjects who provide informed consent for this study. The AES will be used for disposition of study subjects and for all listings.

7 Sample Size Justification

A sample size of at least 230 vessel transections is required to have a minimum of 90% power for rejecting the null hypothesis when the expected rate of Grade 3 hemostatic transections is at least 94.0% based on exact binomial test and a one-sided significance level of 0.025. The hemostatic transection grades for vessels are assumed to be independent within a subject and within a procedure.

In order to achieve a total of 230 vessel transections for analysis with a minimum of 27 vessel transections in each group (including 4 procedure subgroups in upper GI procedure), a minimum of 122 subjects (a maximum of 149 subjects) will be enrolled in the study.

The original sample size of the study was based on the assumption of one vessel transection per subject. At the time of amendment 5 the number of transections per subject was estimated to be 1.9 on average. The primary endpoint and the study hypothesis are based on hemostasis of vessel transection; therefore, the number of subject to be enrolled was updated to ensure 230 vessel transections.

Given that the primary endpoint is being evaluated intra-operatively, it is not anticipated that there will be subject dropout prior to evaluating this endpoint, thus no adjustment or increase in subject enrollment is planned to account for dropout. A minimum of 27 vessel transections in each group (including 4 procedure subgroups in upper GI procedure) is planned to attain optimum representation of each of the procedure groups to the whole study sample.

From a safety perspective on the pooled analysis of 133 subjects and in consideration of rare AEs that may occur (e.g., bleeding requiring blood product transfusion), for an event that has an incidence rate of, for example, 1%, then in a sample of 133 subjects, the probability of observing at least 1 event is 73.7% under a binomial probability model. Thus, this sample size provides a high probability of observing rare events if they do occur, and provides reasonable assurance to conclude that the likelihood of such AEs is less than 2.8% if they do not occur based on the upper limit of an exact 95% confidence interval when 0 events out of 133 subjects are observed.

8 Analyses to be Conducted

8.1 General Conventions

Subject data will be summarized in tables and further details will be provided in listing. All eCRF data will be listed per subject for all subjects. Descriptive statistical analyses will be provided for pre-specified study endpoints. Summaries for continuous variables will include number of observations (n), mean, standard deviation, median, minimum, and maximum. Summaries for categorical variables will include total and counts for each category and their corresponding percentages.

Data recorded at the nominal visits will be presented in summary tables; however, unscheduled visits will not be included in summary tables. Listings will include both scheduled and unscheduled visits.

Analyses will be conducted using SAS software. During the course of programming of tables that are mocked up in this SAP, minor modifications may become necessary. Examples of these minor modifications include, but are not limited to, re-wording of a footnote, addition of a footnote, re-labeling of a column, or addition or removal of a column from a table or listing. In cases where modifications to tables or listings are not related to a change in statistical analysis methodology or conclusions that could be made on the originally proposed methodology, then no amendment of the SAP is necessary. Any final analyses that differ from what has been specified in this document will be identified within the final statistical output and documented within the clinical study report.

8.2 Disposition of Study Subjects

Subject disposition will be summarized by procedure group, procedure subgroup, and in total using counts and percentages. The number and percentage of subjects in the AES who completed, screen failed and discontinued will be tabulated along with the specific reasons for discontinuation.

8.3 Demographic, Vital Signs, and Surgical Characteristics

Summary statistics of subject demographics (age, sex, childbearing potential, race, and ethnicity) and vital signs (height, weight, and body mass index) will be presented by procedure group, procedure subgroup and in total. Background information (smoking history, ASA score) and pregnancy test result will be summarized in a similar manner. Listings will be presented for subject's inclusion/exclusion criteria, demographic, vital sign, and background information.

Background information for upper GI, lower GI, and gynecological will be summarized separately. A listing will be provided for background information of each procedure group.

Medical history will be summarized by Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred term. A listing will be presented for medical history. Treatment history will be listed. Prior and concomitant medications and concomitant procedures will be listed only.

Surgical characteristics will be summarized by procedure group, procedure subgroup, and in total as collected on the following forms: blood transfusion, intra-operative data, vessel transected, prophylactic use of clips, grade 3 form, and grade 4 form.

8.4 Primary and Secondary Endpoints and Associated Hypotheses

8.4.1 Primary Endpoint and Associated Hypotheses

The primary performance endpoint in this study is the number and percentage of vessels where hemostasis (≤ Grade 3) is achieved using the ENSEAL X1 device. The hemostasis grading scale is defined as:

- Grade 1: no bleeding at transection site;
- Grade 2: minor bleeding at transection site, no intervention needed;
- Grade 3: minor bleeding at transection site, mild intervention needed, use of compression, basic energy devices (monopolar and/or bipolar device), and/or touch-ups with ENSEAL X1.
- Grade 4: significant bleeding (e.g., pulsatile blood flow, venous pooling) requiring intervention such as extensive coagulation or ligation with use of additional hemostatic measures (e.g., hemoclips, staples, sutures, fibrin sealants, other advanced energy products).

The primary performance endpoint will be summarized at the vessel transection level as multiple vessel transections per subject is expected; that is, the denominator for the primary endpoint will be the total number of vessel transections and the numerator will be the number of vessel transections where hemostasis (≤ Grade 3) is achieved.

The following hypothesis will be evaluated for the primary endpoint:

$$H_0: p \leq 87.5\%$$
$$H_1: p > 87.5\%$$

Where p is the percentage of transections achieving a Grade 3 or lower hemostasis rating and 87.5% is set as a performance goal for the lower bound of acceptable hemostasis. A 95% confidence interval will be calculated for p based on the proportion of vessel transections where Grade 3 or lower hemostasis is achieved using Clopper-Pearson's method and the lower limit of this confidence interval will be compared to 87.5% to evaluate the above hypotheses. A p-value will be determined based on an exact binomial test. Primary endpoint will be evaluated for the total sample. For procedure group and procedure subgroup 95% CI will be provided using Clopper-Pearson's method for proportion of vessel transections where Grade 3 or lower hemostasis is achieved.

8.4.2 Secondary Endpoints and Associated Hypotheses

No formal hypotheses are specified for the secondary endpoints of this study.

Counts and percentages will be provided for the following secondary endpoints:

- Categories of 5-point scale scores for various tasks completed by the ENSEAL X1 device (adhesion removal or division, lymphatics or tissue bundles divided, tissue grasping, tissue cutting, or tissue dissection). The scale will be a 5-point scale (very dissatisfied, dissatisfied, neither satisfied or dissatisfied, satisfied, or very satisfied) asking how

satisfied the surgeon was with the use of the device for each of the tasks as collected on the "ENSEAL X1 Usage form in eCRF;
- Categories of hemostasis grading scale for each vessel transected; and
- Type, name, and number of additional hemostasis products required to achieved hemostasis for Grade 4 vessel transections.

Counts and percentages will also be provided for type, size, and number of vessels transected. Listing will be provided for ENSEAL X1 usage and vessel transected forms.

8.4.3 Summary of additional key data

Summary statistics will be presented for the following additional key data:

- Procedure duration;
- Use of any other energy device (basic [monopolar and traditional bipolar], advanced bipolar, ultrasonic) in primary procedure (type, name, and number of device and reason for use), if applicable;
- Overall assessment questionnaire of how device performed in various tasks for lower GI/large intestine resection and gynecological procedures;
- Surgeon questionnaire administered once per investigator;
- Task questionnaire after each lower GI/large intestine resection and gynecological procedure;
- Generator questionnaire after each procedure for each GEN11 used;
- Surgical procedure conducted;
- Hospital stay duration;
- Name and number of vessels that were transected, surgeon determination of diameter size range (< 3 mm, 3 to 5 mm, and > 5 to 7 mm);
- Occurrence and location of cancer and occurrence of pre-surgical radiation/chemotherapy within 90 days prior to surgery, if applicable;
- Occurrence of vessel skeletonization;
- Presence of inflamed tissue, calcified tissues/vessels, atherosclerotic tissue, fibrotic tissue, or presence of adhesions, if applicable;
- Volume of estimated intra-operative blood loss;
- Occurrence of blood transfusion, if applicable (record the total required units of blood and rationale);
- Type of additional mild interventions (use of compression, basic energy devices [monopolar and/or bipolar] and/or touch-ups with ENSEAL X1) required to achieve hemostasis for Grade 3 vessel transections including number of times when ENSEAL X1 touch-ups were used; and
- Protocol deviation

Listing will be provided for task questionnaire, surgeon questionnaire, generator questionnaire, and protocol deviation,

8.5 Safety Analyses

The primary safety endpoint in this study is the occurrence of device-related adverse events (AEs). As per the study protocol, device-related AEs are those identified as having a relationship of possibly, probably, or causally with the ENSEAL X1 or GEN11 devices. AEs unrelated to the study device are recorded as 'not related' on the CRF. Both device-related and procedure-related AEs reported during the study will be coded to MedDRA. All reported AEs will be summarized by MedDRA system organ class and preferred term by procedure group, procedure subgroup, and in total. Separate summaries will be provided for device-related and procedure-related AEs. Serious AEs will be summarized in a similar manner. All safety endpoints will be summarized by procedure group, procedure subgroup, and in total. All reported adverse events will be listed. Listings will also be provided for blood transfusion details, concomitant procedures, and concomitant medications.

Safety endpoints are as follows:

- All AEs
- Serious AEs
- All AEs related to the study device
- Serious AEs related to the study device
- All AEs related to the study procedure
- Serious AEs related to the study procedure

8.5.1 Safety Outcomes Reported in the CER

Safety outcomes identified in the CER # SCN060262 (ref. Table 33) will be summarized by procedure group, procedure subgroup, and in total. Only key safety outcomes that include major bleeding as defined as hemorrhage > 400 mL and thermal damage/injury will be presented. The observed event rates for the key safety outcomes from current study will be presented along with the median event rates from the CER for descriptive comparison. No statistical test will be conducted.

8.6 Plans for Interim Analysis

No interim analyses are planned for this study.

8.7 Handling of Missing Data

All summaries will be performed for enrolled subjects only and with observed data. There will be no imputation of data for early terminated subjects or for missing data within the database.

8.8 Sensitivity Analyses

The analysis of the primary performance endpoint described above in Section 8.4.1 makes the assumption of independence of activations within a subject in estimating the variance for the confidence interval. Achieving hemostasis (≤ Grades 3) may be correlated within a patient for those with two or more vessel transections. To account for the potential dependence in achieving

hemostasis in vessels within a subject, a sensitivity analysis will be performed where the 95% confidence interval will be estimated using a generalized linear mixed model. The underlying distribution of the dependent variable in the model is logistic as the outcome variable is binary (i.e., hemostasis achieved or not achieved). A random intercept term at subject-level will be used in the generalized linear mixed model to account for the within subject correlation in achieving hemostasis. The distribution of the random intercept is assumed to be Gaussian.

If the inference from the mixed model is not consistent with the inference from the primary endpoint analysis as described in Section 8.4.1 then the inference from the mixed model will be used to evaluate success.

Example SAS code:

```
*Create a pseudo variable group so that the 95% CI for intercept can be estimated;
data mydata; set mydata; group="pseudo"; run;

PROC GLIMMIX DATA = mydata;
CLASS id group;
MODEL OUTCOME(Event='0') = group / S DIST=BINARY LINK=LOGIT;
RANDOM intercept / SUBJECT = id;
LSMEANS group / CL ILINK; *The results of interest (95% CI of
rate of hemostasis) are presented on the last two columns;
RUN;
```

8.9 Subgroup Analysis

Subgroup analyses are planned to be performed for the subgroup of subjects who have a medical history of treatment for cancer (e.g. chemotherapy or radiation), BMI classes (i.e., underweight, healthy weight, overweight, and obese) and sex. Subjects who reported “neoadjuvant chemotherapy” or “neoadjuvant radiation therapy” within 90 days prior to surgery are identified as subjects with a medical history of treatment for cancer as collected on the “Treatment History” form on eCRF. These analyses will be exploratory and summary statistics for the procedure-related parameters will be provided for each subgroup. Summary statistics for the following procedure-related parameters will be presented by subgroups:

a) Hemostasis grade (achieved or not and distribution of grade)
b) Distribution of 5-point scale scores for various tasks completed by the ENSEAL X1 device
c) Procedure duration
d) Hospital stay duration;
e) Size of vessels
f) Occurrence of vessel skeletonization
g) Presence of inflamed tissue, calcified tissues/vessels, atherosclerotic tissue, fibrotic tissue, or presence of adhesions
h) Volume of estimated intra-operative blood loss;
i) Occurrence of blood transfusion.

8.10 Assessment of Site Homogeneity

No summaries or adjustments by study site are planned for this study.

9 Data Monitoring Committee (DMC)

No Data Monitoring Committee was planned or utilized during this study.

Appendix: Shells for Table, Figures, and Listings to be Generated

Table shells are provided in a separate document for all summaries to be generated for this study. These shells are a guide to the general layout of data to be presented. Minor modifications can be made to suit existing programs or macros that are available. Additionally, a list of all listings to be created is provided corresponding to the eCRFs that are used in this study. All fields collected will be listed.