STATISTICAL ANALYSIS PLAN

Protocol Title:

SAFETY AND FEASIBILITY OF ENDOSCOPIC APPLICATION OF A NOVEL THERAPY FOR DUODENAL MUCOSAL REGENERATION IN THE TREATMENT OF TYPE II DIABETES (REGENT-1-US STUDY)

PROTOCOL NUMBER: 346

STUDY SPONSOR:
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REGENT-1-US study Annotated CRF Dated September 19, 2023 (Footer Date Generated: 19-Sep-2023 16:47:34 (UTC))
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TABLE OF CONTENTS

1. LIST OF ABBREVIATIONS AND DEFINITIONS

Abbreviation	Abbreviated Defined
AACE	American Association of Clinical Endocrinologists
ADA	American Diabetes Association
AAE	Anticipated Adverse Event
ADE	Adverse Device Effect
AE	Adverse Event
AESIs	Adverse Events of Special Interest
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ASADE	Anticipated Serious Adverse Device Effect
AST	Aspartate Aminotransferase
BMI	Body Mass Index
BUN	Blood Urea Nitrogen
CEC	Clinical Events Committee
CFR	Code of Federal Regulations
CGM	Continuous Glucose Monitoring
COVID-19	Coronavirus Disease 2019
CRF	Case Report Form
CSR	Clinical Study Report
Diabetes Site	The site where the Investigator performs study follow up visits and diabetes management.
DMR	duodenal mucosal resurfacing
DSMB	Data Safety and Monitoring Board
DTSQ	Diabetes Treatment Satisfaction Questionnaire
EKG	Electrocardiogram
eGFR	Estimated Glomerular Filtration Rate eGFR calculated by Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) Equation (2021)
Endoscopy Site	The site where the Index Procedure is performed.
FPG	Fasting Plasma Glucose
GCP	Good Clinical Practice
GI	Gastrointestinal
GLMs	Glucose Lowering Medications
HbA1c	Glycosylated Hemoglobin
HDL	High-Density Lipoprotein
HOMA-IR	Homeostatic Model Assessment of Insulin Resistance
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
ICH	International Conference for Harmonization
IDE	Investigational Device Exemption

Abbreviation	Abbreviated Defined
I/E	Inclusion/Exclusion Criteria
IP	Investigational Plan
IRB	Institutional Review Board
ISO	International Organization for Standardization
ITT	Intent-to-Treat
LDL	Low-Density Lipoprotein
MedDRA	Medical Dictionary for Regulatory Activities
PP	Per Protocol
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SU	Sulfonylurea
T2D	Type 2 Diabetes Mellitus
% TBWL	% Total Body Weight Loss
TIR	Time in range
UADE	Unanticipated Adverse Device Effect
ULN	Upper Limit of Normal

2. REVISION HISTORY

Version 1.0 of the Statistical Analysis Plan is the initial version of this document that has been released for production.

3. INTRODUCTION

This statistical analysis plan (SAP) describes the planned statistical methods to be used during the reporting and analysis of data collected under the Clinical Investigation Protocol entitled *Safety and Feasibility of Endoscopic Application of a Novel Therapy for Duodenal Mucosal Regeneration in the Treatment of Type II Diabetes (REGENT-1-US Study), Doc. No. 346*. This SAP should be read in conjunction with the study protocol and case report forms (CRFs).

The REGENT-1-US study is a multicenter, open-label, treatment-only study conducted in Australia. The study is designed to assess the feasibility and preliminary safety of the Endogenex device for endoscopic duodenal cellular regeneration in patients with type 2 diabetes (T2D) inadequately controlled on glucose-lowering medications. The protocol enrolled patients who were treated with non-insulin glucose-lowering agents; a tabulation of the treatment and number of patients is presented below.

Device Generation 1 / 600 Volts / Single Treatment (n)	Device Generation 1 / 600 Volts / Double Treatment (n)	Device Generation 2 / 750 Volts / Double Treatment (n)	All Patients (n)
3	7	10	20

This plan is developed for analysis and reporting of the 48-week follow up data. The SAP may be revised in the future to address additional follow up data analysis beyond 48 weeks, if necessary.

Patients are considered enrolled in the study once the patient has passed endoscopic screening and proceeded to the Index procedure. ***Screen failures*** are defined as patients who consented to participate in the clinical study and started the screening tests specified by the protocol but are not subsequently enrolled into the study. Procedure success was defined as at least 6cm of duodenum was successfully treated.

The following analysis populations are defined for the presentation of the results from this study: *Intent-to-Treat* (ITT), *Full Analysis Set* (FAS) [referred to in the study protocol as the modified Intent-to-Treat (mITT) population], *Per-Protocol* (PP) and *Completed Cases* (CC). (Ref. Section 11.3 of the study protocol).

The primary and secondary safety analyses will be performed using the ITT population. The primary effectiveness analyses will be performed using the FAS population. The Per-Protocol population and Completed-Cases population will be used for the sensitivity analyses of the primary and secondary effectiveness endpoints.

Intent-to-Treat: The Intent-to-Treat population includes all enrolled patients, regardless of the patient having received the target treatment (at least 6cm of duodenum treated). The point of enrollment occurs when a patient has provided written informed consent and an energy delivery has been attempted during the index procedure.

Full Analysis Set: The FAS population consists of the ITT population patients who received the target treatment (at least 6 cm of duodenum treatment) and that have at least one post-treatment follow-up examination.

Per-Protocol: The Per-Protocol population is a subset of the FAS population and includes all patients who received the target treatment, do not have any major eligibility violations, and maintained stable glucose-lowering medications for 24 weeks post-procedure. The definition of what constitutes a major eligibility violations will be established before the study database is locked.

Completed Cases: The Completed Cases population is a subset of the Per-Protocol population and includes all patients who received the target treatment, do not have any major eligibility violations, and maintained stable glucose-lowering medications for 24 weeks post-procedure, and completed the final Week 48 End of Study Visit.

The details contained in this plan include the source code for the assessment of poolability across a myriad of factors and the analysis of each of the endpoints. Additionally, the structure of the table designs and a comprehensive index of the tables and listings has been provided.

This document contains information to support the generation of a Clinical Study Report (CSR). The planned analyses identified in this SAP may be included in regulatory submissions, medical presentations, and manuscripts. Exploratory analyses, not identified in this SAP, may be performed to support the clinical development program. Any post-hoc or unplanned analyses that are performed, but not identified in this SAP, will be clearly identified in the final report of the results. The structure and content of this SAP are designed to meet the requirements identified by the FDA and the International Conference on Harmonization (ICH) Guidance on Statistical Principles for Clinical Trials.

4. STUDY OBJECTIVES AND ENDPOINTS

4.1. Study Objectives

The objective of this first-in-human study is to assess the feasibility and preliminary safety of the Endogenex device for endoscopic duodenal cellular regeneration in individuals with type 2 diabetes inadequately controlled on glucose-lowering medications.

The study will also assess, treatment efficacy, evaluated by changes in glycemic control and liver enzymes following the study index procedure.

The primary objective of the study is to assess the safety of the Endogenex device.

The 3 secondary objectives, in order of presentation are as follows:

- To assess the technical feasibility of the Endogenex device for duodenal cellular regeneration
- To assess changes in glycemic control following the procedure
- To assess changes in liver enzymes following the procedure

(Ref. Section 3.0 of the study protocol)

4.2. Endpoints

There is a single primary endpoint predicated on safety and 18 secondary endpoints. The primary safety endpoint is the proportion of patients experiencing device-related or procedure-related serious adverse events within 12 weeks of the procedure.

For a complete presentation of safety, a tabulation of all adverse events over the course of the clinical investigation will be presented. Adverse events will be summarized as follows:

- All adverse events
- All procedure-related adverse events
- All device-related adverse events
- All serious adverse events
- All serious procedure-related adverse events
- All serious device-related adverse events
- All Unanticipated Adverse Device Effects (UADE)
- All Unanticipated Serious Adverse Device Effects (USADE)

The following elements (variable – label) will be presented in the supportive data listing (Ref. Case Report Form)

AESEV - Severity

- Mild
- Moderate

- Severe

AEOUT - Outcome
- Ongoing
- Resolved
- Resolved with sequalae
- Stabilized
- Death
- Unknown

AEDREL - Relationship to Device
- Definitely related
- Possibly related
- Unlikely related

Not Related

AEPREL - Relationship to Procedure
- Definitely related
- Possibly related
- Unlikely related
- Not Related

AESER - Is this event a Serious Adverse Event?
- Yes
- No

AESDTH - Led to death?
- Yes
- No

AESHOSP - Resulted in hospitalization (hospital stay >24 hours) or prolongation of an existing hospitalization?
- Yes
- No

AESLIFE - Led to life threatening illness or injury?
- Yes
- No

AESMIE - Required intervention to prevent life-threatening illness or injury or permanent impairment of a body structure or body function?
- Yes
- No

AESDISAB - Resulted in permanent impairment of a body structure or body function?
- Yes

- No

AESCONG - Led to fetal distress, fetal death or a congenital abnormality or birth defect?
- Yes
- No

AEUADE - Is this event considered by the investigator to be an UADE/USADE?
- Yes
- No

4.2.1. Secondary Endpoints

First Secondary Endpoint: Procedure success: defined as successful treatment of at least 6 cm of duodenum segment.

Second Secondary Endpoint: Procedure time: defined as the time between the Endogenex catheter insertion and the catheter removal.

Third Secondary Endpoint: Change from baseline (post-baseline minus baseline) in HbA1c reported for each pre-specified study visit.

Note: The estimates will be derived using a mixed model repeated measure procedure; the 24 week result will be the principal time point of interest.

Fourth Secondary Endpoint: Change from baseline (post-baseline minus baseline) in Fasting plasma glucose (FPG) reported for each pre-specified study visit.

Note: The estimates will be derived using a mixed model repeated measure procedure; the 24 week result will be the principal time point of interest.

Fifth Secondary Endpoint: Change from baseline (post-baseline minus baseline) in Insulin-resistance by HOMA-IR reported for each pre-specified study visit.

Note: The estimates will be derived using a mixed model repeated measure procedure; the 24 week result will be the principal time point of interest.

Sixth Secondary Endpoint Part 6a: Change from baseline (post-baseline minus baseline) in Post-prandial plasma glucose (PPG) based on mixed meal tolerance test (MMTT) reported for each pre-specified study visit.

Note: The estimates will be derived using a mixed model repeated measure procedure; the 12 week result will be the principal time point of interest.

Sixth Secondary Endpoint Part 6b: Change from baseline (post-baseline minus baseline) in beta cell function based on mixed meal tolerance test (MMTT) reported for each pre-specified study visit.

Note: The estimates will be derived using a mixed model repeated measure procedure; the 12 week result will be the principal time point of interest.

Sixth Secondary Endpoint Part 6c: Change from baseline (post-baseline minus baseline) in the disposition index based on mixed meal tolerance test (MMTT) reported for each pre-specified study visit.

Note: The estimates will be derived using a mixed model repeated measure procedure; the 12 week result will be the principal time point of interest.

Seventh Secondary Endpoint: o Time in range, glucose variability by continuous glucose monitoring (CGM)

Eighth Secondary Endpoint: Proportion of treated patients with an HbA1c improvement of ≥0.5% points from baseline at 24 weeks (24 week value minus the baseline value).

Ninth Secondary Endpoint: Proportion of treated participants with an HbA1c improvement of ≥0.5 points or more at 24 weeks from baseline and maintained at 48 weeks.

Note: Proportion of treated patients who achieve a HbA1c improvement of ≥0.3% or more at 24 weeks from baseline and maintained at 48 weeks. Patients who fail to maintain HbA1c improvement ≥0.5% at 48 weeks, for any reason, will be counted as not having achieved this endpoint. Patients who fail to achieve a HbA1c ≥0.5% improvement at 24 weeks will be excluded from the tabulation.

Tenth Secondary Endpoint: Change in weight from baseline (post-baseline minus baseline) by visit. Weight change will be reported in both kilograms and %TBWL.

Eleventh Secondary Endpoint: Change in glucose-lowering medication usage.

Twelfth Secondary Endpoint: Change in liver enzyme from baseline at 24 weeks (post-baseline minus baseline) for Alanine Aminotransferase (ALT).

Thirteenth Secondary Endpoint: Change in liver enzyme from baseline at 24 weeks (post-baseline minus baseline) for Aspartate Aminotransferase (AST).

Fourteenth Secondary Endpoint: Change from baseline in blood pressure by visit (systolic and diastolic run separately).

Fifteenth Secondary Endpoint: Change in lipid profile from baseline by visit: total cholesterol

Sixteenth Secondary Endpoint: Change in lipid profile from baseline by visit: triglycerides

Seventeenth Secondary Endpoint: Change in lipid profile from baseline by visit: HDL

Eighteenth Secondary Endpoint: Change in lipid profile from baseline by visit: LDL

4.2.2. Exploratory Endpoints

There are no exploratory endpoints.

5. STUDY OVERVIEW

5.1. Study Design and Description of the Study Device

This is a multicenter, open-label, treatment-only study conducted in the United States. A total of 20 participants is planned for the study. The study will test two treatment parameters. The first 10 participants will be treated at a generator setting of 600 Volts/13 bursts/350 KHz (600V) and the second group of 10 participants at 750 Volts/8 bursts/350KHz (750V). In the 600V group, the first 5 participants will be enrolled/treated with the investigational device sequentially with at least 14 days observation time between each procedure. In the 750V group, the first participants will be enrolled/treated with the investigational device sequentially with at least 6 days observation time between each procedure.

Participants with T2D inadequately controlled on 2-3 non-insulin glucose-lowering medication(s) will be screened for study eligibility. Eligible participants who consent to participate in the study will maintain his/her background glucose-lowering medication(s) stable (no medication or dose change) for at least 12 weeks prior to baseline visit.

The index procedure will be performed under general anesthesia or deep sedation and within 21 days from the baseline visit. Participants will undergo endoscopic screening immediately prior to the DMR procedure, and eligible participants will undergo the DMR procedure. Participants may be discharged per local hospital's guideline; an overnight stay is not required but allowed per local policy and investigator's clinical judgement. A participant is enrolled in the study when the Endogenex catheter insertion is attempted. Participants excluded during endoscopic screening will be considered a screen failure and will be followed for four weeks after the procedure for safety.

Post index procedure, participants will be on a transitional diet consisting of clear liquids for 24 hours followed by a full liquid diet for 3 days, pureed food for 3 days, and soft food for one week, and then return to normal food as tolerated.

Background medication will be titrated to the pre-procedure dose and maintained for 24 weeks post index procedure and the transitional diet period per Section 6.2. After the 24-week follow-up visit, participants will be managed according to the current (2021) guidelines of the American Diabetes Association2 and their glucose-lowering medications will be optimized to achieve individualized A1c goals, which for most individuals is a target of less than 7.0%.

Participants will receive lifestyle-modification counseling sessions at scheduled intervals to promote adherence to a diet and lifestyle suitable for individuals with diabetes. Counseling will be provided by a member of the research team (endocrinologist, dietitian, nurse, etc.) trained in the delivery of lifestyle counseling for diabetes.

Participants will be followed up for 48 weeks after the index procedure. The primary endpoint will be evaluated at 12 weeks post procedure.

5.2. Schedule of Assessments

Reference Appendix 2. Schedule of Activities in the study protocol for the complete schedule of assessments.

5.3. Sample Size Justification

The study plans to enroll 20 participants and test two treatment parameters (600 volts and 750 volts), with 10 participants treated in each group. As this study is intended to characterize device safety and feasibility outcomes, formal sample size and power calculations based on hypothesis testing against a priori statistical objectives are not relevant; a sample size of 10 in each group and 20 in total is considered to be sufficient for the objectives of this investigation.

5.4. Estimated Duration of Patient Participation

Total duration on study will be calculated as the difference between the date of informed consent and the last on-study observation. All calculations defining the duration on study will be performed relative to the date of informed consent and follow the algorithm DURATION = ([STUDY COMPLETION OR WITHDRAW DATE – INFORMED CONSENT DATE])+1.

The first participant enrolled was in Q4, 2021; the estimated enrollment duration is 18 months.

6. ANALYSIS POPULATIONS

Patients will be considered enrolled in the study once the patient has passed endoscopic screening. Screen failures are defined as patient who consented to participate in the clinical study and started the screening tests specified by the protocol but are not subsequently enrolled in the study.

The primary and secondary safety analyses will be performed using the ITT. The primary effectiveness analyses will be performed using the FAS population. The Per-Protocol population and Completed-Cases population will be used for the sensitivity analyses of the primary and secondary effectiveness endpoints.

Intent-to-Treat: The Intent-to-Treat population includes all enrolled patients, regardless of the patient having received the target treatment (at least 6cm of duodenum treated). The point of enrollment occurs when a patient has provided written informed consent and an energy delivery has been attempted during the index procedure.

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Completed Cases: The Completed Cases population is a subset of the Per-Protocol population and includes all patients who received the target treatment, do not have any major eligibility violations, and maintained stable glucose-lowering medications for 24 weeks post-procedure, and completed the final Week 48 End of Study Visit.

7. GENERAL CONSIDERATIONS

Post-text Tables and Listings will be prepared in accordance with the current ICH Guidelines. The header of each Table and Listing will include the sponsor's name and the study number. The information and explanatory notes to be provided in the "footer" or bottom of each Table and Listing will include the following information:

1. Date and time of output generation.
2. SAS® program name, including the path that generates the output.
3. Any other output specific details that require further elaboration.

In general, tables will be formatted with a column displaying findings for all patients combined. Row entries in tables are made only if data exist for at least one (1) patient (*i.e.*, a row with all zeros will not appear). The only exception to this rule applies to tables that list the termination status of patients (*e.g.*, reasons for not completing the study). In this case, zeros will appear for study termination reasons that no patient satisfied. The summary tables clearly indicate the number of patients to which the data apply, and unknown or not performed are distinguished from missing data. Tables, Listings, and Figures will provide the units of measurement, unless there are no units. Results recorded at single times during the study will be presented using the *Level 1* displays for the ITT Population; the example structure is presented below.

Level 1a Display

Parameter and Statistic	Device Generation 1 / 600 Volts / Single Treatment	Device Generation 1 / 600 Volts / Double Treatment	Device Generation 2 / 750 Volts / Double Treatment	All Patients
Age				
Sex				

Level 1b Display

Parameter and Statistic	Device Generation 1 / 600 Volts / Single Treatment	Device Generation 1 / 600 Volts / Double Treatment and Device Generation 2 / 750 Volts / Double Treatment	All Patients
Age			
Sex			

The *Level 2* displays will be used for summarizing the incidence of AEs. An example of the layout for AEs by severity is presented below.

Level 2a Display

System Organ Class Preferred Term	Device Generation 1 / 600 Volts / Single Treatment	Device Generation 1 / 600 Volts / Double Treatment	Device Generation 2 / 750 Volts / Double Treatment	All Patients
SOC				
PT				

Level 2b Display

System Organ Class Preferred Term	Device Generation 1 / 600 Volts / Single Treatment	Device Generation 1 / 600 Volts / Double Treatment and Device Generation 2 / 750 Volts / Double Treatment	All Patients
SOC			
PT			

The *Level 3* display will be used for summarizing the parameters recorded multiple times during the follow-up visits. An example of the layout is presented below; rows will be repeated for all visits where a measurement is recorded using the expanded time windows.

Level 3a Display

Parameter and Statistic	Observation Time	Device Generation 1 / 600 Volts / Single Treatment	Device Generation 1 / 600 Volts / Double Treatment	Device Generation 2 / 750 Volts / Double Treatment	All Patients
HbA1c	Baseline				
HbA1c	Post-Procedure Visit xxx				
HbA1c	Change from Baseline				

Level 3b Display

Parameter and Statistic	Observation Time	Device Generation 1 / 600 Volts / Single Treatment	Device Generation 1 / 600 Volts / Double Treatment and Device Generation 2 / 750 Volts / Double Treatment	All Patients
HbA1c	Baseline			
HbA1c	Post-Procedure Visit xxx			
HbA1c	Change from Baseline			

There will be 2 sets of comparative analyses prepared, each predicated on different combinations of device generation, voltage, and single vs. double treatment. The planned comparisons are outlined below.

Comparison Set 1
Device Generation 1 / 600 Volts / Single Treatment vs.
Device Generation 1 / 600 Volts / Double Treatment vs.
Device Generation 2 / 750 Volts / Double Treatment

Comparison Set 2
Device Generation 1 / 600 Volts / Single Treatment vs.
Device Generation 1 / 600 Volts / Double Treatment plus Device Generation 2 / 750 Volts / Double Treatment

Supportive individual patient data Listings will be sorted and presented by site number, patient number and visit date, if applicable. Listings will also include the number of days relative to the DMR index procedure. Specific algorithms are discussed for imputing missing or partially missing data, if deemed appropriate, under specific data topics. Imputed or derived data will be flagged in the individual patient data Listings. Imputed data, restricted to dates, will not be incorporated into any raw or primary datasets from the electronic capture system. The imputed data will be retained in the derived / analysis datasets.

Summary statistics will consist of the number and percentage of responses or counts at each level for categorical variables (e.g. race). For continuous variables, and the sample size (n), mean, median, standard deviation (SD), minimum, and maximum values will be presented.

All mean and median values will be formatted to one more decimal place than the measured value. Standard deviation values will be formatted to two more decimal places than the measured value. Minimum and maximum values will be presented with the same number of decimal places as the measured value.

The number and percentage of responses will be presented in the form XX (XX.X%).

- All summary tables will include the analysis population sample size (i.e., number of patients).

- Relative Study Day 1 is defined as the day the patient underwent the DMR study procedure. All study days are determined relative to the day the patient underwent the DMR study procedure.

- Baseline values will be defined as those values recorded immediately prior to the DMR study procedure.

- Change from baseline for ratio data will be calculated as follows:
  Change = Post-Procedure value / baseline value.
- Change from baseline for differences will be calculated as follows:
  Change = Post- Procedure value - baseline value.
- Missing data may have an impact upon the interpretation of the trial data. However, given the feasibility nature of this study, coupled with the number of patients within a Comparison Set, multiple imputation will not be attempted. The primary presentation of the results will be based on the observed data. A methodology is defined in this section for addressing missing dates.

- Date variables will be formatted as DDMMMYYYY for presentation; SAS Date9. format.

- Months will be converted to days by dividing by 30.42 and rounding up to achieve an integer value.

- SAS® Version 9.4 will be the statistical software package used for all data analyses.

- All data from this study will be presented in a listing.

- Table and listing numbering will follow ICH guidelines for post-text table and listing numbering.

For Adverse Event reporting, which includes primary and secondary variables, the primary analysis will be based on Patient counts (e.g., the number and percentage of Patients with events among the total number of Patients). The data will be presented in the format of p% (x/N) [e], with p and x being the percentage and number of Patients with events, respectively, N being the sample size of the analysis population, and e being the total number of events occurred in the x Patients. Asymptotic confidence limits will be presented based on the normal approximation to the binomial distribution for differences in proportions. Exact confidence intervals will be used for all other presentations.

7.1. Multiple Comparison/Multiplicity

This is a feasibility study and the hypothesis testing that is being performed is strictly for informative purposes. There will not be any adjustment for multiplicity.

7.2. Adjustments for Covariates and Stratification Factors

Data will be presented by individual subgroups if there are a sufficient number of patients to warrant the breakdown. There are no planned stratification factors to be included in the models of the 5 different Comparison Sets.

7.3. Handling of Missing Data

7.3.1. Missing and Censored Data

All tabulations and analyses will be based on the observed data without imputation, with the exception of dates.

7.3.2. Subgroup Analyses: Assessing the Effect of Pre-Specified Factors on a Continuous Parameter

Based on the limited enrollment and sample size from the clinical investigation, the proposed tabulations for the individual subgroups may not be possible. Subgroup analyses will follow the follow approach where possible and if it is clinically indicated to address a specific research question.

The breakdown of safety and effectiveness will follow the FDA Guidance entitled *Evaluation and Reporting of Age-, Race-, and Ethnicity-Specific Data in Medical Device Clinical Studies* (Document issued on September 12, 2017). Specifically, the guidance provided in Section VI. entitled *Recommendations for Submitting Age-, Race-, and Ethnicity-Specific Data in Submissions to the Agency and Reporting in Public Documents*, Part A: Enrollment Demographics, Baseline Characteristics & Co-Morbidities.

Subgroup analyses by the following baseline characteristics will be provided if there are a sufficient number of patients that warrant this breakdown:

- age group (<65, ≥65 years)
- race
- sex
- ethnicity
- duration of diabetes (<median, ≥median)
- duration of diabetes (≤5, >5 to ≤10, >10 years)
- HbA1c (≤8.5%, >8.5%)
- renal impairment (eGFR <60, ≥60 mL/min/1.73m2), and
- BMI group (<30, ≥30 to <35, ≥35 kg/m2).

7.3.3. Safety Measures

Descriptive summaries for all safety measures will be based on observed data. No imputation of missing scores or observations will be implemented for safety outcomes.

7.3.4. Dates for Medical Events

The completely or partially missing onset and resolution dates of medical events including AEs will be imputed in a conservative fashion as follows:

Date	***Type of Missing Date***	***Handling of Missing Date***
Event onset date (e.g., YYYY-MM-DD)	Completely missing	No imputation will be applied.
	Only YYYY is available	Use the first day of YYYY to impute the missing month and date parts of the onset date
	YYYY and MM are available but DD is missing	Use the first day of MM to impute the missing date part of the onset date
Event resolution date (e.g., YYYY-MM-DD)	Completely missing	No imputation will be applied. The event will be considered ongoing (i.e., not resolved) at the Study Exit date.

8. PATIENT ACCOUNTING AND DISPOSITION

8.1. Patient Disposition

Information for this presentation of the recorded data will come from the **Study Exit** case report form and the ***Procedure*** form. A complete accounting of patient participation in the study by analysis population will be presented in Table 14.1.1a entitled *Patient Accounting* using the Level 1 table design. The purpose of this table is to provide an accounting of patients from their entrance into the study through the final visit and to account for the evaluations of patients in the analyses of efficacy and safety, including reasons for early study termination. The overall number of patients reported in this table will be based on the number of patients consented and the reasons for screen failure.

Each listing will contain separate flags to indicate if the patient is part of the ITT, FAS and Per-Protocol populations, respectively. Listing 16.1 entitled *Patient Disposition* supports Tables 14.1.1a through 14.1.1.2. This listing will be sorted by site number and patient number. Listing 16.2.1 entitled *Inclusion Criteria* displays the data from the Inclusion Criteria case report form. The data will be displayed for each patient and for each inclusion criterion. Listing 16.2.2 entitled *Exclusion Criteria* displays the data from the Exclusion Criteria case report form. The data will be displayed for each patient and for each exclusion criterion. Listing 16.3.1 entitled *Protocol Deviations* will list all protocol deviations for each patient, and identify if they are major. The deviation code and description, visit and action, will also be included in the listing. The list of what constitutes a major deviation will be finalized prior to database lock.

8.2. Patient Demographics Recorded at Baseline

Case Report Form Data Source: Demographics [Date of Birth, Sex, Child-bearing potential, Ethnicity, Race, age, Date of ICF] / Visit: Screening and Baseline

Data will be summarized and reported in Table 14.1.2 entitled *Summary of Patient Demographics* (ITT population) using the Level 1 table design; Table 14.1.2a will be restricted to the ITT population. This table summarizes the patient population with respect to age at entry into the study, sex, weight, height, and BMI. Age will be reported in years. Age, weight (lbs.), height (inches) and BMI will be summarized using descriptive statistics: n, arithmetic mean, standard deviation, median, and range (*i.e.*, minimum and maximum values). Age will also be presented in mutually-exclusive categories: >=65 to <65, years of age. Sex will be summarized using counts and percentages. Patients with missing data that cannot be resolved prior to database lock will not be included in the tabulation and excluded from the summary statistics; all demographic data will be presented in a listing. Sites that do not provide the full date of birth for a patient will not be considered missing data if the day of birth is not provided. Under this scenario, the first day of the month will be used in the calculations.

The supportive data for Tables 14.1.2 and 14.1.2a will be presented in Listing 16.4.1 entitled *Patient Demographics*. This listing will be sorted by site number and patient number and contain a separate flag to indicate if the patient is part of the FAS and Per-Protocol populations, respectively.

8.3. Medical History Recorded at Baseline

Information for this presentation of the recorded data will come from the **Medical History** case report form. Data will be summarized and reported in Table 14.1.3 entitled *Summary of Patient Medical History* (ITT population) using the Level 1 table design; Table 14.1.3a will be restricted to the FAS population. This table summarizes the patient population with respect to risk factors using counts and percentages. Patients with missing data that cannot be resolved prior to database lock will not be included in the tabulation and excluded from the summary statistics; all risk factor data will be presented in a listing.

The supportive data for Tables 14.1.3 and 14.1.3a will be presented in Listing 16.4.2 entitled *Medical History*. This listing will be sorted by Diabetes Site number, Endoscopy Site number and patient number and contain a separate flag to indicate if the patient is part of the FAS and PP populations, respectively.

8.4. Index Procedure and Hospital Admission Details

Information for this presentation of the recorded data will come from the Index **Procedure** case report form. Data will be summarized and reported in Table 14.1.4 entitled *Summary of the Index Procedure and Hospital Admission Details* (ITT population) using the Level 1 table design; Table 14.1.4a will be restricted to the FAS population.

The supportive data for Tables 14.1.4 and 14.1.4a will be presented in Listing 16.4.3 entitled *Index Procedure and Hospital Admission Details*. This listing will be sorted by site number and patient number and contain a separate flag to indicate if the patient is part of the FAS and PP populations, respectively.

8.5. Laboratory Tests

Information for this presentation of the recorded data will come from the **Laboratory Tests** case report form. Data will be summarized and reported in Table 14.1.5 entitled *Summary of the Laboratory Tests Recorded Prior to the Procedure* (ITT population) using the Level 1 table design; Table 14.1.5a will be restricted to the FAS population. The following laboratory values will be summarized based on the construct of the variable using the ITT population: continuous, multinomial, or binary.

Each laboratory parameter recorded on a continuous scale will be summarized using descriptive statistics: n, mean, standard deviation, median, minimum and maximum values. Patients with missing data that cannot be resolved prior to database lock will not be included in the tabulation and excluded from the summary statistics.

The supportive data for Tables 14.1.5 and 14.1.5a will be presented in Listing 16.4.4 entitled *Laboratory Tests*. This listing will be sorted by site number and patient number and contain a separate flag to indicate if the patient is part of the FAS and Per-Protocol populations, respectively. Unscheduled laboratory tests entered into the EDC system will also be contained within the listing.

8.6. Unscheduled Visit Information

Information for this presentation of the recorded data will come from the individual datasets where the visit name is listed as *Unscheduled*. Listing 16.4.9 entitled *Unscheduled Visit Information* will be sorted by site number, and patient.

The table below provides the specification for assignment of an unscheduled visit. If there are multiple records within an interval, date of the latest record will be used.

			Protocol Visit Window			Expanded Visit Window		
Visit Name	**Clinic (Visit) / (R)emote Visit**	**Timing of the Visit (weeks)**	**Protocol Visit Window (days)**	**First Interval Day**	**Last Interval Day**	**First Interval Day**	**Last Interval Day**	**Expanded Visit Window (days)**
Screening	R1	-12	-84 to -5	-84	-5			
Baseline[1]	V2	-3	-28 to -1	-28	-1			
Index Procedure	V3	0						
Week 1	R4	1	±2	5	9	5	9	2
Week 2	R5	2	±3	11	17	10	18	4
Week 4	V6	4	±5	23	33	19	37	9
Week 8	R7	8	±7	49	63	38	74	18
Week 12	R8	12	±7	77	91	73	95	11
Week 16	R9	16	±7	105	119	96	128	16
Week 20	R10	20	±7	133	147	129	151	11
Week 24	V11	24	±7	161	175	152	184	16
Week 28	R12	28	±7	189	203	185	207	11
Week 32	R13	32	±7	217	231	208	240	16
Week 36	V14	36	±7	245	259	241	263	11
Week 40	R15	40	±17	273	287	264	296	16
Week 44	R16	44	±7	301	315	295	321	13
Week 48 (End of Study)	V17	48	30	306	366	322	366	14

Visit Name	Clinic (Visit) / (R)emote Visit	Timing of the Visit (weeks)	Target Visit Day	Number of Days on Either Side of the Target Day to define the Expanded Time Window
Screening	R1	-12		
Baseline[1]	V2	-3		
Index Procedure	V3	0		
Week 1	R4	1	7	2
Week 2	R5	2	14	4
Week 4	V6	4	28	9
Week 8	R7	8	56	18
Week 12	R8	12	84	11
Week 16	R9	16	112	16
Week 20	R10	20	140	11
Week 24	V11	24	168	16
Week 28	R12	28	196	11
Week 32	R13	32	224	16
Week 36	V14	36	252	11
Week 40	R15	40	280	16
Week 44	R16	44	308	13
Week 48 (End of Study)	V17	48	336	14

8.7. Vital Signs Recorded Over the Course of the Study

Vital signs will include blood pressure and heart rate and be presented using the Level 3 table format. Data will be summarized and reported in Table 14.1.7 entitled *Summary of the Vital Sign Results* (ITT population) using the Level 3 table design; Table 14.1.7a will be restricted to the FAS population. Listing 16.4.10 entitled *Vital Sign Results* provides supportive data for Tables 14.1.7 and 14.1.7a and will be sorted by site number, and patient number.

9. ENDPOINTS ANALYSES

There is a single primary endpoint and 18 secondary endpoints. Based on the feasibility nature of this study, there are no formal hypothesis tests.

Primary Endpoint
The primary endpoint of the study is predicated on safety; the distribution of this endpoint is binary. The primary population for analysis of this endpoint will be the ITT population.

Proportion of patients experiencing one or more device- or procedure-related serious adverse events at 12 weeks post-procedure.

All device-related or procedure-related serious adverse events from the start of the study procedure through relative study day 84 will be used in the tabulation.

The secondary endpoints are listed below:

First Secondary Endpoint
The distribution of this endpoint is binary. The primary population for analysis of this endpoint will be the FAS population.

Procedure success: defined as successful treatment of at least 6 cm of duodenum segment.

Immediately following the study procedure, a determination will be made regarding treatment of ≥ 6 cm of the duodenum. Patients who fail to have ≥ 6 cm of the duodenum treated, for any reason, will be counted as not having achieved ***Procedure Success***.

Second Secondary Endpoint
The distribution of this endpoint is continuous. The primary population for analysis of this endpoint will be the FAS population.

Procedure time: defined as the time between the Endogenex catheter insertion and the catheter removal.

Procedure Time will be reported in minutes.

Third Secondary Endpoint
The distribution of this endpoint is continuous. The primary population for analysis of this endpoint will be the FAS population.

Change from baseline (post-baseline minus baseline) in HbA1c reported for each pre-specified study visit.

The pre-specified study visits where HbA1c is recorded is Week 4, 12, 24, 36, 48.

Fourth Secondary Endpoint
The distribution of this endpoint is continuous. The primary population for analysis of this endpoint will be the FAS population.

Change from baseline (post-baseline minus baseline) in Fasting plasma glucose (FPG) reported for each pre-specified study visit.

The pre-specified study visits where FPG is recorded is Week 4, 12, 24, 36, 48.

Fifth Secondary Endpoint
The distribution of this endpoint is continuous. The primary population for analysis of this endpoint will be the FAS population.

Change from baseline (post-baseline minus baseline) in Insulin-resistance by HOMA-IR reported for each pre-specified study visit.

The pre-specified study visits where HOMA-IR is recorded is Week 4, 12, 24, 36, 48.

Sixth Secondary Endpoint 6a
The distribution of this endpoint is continuous. The primary population for analysis of this endpoint will be the FAS population. The estimates will be derived using a mixed model repeated measure procedure; the 12 week result will be the principal time point of interest.

Change from baseline in glycemic parameters [Post prandial plasma glucose (PPG) by mixed meal tolerance test (MMTT)] post index procedure, by visit

Sixth Secondary Endpoint 6b
The distribution of this endpoint is continuous. The primary population for analysis of this endpoint will be the FAS population. The estimates will be derived using a mixed model repeated measure procedure; the 12 week result will be the principal time point of interest.

Change from baseline in glycemic parameters [Beta cell function by mixed meal tolerance test (MMTT)] post index procedure, by visit

Sixth Secondary Endpoint 6c
The distribution of this endpoint is continuous. The primary population for analysis of this endpoint will be the FAS population. The estimates will be derived using a mixed model repeated measure procedure; the 12 week result will be the principal time point of interest.

Change from baseline in glycemic parameters [Disposition Index (DI) by mixed meal tolerance test (MMTT)] post index procedure, by visit

The pre-specified study visits where PPG is recorded is Week 4, 12, 24, 36, 48.

Seventh Secondary Endpoint
The distribution of this endpoint is continuous. The primary population for analysis of this endpoint will be the FAS population. The estimates will be derived using a mixed model repeated measure procedure; the 12 week result will be the principal time point of interest.

Time in range, glucose variability by continuous glucose monitoring (CGM)

Eighth Secondary Endpoint
The distribution of this endpoint is binary. The analysis will be based on the proportion of patients that meet the endpoint at 24 weeks post-procedure. The primary population for analysis of this endpoint will be the FAS population.

Proportion of treated patients with an HbA1c improvement of ≥0.5% from baseline at 24 weeks (24 week score minus baseline score). Patients who fail to have HbA1c improvement of ≥0.5 points from baseline, for any reason, will be counted as not having achieved this endpoint.

Ninth Secondary Endpoint
The distribution of this endpoint is binary. Proportion of treated patients who achieve a HbA1c improvement of ≥0.5% or more at 24 weeks from baseline and maintained at 48 weeks. Patients who fail to maintain HbA1c improvement ≥0.3% at 48 weeks, for any reason, will be counted as not having achieved this endpoint. Patients who fail to achieve a HbA1c ≥0.5% at 24 weeks will be excluded from the tabulation. The primary population for analysis of this endpoint will be the FAS population.

Proportion of treated patients with an HbA1c improvement ≥0.5% from baseline at 24 weeks maintained at 48 weeks.

Tenth Secondary Endpoint: The distribution of this endpoint is continuous. The primary population for analysis of this endpoint will be the FAS population. Change in weight from baseline (post-baseline minus baseline) by visit. Weight change will be reported in both kilograms and %TBWL.

Eleventh Secondary Endpoint: Change in glucose-lowering medication usage.

Twelfth Secondary Endpoint: The distribution of this endpoint is continuous. The primary population for analysis of this endpoint will be the FAS population. Change in liver enzyme from baseline at 24 weeks (post-baseline minus baseline) for Alanine Aminotransferase (ALT).

Thirteenth Secondary Endpoint: The distribution of this endpoint is continuous. The primary population for analysis of this endpoint will be the FAS population. Change in liver enzyme from baseline at 24 weeks (post-baseline minus baseline) for Aspartate Aminotransferase (AST).

Fourteenth Secondary Endpoint: The distribution of this endpoint is continuous. The primary population for analysis of this endpoint will be the FAS population. Change from baseline in blood pressure by visit (systolic and diastolic run separately).

Fifteenth Secondary Endpoint: The distribution of this endpoint is continuous. The primary population for analysis of this endpoint will be the FAS population. Change in lipid profile from baseline by visit: total cholesterol

Sixteenth Secondary Endpoint: The distribution of this endpoint is continuous. The primary population for analysis of this endpoint will be the FAS population. Change in lipid profile from baseline by visit: triglycerides

Seventeenth Secondary Endpoint: The distribution of this endpoint is continuous. The primary population for analysis of this endpoint will be the FAS population. Change in lipid profile from baseline by visit: HDL

Eighteenth Secondary Endpoint: The distribution of this endpoint is continuous. The primary population for analysis of this endpoint will be the FAS population. Change in lipid profile from baseline by visit: LDL

9.1. Analysis of the Primary Safety Endpoint

Each table number and population will clearly state; results will be presented using the Table 1a design. Results will be tabulated based on the number of patients experiencing one or more device-related or procedure-related serious adverse events at 12 weeks post-procedure.

The statement of the primary research question that will be addressed is as follows:

What percentage of the patients in the ITT population experienced one or more device-related or procedure-related serious adverse events within 12 weeks (84 days) of the index study procedure?

The statement of the secondary research question is specific below:

Is there a difference in the percentage of patients in the ITT population who experienced one or more device-related or procedure-related serious adverse events within 12 weeks (84 days) of the index study procedure based on the generation of the device, voltage, and single vs. double treatment?

The following model will be used to compare the groups identified within each Comparison Set. The dependent variable is the classification of each patient relative to experiencing a device-related or procedure-related serious adverse events at within 12 weeks (84 days) of the index study procedure [variable: DRPRSAE]. Contrast statements will be used to derive the estimates for each pair-wise comparison of a group.

```
PROC GLIMMIX DATA=COMP_SET_1 ;
        CLASS COMP_SET_1_GROUP;
        MODEL DRPRSAE = COMP_SET_1_GROUP / DIST=BINARY LINK=LOGIT
SOLUTION;
        RANDOM INTERCEPT / SUBJECT=SUBJID_N ;
        LSMEANS TRTAN / DIFF CL;
RUN;
```

Sensitivity analyses will be performed using the FAS and PP populations. Results will be presented in the analysis table 14.4.1 entitled *Summary of the Device-Related or Procedure-Related Serious Adverse Events Within 12 weeks (84 days) of the index study procedure (ITT Population)* and table 14.4.1.1 entitled *Summary of the Device-Related or Procedure-Related Serious Adverse Events Within 12 weeks (84 days) of the index study procedure (FAS Population)* and table 14.4.1.2 entitled *Summary of the Device-Related or Procedure-Related Serious Adverse Events Within 12 weeks (84 days) of the index study procedure (PP Population).* Listing 16.4.11 entitled *Adverse Events* provides supportive data for Tables 14.4.1, 14.4.1.1, and 14.4.1.2 will be sorted by site number and patient number.

9.2. Analysis of the Secondary Effectiveness Endpoints

Endpoints have been classified relative to their distribution (binary, multinomial, or continuous), and the number of times the variable was recorded.

Binary Variable Assessed at a Single Time Point (3 endpoints):

- **Secondary Endpoint:** Procedure success: defined as successful treatment of at least 6 cm of duodenum segment.
- **Secondary Endpoint:** Proportion of treated patients with an HbA1c improvement of ≥0.5% from baseline at 24 weeks (24 week score minus baseline score).
- **Secondary Endpoint:** Proportion of treated patients with an HbA1c improvement of ≥0.5% from baseline at 24 weeks maintained at 48 weeks.

For each set of results for each Comparison Set, the following 2 research questions will be addressed. Results will be presented using the Level 1 tables b through e.

For the endpoints measured on a binary scale, what are the overall estimates in the FAS population.

For the endpoints measured on a binary scale, is there a difference in the estimates in the FAS population based on the generation of the device, voltage, and single vs. double treatment?

Multinomial Variable Assessed at a Single Time Point (1 endpoint):

- **Secondary Endpoint:** Proportion of patients that have a change in glucose-lowering medication usage from baseline.

For each set of results for each Comparison Set, the following 2 research questions will be addressed. Results will be presented using the Level 1 tables b through e.

For this endpoint measured on a multinomial scale, what are the overall estimates in the FAS population.

For this endpoint measured on a multinomial scale, is there a difference in the estimates in the FAS population based on the generation of the device, voltage, and single vs. double treatment?

Continuous Variable Assessed at a Single Time Point (3 endpoints):

- **Secondary Endpoint:** Procedure time: defined as the time between the Endogenex catheter insertion and the catheter removal.
- **Secondary Endpoint:** Change in liver enzyme from baseline at 24 weeks [Alanine Aminotransferase (ALT)].
- **Secondary Endpoint:** Change in liver enzyme from baseline at 24 weeks [Aspartate Aminotransferase (AST)].

For each set of results for each Comparison Set, the following 2 research questions will be addressed. Results will be presented using the Level 1 tables b through e.

For each endpoint measured on a continuous scale, what are the overall estimates in the FAS population.

For each endpoint measured on a continuous scale, is there a difference in the estimates in the FAS population based on the generation of the device, voltage, and single vs. double treatment?

Continuous Variable Assessed at Multiple Time Points (11 endpoints):

- **Secondary Endpoint:** Change from baseline (post-baseline minus baseline) in HbA1c reported for each pre-specified study visit.
- **Secondary Endpoint:** Change from baseline (post-baseline minus baseline) in Fasting plasma glucose (FPG) reported for each pre-specified study visit.
- **Secondary Endpoint:** Change from baseline (post-baseline minus baseline) in Insulin-resistance by HOMA-IR reported for each pre-specified study visit.
- **Secondary Endpoint 6a:** Change from baseline (post-baseline minus baseline) in Post-prandial plasma glucose (PPG) reported for each pre-specified study visit.
- **Secondary Endpoint 6b:** Change from baseline (post-baseline minus baseline) in beta cell function reported for each pre-specified study visit.
- **Secondary Endpoint 6c:** Change from baseline (post-baseline minus baseline) in disposition index reported for each pre-specified study visit.
- **Secondary Endpoint:** Change from baseline in blood pressure by visit.
- **Secondary Endpoint:** Change in lipid profile from baseline by visit: total cholesterol
- **Secondary Endpoint:** Change in lipid profile from baseline by visit: triglycerides

- **Secondary Endpoint:** Change in lipid profile from baseline by visit: HDL
- **Secondary Endpoint:** Change in lipid profile from baseline by visit: LDL
- **Secondary Endpoint:** Change in weight from baseline (post-baseline minus baseline) by visit. Weight will be evaluated based on the intra-patient percent change from baseline. (% TBWL: % Total Body Weight Loss)
- **Secondary Endpoint:** Time in Range (TIR) based on Continuous Glucose Monitoring (CGM) by visit

For each set of results for each Comparison Set, the following 2 research questions will be addressed. Results will be presented using the Level 3 tables b through e.

For each endpoints measured on a continuous scale, what are the overall estimates in the FAS population assessed over time.

For each endpoint measured on a continuous scale, is there a difference in the estimates in the FAS population based on the generation of the device, voltage, and single vs. double treatment assessed over time?

The list of the top-line tables to be generated are presented below:
Table 14.4.1 entitled *Overall Summary of Procedure Success and Procedure Time (FAS Population)*

Table 14.4.2 entitled *Overall Summary of HbA1C, Fasting plasma glucose (FPG), Insulin-resistance by HOMA-IR, and Post-prandial plasma glucose (PPG) by Visit (FAS Population)*

Table 14.4.3 entitled *Overall Summary of Beta Cell Function by Visit (FAS Population)*

Table 14.4.4 entitled *Overall Summary of HbA1c improvement ≥0.3 points by Visit (FAS Population)*

Table 14.4.5 entitled *Overall Summary of Percent Change in Body Weight by Visit (FAS Population)*

Table 14.4.6 entitled *Overall Summary of Glucose-Lowering Medications by Visit (FAS Population)*

Table 14.4.7 entitled *Overall Summary of Liver Enzymes and Lipids by Visit (FAS Population)*

Table 14.4.8 entitled *Overall Summary of Blood Pressure Measurements by Visit (FAS Population)*

Table 14.4.9 entitled *Overall Summary of Continuous Glucose Monitoring (CGM) by Visit (FAS Population)*

10. SAFETY

The following sections describe how the safety results will be analyzed and reported. The safety analyses will be conducted using the ITT population, defined as all patients in whom the endoscopic screening procedure was initiated. In addition to the reporting of adverse events, Safety will include an examination of hypoglycemia, pancreatic enzymes, and endoscopic follow-up.

10.1. Adverse Events

10.1.1. Definition of Adverse Event

An Adverse Event (AE) is defined as any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in patients, users or other persons, whether or not related to the investigational medical device. (ISO 14155:2011 3.2)

The following information regarding each AE will be obtained: date and time of onset and resolution (duration), severity, whether it was serious, any required treatment or action taken, outcome, relationship to the investigational device, relationship to the procedure, and whether the AE caused withdrawal from the study. Hypoglycemic events, as defined in the protocol, will be summarized and compared between the 2 randomized treatment groups.

10.1.2. Handling of Missing or Partial Adverse Event Dates

Handling of Missing AE Start-dates (missing AE stop-dates are not filled)

Rules for assuming a full date for AEs with incomplete or missing start-dates are addressed below. In the unusual case that the month portion of an AE start-date is missing but the day portion is not missing, the day portion of the AE will be assumed to be missing. Likewise in the case where the year portion of an AE start-date is missing but the month and/or day portion is not missing, the month and/or day portion of the AE will be assumed to be missing. All missing portion(s) of the AE start-dates will be handled using the same rules.

- In the event that the day portion (and only the day portion) of the AE onset date is missing:
    - If the AE started in the same month and year as the study procedure, the AE onset date will be assumed to be the date of the study procedure (*i.e.*, Study Day 1);
    - Otherwise, the AE onset date will be assumed to be the 15th day of the given month and year, *e.g.*, XX–DEC-2005 → 15-DEC-2005 where XX represents an unknown value.
- In the event that the day and month portion (and only the day and month portion) of the AE onset date are missing:
    - If the AE started in the same year as the study procedure, the AE onset date will be assumed the study procedure (*i.e.*, Study Day 1);
    - Otherwise, the AE onset date will be treated as June 15th of the given year, *e.g.*, XX-XXX-2005 → 15-JUN-2005.

- In the event that the day, month, and year portion of the AE onset date are missing, the start-date of the AE will be assumed to be the study procedure (*i.e.*, Study Day 1).

Special Cases on Missing AE Start-dates

- If the assumed AE onset date using the above rules for handling of missing AE dates
    - is earlier than the screening date, the assumed AE onset date will be reset and assumed to be the screening date.
    - is later than the reported AE stop-date, the assumed AE onset date will be reset and assumed to be the AE stop-date.
    - is later than the database lock date and AE stop-date missing, the AE will be assumed to be a follow-up AE and not treatment-emergent.

Several Examples of Handling Missing AE Start-dates

Assume that the study procedure for a patient is 04-FEB-2005 and the Screening Date is 18-JUL-2004

- Example: The day portion (and only the day portion) of the AE onset date is missing:
    - If the AE onset date is XX-DEC-2004 then the assumed AE onset date is 15-DEC-2004.
    - If the AE onset date is XX-FEB-2005 then the assumed AE onset date is 04-FEB-2005, as the AE started in the same month and year as the study procedure.
- Example: The day and month portion (and only the day and month portion) of the AE onset date are missing
    - If the AE onset date is XX-XXX-2004:
        - then the assumed AE onset date is 15-JUN-2004 using the rules;
        - but this is a special case since the assumed date 15-JUN-2004 is before the patient's screening date 18-JUL-2004. Therefore, the assumed AE onset date will be reset and assumed to be 18-JUL-2004.
    - If the AE onset date is XX-XXX-2005 then the assumed AE onset date is 04-FEB-2005, as the AE started in the same year as the study procedure.
- Example: The day, month, and year portion of the AE onset date are missing (*i.e.*, if the AE onset date is XX-XXX-XXXX), then the assumed AE onset date is 04-FEB-2005).

10.1.3. Summaries of Adverse Events

All summaries of adverse events will be based on events that occurred during the study and reported for the ITT population. Adverse events will be mapped to preferred terms and body systems using the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary. The number and percentage of patients experiencing 1 or more adverse events will be presented by preferred term using counts, percentages, and 2-sided 95% exact binomial confidence intervals. The relationship of the adverse event relative to the *device* and *procedure* will be presented

separately. The number and percentage of patients experiencing 1 or more events will be presented by the event description using counts, percentages, and 2-sided 95% exact binomial confidence intervals.

Table 14.3.2 entitled *Overall Summary of Adverse Events (ITT Population)* contains the primary presentation of the adverse event data, independent of the type of event. This table is prepared without regard to causality or relationship to the study procedure or device. Patients will be counted only once for each event type; multiple occurrences of the same event type for a patient will only be counted once. Event types will be displayed alphabetically. The overall incidence of adverse events will be summarized using counts, percentages, and 2-sided 95% exact binomial confidence intervals.

Table 14.3.3 entitled *Summary of Adverse Events by Event Type (ITT Population)* contains the primary presentation of the adverse event data. This table is prepared without regard to causality or relationship to the study procedure or device. Patients will be counted only once for each event type; multiple occurrences of the same event type for a patient will only be counted once. Event types will be displayed alphabetically. The overall incidence of adverse events will be summarized using counts, percentages, and 2-sided 95% exact binomial confidence intervals.

Table 14.3.4 entitled *Summary of Post-Procedural Adverse Events by Event Type and Relationship to the Study Device (ITT Population)* provides the presentation of adverse events by relationship to study device. This table will have the same structure as that of Table 14.3.2, however, only those adverse events that were determined to be related to study device will be displayed. Patients with multiple occurrences of the same event will be summarized using the strongest relationship to study device. The number and percentage of patients experiencing each event type will be displayed.

Table 14.3.4a entitled *Summary of Post-Procedural Adverse Events by Event Type and Relationship to the Study Device by Device Generation, Voltage, and Single vs. Double Treatment (ITT Population)* provides the presentation of adverse events by relationship. This table will follow the Level 2a format for the IS population and Level 2b format for the population. Patients with multiple occurrences of the same event will be summarized using the strongest relationship to study device. The number and percentage of patients experiencing each event type will be displayed.

Table 14.3.5 entitled *Summary of Post-Procedural Adverse Events by Event Type and Relationship to the Study Procedure (ITT Population)* provides the presentation of adverse events related to the study procedure. This table will have the same structure as that of Table 14.3.2, however, only those adverse events that were determined to be related to the study procedure will be displayed. Patients with multiple occurrences of the same event will be summarized using the strongest relationship to study procedure. The number and percentage of patients experiencing each event type will be displayed.

Table 14.3.5a entitled *Summary of Post-Procedural Adverse Events by Event Type and Relationship to the Study Procedure by Device Generation, Voltage, and Single vs. Double Treatment (ITT Population)* provides the presentation of adverse events by relationship. This table

will follow the Level 2a format for the IS population and Level 2b format for the population. Patients with multiple occurrences of the same event will be summarized using the strongest relationship to study device. The number and percentage of patients experiencing each event type will be displayed.

Table 14.3.5.1 entitled *Summary of Post-Procedural Adverse Events by Event Type and Relationship to the Study Device or Procedure (ITT Population)* provides the presentation of adverse events related to the study device or the study procedure. This table will have the same structure as that of Table 14.3.2, however, only those adverse events that were determined to be related to the study device or procedure will be displayed. Patients with multiple occurrences of the same event will be summarized using the strongest relationship to study device or procedure. The number and percentage of patients experiencing each event type will be displayed.

Table 14.3.5.1a entitled *Summary of Post-Procedural Adverse Events by Event Type and Relationship to the Study Device or Study Procedure by Device Generation, Voltage, and Single vs. Double Treatment (ITT Population)* provides the presentation of adverse events by relationship. This table will follow the Level 2a format for the IS population and Level 2b format for the population. Patients with multiple occurrences of the same event will be summarized using the strongest relationship to study device. The number and percentage of patients experiencing each event type will be displayed.

Table 14.3.6 entitled *Summary of Adverse Events Leading to Study Discontinuation (ITT Population)* displays all adverse events resulting in the completion status defined as premature discontinuation due to an adverse event. This table will have the same structure as Table 14.3.6, however, only those adverse events that led to discontinuation will be displayed. Patients will be counted only once by event type; multiple occurrences of the same event for a patient will be counted only once. The number and percentage of patients experiencing each type of event leading to premature discontinuation will be displayed.

Listing 16.7.2 entitled *Adverse Events* provides supportive data for Tables 14.3.1 through 14.3.6 and is sorted by site number and patient number. Listing 16.7.3 entitled *Serious Adverse Events* is a subset of 16.7.2 and contains just the serious events; this listing will be sorted by site number and patient number.

10.1.4. Summaries of Serious Adverse Events

The tables outline above will be repeated, restricted to just serious adverse events. All summaries of serious adverse events will be based on events that occurred during the study. Adverse events will be mapped to preferred terms and body systems using the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary. The number and percentage of patients experiencing 1 or more adverse events will be presented by preferred term using counts, percentages, and 2-sided 95% exact binomial confidence intervals. The relationship of the adverse event relative to the *device* and *procedure* will be presented separately. The number and percentage of patients experiencing 1 or more events will be presented by the event description using counts, percentages, and 2-sided 95% exact binomial confidence intervals.

Table 14.3.7 entitled *Overall Summary of Serious Adverse Events (ITT Population)*

Table 14.3.8 entitled *Summary of Serious Adverse Events by Event Type (ITT Population)*

Table 14.3.9 entitled *Summary of Post-Procedural Adjudicated Serious Adverse Events by Event Type and Relationship to the Study Device (ITT Population)*

Table 14.3.10 entitled *Summary of Post-Procedural Adjudicated Serious Adverse Events by Event Type and Relationship to the Study Procedure (ITT Population)*

Table 14.3.10.1 entitled *Summary of Post-Procedural Adjudicated Serious Adverse Events by Event Type and Relationship to the Study Device or Procedure (ITT Population)*

Table 14.3.11 entitled *Summary of Serious Adverse Events Leading to Study Discontinuation (ITT Population)*

11. PRE-PROCEDURE AND POST-PROCEDURE MEDICATIONS

Concomitant medications are to be collected and documented starting at enrollment and through the duration of the study.

Medications with missing start and stop dates, or having a start date prior to the start of study procedure and missing a stop date, will be counted as concomitant. Partial dates will be handled as follows:

- if the year of the study procedure is ≤ the year of start of concomitant medication AND if the month and day of start of concomitant medication are missing AND if the medication stop date is not prior to the date of the study procedure, then the medication is considered concomitant;
- if the year of the study procedure = the year of start of concomitant medication AND if the month of the study procedure is ≤ the month of start of concomitant medication AND if the day of start of concomitant medication is missing AND if the medication stop date is not prior to date of the study procedure, then the medication is considered concomitant.

A summary of the concomitant medications will be presented in Table 14.5.1 entitled *Summary of Concomitant Medications (ITT Population)*, containing a clear declaration regarding the start date of the medication relative to the study procedure. The concomitant medications taken by the ITT population will be displayed in Listing 16.8.1 entitled *Concomitant Medications*.

11.1. Deviations

Protocol Deviations will be displayed in Listing 16.3.1 entitled *Protocol Deviation,* supporting Table 14.1.1.3 entitled *Summary of Protocol Deviations.* This listing will be sorted by patient number and the type of deviation.

12. REFERENCES

SAS Institute Inc., SAS® Version 9.4 software, Cary, NC.