Safety and Feasibility of Endoscopic Application of a Novel Therapy for Duodenal Mucosal **Regen**eration in the **T**reatment of Type II Diabetes

(**REGENT-1-US Study**)

Protocol number**: 346**

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LIST OF ABBREVIATIONS

AACE	American Association of Clinical Endocrinologists
ADA	American Diabetes Association
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ANI	Alcoholic Liver disease/Nonalcoholic Fatty Liver Disease Index
AST	Aspartate Aminotransferase
BMI	Body Mass Index
BUN	Blood Urea Nitrogen
CRF	Case Report Form
COVID-19	Coronavirus Disease 2019
DPP-4	Dipeptidyl Peptidase 4
DMR	Duodenal Mucosal Regeneration/Resurfacing
DSMB	Data Safety Monitoring Board
EKG	Electrocardiogram
eCRF	Electronic Case Report Form
eGFR	Estimated Glomerular Filtration Rate
eGFR (MDRD)	Estimated Glomerular Filtration Rate calculated using The Modification of Diet in Renal Disease (MDRD) Study equation
FIH	First-in-Human
FPG	Fasting Plasma Glucose
GCP	Good Clinical Practice
GI	Gastrointestinal
GLP-1	Glucagon-Like Peptide-1
GLP-1 RA	Glucagon-Like Peptide-1 receptor agonist
HbA1c	Glycosylated Hemoglobin
HDL	High-Density Lipoprotein
HOMA-IR	Homeostatic Model Assessment of Insulin Resistance
IB	Investigator's Brochure
ITT	Intent-to-Treat
IRB	Institutional Review Board
LDL	Low-Density Lipoprotein
mITT	Modified Intent-to-Treat
NYHA	New York Heart Association

OAD	Oral Anti-diabetic Drug
PEF	Pulsed Electric Field
PP	Per Protocol
PPG	Post-prandial Plasma Glucose
SAE	Serious Adverse Avent
SGLT2i	Sodium-Glucose Cotransporter-2 Inhibitors
SoA	Schedule of Activities
SU	Sulphonylurea
T2D	Type 2 Diabetes Mellitus
TIBC	Total Iron Binding Capacity
UADE	Unanticipated Serious Adverse Device Effect

PROTOCOL SUMMARY

Protocol Title	Safety and Feasibility of Endoscopic Application of a Novel Therapy for Duodenal Mucosal **Regen**eration in the **T**reatment of Type II Diabetes (**REGENT-1-US Study**)
Protocol Number	346
Investigational Device	Endogenex Device
Proposed Indication	The Endogenex Device is indicated for endoscopic treatment of the duodenum in adult patients with type 2 diabetes inadequately controlled by glucose-lowering medications.
Regulatory Status	The Endogenex device does not have approval for commercial distribution in any geography.
Objectives	The objective of this early feasibility study is to assess the feasibility and preliminary safety of the Endogenex Device for endoscopic duodenal mucosal regeneration in patients with type 2 diabetes (T2D) inadequately controlled on 2-3 non-insulin glucose-lowering medications.
Study Design	This is a multicenter, open-label, treatment-only study conducted in the United States. The study plans to enroll 20 participants and test two treatment parameters. The first group of 10 participants will be treated at an energy setting of 600V and the second group of 10 participants at 750V. The first 5 participants in the 600V group will be enrolled/treated sequentially with at least 14 days observation time between each procedure. The first 5 participants in the 750V group will be enrolled/treated sequentially with at least 6 days observation time between each procedure. Patients with T2D inadequately controlled on 2-3 non-insulin glucose-lowering medication(s) will be screened for study eligibility. Eligible patients 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 after the baseline visit. Patients will undergo an endoscopic screening immediately prior to the index procedure. The index procedure will be performed under fluoroscopic and endoscopic guidance. Patients may be discharged the same day per the local hospital's guideline. A patient is enrolled in the study when the Endogenex catheter insertion is attempted. Patients excluded during endoscopic screening will be considered screen failures and will be followed for four weeks after the procedure for safety. Post index procedure, participants will be placed 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 before transitioning to normal diet. Background medication(s) may be decreased peri-procedurally per Section 6.2.2 but will be titrated to the pre-procedure dose and maintained for 24 weeks post index procedure and during the transitional diet period. Background medications may be

	adjusted to manage hypoglycemic risks (Section 6.2.2) or hyperglycemic risks (Section 6.2.2). After the 24-week follow-up visit, participants will be managed according to the current guidelines of the American Diabetes Association and their glucose-lowering medications will be optimized to achieve their 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 healthy diet and a healthy lifestyle. The counseling will be provided by a member of the research team (endocrinologist, dietitian, nurse, etc.) trained in the delivery of lifestyle counseling for diabetes.
Patient Population	Male and female participants, 22-65 years of age, with T2D treated with 2-3 non-insulin glucose-lowering medication(s), and a HbA1C 7.5% -10.0%, inclusive.
Primary Endpoint	Proportion of participants experiencing device- or procedure-related serious adverse events through 12 weeks post procedure.

Secondary Endpoints	• Procedure success rate defined as the proportion of participants who successfully received the target treatment of at least 6 cm of duodenum treatment
	• Procedure time defined as the time between the Endogenex catheter insertion and catheter removal.
	• Change from baseline in glycemic parameters post procedure by visits
	  o HbA1c
	  o Fasting plasma glucose (FPG)
	  o Insulin resistance by HOMA-IR
	  o Post prandial plasma glucose (PPG), Beta cell function, disposition index by mixed meal tolerance test (MMTT)
	  o Time in range, glucose variability by continuous glucose monitoring (CGM)
	• Proportion of treated participants with an HbA1c improvement ≥0.5 points from baseline at 24 weeks
	• Proportion of treated participants with an HbA1c improvement ≥0.5 points from baseline at 24 weeks and maintained at 48 weeks
	• Change in weight from baseline by visit
	• Change in glucose-lowering medication usage
	• Change in liver enzymes from baseline at 24 weeks
	  o Alanine Aminotransferase (ALT)
	  o Aspartate Aminotransferase (AST)
	• Change from baseline in blood pressure and lipid profile by visit

Safety Evaluation	Safety will be characterized through a summary of the incidence of adverse events, device- or procedure-related adverse events, and serious device- or procedure-related adverse events.
Inclusion Criteria	1. 22- 65 years of age 2. Current diagnosis of T2D 3. History of T2D for at least 3 years and less than or equal to 10 years

	4. HbA1C of 7.5-10.0%, inclusive 5. BMI 24-40 kg/m^2, inclusive 6. On two to three non-insulin glucose lowering mediations, with one at maximum tolerated dose and another at half-maximum dose at least, with no changes in medication for at least 12 weeks prior to baseline visit prior to baseline visit 7. History of failed attempt to reach glycemic goal by lifestyle modifications 8. Weight stability (defined as a < 5% change in body weight) for at least 12 weeks prior to the screening visit 9. Agree not to donate blood during participation in the study. 10. Able to comply with study requirements and understand and sign the Informed Consent Form 11. Women of childbearing potential must be using an acceptable method of contraception throughout the study 12. Willing and able to use CGM for the duration of the study and comply with study visits and study tasks as required per protocol. 13.
Exclusion Criteria	1. Diagnosed with type 1 diabetes 2. History of diabetic ketoacidosis or hyperosmolar nonketotic coma 3. Probable insulin production failure, defined as overnight fasting C-peptide serum <1 ng/mL (333pmol/l). 4. Previous use of any types of insulin for >1 month (at any time, except for treatment of gestational diabetes) in last 2 years. 5. Current use of insulin 6. Hypoglycemia unawareness 7. History of ≥1 severe hypoglycemia episode (defined by needing for third-party assistance) in past 6 months from the screening visit 8. Known autoimmune disease, as evidenced by a positive anti-glutamic acid decarboxylase (GAD) test, including but not limited to celiac disease, or pre-existing symptoms of systemic lupus erythematosus, scleroderma or other autoimmune connective tissue disorder. (Participants with adequately controlled primary hypothyroidism may be included). 9. Previous GI surgery that has changed GI anatomy or could limit treatment of the duodenum, such as Billroth 2, Roux-en-Y gastric bypass, gastric band or other similar procedures or conditions. 10. Known history of a structural or functional disorder of the upper GI tract that may impede passage of the device through the upper GI tract or increase risk of tissue damage during an endoscopic procedure, including esophagitis, stricture/stenosis, varices, diverticula, or other disorder of the esophagus, stomach and duodenum. 11. Active H. pylori infection (Participants with active H. pylori may continue with the screening process if they are treated with an appropriate antibiotic regimen) 12. History of, or gastrointestinal symptoms suggestive of gastroparesis. 13. Acute gastrointestinal illness in the previous 7 days 14. Known history of irritable bowel syndrome, radiation enteritis or other inflammatory bowel disease, such as Crohn's disease and Celiac disease

	15. History of chronic or acute pancreatitis. 16. Known active hepatitis or active liver disease other than NASH/NAFLD. 17. Alcoholic liver disease, as indicated by a history of alcohol consumption and ANI > 0. 18. Current use of anticoagulation therapy (such as warfarin) that cannot be safely discontinued periprocedurally. 19. Current use of P2Y12 inhibitors (clopidogrel, prasugrel, ticagrelor) that cannot be discontinued for 7 days before the procedure. 20. Unable to discontinue non-steroidal anti-inflammatory drugs (NSAIDs) during treatment through 4 weeks following the procedure. Use of acetaminophen and low dose aspirin is allowed. 21. Use of systemic glucocorticoids (excluding topical or ophthalmic application or inhaled forms) for more than 10 consecutive days within 12 weeks prior to the baseline visit. 22. Use of drugs known to affect GI motility (e.g. Metoclopramide) 23. Use of weight loss medications such as Meridia, Xenical, Phentermine or over-the-counter weight loss medications (prescription medication) 24. Currently taking, or unable to stop taking dietary supplements or herbal agents, including vitamin C or multivitamins containing vitamin C at >500 mg per day, multivitamins containing biotin (vitamin B7), and supplements for hair, skin, and nail growth. Multivitamins not containing biotin are permitted. 25. Persistent anemia, defined as hemoglobin <10 g/dL. 26. Known history of hemoglobinopathy. 27. Known history of blood donation or transfusion within 3 months prior to the Screening Visit. 28. Known history of cardiac arrythmia 29. Significant cardiovascular disease, including known history of valvular disease, or myocardial infarction, heart failure, transient ischemic attack, or stroke within 6 months prior to the Screening Visit. 30. Estimated glomerular filtration rate (eGFR) ≤ 60 ml/min/1.73m^2 (estimated by MDRD). 31. Known immunocompromised status, including but not limited to individuals who have undergone organ transplantation, chemotherapy, or radiotherapy within the past 12 months, who have clinically significant leukopenia, who are positive for the human immunodeficiency virus (HIV) or whose immune status makes the participant a poor candidate for clinical trial participation in the opinion of the investigator. 32. History of secondary hypothyroidism or inadequately controlled primary hypothyroidism (TSH value outside the normal range at screening) 33. With any implanted electronic devices that cannot be turned off during the procedure,or duodenal or biliary stents. 34. Not a candidate for upper GI endoscopy or general anesthesia. 35. Active illicit substance abuse or alcoholism (>2 drinks/day regularly) 36. Active malignancy within the last 5 years (excluding non-melanoma skin cancers)

	37. Women breastfeeding 38. Participating in another ongoing clinical trial of an investigational drug or device. 39. Any other mental or physical condition which, in the opinion of the study investigator, makes the participant a poor candidate for clinical trial participation. 40. Critically ill or has a life expectancy <3 years Additional exclusion criteria to be confirmed during the screening process: 41. HbA1c < 7.5% or > 10% at baseline visit 42. Any severe hypoglycemic event since the screening visit 43. CGM readings <54 mg/dl in more than 1% of time since the screening visit with at least 5 days of CGM data. 44. CGM readings > 360 mg/dL in more than 1% of time since the screening visit with at least 5 days of CGM data. 45. Mean of 3 separate blood pressure measurements >180 mmHg (systolic) or >100 mmHg (diastolic) 46. Women of child-bearing potential with a positive urine pregnancy test at baseline visit 47. LA Grade C or greater esophagitis on endoscopy 48. Abnormalities of the GI tract preventing endoscopic access to the duodenum 49. Anatomic abnormalities in the duodenum that would preclude the completion of the treatment procedure, including tortuous anatomy 50. Endoscopic observation of upper gastrointestinal abnormality such as ulcers, duodenal polyps in the area to be treated, varices, strictures, congenital or intestinal telangiectasia 51. Any other anatomical or endoscopic abnormalities/characteristics that, in the opinion of the investigator, would preclude safe use of the investigational device or procedure
Assessment Schedule	• Visits: Screening, Baseline, Index Procedure, Week 1, Week 2, Week 4, and every 4 weeks thereafter • Pancreatic enzyme: Baseline, Week 1, 12 • Glycemic parameters: Baseline, Week 4, 12, 24, 36, 48 • Liver enzyme: Baseline, Week 12, 24, 48 • Fasting lipid panel: Baseline, Week 24, 48 • Continuous blood glucose monitoring: Baseline, and for 48 weeks post procedure • Endoscopic follow up: Week 4 • Diabetes review and medication titration will be performed by the treating physician at all visits (see Schedule of Activities)
Peri-Procedural Medications	• Titration for Sulfonylureas and Meglitinides: o Dose reduction by 50% (or discontinuation if on the lowest recommended dose) starting on the day before index procedure through two-week transitional diet period post procedure.

	○ If a hypoglycemic episode is experienced (symptomatic or documented), the dose must be further reduced by 50% again or discontinued if the participant is on the lowest dose. ○ Following the transitional diet period and a review of CGM readings, the medication will be returned to pre-procedure dose if deemed safe and appropriate by the principal investigator. • Titration for other medications: ○ Metformin should be held the day prior to endoscopy and resumed post procedure when the patient tolerates oral intake. ○ SGLT2i should be held three (3) days prior to the index procedure and resumed when the patient transitions to normal diet (after the 2-week transitional diet period). ○ GLP-1 Receptor agonists and DPP-4 inhibitors should be held in the peri-procedure period if the subject experiences significant nausea and/or vomiting and can be resumed once symptoms resolve at the discretion of the principal investigator. ○ Generally, the dosage of other medications may remain unchanged peri-procedurally unless a hypoglycemic risk is identified by blood glucose monitoring. • Proton Pump Inhibitor (PPI) ○ Patients will be placed on PPI (Omeprazole 40 mg daily or equivalent) 1 week prior to the index procedure • Antiemetics and antispasmodics ○ Patients will be provided with antiemetics and antispasmodics on standby post procedure
Post Procedural Diet and Lifestyle Modification	• Patient will be on clear liquid diet for 24 hours, followed by a full liquid diet for 3 days, pureed food for 3 days, soft food for one week, and then transitioned to normal diet as tolerated. • Following the transitional diet period, patient will participate in monthly lifestyle modification counseling sessions to promote adherence to a diet and lifestyle suitable for diabetes.
Safety Monitoring	Safety will be monitored throughout the study. The enrollment will be staged with pre-defined stopping rules to ensure participant's safety. The investigators will assess the occurrence of adverse events at each follow up visit. A data safety monitoring board (DSMB) will review and monitor the safety data throughout the study. Changes in amylase, lipase levels post procedure will be evaluated for any potential pancreatic injury.
Timeline	• First Participant Enrolled: Q4, 2021 • Estimated Enrollment Duration: 18 months (Q2 2023) • Last Participant to Primary Endpoint Follow-up: (Q4 2023) • Study Duration: 30 months

1 BACKGROUND

1.1 Type 2 Diabetes

Type 2 diabetes (T2D) is an expanding global health problem that causes significant health economic burden worldwide. It is a progressive metabolic disease primarily characterized by abnormal glucose metabolism and chronic hyperglycemia. The pathophysiological disturbances responsible for impaired glucose homeostasis involves peripheral tissue insulin resistance, impaired insulin secretion due to abnormal β-cell function and abnormal glucose metabolism in the liver[1].

Individuals with T2D are at high risk for microvascular complications (such as retinopathy, nephropathy and neuropathy) and macrovascular complications (such as cardiovascular comorbidities). Optimizing individualized glycemic control is the therapeutic goal in these individuals with diabetes and has been shown to prevent long-term complications[2]. Health economic studies have found that an A1C decrease of 1% or more was associated with lower total healthcare costs than those without an improvement in the A1C value[3], and a 1% increase in A1C was associated with a 7% increase in healthcare costs over the next 3 years[4].

Despite an increasing number of pharmaceutical agents available to treat Type 2 diabetes , close to 50% of all patients do not achieve the recommended glycemic target of an HbA_{1c} <7% and exposing them to increased risk of T2D-related complications[5].

Bariatric surgery induces dramatic improvement in glycemic control in patients with T2D and obesity. Diabetes remission can be achieved in 30-60% of patients in the 1-5 years following bypass surgery[6], surpassing any combination of pharmacotherapies available to date. However, bariatric surgery is associated with significant morbidities, and therefore its use has been limited to a small portion of patients.

1.2 Duodenal Mucosal Resurfacing

The duodenum as a potential therapeutic target stems from evidence developed following bariatric surgeries. Surgical procedures involving bypassing a portion of the proximal intestine (such as Roux-en-Y Gastric Bypass, and Biliopancreatic Diversion) showed greater diabetes remission rate than gastric volume restrictive procedures such as sleeve gastrectomy, which implicates the important role of upper small intestine in blood glucose regulations.

Studies have found that the duodenal mucosa exhibits abnormal hypertrophy and endocrine hyperplasia in the presence of diabetes[7,8]. It has been hypothesized that duodenal mucosal ablation followed by mucosal regeneration can improve glycemic control in T2D patients.

A duodenal mucosal resurfacing (DMR) procedure using hydrothermal ablation technique (Revita® DMR, Fractyl Laboratories, Lexington, MA., USA) has been studied in patients with T2D in a number of clinical trials. Rajagopalan et al[9]. reported results from 39 patients treated with DMR among 44 patients enrolled in a first-in-human study. Patients were 38 to 65 years old, had a mean diabetes duration of 5.7 years (0.2-9.7) and mean baseline hemoglobin A1c (HbA1c) of 9.5% (range 7.5% to 12%). Patients were required to be on at least one oral antidiabetic medications (OAD), 98% of them were on metformin and 37% on sulfonylurea before the procedure. The ablation length was between 3 and 15 cm of the post papillary duodenal mucosa. FPG reduction was noted within one week of the procedure and HbA1C reduction was observed as early as one month post intervention. HbA1C reduction was 1.2% at 6 months in the full cohort. Ablation length of ≥9 cm was associated with greater HbA1C reduction compared to shorter ablation length (1.4% vs. 0.7% at 6 months). The most common adverse event was transient, postprocedural abdominal pain that resolves without the need of analgesic medications. There was no gastrointestinal bleeding, perforation, pancreatitis, severe hypoglycemia, or evidence of malabsorption (i.e., calcium abnormalities or iron deficiency anemia).

Three patients developed a duodenal stenosis that presented as epigastric pain and vomiting 2–6 weeks after the procedure. They were successfully treated with endoscopic balloon dilation without sequelae. The authors attributed the cause of stenosis to early device and procedure issues that were improved subsequently.

A subsequent study[10] enrolled 46 patients, among them 37 completed the DMR procedure. Patients were 31-69 years old, 63% of them were male, had a mean BMI of 31.6 kg/cm2 and a baseline HbA1C of 8.6%. Improvements in HbA1c, FPG and HOMA-IR levels were observed as early as 4 weeks and sustained out to 12 months. Mean HbA1C reduction was 0.9% at 24 weeks, which was preserved up to 12 months. HOMA-IR was reduced by 2.9±1.1 at 24 weeks and by 3.3±0.9 at 12 months from baseline. The study also observed a statistically significant decrease in alanine transaminase (ALT) levels at 24 weeks and 12 months post procedure. Patients had a modest weight loss of 2.5kg at 24 weeks and 2.4 kg at 12 months. Most common study-related adverse events were GI symptoms. One study-related serious adverse event involved a patient with general malaise, mild fever (38°C), and increased c-reactive protein (CRP) level on the first day after DMR. The mild fever resolved within 24 hours and CRP level normalized within 3 days. No stenosis was reported in this study.

The above data supports the hypothesis that interventions targeting duodenal mucosa can improve glycemic control in T2D patients inadequately controlled by OAD. One limitation of hydrothermal ablation is the need to inject saline into the submucosal layer (mucosal lifting) during the ablation procedure for the purpose of preventing thermal penetration into deeper tissue. In addition to technical demand, mucosal lifting potentially creates an irregular contact surface between the ablation balloon and mucosa, resulting in uncontrolled and nonuniform ablation. One potential solution to address this limitation is to use a regeneration technology that does not require mucosal lifting.

Endogenex has developed a duodenal mucosal treatment device using a pulsed electric field (PEF) with bipolar pulse technology for the treatment of T2D. The treatment does not require mucosal lifting to protect muscularis from thermal damage, and therefore results in a simpler procedure and potentially more uniform tissue treatment.

2 DEVICE DESCRIPTION

2.1 System Description

A summary device description is provided below. More detailed information is provided in the Investigator's Brochure.

The Endogenex device consists of a pulsed electric field generator, a system controller (including PC for user interface), connecting cables, an optional switchbox and a disposable catheter (***Figure 1***).

The Endogenex catheter is provided sterile and designed for single use only.

[redacted]

[redacted]

2.2 Proposed Mechanism of Action

The proposed mechanism of action of the Endogenex device is to elicit mucosal renewal via PEF-induced cell death and regeneration of the pathological mucosal tissue for improvement of glycemic control in patients with T2D. Studies have shown that duodenal hydrothermal ablation can improve HbA1C and insulin sensitivity in T2D patients inadequately controlled by OADs[9,10]. It is hypothesized that the Endogenex device using the PEF technology will result in precise control of treatment depth, uniform treatment surface, favorable procedure safety and ease of use.

2.3 Proposed Indication

The Endogenex device is indicated for endoscopic treatment of duodenum in adult patients with type 2 diabetes inadequately controlled by glucose-lowering medications.

2.4 Prior Investigations

The device has undergone extensive bench and animal testing during product development. The results demonstrated that the system met all performance requirements under Endogenex's design control procedures. Please refer to the Investigator's Brochure for details on the tests performed and their associated results.

Since this is an early feasibility study, no clinical data exists with this device.

2.5 Risks and Benefits

2.5.1 Potential Benefits

There are no guaranteed benefits from participation in this study; however, there are potential benefits for individuals who participate in this clinical study. Participants to be included in the present study have type 2 diabetes and have been treated with medications but still have inadequately controlled blood glucose levels. By participating in this study, participants will have an opportunity to achieve better glycemic control through a combination of structured lifestyle modification. counseling, continuous glucose monitoring, and medication monitoring in addition to the device intervention.

2.5.2 Anticipated Adverse Events Associated with the DMR Procedure

Anticipated AEs associated with the DMR procedure may include, but are not limited to, the following:

- Complications associated with upper GI endoscopy, including but not limited to, aspiration of gastric contents, aspiration pneumonia
- Complications related to sedation and anesthesia
- Cardiac or respiratory arrest during endoscopy
- Cardiac arrythmia, muscle spasm, or electrical shock during the procedure
- Death
- Duodenal mucosal inflammation, erythema, erosion, ulcer, bleeding, perforation and their associated complications
- Duodenum motility disorder
- Duodenum stricture and/or obstruction, and their associated complications or interventions
- Excess reduction in oral intake, resulting in dehydration, ketoacidosis, and their associated complications
- GI symptoms post procedure, including nasopharyngeal pain, abdominal pain, cramps, abdominal discomfort, nausea, vomiting, diarrhea, and other GI symptoms
- Inability to endoscopically remove part or all of the device, which may result in the need for surgery
- Infection, systemic or of GI tract and their associated complications

- Injury to the area of ampulla, leading to biliary and/or pancreatic complications such as biliary obstruction, pancreatitis, etc.
- Injury to peripheral tissue and their associated complications, such as peripancreatic fluid collections, pseudocyst, pancreatic and peripancreatic necrosis, peri-duodenal inflammation or abscess, vascular injuries, pseudoaneurysm, etc.
- Interfere with absorption resulting in nutritional deficiencies
- Undesired metabolic response such as hypoglycemia
- Upper GI tract trauma, including sore or irritated throat, bleeding, perforation, and their associated complications

2.5.3 Residual Risks Associated with the Investigational Device, as Identified in the Risk Analysis Report

Endogenex has conducted extensive assessment of the potential risks associated with the device and its use through Hazard Analysis and FMEA (failure mode and effects analysis) per ISO 14971. A number of safeguards have been built into the device to mitigate risks. The risk assessment concludes that, when used as intended and with mitigation measures implemented, there are no unacceptable risks to the intended patient population.

2.5.4 Risks Associated with Participation in the Clinical Investigation

There are risks associated with participation in a clinical investigation. This is an early feasibility study and therefore no clinical data with the device exists. Unanticipated adverse events associated with the device may occur. There are protocol-defined tests and follow-up studies such as endoscopy that may carry additional risk to the subjects.

2.5.5 Possible Interactions with Concomitant Medication

The effect of the DMR treatment to the absorption of orally administered medication is unknown. Published literature on DMR procedures has not reported changes in medication absorption following the DMR procedure. Participants in this study are taking glucose-lowering medications. Specific risk mitigation measures are included in the protocol, including guidelines on medication management (**Section 6.2**) and the use of CGM (**Section 7.11**) during the study.

For participants who are taking concomitant medications for other conditions, the physician should evaluate the risk and benefit of this procedure, and monitor patients closely post procedure.

2.5.6 Minimization of Risks

The following steps have been taken to further minimize the risks of the study:

- The study protocol has built in measures to control potential adverse effects, including study inclusion/exclusion criteria, staged enrollment, prophylactic medications, clinical and endoscopic surveillance, use of CGM, and guidelines for post-procedure management.
- The protocol minimizes participant's onsite visits to mitigate potential COVID-19 associated risks by allowing for a combination of virtual visits, remote monitoring, and in-home test sample collections.
- Patient informed consent contains sufficient information on the potential risks.
- Participants will be provided with study information cards that contain study and physician contact information if needed.

- Training and technical support will be provided for the DMR procedure during the study
- An DSMB will monitor the safety of the study.

In summary, participants included in the present study have a clinical indication for treatment to achieve better glycemic control. The risks associated with the device have been mitigated to the extent possible. The current study design includes additional measures to further minimize risks. These data and study design features indicate a favorable risk-benefit profile for the participants to be included in the present study.

3 STUDY OBJECTIVES AND ENDPOINTS

The objective of this FIH study is to assess the feasibility and preliminary safety of the Endogenex Device for endoscopic duodenal mucosal regeneration in individuals with type 2 diabetes inadequately controlled on 2-3 non-insulin glucose-lowering medications.

The study will also assess, as exploratory endpoints, treatment efficacy, evaluated by changes in glycemic control and liver enzymes post procedure from baseline.

Objectives	Endpoints
Primary	
• To assess the safety of the Endogenex Device for DMR procedure	• Proportion of participants experiencing one or more device- or procedure-related serious adverse events at 12 weeks post procedure.
Secondary	
• To assess the technical feasibility of the Endogenex Device for DMR procedure • To assess changes in glycemic control • To assess changes in liver enzymes	• Procedure success: defined as successful treatment of at least 6 cm of duodenum segment. • Procedure time: defined as the time between the Endogenex catheter insertion and the catheter removal. • Change from baseline in glycemic parameters post index procedure, by visits o HbA1c o Fasting plasma glucose (FPG) o Insulin-resistance by HOMA-IR o Post prandial plasma glucose (PPG), Beta cell function, disposition index by mixed meal tolerance test (MMTT) o Time in range, glucose variability by continuous glucose monitoring (CGM) • Proportion of treated participants with an HbA1c improvement of 0.5% or more at 24 weeks from baseline • Proportion of treated participants with an HbA1c improvement of 0.5% or more at 24 weeks from baseline and maintained at 48 weeks • Change in weight from baseline by visit • Change in glucose-lowering medication usage • Change in liver enzyme from baseline at 24 weeks o Alanine Aminotransferase (ALT)

	○ Aspartate Aminotransferase (AST) • Change from baseline in blood pressure and lipid profile by visit

4 STUDY DESIGN

4.1 Study Design

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 Association[2] 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.

A schematic diagram of the study design is shown in **Figure 7**.

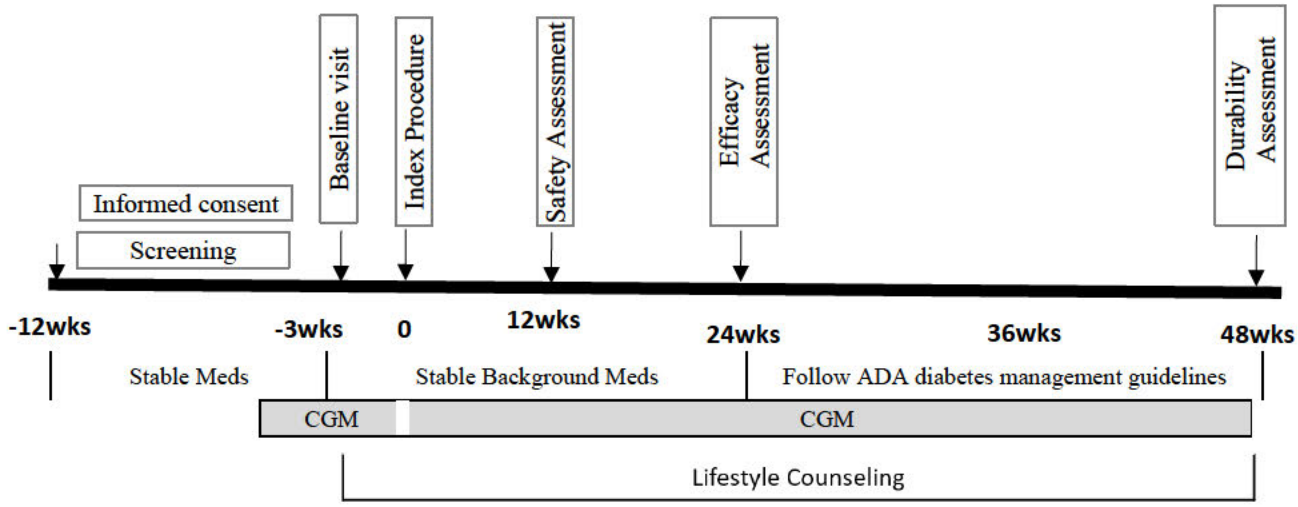

Figure 8. Study Diagram

4.2 Participant Recruitment and Enrollment

Participants will be recruited by investigators at study sites. Potential candidates may be identified through review of hospital medical records, and/or querying an existing database, if available, and contacted by the site staff about the study. Candidates may also be recruited during routine office visits or by use of IRB-approved advertisements such as brochures, flyers, letters, digital media and other methods. Candidates who are potentially eligible for the study will be scheduled for a screening visit.

After giving written informed consent, participants will undergo screening assessments. Screening data will be reviewed to determine participant eligibility. Participants who meet all inclusion criteria and none of the general exclusion criteria will be scheduled for a baseline visit within 21 days of the planned procedure. Participants who remain eligible at the baseline visit will be scheduled for the procedure.

On the day of the procedure, participants will undergo endoscopic assessment to confirm endoscopic eligibility. Participants who meet the endoscopic eligibility will receive the DMR procedure. Participants who are excluded during endoscopic screening will be considered a screening failure and be followed for four weeks for safety.

A participant is considered enrolled in the study when the participant has given written informed consent and the Endogenex catheter insertion is attempted.

4.3 End of Study Definition

A participant is considered to have completed the study if he/she has completed all phases of the study including the last scheduled visit at week 48 in the Schedule of Activities (SoA, **Appendix 2**).

The end of the study is defined as the date of the last visit or the last scheduled procedure of the last participant in the study.

4.4 Staged Enrollment

The study will employ a staged enrollment approach to ensure participants' safety. The first group of 10 participants will be treated at 600V followed by the second group of 10 treated at 750V.

In the 600V group, the initial 5 participants will be treated sequentially with the investigational device and with a compulsory observation time of at least 14 days between each case. In the 750V group, the initial 5 participants will be treated sequentially with the investigational device and with a compulsory observation time of at least 6 days between each case. A DSMB review will be conducted after the first 5 participants have completed the treatment. Investigators should not treat additional participants until the DSMB has given the direction to do so. Based on DSMB recommendation (Section 11), enrollment of subsequent participants may occur at its natural pace without a compulsory observation time.

Additional DSMB reviews are planned at the following time as shown in **Figure 8**.

- Ten (10) participants treated and at least 5 reached the 4-week visit in the 600V group
- Five (5) participants treated in the 750V group
- All 20 participants reached the 4-week visit

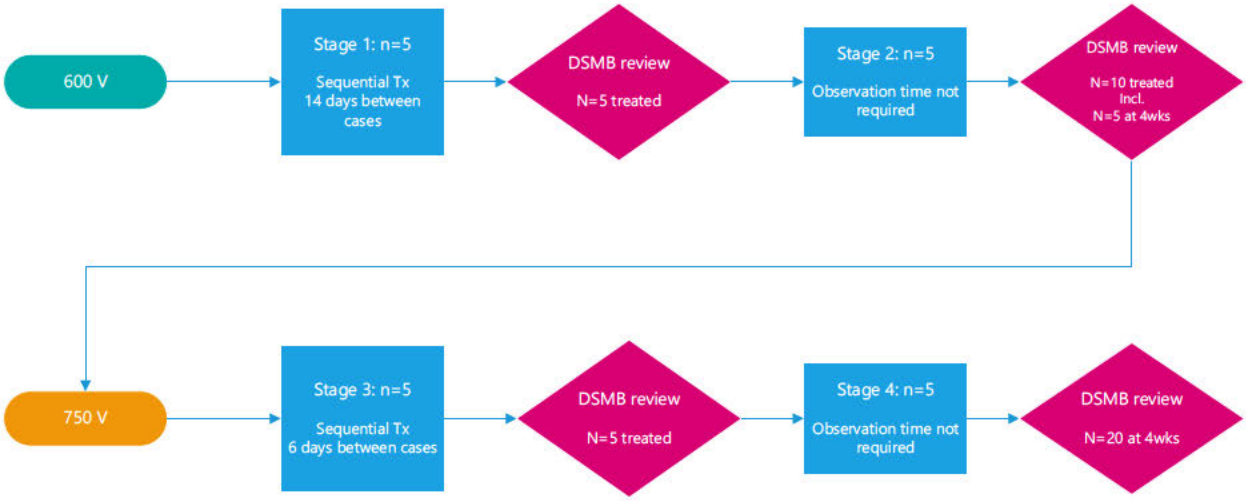

Figure 9. Staged Enrollment

A safety report will be submitted to FDA after the first 5 participants in the study have completed their Week 4 visits. An additional safety report will be submitted to FDA after the first 5 participants have been treated with 750V. Enrollment may continue as described above during the submission and review period.

4.5 Stopping Rules

To protect participants' safety, stopping rules are specified as follows:

A. Any of the following events occurring once:

1) Death related or possibly related to the device or procedure
2) Any device- or procedure-related event requiring intensive care unit management
3) Perforation requiring radiographic/endoscopic/surgical intervention
4) Refractory duodenal stricture requiring multiple dilatations (>2) or surgical intervention

5) Significant mucosal injury (ulcer or inflammation) with bleeding defined as (i) overt bleeding plus hemoglobin drop > 3 g/dL (provided hemoglobin drop is related to bleed). Or (ii) bleeding requiring endoscopic, radiographic or surgical treatment
6) Off-target tissue injury related- or possibly related to the device or procedure requiring endoscopic, radiographic or surgical treatment

B. Other device- or procedure-related SAEs not listed above and occurring more than once.
C. Rescue criteria invoked due to severe hyperglycemia, occurring in 2 out the first 5 participants.
D. Severe hypoglycemia (requiring assistance of another person) occurring in 1 out of the first 5 participants.

If the stopping rule is triggered, the enrollment will be paused and a DSMB review will be conducted. Based on DSMB recommendation, Sponsor will implement necessary actions which may range from continuous monitoring, protocol modification, stopping enrollment to terminate study. Sponsor will report such events to FDA as soon as possible but no later than 10 working days after the investigator first learns of the event.

5 STUDY POPULATION

Patients suffering from type 2 diabetes who meet the inclusion and exclusion criteria will be evaluated for participation in the study. To ensure participant safety in this early feasibility study, we aim to enroll individuals without significant cardiovascular conditions or other serious internal organ diseases.

A total of 20 participants will be enrolled at up to 5 study sites.

5.1 Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

1. 22-65 years of age
2. Current diagnosis of T2D
3. History of T2D for at least 3 years and less than or equal to 10 years
4. HbA1C of 7.5- 10.0%, inclusive
5. BMI 24-40 kg/m^2, inclusive
6. On two to three non-insulin glucose lowering mediations, with one at maximum tolerated dose and another at half-maximum dose at least, with no changes in medication for at least 12 weeks prior to baseline visit
7. History of failed attempt to reach glycemic goal by lifestyle modifications
8. Weight stability (defined as a < 5% change in body weight) for at least 12 weeks prior to the screening visit
9. Agree not to donate blood during participation in the study.
10. Able to comply with study requirements and understand and sign the Informed Consent Form
11. Women of childbearing potential must be using an acceptable method of contraception throughout the study
12. Willing and able to use CGM for the duration of the study and comply with study visits and study tasks as required per protocol.

5.2 Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

1. Diagnosed with type 1 diabetes
2. History of diabetic ketoacidosis or hyperosmolar nonketotic coma
3. Probable insulin production failure, defined as overnight fasting C-peptide serum <1 ng/mL (333pmol/l).
4. Previous use of any types of insulin for >1 month (at any time, except for treatment of gestational diabetes) in last 2 years.
5. Current use of insulin
6. Hypoglycemia unawareness
7. History of ≥1 severe hypoglycemia episode (defined by needing for third-party assistance) in past 6 months from the screening visit
8. Known autoimmune disease, as evidenced by a positive anti-glutamic acid decarboxylase (GAD) test, including but not limited to celiac disease, or pre-existing symptoms of systemic lupus erythematosus, scleroderma or other autoimmune connective tissue disorder. (Participants with adequately controlled primary hypothyroidism may be included).
9. Previous GI surgery that has changed GI anatomy or could limit treatment of the duodenum, such as Billroth 2, Roux-en-Y gastric bypass, gastric band or other similar procedures or conditions.
10. Known history of a structural or functional disorder of the upper GI tract that may impede passage of the device through the upper GI tract or increase risk of tissue damage during an endoscopic procedure, including esophagitis, stricture/stenosis, varices, diverticula, or other disorder of the esophagus, stomach and duodenum.
11. Active H. pylori infection (Participants with active H. pylori may continue with the screening process if they are treated with an appropriate antibiotic regimen)
12. History of, or gastrointestinal symptoms suggestive of gastroparesis.
13. Acute gastrointestinal illness in the previous 7 days
14. Known history irritable bowel syndrome, radiation enteritis or other inflammatory bowel disease, such as Crohn's disease and Celiac disease
15. History of chronic or acute pancreatitis.
16. Known active hepatitis or active liver disease other than NASH/NAFLD.
17. Alcoholic liver disease, as indicated by a history of alcohol consumption and ANI >0
18. Current use of anticoagulation therapy (such as warfarin) that cannot be safely discontinued periprocedurally.
19. Current use of P2Y12 inhibitors (clopidogrel, prasugrel, ticagrelor) that cannot be discontinued for 7 days before the procedure.
20. Unable to discontinue non-steroidal anti-inflammatory drugs (NSAIDs) during treatment through 4 weeks following the procedure. Use of acetaminophen and low dose aspirin is allowed.
21. Use of systemic glucocorticoids (excluding topical or ophthalmic application or inhaled forms) for more than 10 consecutive days within 12 weeks prior to the baseline visit.
22. Use of drugs known to affect GI motility (e.g. Metoclopramide)

23. Use of weight loss medications such as Phentermine, Meridia, Xenical, or over-the-counter weight loss medications (prescription medication)
24. Currently taking, or unable to stop taking dietary supplements or herbal agents, including vitamin C or multivitamins contained vitamin C at >500 mg per day, multivitamins containing biotin (vitamin B7), and supplements for hair, skin, and nail growth. Multivitamins not containing biotin are permitted.
25. Persistent anemia, defined as hemoglobin <10 g/dL.
26. Known history of hemoglobinopathy.
27. Known history of blood donation or transfusion within 3 months prior to the Screening Visit.
28. Known history of cardiac arrythmia
29. Significant cardiovascular disease, including known history of valvular disease, or myocardial infarction, heart failure, transient ischemic attack, or stroke within 6 months prior to the Screening Visit.
30. Estimated glomerular filtration rate (eGFR) ≤ 60 ml/min/1.73m^2 (estimated by MDRD)
31. Known immunocompromised status, including but not limited to individuals who have undergone organ transplantation, chemotherapy, or radiotherapy within the past 12 months, who have clinically significant leukopenia, who are positive for the human immunodeficiency virus (HIV) or whose immune status makes the participant a poor candidate for clinical trial participation in the opinion of the investigator.
32. History of secondary hypothyroidism or inadequately controlled primary hypothyroidism (TSH value outside the normal range at screening)
33. With any implanted electronic devices that can't be turned off during the procedure, or duodenal or biliary stents.
34. Not a candidate for upper GI endoscopy or general anesthesia.
35. Active illicit substance abuse or alcoholism (> 2 drinks/day regularly).
36. Active malignancy within the last 5 years (excluding non-melanoma skin cancers)
37. Women breast feeding
38. Participating in another ongoing clinical trial of an investigational drug or device.
39. Any other mental or physical condition which, in the opinion of the study investigator, makes the participant a poor candidate for clinical trial participation.
40. Critically ill or has a life expectancy <3 years

Additional exclusion criteria to be confirmed during the screening process:

41. HbA1c < 7.5% or > 10% at baseline visit
42. Any severe hypoglycemic event since the screening visit
43. CGM readings of <54 mg/dl in more than 1% of time since the screening visit with at least 5 days of CGM data.
44. CGM readings of >360 mg/dl in more than 1% of time since the screening visit with at least 5 days of CGM data.
45. Mean of 3 separate blood pressure measurements >180 mmHg (systolic) or >100 mmHg (diastolic)

46. Women of child-bearing potential with a positive urine pregnancy test at baseline visit
47. Grade III or greater esophagitis on endoscopy
48. Abnormalities of the GI tract preventing endoscopic access to the duodenum
49. Anatomic abnormalities in the duodenum that would preclude the completion of the treatment procedure, including tortuous anatomy
50. Endoscopic observation of upper gastrointestinal abnormality such as ulcers, duodenal polyps in the area to be treated, varices, strictures, congenital or intestinal telangiectasia
51. Any other anatomical or endoscopic abnormalities/characteristics that, in the opinion of the investigator, would preclude safe use of the investigational device or procedure.

5.3 Point of Enrollment

The point of enrollment occurs when a participant has provided written informed consent and the Endogenex catheter insertion has been attempted during the index procedure.

5.4 Screen Failures

Screen failures are defined as participants 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. Screen failure information including demography, screen failure details, eligibility criteria, and any serious adverse event (SAE) will be documented on eCRFs.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened. Data from all screen and re-screen visits will be captured on eCRFs.

Individuals who failed at endoscopic screening will be followed for four weeks for safety.

6 STUDY INTERVENTION AND CONCOMITANT THERAPY

6.1 Study Intervention (Index Procedure)

The study intervention is the duodenal mucosal regeneration (DMR) procedure using the Endogenex Device.

The DMR procedure is performed under general anesthesia or deep sedation. Participants will be prepared for anesthesia and upper endoscopy according to institution's standard practice.

At the beginning of the procedure, participants will undergo endoscopic assessment to confirm endoscopic eligibility. Participants who meet the endoscopic eligibility will undergo the DMR procedure following the procedure steps described in the Instruction for Use (IFU). In brief, the catheter is inserted trans-orally into the participant's duodenum under endoscopic visualization. Fluoroscopy maybe used to guide the catheter insertion when needed. The catheter's flex circuit section is positioned approximately 2cm distal to the Papilla of Vater. The flex circuit board is deployed to achieve contact between the duodenal wall and the electrodes on the circuit board. Energy delivery is initiated by pressing the "Start" button on the generator. Upon completion of energy delivery, the circuit board is retracted into the housing in a compressed configuration and moved distally to the next treatment zone. The procedure is repeated until the treatment length is up to 14cm approximately. Upon completion of the treatment, the catheter is removed, and a final endoscopic inspection is performed.

Participant will be recovered from anesthesia and discharged according to local institution's discharge criteria and procedures. An overnight stay is not required but permitted per investigator's clinical judgement.

Before the participant is discharged, s/he is to be provided with a study information card. This card provides the phone number and name of the person to contact in case s/he needs medical attention related to the therapy. Additionally, the participant can provide this card to an emergency room doctor, allowing them to contact the Primary Investigator and obtain information about the study. A sample of the card is provided in **Appendix 3**.

The participant will be placed on a clear liquid diet for 24 hours, followed by a full liquid diet for 3 days, pureed food for 3 days, soft food for one week, and then return to normal food as tolerated.

Antiemetic (such as Ondansetron) and antispasmodics (such as hyoscyamine) may be provided on standby following the DMR procedure, and the participants should be educated on their use.

Participants who are excluded during endoscopic screening will be considered a screening failure and be followed for four weeks for safety.

A participant is considered enrolled in the study when the participant has given written informed consent and the Endogenex catheter insertion is attempted.

6.2 Glucose-Lowering Medications

Diabetes review and medication management will be conducted by the treating physician starting from screening visits and throughout the study. The treating physician is a member of the site study team who has been expertise in managing patients with type 2 diabetes.

6.2.1 Background Glucose-Lowering Medications

Eligible participants must be on two to three non-insulin glucose-lowering medication(s), one at maximum tolerated dose and another at half-maximum dose at least, without a severe hypoglycemic event within the past six months of the screening visit.

Participant's background medication will be kept stable (no change in medication or dose) for at least 12 weeks prior to the Baseline Visit.

Peri-procedurally, the dose of medications with hypoglycemic risks will be adjusted per guidelines provided in **Section 6.2.2** .

Following the transitional diet period, participant's medication will be titrated to the background level and maintained stable until the Week 24 Visit has been completed. Medication and/or dose change necessary for managing hypoglycemia, hyperglycemia, or other safety concerns is permitted. Reason for the medication change must be documented on eCRF.

Following the Week 24 Visit, participants will be managed according to the current (2021) guidelines of the American Diabetes Association[2] and their glucose-lowering medications will be optimized as necessary to reach an HbA1c target of 7% .

Background medications are non-investigational products. They should be used in accordance with standard of care and their approved labeling. They will not be provided by the sponsor.

6.2.2 Guideline for Managing Hypoglycemic Risks

The following guideline is provided for minimizing hypoglycemic risks during the study. The treating physicians should exercise their clinical judgment for the treatment of individual patients.

6.2.2.1 Peri-procedure

The dose of sulfonylureas or meglitinides will be reduced by 50% (or discontinued if on the lowest recommended dose) one day before the index procedure to avoid potential hypoglycemic risks. If an episode of documented or symptomatic hypoglycemia is experienced during the peri-procedure or transitional diet period, further reduction of sulfonylurea or meglitinide dose by 50% or discontinuation if on the lowest dose should occur.

Metformin should be held the day prior to endoscopy and resumed post procedure when the patient tolerates oral intake.

SGLT2i should be held three (3) days prior to the index procedure and resumed when the patient transitions to normal diet (after the 2-week transitional diet period).

GLP-1 Receptor agonists and DDP-4 inhibitors should be held in the peri-procedure period if the subject experiences significant nausea and/or vomiting and can be resumed once symptoms resolve at the discretion of the principal investigator.

6.2.2.2 During Diet Transition Period

During the diet transition period, CGM data will be reviewed by the treating physician and used to guide medication titration.

If the risk of hypoglycemia has not been adequately reduced, doses of sulfonylureas, meglitinides, or possibly other glucose-lowering medication(s) should be further reduced or discontinued if appropriate and in the clinical judgment of the participant's treating physician.

In the event of severe hypoglycemia, study staff will document these episodes on the Adverse Event form.

6.2.3 Guidelines for Managing Hyperglycemia

After the background medications have been titrated back to baseline level following the transitional diet period, participants with severe, persistent hyperglycemia should be offered treatment intensification.

In the event of suspected persistent hyperglycemia in a subject based on either symptoms of hyperglycemia (eg, thirst, polyuria, blurred vision), CGM readings of >250 mg/dL for > 30% of the time, or repeated fasting CGM readings above 270 mg/dL (e.g. occurring 3 days in a week), the investigator should perform additional laboratory tests to assess whether rescue therapy is warranted .

Participants meeting the following criteria should be offered rescue medication (i.e. intensification of glucose-lowering background medication and/or initiation of basal insulin).

- FPG > 270 mg/dL, confirmed by repeated measures more than 3 days apart, and no intercurrent cause can be identified, or
- HbA1c is >8.0% AND the interval improvement is <0.5% from baseline, by Week 12

After Week 24, participants should be offered treatment intensification if they do not reach their HbA1c target, which for most individuals is 7.0%.

The above criteria and medications are provided as a guideline. Investigators should always exercise his/her clinical judgement based on individual conditions to protect participant's safety and wellbeing.

Participants who meet rescue criteria before Week 24 should first complete the Week 24 visit activities within 5 days before initiation of the rescue medication to ensure that important trial endpoint measurements are collected and be provided the rescue therapy.

Medication changes and reasons for the changes will be documented on the eCRFs. Medications used to manage hyperglycemia are non-investigational and will not be provided by the sponsor.

6.3 Proton Pump Inhibitor

Participants will be placed on PPI (Omeprazole 40 mg daily or equivalent) at least one week prior to the index procedure.

6.4 NSAIDs (Non-Steroidal Anti-inflammatory Drugs)

Participants must be off NSAIDs for four weeks after the index procedure. Low dose aspirin (81 mg/day) may be used if needed in combination with prophylactic PPI. If unable to discontinue NSAID for four weeks, the participant should be excluded from the study.

6.5 Anticoagulant and Antiplatelet Medications

If a participant is taking anticoagulant or antiplatelet medications, the anticoagulant must be stopped until the International normalized ratio (INR) returns to normal or bridged with low molecular weight heparin (LMWH) prior to the index procedure. The antiplatelet medications must be stopped for 7 days prior to the index procedure. Post procedure, the anticoagulant or antiplatelet medications may be resumed after 48 hours if there is no evidence of bleeding.

The investigator must evaluate the risks of discontinuing these medications based on the overall clinical judgement. If these medications can't be discontinued safely, the participant should be excluded from the study.

6.6 Prohibited Concomitant Medications

6.6.1 Weight-Loss Medications

Study participants will not be allowed to take any weight-loss products during the course of the study, including prescription or over-the-counter (OTC) weight loss medications and herbal products.

6.7 Other Concomitant Medications

For participants on oral thyroid replacement therapy, TSH should be tested at month 3, 6, 9, and 12, and medication adjusted as necessary per clinical guidelines.

Concomitant medications deemed medically necessary for the participant will be allowed during the course of the study; however, any changes in medications will be documented on the Concomitant Medication Log. Medications used during the DMR procedure, such as anesthesia, will not be tracked via the Concomitant Medication Log.

6.8 Participant Education and Lifestyle Counseling

6.8.1 Hypoglycemia

At the onset of the study, participants will be provided a Freestyle Libre 2 CGM device and an instruction (**Appendix** 4) on how to monitor glucose levels during the study. Participants should be educated on the potential for development of hypoglycemia, the symptoms and signs of hypoglycemia, the use of CGM and how to detect hypoglycemia, and instruction on treating hypoglycemia. Participants (especially those receiving a sulfonylurea) should be instructed to monitor for hypoglycemia.

Symptoms suggestive of hypoglycemia include lightheadedness, tremor, shaking, sweating, tingling, blurred vision, difficulty concentrating, and confusion. With marked hypoglycemia, patients may develop altered consciousness, coma, or seizures.

Participants will use CGM for at least 5 days at baseline and for 48 weeks after the procedure.

Participants should also be instructed to confirm blood glucose level with a finger stick if they receive CGM alerts indicating hypoglycemia and contact his/her treating physician to discuss whether the dosage of glucose-lowering medication(s) should be adjusted to prevent hypoglycemic events.

Participants should also be instructed to promptly contact site staff if they experience symptoms of hypoglycemia, CGM readings of <70mg/dL for >4% of time[11], or CGM readings of <54 mg/dL for >1% of time[11].

6.8.2 Hyperglycemia

Participant should be instructed to contact site staff in the event of suspected persistent hyperglycemia based on symptoms of hyperglycemia (e.g, thirst, polyuria, blurred vision), CGM readings above 250 mg/dL for >30% of time, or repeated fasting CGM readings >270 mg/dL (e.g. occurring 3 days in a week).

The investigator will perform additional laboratory tests as necessary to further investigate and may decide to offer rescue medications as necessary per Section 6.2.3.

6.8.3 Transitional Diet

Participants will be educated on the post-procedure transitional diet comprised of 24 hours of clear liquids (water, clear broth, sugar-free popsicles, tea) followed by a full liquid diet (dairy-free milk, protein shakes, strained soups) for 3 days, pureed food diet (pureed soup, sugar-free pudding, fat-free yogurt) for 3 days, and soft food diet (such as stew, fish, soft lean meat) for one week, and then transition to a normal diet as tolerated. Participants should be educated on the importance of hydration, especially during the transitional diet period to prevent hypovolemia. Participants should be instructed to contact the study team if s/he is unable to take food and unable to take at least 2 liters of water per day. Participants should also be instructed to avoid dairy products if experiencing any diarrhea during the transitional diet period.

6.8.4 Lifestyle Modification Counseling

The lifestyle modification counseling will follow standard of care as outlined in the Standard of Medical Care in Diabetes 2021[2]. The goal is to promote use and adherence to healthy eating patterns, increase physical activity (primarily through daily walking), and to recommend behavioral modification strategies.

6.8.4.1 Nutritional Recommendations

Participants will be educated on healthful eating patterns to improve overall health, emphasizing a variety of nutrient-dense foods in appropriate portion sizes. The nutritional recommendations will be individualized to achieve and maintain healthy body weight goals; to attain individualized glycemic control, and blood pressure, and lipid goals; and to delay or prevent the complications of diabetes. Participants will be educated on controlling portion sizes and intake of carbohydrates/starchy foods; increasing intake of low glycemic index and high-protein foods, as well as vegetables; and reducing intake of foods high in fat and sugar, and alcohol. The calorie recommendation will follow the recommendations of the Diabetes Prevention Program[12]. Participants who weigh ≤ 114 kg (≤ 250 lb) will be prescribed 1200-1500 kcal/d and those > 114 kg (> 250 lb) 1500-1800 kcal/d.

6.8.4.2 Physical Activity Recommendations

Participants will be encouraged to include more physical activity in their daily routine for example: walk more every day, climb the stairs instead of taking the lift or escalators, walk to the next bus stop, walk to shops, ride an exercise bike while watching TV. They will also be encouraged to do more activity in their leisure time such as: going for a walk, bicycling or swimming. They will be asked to start with short periods

of low-intensity exercise and increase the intensity and duration slowly. Their goal will be to include 150 minutes a week of moderate intensity and 75 minutes a week of vigorous intensity aerobic activity and muscle strengthening activities more than 2 days a week. Tools such as pedometers or mobile apps maybe recommended (but are not provided) to help individuals increasing their exercise. Any exercise will be adjusted to individual needs and activity levels.

Because of the variation in glycemic response to exercise bouts, participants who are on medications with hypoglycemic risks should be educated to check glucose levels before and after periods of exercise and about the potential prolonged effects (depending on intensity and duration).

6.8.4.3 Behavior Modification

At the same time as the nutritional recommendations and activity advice, participants will be instructed in behavioral modification strategies to promote adherence. Examples of these strategies include estimating portion size by using diabetes plates, reducing consumption of high sugar, high calorie beverages, putting the fork down between bites, etc.

CGM data will be reviewed with the participant to educate the participant as to what food choices minimize postprandial plasma glucose (PPG) and what physical activity choices directly lower PPG; troubleshoot for those with glucose out of their desired range; and reinforce choices that resulted in desirable glucose consequences.

7 STUDY EVALUATION AND STUDY VISITS

This protocol is developed at the time of the COVID-19 pandemic. To mitigate the risks of potential patient exposure, study assessments and visits may be performed remotely if necessary using the site's telehealth platform, and onsite visits can be limited to the ones necessary for study intervention and the integrity of the study. Participants will be provided with a scale to enable remote weight data collection. If necessary, nurse in-home visits may be used for in-home blood sample collections and vital signs data collection.

7.1 Demographics

Baseline demographic data will be collected to assess participant characteristics that include age, gender, race and ethnicity.

7.2 Medical History and Concomitant Medication

Participants' medical history and baseline medications will be reviewed and documented at screening visit. Changes in medical condition and medication usage will be reviewed, assessed, and documented at each study visit.

7.3 Anthropometric measurements

For onsite visits:

Height is measured without shoes in centimeter or inch and recorded in the eCRF to the nearest ½ cm or ¼ inch.

Body weight should be measured in kilograms (kg) or pound (Ib), to one decimal, without shoes and only wearing undergarments and an exam gown.

The BMI is calculated in the eCRF using the following

BMI = body weight (kg)/(height (m) x height (m)) [$kg/m^2 = lb/in^2 \times 703$].

Waist circumference is measured with the participant in a standing position with arms down their side and feet together. The measurement is taken at the midway between the lower rib

margin and the iliac crest using a non-stretchable measuring tape. The tape should touch the skin but not compress soft tissue. The participant should be asked to breathe normally and the measurement should be taken when the participant is breathing out gently.

The measurement will be recorded to the nearest ½ cm or ¼ inch using the same measuring tape throughout the trial.

For remote visits:

Participants will be provided with a scale to enable weight assessment at home. Participants will be instructed to wear only undergarments and no shoes when measuring weight.

Waist circumference will be measured by the nurse who also performs in-home blood sample collection.

7.4 Vital Signs

Systolic and diastolic blood pressure, pulse rate and respiratory rate should be measured in a sitting position after the participant has been resting for at least 5 minutes and by using standard clinical practice at the trial site. For remote visits, the measurements will be performed by a nurse who also performs in-home blood sample collection.

7.5 Physical examination

A physical examination will be performed during onsite visit and will include the following:

- General appearance
- Skin
- Thyroid gland
- Respiratory system
- Cardiovascular system
- Gastrointestinal system including mouth
- Central and peripheral nervous system
- Lymph node palpation

7.6 Electrocardiogram

A 12-lead ECG will be performed and interpreted locally by the investigator or delegate.

An ECG performed for any reason unrelated to the study within 7 days prior to the screening visit is acceptable provided no clinical symptoms suggestive of cardiac disease have occurred in the meantime. If the ECG was performed as a part of routine clinical practice on/before the date when the participant has signed the informed consent, it must be documented in the medical records that the reason for performing the procedure is not related to this study.

7.7 Laboratory Assessments

Local laboratories with appropriate accreditation will be used for all laboratory tests. Specific tests required at each visit are outlined in SoA (**Appendix 2**).

Fasting blood samples will be obtained at the screening and baseline visits, and at Week 1, 4, 12, 24, 36, and 48.

At these fasting visits, participants will not take any food or liquid within the last 8 hours prior to blood sampling, however water is allowed up until 2 hours prior to blood sampling. Participants can take their regular morning medications but should be advised not to take any of their diabetes medications on the

morning of their study visit. Participants should bring their diabetes medications to their study visits and take them after blood sampling.

7.8 Estimated Glomerular Filtration Rate (eGFR)

eGFR is calculated according to the MDRD equation[13]:

eGFR (ml/min/1.73m^2) = 175 x (standardized sCr)$^{-1.154}$ x (Age)$^{-0.203}$ x (0.742 if female) x (1.212 if Black)

Where sCr is serum creatinine reported in mg/dL

7.9 Mixed Meal Tolerance Test

Following a minimum of 8-hour fast, the participant will undergo an MMTT which involves the consumption of a standardized mixed meal, consisting of 200ml of Ensure Plus and an Optifast bar with a combined calorie of 533 Cal (carbohydrate 63.4g, protein 31.8g, fat 17.4g, Fiber 6.7g) , and collection of timed serial blood samples for measurement of plasma glucose, insulin and C-peptide through 180 minutes after consumption of the standardized meal (with no additional food intake during this time).

Participants will wear a CGM during the test. Prior to the test, the fasting glucose level between 70 mg/dL and 200 mg/dL will be confirmed via CGM reading or a capillary blood glucose measurement. The MMTT will only be performed if fasting glucose is within the range. If the fasting glucose is outside of this range, the test may be rescheduled once within the time window for this visit.

The participant should not take his/her glucose-lowering medications in the morning but instead bring the medications to the test. The medications should be taken after the test.

The MMTT should be performed in a laboratory with adequate emergency supplies in the event of severe hypoglycemia or severe hyperglycemia. The test should be started between 7AM and 11AM. A cannula is placed in a forearm vein. The standardized meal will be consumed within 5 minutes, and the blood samples will be collected within 15 minutes before consuming the standardized meal (ie, “0 minutes”), and at 10, 20, 30, 60, 90, 120, and 180 minutes after consumption. Blood sampling should occur as close as possible to the specified times (± 5 minutes) for the MMTT. After the test is completed, the participant may eat food and take his/her medications as prescribed by the investigator. Stable and acceptable glucose levels (glucose between 70 – 270 mg/dL over a 15 minutes) should be confirmed via CGM reading or a capillary blood glucose measurement prior to participant’s discharge. For participants with glucose levels ≤100 mg/dL, the glucose level should not be trending down in the 15-minute observation period and if it is, it should be treated until the glucose level is rising prior to discharge.

The MMTT will be performed at the time points specified in the SoA (Appendix 2). The test requires the participant to visit to the testing laboratory. If the risk of potential COVID-19 exposure overweighs the benefit of performing the test in the opinion of the Investigator, the investigator may decide not to perform this test but perform tests for HbA1c, FPG and insulin instead. Follow-up MMTT will only be scheduled in participants who had baseline MMTT data.

7.10 Test for Helicobacter Pylori

A negative urea breath test or stool antigen test for *H. pylori* is required for study inclusion. The participant should be off antibiotics, antacids, and bismuth for 2 weeks, and not be bleeding before the testing. If the test reveals the participant is positive for *H. pylori*, the participant will be treated accordingly and retested using a stool antigen test. If a stool retest is negative following completion of the treatment, the participant may be entered into the study. If, after treatment, the participant tests positive for *H. pylori* at the retest, s/he is to be excluded from the study.

7.11 Continuous Glucose Monitoring

Participants will receive a Freestyle Libre 2 CGM device and be educated on its use after their screening eligibility is confirmed. The first sensor should be placed and at least 5 days of CGM data collected within the baseline visit window. The CGM device will be placed according to the manufacture's standard instructions. Site staff will assist each participant to set up the CGM alert triggers, and train participants on how to use the reader, access and share the reports in LibreView on a computer.

Participants should be educated on not taking any supplements or medications containing high dose vitamin C (>500mg per day), including cold remedies such as Airborne® and Emergen-C® while wearing the CGM sensor.

The CGM Sensor should be removed prior to the DMR procedure. After the DMR procedure and prior to discharge, the Sensor should be placed on participants and the CGM will be used throughout the follow-up duration. The CGM data will be reviewed at each follow up visits by the treating physician for monitoring hypoglycemic events and prompting for further assessment on necessary therapeutic changes per Sections 6.2.1 and 6.2.2.

Additionally, the CGM data will be reviewed by the dietitian and participant during the lifestyle modification counseling sessions.

7.12 Endoscopic Follow-up

An endoscopic assessment will be performed at week 4 (±7 days) post procedure. It will be performed when the benefits of performing the test outweigh the risk of potential COVID-19 exposure in the opinion of the Investigator. The procedure and peri-procedural patient care will follow site's routine practice for diagnostic upper GI endoscopy.

In case of positive findings in the treated area on endoscopy, biopsy should be performed, and the samples sent to local laboratory for histological evaluation. Further endoscopic follow up should be performed when appropriate, at a minimum one assessment at 24 weeks, to confirm resolution of any clinically significant findings. Clinically significant findings include erosions, ulcers, scalloping of the duodenal mucosa, nodularity of duodenal mucosa, patchy or diffuse erythema, patchy or diffuse petechiae, blanching or discoloration of the duodenum.

7.13 Visit Schedule

A summary of all visits and procedures can be found in SoA (**Appendix 2**). A more detailed description of each visit and accompanying procedures is described below.

7.13.1 Screening Visit – Visit 1 (within 84 days from the Index Procedure)

To limit in-person visit, the screening visit may be performed remotely. Screening BMI eligibility will be based on self-reported height and weight. Potentially eligible participants will be scheduled for laboratory tests at the study laboratory. The following procedures/assessments will be performed during this visit:

- Informed consent prior to the conduct of any study-related procedures
- Inclusion and exclusion criteria
- Demographics
- Medical history including diseases, disorders and medications
- Diabetes history including diabetes medications
- Laboratory tests:
    - Hematology (CBC with differentials)
    - Metabolic panel (liver and renal function)
    - Fasting serum C-peptide, FPG, HbA1C

    - GAD antibodies
    - TSH
- H. Pylori (breath or stool test)
- Pregnancy test for females capable of becoming pregnant
- Registration on screening log

Once all data including testing results related to the screening have been obtained, the investigator will review the participant's eligibility for the study. If deemed eligible, participant will be scheduled for the baseline visit.

Eligible participant must meet all the inclusion criteria and none of the exclusion criteria with one exception. If a participant has met all other criteria except that s/he has been on stable glucose-lowering medication(s) for less than 12 weeks at the time of screening visit, the participant can be scheduled for baseline visit such that s/he will be on stable medication for 12 weeks at the time of baseline visit.

It is recognized that COVID-19 restrictions may cause delays in scheduling the index procedure, resulting in the screening visit being out of window. In case the screening visit is out of the visit window, the investigator will reassess the participant's eligibility by evaluating any changes in the participant's medical history and medications. The investigator may decide to repeat certain screening tests based on his/her medical judgement. If the investigator determines that the participant remains eligible for participating in the study, the participant may proceed to Baseline visit. Investigator's assessment and any repeated test results will be documented on eCRFs.

7.13.2 Baseline Visit – Visit 2 (within 21 days prior to the Index Procedure)

This visit will be performed onsite. The following evaluations/procedures are to be performed. Participant's study eligibility will be reconfirmed at this visit.

- Physical examination
- Anthropometric measurements including height, weight and waist circumference
- Vital signs
- Adverse event (changes in medical history)
- Concomitant medications
- 12-lead EKG
- Laboratory tests:
    - Hematology (CBC with differentials)
    - Metabolic panel
    - Glycemic parameters (HbA1C, MMTT, HOMA-IR)
    - Fasting lipid panel
    - Lipase, Amylase
    - Serum iron, ferritin, transferrin, saturation, serum folate, Vitamin D, Vitamin B12
    - International normalized ratio (INR) for participants on Warfarin (may be performed on Day 0)
- H. Pylori breath or stool test
- Pregnancy test for females capable of becoming pregnant
- Assessment for eligibility
- Preparation with gastroenterologist for procedure, medication management per Section 6.
- Diabetes education, including instruction on CGM use
- Treating physician review of diabetes history and titration of glucose-lowing medications per Section 6.2
- Review CGM data
- Lifestyle counselling

If the participant is no longer eligible for the study due to a change in the participant's condition, such as pregnancy, abnormal blood test values, HbA1C outside of the protocol range, or weight change resulting in a BMI outside of the protocol range, the participant will be excluded from the study and documented as a screen failure.

The screening and baseline visit may be combined if the screening visit falls within the baseline visit window. In this case, data collected during the combined visit will serve as both screen and baseline data.

It is recognized that new COVID-19 restrictions may cause delays in scheduling the index procedure, resulting in the baseline visit out of window. In case the baseline visit is out of visit window, investigator will reassess participant's eligibility by evaluating any changes in participant's medical history and medications, Investigator's assessment will be documented on eCRF. The following tests will be repeated for safety considerations or to serve as baseline data:

- Laboratory tests:
    - Hematology (CBC with differentials)
    - Glycemic parameters (FPG, HbA1C, insulin, HOMA-IR)
- Pregnancy test for females capable of becoming pregnant (may be performed on Day 0)
- Anthropometric measurements including weight and waist circumference (may be collected on Day 0)
- Vital signs (may be collected on Day 0)
- International normalized ratio (INR) for participants on Warfarin (may be performed on Day 0)

7.13.3 Index Procedure Visit – Visit 3 (Day 0)

See **Section 6.1** for details of the index procedure and post procedure instructions.

The following assessments/procedures will be performed.

- Handout participant study ID card
- Vital signs prior to discharge
- Concomitant medications
- Assessment of AEs
- Diabetes review and medication titration by treating physician

Participants will be instructed on transitional diet, the importance of hydration, use of CGM for the duration of the study, monitoring and preventing hypoglycemic events.

7.13.4 Follow-up Visits

Study follow up visits will be performed at Week 1, 2, 4, and every 4 weeks thereafter. The last study visit is Week 48. The visit windows and assessments/procedures to be performed at each visit are shown in SoA (**Appendix 2**).

To minimize COVID-19 risks, follow up visits may be performed remotely if necessary as below (note: "at home" denotes to participant's home or location of choice). Onsite visit is preferred and will not be considered as a protocol deviation.

- Body weight may be measured at home using the scale provided to participants
- Vital signs and waist circumference may be measured by a visiting nurse at home
- Testing samples (blood, stool, urine) may be collected by a visiting nurse at home
- Assessment of AEs, medication changes, CGM and diabetes review may be performed remotely using site's virtual visit platform
- Lifestyle modification counseling may be performed remotely at each visit.

If situation permits, visits at Week 24 and 48 should be performed onsite. However remote visits at these timepoints will not be considered as protocol deviation.

7.13.5 Unscheduled Visits

If a participant is hospitalized, seen in the emergency room, or has an unscheduled clinic visit, efforts should be made to collect the following data:

- Relevant medical history, physical examination, and laboratory test findings
- Concomitant medications
- Assessment of AEs

These assessments should be documented on the eCRFs as appropriate.

7.13.6 Premature Discontinuation

If a participant discontinues the study prematurely prior to his/her 24-week visit, to the extent possible, the participant should be scheduled for an onsite visit (V17A on SoA, Appendix 2), and the following assessments/procedures should be performed.

- Body weight, calculation of BMI, waist circumference
- Vital signs
- Concomitant medications
- Assessment of AEs that occurred since the last visit
- Hematology (CBC)
- Glycemic parameters (FPG, HbA1C, fasting insulin, HOMA-IR, MMTT)
- Metabolic panel
- Fasting lipid panel
- Serum iron, ferritin, transferrin, saturation, serum folate, Vitamin D, Vitamin B12
- CGM data
- Diabetes and medication review by treating physician
- Lifestyle modification counseling
- Study exit

If premature discontinuation is decided during a scheduled visit, the visit will be converted into a V17A and assessment procedures must be performed accordingly.

If a participant discontinues the study prematurely after his/her 24-week visit, a remote visit (R17A) should be scheduled. The following tasks will be performed.

- Concomitant medications
- Assessment of AEs that occurred since the last visit
- CGM data, if available
- Study exit

The primary reason for premature study discontinuation must be documented on the eCRF.

8 STUDY AND PARTICIPANT DISCONTINUATION

8.1 Early Study Termination

Sponsor may discontinue the study at any stage for any reason or no reason. Possible reasons for early termination may include unanticipated adverse device effects that may present unreasonable patient risk.

If the study is terminated early, the sponsor will provide a written statement describing why premature termination has occurred, and notify the investigator, IRB and the regulatory authority (if applicable). All applicable clinical study documents will be subject to the same retention policy as detailed in **Section 14.3**.

8.2 Participant Discontinuation

A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, or compliance reasons.

The following events will result in terminating the participant's participation in remaining follow-up:

- Participant voluntary withdrawal
- Participant withdrawn by the investigator as clinically indicated
- Participant becomes pregnant
- Participant has symptomatic COVID19 requiring medical treatment
- Participant lost to follow-up
- Participant death

At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted. See **Section 7.13.6** for data to be collected at the time of study discontinuation.

The sponsor must be notified of the reason for participant discontinuation. The site will document this information on the electronic case report form (eCRF) and make every effort to give a full description of the reason for withdrawal. Investigator will also report this information to the EC if required per local requirements.

Participants who exit the study early will not be replaced by enrolling additional participants.

8.3 Lost to Follow-up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site; this term does not apply to missed visits.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone or email contacts and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Efforts to regain contact should continue until the end of the participant's last scheduled visit.
- Only if contact with the participant is not regained by the end of the visit window of the last scheduled visit can the participant be considered lost to follow up.

9 SAFETY ASSESSMENT

9.1 Adverse Events

An AE is any untoward medical occurrence in a clinical investigation participant that occurs during any part of the clinical study, whether related to the investigational device or not. Pre-existing conditions are

not reported as AEs unless there has been a worsening in severity or frequency which cannot be attributed to the disease's natural history or progression.

For AEs, the event description, severity (See Appendix 1 for definitions), date of onset, treatment, outcome, and relationship to device will be collected on the AE eCRF. When reporting an AE, if a clinical diagnosis is available, the diagnosis should be reported instead of individual symptoms.

All procedure- and device-related AEs must be followed until resolution or stabilization (the investigator does not expect any further improvement or worsening of the event).

An Adverse Device Effect (ADE) is any adverse event that is considered possibly-related or related to the device. An ADE may occur at any time after exposure to the investigational device.

Determination of whether there is a reasonable possibility that the investigational device caused or contributed to an AE will be reported by the investigator and reviewed by the medical monitor .

Determination will be based on assessment of temporal relationships, biologic plausibility, association (or lack of association) with underlying disease, and presence (or absence) of more-likely cause.

9.1.1 Serious Adverse Event

A SAE is an event that:

- Led to a death
- Led to a serious deterioration in health resulting in
    - a life-threatening illness or injury
    - a permanent impairment of a body structure or body function
    - in-patient hospitalization (>24 hours) or prolongation of an existing hospitalization
    - requires medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment of a body structure or body function
- Led to fetal distress, fetal death or a congenital abnormality or birth defect

Here, "life-threatening" refers to an event when the patient is at substantial risk of dying at the time of the adverse event, it does not refer to an event that hypothetically might have caused death if it were more severe; "permanent" is defined as irreversible impairment or damage to a body structure or function, excluding trivial impairment or damage.

For the purpose of this study, diagnostic endoscopy is not considered as "intervention" in the context of SAE. Planned hospitalization for a pre-existing condition is not considered as a SAE.

9.1.2 Serious Adverse Device Effect

An SADE is an SAE that is possibly related or related to the device.

9.1.3 Unanticipated Serious Adverse Device Effects

Unanticipated Serious Adverse Device Effects (UADE) are any serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in any of study documents such as the investigational plan, investigator's brochure, Instruction for Use (IFU), or Informed Consent.

When an AE meets the definition of a UADE or that relationship is unknown, the investigator will report the event to sponsor within 24 hours but no later than five (5) working days after the investigator first learns of the effect and reports to the reviewing EC as required.

9.1.4 Abnormal Pancreatic Enzyme Levels

Changes in serum amylase, lipase levels post procedure should trigger assessment for potential pancreatic injury.

The diagnosis of acute pancreatitis requires two of the following three features[3]:

- Abdominal pain consistent with acute pancreatitis (acute onset of a persistent, severe, epigastric pain often radiating to the back)
- Serum lipase and/or amylase level at least three times greater than the upper normal limit
- characteristic findings of acute pancreatitis on imaging.

For all confirmed events of pancreatitis, the following additional information should be reported if available:

- Signs and symptoms of pancreatitis
- Specific laboratory test supporting a diagnosis of pancreatitis:
- Imaging performed and consistency with pancreatic disease
- Treatment for and complications of the event
- Relevant risk factors for pancreatic disease
- Family history of pancreatitis

Participants with an increase in pancreatic enzyme levels (>3 x ULN) post procedure should be followed until their levels return to the baseline level.

9.1.5 Hypoglycemia

Hypoglycemia is defined as follows (ADA 2020):

- Level 1 hypoglycemia is a blood glucose concentration 54–70 mg/dL (3.0–3.9 mmol/L).
- Level 2 hypoglycemia is a blood glucose concentration <54 mg/dL (3.0 mmol/L), which is typically the threshold for neuroglycopenic symptoms.
- Level 3 hypoglycemia is a clinical event characterized by altered mental and/or physical functioning that requires assistance from another person for recovery

Documented symptomatic hypoglycemia: An episode during which typical symptoms of hypoglycemia are accompanied by a measured plasma glucose concentration ≤ 3.9 mmol/L (70 mg/dL).

Probable symptomatic hypoglycemia: An episode during which symptoms of hypoglycemia are not accompanied by a plasma glucose determination but that was presumably caused by a plasma glucose concentration ≤ 3.9 mmol/L (70 mg/dL).

Blood glucose concentration may be determined by a laboratory test or capillary blood glucose measurement using a glucose meter and test strips. CGM alerts must be confirmed by blood glucose values.

Level 3 hypoglycemia is defined as **severe hypoglycemia** and should be reported as adverse event. Other non-severe hypoglycemia will be recorded on hypoglycemia eCRF.

To avoid duplicate reporting, all consecutive blood glucose values ≤ 70mg/dL occurring within an 1-hour period may be considered to be a single hypoglycemic event.

9.2 Device Relationship (Causality)

Causality assessment is required for AEs (and SAEs) that occur during clinical investigations. The following terms will be used during this study:

- Related - An AE that is directly and clearly related to the Investigational Device
- Possibly Related - There is a reasonable likelihood that the event is due to the Investigational Device, as evidenced by the following:
    - There may be temporal association with the Investigational Device (e.g., within 24 hours of the DMR procedure)
    - The event, or level of severity of the event, is unlikely to be explained by other etiologies (known to be related to the study disease, patient's baseline medical condition, or concomitant medications)
- Unlikely Related - The AE is not temporally related to the Investigational Device, or is known to be related to one of the following:
    - Morbidity associated with underlying medical condition
    - Anesthesia
    - Upper GI endoscopy
    - Concomitant medication
    - A relationship to the Investigational Device is not biologically plausible
- Not related - The AE is definitely not related to the Investigational Device

9.3 Adverse Event Reporting

9.3.1 Sponsor Reporting Requirements

The Sponsor will conduct an evaluation of any reported UADEs and will report the results of this evaluation to the FDA, IRBs, and participating Investigators within 10 working days after first receiving notice of the event. In addition, if any of the stopping rules are triggered (Section 4.5), it will be reported to FDA, IRB, and participating investigators following the UADE reporting timeline.

9.3.2 Clinical Site Reporting Requirements

- All AEs and ADEs will be recorded by the investigator or designee on the eCRFs provided
- UADE or suspected UADE, or any event that can potentially trigger the stopping rules as described in Section 4.5, will be reported to the sponsor within 24 hours of knowledge of the event, followed by a written confirmation by the investigator within 5 working days
- Any other SAEs are to be reported to the sponsor within 36 hours
- The investigator at each site is ultimately responsible for reporting AEs, SAEs and UADEs to the IRB according to IRB requirements

10 MEDICAL MONITORING

Device relationship of the SAEs will be reviewed and adjudicated by an independent medical monitor who has relevant expertise and is not affiliated with the sponsor or the study site. The medical monitor may require additional explanatory or supportive documents, which may include source documents from the hospital, as needed, when reviewing the events. The medical monitor will also monitor the overall safety of the study and recommending appropriate actions to the sponsor, when necessary.

11 DATA SAFETY MONITORING BOARD

The DSMB is composed of independent physicians who are not participating in the study and will not be affiliated with the sponsor, the Investigators, or the investigational sites. The DSMB will review the study on a periodic basis and per requirements defined in Section 4.4 and 4.5, is responsible for making recommendations regarding any safety or compliance issues throughout the course of the study and may recommend to the sponsor to modify or stop the study. However, all final decisions regarding study modifications or study termination rest with the sponsor.

Cumulative safety data will be reported to the DSMB and reviewed on an ongoing basis throughout enrollment and follow-up periods to ensure subject safety. DSMB will also review individual events when stopping rules (Section 4.5) are triggered. Every effort will be made to allow the DSMB to conduct an unbiased review of subject safety information. All DSMB reports will be made available to the FDA upon request, but will otherwise remain strictly confidential.

DSMB will meet according to the following schedule:

a. Initial meeting will commence before the study start or shortly after the study start.

b. DSMB will convene as often as necessary but at a minimum at the schedule described in Section 4.4.

c. Additionally, a DSMB meeting may be requested by DSMB member, the Sponsor, or IRB at any time to discuss safety concerns if it arises.

DSMB recommendation may include the following

- Continue study without modification
- Continue study with conditions
- Suspend or terminate the enrollment
- Permit re-commencement of enrollment following a suspension

12 STATISTICAL DESIGN AND ANALYSIS

12.1 Statistical Overview

The primary endpoint, defined as the proportion of participants experiencing one or more device- or procedure-related serious adverse events, will be evaluated at week 12. Secondary endpoints will be assessed at times specified in Section 3, including presentation of change from baseline by visits for glycemic parameters, liver enzymes and other cardiometabolic metrices.

12.2 Sample Size Considerations

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.

12.3 Analysis Populations

The following analysis populations are defined for the study: Intent-to-Treat (ITT), modified Intent-to-Treat (mITT), Per-Protocol (PP) and Completed Cases (CC). The primary safety analysis will be performed on the ITT population. The primary effectiveness analysis will be performed on mITT population.

- Intent-to-Treat: The Intent-to-Treat population includes all enrolled participants as defined in Section 5.3 regardless of whether or not the participant received the full treatment.
- Modified Intent-to-Treat: The mITT population consists of the ITT population participants who received the target treatment (at least 6 cm of duodenum treatment) and that have at least one post-treatment follow-up.
- Per-Protocol: The Per-Protocol population is a subset of the mITT population and includes all participants who received the target treatment (at least 6 cm of duodenum treatment), have at least one post-treatment follow-up, do not have any major eligibility violations, and maintained stable glucose-lowering medications for 24 weeks post procedure.

12.4 Statistical Analysis

12.4.1 General Statistical Considerations

Analyses will be performed according to the general principles and directions outlined in these methods.

- Continuous data will be summarized using descriptive statistics: mean, standard deviation, median and range or interquartile range. Categorical variables will be summarized using frequency counts and percentages.
- For events which can occur multiple times in a single subject (e.g., adverse events), summaries will be comprised of the number and percentage of subjects with an event and the total number of such events. The proportion of subjects with events will be considered primary for analysis purposes.
- In general, available data will be used for all analyses, and missing data will not be replaced or otherwise imputed in summaries and analyses of study outcomes. However, to avoid biasing results due to confounding therapies, effectiveness data collected after an identified initiation of rescue medication for hyperglycemia will be replaced by the last value collected prior to such rescue intervention.
- Although the study is not explicitly powered to test *a priori* statistical objectives, comparisons citing p-values may be made between baseline metrics to values collected post-intervention, and between subgroups including the two treatment arms. In such cases, p-values will be presented using two-sided tests at a 0.05 level of significance or equivalently one-sided tests at a 0.025 level of significance.

12.4.2 Accountability and Demographics

The number of participants completing the study and withdrawing from the study will be presented along with reasons for withdrawal.

Descriptive summaries for baseline medical history and demographic characteristics including age, gender, height, weight, baseline BMI, diabetes history, glycemic parameters, and baseline medications will be presented.

12.4.3 Primary Endpoint Analysis

The primary endpoint of the study is the proportion of participants experiencing one or more device- or procedure-related serious adverse events within 12 weeks post-procedure. The analysis will be performed using the ITT population, then tabulated and reported for each treatment arm and overall. Fisher's exact test will be used to assess differences which may be present between groups

Additionally, an overall summary of AEs will be provided including the number of events and percent of participants with any AEs, SAEs, and UADEs. For each type of event, the number of events and number and percent of participants with the event will be provided. Separate summaries of all adverse events will be summarized by seriousness and by relationship to device and procedure.

Only events occurring at or after the index procedure will be counted for the purpose of safety analysis. Events occurring prior to the index procedure will be considered as medical history.

12.4.4 Effectiveness Analysis

Secondary endpoints are summarized in Section 3. The primary analysis of the study's secondary endpoints will be performed using the mITT population. The analysis will also be performed using the PP population when appropriate.

Results for these endpoints will be tabulated and reported for each treatment arm at each timepoint for which data were specified to be collected, using change scores from baseline where appropriate. For binary outcomes, Fisher's exact test will be used to assess differences which may be present between groups, while t-tests or Wilcoxon's rank-sum will be applied for continuous outcomes depending on the normality assumption. Effectiveness endpoints collected at multiple timepoints post-intervention (e.g., HbA1c) will also be assessed longitudinally using repeated-measures mixed-effects models with time as the repeated measure and treatment arm as a factor variable. Assessment of overall change from baseline and comparisons between treatment arms will then be predicated principally upon these repeated-measures analyses.

12.4.5 Subgroup Analysis

Subgroup analyses of the primary and key secondary endpoints will be performed a priori for the following pair of subgroups:

- FPG ≥180 at baseline
- FPG < 180 at baseline

The study is not formally powered to detect statistical significance within or among subgroups, and hence any hypothesis testing comparing results within or between these cohorts will be considered in that context. Observance of trends and qualitative comparisons between the subgroups will therefore be of greatest interest.

13 QUALITY CONTROL AND QUALITY ASSURANCE

13.1 Selection of Study Sites and Investigators

The sponsor will select investigators who are qualified by training and experience to perform clinical research in this field and to participate in the clinical investigation. Sites will be selected based upon an assessment of the qualifications of the Primary Investigator and the facilities at each site. All investigators will be trained on the device, the protocol and all study procedures prior to enrolling participants.

A pre-investigation visit will be conducted at each study site to assure that the investigator and the study staff understand the obligations for using and managing the investigational device, following the study protocol, obtaining informed consent, adhering to GCP and FDA regulations, and conducting clinical research.

13.2 Training

13.2.1 Site Training

All investigators/study personnel are required to attend sponsor training sessions, which may be conducted at a site initiation visit or other appropriate training sessions. Remote over-the-phone or web-based training will take place as necessary. Training of investigators/study personnel will include, but is not limited to, the investigational plan, participant recruitment, enrollment (including review of inclusion and exclusion criteria), participant retention, investigational device usage, protocol requirements, case report form completion, and study personnel responsibilities. All investigators/study personnel that are trained must sign a training log (or an equivalent) upon completion of the training. Investigator/study personnel must not perform any study-related procedures prior to being trained.

Investigators who perform the Endogenex procedure will be trained on device use. Sponsor personnel will provide technical support for all the Endogenex procedures during the study.

13.2.2 Monitor Training

The sponsor or designee will engage monitors that are qualified by appropriate training and experience to review the conduct and quality of the study. Prior to working on the study, monitors will be trained to the investigational plan, case report forms, and the device/procedure knowledge. Such training will be documented.

13.3 Study Monitoring

Sponsor and/or a designee (e.g., a Contract Research Organization), will monitor the clinical study in a manner consistent with FDA regulations and the Good Clinical Practice (GCP) standards adopted by the sponsor.

The investigator is required to ensure compliance with all procedures required by the Investigational plan and by study procedures provided by the sponsor. The investigator agrees to provide reliable data and all information requested by the Investigational Plan including eCRFs, discrepancy clarification requests or other appropriate instruments according to the instructions provided, and to ensure direct access to source documents by sponsor representatives.

Study monitoring provides the sponsor with the opportunity to evaluate the progress of the study, to verify the accuracy and completeness of eCRFs, to resolve any inconsistencies in the study records, and to ensure that all protocol requirements, applicable regulatory requirements, and investigator's obligations are being fulfilled. Centralized data review will be performed to identify missing data, data inconsistencies, potential protocol deviations, unusual trends, site performance, etc. Source data verification (SDV) will be performed remotely and/or onsite to ensure data accuracy. Periodical onsite monitoring visit will be performed to ensure study compliance, adequate adverse event reporting, and to perform other tasks that can't be accomplished remotely.

The investigator and his/her staff will be expected to cooperate with sponsor's personnel or designee and to be available during the monitoring visits to answer questions sufficiently and to provide any missing information. Monitoring visits may be performed remotely, especially in consideration of COVID-19. The Investigator and his/her staff will provide necessary assistance to facilitate remote monitoring.

13.4 Source Data Verification

Source data verification ensures accuracy and credibility of the data obtained. During monitoring, reported data is reviewed with regard to being accurate, complete, and verifiable from source documents (e.g., participant files, physician notes, discharge summaries, operative records, study worksheets, etc.). All data reported on the eCRF should be supported by source documents, unless the eCRF also serves as a source document. Source data verification may be performed remotely.

13.4.1 Definition of Source Data

Source data includes all information in source documents (original records, certified copies of original records, appointment books, original laboratory records, CGM data, and original data recorded on customized worksheets) and includes all original recordings or copies of clinical findings, observations, or other activities in a clinical study necessary for the reconstruction and evaluation of the study. Certain data may be directly entered into eCRF. In this case, the eCRF serves as source document.

13.4.2 Direct Access to Source Data/Documents

The investigator(s)/institution(s) will permit direct access to source data/documents for study-related monitoring, audits, IRB and regulatory inspection(s). For remote source data verification, the Investigator and his/her staff will provide the study monitor remote access to source records.

Consenting participants are agreeing to allow the sponsor or designee access and copying rights to pertinent information in their medical records and their CGM data relevant to study participation. As part of the informed consent, the investigator or designee will obtain permission for regulatory authorities to review any records identifying participants in this study. The sponsor will not otherwise release any personal information (refer to **Section 15.3** Confidentiality).

13.5 Protocol Deviations

It is the investigator's responsibility to ensure that there are no deviations from the protocol except in cases of medical emergencies, when the deviation is necessary to protect the life or physical well-being of the participant. In the event of any deviation from the protocol, a Protocol Deviation Form will be completed. The occurrence of protocol deviations will be monitored by the sponsor for evaluation of investigator compliance to the protocol, Good Clinical Practice (GCP), and regulatory requirements. The investigator will inform the IRB of protocol deviations according to requirements of each reviewing IRB.

A protocol deviation for this protocol consists of, but is not limited to, the following:

- Failure to obtain participant’s informed consent prior to any study-specific activities and the index procedure
- Enrollment of participants who do not meet all eligibility requirements
- Failure to conduct protocol required clinical follow-ups and within time windows
- Failure to report SAEs according to protocol requirements

In the event of any deviation from the protocol, the investigator will be notified of the site’s non-compliance. Corrective actions will be advised if necessary and the methods, plan or other activities put in place to ensure non-recurrence will be documented by the investigator and forwarded to the sponsor or their designee. Continued protocol deviations despite re-education of study site personnel and/or persistent protocol deviations may result in termination of the site’s study participation. Participants already enrolled at these sites will continue to be followed per protocol guidelines.

13.6 Termination of Study Site Participation

The sponsor reserves the right to stop study enrollment at a study center at any time during the study. Specific instances that may precipitate terminating a study center may include the following:

- Unsatisfactory participant enrollment
- Failure to comply with protocol
- Failure to obtain informed consent
- Inaccurate and/or incomplete data recording on a recurrent basis

- Failure to report SAEs in timely manner on a recurrent basis
- Loss of (or unaccounted for) investigational product inventory
- Severe protocol deviations without justification or failure to implement corrective actions

14 DATA HANDLING AND RECORD KEEPING

For the study duration, the investigator will maintain complete and accurate documentation including but not limited to the following: medical records, study progress records, laboratory reports, CGM data, case report forms, signed informed consent forms, device records, and correspondence with the IRB and study monitor/sponsor, AE reports, and information regarding participant discontinuation or study completion.

14.1 Source Documentation

For the duration of the study, the investigator shall take responsibility for maintaining complete and accurate source documentation.

The following materials should be included in the patient record:

- Participant medical history/physical condition prior to study involvement
- Dated and signed notes on the day of entry into the study referencing the study, the sponsor, participant study ID number, and a statement confirming informed consent
- Dated and signed notes from each participant's visit (for specific results of procedures and exams)
- AEs reported and their outcome including supporting documents
- Participant's condition upon study completion or withdrawal

14.2 Case Report Form Completion

Data will be collected primarily using the electronic case report forms (eCRF). Laboratory data and CGM data may be collected separately and integrated into the data analysis.

Primary data collection will be performed by site staff trained on the protocol and eCRF completion. All data fields will be completed where appropriate. However, if data are not available (i.e., missed visit, etc.), the site will receive instruction regarding electronic documentation. As data are entered, automated cross-check programs will search for any data discrepancies in the eCRFs. Appropriate error messages will be generated, allowing for the modification and/or verification of the entered data. Queries will generally be sent to the investigational site using an electronic data query system that includes an automated audit trail of the corrections. The investigator, or designee, will certify that the data are complete and accurate by applying an electronic signature to the eCRF. Any subsequent alterations, corrections, or additions will be reviewed and electronically signed by the investigator prior to the database lock.

The sponsor or designee will provide clinical monitoring to include eCRF review and parity checks with the source documentation, including operator worksheets retained with eCRF documentation and health care facility charts.

14.3 Record Retention

The investigator/site will maintain all records pertaining to this study for the later of (a) ten years following study completion, or (b) ten years after the study has been terminated by the sponsor, or (c) as otherwise instructed by the sponsor. Investigator will be notified by sponsor of the date of completion or discontinuation of the study.

To comply with these requirements, the investigator will not dispose of or transfer any records relevant to this study without either (1) written permission from the sponsor, or (2) providing an opportunity for the sponsor to archive the records with an external vendor.

15 ETHICAL CONSIDERATIONS

15.1 Institutional Review Board

IRB approval for the protocol and informed consent form will be obtained by the investigator prior to study participation by participants. The approval letter must be obtained prior to beginning this study and a copy must be provided to the sponsor. No changes will be made to the protocol or informed consent form without appropriate approval from the IRB, the sponsor and/or the regulatory agencies. Additionally, the investigator or representative will provide an IRB membership list or assurance number to the sponsor or its designee.

As per oversight IRB requirements, the investigator will report study progress until it is completed. Further, any protocol amendments as well as associated informed consent changes will be submitted to the IRB and written approval must be obtained prior to implementation.

15.2 Informed Consent

Written informed consent must be obtained prior to any study-related activities and the index procedure.

The investigator should clearly explain that this is an elective procedure and should discuss the potential risks and benefits associated with participation in this study.

Participants providing informed consent agree to permit the sponsor or designee access to pertinent information in their medical records and other study related data concerning their participation in this study. This confidential patient information may be shared with regulatory agencies as required; however, the sponsor undertakes not to otherwise release the participant's personal and private health information.

15.3 Confidentiality

The identity of participants enrolled in the study and the information contained in their study records will be kept confidential by the sponsor. As part of the investigator training session, investigators will be instructed in the importance of confidentiality and the techniques for protecting participant's privacy and rights. Participant's personal information will be handled at all times in accordance with appropriate confidentiality standards and applicable data protection and local privacy laws.

Each participant will be assigned a study identification number to be used on eCRFs and other study records sent to the sponsor or its designee. Initials will also be used to track study participants.

Confidentiality will be protected as much as possible throughout the study. Medical records will be reviewed by representatives of the sponsor and/or its designee and will be made available for review as required by the IRB and FDA regulations. Results of data collected will be reported as statistical information only. The participant's name will not be used or otherwise disclosed unless required by law or regulation.

16 INVESTIGATIONAL DEVICE MANAGEMENT

16.1 Device Accountability

The sponsor will only distribute investigational devices to sites that are part of the clinical investigation. The sponsor will maintain complete, current and accurate records pertaining to the distribution of the investigational devices and follow record keeping requirements in accordance with Good Clinical Practices and FDA regulations.

The investigator is responsible for maintenance of adequate records of the receipt, disposition, and/or return of all investigational devices distributed to their site. At study termination, or termination of the site from

participation in the study the sponsor will provide specific instructions to the study sites on unused investigational devices.

Use of the investigational device outside of the protocol (e.g., compassionate use) without prior written approval is strictly forbidden and may constitute grounds for removal of the investigator/site from the study.

16.2 Device Return

All unused investigational devices, including those unused due to malfunction, device failure, device complaint or device dropped on the floor, must be returned to the sponsor or its designee immediately according to the returned goods process. All devices and/or remaining components that are associated with a device malfunction or clinical procedural failure should be returned to the sponsor.

17 REFERENCES

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APPENDIX 1. DEFINITIONS

Adverse Event Severity

- **Mild:** no or transient symptoms, no interference with the participant's daily activities
- **Moderate:** marked symptoms, moderate interference with the participant's daily activities.
- **Severe:** incapacitating with inability to perform daily activities; unacceptable.

The Los Angeles Classification of esophagitis[14]

- Grade A: One (or more) mucosal break no longer than 5 mm that does not extend between the tops of two mucosal folds
- Grade B: One (or more) mucosal break more than 5 mm long that does not extend between the tops of two mucosal folds
- Grade C: One (or more) mucosal break that is continuous between the tops of two or more mucosal folds but which involve less than 75% of the circumference
- Grade D: One (or more) mucosal break which involves at least 75% of the esophageal circumference

Hypoglycemia (ADA 2020)

- Level 1 hypoglycemia is a blood glucose concentration 54–70 mg/dL (3.0–3.9 mmol/L).
- Level 2 hypoglycemia is a blood glucose concentration <54 mg/dL (3.0 mmol/L), which is typically the threshold for neuroglycopenic symptoms.
- Level 3 hypoglycemia is a clinical event characterized by altered mental and/or physical functioning that requires assistance from another person for recovery

Severe hypoglycemia: Level 3 hypoglycemia per ADA 2020 definition.

Documented symptomatic hypoglycemia: An episode during which typical symptoms of hypoglycemia are accompanied by a measured plasma glucose concentration ≤ 3.9 mmol/L (70 mg/dL).

Probable symptomatic hypoglycemia: An episode during which symptoms of hypoglycemia are not accompanied by a plasma glucose determination but that was presumably caused by a plasma glucose concentration ≤ 3.9 mmol/L (70 mg/dL).

Severe hyperglycemia: for purpose of this study, severe hyperglycemia is defined as FPG > 270 mg/dL confirmed by repeated measures more than 3 days apart

Diabetic ketoacidosis (DKA): an acute, major, life-threatening complication of diabetes characterized by hyperglycemia, ketoacidosis, and ketonuria.

APPENDIX 2. SCHEDULE OF ACTIVITIES

	Screening	Baseline[1]	Index Procedure	Week 1	Week 2	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 28	Week 32	Week 36	Week 40	Week 44	Week 48 End of Study	Premature discontinuation within 24 weeks	Pre-mature discontinuation post 24
Clinic Visit(V)/Remote Visit (R)	R1	V2	V3	V/R4	R5	V/R6	R7	V/R8	R9	R10	V11	R12	R13	V/R14	R15	R16	V17	V17A	R17A
Timing of visit (weeks)	-12	-3	0	1	2	4	8	12	16	20	24	28	32	36	40	44	48		
Visit window (days)	-84 to -5	-21 to -1		±2	±3	±5	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	+30		
SUBJECT RELATED INFO/ASSESMENTS																			
Informed consent	X																		
In/exclusion criteria	X	X																	
Medical history/Diabetes history	X																		
Concomitant medication	X	X	X	X		X		X			X			X			X	X	X
Demographics	X																		
Treating physician diabetes assessment and medication review		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Lifestyle Counseling		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Diabetes education, Handout and instruct in CGM use		X																	
Handout ID card			X																
Study Exit																	X	X	X
VITAL SIGNS AND PHYSICAL EXAMINATION																			
Height		X																	
Body weight		X		X		X		X			X			X			X	X	
BMI		X		X		X		X			X			X			X	X	
Waist circumference		X						X			X			X			X	X	
Blood pressure and pulse rate		X	X	X		X		X			X			X			X	X	
Physical examination		X															X	X	
LABORATORY TESTINGS																			
Fasting plasma glucose	X	X				X		X[6]			X			X			X[6]	X	
HbA_{1c}	X	X				X		X			X			X			X	X	
Fasting insulin		X				X		X[6]			X			X			X[6]	X	
Fasting serum C-peptide	X																		

	Screening	Baseline[1]	Index Procedure	Week 1	Week 2	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 28	Week 32	Week 36	Week 40	Week 44	Week 48 End of Study	Premature discontinuation within 24 weeks	Pre-mature discontinuation post 24
Clinic Visit(V)/Remote Visit (R)	R1	V2	V3	V/R4	R5	V/R6	R7	V/R8	R9	R10	V11	R12	R13	V/R14	R15	R16	V17	V17A	R17A
Timing of visit (weeks)	-12	-3	0	1	2	4	8	12	16	20	24	28	32	36	40	44	48		
Visit window (days)	-84 to -5	-21 to -1		±2	±3	±5	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	+30		
MMTT (Mixed meal tolerance test)		X						X									X	X	
HOMA-IR		X				X		X			X			X			X	X	
Fasting lipid panel		X									X						X	X	
Metabolic Panel [2]	X	X		X				X			X			X			X	X	
Pancreatic Enzyme (Lipase, Amylase)		X		X				X											
Serum Iron, ferritin, transferrin, saturation, serum folate, Vitamin D, Vitamin B12		X									X						X	X	
CBC with differential	X	X		X		X		X			X			X			X	X	
Serum Glutamic acid decarboxylase antibody (Anti-GAD)	X																		
Thyroid-stimulating hormone (TSH)	X							X[3]			X[3]			X[3]			X[3]		
H. Pylori test	X	X																	
Pregnancy test [4]	X	X																	
International Normalized Ratio (INR)[7]		X																	
EKG		X																	
ENDOSCOPIES																			
DMR procedure			X																
Endoscopic follow up						X					X[5]								
SAFETY																			
Hypoglycaemic episodes	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CGM		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

[1] Screening and baseline visits may be combined if screening visits or tests falls within baseline visit window.

[2] Metabolic panel includes albumin, total protein, ALP, ALT, AST, bilirubin, BUN, creatinine, BUN/creatinine ratio, eGFR.

[3] For participants on oral thyroid replacement therapy only.

[4] For women with child-bearing potential.

[5] Required if there were positive findings in the treated area at the 4-week endoscopy.

[6] Only when MMTT is not performed.

[7] INR is required prior to procedure only if participant is on Warfarin.

APPENDIX 3. SAMPLE PATIENT INFORMATION CARD

If you are required to see your doctor for other medical conditions, please show this card to your doctor.
PLEASE CARRY THIS CARD AT ALL TIMES

Study Participant Card for the REGENT-1 Study

Date of Procedure: _____

Investigator Physician's contact information: _____ at _____

*This person is participating in a clinical study and had undergone an endoscopic duodenal mucosal regeneration procedure with a device that delivers microprocessor-controlled pulsed electric field to the mucosa and submucosa of the duodenum in the treatment of T2D. For questions regarding the study, please contact the Investigator.

Endogenex Inc. 151 Cheshire Ln N # 400, Plymouth, MN 55441. Telephone: +1 763-251-6820

APPENDIX 4. PARTICIPANT GLUCOSE MONITORING INSTRUCTIONS

(Note: this instruction is to be handout to participants when they are trained to use the CGM at baseline)

1. Why do I need to monitor my glucose levels?

   Individuals with type 2 diabetes can develop hypoglycemia (blood sugar levels that aretoo low) or hyperglycemia (blood sugar levels that are too high), especially at the times of medication changes, diet changes, exercise, illness or physical stress. You are participating in a study that tests a new treatment procedure for diabetes. To decrease your risk of developing severe hypoglycemia or severe hyperglycemia, your glucose levels will be monitored closely during your participation in the study using a Continuous Glucose Monitoring System.

2. What is Continuous Glucose Monitoring?

   Continuous Glucose Monitoring (CGM)) is a device with a glucose sensor placed under the skin that communicates back to a reader device track glucose levels throughout the day and night and can alert you if your levels go too high or too low.

   The CGM that will be used in this study is called Freestyle Libre 2 from Abbott Diabetes Care. It is approved for clinical use in the US.

3. When to check blood glucose levels using a finger stick?

   The Freestyle Libre 2 Reader has a built-in blood glucose meter that can be used to test blood glucose using blood from a finger stick if needed. It uses only FreeStyle Precision Neo test strips which will be provided to you.

   You should check your blood glucose level using the strip and the meter in the following situations:

   - when you see the symbol  on your reader during the first 12 hours of wearing a Sensor,
   - when your CGM reading does not match your symptoms
   - when your CGM reading does not include a number
   - when you want to check or confirm whether your level is too low

4. Where can I find more information about the Freestyle Libre 2 CGM?

   When you receive the device, it comes with a package insert. Please make sure you review all product information and follow the manufacturer's instructions.

   You can also find more information on this device at https://www.freestyle.abbott/us-en/support/overview.html.

5. Do I need to wear the CGM device for the duration of the study? Why?

   Yes. You will wear the CGM for at least 5 days before the Endogenex procedure.

   After the Endogenex procedure, you will wear the CGM device for the duration of the study to closely monitor your glucose levels. This is to make sure that if your levels are too high or too low, you will be alerted and you can contact your study doctor as soon as possible.

6. Is there anything that I should not take while wearing the Freestyle Libre 2 CGM?

You should not take any supplements or medications containing high dose vitamin C (>500mg per day), including cold remedies such as Airborne® and Emergen-C® while wearing the CGM sensor. High dose vitamin C may interfere with the sensor readings.

7. What to do if I get alarms?

   Freestyle Libre 2 has default glucose alarm settings. Low Glucose Alarm is set to 70 mg/dL. High Glucose Alarm is set to 240 mg/dL. If you get a Low or High Glucose Alarm, you must obtain a glucose reading on your CGM and check your blood glucose using a finger stick.

   If your level is confirmed low (at or below 70 mg/dL), you should eat or drink 15 grams of carbs and recheck your level in 15 minutes (15-15 rule). If your level is still low, recheck it, repeat the steps until it's back to normal. When your level is normal again, you may eat a meal or snack to keep it stable and prevent another low.

   Options like below can give you 15 grams of carbs:

   - Half a cup of fruit juice
   - Half a cup of full-sugar soda
   - 6 large jelly beans
   - 1 tablespoon of sugar or honey

   If you receive alarms multiple times a day, you should check your report and see if you should contact your study doctor (see #7 and #8 below).

   The Reader will automatically communicate with the Sensor when in range (within 20 feet of you). For your safety, please make sure your Reader is always within 20 feet of you, and the alarm function is always on.

8. When should I contact my study doctor?

   You should contact your doctor if you experience the following:

   - You experience symptoms of hypoglycemia (levels too low). Symptoms suggestive of hypoglycemia include lightheadedness, tremor, shaking, sweating, tingling, blurred vision, difficulty concentrating, and confusion. With severe hypoglycemia, patients may develop altered consciousness, coma, or seizures.
   - You experience symptoms of hyperglycemia (levels too high). Symptoms suggestive of hyperglycemia includes increased thirst, frequent urination (peeing), blurred vision, headache.
   - Your CGM readings "Very High (>250 mg/dL)" for >30% of time.
   - Your CGM readings "Low (54-69)" for >4% of time.
   - Your CGM readings "Very Low (<54 mg/dL)" for >1% of time.
   - Your CGM readings are above 270 mg/dL before breakfast for 3 days in a week.
   - You have skin reactions at the location of the sensor placed or any other issues or questions about your CGM use, health conditions, or medications.
   - You are unable to take food and unable to drink at least 2 liters of water per day (about 8 glasses).

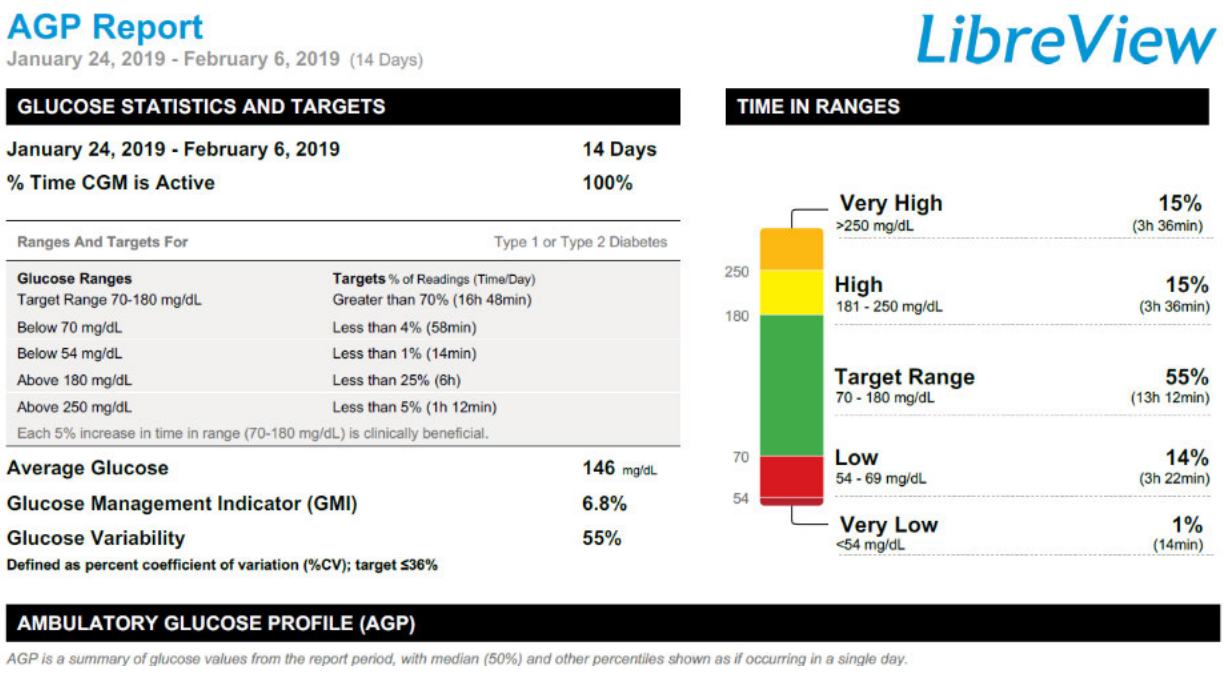
9. Where can I find these CGM readings?

Your CGM device comes with a Reader that will show your levels and send you alerts if your level is too high or too low. You must scan the Sensor to get your real-time current glucose level as the Reader will not provide this information without a scan. It is recommended that you check your levels when you first wake up in the morning, during the day, and before you go to bed. The Sensor can hold 8 hours of data. You can scan the Sensor as frequently as you like but at least once every 8 hours to make sure you don't lose data. You should also check your levels before and after exercise.

Your CGM device comes with instructions on how to connect with a computer and download LibreView, a software application that works with your CGM device. You can find more detailed information in LibreView on your computer. You will be taught how to find reports like the one below. On the report below, you can find the information you need to decide whether you should contact your study doctor.

You should review your CGM reports on your LibreView account and share them with your study doctor or his/her staff at least once a week for the first 4 weeks after the Endogenex procedure. Afterwards, you should review the reports at least once every two weeks. Of course, you can review the reports as frequently as you like.

Please make sure you do share your reports with your study team as described above. This will allow your study doctor and his/her staff to closely monitor your levels.



AGP Report

January 24, 2019 - February 6, 2019 (14 Days)

LibreView

GLUCOSE STATISTICS AND TARGETS

January 24, 2019 - February 6, 2019	14 Days
% Time CGM is Active	100%

Ranges And Targets For	Type 1 or Type 2 Diabetes
Glucose Ranges	**Targets** % of Readings (Time/Day)
Target Range 70-180 mg/dL	Greater than 70% (16h 48min)
Below 70 mg/dL	Less than 4% (58min)
Below 54 mg/dL	Less than 1% (14min)
Above 180 mg/dL	Less than 25% (6h)
Above 250 mg/dL	Less than 5% (1h 12min)

Each 5% increase in time in range (70-180 mg/dL) is clinically beneficial.

Average Glucose	146 mg/dL
Glucose Management Indicator (GMI)	6.8%
Glucose Variability	55%

Defined as percent coefficient of variation (%CV); target ≤36%

TIME IN RANGES

250
180
70
54

Very High	>250 mg/dL	15% (3h 36min)
High	181 - 250 mg/dL	15% (3h 36min)
Target Range	70 - 180 mg/dL	55% (13h 12min)
Low	54 - 69 mg/dL	14% (3h 22min)
Very Low	<54 mg/dL	1% (14min)

AMBULATORY GLUCOSE PROFILE (AGP)

AGP is a summary of glucose values from the report period, with median (50%) and other percentiles shown as if occurring in a single day.