Evaluation of the Fractyl Duodenal Remodeling System for the Treatment of Type 2 Diabetes

Protocol Number: C-10000

Sponsor:
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Protocol Summary

Title:	Duodenal Remodeling for the Treatment of Type 2 Diabetes
Protocol ID#:	C-10000
Device:	Fractyl Duodenal Remodeling System (DMR) is an endoscopic treatment consisting of mucosal lift with saline and circumferential thermal ablation along a length of the duodenum. The submucosal expansion step is designed to provide a uniform ablative surface and a thermally protective layer of saline between the duodenal mucosa that is to be ablated and deeper tissue layers that are to be protected.
Study Objective:	The primary objective is to investigate the preliminary safety and effectiveness of the Fractyl Duodenal Remodeling System for the treatment of Type 2 Diabetes through 36 months follow up period by assessing participant response to a Mixed Meal Tolerance Test, HbA1c levels and adverse event profile. This study will be used to support expanded clinical assessment in future evaluations
Study Design:	• Proposed Start Date: March 2013 • Up to 3 Investigational Sites • Maximum enrollment of 60 participants • Single arm, non-randomized open label trial • Participant follow up at 2, 7, 14, days and 1, 2, 3 6, 9, 12, 18, and 24months post procedure
Indication for Use:	The Fractyl Duodenal Remodeling System is intended for use on participants with Type 2 Diabetes who are poorly controlled with oral medications and disease diagnosed less than 10 years before study entry
Inclusion Criteria	1. Participants Age > 28 years and ≤ 75 years 2. Male or Female 3. Participants with Type 2 Diabetes who have been treated for ≤ 10 years and are on stable oral diabetic medications for a minimum of 3 months 4. Participants with an HbA1c ≥ 7.5 and ≤ 10.0 % 5. Participants with a BMI > 24 and < 40 6. Participants willing to comply with study requirements and able to understand informed consent

7. Participants who have signed an informed consent form

Exclusion Criteria

1. Participants diagnosed with Type 1 Diabetes or with a history of ketoacidosis
2. Participants using insulin for more than 12 months
3. Participants with probable insulin production failure (defined as fasting C Peptide serum <1ng/mL)
4. Participants that have known autoimmune disease as evidenced by a positive anti-GAD blood test
5. Participants requiring prescription anticoagulation therapy and/or dual anti-platelet therapy including aspirin who cannot discontinue their medication for 14 days before and 14 days after the procedure
6. Participants with iron deficiency anemia - either currently or in their history
7. Participants with current symptomatic hypocalcemia or vitamin D deficiency (routine calcium and/or vitamin D supplementation is acceptable)
8. Participants with abnormalities of the GI tract preventing endoscopic access to the duodenum
9. Participants with symptomatic gallstones or kidney stones at the time of screening
10. Participants with a history of pancreatitis
11. Participants with an active systemic infection
12. Participants with or a history of coagulopathy, upper gastro-intestinal bleeding conditions such as ulcers, gastric varices, strictures, congenital or acquired intestinal telangiectasia
13. Participants with celiac disease
14. Participants with active malignancy. Those who have had remedial treatment and/or are cancer free for 5 years can be enrolled
15. Participants with known active hepatitis or active liver disease
16. Participants emotionally unstable or exhibiting psychological characteristics which, in the opinion of the Investigator, makes the Participant a poor candidate for clinical trial participation
17. Participants with previous GI surgery that could affect the ability to treat the duodenum such as participants who have had a Bilroth II, Roux-en-Y gastric bypass, or other similar procedures or conditions
18. Participants unable to discontinue NSAIDs (non-steroidal anti-inflammatory drugs) during treatment through 2 weeks post-procedure
19. Participants receiving weight loss medications such as

Meridia, Xenical, or over the counter weight loss medications
20. Participants with known diagnosis or pre-existing symptoms of systemic lupus erythematosus, scleroderma or other autoimmune connective tissue disorder
21. Participants with active and uncontrolled GERD defined as grade II esophagitis or higher
22. Participants who are current illicit substance abusers or alcoholics
23. Participants participating in another ongoing investigational clinical trial
24. Participants taking corticosteroids or drugs known to affect GI motility (i.e. Reglan)
25. Participants who are not potential candidates for duodenal exclusion surgery (such as Roux-en-Y gastric bypass surgery) or general anesthesia

Outcomes:

- HbA1c
- Mixed Meal Tolerance Test
- Fasting blood glucose
- Serum lipid panel (LDL, HDL, triglycerides, total cholesterol)
- Blood Pressure
- Weight
- Blood chemistry analysis
- Amylase, lipase
- Serum, plasma for data collection
- Adverse Events
- Symptomatic hypoglycemic events

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List of Abbreviations and Definition of Terms

ACRONYM	DESCRIPTION
AE	Adverse Event
BMI	Body Mass Index
CBC	Complete Blood Count
CRF	Case Report Form
DMR	Fractyl Duodenal Remodeling System
GI	Gastrointestinal
GIP	Gastric Inhibitory Peptide
GLP-1	Glucagon-like peptide 1
HbA1c	Glycated Hemoglobin
IHF	International Conference on Harmonization
ICF	Informed Consent Form
IEC	Independent Ethics Committee
IV	Intravenous
mg/dL	Milligrams per Deciliter
MMTT	Mixed Meal Tolerance Test
ng/mL	Nanograms per milliliter
QA	Quality Assurance
NPO	Nil per os (withhold oral food and fluids)
SAE	Serious Adverse Event
UADE	Unanticipated Adverse Device Effect

1.0 Introduction

1.1 Background

Type 2 diabetes is an endocrine disorder linked to the obesity epidemic that is characterized by chronically elevated blood sugars the downstream complications of hyperglycemia. There are approximately 300 million type 2 diabetics throughout the world (1). The disease has spread rapidly in rich and poor nations and has been associated with the explosion of Western dietary influences around the globe. In the United States alone, there are 26 million type 2 diabetics – and this number is expected to triple by 2050 (2). The UK National Health Service (NHS) apportions 10% of its budget to the disease and its complications. Type 2 diabetes is the most prevalent and costly pandemic of our time.

Type 2 Diabetes is also an imperfectly understood chronic and progressive condition (3). Early in the disease, participants display intolerance to ingested glucose and resistance to insulin function. Insulin secretion from the pancreatic beta cells initially increases to compensate for the body's own acquired resistance. This maintains euglycemia through the early course of the illness. Physiologic studies during this time reveal insulin resistance in peripheral tissues and impaired capacity for insulin to suppress glucose production in the liver. However, as the disease progresses, beta cells eventually fail and the body's endogenous insulin secretion proves inadequate to maintain effective glucose homeostasis.

The hyperglycemia that results from this complex metabolic disturbance exerts its pathologic effect in small and large blood vessels. The impairment of small blood vessels can lead to renal failure, retinopathy, and peripheral neuropathy. As a consequence, diabetes is the leading cause of renal failure, blindness, and non-traumatic amputations in developed nations. In addition, type 2 diabetes contributes significantly to large vessel atherosclerotic diseases, increasing the risk of myocardial infarctions, stroke, and peripheral vascular disease.

The current paradigm for medical therapy for type 2 diabetics begins with improvements in diet and exercise. The vast majority of participants do not achieve improved glycemic control with lifestyle changes alone. There are also several classes of pharmacologic therapy, including drugs that increase insulin secretion from the pancreas, drugs that enhance the body's sensitivity to insulin, and a variety of other drug classes. Many participants still do not achieve good glycemic control despite the wide variety of drugs available to them. These participants, despite tremendous antipathy to injectable agents, often must proceed to insulin therapy (4). All told, however, nearly 50% of participants remain poorly controlled despite all of these measures.

In contrast to the inadequacy of drugs and insulin therapy, certain forms of bariatric surgery have a profound anti-diabetic effect in ways that clinicians have

only begun to appreciate and characterize (5,6). Though the mechanisms underlying this improvement in glucose homeostasis are not well understood, certain compelling observations have been made. In particular, surgeries that divert the passage of nutrients around the duodenum, or first portion of the small intestine, appear to lead to nearly immediate, extremely durable, and weight-independent anti-diabetic effects (7). Because the GI tract is the largest endocrine organ in the body, the bypass of the proximal small bowel leads to dramatic hormonal changes that improve glucose homeostasis (8,9). This appears to occur without dramatic changes in absorption from the intestine. Rather, these hormonal changes restore the ability of the liver to suppress endogenous glucose production in response to insulin, a physiologic process that is otherwise impaired in diabetic participants.

How does bypass of the proximal small bowel exert such a strong anti-diabetic effect? There are two main theories, both of which are likely at least partial contributors (10). First, some believe that the delivery of excess nutrients to the distal small bowel leads to enhanced secretion of GLP-1 (and perhaps additional related insulin secreting hormones) from the GLP-1-rich entero-endocrine cells of the terminal ileum and colon. Enhanced GLP-1 release into the blood stream after an ingested meal has a number of beneficial effects on glucose homeostasis.

A second theory is that diabetics acquire mucosal alterations in their proximal small bowel that contribute to insulin resistance and glucose intolerance. Data from rats and humans suggest that prolonged exposure to a Western diet leads to a dramatic increase in enteroendocrine cell numbers and subsequent hormone production after a meal (11). Other studies have demonstrated hypertrophy of the mucosa of the small bowel in diabetic participants (12). In this way, the body's insulin resistance arises from hormones produced by the proximal small bowel as a consequence of these mucosal alterations. Bypass of nutrients around the duodenum prevents the release of these hormones and therefore immediately leads to an improvement in glucose tolerance after surgery.

Unfortunately, as effective as these surgeries are, one cannot imagine that surgery can be offered to enough participants to adequately address the scope of the diabetes pandemic. There are several reasons for this. The primary indication for bariatric surgery remains morbid obesity, and yet most diabetics are not morbidly obese. Also, the risks (of major morbidity, mortality, and need for re-operation) from bypass surgeries are quite real and pose a significant barrier to its wholesale adoption as a treatment for type 2 diabetes. In addition, surgery is extremely invasive, psychologically traumatic, and physically demanding. For all these reasons, only a minority of diabetics currently undergoes surgery as a treatment for their diabetes. Given the constraints just outlined, it is also hard to imagine that this number can increase substantially.

A scalable solution that leverages the physiologic learning from bariatric surgery but can be cost-effectively delivered to a much larger segment of the population is surely needed. Some medical devices have been developed that aim to mimic aspects of bariatric surgery for the treatment of diabetes and obesity (13). In particular, the GI Dynamics *Endobarrier* is an endoluminal semi-permanent implant sleeve that anchors in the duodenal bulb and prevents the interaction of food with the duodenal and proximal jejunum (14). It has achieved CE Mark approval for sale in Europe and Australia. Like in the surgeries described above, diabetic participants who receive a GI Dynamics implant enjoy a remarkable improvement in their glucose control.

The Fractyl Laboratories Duodenal Remodeling System allows physicians to safely and effectively ablate the duodenal mucosa in type 2 diabetic participants. The objective is to alter the body's hormonal response to food intake in a similar way to that achieved with bypass surgery or *Endobarrier* implantation, but without the challenges associated with endoluminal surgery or long-term gastrointestinal implants.

1.2 Device Name

The device used for execution of this protocol is the Fractyl Duodenal Remodeling System. The system consists of two main components: the Revita Catheter and a console.

1.3 Purpose

The purpose of this protocol is to evaluate the initial safety profile of the Fractyl System and its effect on participants with Type 2 Diabetes. This will be determined through the monitoring of adverse events and outcome measures including Mixed Meal Tolerance Test (MMTT) and blood serum HbA1c concentration.

1.4 Intended Use

The Fractyl Duodenal Remodeling System is intended for use on participants with Type 2 Diabetes who are poorly controlled with oral medications and disease diagnosed less than 10 years before study entry.

1.5 Study Objectives

The objectives of this evaluation are to evaluate the initial safety profile and efficacy outcome measures of the Fractyl Duodenal Remodeling System through the 6 month post treatment period on participants with Type 2 Diabetes Mellitus.

The safety objective will be evaluated through the adverse event profile and their associations to the study device or procedure during the study follow up period.

The efficacy objective will be evaluated through the testing of blood HbA1c and MMTT. As this is an initial clinical evaluation, no specific minimum outcome requirement is set.

2.0 Device Description and Endoscopic Technique

2.1 Device Description

The Fractyl Laboratories Duodenal Mucosal Resurfacing (DMR) Technology consists of a Revita Catheter and a console.

Revita Catheter

The Revita Catheter is a sterile, single use device that performs two functions: 1) it places saline into the submucosa of the duodenum to create a thermal barrier while also lifting the mucosa with saline to create a more uniform surface for ablation and 2) ablates the mucosal surface using heated water recirculating inside a balloon.

To achieve its function, the Revita Catheter is constructed of a multi-lumen shaft with a balloon affixed to its distal end. Affixed to the outside of the balloon are three narrow shafts with a port that are used to draw a vacuum and place the saline during the mucosal lifting portion of the procedure. Within each shaft is a fluid lumen with a miniaturized needle affixed to the distal end. Each needle is wholly constrained within the port ensuring its safe use. The opposite proximal end of the shaft is fitted with a handle and saline and vacuum lines that are affixed to a console unit to control its function. The catheter will be available with 1 balloon diameter: 24mm.

Console:

The console is a reusable piece of capital equipment that provides the functionality to perform the mucosal lift and hot fluid ablation steps of the procedure. It is controlled through the use of a software \ user interface monitor. Prior to use, it is fitted with a sterile single use line set that serves as the pathway for the saline to be placed into the duodenal submucosa.

For mucosal lifting the console passes a vacuum through each of the vacuum lumens, delivers saline to each of the 3 fluid delivery lumens, and inflates and deflates the balloon at the end of the catheter. Pressure transducers in the console monitor the balloon pressure as a function of infused water.

The console also contains a pump system that is used to deliver the hot fluid to the Catheter. The system is fitted with thermistors for temperature measurement, solenoid valves to direct fluid in and out of the catheter and one hot and one cold water reservoir.

2.2 Duodenal Resurfacing Technique (DMR)

After an overnight fast, participant will arrive 1 hour prior to the scheduled procedure in the gastroenterology endoscopy suite. Intravenous (I.V.) access will be obtained and I.V. antibiotics (1 g of I.V. cefazolin or equivalent) will be

administered if deemed appropriate by the investigator. I.V. sedation with fentanyl, meperidine, propofol or midazolam or other combinations and will be administered using American Society for Gastrointestinal Endoscopy (ASGE) guidelines and per standard hospital protocol. Alternatively, general anesthesia can be used during those cases where appropriate sedation cannot be achieved.

The DMR procedure is performed endoscopically by a trained endoscopist, assisted by other physicians or nurses trained in performing the procedure. A thorough examination of the upper gastrointestinal tract will be performed using a standard endoscope.

The Investigator will make the decision on the length of the treatment in the duodenum based on the specific patient's anatomy. The treatment response will be based on data gathered during the course of the evaluation. A second treatment in the same participant may be completed if the participant does not experience improvement in their Type 2 Diabetes symptoms a minimum of 30 days after the initial treatment.

Mucosal Lift and Ablation:
The The Revita Catheter is placed in the proximal duodenum distal to the papilla. Using the console interface, the balloon is inflated and vacuum delivered to draw the intestinal mucosal tissue onto the ports located on the balloon. The Operator actuates the handle mechanism to advance the needle into the submucosal space within each of the ports. The console delivers saline into the submucosa through the needles within the lumens of the Catheter resulting in complete circumferential lift of the mucosa. Once complete, the ablation cycle is started and hot water is circulated into the balloon to complete an ablation of the previously expanded tissue. The balloon is deflated and the catheter repositioned distally to the next segment to be treated. The process of expansion, ablation and repositioning is repeated until the needed length of duodenum is treated. The Revita Catheter and endoscope are then removed.

3.0 Study Design and Methodology

3.1 Study Design

This protocol is a Phase I, open label, first in human evaluation and will be accomplished using a single arm, non-randomized study design. The results of this evaluation will be used to evaluate initial safety and performance characteristics of the Fractyl Duodenal Remodeling System and help define future pilot and randomized trials. A maximum of 60 participants will all receive the investigational treatment and will be followed in accordance with the follow up procedures outlined in this protocol.

3.2 Study Scope

3.2.1 Participating Institutions

This evaluation will utilize a maximum of 3 clinical sites. A list of participating institutions will be maintained in the Trial Master File and provided annually to regulatory authorities as required.

3.2.2 Participant Population

The Fractyl Duodenal Remodeling Study will include Participants as specified in the inclusion/exclusion criteria. Study participants will have Type 2 Diabetes for less than 10 years with an HbA1c between 7.5% and 10%. Detailed enrollment criteria can be found in the Participant Selection section of this protocol.

3.3 Study Duration

It is anticipated that the overall duration of this investigation will be approximately 60 months including all participant enrollment, collection of follow up assessments, and data analysis. The trial will be initiated at each institution following approval of the country regulatory authorities and the respective Independent Ethics Committees. Enrollment of participants will take approximately 24 months based on two sites accruing 2 participants per month. Follow up visits will occur for an additional 24 months with final data collection and analysis taking up to an additional 6 months.

3.4 Study Endpoints

This protocol is designed as a single arm non-controlled evaluation. As such, this protocol will not specify a specific primary endpoint that defines participant and study success. Instead the results of this evaluation will be used to further define the clinical procedures and participant populations that will best respond to the treatment with an optimum safety profile to ensure future success.

The efficacy endpoints that will be analyzed will include:

- Reduction in HbA1c levels over the 12 month study period
- Improvement in Mixed Meal Tolerance Test between Screening and 3 months
- Reduction in Fasting Blood Glucose levels over the 12 month study period
- Reduction in medications to control Type 2 Diabetes over the 12 month study period

The safety endpoints that will be analyzed will include:

- Incidence of device and procedure related adverse events
- Increase in pancreatic enzymes indicative of pancreatitis (amylase and lipase)
- Incidence rate of significant and/or symptomatic hypo-glycemic events

3.5 Control of Bias and Validity

The following measures have been included in the study to control bias and increase study validity

- The study design utilizes multiple investigators.
- The study design utilizes objective endpoints that are measured by validated test methods. These include Mixed Meal Tolerance Test, Fasting Blood Glucose and HbA1c. Standardized methods and protocols for performing and evaluating tests and examinations have been incorporated into the study protocol.
- The study monitor will review data collection forms as they are received from the study sites to assure there are no missing or incorrect data. Missing or incorrect data will be corrected before the data forms are entered into the database. Site re-training will take place as required to ensure compliance with the protocol.

4.0 Participant Selection and Enrollment

All participants presenting with Type 2 diabetes for less than 10 years and who are not on insulin are potential study candidates and will be approached for consent prior to any data collection by a member of the institution's research team. A screening and enrollment log will be provided to study sites to maintain a cumulative log of all screened participants.

Every effort will be made to establish eligibility of the participants prior to enrollment. Only participants who meet all eligibility criteria will be enrolled in the study. Reasons for screening failure will be documented on the site screening log. Actual study enrollment is defined as the time of initiation of the Fractyl procedure.

Participants may not be enrolled in the investigation without first granting consent. The informed consent process is accomplished by providing the participants with a copy of the Informed Consent Form. The contents of this form are discussed with the participant allowing adequate time for questions. If participants are willing to participate in the study, they indicate their willingness by signing the form.

All participants enrolled in the study are considered follow-up eligible and will be required to adhere to the follow-up schedule outlined in this protocol. Participants withdrawing consent after treatment will not be required to undergo follow-up after withdrawal.

4.1 Inclusion Criteria

Before entry into this study, each participant will be evaluated by the investigator to determine if the participant satisfies the eligibility criteria for this trial. To be eligible, the participant must meet all of the characteristics in the "Inclusion

Criteria" and none of the characteristics listed in the "Exclusion Criteria" listed below.

1. Participants Age > 28 years and ≤ 75 years
2. Male or Female
3. Participants with Type 2 Diabetes who are treated for ≤ 10 years and are on stable oral diabetic medications for a minimum of 3 months
4. Participants with an HbA1c ≥ 7.5 and ≤ 10.0%
5. Participants with a BMI > 24 and < 40
6. Participants willing to comply with study requirements and able to understand and comply with informed consent
7. Participants who have signed an informed consent form

4.2 Exclusion Criteria

1. Participants diagnosed with Type I Diabetes or with a history of ketoacidosis
2. Participants using insulin for more than 12 months
3. Participants with probable insulin production failure (defined as fasting C Peptide serum <1ng/mL)
4. Participants that have known autoimmune disease as evidenced by a positive anti-GAD blood test
5. Participants requiring prescription anticoagulation therapy and/or dual anti-platelet therapy including aspirin who cannot discontinue their medication for 14 days before and 14 days after the procedure
6. Participants with iron deficiency anemia – either currently or in their history
7. Participants with current symptomatic hypocalcemia or vitamin D deficiency (routine calcium and/or vitamin D supplementation would not be excluded)
8. Participants with or a history of abnormalities of the GI tract preventing endoscopic access to the duodenum,
9. Participants with symptomatic gallstones or kidney stones at the time of screening
10. Participants with a history of pancreatitis
11. Participants with an active systemic infection
12. Participants with or a history of coagulopathy, upper gastro-intestinal bleeding conditions such as ulcers, gastric varices, strictures, congenital or acquired intestinal telangiectasia
13. Participants with celiac disease
14. Participants with active malignancy. Those who have had remedial treatment and/or are cancer free for 5 years can be enrolled
15. Participants with known active hepatitis or active liver disease
16. Participants emotionally unstable or who exhibit psychological characteristics which, in the opinion of the Investigator, make the participant a poor candidate for clinical trial participation

17. Participants with previous GI surgery that could affect the ability to treat the duodenum such as participants who have had a Bilroth 2, Roux-en-Y gastric bypass, or other similar procedures or conditions
18. Participants unable to discontinue NSAIDs (non-steroidal anti-inflammatory drugs) during treatment through 2 weeks post procedure phase
19. Participants receiving weight loss medications such as Meridia, Xenical, or over the counter weight loss medications
20. Participant with a known diagnosis or pre-existing symptoms of systemic lupus erythematosus, scleroderma or other autoimmune connective tissue disorder
21. Participants with active and uncontrolled GERD defined as grade II esophagitis or greater
22. Participants with active illicit substance abuse or alcoholism
23. Participants participating in another ongoing investigational clinical trial
24. Participants taking corticosteroids or drugs known to affect GI motility (i.e. Reglan)
25. Participants who are not potential candidates for duodenal exclusion surgery or general anesthesia

5.0 Study Procedures

The Fractyl Duodenal Remodeling System will be clinically evaluated utilizing a standardized protocol as described below. The protocol has been designed to minimize variations in participant selection, endoscopic technique, post-procedure management, participant evaluation, and documentation of results. To further assure consistency, each investigator will be trained in all aspects of the protocol, including the endoscopic technique and appropriate documentation.

Study participants will be evaluated pre-procedure, post-procedure, upon discharge, and at 7, 14 days, 1, 3, 6, 9, 12, 18, and 244 months post-operatively in the Investigator's office. In addition follow up phone calls will be completed at 2 days and 2 months post procedure. The evaluations to be completed at each study visit will include evaluation of treatment response, standard blood analysis for metabolic function, serum hormone analysis and post treatment endoscopic assessment. A summary of the data collection requirements is presented in Appendix 1. Included in this section are the acceptable time windows for participant follow-up to be completed at each study time point. A detailed description of the assessment to be performed at each study visit is provided below.

5.1 Visit 1: Screening

Participants presenting with Type 2 Diabetes will potentially be eligible for participation in the study. Before being considered for enrollment into this clinical evaluation or receiving any study-specific diagnostic tests to further determine eligibility, the Informed Consent Form must be completed and signed by the participant.

Once an Informed Consent Form has been successfully completed, the participant will be evaluated for his or her ability to meet the inclusion and exclusion criteria. Only those individuals who meet all of the inclusion criteria and none of the exclusion criteria are to be enrolled in the study. A list of participants excluded from enrollment into this study, or considered participant screen failures will be maintained for each investigation site. The following screening procedures and baseline data are collected for all participants.

5.1.1 Participant History/Physical Exam

Participant demographics and medical history will be completed by the physician or assigned medical personnel. Specific parameters include:

- Age
- Gender
- Height/Weight/BMI
- Duration of diabetic symptoms
- Concurrent health conditions
- Medication Use
- Previous surgeries/treatments

Female participants of childbearing potential must have a negative pregnancy test within 14 days prior to treatment and must agree to avoid pregnancy during the course of the study.

5.1.2 Standard Blood Analysis

All participants being screened for inclusion for this study will have sufficient blood drawn to complete the following tests. As indicated in the table below, the test name will have the associated specific evaluations included. This data will provide a baseline for comparison at future follow up visits.

Test Name	Evaluation to be included
Complete Blood Count	White Blood Cell Count and Differential Total Hemoglobin Hematocrit
Blood Chemistry	Blood Urea Nitrogen Calcium Chloride Creatinine Glucose Potassium Sodium
Liver Enzymes	Alanine Aminotransferase Aspartate Aminotransferase Total Billirubin

	Alkaline Phosphatase
Pancreatic Enzymes	Amylase Lipase
Fasting Lipid Panel	Total Cholesterol High Density Lipoprotein Low Density Lipoprotein Triglycerides
Fasting Glucose	Same
Glycolated hemoglobin (HbA1c)	Same
Fasting Insulin	Same

Participants with test results outside acceptable ranges that are indicative of an underlying condition that would compromise their participation in the study based on the Investigator's expertise are excluded from the study

In addition participants with an HbA1c below 7.5% and above 10.0% are also excluded. The reason for a participant's exclusion are documented in the site screening log.

One extra tube of blood will be taken and stored at -20 degrees C as a back-up for use as needed.

5.1.3 Mixed Meal Tolerance Test

All participants will be administered a Mixed Meal Tolerance Test at screening to establish their hormone response to nutrients by measuring the concentration of glucose, gut and pancreatic hormones, and metabolic substrates. Results will be compared to post procedure follow up values.

Results will be compared to post procedure follow up values.

The mixed meal tolerance test will be performed after a 10 hour overnight fast using Ensure (200 ccl) ingested over 10 minutes, with assays measured at 0 (fasting), 15, 30, 45, 60, 90, 120 and 180 min after oral ingestion via blood analysis.

5.1.4 Participant Questionnaires

Participants will be administered one outcome questionnaires at baseline for comparison to follow up visits.

The SF-36 will be used to assess the participant's Quality of Life. All questionnaires will be completed by the participant.

5.1.5 Endoscopy/Biopsy

A screening endoscopy is performed to visually examine the participant's GI tract to ensure they meet the requirements of the exclusion criteria concerning anatomical anomalies that would preclude the ability to complete the treatment. A biopsy is also taken to evaluate the baseline tissue.

Participants with active H. pylori during screening endoscopy may be enrolled if they are treated via medication.

5.2 Visit 2: Procedure/Enrollment

The Fractyl Duodenal Remodeling procedure utilizes both a trans-oral over the wire and endoscopic approach to minimally invasively ablating and remodeling the duodenum. The procedure may be completed in an endoscopic suite or in an operating room depending on the facilities and support at each investigative site. All participants will be monitored and anesthetized per each facility's standard protocol. Information about the devices and endoscopic technique are detailed in section 2.0 above

Prior to the start of the Duodenal Remodeling Procedure, the following evaluations will be completed to establish an accurate baseline measurement and documented on the appropriate CRFs:

- Weight
- Standard Blood Analysis per section 5.1.2

All participants will be administered prophylactic antibiotics and proton pump inhibitors. Antibiotics will consist of 1 g of Cefazolin (or equivalent) administered via IV the day of the procedure and continuing orally on a daily basis for 3 days.

Proton Pump Inhibitors can consist of 40mg Omeprazole (or equivalent) and is administered 7 days in advance of the procedure and continuing for 30 days post post-procedure.

Immediately before completing the Fractyl procedure, an endoscopic assessment of the esophagus, stomach, duodenum and associated structures is completed to ensure there are no conditions that would exclude the participant from the study.

The actual length of duodenum treated will be per the Investigator's discretion based on patient anatomy and results from this study.

Details of the procedure are documented on the applicable CRF including:

- Operative date
- Investigator and assist personnel
- Devices used
- Procedural notes and length of treatment
- Total procedure time

- Procedural complications

Unforeseen events (findings or procedures) may occur during the procedure. These unforeseen events are those that are not planned as part of this procedure (eg, a drop in oxygen saturation or evidence of intestinal bleeding, etc). Unforeseen events that are emergent in nature should be recorded as adverse events and the investigator should reassess the participant's suitability for continued participation in this study.

Immediately following the procedure, the participant is transported to the recovery area and monitored according to the hospital/physician protocol for procedures of this nature. The participant may be released from the recovery room to the nursing unit when they have met the hospital's criteria for discharge from the recovery area. Immediate postoperative care will be dictated by the hospital or physician's standard care protocol regarding post-anesthesia recovery.

Pain and other medications may be administered at the discretion of the Investigator.

A second treatment may be completed by the Investigator if the participant does not demonstrate an improvement in their symptoms a minimum of 30 days after the primary treatment.

5.3 Discharge (Day will vary)

Prior to discharge all participants are examined and evaluated for the presence of any adverse events that may have occurred between the procedure and discharge. Participant discharge from the hospital will be accomplished according to standard hospital/physician practice.

Participants are also instructed to stay on their current diabetes medication. Glucose levels will be monitored once per day using a glucose monitor after discharge. If the Participant does not routinely monitor their glucose level, a glucose monitor and proper instruction is provided by the site.

A continuous glucose monitoring device may also be used in addition to the standard monitor for 7 days pre and post procedure if available at the investigational site.

Participants are eligible to be discharged after the procedure provided they meet the following minimum discharge requirements:

- Participant is able to ambulate
- No signs of infection
- Participant bodily functions are active
- Participant is not hypoglycemic (defined as glucose < 70 mg/dL)

A Participant's hospital stay can be extended based on need as determined by the Study Investigator.

Guidelines for post procedure diet are as follows. Actual diet can be modified as needed by the study Investigator:

- Day 0: NPO
- Day 1-5: Clear liquids
- Day 6-14: Soft Diet
- Day 15 and beyond: Diet as tolerated

5.4 Participant Follow Up

Participant follow-up will be completed at 2, 7, 14 days, and 1, 2, 3, 6, 9, 12, 18, and 24months post procedure as outlined in the Assessment Schedule located in **Appendix 1.** The 2 day and 2 month visits will be completed via phone call. All other visits will be office visits completed at the Investigator's office. The study assessments required at each follow-up visit are detailed below.

5.4.1 Visit 3: 2 Day Phone Call (+1/-0 days)

At day 2 post procedure, the participant will be contacted via phone, no office visit is required. The following information will be collected during the call:

- Medication Use: All medication use will be recorded on the appropriate CRF.
- Any adverse events reported by the participant.

5.4.2 Visit 4: 7 Day Office Visit (+/- 2 days)

The following evaluations will be completed at the 7 day office visit and documented on the appropriate CRFs:

- Weight
- Blood Pressure
- Targeted Physical Exam: All symptoms noted as abnormal on baseline physical exam will be evaluated. New signs or symptoms not previously reported will be evaluated.
- Medication Use: All medication use will be recorded on the appropriate CRF.
- Standard Blood Analysis per section 5.1.2
- Participant Questionnaires (SF-36) per section 5.1.4
- Any adverse events reported by the participant or dictated by blood tests and office evaluation

5.4.3 Visit 5: 14 Day Office Visit (+/- 2 days)

The following evaluations will be completed at the 14 day visit and documented on the appropriate CRFs:

- Weight
- Blood Pressure
- Targeted Physical Exam: A symptom directed physical examination will be conducted if a participant has reported signs or symptoms not previously identified during the screening process. All findings on-going on the previous exam will be reevaluated. Any abnormal findings will be recorded on the appropriate CRF.
- Medication Use: All medication use will be recorded on the appropriate CRF.
- Standard Blood Analysis per section 5.1.2
- Participant Questionnaires (SF-36) per section 5.1.4
- Any adverse events reported by the participant or dictated by blood tests and office evaluation

5.4.4 Visit 6: 1 Month Office Visit (+/- 5 days)

The following evaluations will be completed at the 1 month visit and documented on the appropriate CRFs:

- Weight
- Blood pressure
- Targeted Physical Exam: A symptom directed physical examination will be conducted if a participant has reported signs or symptoms not previously identified during the screening process. All findings ongoing on the previous physical exam will be reevaluated. Any abnormal findings will be recorded on the appropriate CRF.
- Medication Use: All medication use will be recorded on the appropriate CRF.
- Standard Blood Analysis per section 5.1.2
- Participant Questionnaires (SF-36) per section 5.1.4
- Any adverse events reported by the participant or dictated by blood tests and office evaluation

5.4.5 Visit 7: 2 Month Call (+/- 7 days)

At 2 months post procedure, the participant will be contacted via phone, no office visit is required. The following will be collected during the call:

- Medication Use: All medication will be recorded on the appropriate CRF.
- Any Adverse events reported by the participant.

5.4.6 Visit 8: 3 Month Office Visit (+/- 7 days)

The following evaluations will be completed at the 3 month visit and documented on the appropriate CRFs:

- Weight
- Blood pressure
- Targeted Physical Exam: A symptom directed physical examination will be conducted if a participant has reported signs or symptoms not previously identified during the screening process. All findings ongoing on the previous physical exam will be reevaluated. Any abnormal findings will be recorded on the appropriate CRF.
- Medication Use: All medication use will be recorded on the appropriate CRF.
- Standard Blood Analysis per section 5.1.2
- Mixed Meal Tolerance Test per 5.1.3
- Participant Questionnaires (SF-36) per section 5.1.4
- Endoscopy/Biopsy: A follow up endoscopy is performed during the visit to visually examine the treatment site and adjacent tissues. Video of the procedure is captured as well as any Investigator notes detailing observations.
  During the Endoscopy, a biopsy of the treatment site is taken using Biopsy Forceps. The tissue is fixed in 10% formalin and evaluated via Hematoxylin and Eosin stain.
- Any adverse events reported by the participant or dictated by blood tests and office evaluation

5.4.7 Visit 9: 6 Month Office Visit (+/- 14 days)

The following evaluations will be completed at the 6 month visit and documented on the appropriate CRFs:

- Weight
- Blood pressure
- Targeted Physical Exam: A symptom directed physical examination will be conducted if a participant has reported signs or symptoms not previously identified during the screening process. All findings ongoing on the previous physical exam will be reevaluated. Any abnormal findings will be recorded on the appropriate CRF.
- Medication Use: All medication use will be recorded on the appropriate CRF.
- Standard Blood Analysis per section 5.1.2
- Participant Questionnaires (SF-36) per section 5.1.4
- Any adverse events reported by the participant or dictated by blood tests and office evaluation

5.4.7 Visit 10: 9 Month Office Visit (+/- 14 days)

The following evaluations will be completed at the 9 month visit and documented on the appropriate CRFs:

- Weight
- Blood pressure
- Targeted Physical Exam: A symptom directed physical examination will be conducted if a participant has reported signs or symptoms not previously identified during the screening process. All findings ongoing on the previous physical exam will be reevaluated. Any abnormal findings will be recorded on the appropriate CRF.
- Medication Use: All medication use will be recorded on the appropriate CRF.
- Standard Blood Analysis per section 5.1.2
- Any adverse events reported by the participant or dictated by blood tests and office evaluation

5.4.8 Visit 11: 12 Month Office Visit (+/- 14 days)

The following evaluations will be completed at the 12 month visit and documented on the appropriate CRFs:

- Weight
- Blood pressure
- Targeted Physical Exam: A symptom directed physical examination will be conducted if a participant has reported signs or symptoms not previously identified during the screening process. All findings ongoing on the previous physical exam will be reevaluated. Any abnormal findings will be recorded on the appropriate CRF.
- Medication Use: All medication use will be recorded on the appropriate CRF.
- Standard Blood Analysis per section 5.1.2
- Participant Questionnaires (SF-36) per section 5.1.4
- Any adverse events reported by the participant or dictated by blood tests and office evaluation

5.4.7 Visits 12-13: 18 and 24Month Office Visits (+/- 1 month)

The following evaluations will be completed at the 18 and 24month visit and documented on the appropriate CRFs:

- Weight
- Blood pressure
- Targeted Physical Exam: A symptom directed physical examination will be conducted if a participant has reported signs or

symptoms not previously identified during the screening process. All findings ongoing on the previous physical exam will be reevaluated. Any abnormal findings will be recorded on the appropriate CRF.
- Medication Use: All medication use will be recorded on the appropriate CRF.
- Standard Blood Analysis per section 5.1.2
- Any adverse events reported by the participant or dictated by blood tests and office evaluation

At the completion of the 36 month visit, the site also completes the End of Study Case Report Form and the Investigator signs the Investigator Signature Page Case Report Form.

5.5 Participant Discontinuation

All participants enrolled into the study and who have undergone the endoscopic procedure, will be followed for 6 months post-procedure. Acceptable reasons for not evaluating a participant through the follow-up period include:

a) Lost to Follow-Up: Unable to locate the participant despite documented attempts to notify via telephone, email or mail. A participant will not be considered lost to follow-up until the last scheduled follow-up visit (24-month study time point).

b) Request to Terminate: The participant requests to terminate his/her involvement in the study, therefore withdrawing his/her consent to participate in the study (the investigator must thoroughly document the reasons for termination).

c) Death: If possible, an autopsy and/or death certificate should be obtained in order to document the cause of death.

If a participant discontinues from the study (regardless of the reason), the investigator will record the reason for withdrawal on the appropriate CRFs.

6.0 Adverse Event Reporting

6.1 Adverse Events

An Adverse Event is any undesirable clinical occurrence in a participant whether it is considered to be device related or not.

Events will be classified and tabulated by relationship to procedure, device, severity, and body system. Serious adverse events, deaths and unanticipated adverse device effects will be listed separately. All reports will be filed as required by country regulations.

The determination of whether an adverse event is classified as a Serious Adverse Event or Unanticipated Adverse Device Effect will be based on the definitions contained in this section taking into account the clinical judgment of the investigator.

Potential adverse events may include the following:

Device related adverse events

- Device breakage
- Device disarticulation
- Device/Component lost in GI tract
- Control module delivers incorrect ablation time and temperature profile
- Wrong balloon size chosen due to sizing catheter error
- Component degradation;
- Allergic reaction to device materials or injectate

Procedure related adverse events

- Vessel damage/bleeding;
- Infection
- Pain
- Bowel obstruction
- Perforation
- Stricture
- Ileus
- Pancreatitis

6.2 Serious Adverse Events

Serious adverse events (SAE) are defined as adverse events that are life-threatening, or ones that result in permanent impairment of a body function or permanent damage to a body structure, or they necessitate medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure.

A SAE is any untoward medical occurrence that:

- Results in death,
- Is immediately life-threatening,
- Results in disability or permanent damage
- Requires intervention to prevent permanent impairment or damage
- Requires participant hospitalization or prolongation of existing hospitalization,
- Is a congenital anomaly/birth defect or
- Is any other serious or important medical event

The definition of Other Serious or Important medical event is any event that does not fit the other outcomes, but the event may jeopardize the patient and may require medical or surgical intervention (treatment) to prevent one of the other outcomes. Examples include allergic brochospasm (a serious problem with breathing) requiring treatment in an emergency room, serious blood dyscrasias (blood disorders) or seizures/convulsions that do not result in hospitalization. The development of drug dependence or drug abuse would also be examples of important medical events.

Any Serious Adverse Event must be reported to Fractyl by the investigator or designee within 24 hours of first learning about the event. A written report must be made within 10 working days of knowledge of the event to the individual listed below and on the Serious Adverse Event/Unanticipated Adverse Device Effect Case Report Form.

Fractyl Laboratories, Inc.
Eric Bannon
Office 781-902-8812
Fax 781-609-2290
Cell 781-710-8243
Email Eric@fractyl.com

Participating Ethics Committees will be notified in accordance with their respective reporting requirements.

6.3 Unanticipated Adverse Device Effects

An unanticipated adverse device effect is defined as any serious adverse effect on health or safety or any life threatening problem or death caused by or associated with the device if that effect, problem or death was not previously identified in nature, severity or degree of incidence in the investigational plan, or any other unanticipated serious problem associated with the device that relates to the rights, safety or welfare of participants.

Any unanticipated adverse device effects must be reported to Fractyl within 24 hours of first learning about the event. A written report must be made to Fractyl within 10 working days of knowledge of the event to the fax number listed above and on the Serious Adverse Event/Unanticipated Adverse Device Effect Case Report Form. The Ethics Committee must also be notified within ten working days or sooner depending on their requirements.

Fractyl will also notify the appropriate regulatory agencies, and all participating investigators and Ethics Committees in writing within 10 working days after learning of any unanticipated adverse device effects.

6.4 Non-Serious Adverse Events

For non-serious adverse events (whether device-related or not), complete all sections of the appropriate Adverse Event Form(s).

6.5 Participant Death

Participant death during the investigation must be reported by fax to Fractyl within 24 hours of investigator's knowledge of the death. Notification of death must include a brief statement of the relevant details and be signed by the investigator or co-investigator. A copy of the death records, death certificate and an autopsy report (if performed) must be sent to Fractyl.

7.0 Statistical Considerations

7.1 Analysis Plan

The data from this pilot study will not be analyzed to draw conclusions on accepting or rejecting specific outcome measures or study hypothesis.

Safety data including adverse events and surgical interventions will be summarized by event, relationship to the procedure and severity. Outcome measures will be summarized using descriptive statistics. Participant demographic characteristics will be descriptively summarized.

The data generated during this evaluation will be used to define future studies and potential participant populations.

Interim Analyses

An interim analysis of 40 cases at 12 months is performed for regulatory purposes and approval. The details of the interim analyses will be provided in the Statistical Analysis Plan. This analysis will not be used to modify the trial in any way and as such will not require an alpha-spending function. Analysis also identifies any potential learning curve in the use of the device by assessing the results of these cases relative to those obtained in previous investigations.

7.2 Sample Size

This pilot evaluation will enroll a maximum of 60 participants. If additional enrollment is required, proper notification to the Investigator and associated Ethics Committee will be completed.

8.0 Risk Benefit Analysis

There are certain risks associated with the use of the Fractyl Duodenal Remodeling System including risks that are associated with any endoscopic procedure, risks that are associated with interventional procedures in the duodenum and risks that are unique to the use of the Remodeling System itself.

A detailed explanation of these potential risks and the means by which they may be minimized, as well as a justification for conducting the study are detailed below.

8.1 Procedure Risks

There are risks related to any endoscopic procedure as well as procedures specific to this treatment for Type 2 Diabetes. Specific risks associated with this procedure include:

abscess formation
abdominal pain
achalasia
bleeding
delayed gastric emptying
dental injury
diarrhea
difficulty swallowing
fever
gastric dumping syndrome
headache
hypoxia
infection
injury to esophageal
nausea
non-healing ulcer
nutritional mal-absorption
pancreatitis
perforation
pnuemoperitoneum
pulmonary aspiration
sore throat
stomach or duodenal mucosa
stricture and obstruction
structural damage to the GI tract
tightness and cramping
worsening diabetic symptoms including hypoglycemia

Many of these risks and complication rates associated with the procedure would be similar to those associated with other commonly performed endoscopic procedures such as duodenal biopsies and endoscopic mucosal resection.

8.2 Device Risks

In addition to the risks listed above, the Fractyl Duodenal Remodeling System may have unique risks associated with its catheters and control consoles used to complete the procedure. This includes risks associated with the materials selected, its design and construction. These risks include:

allergic reaction to the device materials or methylene blue
device breakage
disarticulation of components from the device
hole in hot fluid catheter balloon resulting in leakage of hot fluid
lost component in the GI tract or wall
thermal damage to the duodenum wall or surrounding structures

8.3 Minimizing Study Risks

The following steps have been taken to minimize risks associated with the procedure and the use of the Fractyl Duodenal Remodeling system:

- The patient contact materials used in the construction of the sizing, sub-mucosal injection and hot fluid ablation catheters all use known medical grade materials that are well characterized and have a long history of use.
- Device designs use known technologies including sub-mucosal injection and hot fluid balloon to complete the procedure. Similar technologies are currently in use for such accepted procedures as endoscopic mucosal resection and treatment of menorrhagia.
- Device designs have been rigorously tested in the laboratory as well as animal models to characterize their performance and ensure high confidence in the procedure.
- All investigators receive detailed training in the use of the Fractyl Duodenal Remodeling System. The training includes hands on use of the system in a lab setting.

8.4 Justification for Investigation

As with any product developed for use in a medical procedure, there are risks associated with the Fractyl Duodenal Remodeling procedure. Many of these risks are similar to those seen with other endoscopic devices that are passed either over the wire or through an endoscope for treatment in the esophagus, stomach or duodenum. From a procedural standpoint, devices such as Carr-Locke needles, Biopsy Forceps and Endoscopic Mucosal Resection systems have shown a satisfactory history of clinical use. In addition, appropriate steps have been taken to minimize the risks associated with the device design and materials.

The medical consequences and morbidity associated with Type 2 diabetes has been well studied and documented and includes renal failure, blindness, peripheral neuropathy, amputation, increased risk of myocardial infarctions, stroke, and peripheral vascular disease. A successful Fractyl procedure may enable patients to more effectively control their glycemic levels or even reduce or discontinue use of medications needed to treat their disease. This procedure and device potentially allows patients to reduce the morbidity of the disease and through improved glycemic control.

As noted above, there are substantial potential benefits associated with the Fractyl procedure and the risks associated with the devices and procedure have been identified and minimized where possible. Thus, the balance of potential risks and benefits associated with the Fractyl Duodenal Remodeling System warrants further clinical research and justifies this investigation.

9.0 Administrative Responsibilities

9.1 Ethics Committee Information

The investigation must be reviewed and approved by the appropriate Ethics Committees before participant enrollment may begin. All proposed changes to the investigational plan must be reviewed and approved by Fractyl. Fractyl will also obtain any necessary in country approvals before initiation of the study.

9.1.1 Ethics Committee Approval

Ethics Committee approval is required for each institution participating in this clinical investigation. Prior to shipment of investigational devices, a signed copy of the Ethics Committee approval letter identifying the clinical study must be submitted to Fractyl, signifying study approval. Investigators are responsible for obtaining and maintaining approval of the study by their institution's Ethics Committee.

9.1.2 Informed Consent

Written informed consent is mandatory and must be obtained from all participants prior to participation in this clinical study. Informed consent shall inform the participant as to the objective and procedures of the study and possible risks involved. The participants must be informed about their right to withdraw from the study at any time and for any reason without sanction, penalty, or loss of benefits to which the participant is otherwise entitled and that withdrawal from the study will not jeopardize their future medical care. The clinical study informed consent must be used in addition to the institution's standard consent form for procedures of this nature. The institutional standard participant consent form does not replace the study consent form. The Ethics Committee approved Informed Consent must be retained at the investigational site along with the other investigational case report forms. A signed copy of the consent form must be given to each participant enrolled in the study.

Modifications to the Fractyl Clinical Study Informed Consent and any written participant information must be approved by Fractyl and, the Ethics Committee as appropriate.

9.2 Confidentiality

All information and data sent to Fractyl or their authorized representatives, concerning participants or their participation in this study will be considered

confidential. All data used in the analysis and reporting of this evaluation will be used in a manner without identifiable reference to the participant.

9.3 Data Monitoring and Quality Control

9.3.1 Training

The training of investigational site personnel will be the responsibility of Fractyl. To ensure uniform data collection and protocol compliance, Fractyl appointed clinical monitors will review the clinical protocol, techniques for the identification of eligible participants, instructions on in-hospital/office visit data collection with the research coordinators.

9.3.2 Case Report Forms

Fractyl Case Report Forms (CRFs) will be used to collect participant data during the study. CRFs must be completed fully for each participant, signed by the Investigator, and available for review by regulatory authorities, Fractyl and/or its designees.

All CRF's and supporting original data must be reviewed by Fractyl and/or it's designees at the institution. After review the CRF's will be forwarded to data collection for input into the study database. The original CRF will be provided to Fractyl for archiving and a final copy will be provided to the site for site archives.

9.3.3 Data Reporting

The investigator, or an individual designated by him/her, is responsible for recording all study data on the CRFs supplied by Fractyl. The required study data will also be documented in the participant's medical record. The data on each CRF must be legibly handwritten.

The investigator is required to sign the CRF on the appropriate page(s) to verify that he/she has reviewed the recorded data.

Completed CRFs will be verified by a Fractyl appointed monitor at the site at regular intervals throughout the study. To this end, the investigator must permit inspection of the study files, participant CRF's, and participant medical records by Fractyl appointed monitors and authorized government agencies, as indicated.

9.3.4 Investigational Site Monitoring

Fractyl Inc. is the sponsor of this study. The study will be monitored according to applicable provisions of Fractyl Monitoring Procedures, and in conformance with Good Clinical Practices. Responsibility for monitoring is assigned to:

Eric Bannon
Fractyl Laboratories, Inc.
203 Crescent St, Suite 303

Waltham, MA 02453

Office 781-902-8812
Fax 781-609-2290
Cell 781-710-8243
Email Eric@fractyl.com

Monitoring will include pre-study site qualification, on-going site study monitoring and study closure monitoring. The major function of the clinical monitor is to observe and assess the quality of the clinical study. In addition, the study will be monitored to ensure that potential adverse trends are quickly identified allowing immediate corrective action. The monitor's duties include: on-site visits, observation of treatment with the study devices and review of study documents and results.

9.4 Record Maintenance

9.4.1 Records and Retention

The following records must be maintained in designated Fractyl Clinical Study administrative files:

- Clinical protocol and all amendments
- Signed Clinical Study Agreement
- Signed Non-Disclosure Agreement
- Ethics Committee Roster
- Ethics approval letter(s) and approved informed consent(s) (including any revisions)
- Approved advertisements for subject recruitment (if applicable)
- Financial Disclosure Forms
- Correspondence relating to this study (with Sponsor, clinical monitors, other Investigators, etc.)
- Correspondence with the Ethics Committee
- Instructions for Use
- Curriculum vitae for all investigators
- Investigational device log
- Investigational Device Brochure
- Investigational device related paperwork (including shipping documents, invoices, device return log, etc.)
- Normal value(s)/Range(s) for all laboratories used
- Laboratory certification(s) for all laboratories used
- Shipping records for investigational device(s)
- Sample of investigational device label(s)
- Monitoring Report(s)
- Monitor sign-in log
- Site authorized personnel signature list/Delegation of Authority Log

- Blank set of CRFs and instructions for completion
- Reports (including Adverse Event reports, annual reports and final reports from Investigator and Sponsor)

The following records must be maintained for each participant enrolled in the study:

- Signed participant consent form
- All completed CRFs
- Record of any side effects, device malfunction, and treatment failures (with supporting documentation)
- Procedure reports, nursing notes, and participant office files
- Copies of all radiographs
- Records of any interventions (procedure reports, nursing notes, etc.)
- Records related to participant deaths during the investigation (including death records, death certificate and autopsy report, if performed).

The Investigator or Investigational site will maintain, at the investigative site, in original format all essential study documents and source documentation that support the data collected on the study subjects in compliance with ICH/GCP guidelines. Documents must be retained for at least 2 years after the last approval of a marketing application or until at least 2 years have elapsed since the formal discontinuation of the clinical investigation of the product. These documents will be retained for a longer period of time by agreement with Fractyl or in compliance with other local regulations. It is Fractyl's responsibility to inform the Investigator when these documents no longer need to be maintained. The Investigator will take measures to ensure that these essential documents are not accidentally damaged or destroyed. If for any reason the Investigator withdraws responsibility for maintaining these essential documents, custody must be transferred to an individual who will assume responsibility and Fractyl must receive written notification of this custodial change.

9.4.2 Reports

Investigators are required to prepare and submit the following complete, accurate, and timely reports as outlined in the following table:

Responsibilities for Preparing & Submitting Reports

Type of Report	Prepared by Investigator for	Time of Notification (From Documented Event)
Case Report Forms (working copy)	Fractyl	Ready for monitoring within 10 working days
Serious Adverse Event (device related or not)	Fractyl, Ethics (as required)	Within 24 hours of knowledge

Device Malfunction	Fractyl	Within 24 hours of knowledge
Participant death during the investigation	Fractyl and Ethics	Within 24 hours of knowledge
Unanticipated Adverse Device Effects	Fractyl, Ethics (as required)	Within 24 hours of knowledge
Participant withdrawal	Fractyl	Within 7 days of knowledge
Withdrawal of Ethics approval	Fractyl	Within 24 hours of knowledge
Deviations from investigational protocol	Fractyl, Ethics (as required)	Within 7 days of knowledge
Informed consent not obtained from participant	Fractyl and Ethics	Within 24 hours of knowledge
Annual Progress report	Fractyl and Ethics	Within 1 month of annual Ethics approval date
Final summary report	Fractyl, Ethics (as required)	Within 3 months of study completion
Other information as requested by Fractyl, Ethics	As appropriate	As requested

Investigator files containing all records and reports of the investigation should be retained for a minimum of two years after the site has been notified in writing by the Sponsor that the records are no longer needed to support regulatory filings. They may be discarded upon notification by Fractyl. To avoid any error, the investigator should contact Fractyl before destroying any records and reports pertaining to the study to ensure they no longer need to be retained.

In addition, in accordance with the Clinical Study Agreement, Fractyl should be contacted if the investigator plans to leave the investigational site so that appropriate arrangements can be made.

9.4.3 Investigator's Annual and Final Reports

Each year a summary report shall be prepared by the investigator providing a synopsis of the participants treated to date as well as other pertinent clinical information associated with the device usage. The report must be signed by all participating Investigators at the site involved in the study and will be provided to the Ethics Committee and Fractyl.

Upon completion or termination of the study a final report will be prepared. This report will contain a critical evaluation of all data collected during the course of the investigation at each institution. The report must be signed by all participating Investigators at the site involved in the study and will be provided to the Ethics Committee and Fractyl. Any modifications to this final report must be reviewed and approved by Fractyl.

9.5 Device Accountability

All investigational devices received and used by the investigator will be inventoried and accounted for throughout the study. The devices will be stored in a secure area, separate from other devices. Upon request by the sponsor or study completion, all unused devices will be returned to Fractyl. No devices will be used except by authorized investigators in accordance with the protocol.

Devices that do not function properly during use or others that may be determined by the sponsor to be needed for post use evaluation will be retained by the site until the evaluation is complete at which time they will be returned to the Sponsor.

9.6 Deviations from Protocol & Medical Emergencies

The investigator will not deviate from the protocol without the prior written approval of Fractyl except in medical emergencies or in unforeseen, isolated instances where minor changes are made that will not increase the participant's risk or affect the validity of the study. In medical emergencies, prior approval for protocol deviations will not be required, but Fractyl must be notified within 24 hours of occurrence.

9.7 Investigational Site Termination

Fractyl reserves the right to terminate an investigational site for any of the following reasons:

- Repeated failure to complete Case Report Forms
- Failure to obtain Informed Consent
- Failure to report Serious Adverse Events within 24 hours of knowledge
- Loss of or unaccounted for investigational device inventory
- Repeated protocol violations
- Failure to enroll an adequate number of participants

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Appendix 1: Schedule of Study Events

Intervention - test or assessment	Screening	Endoscopic Procedure	2 Day Call	7 Day	14 Day	1 Month	2 Month Call	3 Month	6 Month	9 Month	12 Month	18 & 24 Month
	VISIT 1	VISIT 2	VISIT 3	VISIT 4	VISIT 5	VISIT 6	VISIT 7	VISIT 8	VISIT 9	VISIT 10	Visit 11	Visits 12-13
Visit Windows			*+1/-0 days*	*+/- 2 days*	*+/- 2 days*	*+/- 5 days*	*+/- 7 days*	*+/- 7 days*	*+/- 14 days*	*+/- 14 days*	*+/- 14 days*	*+/- 1 month*
Informed Consent	X											
History and Full Physical Examination	X	X (Weight only)										
Targeted Physical Exam				X	X	X		X	X	X	X	X
Medication Use	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy test (if applicable)	X											
Standard Blood Analysis	X	X		X	X	X		X	X	X	X	X
Mixed Meal Tolerance Test	X							X				
Outcome Questionnaire (SF-36)	X			X	X	X		X	X		X	
Participant Enrollment		X										
Endoscopy	X	X						X				
Biopsy	X							X				
Adverse Events		X	X	X	X	X	X	X	X	X	X	X