Evaluation of the effect of Duodenal Mucosal Resurfacing (DMR) using the Revita® System in the treatment of Type 2 diabetes (T2D)

REVITA-2 Study

Protocol Number: C-30000

Sponsor:

Fractyl Laboratories
17 Hartwell Avenue
Lexington, MA 02421

Version 5.0
Date 05 May 2019

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Sponsor Protocol Approval Page

Karen Hager Director of Clinical Operations	DocuSigned by: FF70667F401F458...
	Date: May 13, 2019
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	Date: May 10, 2019

STUDY TITLE:	**Evaluation of the effect of Duodenal Mucosal Resurfacing (DMR) using the Revita® System in the treatment of Type 2 diabetes (T2D)** REVITA-2 Study
PROTOCOL NUMBER:	C-30000
VERSION NUMBER:	5.0

We, the undersigned, have read and approve the protocol specified above and agree on its content.

Investigator Protocol Approval Page

Evaluation of the effect of Duodenal Mucosal Resurfacing (DMR) using the Revita® System in the treatment of Type 2 diabetes (T2D)

REVITA-2 Study
C-30000

Protocol Version 5.0

I hereby agree to participate in this evaluation of the Fractyl Revita® System sponsored by Fractyl Laboratories, Inc. (here in after "Study Sponsor"). I agree to conduct this investigation according to the requirements of the protocol provided by the Study Sponsor in accordance with applicable local regulations, and in accordance with the conditions imposed by the reviewing Institutional Review Board (IRB) or Ethics Committee (EC). I agree to supervise all use of the investigational devices and to ensure appropriate informed consent is obtained from all subjects prior to inclusion in this study.

I understand that this investigation will be monitored by the Study Sponsor and/or a designee employed by the Study Sponsor. This monitoring will involve periodic inspection of my investigational site and ongoing review of the data that are submitted by me to the Study Sponsor.

I am aware that the Study Sponsor reserves the right to discontinue this investigation at any time.

I understand this study protocol and trial results are confidential, and I agree not to disclose any such information to any person other than a representative of the Study Sponsor, the IRB/EC, or regulatory authorities without the prior written consent of the Study Sponsor.

Accepted by:

_____ _____
Principal Investigator Date

_____
Printed Name

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Protocol Summary

Title: **Evaluation of the effect of Duodenal Mucosal Resurfacing (DMR) using the Revita® System in the treatment of Type 2 diabetes (T2D)**

Short Title: Revita-2

Protocol ID#: **C-30000**

Device: The Fractyl Revita® System is an endoscopic treatment consisting of duodenal mucosal lift with saline and circumferential thermal ablation.

Study Objective:

Phase 1 (0 - 24 Weeks) Objective:
To study the effect of DMR on glycemic and mechanistic endpoints 24 weeks post-procedure in subjects with T2D.

Phase 2 (24 - 48 Weeks) Objective:
To study the effect of DMR on glycemic endpoints for assessment of durability for patients who received DMR at Visit 3.

Study Design: Randomized double-blind sham-controlled prospective multicenter clinical investigation of subjects with type 2 diabetes sub-optimally controlled on one or more oral anti-diabetic medications.

- Up to 15 Investigational Sites in EU and global geographies
- Maximum of 50 training and up to 120 randomized subjects
- 1:1 randomized, double blind (subject and endocrinologist) trial comparing DMR treatment to sham procedure
- 4 week oral anti-diabetic medication run-in to assess stability of blood glucose control in conjunction with medication compliance and nutritional counseling
- Oral diabetic medications held constant from start of run in period through 24 Week endpoint with predefined rescue algorithm for hypo and hyper glycemia
- Unblinding to occur at 24 Weeks and:
    - Sham treatment arm to cross-over to receive DMR treatment at 24 Weeks with background medications held constant from 24 - 48 Weeks of follow up (cross-over 24 Weeks / Visit 9C)
    - DMR treatment arm to be managed according to current diabetes standard of care for 24 - 48 Weeks of follow up
- Mechanism of action assessments, conducted in a subset of Study Sites, include: ambulatory blood pressure monitoring (ABPM) in training case only, Mixed Meal Tolerance Test

(MMTT), Urine Micro Albumin, and Radiological Hepatic Status(MR-PDFF, MR-LIC)

- DMR: Subject follow-up visits will occur at 7 and 14 Days (by phone) and 4, 12, 18, 24, 36 and 48 Weeks (in clinic), and 15, 21, 30 and 42 weeks (by phone) post procedure.
- Sham: Subject follow-up visits will occur at 7 and 14 Days (by phone) and 4, 12, 15 (phone),18, and 24 weeks after the initial procedure. Sham patients who complete the cross-over DMR procedure at Visit 3C (7-14 days after Week 24) follow up will occur at 7 and 14 Days (by phone) and 4, 12, 18 and 24 Weeks (in clinic), and 15 and 21 weeks (by phone) post cross-over DMR procedure.

Indication for Use:

The Revita® System is intended to improve glycemic control in patients with Type 2 diabetes who have preserved pancreatic beta cell function and whose diabetes is poorly controlled with oral glucose lowering medications.

Inclusion Criteria

1. 28-75 years of age
2. Diagnosed with Type 2 Diabetes and evidence of preserved insulin secretion. Fasting insulin > 7.0 μU/ mL.
3. HbA1c of 7.5 - 10.0% (59-86 mmol/mol)
4. Body Mass Index (BMI) ≥ 24 and ≤ 40 kg/m^2
5. Currently taking one or more oral glucose lowering medications, of which one must be Metformin, with no changes in dose or medication in the previous 12 Weeks prior to study entry.
6. Able to comply with study requirements and understand and sign the informed consent

Exclusion Criteria

Screening Visit (Pre-Medication Run-In, Visit 1)

1. Diagnosed with Type 1 Diabetes or with a history of ketoacidosis
2. Current use of Insulin
3. Current use of GLP-1 analogues
4. Hypoglycemia unawareness or a history of severe hypoglycemia (more than 1 severe hypoglycemic event, as defined by need for third-party-assistance, in the last year)
5. Known autoimmune disease, as evidenced by a positive Anti-GAD test, including Celiac disease, or pre-existing symptoms of systemic lupus erythematosus, scleroderma or other autoimmune connective tissue disorder
6. Active H. pylori infection (Participants with active H. pylori may continue with the screening process if they are treated via medication.)

7. Previous GI surgery that could affect the ability to treat the duodenum such as subjects who have had a Bilroth 2, Roux-en-Y gastric bypass, or other similar procedures or conditions
8. History of chronic or acute pancreatitis
9. Known active hepatitis or active liver disease
10. Symptomatic gallstones or kidney stones, acute cholecystitis or history of duodenal inflammatory diseases including Crohn's Disease and Celiac Disease
11. History of coagulopathy, upper gastro-intestinal bleeding conditions such as ulcers, gastric varices, strictures, congenital or acquired intestinal telangiectasia
12. Use of anticoagulation therapy (such as warfarin) which cannot be discontinued for 7 days before and 14 days after the procedure
13. Use of P2Y12 inhibitors (clopidogrel, pasugrel, ticagrelor) which cannot be discontinued for 14 days before and 14 days after the procedure. Use of aspirin is allowed.
14. Unable to discontinue NSAIDs (non-steroidal anti-inflammatory drugs) during treatment through 4 weeks post procedure phase
15. Taking corticosteroids or drugs known to affect GI motility (e.g. Metoclopramide)
16. Receiving weight loss medications such as Meridia, Xenical, or over the counter weight loss medications
17. Persistent Anemia, defined as Hgb<10 g/dl
18. eGFR or MDRD <30 ml/min/1.73m^2
19. Active systemic infection
20. Active malignancy within the last 5 years
21. Not potential candidates for surgery or general anesthesia
22. Active illicit substance abuse or alcoholism
23. Participating in another ongoing clinical trial of an investigational drug or device
24. Any other mental or physical condition which, in the opinion of the Investigator, makes the subject a poor candidate for clinical trial participation

Baseline Visit (Post Medication Run-In, Visit 2)

1. HbA1c post run-in phase < 7.5% (59 mmol/mol) or > 10.0% (86 mmol/mol)
2. One or more clinically significant hypoglycemic events defined as self-monitored or laboratory plasma glucose level of < 54 mg/dL (3.0 mmol/L), or at least 2 such events if a clear correctable precipitating factor can be identified; or a severe hypoglycemic event, as defined as hypoglycemia requiring third-party-assistance, since the screening visit (Visit 1)
3. Hyperglycemic event defined as three self-monitored finger sticks in 1 day during the run-in period with fasting blood

glucose measurements >15 mmol/L (270 mg/dL) or non-fasting blood glucose measurements >20 mmol/L (360 mg/dL) or any combination of the two. Fasting glucose hyperglycemia is not an exclusion if measured at the actual baseline visit (Visit 2) blood analysis test.
4. Those who are pregnant, nursing or expect to become pregnant over the course of the study

Procedure (Visit 3)

1. Active and uncontrolled GERD defined as grade III esophagitis or greater
2. Abnormalities of the GI tract preventing endoscopic access to the duodenum
3. Anatomic abnormalities in the duodenum that would preclude the completion of the DMR procedure, including tortuous anatomy
4. Malignancy newly diagnosed by endoscopy
5. Upper gastro-intestinal conditions such as ulcers, polyps, gastric varices, strictures, congenital or acquired intestinal telangiectasia

Study Endpoints:

Primary Efficacy Endpoint:

1) the change from baseline at 24 weeks in HbA1c, DMR vs Sham, and

2) The absolute change from baseline at 12 weeks in MR-PDFF in patients with baseline MR-PDFF > 5% , DMR vs Sham

Primary Safety Endpoints:

Incidence rates of device or procedure related Serious Adverse Events (SAEs), Unanticipated Adverse Device Effects (UADEs), and Adverse Events of Special Interest (AESIs) through 24 Weeks.

Secondary Endpoints:

1. HbA1c change from baseline to Week 24 (Visit 9) by visit over time, DMR vs. Sham
2. The relative MR-PDFF change from baseline to Week 12 in patients with baseline MR-PDFF > 5%, DMR vs. Sham
3. Proportion of randomized-DMR-treated subjects with an HbA1c improvement from baseline at 24 weeks (Visit 9) that maintain an HbA1c improvement relative to baseline at 48 weeks
4. Proportion of randomized-DMR-treated subjects with an MR-PDFF > 5% at baseline and MR-PDFF improvement from baseline at 24 weeks (Visit 9) that maintain an MR-PDFF improvement relative to baseline at 48 weeks

5. Fasting Plasma Glucose (FPG) change from baseline at 24 weeks DMR vs. Sham
6. FPG change from baseline to Week 24 by visit over time, DMR vs. Sham
7. Weight change from baseline at 24 weeks DMR vs. Sham
8. In randomized-DMR-treated subjects with an HbA1c improvement from baseline at 24 weeks, average HbA1c improvement from baseline at 48 weeks
9. In randomized-DMR-treated subjects with an MR-PDFF > 5% at baseline and MR-PDFF improvement from baseline at 12 weeks, average MR-PDFF improvement at 48 weeks
10. HOMA-IR change from baseline at 24 weeks DMR vs. Sham

Exploratory Endpoints

- Change from the baseline in the following by visit out to 24 weeks in DMR vs. Sham
    - FPI
    - Fasting C-peptide
    - Weight
    - ALT
    - AST
    - FIB-4
    - Ferritin
    - UACR
    - eGFR
    - Triglycerides
    - HDL
    - TG/HDL

- Change from baseline in the following at 12 weeks, DMR vs. Sham:
    - MMTT change from baseline (glucose AUC through 2 hours)
    - Change in MMTT measure of Insulin secretion
    - Change in MMTT measure of Insulin resistance
    - MR-LIC Liver Iron Content

- Proportion of randomized-DMR-treated subjects with an abnormal MR-LIC at baseline and MR-LIC improvement from baseline at 12 weeks that maintain an MR-LIC improvement at 48 weeks.

- In randomized-DMR-treated subjects with an abnormal MR-LIC at baseline and MR-LIC improvement from baseline at 12, average MR-LIC improvement at 48 weeks.

- Training Cohort only:
    - Change in SBP by ABPM from baseline in training cohort, at 12 weeks
    - Change in DBP by ABPM from baseline in training cohort, at 12 weeks

Additional exploratory endpoint and ad-hoc analyses of interest will be defined in the study Statistical Analysis Plan (SAP).

Study Sponsor: Fractyl Laboratories Inc.
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List of Abbreviations

ACRONYM	DESCRIPTION
AE	Adverse Event
AESI	Adverse Event of Special Interest
ABP	Ambulatory Blood Pressure
ABPM	Ambulatory Blood Pressure Monitoring
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
AUC	Area Under Curve
BMI	Body Mass Index
AUC	Area Under the Curve
CBC	Complete Blood Count
CRF	Case Report Form
DMC	Data Monitoring Committee
DMR	Duodenal Mucosal Resurfacing
EC	Ethics Committee
EW	Excess Weight
FA	Flip angle
FIB-4	Fibrosis-4 Index for Liver Fibrosis
FPG	Fasting Plasma Glucose
GI	Gastrointestinal
GIP	Gastric Inhibitory Peptide
GLP-1	Glucagon-like peptide 1
HbA1c	Glycated Hemoglobin
ICH	International Conference on Harmonization
ICF	Informed Consent Form
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IS	Insulin Sensitivity
ITT	Intent-to-Treat
IV	Intravenous
LOCF	Last Observation Carried Forward
mg/dL	Milligrams per Deciliter
Mmol	Millimoles
mmol/L	Milimoles per liter
MMTT	Mixed Meal Tolerance Test
MR-PDFF	Magnetic Resonance Fat Fraction
ng/mL	Nanograms per milliliter
NPO	Nil per os (withhold oral food and fluids)
OAD	Oral antidiabetic medications
OD	Outer diameter
pmol/l	Picomole/liter
PP	Per Protocol
QA	Quality Assurance
SAE	Serious Adverse Event

SAP	Statistical Analysis Plan
SMBG	Self-Monitored Blood Glucose
SSR	Sample size re-estimation
T2D	Type 2 Diabetes
UACR	Urine Albumin/Creatinine Ratio
UADE	Unanticipated Adverse Device Effect
UPE	Urinary Protein Excretion

List of Definitions

Term	Definition
Clinically Significant	A clinical observation or a laboratory result that leads to a new intervention or a change in therapy. In the context of this study, improvements in clinical observation or laboratory result will not be reported as clinically significant.
End-of-study	The end-of-study date is when all subjects have completed all study visits or have otherwise discontinued from the study.
Enrolled Subject	Study enrollment is defined as successful completion of the endoscopic evaluation and initiation of the index procedure, Fractyl DMR or sham.
Hyperglycemic Events	Hyperglycemic events defined as three self-monitored finger sticks in 1 day with fasting blood glucose measurements >15 mmol/L (270 mg/dL) or non-fasting blood glucose measurements >20 mmol/L (360 mg/dL) or any combination of the two. Fasting glucose hyperglycemia is not an exclusion if measured at the actual baseline visit (Visit 2) blood analysis test.
Hypoglycemic Events	Serious, clinically important hypoglycemia is defined as a plasma glucose of < 3.0 mmol/L (54 mg/dL). Severe hypoglycemia is defined as denoting severe cognitive impairment requiring external assistance for recovery A glucose alert value is defined as ≤ 3.9 mmol/L (70 mg/dL). All episodes of hypoglycemia should be recorded in the subject's diary, including all glucose alert values.
Intent-to-Treat (ITT) Population	The ITT population includes all randomized subjects. It specifically excludes the training subjects.
Medication Run In	Time period when subjects who have met the Screening criteria and undergo the 4 week Medication Run In period.
Modified Intent-to-Treat (mITT) Population	The mITT population includes all randomized subjects in whom the study procedure (DMR or sham) is attempted and who have a baseline measurement for at least one primary endpoint. The procedure is attempted when all endoscopic exclusion criteria are verified, the catheter is introduced into the subject, and at least one ablation is performed. Subjects will be analyzed according to their randomized group assignment. The mITT population is the primary analysis population for both the primary and secondary efficacy endpoints. The mITT population specifically excludes the training subjects.
On-Study Period	Subject participation in the study will begin from the time of signing the informed consent and concludes after the last study visit is completed.
Per-Protocol (PP) Population	The Per-Protocol (PP) analysis population includes the subset of mITT subjects who received the treatment to which they were randomized, and excluding any subjects with major

	protocol deviations, which include those Fractyl DMR cases that did not undergo the full DMR procedure. The PP population specifically excludes the training subjects.
Screening Period	From the time the subject signs informed consent until the time of randomization will be considered a screening period.
Screen Failure	Patient who signs the informed consent form and fails to meet all eligibility criteria.
Study Subject	Patient who participates in this study in any capacity will be referred to as the “subject”.
Study Participation Duration	From the time the first subject signs informed consent until their completion of the last study visit.
Study Reference Manual	A general term for any information or guideline provided to the study sites on technical aspects or procedural details of the clinical study.
Training Subjects	The training population includes all subjects enrolled as training cases at the site. These cases are described separately from randomized subjects in the final study report and are presented primarily using descriptive statistics.

1. Introduction

1.1 Type 2 Diabetes Mellitus

Type 2 Diabetes is an endocrine disorder linked to the obesity epidemic. It is characterized by chronically elevated blood glucose and subsequent vascular complications. There are approximately 382 million subjects with type 2 diabetes throughout the world (1). The disease has spread rapidly in rich and poor nations and has been associated with increasing age, decreased physical activity and the explosion of Western dietary habits around the globe. In Europe alone, there are 56 million patients with type 2 diabetes – and this number is expected to triple by 2050 (2). The UK National Health Service 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, patients display intolerance to ingested glucose and resistance to insulin. 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 can no longer compensate for the body's resistance to insulin 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 nephropathy, retinopathy, and peripheral neuropathy. As a consequence, diabetes is a 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 diabetes begins with improvements in diet and exercise. The vast majority of patients do not achieve sustained good glycemic control with lifestyle changes alone. Several classes of pharmacologic therapy are available, 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. Despite these oral therapies, diabetes control will usually deteriorate over time and treatment with insulin will become necessary (4). All told, however, a large proportion of patients remain poorly controlled despite all of these measures.

There are many reasons for the limited effectiveness of current pharmacologic interventions in the general population. First, today's medicines may lower blood glucose but they do not address the fundamental pathogenesis of Type 2 Diabetes. Second, poor compliance to complicated pharmacologic regimens is

well documented and a structural barrier to better glycemic control. Third, clinical inertia on the part of physicians prevents drug regimen escalation even in patients with access to excellent medical care. Fourth, psychological resistance to insulin prevents the use of this class of agents. Fifth, hypoglycemia (and the risk thereof) limits the degree of pharmacologic intervention with which physicians and patients feel comfort. Taken together, nearly 50% of patients remain poorly controlled throughout Europe and the United States.

Interestingly, 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). The GI tract is the largest endocrine organ in the body and the bypass of the proximal small bowel leads to hormonal changes that improve glucose homeostasis (8,9). This appears to occur without substantial 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 subjects with diabetes.

Moreover, it is now becoming increasingly recognized that the upstream surgical perturbation of the gastro-intestinal tract, resulting in exclusion of the duodenum, does indeed manifest a compelling anti-diabetic effect but the metabolic state of the patient is also a key determinant of outcome. Studies have now reported that the potency of the anti-diabetic effect manifested with bariatric surgery is contingent on or influenced by innate endogenous beta cell reserve or insulin secretory capacity (10, 11, 12). In other words, bariatric surgery elicits powerful anti-diabetic effects but more notably in the presence of some degree of endogenous beta cell secretory capacity. This raises important questions concerning a more targeted use of such interventions where patients may require certain beta cell reserve characteristics and/or certain companion pharmacological agents that augment beta cell secretor function (e.g. GLP1-receptor agonists) to best optimize outcome.

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 (13). 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 producing 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 patients with diabetes 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 an increase in entero-endocrine cell numbers and subsequent gastric inhibitory peptide (GIP) after a meal (14). Other studies have demonstrated hypertrophy of the mucosa of the small bowel in subjects with diabetes (15). 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 bariatric surgeries are, one cannot imagine that surgery can be offered to enough patients to adequately address the diabetes pandemic. There are several reasons for this. The primary indication for bariatric surgery remains morbid obesity, yet most diabetes patients are not morbidly obese. Also, the risks (of major morbidity, mortality, and need for re-operation) from bypass surgeries pose a significant barrier to its wholesale adoption as a treatment for type 2 diabetes. Finally, surgery is invasive, psychologically difficult, and physically demanding. For all these reasons, only a minority of patients with diabetes currently undergo surgery as a treatment for their diabetes.

A scalable solution that leverages the physiologic lessons from bariatric surgery but can be cost-effectively delivered to a much larger segment of the population would be welcomed. Some medical devices have been developed that aim to mimic aspects of bariatric surgery for the treatment of diabetes and obesity (16). 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 duodenum and proximal jejunum (17). It has achieved CE-marking approval for sale in Europe and Australia. Like in the surgeries described above, subjects with type 2 diabetes who receive a GI Dynamics implant enjoy a remarkable improvement in their glucose control.

The Fractyl Revita® System has achieved CE-marking and allows physicians to safely and effectively ablate the duodenal mucosa in patients with type 2 diabetes. This procedure appears to elicit important lowering of hyperglycemia in Type 2 diabetes, thereby positively impacting metabolic state. Further study of the Fractyl Revita® System in patients with Type 2 diabetes will be performed to continue to optimize characterizing the tolerability, efficacy and safety profile, while observing short and longer term effects on glycemia, and defining patients with optimal outcomes.

1.2 Fractyl Laboratories Revita® System

The Fractyl Revita® System consists of two main components: the Revita Catheter and a console.

Revita Catheter:
The Revita Catheter is a sterile, single use device that performs two functions: 1) it injects 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 when placing 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. During the mucosal lift, the tissue is drawn into the needle port, and saline is injected into the submucosal space through the needles. The 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 a 24 mm OD (outer diameter) balloon.

Console:
The console is a reusable electro-mechanical piece of equipment and provides functionality to the submucosal 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 during the procedure.

1.3 Duodenal Mucosal Resurfacing (DMR) Procedure

The DMR procedure using the Revita® System is completed in the endoscopy suite using either general anesthesia or conscious sedation. The patient is positioned in the left lateral decubitus position used for endoscopic procedures or preferred position as dictated by the site's requirements for endoscopic procedures. A standard endoscope is used to complete an initial endoscopic evaluation and a guidewire is delivered past the ligament of Treitz to assist in delivering the catheter. Anti-peristaltic agents may be used during the procedure. Catheter delivery and device location for treatment is verified using fluoroscopic guidance. The use of fluoroscopy is limited to use during catheter placement and verification of location during treatment. Based on data collected during earlier clinical investigations, the duration of radiation exposure is approximately equivalent to that delivered during an endoscopic retrograde cholangiopancreatography procedure, which is a common endoscopic procedure with an acceptable safety profile. The total procedure time is approximately 70 minutes.

Mucosal Lift and Ablation Procedure
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 actuator

on the handle is moved 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 (approximately 10 cm) of the duodenum is treated. The Revita catheter and endoscope are then removed.

1.4 Clinical Experience

A first in human clinical investigation (C-10000) began in August 2013 at a single site in Santiago, Chile and has enrolled 48 subjects to date. The objective of this investigation is to evaluate the initial feasibility and safety profile of the Fractyl Duodenal Resurfacing (DMR) procedure using the Revita® System and its effect on participants with Type 2 Diabetes. Efficacy is evaluated through the testing of fasting blood glucose and blood HbA1c. Safety is evaluated through the adverse event profile and their associations to the study device or procedure during the study follow up period. The details of study C-10000 can be found in the Revita® System Investigator Brochure.

A second single arm, open label evaluation has enrolled 28 patients in Chile and 4 additional sites in Europe. The objective of this evaluation is to verify the results seen in a single center are generalizable to a mult-center trial in Europe and to further refine the patient profile to define those subjects most likely to see a treatment effect. The details of study C-20000 can be found in the Revita® System Investigator Brochure.

1.5 Risk Analysis

The Fractyl Revita® System will be used within its CE-marking intended use. There are certain residual risks associated with the use of the Fractyl Revita® System and the DMR procedure. As with any endoscopic procedure, there are risks that are associated with interventional procedures in the duodenum. The IFU provides a listing of the device related residual risks. Below is a listing of these risks, the means by which they may be minimized, as well as, a justification for conducting the study.

1.5.1 Procedure Risks

There are risks related to the endoscopic procedure in general, as well as, risks specific to the Fractyl Revita® System procedural treatment for Type 2 Diabetes. Specific risks associated with the procedure include (in alphabetical order):

- abdominal tightness, cramping, pain
- diarrhea
- difficulty swallowing
- infection
- mucosal injury to GI tract

- pancreatitis
- perforation
- sore throat
- stricture
- transient bleeding
- worsening diabetic symptoms including hypoglycemia

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

1.5.2 Device Risks

In addition to the risks listed above, the Fractyl Revita® System may have unique risks associated with its catheter and console 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 endoscopic labeling dye or injectate
- Component degradation
- Control module delivers incorrect ablation time and temperature profile
- Device breakage
- Disarticulation of components from the device
- Device/Component lost in GI tract or wall
- Hole in hot fluid catheter balloon resulting in leakage of hot fluid
- Lost catheter component in the GI tract or wall
- Thermal damage to the duodenum wall or surrounding structures
- Unforeseen adverse events

1.5.3 Minimizing Study Risks

The following steps have been taken to minimize risks associated with the procedure and the use of the Fractyl Revita® System:

- The tissue or fluid contacting materials used in the construction of the Revita Catheter are known medical grade materials that are well characterized and have a long history of use. In addition, biocompatibility testing has proven that the materials are safe.
- The device design uses 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.
- The device design has been rigorously tested in the laboratory, animal models and clinical trials to characterize its performance and comfirm the safety and performance of the procedure.

- All investigators receive detailed training in the use of the Fractyl Revita® System and the DMR procedure. The training includes hands on use of the system in a lab setting.

1.5.4 Justification for Investigation

The Fractyl Revita® System has obtained CE-marking and has shown that the safety and performance of the device provides an acceptable risk/benefit profile. Additional monitoring of the device, as well as, gathering additional patient data is needed to establish a continuous evaluation of the efficacy and safety of the device and to generate additional data to support endocrinologist adoption.

The device will be used as intended and the risks involved in this procedure have been established as part of the CE-marking process. Performing this study under controlled conditions lowers any unknown risks to the patients and will obtain additional confirmation on the efficacy and safety of the device treatment.

As with any medical device, there are risks associated with the Fractyl Revita® System and the DMR 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.

The study will be performed within the intended use of the Fractyl Revita® System. Although the follow-up test requirements are more intensive then the standard of care, no additional invasive tests are included which introduce any additional risk.

It is concluded that the balance of potential risks of participation in the study and benefits associated with the Revita® System warrants further clinical research and justifies this investigation.

2. Study Design

2.1 Overview

The study is a multi-center, randomized, prospective, double-blinded (subject and endocrinologist) trial of type 2 diabetes patients sub-optimally controlled on 1 or more oral anti-diabetic medications comparing the Fractyl DMR procedure to sham procedure. Randomization will be 1:1 DMR treatment to sham. All subjects will participate in a 4 week oral anti-diabetic medication run-in period before the index procedure to confirm lack of blood glucose control in conjunction with medication compliance and nutritional counseling. The Sham treatment arm will cross-over to receive the DMR treatment at 24 weeks with background medications held constant 24weeks of follow up after the cross-over DMR procedure. The DMR treatment arm will be managed according to current diabetes standard of care.

Mechanism of action assessments, conducted in a subset of centers, include:ambulatory blood pressure monitoring (ABPM) in training cases only, Mixed Meal Tolerance Test (MMTT), and Radiological Hepatic Status. Subject follow up visits will occur at 7 and 14 days (by phone), 4, 12, 18 and 24weeks (in clinic), and 15 and 21 weeks (by phone) post procedure. A summary of the assessments and data collection requirements is presented in Appendix 1 (Training Cases), 2 (Randomized to DMR) and 3 (Randomized to Sham).

2.2 Number of study sites and subjects

Up to 15 sites in Europe and global geographies will participate in the study. Each site will complete up to 5 training cases before starting to randomize subjects, for a maximum of 50 training subjects. The decision to allow a site to commence the randomization phase will be made on a site by site basis by Fractyl based on site performance in the training case phase. The total study enrollment in the randomized phase is a maximum of 120 subjects (60 per group).

2.3 Training Cases

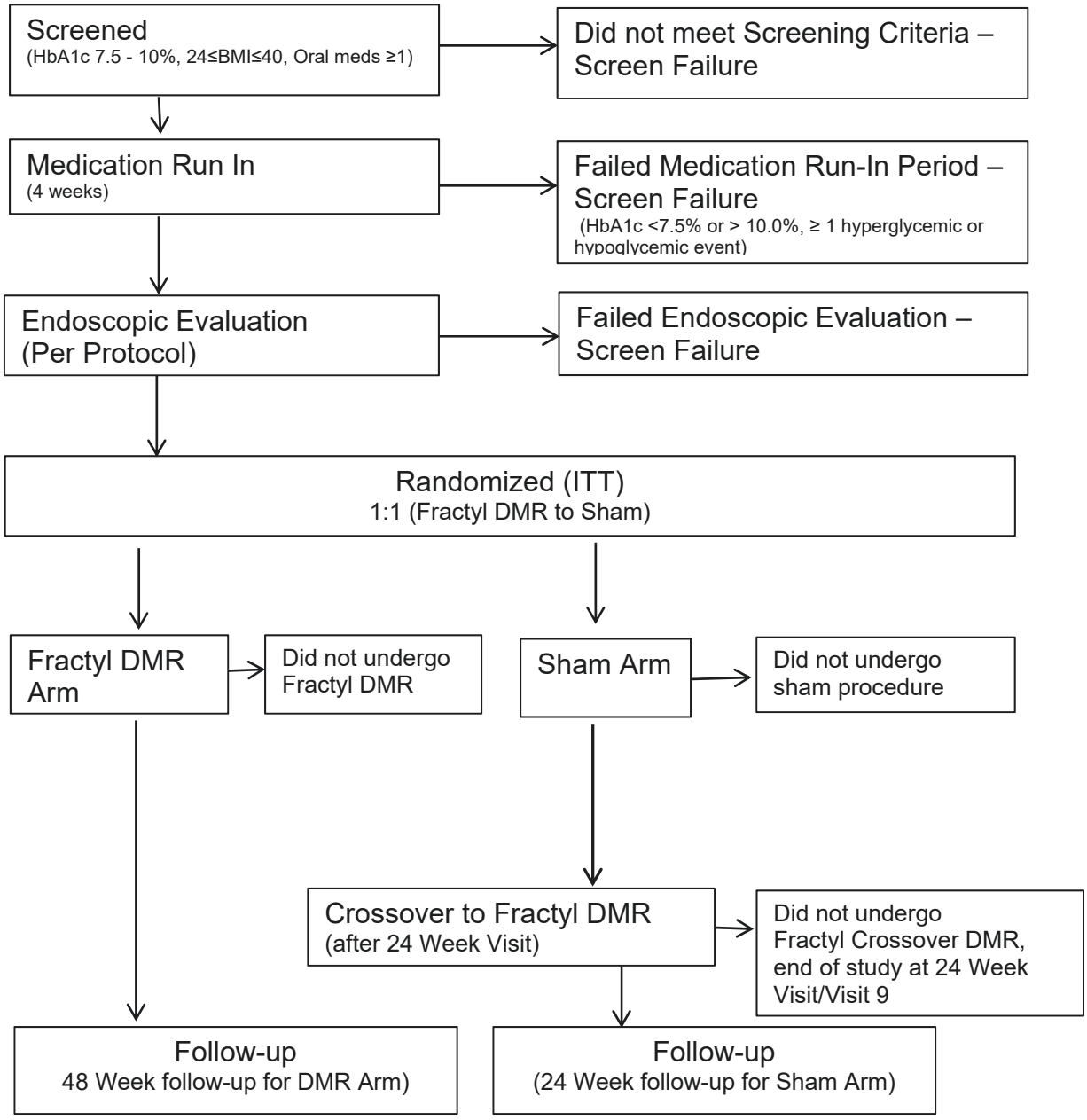
The training phase aims to provide training on the intervention procedure for the endoscopist as well as verify the safety profile before each site begins the randomized protocol. All subjects enrolled as training cases are treated with the Fractyl DMR procedure and followed per protocol for 48 Weeks.

The training cases will be analyzed for safety as outlined in Section 8.2.

2.4 Randomized Cases

After the training cases have been completed at a site, the site will be given permission by Fractyl to begin recruiting and screening for enrollment for the randomized portion of the study. Subjects who meet all criteria after screening are randomized 1:1 (DMR to sham), with double blinding (subject and endocrinologist). The endoscopist is not blinded. Subjects randomized to the DMR procedure are followed per protocol for 48 Weeks. Subjects randomized to the sham procedure are followed for 24 weeks and then offered to cross-over to the DMR procedure. Cross-over subjects are then followed per protocol for an additional 24 Weeks.

Randomized Case Flowchart



The study disposition of study subjects is presented, reflecting the flow diagram above. Subjects randomized to sham who DO NOT cross-over to DMR (Visit 3C) after 24 week/Visit 9 will complete the study at Week 24/Visit 9.

2.5 Intended Use

The Revita® System is intended to improve glycemic control in patients with Type 2 diabetes who have preserved pancreatic beta cell function and whose diabetes is poorly controlled with oral anti-diabetic medications.

2.6 Study Objectives

To demonstrate the efficacy and safety of the Fractyl DMR Procedure using the Revita® System compared to a sham procedure for the treatment of uncontrolled type 2 diabetes.

2.7 Study Duration

It is anticipated that the overall duration of this investigation is approximately 42 months including all training cases, randomized subject enrollment, collection of follow up assessments, and data analysis. The trial is initiated at each institution following approval of the national regulatory authority and the respective Independent Ethics Committee or IRB and a Site Initiation Visit. An estimated 3-5 training cases are performed at each center and take approximately 3 months per site to complete. Enrollment of subjects is expected to take approximately 21 months. Follow up visits occur for an additional 48 Weeks. Sham subjects cross-over to the treatment at 24 Weeks post-index procedure and are followed per protocol for an additional 24 Weeks. Final data collection, analysis and final study report will take an additional 6 months.

2.8 Study Endpoints

The stated objectives of this study are to demonstrate the effectiveness and safety of the Fractyl Revita® System compared to a sham procedure for the treatment of patients with Type 2 Diabetes that are uncontrolled with oral anti-diabetic medication.

2.8.1 Primary Efficacy Endpoints

1) The change from baseline at 24 weeks in HbA1c, DMR vs Sham
2) The absolute change from baseline at 12 weeks in MR-PDFF in patients with baseline MR-PDFF > 5% , DMR vs Sham

2.8.2 Primary Safety Endpoints

The primary safety endpoints are incidence rates of device or procedure related treatment emergent serious adverse events (SAEs), unanticipated device effects (UADEs), and adverse events of special interest (AESIs) through 24 Weeks (Visit 9).

2.8.3 Secondary Endpoints

The secondary endpoints include the following:

1. HbA1c change from baseline to Week 24 (Visit 9) by visit over time, DMR vs. Sham
2. The relative MR-PDFF change from baseline to Week 12 in patients with baseline MR-PDFF > 5%, DMR vs. Sham

3. Proportion of randomized-DMR-treated subjects with an HbA1c improvement from baseline at 24 weeks (Visit 9) that maintain an HbA1c improvement at 48 weeks
4. Proportion of randomized-DMR-treated subjects with an MR-PDFF > 5% at baseline and MR-PDFF improvement from baseline at 24 weeks (Visit 9) that maintain an MR-PDFF improvement at 48 weeks
5. Fasting Plasma Glucose (FPG) change from baseline at 24 weeks DMR vs. Sham
6. FPG change from baseline to Week 24 by visit over time, DMR vs. Sham
7. Weight change from baseline at 24 weeks DMR vs. Sham
8. In randomized-DMR-treated subjects with an HbA1c improvement from baseline at 24 weeks, average HbA1c improvement from baseline at 48 weeks
9. In randomized-DMR-treated subjects with an MR-PDFF > 5% at baseline and MR-PDFF improvement from baseline at 12 weeks, average MR-PDFF improvement at 48 weeks
10. HOMA-IR change from baseline at 24 weeks DMR vs. Sham

2.8.4 Exploratory Endpoints

Change from the baseline in the following by visit out to 24 weeks in DMR vs. Sham

- FPI
- Fasting C-peptide
- Weight
- ALT
- AST
- FIB-4
- Ferritin
- UACR
- eGFR
- Triglycerides
- HDL
- TG/HDL

Change from baseline in the following at 12 weeks, DMR vs. Sham:

- MMTT change from baseline (glucose AUC through 2 hours)
- Change in MMTT measure of Insulin secretion
- Change in MMTT measure of Insulin resistance
- MR-LIC Liver Iron Content

- Proportion of randomized-DMR-treated subjects with an abnormal MR-LIC at baseline and MR-LIC improvement from baseline at 12 weeks that maintain an MR-LIC improvement at 48 weeks.

- In randomized-DMR-treated subjects with an abnormal MR-LIC at baseline and MR-LIC improvement from baseline at 12 weeks, average MR-LIC improvement at 48 weeks.

- Training Cohort only:
  - Change in SBP by ABPM from baseline in training cohort, at 12 weeks
  - Change in DBP by ABPM from baseline in training cohort, at 12 weeks

Additional exploratory endpoint and ad-hoc analyses of interest will be defined in the study Statistical Analysis Plan (SAP).

2.9 Blinding

In this study, both the endocrinologist and the study subject are blinded to the treatment through the 24 Week follow-up visit. While the endoscopist is not blinded to individual treatments, he or she is blinded to cohort level data and is not responsible for managing the Type 2 Diabetes in trial subjects. At the 24 Week Visit, the subject and endocrinologist are unblinded and the subjects who received the sham treatment are offer the to undergo the DMR procedure.

All study staff and associated hospital personnel are instructed that subjects are not to be informed of their randomization assignments until the scheduled time of unblinding and care should be taken to minimize the risk of inadvertent premature unblinding.

2.10 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 and multiple study sites.
- The study design utilizes objective endpoints that are measured by validated test methods. These include HbA1c and Fasting Blood Glucose. Standardized methods and protocols for performing and evaluating tests and examinations have been incorporated into the study protocol.
- The study design utilizes the randomization of subjects and the blinding of both subjects and assessors.
- The blood analysis will be conducted by a central laboratory.
- The study monitor reviews data collection forms as they are received from the study sites to assure there are no missing or incorrect data. Missing or incorrect data is queried and corrected in the database. Site re-training takes place as required to ensure compliance with the protocol.
- The study employs a Data Monitoring Committee (DMC) to evaluate Serious Adverse Events as well as to establish stopping rules to ensure continued safety monitoring. Employing an independent body to oversee evaluation of device and procedure adverse event

relatedness provides added validity to the assessment of study safety endpoints and reduces the potential bias a sponsor might have completing the adjudication process on their own.

3. Study Population

3.1 Subject Selection

A maximum of 120 randomized subjects at up to 15 study sites in Europe and global geographies will be enrolled into this clinical study. The clinical study population will be comprised of males and females, 28 - 75 years of age who satisfy all of the inclusion and exclusion criteria. All subjects taking part in this clinical study must undergo the informed consent process. Subjects must be allowed adequate time to review the consent, have any questions answered, and make a voluntary decision to participate in the clinical study. Each subject must sign and date the IRB/EC approved informed consent form before any clinical study-related procedures are performed. A copy of the signed informed consent form will be provided to the subject for his/her records. A subject's participation in the clinical study begins with the signing and dating of the informed consent form.

Investigational sites may utilize a number of methods to recruit potential subjects into the study including evaluation of existing subjects from their clinical practice, referrals from other physicians and recruitment via external advertising. Advertising materials need to be reviewed and approved by the IRB or EC before use.

3.1.1 Initial Subject Identification

Potential study subjects are identified by the Investigator or their designee(s) through medical record review, referring physicians, and inquiries from interested subjects. Subjects may be screened using a telephone screening script to evaluate potential eligibility for the study. If necessary, the subject's General Practitioner may be asked to provide the required medical information after the subject's authorization. If the subject meets the study's basic entry criteria as verified over the phone using the screening script or through medical record review, the subject is invited to attend an office visit for potential inclusion in the study and completion of the informed consent form.

3.2 Duration of Subject Participation

For subjects randomized to DMR (and all training cases), the total anticipated duration of subject participation in the clinical study will be up to a maximum of 56 weeks (maximum of 6 weeks between Screening and Baseline, maximum of 2 weeks between Baseline and Procedure, and 48 weeks of follow up post procedure).

For subjects randomized to sham who cross-over to DMR at 24 weeks, the total anticipated duration of subject participation in the clinical study will be up to a maximum of 56 weeks (maximum of 6 weeks between Screening and Baseline,

maximum of 2 weeks between Baseline and Procedure, and 24 weeks of follow up, then cross-over and additional 24 weeks of follow up). For subjects randomized to sham who DO NOT cross-over to DMR (Visit 3C) after 24 week/Visit 9 will complete the study at Visit 9.

4. Screening Period and Eligibility Criteria

The screening period is completed in 3 phases: Screening (Visit 1, Pre-Medication Run-In), Baseline (Visit 2, post-medication run-in) and Procedure (Visit 3). The inclusion criteria and additional exclusion criteria for each visit are listed by visit.

4.1 Selection Criteria

Selection criteria are assessed over the first 3 study visits: at the initial Screening visit (Visit 1), at Baseline (Visit 2), and during the endoscopic evaluation at the Procedure Visit (Visit 3).

4.1.1 Inclusion Criteria

Screening Visit (Pre-Medication Run-In, Visit 1)

1. 28 -75 years of age
2. Diagnosed with Type 2 Diabetes and evidence of preserved insulin secretion. Fasting insulin > 7.0 μU/ mL.
3. HbA1c of 7.5 - 10.0% (59-86 mmol/mol)
4. Body Mass Index (BMI) ≥ 24 and ≤ 40 kg/m2
5. Currently taking one or more oral glucose lowering medications, of which one must be Metformin, with no changes in medication in the previous 12 weeks prior to study entry
6. Able to comply with study requirements and understand and sign the informed consent

No additional inclusion criteria are applicable at Baseline Visit (Visit 2) or at Procedure (Visit 3).

4.1.2 Exclusion Criteria

Screening Visit (Pre-Medication Run-In, Visit 1)

1. Diagnosed with Type 1 Diabetes or with a history of ketoacidosis
2. Current use of Insulin
3. Current use of GLP-1 analogues
4. Hypoglycemia unawareness or a history of severe hypoglycemia (more than 1 severe hypoglycemic event, as defined by need for third-party-assistance, in the last year)
5. Known autoimmune disease, as evidenced by a positive Anti-GAD test, including Celiac disease, or pre-existing symptoms of systemic lupus erythematosus, scleroderma or other autoimmune connective tissue disorder
6. Active H.pylori infection (Participants with active H. pylori may continue with the screening process if they are treated via medication

7. Previous GI surgery that could affect the ability to treat the duodenum such as subjects who have had a Bilroth 2, Roux-en-Y gastric bypass, or other similar procedures or conditions
8. History of chronic or acute pancreatitis
9. Known active hepatitis or active liver disease
10. Symptomatic gallstones or kidney stones, acute cholecystitis or history of duodenal inflammatory diseases including Crohn's Disease and Celiac Disease
11. History of coagulopathy, upper gastro-intestinal bleeding conditions such as ulcers, gastric varices, strictures, congenital or acquired intestinal telangiectasia
12. Use of anticoagulation therapy (such as warfarin) which cannot be discontinued for 7 days before and 14 days after the procedure
13. Use of P2Y12 inhibitors (clopidogrel, pasugrel, ticagrelor) which cannot be discontinued for 14 days before and 14 days after the procedure. Use of aspirin is allowed.
14. Unable to discontinue NSAIDs (non-steroidal anti-inflammatory drugs) during treatment through 4 weeks post procedure phase
15. Taking corticosteroids or drugs known to affect GI motility (e.g. Metoclopramide)
16. Receiving weight loss medications such as Meridia, Xenical, or over the counter weight loss medications
17. Persistent Anemia, defined as Hgb<10 g/dl
18. eGFR or MDRD <30 ml/min/1.73m^2
19. Active systemic infection
20. Active malignancy within the last 5 years
21. Not potential candidates for surgery or general anesthesia
22. Active illicit substance abuse or alcoholism
23. Participating in another ongoing clinical trial of an investigational drug or device
24. Any other mental or physical condition which, in the opinion of the Investigator, makes the subject a poor candidate for clinical trial participation

Baseline Visit (Post Medication Run-In, Visit 2)

1. HbA1c post run-in phase < 7.5% (59 mmol/mol) or > 10.0% (86 mmol/mol)
2. One or more clinically significant hypoglycemic events defined as self-monitored or laboratory plasma glucose level of < 54 mg/dL (3.0 mmol/L), or at least 2 such events if a clear correctable precipitating factor can be identified; or a severe hypoglycemic event, as defined as hypoglycemia requiring third-party-assistance, since the screening visit (Visit 1)
3. Hyperglycemic event defined as three self-monitored finger sticks in 1 day during the run-in period with fasting blood glucose measurements >15 mmol/L (270 mg/dL) or non-fasting blood glucose measurements >20 mmol/L (360 mg/dL) or any combination of the two. Fasting

glucose hyperglycemia is not an exclusion if measured at the actual baseline visit (Visit 2) blood analysis test
4. Those who are pregnant, nursing or expect to become pregnant over the course of the study

Procedure (Visit 3)
1. Active and uncontrolled GERD defined as grade III esophagitis or greater
2. Abnormalities of the GI tract preventing endoscopic access to the duodenum
3. Anatomic abnormalities in the duodenum that would preclude the completion of the DMR procedure, including tortuous anatomy
4. Malignancy newly diagnosed by endoscopy
5. Upper gastro-intestinal conditions such as ulcers, polyps, gastric varices, strictures, congenital or acquired intestinal telangiectasia

5. Study Visits

5.1 Visit 1: Screening (Pre-Medication Run-In)

When the subject comes into clinic for the screening visit, the Informed Consent procedure is completed.

Informed Consent

Informed consent shall inform the subject as to the objective and procedures of the study and possible risks involved. The subjects are 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 subject is otherwise entitled and that withdrawal from the study will not jeopardize their future medical care. The informed consent process is accomplished by providing the subjects with a copy of the Informed Consent Form. The contents of this form are discussed with the subject allowing adequate time for questions. If subjects are willing to participate in the study, they indicate their willingness by signing the form. A signed copy of the consent form is given to each subject in the study. The site must make a note in the subject's medical record as to the consent given and the date and time at which the form was signed.

Demographics, Medical History and Full Physical Exam

Subject demographics, medical history and a full physical exam are completed by the physician or assigned medical personnel.

Blood Analysis

All subjects will have sufficient blood drawn to complete the tests outlined in Section 6.3.

Subjects 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 and considered to be

a screen failure. Screen Failure subjects are informed by a phone call from the site staff.

H. pylori Test
A blood sample will be drawn to complete testing of H.pylori on all potential subjects.

Participants with active H. pylori may continue with the screening process if they are treated via antibiotic medication.

Oral Anti-Diabetic Medication Run-In
Individuals who meet all the inclusion criteria and none of the exclusion criteria at the Screening Visit are eligible to start the 4 week medication run-in. The medication run-in period will begin after all of the Visit 1 criteria have been evaluated and the subject is confirmed as eligible. Subjects are instructed to continue their oral anti-diabetic medication without any changes in the prescribed regime.The intent of the medication run-in is to verify a subject's medication regime and associated compliance to establish a baseline for future comparison.

Subject Self-Monitored Blood Glucose / Glycemia Diary
As outlined in Section 6.9, subjects are provided with a Glycemia diary and a home blood glucose monitor. Subjects are instructed to record symptoms and measured blood glucose levels in the event of a hypoglycemic or hyperglycemic episodes in this diary.

Nutritional Counseling
As outlined in Section 6.8, study subjects are provided with nutritional counseling to educate them on the importance of diet in relation to blood glucose control during this visit.

Adverse Event Evaluation
As outlined in Section 7.8, any reported adverse events by the subject or dictated by blood tests and office evaluation are recorded. AEs are collected from the time the Informed Consent is signed.

Concomitant Medication
A complete list of all medications a subject is currently taking will be recorded by the physician or assigned medical personnel.

5.2 Visit 2: Baseline (Post Medication Run-In)

Subjects come into the clinic for the Baseline Visit after completing a minimum of a 4 week (28 days) medication run-in. This visit must occur 4-6 weeks (28 – 42 days) after the Screening Visit. This visit may be conducted the same day as Visit 3 / Endoscopic Procedure/Randomization provided all testing and verification of final inclusion and exclusion criteria are verified before randomization and the index procedure. The maximum allowed time between the Baseline Visit and the Endoscopic Procedure/Randomization visit is 14 days.

At this visit, subjects are assessed for the following additional exclusion criteria:

1. HbA1c post run-in phase < 7.5% (59 mmol/mol) or > 10.0% (86 mmol/mol)
2. One or more clinically significant hypoglycemic events defined as self-monitored or laboratory plasma glucose level of < 54 mg/dL (3.0 mmol/L), or at least 2 such events if a clear correctable precipitating factor can be identified; or a severe hypoglycemic event, as defined as hypoglycemia requiring third-party-assistance, since the screening visit (Visit 1)
3. Hyperglycemic event defined as three self-monitored finger sticks in 1 day during the run-in period with fasting blood glucose measurements >15 mmol/L (270 mg/dL) or non-fasting blood glucose measurements >20 mmol/L (360 mg/dL) or any combination of these. Fasting glucose hyperglycemia is not an exclusion if measured at the actual baseline visit (Visit 2) blood analysis test.

The procedures outlined below are conducted for all subjects and the baseline values are established for comparison with future study visits.

Targeted Physical Exam
As outlined in Section 6.2, weight and blood pressure will be conducted in all subjects. A symptom directed physical examination is conducted if new signs or symptoms are reported by a subject. Findings ongoing since previous physical exam are reevaluated and any abnormal findings are recorded.

A urine pregnancy test for females of childbearing potential will be performed by a local laboratory.

Blood Analysis
As outlined in Section 6.3, Standard Blood Analysis, all subjects continuing to be screened for inclusion for this study will have sufficient blood drawn to complete the standard blood analysis. These data will provide a baseline for comparison at future follow up visits.

Urinary Protein Excretion (UPE) Test
As outlined in Section 6.4, urine albumin & urine creatinine excretion levels in the urine is analyzed to evaluate kidney function. A urine sample is collected (at the same time as the fasting blood sample) from the subject following standard techniques and forwarded to a central laboratory for analysis.

Mixed Meal Tolerance Test (MMTT)
MMTT to be performed at selected study sites.

As Outlined in Section 6.5, all participants will be administered a Mixed Meal Tolerance Test to establish their insulin response to glucose by measuring the concentration of:

- Glucose
- Pancreatic and gut hormones
- Metabolic substrate screen

Ambulatory Blood Pressure
ABPM to be performed in training cases only.

As outlined in Section 6.6, subjects will have an ambulatory blood pressure monitor placed after the MMTT is complete. The monitor will be worn for 24 hours. The subject will return to the study site (Visit 2A) to return the monitor for reading and analysis.

Radiological Hepatic Status using Magnetic Resonance – Proton Density Fat Fraction (MR-PDFF) and Magnetic Resonance – Liver Iron Content (MR-LIC)

MR-PDFF and MR-LIC to be performed at selected study sites.

As outlined in Section 6.7, MR-PDFF and MR-LIC will be conducted to assess the potential effect of DMR on liver fat as measured by the percent of proton density fat fraction, and to assess the potential effect of DMR on liver iron content.

Subject Self-Monitoring Blood Glucose / Glycemia Diary
As outlined in Section 6.9, the diary is reviewed for the occurrence of glycemic events, blood glucose levels, and/or symptoms of hypoglycemia or hyperglycemia. Subjects who have experienced a severe hypoglycemic or hyperglycemic event (defined in section 6.9) since the screening visit are excluded from the study.

Oral Anti-Diabetic Medication Run-In
Subjects are instructed to continue their oral anti-diabetic medication without any changes in the prescribed regime through Visit 3 Procedure.

Nutritional Counseling
As outlined in Section 6.8, study subjects are provided with nutritional counseling to educate them on the importance of diet in relation to blood glucose control during this visit.

Adverse Event Evaluation
As outlined in Section 7.8, any reported adverse events by the subject or dictated by blood tests and office evaluation are recorded.

Concomitant Medication
All concurrent medication reported by the subject is recorded.

All subjects are asked about current oral anti-diabetic medication use. Any changes in medication, including use of rescue medication, are recorded on the medication log.

At the end of the Baseline Visit, the endoscopic procedure is scheduled within the next 14 days.

5.3 Visit 2A: Ambulatory Blood Pressure Monitor Return

ABPM to be performed in training cases only.

Subjects come to the study site 24 hours after the ambulatory blood pressure monitoring device was placed and monitoring was initiated. The device is returned to the study site for reading and analysis.

5.4 Visit 3: Procedure

The procedure visit consists of an endoscopic evaluation, subject randomization, and the completion of the index procedure. This visit may be conducted the same day as the Baseline Visit (Post Medication Run-In, Visit 2) provided all required procedures are complete and inclusion/exclusion criteria are met. This visit may not occur more than 14 days after the Baseline Visit (Visit 2).

Endoscopic Evaluation
On the day of the procedure, an endoscopic evaluation consisting of an assessment of the esophagus, stomach, duodenum and associated structures is completed to ensure there are no conditions that would exclude the subject from having the index procedure.

The following additional exclusion criteria should be assessed via endoscopy prior to randomization:

1. Active and uncontrolled GERD defined as grade III esophagitis or greater
2. Abnormalities of the GI tract preventing endoscopic access to the duodenum
3. Anatomic abnormalities in the duodenum that would preclude the completion of the DMR procedure, including tortuous anatomy
4. Malignancy newly diagnosed by endoscopy
5. Upper gastro-intestinal conditions such as ulcers, gastric varices, strictures, congenital or acquired intestinal telangiectasia

Any subject found to have the conditions listed in the exclusion criteria above is considered a Screen Failure and is not randomized, does not undergo the procedure and is not followed per protocol.

Randomization
Following confirmation of subject eligibility during the endoscopic evaluation, the subject is randomized. Randomization is completed using electronic assignment via a web-based system and is stratified by study center at a 1:1 ratio to:

- Fractyl DMR Procedure: Subjects are blinded and are treated with the DMR procedure
- Sham Procedure: Subjects are blinded and are provided a sham procedure

Immediately following randomization, paracetamol, acetaminophen or equivalent is administered to prevent pain after the procedure and minimize the risk of premature unblinding. Hereafter, the assigned procedure is completed.

Subject Enrollment
Study enrollment is defined as successful completion of the endoscopic evaluation and initiation of the index procedure, Fractyl DMR or sham.

All subjects who are enrolled in the study are are required to adhere to the follow-up schedule outlined in this protocol.

Duodenal Mucosal Resurfacing Procedure
The Fractyl DMR procedure using the Revita® System utilizes an over the wire endoscopic approach to ablate the duodenum as detailed in the Instructions for Use (IFU) and Operators Manual supplied with the study materials. Training is also provided by the Sponsor in advance of initiating the study.

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 subjects are monitored and anesthetized by conscious sedation per each facility's standard protocol. In the training and randomized phase, a full DMR procedure is defined as 5 complete ablations or 9 axial centimeters of circumferentially ablated tissue in the duodenum. In the cross-over phase, a full DMR procedure is defined as at least 5 complete ablations or at least 9 axial centimeters of circumferentially ablated tissue in the duodenum.

Subjects who do not receive any ablations during the DMR procedure will be followed for safety through the 4 week visit and then discontinued from the study.

Sham Procedure
The sham procedure will consist of placing the Revita Catheter as described above into the stomach and leaving it in place for 30 minutes and then removing it from the patient.

Unforeseen events (findings or procedures) may occur during either the DMR or sham procedure. These unforeseen events are those that are not planned as part of this procedure (e.g., 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 subject's suitability for continued participation in this study.

Post-Procedure Care & Discharge
Immediately following the procedure, the subject is transported to the recovery area and monitored according to the hospital/physician protocol for endoscopic procedures. The subject 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 is dictated by the hospital or physician's standard care protocol regarding post-anesthesia recovery.

Prior to discharge, all subjects are examined and evaluated for the presence of any adverse events that may have occurred between the procedure and discharge. A subject's hospital stay can be extended based on need as determined by the Investigator. Subjects are eligible to be discharged when they meet the criteria following the local sedation protocol and discharge requirements.

Post-Procedure Diet & Nutritional Counseling
Study subjects are provided with continued nutritional counseling to educate them on the importance of diet in relation to blood glucose control. Subjects are specifically instructed on appropriate post-procedure diet prior to discharge. Guidelines for post procedure, 2-week diet are as follows. The day of the procedure, abstinence of food is maintained (water is allowed but must be sipped). On Days 1–3 after the procedure, the subject may drink clear liquids such as tea, chicken broth and skimmed (fat-free) milk. Day 4-6 post-procedure, the subject should begin to eat a soft diet such as chicken or beef soup (broth with herbs and semolina), nonfat yogurt, tea and sugar free gelato. Day 7-14 of the diet, the subject may expand their diet to include foods such as stew, fruit puree, yogurt and soda crackers. After finishing the two week diet, normal diet is resumed as tolerated.

Oral Anti-Diabetic Medication, Subject Self-Monitoring Blood Glucose and Glycemia Diary
As outlined in Sections 6.9 and 6.10, subjects continue to take oral anti-diabetic medication post-procedure and record hypoglycemic and hyperglycemic events (as defined in section 6.9) in the glycemia diary.

Adverse Event Evaluation
As outlined in Section 7.8, any reported adverse events by the subject or dictated by blood tests and office evaluation are recorded.

Concomitant Medication
All concurrent medication reported by the subject is recorded.

All subjects are asked about current oral anti-diabetic medication use. Any changes in medication, including use of rescue medication, are recorded on the medication log.

5.5 Visit 4: 7 Day Phone Call (+/-2 days)

At day 7 post-procedure, the subject is contacted via phone; no office/clinic visit is required. The following information are collected during the call:

Nutritional Counseling
As outlined in Section 6.8, study subjects are provided with nutritional counseling to educate them on the importance of diet in relation to blood glucose control during this visit.

Self-Monitoring Blood Glucose / Glycemia Diary
Subjects are reminded to continue to monitor blood glucose and record hypoglycemic and hyperglycemic events (as defined in Section 6.9) in the glycemia diary until the next study visit.

Adverse Event Evaluation
As outlined in Section 7.8, any reported adverse events by the subject or dictated by blood tests and office evaluation are recorded.

Concomitant Medication
All concurrent medication reported by the subject is recorded.

All subjects are asked about current oral anti-diabetic medication use. Any changes in medication, including use of rescue medication, are recorded on the medication log.

5.6 Visit 5: 14 Day Phone Call (+/-2 days)

At day 14 post-procedure, the subject is contacted via phone; no office/clinic visit is required. The following information are collected during the call:

Nutritional Counseling
As outlined in Section 6.8, study subjects are provided with nutritional counseling to educate them on the importance of diet in relation to blood glucose control during this visit.

Self-Monitoring Blood Glucose / Glycemia Diary
Subjects are reminded to continue to monitor blood glucose and record hypoglycemic and hyperglycemic events (as defined in Section 6.9) in the glycemia diary until the next study visit.

Adverse Event Evaluation
As outlined in Section 7.8, any reported adverse events by the subject or dictated by blood tests and office evaluation are recorded.

Concomitant Medication
All concurrent medication reported by the subject is recorded.

All subjects are asked about current oral anti-diabetic medication use. Any changes in medication, including use of rescue medication, are recorded on the medication log.

5.7 Visit 6: 4 Week (28 Day) Clinic Visit (+/- 7 days)

The following evaluations are completed at the 4 Week Visit for both treatment groups:

Targeted Physical Exam
As outlined in Section 6.2, weight and blood pressure will be conducted in all subjects. A symptom directed physical examination is conducted if new signs or symptoms are reported by a subject. Findings ongoing since previous physical exam are reevaluated and any abnormal findings are recorded.

Blood Analysis
As outlined in Section 6.3, Standard Blood Analysis, all subjects continuing to be screened for inclusion for this study will have sufficient blood drawn to complete the standard blood analysis. These data will provide a means for comparison at future follow up visits.

Nutritional Counseling
As outlined in Section 6.8, study subjects are provided with nutritional counseling to educate them on the importance of diet in relation to blood glucose control during this visit.

Subject Self-Monitoring Blood Glucose / Glycemia Diary
As outlined in Section 6.9, the diary is reviewed for the occurrence of glycemic events, blood glucose levels, and/or symptoms of hypoglycemia or hyperglycemia.

Subjects continue to monitor blood glucose and record hypoglycemic and hyperglycemic events (as defined in Section 6.9) in the glycemia diary until the next study visit.

Management of Glycemia and Oral Anti-Diabetic Medication
As outlined in Section 6.9, subjects continue to take oral anti-diabetic medication without any changes to the regime unless rescue criteria is met (outlined in Section 6.10).

Adverse Event Evaluation
As outlined in Section 7.8, any reported adverse events by the subject or dictated by blood tests and office evaluation are recorded.

Concomitant Medication
All concurrent medication reported by the subject is recorded.

All subjects are asked about current oral anti-diabetic medication use. Any changes in medication, including use of rescue medication, are recorded on the medication log.

5.8 Visit 7: 12 Week (84 Days) Clinic Visit (+/- 7 days)

The following evaluations are completed at the 12 Week Visit for both treatment groups:

Targeted Physical Exam
As outlined in Section 6.2, weight and blood pressure will be conducted in all subjects. A symptom directed physical examination is conducted if new signs or symptoms are reported by a subject. Findings ongoing since previous physical exam are reevaluated and any abnormal findings are recorded.

Blood Analysis
As outlined in Section 6.3, Standard Blood Analysis, all subjects continuing to be screened for inclusion for this study will have sufficient blood drawn to complete the standard blood analysis. These data will provide a means for comparison at future follow up visits.

Urinary Protein Excretion (UPE) Test
As outlined in Section 6.4, urine albumin & urine creatinine excretion levels in the urine is analyzed to evaluate kidney function. A urine sample is collected (at the same time as the fasting blood sample) from the subject following standard techniques and forwarded to a central laboratory for analysis.

Mixed Meal Tolerance Test
MMTT to be performed at selected study sites.

As Outlined in Section 6.5, all participants will be administered a Mixed Meal Tolerance Test to establish their insulin response to glucose by measuring the concentration of:

- Glucose
- Pancreatic and gut hormones
- Metabolic substrate screen

Ambulatory Blood Pressure
ABPM to be performed in training cases only.

As outlined in Section 6.6, subjects will have an ambulatory blood pressure monitor placed after the MMTT is complete. The monitor will be worn for 24 hours. The subject will return to the study site (Visit 7A) to return the monitor for reading and analysis.

Radiological Hepatic Status (MR-PDFF and MR-LIC)
MR-PDFF and MR-LIC to be performed at selected study sites.

As outlined in Section 6.7, MR-PDFF and MR-LIC will be conducted to assess the potential effect of DMR on liver fat as measured by the percent of proton density fat fraction, and to assess the potential effect of DMR on liver iron content.

Nutritional Counseling
As outlined in Section 6.8, study subjects are provided with nutritional counseling to educate them on the importance of diet in relation to blood glucose control during this visit.

Subject Self-Monitoring Blood Glucose / Glycemia Diary
As outlined in Section 6.9, the diary is reviewed for the occurrence of glycemic events, blood glucose levels, and/or symptoms of hypoglycemia or hyperglycemia.

Subjects continue to monitor blood glucose and record hypoglycemic and hyperglycemic events (as defined in Section 6.9) in the glycemia diary until the next study visit.

Management of Glycemia and Oral Anti-Diabetic Medication
As outlined in Section 6.9, subjects continue to take oral anti-diabetic medication without any changes to the regime unless rescue criteria is met (outlined in Section 6.10).

Adverse Event Evaluation
As outlined in Section 7.8, any reported adverse events by the subject or dictated by blood tests and office evaluation are recorded.

Concomitant Medication
All concurrent medication reported by the subject is recorded.

All subjects are asked about current oral anti-diabetic medication use. Any changes in medication, including use of rescue medication, are recorded on the medication log.

5.9 Visit 7A: Ambulatory Blood Pressure Monitor Return

ABPM to be performed in training cases only.

Subjects come to the study site 24 hours after the ambulatory blood pressure monitoring device was placed and monitoring was initiated. The device is returned to the study site for reading and analysis.

5.10 Visit 7.1: 15 Week (105 Day) Phone Call (+/- 5 days)

At 15 Weeks post procedure, the subject is contacted via phone; no office/clinic visit is required. The following information is collected during the call:

Nutritional Counseling
As outlined in Section 6.8, study subjects are provided with nutritional counseling to educate them on the importance of diet in relation to blood glucose control during this visit.

Self-Monitoring Blood Glucose / Glycemia Diary review
Subjects are reminded to continue to monitor blood glucose and record hypoglycemic and hyperglycemic events (as defined in Section 6.9) in the glycemia diary until the next study visit.

Adverse Event Evaluation
As outlined in Section 7.8, any reported adverse events by the subject or dictated by blood tests and office evaluation are recorded.

Concomitant Medication
All concurrent medication use reported by the subject is recorded.

All subjects are asked about current oral anti-diabetic medication use. Any changes in medication, including use of rescue medication, are recorded on the medication log.

5.11 Visit 8: 18 Week (126 Day) Clinic Visit (+/- 7 days)

The following evaluations are completed at the 18 Week Visit for both treatment groups:

Targeted Physical Exam
As outlined in Section 6.2, weight and blood pressure will be conducted in all subjects. A symptom directed physical examination is conducted if new signs or symptoms are reported by a subject. Findings ongoing since previous physical exam are reevaluated and any abnormal findings are recorded.

Blood Analysis
As outlined in Section 6.3, Standard Blood Analysis, all subjects continuing to be screened for inclusion for this study will have sufficient blood drawn to complete the standard blood analysis. These data will provide a means for comparison at future follow up visits.

Nutritional Counseling
As outlined in Section 6.8, study subjects are provided with nutritional counseling to educate them on the importance of diet in relation to blood glucose control during this visit.

Subject Self-Monitoring Blood Glucose / Glycemia Diary
As outlined in Section 6.9, the diary is reviewed for the occurrence of glycemic events, blood glucose levels, and/or symptoms of hypoglycemia or hyperglycemia.

Subjects continue to monitor blood glucose and record hypoglycemic and hyperglycemic events (as defined in Section 6.9) in the glycemia diary until the next study visit.

Management of Glycemia and Oral Anti-Diabetic Medication
As outlined in Section 6.9, subjects continue to take oral anti-diabetic medication without any changes to the regime unless rescue criteria is met (outlined in Section 6.10).

Adverse Event Evaluation
As outlined in Section 7.8, any reported adverse events by the subject or dictated by blood tests and office evaluation are recorded.

Concomitant Medication
All concurrent medication reported by the subject is recorded.

All subjects are asked about current oral anti-diabetic medication use. Any changes in medication, including use of rescue medication, are recorded on the medication log.

5.12 Visit 8.1: 21 Week (147 Day) Phone Call (+/- 5 days)

At 21 Weeks post procedure, the subject is contacted via phone; no office/clinic visit is required. The following information is collected during the call:

Nutritional Counseling
As outlined in Section 6.8, study subjects are provided with nutritional counseling to educate them on the importance of diet in relation to blood glucose control during this visit.

Self-Monitoring Blood Glucose / Glycemia Diary review
Subjects are reminded to continue to monitor blood glucose and record hypoglycemic and hyperglycemic events (as defined in Section 6.9) in the glycemia diary until the next study visit.

Adverse Event Evaluation
As outlined in Section 7.8, any reported adverse events by the subject or dictated by blood tests and office evaluation are recorded.

Concomitant Medication
All concurrent medication use reported by the subject is recorded.

All subjects are asked about current oral anti-diabetic medication use. Any changes in medication, including use of rescue medication, are recorded on the medication log.

5.13 Visit 9: 24 Week (168 Day) Clinic Visit (+/- 14 days)

All subjects and the site endocrinologist and staff are unblinded at this visit.

5.13.1 For subjects Treated with the DMR Procedure

The following evaluations are completed:

Targeted Physical Exam

As outlined in Section 6.2, weight and blood pressure will be conducted in all subjects. A symptom directed physical examination is conducted if new signs or symptoms are reported by a subject. Findings ongoing since previous physical exam are reevaluated and any abnormal findings are recorded.

Blood Analysis

As outlined in section 6.3, Standard Blood Analysis, all subjects continuing to be screened for inclusion for this study will have sufficient blood drawn to complete the standard blood analysis. These data will provide a means for comparison at future follow up visits.

Urinary Protein Excretion (UPE) Test

As outlined in Section 6.4, urine albumin & urine creatinine excretion levels in the urine is analyzed to evaluate kidney function. A urine sample is collected (at the same time as the fasting blood sample) from the subject following standard techniques and forwarded to a central laboratory for analysis.

Endoscopy and Endoscopic Evaluation
(Training and randomized DMR subjects only)

On the day of the visit (or within 14 days of Visit 9), a follow up endoscopic evaluation to visually examine the treatment site and adjacent tissues is conducted. Video of the procedure is captured, as well as, any Investigator notes detailing observations.

Nutritional Counseling

As outlined in Section 6.8, study subjects are provided with nutritional counseling to educate them on the importance of diet in relation to blood glucose control during this visit.

Subject Self-Monitoring Blood Glucose / Glycemia Diary

As outlined in Section 6.9, the diary is reviewed for the occurrence of glycemic events, blood glucose levels, and/or symptoms of hypoglycemia or hyperglycemia.

Subjects continue to monitor blood glucose and record hypoglycemic and hyperglycemic events (as defined in Section 6.9) in the glycemia diary until the next study visit.

Management of Glycemia and Oral Anti-Diabetic Medication
Once the subject is unblinded, the subject's diabetes medication regimen is managed according to current diabetes standard of care through the end of the study. Medication changes will be based on Hyperglycemia Rescue Criteria (Section 6.9) that reflect patient-centric approach in the setting of a diabetes clinical trial, as based on International Diabetes Federation Clinical Practice recommendations, the Position Statement of the American Diabetes Association and the European Association for the Study of Diabetes, or other relevant medical society guidelines that can be used as a guide to manage the subject's diabetes.

Any changes in medication, including use of rescue medication, are recorded on the medication log.

Adverse Event Evaluation
As outlined in Section 7.8, any reported adverse events by the subject or dictated by blood tests and office evaluation are recorded.

Concomitant Medication
All concurrent medication reported by the subject is recorded.

All subjects are asked about current oral anti-diabetic medication use. Any changes in medication, including use of rescue medication, are recorded on the medication log.

5.13.2 For subjects Treated with the Sham Procedure

At the 24 Week Visit, all subjects initially treated with the Sham Procedure have the same evaluations as the subjects in the DMR treatment group listed above, except for the 24 Week Follow-up endoscopy and endoscopic evaluation. For patients who are eligible and accept the offer of cross-over, the Endoscopy / DMR procedure is scheduled within 0-14 days of this 24 Week Visit. During the time between the 24 Week Visit and the cross-over to DMR (Visit 3C), medications should be held stable. For subjects randomized to sham who DO NOT cross-over to DMR (Visit 3C) after 24 week/Visit 9 will complete the study at Visit 9.

5.13.3 Visit 3C: Cross-over to DMR Visit (0-14 days from Visit 9)

The endoscopy and the DMR procedure are completed at this visit; Visit 3C assessments and cross-over procedure may be completed the same day as Visit 9 assessments for Sham patients. Video of the procedure is captured, as well as, any Investigator notes detailing observations.

Once a previous-sham subject is treated with the DMR procedure, these subjects complete follow-up study visits 4 through 9 per protocol (repeating Visits 4 – 9 with some modification as indicated in the schedule of assessments and visit descriptions, these are refered to as Visit 4C – 9C). ***Cross-over subjects will not complete a MMTT (Visit 7C) and will not complete anadditional 24 Week follow-up endoscopy and nutritional couseling (Visit 9C) post cross-over to DMR.***

5.14 Visit 9.1: 30 Week (210 Day) Phone Call (+/- 5 days)

At 30 Weeks post procedure, the subject is contacted via phone; no office/clinic visit is required. The following information is collected during the call:

Nutritional Counseling
As outlined in Section 6.8, study subjects are provided with nutritional counseling to educate them on the importance of diet in relation to blood glucose control during this visit.

Self-Monitoring Blood Glucose / Glycemia Diary review
Subjects are reminded to continue to monitor blood glucose and record hypoglycemic and hyperglycemic events (as defined in Section 6.9) in the glycemia diary until the next study visit.

Adverse Event Evaluation
As outlined in Section 7.8, any reported adverse events by the subject or dictated by blood tests and office evaluation are recorded.

Concomitant Medication
All concurrent medication use reported by the subject is recorded.
All subjects are asked about current oral anti-diabetic medication use. Any changes in medication, including use of rescue medication, are recorded on the medication log.

5.15 Visit 10: 36 Week (252 Day) Clinic Visit (+/- 28 days)

The following evaluations are completed at the 36 Week visit:

Targeted Physical Exam
As outlined in Section 6.2, weight and blood pressure will be conducted in all subjects. A symptom directed physical examination is conducted if new signs or symptoms are reported by a subject. Findings ongoing since previous physical exam are reevaluated and any abnormal findings are recorded.

Blood Analysis
As outlined in Section 6.3, Standard Blood Analysis, all subjects continuing to be screened for inclusion for this study will have sufficient blood drawn to complete the standard blood analysis. These data will provide a means for comparison at future follow up visits.

Nutritional Counseling
As outlined in Section 6.8, study subjects are provided with nutritional counseling to educate them on the importance of diet in relation to blood glucose control during this visit.

Subject Self-Monitoring Blood Glucose / Glycemia Diary
As outlined in Section 6.9, the diary is reviewed for the occurrence of glycemic events, blood glucose levels, and/or symptoms of hypoglycemia or hyperglycemia.

Subjects continue to monitor blood glucose and record hypoglycemic and hyperglycemic events (as defined in Section 6.9) in the glycemia diary until the next study visit.

Management of Glycemia and Oral Anti-Diabetic Medication
As outlined in Section 6.9, subjects continue to take oral anti-diabetic medication without any changes to the regime unless rescue criteria is met (outlined in Section 6.10).

Adverse Event Evaluation
As outlined in Section 7.8, any reported adverse events by the subject or dictated by blood tests and office evaluation are recorded.

Concomitant Medication
All concurrent medication reported by the subject is recorded.

All subjects are asked about current oral anti-diabetic medication use. Any changes in medication, including use of rescue medication, are recorded on the medication log.

5.16 Visit 10.1: 42 Week (294 Day) Phone Call (+/- 5 days)

At 42 Weeks post procedure, the subject is contacted via phone; no office/clinic visit is required. The following information is collected during the call:

Nutritional Counseling
As outlined in Section 6.8, study subjects are provided with nutritional counseling to educate them on the importance of diet in relation to blood glucose control during this visit.

Self-Monitoring Blood Glucose / Glycemia Diary review
Subjects are reminded to continue to monitor blood glucose and record hypoglycemic and hyperglycemic events (as defined in Section 6.9) in the glycemia diary until the next study visit.

Adverse Event Evaluation
As outlined in Section 7.8, any reported adverse events by the subject or dictated by blood tests and office evaluation are recorded.

Concomitant Medication
All concurrent medication use reported by the subject is recorded.
All subjects are asked about current oral anti-diabetic medication use. Any changes in medication, including use of rescue medication, are recorded on the medication log.

5.17 Visit 11: 48 Week (336 Day) Clinic Visit (+/- 28 days)

The following evaluations are completed at the 48 Week visit:

Targeted Physical Exam
As outlined in Section 6.2, weight and blood pressure will be conducted in all subjects. A symptom directed physical examination is conducted if new signs or symptoms are reported by a subject. Findings ongoing since previous physical exam are reevaluated and any abnormal findings are recorded.

Blood Analysis
As outlined in Section 6.3, Standard Blood Analysis, all subjects continuing to be screened for inclusion for this study will have sufficient blood drawn to complete the standard blood analysis. These data will provide a means for comparison at future follow up visits.

Radiological Hepatic Status (MR-PDFF and MR-LIC)
MR-PDFF and MR-LIC to be performed at selected study sites.

As outlined in Section 6.7, MR-PDFF will be conducted to assess the potential effect of DMR on liver fat as measured by the percent of proton density fat fraction, and to assess the potential effect of DMR on liver iron content.

Subject Self-Monitoring Blood Glucose / Glycemia Diary
As outlined in Section 6.9, the diary is reviewed for the occurrence of glycemic events, blood glucose levels, and/or symptoms of hypoglycemia or hyperglycemia.

Management of Glycemia and Oral Anti-Diabetic Medication
Any changes in medication, including use of rescue medication, are recorded on the medication log. All subjects should continue taking their OADs until post-study care is implemented (Section 6.10).

Adverse Event Evaluation
As outlined in Section 7.8, any reported adverse events by the subject or dictated by blood tests and office evaluation are recorded.

Concomitant Medication
All concurrent medication reported by the subject is recorded.

All subjects are asked about current oral anti-diabetic medication use. Any changes in medication, including use of rescue medication, are recorded on the medication log.

5.18 Subject Withdrawal & Early Termination

All subjects enrolled into the study and who have undergone the DMR procedure are followed for 48 weeks post-procedure. Subjects who have undergone the sham procedure are followed for 24 weeks post-procedure prior to cross-over and then for an additional 48 weeks post-cross-over. Subjects randomized to sham who DO NOT cross-over to DMR (Visit 3C) after 24 week/Visit 9 will complete the study at Visit 9. While study withdrawal is discouraged, subjects may withdraw from the study at any time, with or without reason, and without prejudice to further treatment. Reasonable efforts are made by the investigational site to obtain a final data set from the subject, corresponding to data captured at Visits 4-11. Acceptable reasons for withdrawal include physician discretion, subject choice to withdraw consent, loss to follow-up and death, as described below.

- Physician Discretion: the investigator determines that, for medical reasons, it is in the best interest of the subject to discontinue participation in the study.
- Loss to Follow-Up: Unable to locate the subject despite documented attempts to notify via telephone, email or mail. A subject will not be considered lost to follow-up until the last scheduled follow-up visit (12 month study time point) or until 3 documented unsuccessful attempts have been made to contact the patient, whichever occurs first. One such contact attempt must include a registered return receipt letter.
- Subject Withdrawal: The subject 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).
- Death: If possible, an autopsy and/or death certificate should be obtained in order to document the cause of death.

All subjects enrolled in the clinical study (including those withdrawn from the clinical study or lost to follow-up) shall be accounted for and documented. If a subject withdraws from the clinical investigation, the reason(s) shall be reported. If such withdrawal is due to problems related to investigational device safety or performance, the investigator shall ask for the subject's permission to follow his/her status/condition outside of the clinical study. All applicable case report forms up to the point of subject withdrawal must be completed. Additional data may no longer be collected after the point at which a subject has been withdrawn from the study or withdraws his/her consent, for whatever reason. All open adverse events should be closed or documented as chronic. Data collected up to the point of subject withdrawal may be used. Withdrawn subjects will not be replaced.

5.19 Post-Study Care

After completing the study, subjects will be followed according to the standard of care to be defined by each responsible investigator. This typically includes a yearly follow up visit with the following assessments to be taken:

Review of diabetes status including blood glucose levels
Review of compliance with prescribed diet & medication regime

At study completion or subject withdrawal, the subjects' status will be assessed and any unresolved SAEs will be evaluated to provide a clarification on planned patient follow up/medical care.

6. Study Procedures & Assessments

6.1 Demographics/Medical History/Physical Exam

Subject demographics, medical history and a full physical exam are completed by the physician or assigned medical personnel. If necessary, the subject's General Practitioner may be asked to provide medical records about the subject's medical history. Specific parameters to be captured include:

- Age
- Gender
- Height, Weight, BMI
- Duration of diabetes
- Concurrent health conditions
- Concurrent and Oral Anti-Diabetic Medication Use
- Previous surgeries/treatments
- Pregnancy test
  - Female subjects of childbearing potential must have a negative pregnancy test within 14 days prior to Procedure Visit (Visit 3) and must agree to avoid pregnancy during the course of the study

6.2 Targeted Physical Exam

Weight and blood pressure will be conducted in all subjects.

- Body weight will be measured to the nearest 0.1 kg on a balanced beam scale in the morning before breakfast after a visit to the lavatory with a subject in light clothing.

- Blood pressure will be measured in sitting position in duplicate after 15 min of rest. The measurement will be repeated in the same arm at that given visit.

A symptom directed physical examination is conducted if new signs or symptoms are reported by a subject.

- Findings ongoing since previous physical exam are reevaluated
- Abnormal findings are recorded These data will provide a means for comparison at future follow up visits.
- Weight
- Blood pressure
- Symptom directed physical examination conducted if new signs or symptoms reported
- Findings ongoing since previous physical exam are reevaluated
- Abnormal findings are recorded

6.3 Blood Analysis

All subjects will have sufficient fasting blood drawn to complete the following tests. As indicated in the table below, the test name will have the associated specific evaluations included. Baseline data will provide a comparison for future follow-up visits. All blood drawn for analysis should be performed after a 10 hour overnight fast.

Test Name	Evaluation to be Included
Complete Blood Count	White Blood Cell Count White Blood Cell Differential Total Hemoglobin Hematocrit Platelet Count
Blood Chemistry	Blood Urea Nitrogen Calcium Chloride Creatinine & calculated eGFR Potassium Sodium Albumin
Liver Panel	Alanine Aminotransferase (ALT) Aspartate Aminotransferase (AST) Total Bilirubin Alkaline Phosphatase Ferritin
Pancreatic Enzymes	Amylase Lipase
Fasting Lipid Panel	Total Cholesterol High Density Lipoprotein Low Density Lipoprotein Triglycerides
Fasting Glucose	Same
Glycosylated hemoglobin (HbA1c)	Same
C-Peptide	Same
Fasting Insulin	Same
Anti-Gad *(Screening Visit Only)*	Same
H.pylori *(Screening Visit Only)*	Same

Subjects 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 and considered to be a screen failure. Screen Failure subjects are informed by a phone call.

Blood analysis will be conducted at a central laboratory.

6.4 Urinary Protein Excretion (UPE) Test

Urine albumin & urine creatinine excretion levels in the urine is analyzed to evaluate kidney function. A urine sample is collected (at the same time as the fasting blood sample) at the Baseline, 12 Week and 24 Week Visits from the

subject following standard techniques and forwarded to a central laboratory for analysis.

6.5 Mixed Meal Tolerance Test (MMTT)

MMTT will be performed at selected study sites only. All enrolled subjects at these sites will be administered a Mixed Meal Tolerance Test to evaluate their hormone response to nutrients by measuring the concentration of glucose, gut and pancreatic hormones, and metabolic substrates.

The Baseline results will be compared to results at 12 Weeks post-procedure.

Before the beginning the assessment, the subject's blood glucose is tested with a glucometer to help assess fasting state. If the reading is above 300 mg/dL (16.7 mmol/L), the subject is asked to confirm time and details of last oral intake. If appropriate fasting cannot be confirmed, the MMTT assessment is rescheduled and subject is reminded of the fasting schedule and procedures. After a 10-hour overnight fast, participants are asked to ingest a liquid meal consisting of Ensure (200 ccl) or equivalent. Meals are to be ingested within 10 min. During the test, blood samples are drawn at 0 mins (fasting) and at 15, 30, 45, 60, 90, 120 and 180 following the start of the meal. Blood samples are labeled with subject ID, date and study visit, and blood draw timepoint (i.e 0, 15, 30 mins, etc.). Samples are sent to the central laboratory for anaylsis.

6.6 Ambulatory Blood Pressure Monitoring (ABPM)

ABPM will be performed in the training cases only.

To assess the potential effect of DMR on blood pressure, 24-hour ambulatory blood pressure will be measured at Baseline and 12 Weeks post procedure visits and compared for analysis.

ABPM monitoring is performed for a period of 24 hours. The blood pressure monitor is placed on the subject after the MMTT is complete (at the Baseline Visit and then the 12 Week Visit). The ABPM device is placed on the patient with the cuff on the non-dominant arm unless there is a 20/10 mmHg difference between arms in which case, the arm with the higher reading is used.

Normal activity should be maintained during ABPM. The patient's arm should be still and held at heart level during measurement. An exception is made while a measurement is being taken while a patient is engaged in certain activities, such as driving. Recordings are programmed for every 30 minutes during the day (07.00 – 22.00) and 60 minutes at night (22.00 to 07.00). These times are adjusted accordingly if the subject works at night. If available, the machine will also record pulse wave velocity.

After 24 hours from the start of monitoring, the subject turns off and removes the monitor and returns it to the study site to return for reading and analysis. The

average systolic and diastolic blood pressures for each subject are calculated and recorded by the study site.

6.7 Radiological Hepatic Status with Magnetic Resonance-Proton Density Fat Fraction (MR-PDFF) and Magnetic Resonance – Liver Iron Content (MR-LIC)

MR-PDFF and MR-LIC will be performed at selected study sites at Baseline, 12 Weeks and 48 Weeks (randomized DMR patients only) post procedure to assess the potential effect of DMR on liver fat as measured by the percent of proton density fat fraction, and to assess the potential effect of DMR on liver iron content.

Subjects are instructed to fast for a minimum of 4 hours in advance of the evaluation. Scans are completed in the supine position with a torso phased-array coil placed over the abdomen using a 1.5-T magnet MR scanner (Signa Echospeed, LX version 8.3; GE Medical Systems, or similar).

To estimate the proton density fat fraction a gradient echo sequence with low flip angle (FA) is employed to minimise T1 bias. Muliple echos are acquired to control for $T2^*$ bias where fat and water signals are nominally in phase or out of phase relative to each other. Estimates of fat and water proton densities are made from which the percent of fat content is calculated.

All MR imaging studies will be performed at the investigator site and imaging results will be interpreted by a single radiology specialist at each site that is blinded to treatment group designation.

Specific instructions for MR-PDFF and MR-LIC are provided in the Study Reference Manual.

6.8 Nutritional Counseling

Study subjects are provided with nutritional counseling to educate them on the importance of diet in relation to blood glucose control during this visit. The details are provided in the Study Reference Manual.

6.9 Subject Self-Monitored Blood Glucose (SMBG) and Glycemia Diary

Subjects are provided with a Glycemia diary and a home blood glucose monitor. Subjects are instructed to test blood sugars according to the schedule below in Table 1, record symptoms and measured blood glucose levels in the event of a hypoglycemic or hyperglycemic episode in the diary.

Adverse events for hypo- or hyper-glycemia will be reported according to the following definitions:

- **Hyperglycemic events**:three self-monitored finger sticks in 1 day with fasting blood glucose measurements >15 mmol/L (270 mg/dL) or non-fasting blood glucose measurements >20 mmol/L (360 mg/dL) or any combination of the two. Fasting glucose hyperglycemia is not an

exclusion if measured at the actual baseline visit (Visit 2) blood analysis test.

- **Hypoglycemic events**: a plasma glucose of < 3.9 mmol/L (70 mg/dL), should be managed medically according to established standards. Subjects who experience a hypoglycemic event during this phase are excluded from the study.

Subjects are instructed to bring the diary to every study visit.

Post-procedure, subjects continue to record hypoglycemic and hyperglycemic events in the glycemia diary.

The table below details the self-monitored glucose plan for study subjects. The plan is based on the results of daily self-monitoring glucose combined with symptoms, and study phase. All study subjects begin routine monitoring at the start of the run-in and adjust their blood glucose monitoring schedule according to the table below. Subjects who experience either hypo- or hyper- glycemia symptoms should immediately test their blood sugars to determine a course of action according to the guidance below:

Table 1 – Self-Monitored Blood Glucose

SMBG Type	Glucose Levels	Action Taken
Routine Monitoring *2x a day, once pre-breakfast (fasting) and once before dinner (non-fasting)*	Low : 1 value < 70 mg/dL High: 1 value > 270 mg/dL (fasting) OR 1 value > 360 mg/dL (non-fasting)	• Treat hypoglycemia (Section 6.11) • Log a blood sugar event for the low or high value • Transition to short term intensive monitoring
Short-term Intensive Monitoring *4 x a day, once pre-breakfast (fasting) AND once before lunch, once before dinner, and once before bed (non-fasting)*	No hypoglycemic or hyperglycemic events for 48 hours	• Return to routine monitoring
	Low: 1 value < 70 mg/dL High: 1 value > 270 mg/dL (fasting) with symptoms OR 1 value > 360 mg/dL (non-fasting) with symptoms	• Treat hypoglycemia (Section 6.11) • Log a blood sugar event for the low or high value • Call the clinic for further evaluation & continue short term intensive monitoring

	Low: 2 or more values < 70 mg/dL with or without symptoms in a 24 hour period	• Treat hypoglycemia (Section 6.11) • Log a blood glucose event to record the low value • Call clinic, schedule visit for assessment of glycemic control • Re-evaluate oral anti-diabetic medication regimen
Post-procedure Intensive Monitoring (0-14 days post-procedure) *4 x a day, once pre-breakfast (fasting) AND once before lunch, once before dinner, and once before bed (non-fasting)*	No hypoglycemic or hyperglycemic events	
	Low: 1 value < 70 mg/dL with or without symptoms	• Treat hypoglycemia (Section 6.11) • Log a blood glucose event to record the low value
	Low: 2 or more values < 70 mg/dL with or without symptoms in a 24 hour period	• Treat hypoglycemia (Section 6.11) • Log a blood glucose event to record the low value • Call clinic, schedule visit for assessment of glycemic control • Re-evaluate oral anti-diabetic medication regimen
	High: 3 values > 270 mg/dL (fasting) with symptoms OR > 360 mg/dL (non-fasting) with or without symptoms in 24 hours	• Call the clinic • Log a blood sugar event to record the high values
	Any low blood sugar or high blood sugar symptoms, regardless of glucose readings	• Obtain SMBG value, if possible • Treat hypoglycemia (Section 6.11) • Log a blood sugar event to record the low or high value • Call the clinic

Additionally, if the subject experiences any symptoms of either low or high blood sugar, they should use the glucometer they were provided to test their blood sugar immediately and complete one journal entry.

Low Blood Sugar Symptoms
- Sweating
- Shaking
- Sudden mood changes (irritated)
- Hunger pangs
- Difficulty speaking
- Rapid heartbeat
- Epileptic seizure
- Loss of consciousness

High Blood Sugar Symptoms
- Frequent urination
- Increased thirst
- Dry mouth

Below are some symptoms that can apply to both high and low blood sugar:

- Fatigue
- Dizziness
- Headache
- Distorted vision
- Nausea
- Concentration problems
- Confusion
- Difficulty standing and walking
- Muscle spasms
- Tired and/or weak feeling

Glucose unit conversions:

Glucose value in mg/dL	Glucose value in mmol/L
70 mg/dL	3.9 mmol/L
270 mg/dL	15 mmol/L
360 mg/dL	20 mmol/L

Journal Definitions:

Fasting: when you have not had any food or drink for at least 8 hours

Non-fasting: when you have had food or drink in the last 8 hours

6.10 Management of Glycemia and Oral Anti-Diabetic Medication

Over the course of the study, subject's glycemia will be managed by measuring the following parameters:

- Recording and managing of anti-diabetic medications
- Self Monitoring of Blood Glucose (SMBG)
- HbA1c measured from blood tests
- Symptoms of hyper- or hypo- glycemia

These are captured across all phases of the study: Run-In, Primary Endpoint, Long-Term Glycemic Follow-Up Phases.

Oral anti-diabetic medication regime established during the run-in period should be continued through the index procedure without change until the 24 week follow-up visit (Visit 9) unless the following criteria apply therefore requiring rescue.

Hyperglycemia Requiring Rescue:

Study Phase	Rescue Criteria	Treatment
Run-in Phase *(between Screening and Procedure)*	3 self-monitored finger sticks in 1 day meeting criteria in Section 6.9	• Call clinic, schedule visit to confirm elevated HbA1c • Subject exclusion from study • Diabetes management as per their physician
Primary Endpoint Phase *(Procedure through 12 weeks)*	• HbA1c >9.0% at 12 weeks	• Subject medications should be modified per rescue criteria below
	• 3 self-monitored finger sticks in 1 day meeting criteria in Section 6.9	• Subject to call clinic, schedule visit to confirm elevated HbA1c • Consider anti-diabetic medication change
Primary Endpoint Phase (12 through 24 weeks)	• HbA1c >8.5% at 24 weeks	• Subject medications should be modified per rescue criteria below
	• 3 self-monitored finger sticks in 1 day meeting criteria in Section 6.98	• Subject to call clinic, schedule visit to confirm elevated HbA1c • Consider anti-diabetic medication change
Long-term Glycemic Follow-up Phase *(after 24 weeks)*	• HbA1c > 8.5% at 36 Weeks	• Subject medications should be modified per rescue criteria below
	• 3 self-monitored finger sticks in 1 day meeting criteria in Section 6.9	• Subject to call clinic, schedule visit to confirm elevated HbA1c • Consider anti-diabetic medication change

Acute Hyperglycemia Requiring Short-Term Rescue:
During study conduct, study subjects are at risk of experiencing a more acute deterioration in glycemic control often associated with the development of an intercurrent illness (e.g. infection). The following steps will accommodate for this eventuality:

Study Phase	Rescue Criteria	Treatment
All study Phases	Hyperglycemia symptoms	• Subject should call clinic, schedule visit to review SMBG and measure HbA1c
	3 self-monitored finger sticks in 1 day meeting criteria in Section 6.9 (Elevated SMBG x 3)	• Subject should call clinic, schedule visit to review symptoms and measure HbA1c
	If 2 of these 3 are met: • Elevated SMBG x3 in 1 day, • HbA1c ≥ 10% • Hyperglycemia symptoms	• Subject should call clinic, schedule visit to assess hyperglycemia • If significant hyperglycemia confirmed, insulin rescue permitted

If the rescue criteria outlined above is met, a confirmatory plasma glucose and HbA1c measurement should be obtained by blood test at a visit to the study site before adjusting or adding oral anti-diabetic medications including insulin as rescue therapy.

Subjects who meet the HbA1c criteria for rescue should have an escalation of treatment according to clinical practice recommendations.

Current Regimen	Dose Adequacy	Rescue Regimen
Metformin only	Submaximal	↑ metformin dose if tolerated
	Maximally tolerated	Add SU or TZD or DPP-4 inhibitor or SGLT2 inhibitor
Metformin + other OAD	Submaximal metformin only	↑ metformin dose if tolerated
	Submaximal OAD only	↑ OAD dose if tolerated
	Submaximal both	↑ metformin dose if tolerated; if not, ↑ OAD dose if tolerated
	Maximally tolerated	Add an OAD that the subject is not taking (SU or TZD or DPP-4 inhibitor or SGLT2 inhibitor) or add GLP-1RA.

If the subject is on triple therapy and requires rescue therapy per Section 6.9, move to basal insulin or GLP-1RA.
Consider initiating insulin therapy when blood glucose is ≥300 mg/dL (16.7 mmol/L) or A1C is ≥10% or if the patient has persistent symptoms of hyperglycemia (i.e., polyuria or polydipsia). As the patient's glucose toxicity resolves, the regimen may, potentially, be simplified.

6.11 Glucose Alert and Hypoglycemic Glucose Values and Treatment

Hypoglycemia is the major limiting factor in the glycemic management of both type 1 and type 2 diabetes. Recommendations from the International Hypoglycaemia Study Group (2017) regarding the classification of hypoglycemia are outlined in Table below:

	Glycemic Criteria	Description
Glucose alert value	≤70 mg/dL (3.9 mmol/L)	Sufficiently low for treatment with fast-acting carbohydrate
Clinically significant hypoglycemia	<54 mg/dL (3.0 mmol/L)	Sufficiently low to indicate serious, clinically important hypoglycemia
Severe hypoglycemia	No specific glucose threshold	Hypoglycemia associated with severe cognitive impairment requiring external assistance for recovery

Glucose (15–20 g) is the preferred treatment for the conscious individual with hypoglycemia at the glucose alert value of ≤70 mg/dL (3.9 mmol/L), although any form of carbohydrate that contains glucose may be used. Fifteen minutes after reatment, if SMBG shows continued hypoglycemia, the treatment should be repeated.Once SMBG returns to normal, the individual should consume a meal or snack to prevent recurrence of hypoglycemia.

The use of glucagon is indicated for the treatment of hypoglycemia in people unable or unwilling to consume carbohydrates by mouth. Glucagon should be prescribed for all individuals at increased risk of clinically significant hypoglycemia, defined as blood glucose, 54 mg/dL (3.0 mmol/L), so it is available should it be needed.

If a subject has symptoms of hypoglycemia, the hypoglycemia should be treated, whether of not it was possible to obtain a confirmatory SMBG value. All glucose values ≤70 mg/dL (3.9 mmol/L), and all symptomatic treated episodes of hypoglycemia, with or without a SMBG value, should be recorded in the subject's Glycemia diary.

6.12 Concomitant Medications

All concomitant medications are recorded at the Screening Visit. Medication use is then checked at each following study visit. All medications are captured in the source documents and on the appropriate Case Report Form. The following information is recorded for each medication: name, indication, dose, frequency, start date, end date.

7. Study Management

7.1 Regulatory Compliance

This clinical trial will be conducted according to 21 CFR Part 812, 21 CFR Part 50, 21 CFR Part 56; EN ISO 14155:2011; 93/42/EEC Medical Device Directive; GCP principles and the principles of the World Medical Association Declaration of Helsinki 1964 (including all amendments and Notes of Clarification, up to and including the Scotland 2000 amendment and Tokyo 2004 Note of Clarification). The Investigator will conduct all aspects of this trial in accordance with all national, state, and local laws or regulations.

7.2 Institutional Review Board (IRB) and Ethics Committee (EC) Review

The study must be reviewed and approved by the appropriate IRB or EC before subject enrollment may begin. All proposed changes to the investigational plan must be reviewed and approved by Fractyl. Fractyl will also obtain any necessary national regulatory approvals before initiation of the study.

IRB or EC approval is required for each institution participating in this clinical investigation. Investigators are responsible for obtaining and maintaining approval of the study by their institution's IRB or EC.

The IRB or EC approved Informed Consent Form must be retained at the investigational site. Modifications to the Informed Consent Form and any written subject information must be approved by Fractyl and the IRB/EC.

7.3 Study Records

All information and data sent to Fractyl or their authorized representatives concerning subjects or their participation in this study is considered confidential. All data used in the analysis and reporting of this evaluation is used in a manner without identifiable reference to the subject.

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

- Clinical protocol and all amendments
- Investigator's Brochure
- IRB / EC Roster
- IRB / EC approval letter(s) and approved informed consent(s) (including any revisions)
- Approved advertisements for subject recruitment (if applicable)
- Correspondence with the IRB / EC

- Signed Clinical Study Agreement
- Site authorized personnel signature list/Delegation of Authority Log
- Signed Non-Disclosure Agreement
- Curriculum vitae for all investigators
- Financial Disclosure Forms
- Correspondence relating to this study (with Sponsor, clinical monitors, other Investigators, etc.)
- Instructions for Use
- Device Accountability Log and 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
- Monitoring Letters/Report(s) and Sponsor Representative Signature Log
- CRF Completion Guidelines
- Reports (including Adverse Event reports, annual reports and final reports from Investigator and Sponsor)

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

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

The Investigator or Investigational site will maintain in original format all essential study documents and source documentation that support the data collected on the study subjects in compliance with GCP guidelines. Investigator files containing all records and reports of the investigation should be retained for a minimum of two years or longer as mandated by site specific requirements 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. It is Fractyl's responsibility to inform the Investigator when these documents no longer need to be maintained. 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. 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.

7.4 Study 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, IRB/EC (as required)	Within 24 hours of knowledge
Device Malfunction	Fractyl	Within 24 hours of knowledge
Subject death during the investigation	Fractyl and IRB/EC	Within 24 hours of knowledge
Unanticipated Adverse Device Effect	Fractyl, IRB/EC (as required)	Within 24 hours of knowledge
Subject withdrawal	Fractyl	Within 7 days of knowledge
Withdrawal of IRB/ECapproval	Fractyl	Within 24 hours of knowledge
Deviation from investigational protocol	Fractyl, IRB/EC (as required)	Within 7 days of knowledge
Informed consent not obtained from subject	Fractyl and IRB/EC	Within 24 hours of knowledge
Annual Progress report	Fractyl and IRB/EC	Within 1 month of annual IRB/ECapproval date
Final summary report	Fractyl, IRB/EC (as required)	Within 3 months of study completion
Other information as requested by Fractyl, Ethics	As appropriate	As requested

Reports generated for this clinical investigation should be stored in accordance with section 7.3.

Investigator's Annual and Final Reports

Each year a summary report is prepared by the Study Principal Investigator and Sponsor providing a synopsis of the subjects treated to date, safety profile, as well as other pertinent clinical information associated with the device usage. The report is provided to each study site Investigator to file reports as required by IRB / EC, local guidelines and government regulations.

Upon completion or termination of the study a final report is prepared. This report contains a critical evaluation of all data collected during the course of the investigation at each institution. The report must be signed by the Principal Investigator at the site and is provided to the IRB / EC and a copy to Fractyl. Any modifications to this final report must be reviewed and approved by Fractyl.

7.5 Device Accountability

All devices received for this trial are inventoried and accounted for throughout the study. The devices must be stored in a secure, limited-access area. Upon request by the sponsor or study completion, all unused devices are returned to Fractyl. No devices may be used outside this trial 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 are retained by the site until the evaluation is complete at which time they are returned to the Sponsor.

7.6 Protocol Deviations

The investigator must not make changes or deviate from the protocol, except to protect the life and physical well-being of a subject in an emergency. The investigator shall notify the sponsor and the reviewing IRB / EC (as applicable) of any deviation from the investigational plan to protect the life or physical well-being of a subject in an emergency, and those deviations which affect the scientific integrity of the clinical investigations. Such notice shall be given as soon as possible, but no later than 24 hours after the emergency occurred, or per prevailing local requirements, if sooner than 24 hours.

All deviations from the investigational plan must be documented and reported to the sponsor using entry onto the eCRF. Sites may also be required to report deviations to the IRB / EC, per local guidelines and government regulations.

Deviations are reviewed and evaluated on an ongoing basis and, as necessary, appropriate corrective and preventive actions (including notification, center re-training, or discontinuation) are put into place by the sponsor.

7.7 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 device inventory
- Repeated protocol deviations
- Failure to enroll an adequate number of subjects
- Business reasons

7.8 Adverse Events (AE)

An AE is any untoward medical occurrence, unintended disease or injury, or any untoward clinical signs (including an abnormal laboratory finding) in subjects, users, or other persons, regardless of whether or not it is related to the investigational medical device.

Adverse events are 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.

Note 1: This definition includes adverse events related to the medical device of this investigation.

Note 2: This definition includes adverse events related to the procedures involved (any procedures in the clinical investigational plan).

Note 3: For adverse events involving “users or other persons”, this definition is restricted to adverse events related to the medical device of this investigation.

Adverse Event information is recorded in the Adverse Event Form.

Adverse events are graded on a 3-point scale and reported as indicated on the CRF. The intensity of an adverse experience is defined as follows:

- **Mild:** Discomfort noticed, but no disruption to daily activity
- **Moderate:** Discomfort sufficient to reduce or affect normal daily activity
- **Severe:** Inability to work or perform normal daily activity

Study Procedure and Device Relationship: the relationship of an adverse event to the device and to the procedure will be assessed by the investigator as follows:

Definitely Related:	Clear-cut temporal association and no other possible cause.
Probably Related:	Clear-cut temporal association and a potential alternative etiology is not apparent.
Possibly Related:	Temporal association is less clear and other etiologies are also possible.
Not Related:	There is no temporal association and/or evidence exists that the event is definitely related to another etiology

All adverse event reports are filed as required by country regulations. For all adverse events (whether device-related or not), all sections of the appropriate

Adverse Event Form(s) must be completed. In this study, all adverse events are collected from the signing of the informed consent.

Potential adverse events may include the following:

Device related adverse events

- Allergic reaction to the device materials or endoscopic labeling dye or injectate
- Component degradation
- Control module delivers incorrect ablation time and temperature profile
- Device breakage
- Disarticulation of components from the device
- Device/Component lost in GI tract or wall
- 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
- Unforeseen adverse events

Procedure related adverse events

- abdominal tightness, cramping, pain
- diarrhea
- difficulty swallowing
- infection
- mucosal injury to GI tract
- pancreatitis
- perforation
- sore throat
- stricture
- transient bleeding
- worsening diabetic symptoms including hypoglycemia

Any procedural or device related adverse events are to be followed until there is evidence of resolution or permanent change.

If a subject experiences combined symptoms of pain, nausea and vomiting, an endoscopic evaluation is recommended as previous serious adverse events have been reported.

The determination of whether an adverse event is classified as a Serious Adverse Event or Unanticipated Adverse Device Effect is based on the definitions contained in sections 7.9 and 7.10, taking into account the clinical judgment of the investigator.

7.9 Serious Adverse Events

A Serious Adverse Event (SAE) is an adverse event that:

- Led to death,
- Led to serious deterioration in the health of the subject, that either resulted in
  - a life-threatening illness or injury, or
  - a permanent impairment of a body structure or a body function, or
  - in-patient or prolonged hospitalization, or
  - medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,

Note: Planned hospitalization for a pre-existing condition, or a procedure required by the protocol, without serious deterioration in health, is not considered a serious adverse event.

A SAE may or may not be considered related to the device.

7.10 Unanticipated Adverse Device Effects

An unanticipated adverse device effect (UADE) 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 subjects.

7.11 Adverse Events of Special Interest (AESI)

Adverse Events of Special Interest are characterized as:

- Specific events that may be related to the mechanism of action of the DMR procedure (eg, hypoglycemia)
- Potential adverse consequences of the procedure (eg, GI adverse events)
- Rare events that may or may not be related to the DMR procedure/device, but are of interest to the Sponsor (eg, unexplained fever)

Irrespective of whether an AE is serious or non-serious, the following events are defined as ‘protocol-specified adverse events of special interest’ and have additional reporting requirements.

Events of Special Interest are:

- Hypoglycemia
- Diarrhea
- Abdominal pain, nausea, vomiting
- Gastrointestinal bleeding
- Unexplained fever
- Stenosis (GI)

7.12 SAE & UADE Reporting

AEs observed during the course of this trial, regardless of severity or relationship to the trial procedure or investigational medical device will be recorded on the appropriate AE Form and reported to the sponsor.

For EU sites, the procedures for handling and reporting/notification of SAEs shall be carried out in accordance with the applicable sections of the Medical Device Directive (MDD), ISO 14155:2011(E), MEDDEV 2.12/1 and local regulations.

For US sites and reporting to FDA, the procedures for handling and reporting/notification of Serious Adverse Events shall be carried out in accordance with the applicable sections of 21 CFR Part 812 and local IRB requirements.

The sponsor will implement and maintain an electronic data capture (EDC) system to ensure that the investigator can report the events to the sponsor. Once the Investigator has completed an initial Adverse Event Form, the Sponsor is automatically notified about the Adverse Event via email.

7.13 Investigator safety reporting requirements

SAEs/UADEs will be recorded in the Adverse Event Form and the event is to be reported to the Sponsor within 24 hours of knowledge of the event. Additional information (subject source data) regarding an already reported SAE/UADE must be forwarded to Fractyl as soon as possible, but no later than three (3) working days of knowledge of the event.

All other AEs will be recorded in the Adverse Event Form within ten (10) days of knowledge of the event.

The Investigator must adhere to all reporting requirement for his IRB / EC and national authorities.

7.14 Sponsor safety reporting requirements

In the U.S., only UADEs wil be reported to the FDA, in accordance with 21 CFR Part 812.

The sponsor will also conduct vigilance reporting to the National Competent Authority according to guideline (MEDDEV 2.12.1). Any event which meets <u>all</u> 3 basic reporting criteria A – C listed below is considered as an ‘incident’ and must be reported to the relevant National Competent Authority.
The criteria are:

Criteria A) An event has occurred.
Criteria B) The manufacturer’s device is suspected to be a contributory cause of the incident.
Criteria C) The event led, or might have led, to one of the following outcomes:

- Death of a subject, user or other person

- Serious deterioration in state of health of a subject, user or other person.

7.15 Data Monitoring Committee

A Data Monitoring Committee (DMC) is convened for the study and is assembled prior to subject enrollment. The group is multidisciplinary and membership includes individuals not participating in the clinical study. The DMC members act independently from both the sponsor and the study investigators. The group consists of an endoscopist, endocrinologist and a biostatistician. The DMC members will be independent from both the sponsor and the study investigators. Full DMC details including structure, roles and responsibilities are included in the DMC Charter.

General responsibilities of the DMC include:

- Review and finalize the DMC Charter
- Review data during the trial regarding safety and regarding quality of trial conduct
- Monitor the quality of the treatment provided at individual sites by reviewing the occurrence of peri-procedural complications and major protocol violations
- Responsible for the review of all serious adverse events that occur over the course of the study and the subsequent classification of these events
- Provide recommendations to the sponsor about modifications in the protocol and/or continuation of the trial necessary to maintain the safety of the subjects

The DMC will establish a set of stopping rules for the study at their first meeting. The study (or study site) will be suspended or prematurely terminated if, in the opinion of the DMC, Sponsor, reviewing IRB / EC or Competent Authority, the safety of patients and/or data is uncertain. The sponsor will make sure that the suspension or premature termination will be communicated through the PI, Competent Authority and reviewing IRB / EC.

The decision to resume study (site) enrollment and treatment will be made by the DMC in consultation with the Sponsor. Additionally, the triggering of the stopping/re-activation rules will promptly be submitted to the involved Competent Authorities and the reviewing IRBs / ECs for approval as required by local law.

8. Data Management

8.1 Data Collection and Quality Control

8.1.1 Site Training

The training of investigational site personnel on proper data collection, documentation practices, and case report form completion is the responsibility of Fractyl. To ensure uniform data collection and protocol compliance, Fractyl appointed clinical monitors review the clinical protocol,

techniques for the identification of eligible subjects, instructions on in-hospital/office visit data collection with the research coordinators. This is completed before or in conjunction with site initiation.

8.1.2 Case Report Forms

Subject data are recorded in a limited access secure electronic data capture (EDC) system. All changes made to the clinical data will be captured in an electronic audit trail and available for review by Fractyl or its representative. The associated software and database are designed to meet regulatory compliance for deployment as part of a validated system compliant with laws and regulations applicable to the conduct of clinical studies pertaining to the use of electronic records and signatures.

The Investigator provides his/her electronic signature on the appropriate electronic case report forms (eCRFs) in compliance with local regulations. A written signature on printouts of the eCRFs is also provided if required by local regulation. Changes to data previously submitted to the sponsor require a new electronic signature by the Investigator acknowledging and approving the changes.

CRFs are completed fully for each subject by the site staff, e-signed by the Investigator, and available for review by regulatory authorities, Fractyl and/or its designees.

8.1.3 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 subject's medical record.

All patient related medical data in the study will be handled confidentially and as per applicable data protection law and local regulations and will not be released without the written consent of the subject (or the subject's guardian). The data will be handled and stored in an anonymous format.

8.1.4 Data Monitoring

Completed eCRFs are 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, subject eCRFs, and subject medical records by Fractyl appointed monitors and authorized government agencies, as indicated.

The study is monitored according to applicable provisions of Fractyl or designee's Monitoring Procedures, and in conformance with Good Clinical Practices.

Monitoring includes pre-study site qualification, site initiation visit, on-going site study monitoring and study closure monitoring as described in the

study monitoring plan. The major function of the clinical monitor is to observe and assess the quality of the clinical study. In addition, the study is 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.

Visual and/or electronic data review is performed by the study monitor to identify possible data discrepancies. The study monitor(s) will verify the data entered into the eCRFs against hostpital records, medical history, or other source documents to ensure accuracy and completeness of the data. Manually generated and/or automatic queries are created in the EDC system and are issued to the site for appropriate response. Site staff is responsible for resolving all queries in the database.

8.2 Statistical Considerations

Prior to locking the database, all data editing is complete and decisions regarding the evaluability of all subject data for inclusion in the statistical analysis are made. The rationale for excluding any data from the statistical analyses is prospectively defined, and classification of all or part of a subjects' data as non-evaluable is completed and documented before the entire database is locked.

Additional details on the analysis as well as any changes from the analyses presented in the protocol are provided in the Statistical Analysis Plan (SAP).

8.2.1 General Considerations

Variables are presented by treatment group using various descriptive statistics. Nominal and ordinal variables for each time period are presented using frequencies and percent of patients in each category. Interval and ratio variables for each time period are presented using means and standard deviations and/or medians and ranges, as appropriate. For variables collected at multiple follow-up time periods, tables which include appropriate descriptive statistics of change from baseline are presented by treatment group at each follow-up interval.

Distributions of each continuous variable are assessed prior to analysis and examined for normality. Data with interval or ratio scales to be analyzed that are not normal are transformed in an appropriate manner (e.g., log transformation), or are analyzed using nonparametric statistics. Statistical tests are performed using two-sided significance levels of 5% unless otherwise specified.

Demographic and baseline data will be summarized using summary statistics of mean, standard deviation, median, min and max for continuous variables and number and percent of patients in each category. These summaries will be performed based on the safety population and modified intent to treat (mITT) analysis population defined

below. Study endpoint analysis are described in further detail below and will be performed in the defined primary analysis population for purposes of study hypothesis testing. Additional presentation of results based on alternative analysis populations will be presented to allow for comprehensive review of the study results.

8.2.2 Determination of Sample Size

Training Phase

For each study site, between 3 to 5 training cases are performed, with up to 15 sites participating. The number of training cases per site is based on training requirements and not statistical considerations. A maximum of 50 cases will be conducted as part of the Training Phase.

Randomization Phase

The primary endpoints are 1) the change from baseline at 24 weeks in HbA1c and 2) The absolute change from baseline at 12 weeks in MR-PDFF in patients with baseline MR-PDFF > 5% , DMR vs Sham.

Assumptions of effect size for the primary efficacy endpoint of change from baseline at 24 weeks in HbA1c in the treatment arm are derived from the Revita 1 study (Fractyl Protocol C-20000). The treated subjects saw a mean change difference in HbA1c of -1.0 at 24 weeks with a standard deviation of 1.0. Based on previous experience, the estimated mean (± sd) sham effect at 24 weeks is -0.3 ± 1.0.

Assumptions are similarly obtained for the primary efficacy endpoint of absolute change from baseline at 12 weeks for MR-PDFF in patients with baseline MR-PDFF > 5%, with an assumed difference between treatment and sham MR-PDFF means of 4.0 and a standard deviation assumption of 6.5 per treatment group.

Under (a) the assumption of a difference in mean change in HbA1c between treatment and control of 0.7 at 24 weeks with equal variance in both groups (standard deviation of 1.0) of the C-30000 study; (b) the assumption of a difference in mean change in MR-PDFF between treatment and control of 4.0 at 12 weeks and a standard deviation of 6.5 per treatment group; (c) approximately 3% of randomized subjects will not be evaluable for HbA1c and approximately 70% of randomized subjects will have baseline MR-PDFF >5% and be evaluable for 12-week MR-PDFF; and (d) the correlation between the two primary endpoints is 0 or very small, then 90 randomized subjects (45 per group) provides at least 90% power that the benefit of treatment over sham will be found for at least one primary endpoint using the Hochberg procedure controlling the experimentwise significance level at a one-sided 0.05 value.

A maximum of 120 patients may be randomized to account for potential patients lost to follow up prior to the primary endpoint assessment.

Table 2: Planned Sample Size

Study Cohort	Fractyl DMR	Sham Arm	Total
Training	up to 50	N/A	**up to 50**
Miminum Randomized	45	45	**90**
Maximum Randomized	60	60	**120**
Combined Training and Randomized	**up to 110**	**up to 60**	**up to 170**

8.2.3 Analysis Populations

Training Subjects: The training population includes all subjects enrolled as training cases at the site. These cases are described separately from randomized subjects in the final study report and are presented primarily using descriptive statistics. These subjects will not be included in the randomized primary efficacy analysis

Intent-to-Treat (ITT): The ITT analysis population includes all randomized subjects.

Modified Intent-to-Treat (mITT): The mITT population includes all randomized subjects in whom the study procedure (DMR or sham) is attempted and who have a baseline measurement for at least one primary endpoint. The procedure is attempted when all endoscopic exclusion criteria are verified, the catheter is introduced into the subject, and at least one ablation is performed. Subjects will be analyzed according to their randomized group assignment. The mITT population is the primary analysis population for both the primary and secondary efficacy endpoints. The mITT population specifically excludes the training subjects.

Per-Protocol (PP): The Per-Protocol (PP) analysis population includes the subset of mITT subjects who received the treatment to which they were randomized, and excluding any subjects with major protocol deviations, which include those Fractyl DMR cases that did not undergo the full DMR procedure.-The full details on "major protocol deviations" that lead to patients being excluded from the PP population will be included in the SAP. The PP population specifically excludes the training subjects.

Safety: This analysis population includes all treated subjects, and these subjects are analyzed by actual treatment received. This analysis population is the primary analysis population used for all safety endpoint analyses.

Cross-over: Control subjects who elect to cross-over to DMR treatment at 24 Weeks will be analyzed separately beginning from the point at which

active treatment is initiated. Safety endpoints will be summarized for this cohort seperately.

8.2.4 Efficacy Analysis

Primary Efficacy Endpoints:

1) The change from baseline at 24 weeks in HbA1c, DMR vs Sham, and 2) in patients with baseline MR-PDFF > 5%, the absolute change from baseline at 12 weeks in MR-PDFFbetween Fractyl DMR and Sham subjects in the mITT analysis population.

The following are the null and alternative superiority hypotheses for the primary efficacy parameter of change in HbA1c.

$$H_0: \mu_{DMR} - \mu_{Sham} > 0$$
$$\text{vs.}$$
$$H_a: \mu_{DMR} - \mu_{Sham} \leq 0$$

where μ_{DMR} and μ_{Sham} are the mean change in HbA1c from Baseline to 24 Weeks.

The following are the null and alternative superiority hypotheses for the primary efficacy parameter of change in MR-PDFF.

$$H_0: \gamma_{DMR} - \gamma_{Sham} > 0$$
$$\text{vs.}$$
$$H_a: \gamma_{DMR} - \gamma_{Sham} \leq 0$$

where γ_{DMR} and γ_{Sham} are the mean change in MR-PDFF from Baseline to 12 Weeks.

The primary analysis will be performed in the mITT analysis population comparing treatment groups with an Analysis of Covariance (ANCOVA) model with Multiple Imputation, that will adjust for study region, the baseline value of the outcome, and the difference between the screening and baseline value of the outcome for only the HbA1c endpoint (region will be specified in the formal statistical analysis plan). The Hochberg procedure will be used to control the experimentwise significance level at a one-sided 0.05 level across the two primary endpoints. With the Hochberg procedure, the experimental treatment is considered beneficial over control for both primary endpoints if the treatment comparison one-sided p-value for each endpoint is <0.05; otherwise, if the one-sided treatment comparison p-value <0.025 for one endpoint, treatment is considered beneficial over control for that given endpoint. A similar analysis will be conducted in the PP analysis population.

If a significant beneficial treatment effect is found in both primary endpoints using the Hochberg approach at the experimentwise one-sided 0.05 level of significance, then both primary endpoints will be compared between treatments using the Hochberg procedure at an experimentwise one-sided 0.025 level of significance. If, however, a significant beneficial treatment effect is found in only one endpoint using the Hochberg approach at the experimentwise one-sided 0.05 level of significance (i.e., the endpoint is significant at the one-sided comparisonwise 0.025 level of significance), then that endpoint alone will be compared between treatments at a one-sided 0.0125 level of significance.

8.2.5 Safety Analysis

The safety analysis is performed separately on the Safety population for the Training Cohort and the Randomization Cohort. The Randomization Cohort analysis is performed by treatment administered and will be presented for safety data collected during the randomized phase (24 weeks from index procedure). As a secondary analysis, analyses will also performed for all subjects undergoing Fractyl DMR after cross-over.

Physical Examination and Vital Signs: Observed measurements and changes in physical exams and vital signs from baseline to study time points are descriptively summarized. Listings of abnormal findings/values are also presented.

Clinical Laboratory Tests: Observed measurements in blood chemistry analysis and changes from baseline to study time points are descriptively summarized. All laboratory values are compared to normal ranges. All data is also presented in listings.

Adverse Events: AEs, AESIs, SAEs,and UADEs are coded using MedDRA and will be summarized for the Training Cohort and Randomization Cohort through 24 weeks for each treatment by number and percentage of patients with at least one treatment emergent adverse event (TEAE) overall and by primary SOC and preferred term. Events occurring throughout the cross-over phase will be detailed in the same approach.

Detailed listings of subjects that experience treatment emergent AEs (TEAEs) and SAEs will be provided. The incidence of these TEAEs will also be tabulated (frequencies and percentages of patients) by severity and relationship to procedure for each of the Training Cohort, the Randomization Cohort through 24 weeks, and the cross-over phase. In tabulating the severity of TEAEs on a per subject basis, the greatest severity should be assigned to a subject should there be more than one occurrence of the same AE with different reported severities. Relationship is categorized as no, possibly, probably and definitely. The highest level of

association is reported for subjects with different relationships for the same TEAE.

The primary safety endpoint is the incidence rate of the device or procedure related SAEs, UADEs and AESIs through the 24 Weeks post treatment initation. The safety endpoint summary will include the number and percentage of subjects in each of the categories overall and by system organ class and preferred term; for the overall counts, the two-sided Clopper-Pearson 95% CI of the percentages will be presented. A formal hypothesis comparing treatments is not planned.

8.2.6 Secondary Endpoint and Additional Analyses

The mITT population is also utilized as the primary analysis population for assessment of secondary endpoints. The secondary endpoints include the following:

1. HbA1c change from baseline to Week 24 (Visit 9) by visit over time, DMR vs. Sham
2. The relative MR-PDFF change from baseline to Week 12 in patients with baseline MR-PDFF > 5%, DMR vs. Sham
3. Proportion of randomized-DMR-treated subjects with an HbA1c improvement from baseline at 24 weeks (Visit 9) that maintain an HbA1c improvement at 48 weeks
4. Proportion of randomized-DMR-treated subjects with an MR-PDFF > 5% at baseline and MR-PDFF improvement from baseline at 24 weeks (Visit 9) that maintain an MR-PDFF improvement at 48 weeks
5. Fasting Plasma Glucose (FPG) change from baseline at 24 weeks DMR vs. Sham
6. FPG change from baseline to Week 24 by visit over time, DMR vs. Sham
7. Weight change from baseline at 24 weeks DMR vs. Sham
8. In randomized-DMR-treated subjects with an HbA1c improvement from baseline at 24 weeks, average HbA1c improvement from baseline at 48 weeks
9. In randomized-DMR-treated subjects with an MR-PDFF > 5% at baseline and MR-PDFF improvement from baseline at 12 weeks, average MR-PDFF improvement at 48 weeks
10. HOMA-IR change from baseline at 24 weeks DMR vs. Sham

Secondary continuous endpoints (endpoints 2, 5, and 7) measured at a given time point in the randomization phase will be tested comparatively using an ANCOVA model to adjust for region and the baseline value of the outcome, and the difference between the screening value and baseline value of the outcome(for endpoints where the screening value is available). Each endpoint will be compared between treatments at a one-sided 0.05 level of significance, where the direction of the alternative hypothesis represents a benefit of DMR over sham. There will be no

adjustment of the significance level across the multiple secondary endpoints.

For the secondary endpoints that are compared between treatments over time (i.e., for secondary endpoints 1 and 6 where the treatment comparison is not just at one time point such as 24 weeks, but where the treatments are compared at all visit time points simultaneously), a mixed model repeated measures approach will be used to compare treatments with respect to mean outcome over time; subject will be a random effect, and region, the baseline value of the outcome measure, and the difference between the screening and baseline value of the outcome will be used as a covariate. Plots of the mean (+/-1) standard error over time will be presented for each treatment group, with both treatment groups presented on the same graph. Each endpoint will be compared between treatments at a one-sided 0.05 level of significance, where the direction of the alternative hypothesis represents a benefit of DMR over sham. There will be no adjustment of the significance level across the multiple secondary endpoints.

Similar analyses will be conducted in the per-protocol analysis population.

8.2.7 Exploratory Endpoints

The following analyses will be performed for the mITT population. There will be no formal treatment compariosons on these endpoints.

- Change from the baseline in the following by visit out to 24 weeks in DMR vs. Sham
- FPI
- Fasting C-peptide
- Weight
- ALT
- AST
- FIB-4
- Ferritin
- UACR
- eGFR
- Triglycerides
- HDL
- TG/HDL

Change from baseline in the following at 12 weeks, DMR vs. Sham:

- MMTT change from baseline (glucose AUC through 2 hours)
- Change in MMTT measure of Insulin secretion
- Change in MMTT measure of Insulin resistance
- MR-LIC Liver Iron Content

Proportion of randomized-DMR-treated subjects with an abnormal MR-LIC at baseline and MR-LIC improvement from baseline at 12 weeks that maintain an MR-LIC improvement at 48 weeks.

In randomized-DMR-treated subjects with an abnormal MR-LIC at baseline and MR-LIC improvement from baseline at 12, average MR-LIC improvement at 48 weeks.

Training Cohort only:

- Change in SBP by ABPM from baseline in training cohort, at 12 weeks
- Change in DBP by ABPM from baseline in training cohort, at 12 weeks

Additional exploratory endpoint and ad-hoc analyses of interest will be defined in the study SAP.

8.2.8 Interim Analyses

There will be no interim analyses for this study.

8.2.9 Handling of Missing Data

All efforts will be made to prevent the occurrence of missing data. The sites will be instructed to identify and obtain contact information for the primary care giver for the subject. Complete site training and regular monitoring will also help to minimize missing data. Nevertheless, it is anticipated that withdrawals will occur and hence there will be missing data on primary and secondary efficacy endpoints. Further, some patients may take rescue medication prior to the end of the study; given that rescue medication may cause mis-estimation of the true effect of randomized treatment, for the primary analysis on the primary endpoints, all efficacy endpoint data measured after the use of rescue medication will be set to missing and treated in the analysis as missing data.

The primary analysis of study data will use multiple imputation using linear regression to impute missing primary endpoint data (including post-rescue medication data that is set to missing). Details, including the covariates to be used in the linear regression imputation model, will be provided in the formal statistical analysis plan. Sensitivity analyses will then be conducted where missing primary endpoint data (including post-rescue medication data set to missing) are not imputed (available case analyses). Then as further sensitivity analyses, all imputation methods (multiple imputation, available case) will be repeated where data collected post-rescue medication are NOT set to missing.

For secondary endpoints, the analysis will be LOCF (where post-rescue values are set to missing). There will be no imputation of missing data for exploratory endpoints (post-rescue medication will be set to missing).

8.2.10 Pooling of Site Data

To evaluate consistency in treatment effect across regions in the trial for the two primary endpoints, summary tables of treatment differences by region on the primary endpoints will be presented and compared. Treatment-by-region interaction on each of the two primary endpoints will be assessed using analysis of covariance with effects for treatment, region, baseline value of the outcome, the difference between the screening and baseline value of the outcome for HbA1c, and treatment-by-region interaction. The details on the grouping of sites into geographic regions will be provided in the formal statistical analysis plan.

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Appendix 1: Schedule of Assessments for Training Cases

Visit #	Visit	*Visit Window / Intervention*	Informed Consent	History & Full PE	Body Weight & Targeted PE	Pregnancy test (if applicable)	Blood Analysis	H.pylori Test	Urinary Protein Excretion (UPE)	MMTT	24-Hour Ambulatory Blood Pressure	Radiological Hepatic Status (MR-PDFF)	Endoscopic Evaluation	Subject Randomization & Enrollment	DMR /Sham Procedure	Nutritional Counseling	Subject Self-Monitoring Blood Glucose/ Glycemia Diary	Adverse Events	Medication Use
1	Screening (Pre Run-In)		X	X			X	X								X		X	X
2	Baseline (Post Run-In)	*Visit to occur 4-6 weeks after Screening*			X	X	X		X	X	X	X				X	X	X	X
2A	Ambulatory Blood Pressure Monitor Return										X Return Monitor								
3	Procedure (DMR)	*Within 14 days of Visit 2*											X	X	X	X	X	X	X
4	7 Day Call	*+/- 2 days*														X	X*	X	X
5	14 Day Call	*+/- 2 days*														X	X*	X	X
6	4 Week (28 Day)	*+/- 7 days*			X		X									X	X	X	X
7	12 Week (84 Day)	*+/- 7 days*			X		X		X	X	X	X				X	X	X	X
7A	Ambulatory Blood Pressure Monitor Return										X Return Monitor								
7.1	15 Week Call (105 Day)	*+/- 5 days*														X	X*	X	X
8	18 Week (126 Day)	*+/- 7 days*			X		X									X	X	X	X
8.1	21 Week Call (147 Day)	*+/- 5 days*														X	X*	X	X
9	24 Week (168 Day)	*+/- 14 days*			X		X		X				X			X	X	X	X
9.1	30 Week Call (210 Day)	*+/- 5 days*														X	X*	X	X
10	36 Week (252 Day)	*+/- 28 days*			X		X									X	X	X	X
10.1	42 Week Call (294 Day)	*+/- 5 days*														X	X*	X	X
11	48 Week (336 Day)	*+/- 28 days*			X		X					X					X	X	X

*During phone calls, subjects are reminded to continue to monitor blood glucose and record hypoglycemic and hyperglycemic events in the glycemia diary until the next study visit. The diary itself is not checked by the site staff during phone calls.

Appendix 2: Schedule of Assessments for DMR

Visit #	Visit	*Visit Window / Intervention*	Informed Consent	History & Full PE	Body Weight & Targeted PE	Pregnancy test (if applicable)	Blood Analysis	H.pylori Test	Urinary Protein Excretion (UPE)	MMTT	Radiological Hepatic Status (MR-PDFF)	Endoscopic Evaluation	Subject Randomization & Enrollment	DMR /Sham Procedure	Nutritional Counseling	Subject Self-Monitoring Blood Glucose/ Glycemia Diary	Adverse Events	Medication Use
1	Screening (Pre Run-In)		X	X			X	X							X		X	X
2	Baseline (Post Run-In)	*Visit to occur 4-6 weeks after Screening*			X	X	X		X	X	X				X	X	X	X
3	Procedure (DMR)	*Within 14 days of Visit 2*										X	X	X	X	X	X	X
4	7 Day Call	*+/- 2 days*													X	X*	X	X
5	14 Day Call	*+/- 2 days*													X	X*	X	X
6	4 Week (28 Day)	*+/- 7 days*			X		X								X	X	X	X
7	12 Week (84 Day)	*+/- 7 days*			X		X		X	X	X				X	X	X	X
7.1	15 Week Call (105 Day)	*+/- 5 days*													X	X*	X	X
8	18 Week (126 Day)	*+/- 7 days*			X		X								X	X	X	X
8.1	21 Week Call (147 Day)	*+/- 5 days*													X	X*	X	X
9	24 Week (168 Day)	*+/- 14 days*			X		X		X			X			X	X	X	X
9.1	30 Week Call (210 Day)	*+/- 5 days*													X	X*	X	X
10	36 Week (252 Day)	*+/- 28 days*			X		X								X	X	X	X
10.1	42 Week Call (294 Day)	*+/- 5 days*													X	X*	X	X
11	48 Week (336 Day)	*+/- 28 days*			X		X				X					X	X	X

*During phone calls, subjects are reminded to continue to monitor blood glucose and record hypoglycemic and hyperglycemic events in the glycemia diary until the next study visit. The diary itself is not checked by the site staff during phone calls.

Appendix 3: Schedule of Assessments for Sham

Visit #	Visit	*Visit Window / Intervention*	Informed Consent	History & Full PE	Body Weight & Targeted PE	Pregnancy test (if applicable)	Blood Analysis	H.pylori Test	Urinary Protein Excretion (UPE)	MMTT	Radiological Hepatic Status (MR-PDFF)	Endoscopic Evaluation	Subject Randomization & Enrollment	DMR /Sham Procedure	Nutritional Counseling	Subject Self-Monitoring Blood Glucose/ Glycemia Diary	Adverse Events	Medication Use
1	Screening (Pre Run-In)		X	X			X	X							X		X	X
2	Baseline (Post Run-In)	*Visit to occur 4-6 weeks after Screening*			X	X	X		X	X	X				X	X	X	X
3	Procedure (DMR)	*Within 14 days of Visit 2*										X	X	X	X	X	X	X
4	7 Day Call	*+/- 2 days*													X	X*	X	X
5	14 Day Call	*+/- 2 days*													X	X*	X	X
6	4 Week (28 Day)	*+/- 7 days*			X		X								X	X	X	X
7	12 Week (84 Day)	*+/- 7 days*			X		X		X	X	X				X	X	X	X
7.1	15 Week Call (105 Day)	*+/- 5 days*													X	X*	X	X
8	18 Week (126 Day)	*+/- 7 days*			X		X								X	X	X	X
8.1	21 Week Call (147 Day)	*+/- 5 days*													X	X*	X	X
9	24 Week [1] (168 Day)	*+/- 14 days*			X		X		X						X	X	X	X

Appendix 3: Schedule of Assessments for Sham CONTINUED

Visit #	Visit	*Visit Window / Intervention*	Informed Consent	History & Full PE	Body Weight & Targeted PE	Pregnancy test (if applicable)	Blood Analysis	H.pylori Test	Urinary Protein Excretion (UPE)	MMTT	Radiological Hepatic Status (MR-PDFF)	Endoscopic Evaluation	Subject Randomization & Enrollment	DMR /Sham Procedure	Nutritional Counseling	Subject Self-Monitoring Blood Glucose/ Glycemia Diary	Adverse Events	Medication Use
3C	Cross-over [1]	*0-14 days of the 24 Week Visit*										X		X	X		X	X
4C	Cross-over 7 Day Call	*+/- 2 days*															X	X
5C	Cross-over 14 Day Call	*+/- 2 days*															X	X
6C	Cross-over 4 Week (28 Day)	*+/- 7 days*			X		X								X	X	X	X
7C	Cross-over 12 Week (84 Day)	*+/- 7 days*			X		X		X		X				X	X	X	X
7.1C	Cross-over 15 Week Call (105 Day)	*+/- 5 days*													X	X*	X	X
8C	Cross-over 18 Week (138 Day)	*+/- 7 days*			X		X								X	X	X	X
8.1C	Cross-over 21 Week Call (147 Day)	*+/- 5 days*													X	X*	X	X
9C	Cross-over 24 Week (168 Day)	*+/- 14 days*			X		X		X							X	X	X

*During phone calls, subjects are reminded to continue to monitor blood glucose and record hypoglycemic and hyperglycemic events in the glycemia diary until the next study visit. The diary itself is not checked by the site staff during phone calls.

1. Sham patients who do not want to cross-over at visit 3C will complete the study at Week 24/Visit 9. Sham patients who do want to cross-over may complete Visit 3C assessments and cross-over procedure the same day as Visit 9 assessments.