March 22, 2022

Clinicaltrials.gov

To Whom it May Concern:

Following please find the final protocol for the study titled “Randomized, Double-Blind, Sham-Controlled, Prospective, Multi-Center Pilot Study to Evaluate the Safety and Effectiveness of Duodenal Mucosal Resurfacing Using the Revita™ System in the Treatment of Type 2 Diabetes”, version date 9Jul2020, NCT03653091.

Sincerely,

DocuSigned by:
Sarah Hackett
FF259F44539D417...

Sarah Hackett
Sr. Director of Clinical Operations
Fractyl Health

Randomized, Double-Blind, Sham-Controlled, Prospective, Multi-Center Pilot Study to Evaluate the Safety and Effectiveness of Duodenal Mucosal Resurfacing Using the Revita™ System in the Treatment of Type 2 Diabetes

The Revita™ US Pilot Study

Protocol Number: C-40000

Sponsor:
Fractyl Laboratories
17 Hartwell Avenue
Lexington MA 02421

Version 3.0
Date 9 July,2020

Confidential **Do Not Copy**

Sponsor Protocol Approval Page

STUDY TITLE:	**Randomized, Double-Blind, Sham-Controlled, Prospective, Multi-Center Pilot Study to Evaluate the Safety and Effectiveness of Duodenal Mucosal Resurfacing Using the Revita™ System in the Treatment of Type 2 Diabetes** **The Revita™ US Pilot Study**
PROTOCOL NUMBER:	C-40000
VERSION NUMBER:	3.0

Sarah Hackett, BS Director of Clinical Operations Fractyl Laboratories USA	 Date:
Sanobar Parkar, MD, MPH Medical Director, Clinical Development Fractyl Laboratories USA	 Date:
Kelly White, PharmD Executive Director, Clinical Development Fractyl Laboratories USA	 Date:
Juan Carlos Lopez-Talavera, MD, PhD Chief Medical Officer Fractyl Laboratories USA	 Date:

Investigator Protocol Approval Page

Randomized, Double-Blind, Sham-Controlled, Prospective, Multi-Center Pilot Study to Evaluate the Safety and Effectiveness of Duodenal Mucosal Resurfacing Using the Revita™ System in the Treatment of Type 2 Diabetes

The Revita™ US Pilot Study

C-40000

Protocol Version 3.0

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). 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 Version 3.0 Rationale for Changes

Section	Change	Rationale for Change
2.1	Subject enrollement # of changes from 18 to 9	Amended to reflect actual number of subjects enrolled.
2.1	Both treatment arms will be followed up for a total of 48 weeks to 24 weeks	Amended for elimination of follow ups out to Week 48 in DMR arm.
2.1	Telephone visits 30 and 42 removed and in-clinic visits 36 and 48 post procedure visits removed.	Amended for elimination of follow ups out to Week 48 in DMR arm.
2.2	Enrollement # changed from 18 to 9	Amended to reflect actual number of subjects enrolled.
2.4	Removed study objective to assess the effect of DMR on glycemic endpoint 48 weeks after the randomized procedure for durability of effect determination	Amended study objective to eliminate 48 week glycemic endpoint in DMR arm.
2.7.1	Removed secondary endpoint proportion of DMR-treated subjects with an A1c improvement from baseline at 24 weeks that maintain an A1c improvement at 48 weeks	Eliminated 48 week secondary endpoints in DMR arm.
2.7.1	Removed additional endpoint interest A1c change from baseline to Week 48 by visit over time, DMR only	Eliminated 48 week additional endpoints of interest in DMR arm.
2.7.1	Removed additional endpoint interest FPG change from baseline to Week 48 by visit over time, DMR only	Eliminated 48 week additional endpoints of interest in DMR arm.
2.7.1	Removed additional endpoint interest UACR change from baseline to Week 48 by visit over time, DMR only	Eliminated 48 week additional endpoints of interest in DMR arm.
2.7.1	Removed additional endpoint interest ALT and AST change from baseline to Week 48 by visit over time, DMR only	Eliminated 48 week additional endpoints of interest in DMR arm.
3.1	Subject enrollement # of changes from 18 to 9	Amended to reflect actual number of subjects enrolled.
3.2	Updated the total anticipated duration of subject participation in the clinical study for a subject randomized to DMR will be up to a maximum of 33 weeks from 57 weeks (maximum of 6 weeks between Screening and Baseline, maximum of 3 weeks between Baseline and Procedure, and 24 weeks from 48 weeks of follow up post procedure).	Revised total study duration to reflect the elimination of follow ups out to Week 48 for DMR arm.

Section	Change	Rationale for Change
5.12.11	Added following language under AE for Week 24 visit “Subjects with an ongoing possibly and probably device and procedure related AEs reported at week 24 follow up visit will be followed until resolution. This will also also include AEs (signs and symptoms) reported during 24 week follow up period but without a definitive diagnosis and/or attribution of the cause at this visit”	This language is added to ensure all ongoing AEs or those without diagnosis or causality will be followed until resolution for subject safety reason.
5.14	Added COVID-19 Expectations for the study	Added language around COVID-19 exceptions to endpoint assessments and crossover procedures.
5.14	Removed Visit 13 Week 30 telelphone call	Amended for elimination of follow ups out to Week 48 in DMR arm.
5.15	Removed Visit 14 Week 36 In Clinic Visit	Amended for elimination of follow ups out to Week 48 in DMR arm.
5.16	Removed Visit 15 Week 42 telelphone call	Amended for elimination of follow ups out to Week 48 in DMR arm.
5.17	Removed Visit 16 Week 48 In Clinic Visit	Amended for elimination of follow ups out to Week 48 in DMR arm.
6.7	Subjects will be provided lifestyle counseling to Week 24 (visit 12)	Amended for elimination of follow ups out to Week 48 in DMR arm.
6.8	SF-36 Quality of Life Questionnaire assessment removed at Week 48 visit	Amended for elimination of follow ups out to Week 48 in DMR arm.
6.9	PROMIS questionnaire removed at Week 48 visit	Amended for elimination of follow ups out to Week 48 in DMR arm.
6.11	Anti Diabetic Regimen will be followed through 24 week Visit 12 instead of Week 48 Visit 16	Amended for elimination of follow ups out to Week 48 in DMR arm.
6.11.1	Hyperglycemia Management from week 24 to week 48 will not be followed	Amended for elimination of follow ups out to Week 48 in DMR arm.
7.9	Added “All possibly and probably device and procedure related AEs reported during 24 weeks follow up will be followed until resolution. This will also also include resolution of all AEs (signs and symptoms) reported upto 24 weeks for which there is not yet a definitive diagnosis and/or attribution of cause by the 24 weeks follow up visit”.	This is added to ensure safety of all subjects with ongoing AE(signs and symptoms) during 24 week followup or without diagnosis or causality at their last or week 24 follow up visit.
7.12.2	Sample size decreased from 18 to 9 subjects	Amended to reflect actual number of subjects enrolled.
7.12.5	Removed safety population analysis through 48 weeks post-DMR; this will include the 48 weeks of the study for patients receiving DMR from the start of the study. Results will be presented separately for the first 24 weeks and the 24-48 weeks.	Revised analysis of safety population due to elimination of follow ups out to Week 48.

Section	Change	Rationale for Change
7.12.6	Secondary efficacy endpoint proportion of DMR-treated subjects with an A1c improvement from baseline at 24 weeks that maintain an A1c improvement at 48 weeks	Eliminated 48 week secondary endpoint in DMR arm.
7.12.6	Additional Endpoint of Interest removed (i) A1c change from baseline to Week 48 by visit over time, DMR only (ii) FPG change from baseline to Week 48 by visit over time, DMR only (iii) UACR change from baseline to Week 48 by visit over time, DMR only (iv) ALT and AST change from baseline to Week 48 by visit over time, DMR only	Eliminated 48 week additional endpoints of interest in DMR arm.
Apprendix 1	Schedule of Assessments for visit #13 to 16 removed	Updated scheduled of assessments to reflect elimination of follow ups out to Week 48 in DMR arm.

Protocol Summary

Title:	**Randomized, Double-Blind, Sham-Controlled, Prospective, Multi-Center Pilot Study to Evaluate the Safety and Effectiveness of Duodenal Mucosal Resurfacing (DMR) Using the Revita™ System in the Treatment of Type 2 Diabetes (T2D)**
Short Title:	**The Revita™ US Pilot Study**
Protocol ID#:	**C-40000**
Device:	The Fractyl Revita™ System is an endoscopic treatment consisting of a single catheter and console designed to lift the duodenal mucosa with saline followed by controlled circumferential hydrothermal ablation of the mucosa.
Study Objectives:	The study objectives are: • to assess the safety of the Fractyl Revita™ System for the treatment of subjects with type 2 diabetes (T2D) suboptimally controlled on 2 to 3 oral antidiabetic medications (OADs) • to assess the effect of Duodenal Mucosal Resurfacing (DMR) versus Sham procedures on glycemic endpoints 24 weeks after the procedure
Study Design:	Randomized, double-blind sham-controlled prospective multicenter clinical investigation of subjects with T2D suboptimally controlled on 2 to 3 OADs, one of which must be metformin. Total post-randomization study duration will be up to 48 weeks. • Up to 6 Study Sites in the US • Maximum of 9 enrolled subjects, with 2:1 randomization scheme • 4 week OAD Run-In Period to assess stability of blood glucose control in conjunction with medication compliance and lifestyle (diet, exercise) counseling • OADs will be held constant from start of Run-In Period through Week 24, with protocol pre-specified treatment algorithms for hypoglycemia and hyperglycemia. Note: Subjects on SU medications will be provided with specific instructions regarding their medication usage pre- and post-DMR/Sham procedure (See 5.3.1). • Following OAD Run-In Period, subjects will be scheduled for an endoscopic evaluation consisting of an assessment

of the esophagus, stomach, duodenum and associated structures to ensure there are no conditions that would exclude the subject from having the index procedure (DMR or Sham).

- Following confirmation of eligibility during the endoscopic evaluation, subjects will be randomized to receive either the DMR or Sham procedure, and post-procedure, will return for follow-up visits as per visit schedule.
- Unblinding will occur at Week 24:
    - Sham treatment arm subjects who accept the offer of crossover will receive DMR treatment at Week 24 with a 24-week follow-up post-procedure
        - Their antidiabetic medications will be held constant from Week 24 through Week 48 with protocol pre-specified treatment algorithms for hypoglycemia and hyperglycemia
        - Subjects will continue to receive lifestyle (diet, exercise) counseling
    - DMR treatment arm will continue to receive lifestyle (diet, exercise) counseling through Week 24.
        - Their antidiabetic medications will be managed with a protocol pre-specified rescue treatment algorithm consistent with current diabetes standard of care
- In subjects randomized to the DMR treatment arm, an ablation site biopsy will be performed at Week 24
- A Data Monitoring Committee (DMC) with pertinent expertise will monitor the safety of study subjects on an ongoing basis
- A Clinical Events Committee (CEC) will adjudicate safety endpoints, and provide an unbiased assessment of adverse event (AE) relatedness and severity

Indication for Use:

The Revita™ System is intended to improve glycemic control in conjunction with diet and exercise in patients with T2D who are inadequately controlled with oral antidiabetic medications.

Inclusion Criteria

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

1. Men and non-pregnant women 28-65 years of age
2. Diagnosed with T2D for at least 3 years
3. Hemoglobin A1C (A1C) of 7.5 - 9.5% (59 - 80 mmol/mol)

4. On two to three OADs (metformin plus one or two additional OADs) with two (see note below) at least at

half maximum labeled dose (or highest tolerated) with no changes in medication in the 12 weeks prior to the Screening Visit (Visit 1) *(Refer to Table 8.3 of the American Diabetes Association [ADA] Standard of Medical Care in Diabetes 2018 for the maximum approved daily dose of non-insulin glucose lowering agents.)* Note: For subjects on sulfonylurea (SU) glucose-lowering drugs for diabetes, the only SUs permitted in the study will be glipizide or glimepiride, and their doses below half maximum labeled dosing will not be an exclusion for study entry. Patients unwilling to reduce the dose of SU at the time of the DMR procedure as described by protocol will be excluded.

5. Agree to use an additional glucose-lowering treatment (eg, liraglutide, other OAD with the exception of glyburide) if recommended by the study investigator in case of persistent hyperglycemia.
6. Agree not to donate blood during their participation in the study
7. Able to comply with study requirements and understand and sign the Informed Consent Form
8. Women of childbearing potential (WOCBP) must be using two acceptable methods of contraception throughout the study
9. Women must not be breastfeeding

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

1. WOCBP must have a negative urine pregnancy test at Baseline Visit

Exclusion Criteria

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

1. Diagnosed with Type 1 Diabetes (T1D)
2. Probable insulin production failure, defined as fasting C Peptide serum <1 ng/mL (333pmol/l)
3. History of diabetic ketoacidosis or hyperosmolar nonketotic coma
4. Previous use of any types of insulin for >1 month (at any time, except for treatment of gestational diabetes)
5. Current use of injectable medications for diabetes (insulin, glucagon-like peptide-1 receptor agonist [GLP-1RA])
6. Current use of glyburide, a sulfonylurea (SU) glucose-lowering drug for diabetes.
7. 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)

8. Known autoimmune disease, including but not limited to celiac disease, or pre-existing symptoms of systemic lupus erythematosus, scleroderma or other autoimmune connective tissue disorders
9. Previous GI surgery that could limit treatment of the duodenum such as Bilroth 2, Roux-en-Y gastric bypass, or other similar procedures or conditions
10. History of chronic or acute pancreatitis
11. History of diabetic gastroparesis
12. Known active hepatitis or active liver disease
13. Acute gastrointestinal illness in the previous 7 days
14. Known history of irritable bowel syndrome, radiation enteritis or other inflammatory bowel disease, such as Crohn's disease
15. Known history of a structural or functional disorder of the esophagus that may impede passage of the device through the gastrointestinal tract or increase risk of esophageal damage during an endoscopic procedure, including Barrett's esophagus, esophagitis, dysphagia, achalasia, stricture/stenosis, esophageal varices, esophageal diverticula, esophageal perforation, or any other disorder of the esophagus
16. Known history of a structural or functional disorder of the esophagus, including any swallowing disorder, esophageal chest pain disorders, or drug refractory esophageal reflux symptoms
17. Known history of a structural or functional disorder of the stomach, including gastric ulcer, chronic gastritis, gastric varices, hiatal hernia (> 2 cm), cancer or any other disorder of the stomach
18. Known history of chronic symptoms suggestive of a structural or functional disorder of the stomach, including any symptoms of chronic upper abdominal pain, chronic nausea, chronic vomiting, chronic dyspepsia or symptoms suggestive of gastroparesis, including post-prandial fullness or pain, post-prandial nausea or vomiting or early satiety
19. Known history of duodenal ulcer, intestinal diverticula (diverticulitis), intestinal varices, intestinal stricture/stenosis, small bowel obstruction, or any other obstructive disorder of the gastrointestinal (GI) tract
20. Currently have ongoing symptoms suggestive of intermittent small bowel obstruction, such as recurrent

bouts of post-prandial abdominal pain, nausea or vomiting

21. Active H. pylori infection (subjects with active H. pylori may continue with the screening process if they are treated with an appropriate antibiotic regimen)
22. History of coagulopathy, upper gastrointestinal bleeding conditions such as ulcers, gastric varices, strictures, congenital or acquired intestinal telangiectasia
23. Current use of anticoagulation therapy (such as warfarin) which cannot be discontinued for 7 days before and 14 days after the procedure
24. Current use of P2Y12 inhibitors (clopidogrel, pasugrel, ticagrelor) which cannot be discontinued for 14 days before and 14 days after the procedure.
25. Unable to discontinue non-steroidal anti-inflammatory drugs (NSAIDs) during treatment through 4 weeks following the procedure. Use of low dose aspirin is allowed.
26. Current use of serotonergic medications (SSRI)
27. Use of systemic glucocorticoids (excluding topical or ophthalmic application or inhaled forms) for more than 10 consecutive days within 90 days prior to the Screening Visit.
28. Use of drugs known to affect GI motility (e.g. Metoclopramide)
29. Receiving weight loss medications such as Meridia, Xenical, or over the counter weight loss medications
30. Untreated/inadequately treated hypothyroidism, defined as an elevated Thyroid Stimulating Hormone (TSH) level at Screening; if on thyroid hormone replacement therapy, must be on a stable dose for at least 6 weeks prior to Screening
31. Persistent anemia, defined as Hemoglobin <10 g/dL
32. Subjects who have donated blood or received a transfusion in the prior 3 months
33. Subjects with conditions that alter red blood cell turnover
34. Subjects with prosthetic joints
35. Significant cardiovascular disease including known history of valvular disease, or myocardial infarction, heart failure, transient ischemic attack or stroke within the last 6 months
36. Moderate or severe chronic kidney disease (CKD), with estimated glomerular filtration rate (eGFR) <45

ml/min/1.73m^2 (estimated by Modification of Diet in Renal Disease [MDRD])

37. Known immunocompromised status, including but not limited to individuals who have undergone organ transplantation, chemotherapy or radiotherapy within the past 12 months, who have clinically-significant leukopenia, who are positive for the human immunodeficiency virus (HIV) or whose immune status makes the subject a poor candidate for clinical trial participation in the opinion of the Investigator
38. Active systemic infection
39. Active malignancy within the last 5 years (with the exception of treated basal cell or treated squamous cell carcinoma)
40. Subjects with a personal or family history of medullary thyroid carcinoma
41. Subjects with Multiple Endocrine Neoplasia syndrome type 2
42. Not a candidate for surgery or general anesthesia
43. Active illicit substance abuse or alcoholism
44. Current smoker
45. Participating in another ongoing clinical trial of an investigational drug or device
46. Any other mental or physical condition which, in the opinion of the Investigator, makes the subject a poor candidate for clinical trial participation
47. Unwilling or unable to perform self-monitoring of blood glucose (SMBG), complete the patient diary, or comply with study visits and other study procedures as required per protocol

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

1. A1c post run-in phase < 7.5% (59 mmol/mol) or > 9.5% (86 mmol/mol)2. Any severe hypoglycemic event, defined as hypoglycemia requiring third-party assistance; or any clinically significant hypoglycemic event, defined as self-monitored or laboratory plasma glucose level < 54 mg/dL (3.0 mmol/L); or ≥ 2 glucose alert values ≤70 mg/dL (3.9 mmol/L), unless a clear correctable precipitating factor can be identified, since the Screening Visit (Visit 1)
2. Uncontrolled hyperglycemia with a glucose level >270 mg/dl (>15 mmol/L) after an overnight fast or >360 mg/dl (>20 mmol/l) in a randomly performed measurement during Medication Run-In Period and

confirmed by a second measurement (not on the same day)
3. Mean of 3 separate blood pressure measurements >180 mmHg (systolic) or >100 mmHg (diastolic)
4. WOCBP with a positive urine pregnancy test at Baseline Visit

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 gastrointestinal conditions such as ulcers, polyps, varices, strictures, congenital or acquired intestinal telangiectasia

Study Endpoints:

Effectiveness Endpoints:

Primary Endpoint:
A1c change from baseline to Week 24, DMR vs Sham

Secondary Endpoints:

(i) A1c change from baseline to Week 24 by visit over time, DMR vs. Sham
(ii) Fasting plasma glucose (FPG) change from baseline to Week 24, DMR vs. Sham
(iii) FPG change from baseline to Week 24 by visit over time, DMR vs. Sham
(iv) Urine Albumin-to-Creatinine Ratio (UACR) change from baseline to Week 24, DMR vs. Sham
(v) Alanine Aminotransferase (ALT) and Aspartate Aminotransferase (AST) change from baseline to Week 24, DMR vs. Sham

Additional Endpoints of Interest:

(i) A1c change from Week 24 (pre-DMR) in Sham cross-over group to Week 48
(ii) FPG change from Week 24 (pre-DMR) in Sham cross-over group to Week 48
(iii) RAND Short Form (36) Health Survey (SF-36) change from baseline at Week 24 (prior to assessments or endoscopy) vs Sham

(iv) PROMIS® (Patient-Reported Outcomes Measurement Information System) change from baseline at Week 24 (prior to assessments or endoscopy) vs Sham

Safety Endpoints:

- Event number and incidence of reported adverse events (AEs) and serious adverse events (SAEs), as well as device- and procedure-relatedness of AEs and SAEs, unanticipated adverse device effects (UADEs), and withdrawals due to AEs
- Other safety
  - assessments including vital signs and weight, physical exam, laboratory values (FPG, HbA1c, ALT, AST and UACR), electrocardiogram [ECG]
  - Duodenal biopsy samples for histological evidence of mucosal regrowth, inflammation and fibrosis
  - Magnetic Resonance Imaging Enterography (MRE) to assess thermal injury in the duodenum

Note: As a pilot evaluation, this study is not statistically powered and only descriptive statistics will be used to assess both primary and secondary endpoints.

Study Assessments:

A1c
FPG
ALT, AST
UACR
Duodenal mucosal biopsy
MRE
SF-36
PROMIS®

Study Sponsor:

Fractyl Laboratories Inc.
17 Hartwell Ave
Lexington, MA 02421 USA

List of Abbreviations

ACRONYM	DESCRIPTION
A1c	Glycated Hemoglobin (HbA1c)
ADA	American Diabetes Association
AE	Adverse Event
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
BMI	Body Mass Index
BP	Blood Pressure
CBC	Complete Blood Count
CEC	Clinical Events Committee
CFR	Code of Federal Regulations
DMC	Data Monitoring Committee
DMR	Duodenal Mucosal Resurfacing
DPP	Diabetes Prevention Program
DPP4	Dipeptidyl peptidase-4 inhibitor
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
eGFR	Estimated Glomerular Filtration Rate
FPG	Fasting Plasma Glucose
GI	Gastrointestinal
GIP	Gastric Inhibitory Peptide
GLP-1	Glucagon-like peptide 1
GLP1-RA	Glucagon-like peptide 1 receptor agonist
HCP	Health Care Provider
HDL	High Density Lipoprotein
HIV	Human Immunodeficiency Virus
HOMA-IR	Homeostatic Model Assessment of Insulin Resistance
ICH	International Conference on Harmonization
ICF	Informed Consent Form
IEC	Independent Ethics Committee
IFU	Instructions for Use
IRB	Institutional Review Board
ITT	Intent-to-Treat
IV	Intravenous
LDL	Low Density Lipoprotein
mg/dL	Milligrams per Deciliter
Mmol	Millimoles
mmol/L	Millimoles per liter
MRE	MRI Enterography
MRI	Magnetic Resonance Imaging
ng/mL	Nanograms per milliliter
NSAIDs	Non-steroidal anti-inflammatory drugs
OAD	Oral antidiabetic medications

OD	Outer diameter
PROMIS®	Patient-Reported Outcomes Measurement Information System
pmol/l	Picomole/liter
PP	Per Protocol
PT	Preferred term
QA	Quality Assurance
QOL	Quality of Life
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
Sc	subcutaneous
SF-36	Short Form (36) Health Survey by RAND
SGLT2i	Sodium-glucose cotransporter-2 inhibitor
SMBG	Self-Monitoring of Blood Glucose
SOC	System organ class
SSRI	Serotonergic medications
SU	Sulfonylurea
TEAE	Treatment Emergent Adverse Event
TZD	Thiazolidinedione
T1D	Type 1 Diabetes
T2D	Type 2 Diabetes
TSH	Thyroid Stimulating Hormone
UACR	Urine Albumin-to-Creatinine Ratio
UADE	Unanticipated Adverse Device Effect
WOCBP	Women of Childbearing Potential

List of Definitions

Term	Definition
As-Treated (AT) Population	The subset of ITT subjects who received at least one ablation or undergo the sham procedure. This is the primary population for efficacy. Subjects are analyzed according to the treatment received.
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, randomization, and initiation of the index procedure, DMR or sham.
Fasting blood glucose level	Blood sample obtained after an overnight fast of at least 8 hours
Hypoglycemic events	A glucose alert value is defined as ≤ 70 mg/dL (3.9 mmol/L). Serious, clinically important hypoglycemia is defined as a plasma glucose of < 54 mg/dL (3.0 mmol/L). Severe hypoglycemia is defined as denoting severe cognitive impairment requiring external assistance for recovery.
Intent-to-Treat (ITT) Population	The ITT population includes all subjects who were randomized after the Medication Run-In phase. This is the secondary analysis population for efficacy (no imputation will be made for missing data, given the nature of the study; i.e., analysis on this population will be performed using only available data). Subjects are analyzed according to the treatment to which they were randomized.
Medication Run-In	Time period when subjects who have met the Screening criteria undergo the 4 week Medication Run-In period.
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.
Safety Population	This population includes all subjects in whom randomized treatment was attempted. Subjects are analyzed according to the treatment received.
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.
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 Population	The study population includes all subjects consented at the site. Within this population there are Screened, Medication Run In, and Safety populations.
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.

1 Introduction

1.1 Type 2 Diabetes (T2D)

T2D is an endocrine disorder that is characterized by chronically elevated blood glucose (hyperglycemia) and subsequent vascular complications. It is a global disease of pandemic proportions and, in the United States alone, there are over 25 million patients with T2D and nearly 2 million newly diagnosed patients every year (1). T2D is the leading cause of blindness (due to diabetic retinopathy, 20,000 cases/year), end-stage renal disease (due to diabetic nephropathy, 50,000 cases/year), and amputation (due to diabetic neuropathy, 70,000 cases/year) (2).

T2D is a complicated condition and its characteristic feature, hyperglycemia, manifests through diminished insulin action in the body. This occurs through two main pathogenic drivers: (i) a failure of the pancreatic beta cells to secrete adequate insulin; and (ii) systemic resistance to insulin action (termed “insulin resistance”). In principle, some patients who are genetically predisposed to disease worsen their degree of insulin resistance through westernized lifestyle behaviors (i.e., excessive caloric consumption of a diet rich in fat and simple sugars, and insufficient physical activity). This insulin resistant state thus imposes a persistent and excessive insulin secretory demand on the pancreatic beta cells (3,4). Over time, the pancreatic beta cell is unable to sustain its capacity to maintain such a high level of insulin secretion, and overt insulin secretory failure ensues. The mismatch between the degree of insulin resistance and the insufficient pancreatic insulin production leads to the onset of frank hyperglycemia and clinical diabetes (5). Unfortunately, once established, the disease continues to run a progressive course as pancreatic beta cell reserve further and inexorably declines over time. This explains why treatment approaches to lower blood glucose early in the disease invariably fail in the face of progressive beta cell failure. This inevitably results in the typical patient requiring more treatment assistance over time, culminating in the advanced state of negligible beta cell secretory reserve and the need for insulin treatment by injection (6,7). Therefore, an ideal new treatment approach for T2D would intervene before pancreatic beta cell function has completely failed with the aim of improving insulin sensitivity, and delaying or reducing the progressive decline in insulin secretory capacity.

1.2 Existing Treatment Options

Existing treatment options for T2D include lifestyle modification, pharmacological therapy and bariatric surgery.

1.2.1 Lifestyle Modification

Lifestyle modification (i.e. diet, exercise) is a well-established intervention that is a critical first treatment step in T2D clinical management. Under carefully controlled clinical trial conditions, intensive lifestyle modification exerts metabolic benefit in subjects with pre-T2D, as demonstrated in the Diabetes Prevention

Program (DPP) (8,9) and in patients with T2D (10,11). However, lifestyle modification alone is a largely ineffective treatment approach in a real world setting in large part due to patient non-compliance over the long term (12).

1.2.2 **Pharmacological Intervention**

Pharmacological intervention is the mainstay of diabetes management, with approximately 45 anti-diabetes therapeutics currently available in the US. Unfortunately, like lifestyle modification, patient non-compliance renders this extensive treatment resource only partially effective. As illustration, a large segment of the US T2D population remains in sub-optimal glycemic control despite access to a wide array of pharmacological options (13,14). Pharmacological treatment of T2D is predominantly founded on increasing insulin action to limit hyperglycemia. This is accomplished by either (1) increasing insulin availability through stimulating endogenous secretion from the pancreatic beta cells or, in advanced disease, by exogenously administering insulin, or (2) increasing the body's sensitivity to insulin action, in other words, insulin sensitization. Pharmacological intervention is also founded on pragmatic ease of implementation and patient acceptance, where orally administered therapies tend to be used earlier in the disease before graduating to the need for injectable therapies (i.e., Glucagon-like peptide 1 receptor agonist [GLP-1RA], insulins).

Increasing insulin availability is realized through well-established pharmacological therapy classes, the sulphonylureas (SUs), GLP-1RAs, and insulin, but two of the three classes (SUs and insulin) do so with potential for causing abnormally excessive circulating insulin levels that can expose patients to the harmful effects of hypoglycemia. It is well-established that iatrogenic hypoglycemia in T2D, through use of either SU or insulin, is associated with detrimental consequences, namely cardiovascular complications and death (15-18). It is also speculated that the excessive hyperinsulinemia observed with both treatment classes, in particular with exogenous insulin use, stimulates abnormal lipogenesis, and this results in weight gain through increased adiposity and increased abnormal fat deposition in critical end organs, such as the liver, thereby worsening co-existent fatty liver disease (19-21).

Insulin sensitization can be elicited by well-established interventions (lifestyle [diet and exercise], metformin, thiazolidinediones [TZDs]) that result in an improvement in overall glycemia. This improvement in glycemia can be observed at all stages of T2D: in conjunction with insulin secretagogues or exogenous insulin later in the disease, or to prevent the progression of beta cell failure when used earlier in the disease (22). It is also recognized that insulin sensitization is often accompanied by metabolic benefits beyond glycemic control through positive effects observed in other insulin sensitive end organs (e.g., cardiovascular system, liver, and ovary) (23-25). With the TZD class as illustration, positive effects have been reported on blood pressure, improvements in fatty liver disease manifestations, and a return to ovulation in anovulatory females (26).

1.2.3 Bariatric Surgery

Bariatric surgery has emerged as an intervention that exerts striking improvements in glycemic control in subjects with T2D, seemingly in a weight-independent manner, and highlights the important role of the gastrointestinal tract in regulating metabolic homeostasis (27,28). It has been shown to exert durable improvements in glycemic control that are superior to that achieved with optimized pharmacological therapy (29,30). However, the notion of surgery itself and its attendant risks, as well as limited surgical capacity, limits the role of bariatric surgery to impact population-level disease.

1.3 Summary of Limitations of Current Therapies

A number of barriers are acknowledged as impediments to achieving optimal glycemic control in T2D with currently available treatment options at both the patient and population level.

1.3.1 By Patient Adherence/Compliance

The treatment of T2D is notable in that the majority, if not all, of the available interventions require some level of compliance on the part of the individual patient on a daily basis (e.g., administering oral medications or injections, sometimes multiple times per day, exercising, eating healthy meals and snacks, blood glucose monitoring). Non-compliance therefore limits greatly the impact of lifestyle modification and most of the pharmacological therapies; and the more complex and labor intensive a given treatment (e.g., exogenous insulin) the more it diminishes real world impact (31). Bariatric surgery has emerged as a very different treatment approach involving a single point in time intervention that exerts a powerful impact on metabolism. It is of course counterbalanced by the short-term effects of an actual surgical procedure and the significant risk of post-surgical complications, but it nevertheless offers a transformative treatment approach that circumvents many of the issues of patient compliance (32,33).

1.3.2 By Specific Treatment Approach

Each pharmacological modality also comes with specific tolerability or adverse event considerations that become a particular impediment to their use and contribute to real world non-compliance.

Treatment	Impediment
Metformin	GI intolerability, certain exclusion criteria, rare lactic acidosis
SUs	Weight gain, hypoglycemia
Dipeptidyl peptidase-4 inhibitors (DPP4s)	Pancreatitis risk, rare angioedema and arthralgia
TZDs	Weight gain, edema, heart failure, bladder cancer
Acarbose	GI intolerability

SGLT2i	GU infection, rare ketoacidosis, amputations
GLP-1RA	GI intolerability, injections, risk of pancreatitis
Insulin	Weight gain, hypoglycemia, edema, injections, blood glucose monitoring

1.3.3 By Disease Progression and Treatment Continuum

T2D is a progressive disease and currently available pharmacological therapies are not designed to address its core pathophysiological abnormalities, and this results in an inability to alter the inexorable course of the disease. In other words, pharmacological treatment has been largely designed to limit the metabolic manifestation of clinical diabetes (hyperglycemia) but without treating the actual underlying disease. The average patient therefore requires more pharmacological treatment over time to control hyperglycemia, culminating in the eventual transition to insulin treatment (34,35). The final step to insulin treatment is especially problematic in that subjects resist this final therapeutic step as the treatment itself carries great negative stigma; it is hard to implement in a real world setting especially among patients with multiple chronic diseases and multiple concomitant chronic medications (see above), and there are inherent harmful side effects of insulin therapy that are often experienced by the patient (e.g., hypoglycemia, fluid retention, weight gain) (36-38).

In summary, the management of T2D, despite an extensive list of treatment modalities, is impeded, given that (i) patient non-compliance limits treatment success at all parts of the disease continuum, (ii) the available treatments only treat the metabolic consequence of the disease (hyperglycemia) and not the underlying disease itself, (iii) the available treatments are unable to safely correct hyperglycemia in a large segment of the population, and (iv) aversion to insulin use means patients suffer needlessly with prolonged hyperglycemia pre-insulin use.

1.4 Emerging Metabolic Role in the Gut

Recent bariatric surgery experience has provided an increasing body of evidence that the gut plays a critical metabolic role in T2D. More specifically, the bypass of the duodenum or prevention of nutrient contact with the duodenal mucosal surface results in a prompt and sustained insulin sensitizing effect. This effect appears to be independent of the short-term calorie restriction and the later reduction in adipose fat mass that is observed in patients who have undergone bariatric surgery.

DMR, using the Revita™ System, is designed to mimic the metabolic benefit of the duodenal exclusion component of bariatric surgery, thereby eliciting an insulin sensitizing effect. The clinical data gathered thus far indicate that DMR exerts a likely insulin sensitizing effect as evidenced by a lowering of Homeostatic Model Assessment of Insulin Resistance (HOMA-IR), an insulin sensitizing metabolic signature by metabolomics testing (e.g., lowering of α-hydroxybutyrate, diacylglycerol, and peroxidase activity), and other related insulin

sensitizing biomarker effects (including lowered hepatic transaminases and urinary albumin).

Unlike bariatric surgery, which involves an anatomical bypass of the duodenum and therefore no exposure of ingested nutrients to the surface of that portion of the GI tract, DMR is designed to ablate and resurface the duodenal mucosal surface, thus allowing nutrients to be exposed to a resurfaced local mucosa. This infers that the duodenal mucosa surface is in some way abnormal in insulin resistant T2D subjects and is therefore emanating a potential 'insulin resisting' effect. This notion is supported by multiple lines of evidence:

(i) the duodenum undergoes a maladaptive hypertrophic response when exposed to unhealthy nutrients (i.e., fat, simple sugars);
(ii) this change appears to be associated with an augmented insulin resistant signal emanating from this portion of the bowel;
(iii) this signal appears to be persistent and reversible in T2D, as revealed in patients after bariatric surgery: in patients in whom metabolic improvement has been established after surgery, the acute re-exposure of the bypassed duodenum to nutrients quickly restores the insulin resistant, hyperglycemic, dysmetabolic condition that had existed pre-surgery; and
(iv) ablation technology applied to other tissue surfaces has shown that the natural tissue response to ablation is re-growth with subsequent healthy tissue surface formation (39-41)

Taken together, there is a strong rationale that the duodenal mucosa of T2D subjects is in some way abnormal and that subjects would likely reap metabolic benefit if the local duodenal mucosa is resurfaced through an ablation technique. Preliminary clinical data gathered in ~100 patients treated with the Revita™ System (discussed in Section 1.7) suggest that DMR does indeed exert a glycemic improvement in T2D subjects, which appears to be mediated through an insulin sensitizing mechanism. The goal of the proposed pilot study is to further advance the DMR clinical evidence in T2D subjects in a controlled clinical setting to better characterize its safety and effectiveness profile.

The Fractyl Revita™ System has achieved CE-marking and allows physicians to safely and effectively ablate the duodenal mucosa in patients with T2D. This procedure decreases hyperglycemia in these patients, thereby positively impacting their abnormal metabolic state. Further study of the Fractyl Revita™ System in patients with T2D will add important new data regarding tolerability, efficacy and safety of the DMR procedure compared to a sham-treated control group, provide both a short- and longer-term metabolic and safety perspective, and better characterize the intended user population.

1.5 Fractyl 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 is delivered transorally over a guidewire into the duodenum using standard techniques, by a therapeutic endoscopist, and performs two functions: 1) 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, each 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 contained 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 is available with a 24 mm outer diameter (OD) balloon.

Console:
The console is a reusable electro-mechanical piece of equipment and provides precisely controlled functionality to the catheter to perform the submucosal lift and hot fluid ablation steps of the procedure. The console continuously monitors its performance to detect fault conditions and mitigate risks to the patient. The console is controlled by the user through the use of a software user interface monitor. Prior to use, the console 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.

1.6 DMR Procedure

The DMR procedure using the Revita™ System is completed in the endoscopy suite or in an operating room using either general anesthesia by a physician who is trained in therapeutic endoscopic procedures involving the use of a guidewire. 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 30 minutes.

Mucosal Lift and Ablation Procedure

The Revita™ catheter is placed in the proximal duodenum distal to the papilla. Both mucosal lift and mucosal ablation of the duodenum are commonly performed in the endoscopy suite, and the Revita™ System is designed to enable a highly controlled lift and ablation of the post-papillary duodenum. Using the console interface, the balloon is inflated and vacuum delivered to draw the intestinal mucosal tissue into 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 colored with methylene blue or similar dye 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 is treated. A full DMR procedure is defined as 5 complete ablations representing 10 axial centimeters of circumferentially ablated tissue in the duodenum. The Revita™ catheter and endoscope are then removed.

1.7 Clinical Experience

A first in human clinical investigation (C-10000) began in August 2013 at a single site in Santiago, Chile and enrolled 57 subjects. The objective of this investigation was to evaluate initial feasibility and the safety profile of the DMR procedure using the Revita™ System, and its effect on subjects with T2D. Efficacy was evaluated with FPG and A1c levels. Safety data included volunteered/elicited AEs and their relatedness to the study device or procedure. Early in the course of the study, three SAEs of duodenal stenosis were reported. All resolved without sequelae. As corrective action, procedural and catheter modifications were implemented with no further reports of stenosis across the entire Revita™ clinical program to date. An additional SAE of jejunal perforation during catheter placement and prior to ablation, was noted. The most frequent AEs were GI-related (abdominal distention, abdominal pain, change of bowel habit and diarrhea). They occurred early following the procedure, were predominately mild in severity, and resolved early during the post-operative period, all without sequelae. Although the study was conducted primarily to demonstrate safety, A1c and FPG lowering and HOMA-IR improvement suggested significant improvement in the metabolic derangements of diabetes (42).

A second single arm, open label evaluation has enrolled 46 subjects in Europe and South America (C-20000). The objective of this multi-center trial was to verify that the results seen in C-10000 at a single center were generalizable to a broader population across Europe, in addition to South America . There were no

device-related SAEs. One procedure-related SAE, a transient low grade fever (38°) with C-reactive protein (CRP) elevation, occurred the day after DMR and required one extra day of hospitalization. Consistent with the C-10000 study, the most frequent AEs were GI-related, occurring early post procedure; they were transient and generally mild. Effectiveness was demonstrated by a robust mean improvement in A1c of 1.0% at 24 weeks, with 71.1% of subjects achieving an improvement of at least 0.5%; mean FPG lowering of 35.7 mg/dL; a durable glycemic response over 52 weeks of observation; and a clinically-relevant decrease in HOMA-IR.

C-30000, a randomized double-blind sham-controlled prospective multicenter clinical investigation in up to 120 T2D subjects was initiated in Europe and Brazil in Q2 2017, and includes mechanistic studies as well as safety and effectiveness assessments.

1.8 Risk Analysis

There are certain residual risks associated with the use of the Fractyl Revita™ System and the DMR procedure. AEs that may result from the DMR System include those commonly associated with gastrointestinal endoscopy procedures, as well as device-related AEs: potential acute and chronic adverse consequences of the device-induced duodenal ablation treatment, or those resulting from device malfunction, device user error, selected materials, device design or device construction. Some AEs may be associated with both the procedure and the device. In addition, device malfunctions may occur which may or may not result in a device-related AE. The Instructions for Use (IFU) provide a listing of these 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.

1.8.1 Procedure Risks

Potential AEs associated with the endoscopic procedure and sedation include the following (in alphabetical order):

- Abdominal cramps, discomfort, or pain
- Allergic or adverse reaction to sedation or anesthesia
- Abdominal bloating
- Cardiac or respiratory arrest
- Death
- Delayed gastric emptying
- Dental injury
- Difficulty swallowing
- Digestive tract injury or perforation
- Fever
- Gastrointestinal bleeding
- Headache
- Hyperglycemia
- Hypoglycemia

- Hypotension
- Hypoxia
- Impaired judgment or reactions
- Indigestion
- Infection
- Injury to esophagus
- Laryngospasm
- Mucosal injury to GI tract
- Nausea
- Pancreatitis
- Perforation
- Pneumoperitoneum
- Pulmonary aspiration
- Sore or irritated throat
- Vomiting

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

1.8.2 **Device Risks**

Potential AEs associated with the device include the following:

- Abdominal cramps, discomfort, or pain
- Abscess formation
- Allergic reaction to the device materials or methylene blue
- Death
- Delayed gastric emptying
- Diarrhea
- Digestive tract injury
- Duodenal stenosis
- Fever
- Gastric dumping syndrome
- Gastritis
- Gastrointestinal bleeding
- Hyperglycemia
- Hypoglycemia
- Infection
- Mucosal injury to GI tract
- Nausea
- Nutritional malabsorption
- Pancreatitis
- Perforation
- Stomach or duodenal obstruction
- Stricture

- Structural damage to the GI tract
- Thermal damage to the duodenum wall or surrounding structures
- Ulcer
- Vomiting

Device malfunctions that lead to device-related AEs include:

- Console delivers incorrect ablation time and temperature profile resulting in GI tract injury or perforation
- Hole in hot fluid catheter balloon resulting in leakage of hot fluid that results in GI tract injury or perforation
- Lost catheter component in the GI tract or wall that results in GI tract injury or perforation

Device malfunctions that may or may not result in device-related AEs include:

- Component degradation
- Device breakage
- Device disarticulation

1.8.3 **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 confirm the safety and performance of the procedure.
- All endoscopists 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.

1.8.4 **Justification for Investigation**

As with any medical device developed for use in a procedure, 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 risk profile of such devices in the hands of experienced therapeutic endoscopists has improved dramatically over time with dedicated training, implementation of best practices in therapeutic technique

(e.g. use of endoscopic guidewires), improved endoscopic visualization, and improved fluoroscopic capabilities in endoscopic suites. From a procedural standpoint, devices such as achalasia-pneumodilatation balloons, injection needles, RF ablation devices and endoscopic mucosal resection systems have shown a satisfactory history of safe and effective clinical use. Attempts have been made to limit procedural risks by limiting study participation to subjects in general good health as per the stringent inclusion/exclusion criteria, having the DMR procedure conducted only by physicians and procedural teams trained in advanced therapeutic endoscopic procedures, and by conducting didactic and hands-on animal labs. In addition, appropriate steps have been taken to minimize the risks associated with the device design and materials, as listed above.

The medical consequences and morbidity associated with T2D have been well studied and documented, and include microvascular and macrovascular complications such as renal failure, blindness, peripheral neuropathy, amputation, increased risk of myocardial infarctions, stroke, and peripheral vascular disease. A successful DMR procedure is expected to lower A1c in T2D patients with inadequate glycemic control despite the use of oral glucose-lowering medications, given its potential for increasing insulin sensitivity and action, thereby decreasing glucose toxicity and enabling more effective glycemic control. In addition to its beneficial effect on the pathophysiological drivers of metabolic dysfunction, the DMR procedure has a key therapeutic advantage in that its effectiveness is not compliance-dependent, in contrast to all other currently available T2D therapies. Because poor adherence to medications is a significant barrier to glycemic control in the general population, a DMR procedure which does not require daily compliance with additional medications may prove to be particularly helpful in achieving superior real world results, as has been observed with bariatric surgery. In conjunction with an appropriate lifestyle (eg, healthy diet, exercise), a DMR procedure performed in patients who have not achieved target glycemic goals with their current regimen of OADs should help optimize glycemic control and support endogenous beta cell function. Removing compliance as an impediment to glycemic control, and given its mechanistic plausibility, the DMR procedure and device offer an important new therapy to patients with T2D to help reduce the morbidity and end-organ damage from this debilitating chronic illness.

As noted above, there are potential benefits associated with the DMR procedure, and the risks associated with the device and procedure have been identified and minimized where possible. Thus, the benefit/risk profile associated with the Revita™ System warrants further clinical research and justifies this investigation.

2 Study Design

2.1 Overview

In two clinical trials conducted to date, the Fractyl Revita™ System has been studied as an open-label device intervention without a pre-specified control arm. Additionally, the first randomized, double-blind, sham controlled study was initiated in Q2, 2017 in Europe and South America and is in the process of being closed out.

The US Pilot study is a prospective, randomized, double-blind (subject and endocrinologist), 24-week, sham-controlled, multi-center, pilot trial in a maximum of 9 enrolled subjects with T2D suboptimally controlled on 2 to 3 OADs, one of which must be metformin. The randomization scheme will be 2:1 DMR treatment:Sham procedure. Total post-randomization study duration will be 24 weeks for DMR subjects and 48 weeks for Sham subjects who undergo the crossover procedure within 21 days of Week 24 visit.

All eligible subjects will participate in a 4-week antidiabetic medication Run-In Period before randomization to the index procedure to assess stability of blood glucose control in conjunction with medication compliance and lifestyle (diet, exercise) counseling. OADs will be held constant from start of Run-In Period through Week 24, with protocol pre-specified treatment algorithms for hypoglycemia and hyperglycemia.

Following the medication run-in period, subjects will be scheduled for an endoscopic evaluation consisting of an assessment of the esophagus, stomach, duodenum and associated structures to ensure there are no conditions that would exclude the subject from having the index procedure (DMR or Sham).

Following confirmation of subject eligibility during the endoscopic evaluation, subjects will be randomized to receive the DMR or Sham procedure. Post procedure the subjects will be required to return for follow-up visits as per visit schedule.

Both treatment arms will be followed up for a total of 24 weeks from the index procedure and will continue to receive lifestyle counseling through the end of the study. At the Week 24 Visit, subjects randomized to the DMR treatment arm will have an ablation site biopsy and will be followed for an additional 24 weeks. At the Week 24 Visit, the Sham treatment arm will be provided the opportunity to cross-over to receive the DMR treatment. Sham subjects will then repeat all study visits from the DMR procedure through 24 weeks post crossover. Sham subjects that choose not to crossover and have the DMR study will be withdrawn from the study.

On an ongoing basis, study subjects will be provided with healthy lifestyle counseling to educate them on the importance of exercise and diet in relation to

blood glucose control. They will receive blood glucose meters at the Screening Visit and will be instructed how to perform self-monitoring of blood glucose (SMBG) at a schedule as outlined in Section 6.10. Subjects will be provided diaries in which they will record any changes in medication use, SMBG results, and any symptoms of hypoglycemia or hyperglycemia.

Study assessments include: A1c, FPG, ALT, AST, UACR, Duodenal mucosal biopsy, MRE, SF-36 Questionnaire, PROMIS®.

Subject follow up visits conducted by telephone will occur at 7 and 14 days and at Weeks 8,15 and 21 post procedure. Subject follow up visits conducted in clinic will occur at Week 4, 12, 18 and 24 post procedure. A summary of the assessments and data collection requirements is presented in Appendix 1 (DMR) and Appendix 2 (Sham).

2.2 Number of Study Sites and Subjects

Up to 6 sites in the US will participate in the study. The total study enrollment is a maximum of 9 enrolled subjects in a randomized scheme of 2:1 (DMR:Sham)

2.3 Intended Use

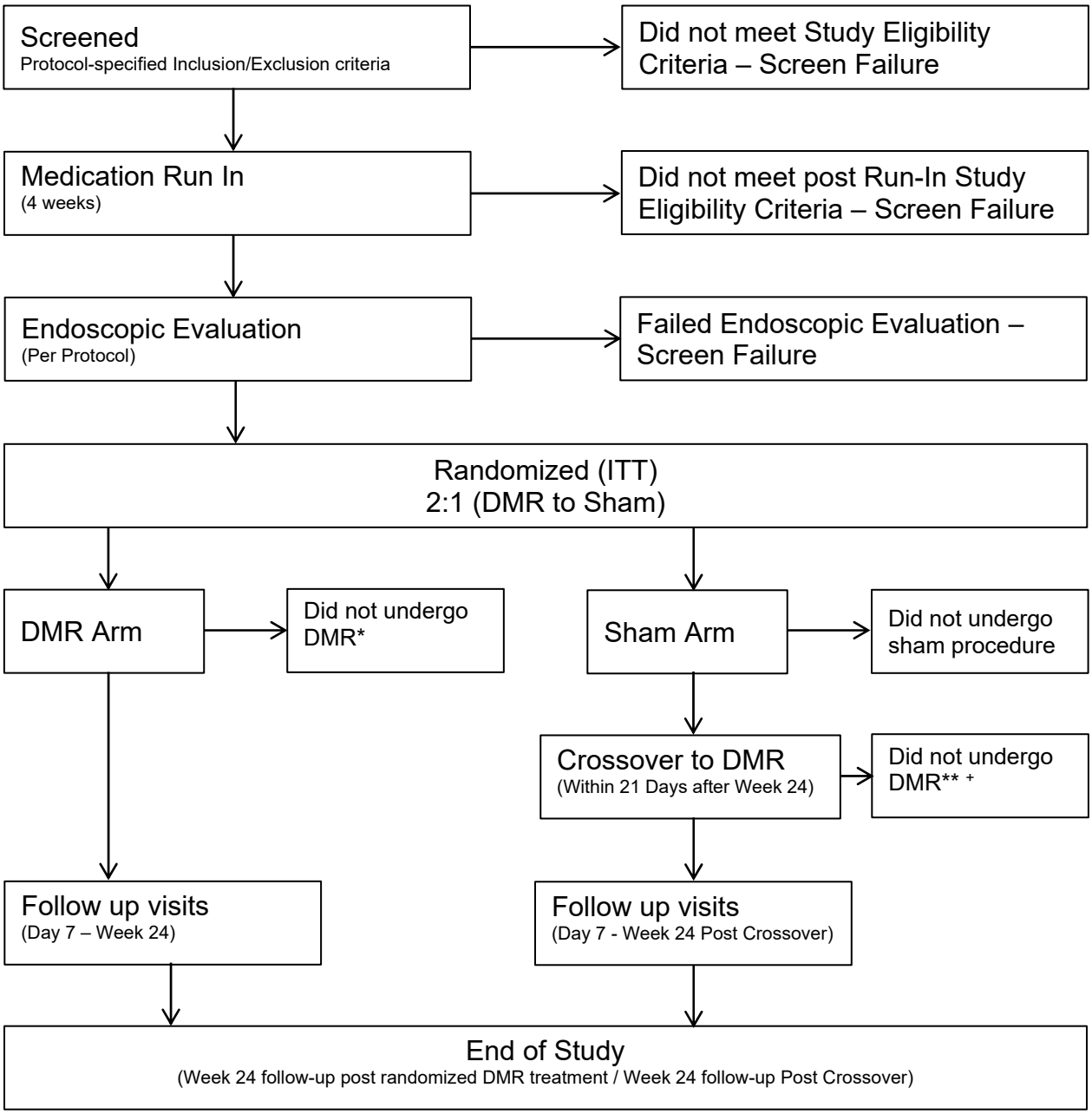
The Fractyl Revita™ System is intended to improve glycemic control in conjunction with diet and exercise in patients with T2D who are inadequately controlled with oral antidiabetic medications.

2.4 Study Objectives

The study objectives are:

- to assess the safety of the Fractyl Revita™ System for the treatment of subjects with T2D suboptimally controlled on 2 to 3 oral antidiabetic medications
- to assess the effect of DMR versus Sham procedures on glycemic endpoints 24 weeks after the procedure

2.5 Study Workflow



**Subjects randomized to DMR who do not receive any ablations during the DMR procedure will have all clinical findings documented, and will be followed for safety through the Week 4 visit and then discontinued from the study.*

***Subjects randomized to Sham who crossover to DMR but do not receive any ablations during the DMR procedure will have all clinical findings documented, and will be followed through the Week 4 post crossover visit and then discontinued from the study.*

+Subjects that choose not to crossover from sham to DMR will be discontinued from the study and the End of Study Electronic Case Report Forms (eCRFs) will be completed.

2.6 Study Duration

It is anticipated that the overall duration of this investigation will be approximately 23 months including subject enrollment, collection of follow-up assessments, and data analysis. The study will be initiated at each institution following approval of the respective independent Institutional Review Board (IRB) and after a Site Initiation Visit has been performed. Enrollment of subjects will take approximately four (4) months based on six (6) sites accruing a maximum of 9 enrolled subjects. Subjects will be follow for 24 weeks after initial randomization to DMR/Sham procedure or following Sham crossover to DMR procedure. Final data collection, analysis and final study report will take an additional 4 months.

2.7 Study Endpoints

This study is designed as a multi-center pilot evaluation of safety and effectiveness of the DMR procedure. It is not powered to demonstrate a statistically significant difference in effectiveness parameters between the treatment groups, and these endpoints will not formally define subject and study success. Instead, the results of this evaluation will be used to better understand the safety profile of the DMR procedure and to examine the reduction in A1c to aid in powering the future pivotal study which will serve as the basis for marketing authorization in the US.

2.7.1 Effectiveness Endpoints

Primary Endpoint

A1c change from baseline to Week 24, DMR vs Sham

Secondary Endpoints

(i) A1c change from baseline to Week 24 by visit over time, DMR vs. Sham
(ii) FPG change from baseline to Week 24, DMR vs. Sham
(iii) FPG change from baseline to Week 24 by visit over time, DMR vs. Sham
(iv) UACR change from baseline to Week 24, DMR vs. Sham
(v) ALT and AST change from baseline to Week 24, DMR vs. Sham

Additional Endpoints of Interest

(i) A1c change from Week 24 (pre-DMR) in Sham cross-over group to Week 48
(ii) FPG change from Week 24 (pre-DMR) in Sham cross-over group to Week 48
(iii) Short Form (36) Health Survey Version 2 (SF-36) change from baseline at Week 24 (pre- assessments and endoscopy) vs Sham
(iv) Promis® (Patient-Reported Outcomes Measurement Information System) change from baseline at Week 24 (pre- assessments and endoscopy) vs Sham

2.7.2 Safety Endpoints

- Event number and incidence of reported AEs and SAEs, as well as device- and procedure-relatedness of AEs and SAEs, UADEs, and withdrawals due to AEs
- Other safety
    - assessments including vital signs and weight, physical exam, laboratory values (FPG, HbA1c, ALT, AST and UACR), ECG
    - Duodenal biopsy samples for histological evidence of mucosal regrowth, inflammation and fibrosis
    - MRE to assess thermal injury to the duodenum.

2.8 Blinding

In this study, the endocrinologist and the associated site personnel and the subjects will be blinded to the treatment through the Week 24 follow-up visit, as will the Sponsor study team (except the proctors and technichians who will be present at the procedure). While the endoscopist will not be blinded to individual treatments, he or she will be blinded to cohort level data and will not be responsible for the diabetes management of the subjects. At the Week 24 Visit, the subjects, the endocrinologist and the blinded study site staff, as well as the blinded Sponsor study team will be unblinded.

Subjects who received the Sham treatment will be offered the option to crossover and undergo the DMR procedure at the Week 24 Visit post randomization.

Sham-treated subjects who do not choose to crossover and receive DMR will be discontinued (withdrawn) from the study and the End of Study eCRFs will be completed.

No study staff, associated hospital personnel, or study subjects will be informed of the randomization assignments until the scheduled time of unblinding at Week 24, and care will be taken to minimize the risk of inadvertent premature unblinding. The unblinding occurs after all assessments have been conducted at the Week 24 Visit.

2.9 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 in a central laboratory using validated methodology, these include A1c and FPG. Standardized methods and protocols for performing and evaluating tests and examinations have been incorporated into the study protocol.
- The use of a randomized controlled study design minimizes the bias in the findings and is considered the gold standard to demonstrate the true treatment effect.
- The study monitor will review data collection forms as they are received from the study sites to assure there are no missing or incorrect data. Missing or

incorrect data are queried and corrected in the database. Site re-training will take place as required to ensure compliance with the protocol.
- The DMC will evaluate SAEs and other pertinent safety parameters to ensure unbiased ongoing safety surveillance.
- The CEC will adjudicate SAEs, and provide an unbiased assessment of AE relatedness and severity. Employing an independent body to oversee AE causality provides added validity to the assessment of study safety endpoints, reduces potential Sponsor or Investigator bias, and increases the consistency of all safety determinations.

3 Study Population

3.1 Subject Selection

A maximum of 9 subjects at up to six (6) study sites in the US will be enrolled into this clinical study. The clinical study population will be comprised of males and females, 28 - 65 years of age who satisfy all of the inclusion and exclusion criteria, as defined in Section 4.1. 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-approved Informed Consent Form (ICF) before any clinical study-related procedures are performed. A copy of the signed ICF 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 ICF.

Study 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 before use.

3.1.1 Initial Subject Identification

Potential subjects are identified by the Investigator or their designee(s) through medical record review, referring physicians, and inquiries from interested subjects. Subjects may be pre-screened using a telephone screening script to evaluate potential eligibility for the study. If the subject meets the study's basic entry criteria as verified over the telephone 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 consent to participate in the study by signing the ICF.

3.2 Duration of Subject Participation

The total anticipated duration of subject participation in the clinical study for a subject randomized to DMR will be up to a maximum of 33 weeks (maximum of 6 weeks between Screening and Baseline, maximum of 3 weeks between Baseline and Procedure, and 24 weeks of follow up post procedure).

The total anticipated duration of subject participation in the clinical study for a subject randomized to Sham will be up to a maximum of 60 weeks (maximum of 6 weeks between Screening and Baseline, maximum of 3 weeks between Baseline and Procedure, 24 weeks (to max of 27 weeks) to Crossover and 24 weeks of follow up post crossover procedure).

4 Screening Period and Eligibility Criteria

The screening period will be completed in 3 phases and the eligibility confirmed at each of these visits: 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 in the following section below.

4.1 Selection Criteria

Selection criteria will be assessed and eligibility confirmed 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). Details of any subject who is screened for the study but is found to be ineligible at any of these 3 visits, based on medical history, medication use, physical exam, laboratory or ECG findings, will be considered a screen failure and the data collected must be entered in the Screening/Enrollment Log and documented in the eCRF. Screen Failure subjects will be informed by a telephone call from the site staff that they are ineligible for continued study participation.

4.1.1 Inclusion Criteria

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

1. Men and non-pregnant women 28-65 years of age
2. Diagnosed with T2D for at least 3 years
3. A1C of 7.5 - 9.5% (59-80 mmol/mol)
4. BMI ≥ 28 and ≤ 40 kg/m^2
5. On two to three oral OADs (metformin plus one to two additional OADs) with two (see note below) at least at half maximum labeled dose (or highest tolerated) with no changes in medication in the 12 weeks prior to the Screening Visit (Visit 1) *(Refer to ADA Standard of Medical Care in Diabetes 2018, Table 8.3 for the maximum approved daily dose of non-insulin glucose lowering agents)* (43). Note: For subjects on sulfonylurea (SU) glucose-lowering drugs for diabetes, the only SUs permitted in the study will be glipizide or glimepiride, and their doses below half maximum labeled dosing will not be an exclusion for study entry. Patients unwilling to reduce the dose of SU at the time of the DMR procedure as described by protocol will be excluded.
6. Agree to use an additional glucose-lowering treatment (eg, liraglutide, other OAD with the exception of glyburide) if recommended by the study investigator in case of persistent hyperglycemia.

7. Agree not to donate blood during their participation in the study
8. Able to comply with study requirements and understand and sign the Informed Consent Form
9. Women of childbearing potential (WOCBP) must be using two acceptable methods of contraception throughout the study
10. Women must not be breastfeeding

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

1. WOCBP must have a negative urine pregnancy test at Baseline Visit

4.1.2 Exclusion Criteria

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

1. Diagnosed with Type 1 Diabetes (T1D)
2. History of diabetic ketoacidosis or hyperosmolar nonketotic coma
3. Probable insulin production failure, defined as fasting C Peptide serum <1 ng/mL (333pmol/l)
4. Previous use of any types of insulin for >1 month (at any time, except for treatment of gestational diabetes)
5. Current use of injectable medications for diabetes (insulin, GLP-1RA)
6. Current use of glyburide, a sulfonylurea (SU) glucose-lowering drug for diabetes
7. 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)
8. Known autoimmune disease, including but not limited to celiac disease, or pre-existing symptoms of systemic lupus erythematosus, scleroderma or other autoimmune connective tissue disorder
9. Previous GI surgery that could limit treatment of the duodenum such as Bilroth 2, Roux-en-Y gastric bypass, or other similar procedures or conditions
10. History of chronic or acute pancreatitis
11. History of diabetic gastroparesis
12. Known active hepatitis or active liver disease
13. Acute gastrointestinal illness in the previous 7 days
14. Known history irritable bowel syndrome, radiation enteritis or other inflammatory bowel disease, such as Crohn's disease
15. Known history of a structural or functional disorder of the esophagus that may impede passage of the device through the gastrointestinal tract or increase risk of esophageal damage during an endoscopic procedure, including Barrett's esophagus, esophagitis, dysphagia, achalasia, stricture/stenosis, esophageal varices, esophageal diverticula, esophageal perforation, or any other disorder of the esophagus
16. Known history of a structural or functional disorder of the esophagus, including any swallowing disorder, esophageal chest pain disorders, or drug refractory esophageal reflux symptoms

17. Known history of a structural or functional disorder of the stomach including gastroparesis, gastric ulcer, chronic gastritis, gastric varices, hiatal hernia (> 2 cm), cancer or any other disorder of the stomach
18. Known history of chronic symptoms suggestive of a structural or functional disorder of the stomach, including any symptoms of chronic upper abdominal pain, chronic nausea, chronic vomiting, chronic dyspepsia or symptoms suggestive of gastroparesis, including post-prandial fullness or pain, post-prandial nausea or vomiting or early satiety
19. Known history of duodenal ulcer, intestinal diverticula (diverticulitis), intestinal varices, intestinal stricture/stenosis, small bowel obstruction, or any other obstructive disorder of the GI tract
20. Currently have ongoing symptoms suggestive of intermittent small bowel obstruction, such as recurrent bouts of post-prandial abdominal pain, nausea or vomiting
21. Active H. pylori infection (Subjects with active H. pylori may continue with the screening process if they are treated with an appropriate antibiotic regimen)
22. History of coagulopathy, upper gastrointestinal bleeding conditions such as ulcers, gastric varices, strictures, congenital or acquired intestinal telangiectasia
23. Current use of anticoagulation therapy (such as warfarin) which cannot be discontinued for 7 days before and 14 days after the procedure
24. Current use of P2Y12 inhibitors (clopidogrel, pasugrel, ticagrelor) which cannot be discontinued for 14 days before and 14 days after the procedure.
25. Unable to discontinue non-steroidal anti-inflammatory drugs (NSAIDs) during treatment through 4 weeks following the procedure. Use of low dose aspirin is allowed.
26. Current use of serotonergic medications (SSRI)
27. Use of systemic glucocorticoids (excluding topical or ophthalmic application or inhaled forms) for more than 10 consecutive days within 90 days prior to the Screening Visit
28. Use of drugs known to affect GI motility (e.g. Metoclopramide)
29. Receiving weight loss medications such as Meridia, Xenical, or over the counter weight loss medications
30. Untreated/inadequately treated hypothyroidism, defined as an elevated Thyroid-Stimulating Hormone (TSH) level at Screening; if on thyroid hormone replacement therapy, must be on stable dose for at least 6 weeks prior to Screening
31. Persistent Anemia, defined as Hemoglobin <10 g/dL
32. Subjects who have donated blood or received a transfusion in the prior 3 months
33. Subjects with conditions that alter red blood cell turnover
34. Subjects with prosthetic joints
35. Significant cardiovascular disease including known history of valvular disease, or myocardial infarction, heart failure, transient ischemic attack or stroke within the last 6 months

36. Moderate or severe chronic kidney disease (CKD), with estimated glomerular filtration rate (eGFR) <45 ml/min/1.73m^2 (estimated by MDRD)
37. Known immunocompromised status, including but not limited to individuals who have undergone organ transplantation, chemotherapy or radiotherapy within the past 12 months, who have clinically-significant leukopenia, who are positive for the human immunodeficiency virus (HIV) or whose immune status makes the subject a poor candidate for clinical trial participation in the opinion of the Investigator
38. Active systemic infection
39. Active malignancy within the last 5 years (with the exception of treated basal cell or treated squamous cell carcinoma)
40. Subjects with a personal or family history of medullary thyroid carcinoma
41. Subjects with Multiple Endocrine Neoplasia syndrome type 2
42. Not a candidate for surgery or general anesthesia
43. Active illicit substance abuse or alcoholism
44. Current smoker
45. Participating in another ongoing clinical trial of an investigational drug or device
46. Any other mental or physical condition which, in the opinion of the Investigator, makes the subject a poor candidate for clinical trial participation
47. Unwilling or unable to perform SMBG, complete the patient diary, or comply with study visits and other study procedures as required per protocol

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

1. A1c post Run-In Phase < 7.5% (59 mmol/mol) or > 9.5% (86 mmol/mol)
2. Any severe hypoglycemic event, defined as hypoglycemia requiring third-party assistance; or any clinically significant hypoglycemic event, defined as self-monitored or laboratory plasma glucose level < 54 mg/dL (3.0 mmol/L); or ≥ 2 glucose alert values ≤70 mg/dL (3.9 mmol/L), unless a clear correctable precipitating factor can be identified, since the screening visit (Visit 1)
3. Uncontrolled hyperglycemia with a glucose level >270 mg/dl (>15 mmol/L) after an overnight fast or >360 mg/dl (>20 mmol/l) in a randomly performed measurement during Medication Run-In Period and confirmed by a second measurement (not on the same day)
4. Mean of 3 separate blood pressure measurements >180 mmHg (systolic) or >100 mmHg (diastolic)
5. WOCBP with a positive urine pregnancy test at Baseline Visit

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 gastrointestinal conditions such as ulcers, polyps, 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.

5.1.1 Informed Consent

The informed consent shall inform the subject as to the objective and procedures of the study and possible risks involved. The subject will be informed about his/her 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 contents of the Informed Consent Form (ICF) will be discussed with the subject allowing adequate time for questions. If a subject is willing to participate in the study, they will indicate their willingness by signing the form. A signed copy of the ICF will be given to each subject in the study. The site must make a note in the subject's medical record that consent was given, and the date and time at which the form was signed.

5.1.2 Demographics, Medical History and Full Physical Exam

As outlined in Section 6.1, subject demographics, medical history and a full physical exam will be completed by the Investigator or designated study site personnel.

5.1.3 Blood Analysis

As outlined in Section 6.3, subjects will have sufficient blood drawn to complete the required tests.

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 protocol-specified Exclusion Criteria or Investigator expertise will be excluded from the study and considered to be Screen Failures.

5.1.4 H. pylori Test

As outlined in Section 6.3, 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 with an appropriate antibiotic regimen (A positive result will not be considered and Adverse Event).

5.1.5 ECG

As outlined in Section 6.4, a 12-lead ECG will be performed on all potential subjects.

5.1.6 Lifestyle Counseling

As outlined in Section 6.7, the subject will be provided with diabetic nutrition, healthy lifestyle and exercise guidance during this visit that is consistent with the standards of the American Diabetes Association (ADA) in order to educate them on the importance of a healthy lifestyle to blood glucose control.

5.1.7 Medication Run-In Period

Individuals who meet all the Inclusion Criteria and none of the Exclusion Criteria at the Screening Visit (Visit 1) will be eligible to start the 4 week Medication Run-In. Subjects will be instructed to continue their OAD regimen without change. The intent of the Medication Run-In Period is to verify a subject's medication regimen and associated compliance, and to assess stability of glycemic control to ensure a stable baseline for subsequent comparisons.

5.1.8 SMBG / Glycemia Diary

As outlined in Section 6.10, subjects will be provided with a home blood glucose meter, taught to perform SMBG (per the schedule outlined in Section 6.10) and asked to record the glucose values in the Glycemia Diary provided by the site. Subjects will be instructed to record the occurrence and blood glucose values (if possible) of all hypoglycemic episodes. They will also record their daily OAD intake.

5.1.9 Concomitant Medication

As outlined in Section 6.12, a complete list of all medications a subject is currently taking will be recorded by the Investigator or designated study site personnel.

5.1.10 Adverse Events (AEs)

As outlined in Section 7.8, any reported/elicited adverse events or as dictated by blood tests and office evaluation will be recorded in the eCRF. AEs are collected from the time the ICF is signed.

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

Subjects will come into the clinic for the Baseline Visit after completing a minimum of a 4 week (28 day) Medication Run-In. This visit must occur 4-6 weeks (28 – 42 days) after the Screening Visit (Visit 1).

At this visit, subjects will be assessed for the following additional Inclusion Criteria:

1. WOCBP must have a negative urine pregnancy test at Baseline Visit

At this visit, subjects will be assessed for the following additional Exclusion Criteria:

1. A1c post Run-In Phase < 7.5% (59 mmol/mol) or > 9.5% (86 mmol/mol)
2. Any severe hypoglycemic event, defined as hypoglycemia requiring third-party assistance; or any clinically significant hypoglycemic event, defined as

self-monitored or laboratory plasma glucose level < 54 mg/dL (3.0 mmol/L); or ≥ 2 glucose alert values ≤70 mg/dL (3.9 mmol/L), unless a clear correctable precipitating factor can be identified, since the Screening Visit (Visit 1)
3. Uncontrolled hyperglycemia with a glucose level >270 mg/dl (>15 mmol/L) after an overnight fast or >360 mg/dl (>20 mmol/l) in a randomly performed measurement during Medication Run-In Period and confirmed by a second measurement (not on the same day)
4. Mean of 3 separate blood pressure measurements >180 mmHg (systolic) or >100 mmHg (diastolic).
5. WOCBP with a positive urine pregnancy test

At the end of the Baseline Visit, the endoscopic procedure will be scheduled for subjects who are still eligible for study participation. The maximum time allowed between the Baseline Visit (Visit 2) and the Endoscopic Procedure Visit (Visit 3) is 21 days. Provide subjects on SU medications with specific instructions regarding their medication usage pre- and post-DMR/Sham procedure (See 5.3.1).

The study procedures outlined below will be performed at this Baseline (Post Medication Run-In) Visit in all subjects.

5.2.1 **Body Weight, Blood Pressure & Targeted Physical Exam**

As outlined in Section 6.2, weight and blood pressure will be measured in all subjects. A symptom-directed physical examination will be performed if new signs or symptoms are reported by a subject. Abnormal findings noted at the previous physical exam will be reevaluated and any abnormal findings recorded.

5.2.2 **Pregnancy Test**

A urine pregnancy test for WOCBP will be performed by a local laboratory.

5.2.3 **Blood Analysis**

As outlined in Section 6.3, subjects continuing to be screened for study inclusion will have sufficient blood drawn to complete the standard blood analysis and forwarded to a central laboratory for analysis.

A subject with test results outside acceptable ranges that are indicative of an underlying condition that would compromise their participation in the study based on the protocol-specified Exclusion Criteria or Investigator expertise will be excluded from the study and considered to be a Screen Failure.

5.2.4 **Renal Function**

As outlined in Section 6.5, urinary albumin and creatinine levels will be analyzed to determine the UACR for evaluation of kidney function. A urine sample will be collected (at the same time as the fasting blood sample) from the subject and forwarded to a central laboratory for analysis.

5.2.5 MRE

As outlined in Section 6.7, subjects will undergo a MRE.

5.2.6 Lifestyle Counseling

As outlined in Section 6.7, a member of the nutrition staff will query the subject regarding his/her adherence to a healthy lifestyle regimen, and provide the subject with advice regarding improvement in his/her diet and exercise regimen, if needed. Subjects will be reminded of the importance of a healthy lifestyle to blood glucose control.

5.2.7 SF-36 Quality of Life Questionnaire

As outlined in Section 6.8, subjects will complete the SF-36 for a health status and QOL assessment.

5.2.8 PROMIS® Patient Reported Outcomes

As outlined in Section 6.9, subjects complete PROMIS® questionnaires to evaluate physical health.

5.2.9 OAD Use, SMBG / Glycemia Diary Review

The subject's Glycemia Diary will be reviewed by the study site personnel for the occurrence of any exclusionary glycemic events, and OAD adherence. Subjects who meet the hypoglycemia or hyperglycemia exclusion criteria as outlined in Section 5.2 be excluded from the study.

Subjects still eligible for the study will continue to perform SMBG, record occurrence of hypoglycemia, and continue their OADs without any changes through Visit 3 (Procedure).

5.2.10 Concomitant Medication

As outlined in Section 6.12, all concurrent medication use reported by the subject will be recorded. Any changes in medication will be recorded on the medication log.

5.2.11 Adverse Events (AEs)

As outlined in Section 7.8, any reported adverse events by the subject or dictated by blood tests or office evaluation will be recorded.

5.3 Visit 3: Procedure (within 21 days from Visit 2)

The procedure visit will consist of endoscopy, randomization of eligible subjects, and the completion of the index procedure (DMR or Sham). All assessments are to be completed during a single clinic visit. This visit may not occur more than 21 days after the Baseline Visit (Visit 2).

5.3.1 Endoscopic Evaluation

Prior to the procedure, subjects who are on SU medication will be instructed by the site regarding specific pre- and post-procedure (DMR or Sham) SU

management. They will be asked to take half their regular dose of SUs the day before the procedure, and omit taking any SU the day of the procedure. On the day of the procedure,the subject will undergo endoscopy with an assessment of the esophagus, stomach, duodenum and associated structures in order to ensure there are no conditions that would exclude the subject from receiving the index procedure (DMR or Sham).

The following additional exclusion criteria should be assessed via endoscopy prior to subject study enrollment:

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 gastrointestinal conditions such as ulcers, polyps, varices, strictures, congenital or acquired intestinal telangiectasia

Any subject found to have the conditions listed in the Exclusion Criteria above will be considered a Screen Failure and will be excluded from further study participation.

5.3.2 **Randomization**

Following confirmation of subject eligibility during the endoscopic evaluation, the subject will be randomized using electronic assignment via a web-based system at a 2:1 ratio to:

- DMR Procedure
- Sham Procedure

The endocrinologist and the associated site personnel and the subjects will be blinded to the treatment through the Week 24 follow-up visit, as will the Sponsor study team (except the proctors and technichians who will be present at the procedure). While the endoscopist will not be blinded to individual treatments, he or she will be blinded to cohort level data and will not be responsible for the diabetes management of the study subjects.

Immediately following randomization, paracetamol, acetaminophen or equivalent will be administered to prevent pain after the procedure and to minimize the risk of premature unblinding.

5.3.3 **Subject Enrollment**

Study enrollment is defined as successful completion of the endoscopic evaluation, randomization, and initiation of the index procedure, DMR or Sham.

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

5.3.4 Duodenal Mucosal Resurfacing Procedure

The 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 will also be provided by Fractyl 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 will be monitored before and during anesthetization by general anesthesia or conscious sedation per each facility's standard protocol. A complete DMR procedure is defined as 5 complete ablations representing 10 axial centimeters of circumferentially ablated tissue in the duodenum.

During the DMR procedure, a measurement is made by the endoscopist to approximate the distance in centimeters from the papilla to the proximal edge of the first completed ablation. This data will be used to assist the endoscopist in the location for the biopsies at the Week 24 Visit.

For subjects randomized to DMR who do not receive any ablations during the DMR procedure, due to items such as tortuous anatomy precluding distal catheter delivery or erosive duodentitis, all clinical findings noted during the procedure will be documented in the medical record and in the CRFs. If the diameter of the subject's duodenum prohibits the use of the single Revita catheter it will be noted in the medical record and in the CRFs. The subjects will be followed for safety through the Week 4 visit and then discontinued from the study.

5.3.5 Sham Procedure

The Sham procedure will consist of placing the Revita™ Catheter as described above into the duodenum for a minimum of 30 minutes and then removing it from the patient.

5.3.6 Post-Procedure Care & Discharge

Unforeseen events (findings or procedures) may occur during either the DMR or Sham procedures. 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.

Immediately following the procedure, the subject will be 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 will be dictated by the hospital or physician's standard care protocol regarding post-anesthesia recovery.

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

5.3.7 **Post-Procedure Glucose and Diet Management**

For people with diabetes, any procedure that causes them to miss a meal or change their usual meal plan will require special planning to safely manage blood glucose. Subjects will be specifically instructed on appropriate post-procedure diet and glycemic management prior to discharge. Intensified glucose monitoring will be implemented during this period, as discussed in Section 6.10. Subjects will be instructed to maintain adequate caloric intake and hydration during the entire post-procedure period. 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, and 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. Training of the site personnel regarding the principles of nutritional management during this peri- and post-procedure period will be performed at every site prior to subject study entry. Site personnel training will include the composition and adequacy of dietary intake, attention to appropriate hydration, and relevance of intake to glycemic control.

Following the DMR/Sham procedure, subjects on SU medications will be instructed to restart their medicines in an incremental fashion (step-wise increase to pre-procedure dose) guided by how well their dietary intake is progressing (eg, tolerability of full soft diet, calorie intake) and by their blood glucose levels as noted during their intense glucose monitoring efforts (refer to section 6.10 for additional instructions on SMBG and section 6.11 for additional instructions on Management of Glycemia and Antidiabetic Medication).

After finishing the 14 day diet, a standard diabetic diet, outlined by the registered dietitian, will be resumed as tolerated.

5.3.8 **OAD Use, SMBG and Glycemia Diary Review**

As outlined in Sections 6.10 and 6.11, subjects will continue on their standard OAD regimen post-procedure, and record OAD use, blood glucose levels, and any hypoglycemia in the Glycemia Diary.

5.3.9 Concomitant Medication

As outlined in Section 6.12, all concurrent medication reported by the subject will be recorded. Any changes in medication will be recorded on the medication log.

5.3.10 Adverse Events (AEs)

As outlined in Section 7.8, any AEs reported by or elicited from the subject, or dictated by blood tests or office evaluation will be recorded in the eCRF. Those that occur after the DMR or Sham procedure will be considered to be Treatment-Emergent Adverse Events (TEAEs).

5.4 Visit 4: Day 7 Telephone Call (+/-2 days)

At Day 7 post-procedure, the subject will be contacted via telephone; no office/clinic visit is required. The following reminders will be given and information collected during the call:

5.4.1 Post-Procedure Diet Reminder

The subjects will be reminded about the specific 14 day post-procedure diet.

5.4.2 OAD and Rescue Medication Use, SMBG, and Glycemia Diary Review

The subject's Glycemia Diary will be reviewed by the study site personnel for OAD adherence, the addition of rescue medication for hyperglycemia, the occurrence of any hypoglycemia event, and SMBG levels (as outlined in Section 6.10 and section 6.11). For subjects who had been on SU medications prior to the DMR/Sham procedure, a review of dietary as well as glycemic and medication history will be performed to assess adequacy of their current SU dose and to provide further dosing recommendations, as needed.

5.4.3 Concomitant Medication

As outlined in Section 6.12, all concurrent medication reported by the subject will be recorded. Any changes in medication will be recorded on the medication log.

5.4.4 Adverse Events (AEs)

As outlined in Section 7.8, any AEs reported by or elicited from the subject, or dictated by blood tests or office evaluation, will be recorded in the eCRF.

5.5 Visit 5: Day 14 Telephone Call (+/-2 days)

At Day 14 post-procedure, the subject will be contacted via telephone; no office/clinic visit will be required. The following reminders will be given and information collected during the call:

5.5.1 Post-Procedure Diet Reminder

The subjects will be reminded to discontinue the specific 14-day post-procedure diet. As outlined in Section 6.7, subjects will return to a standard diabetic diet as tolerated, as outlined by the study nutritionist.

5.5.2 OAD and Rescue Medication Use, SMBG, and Glycemia Diary Review

The subject's Glycemia Diary will be reviewed by the study site personnel for OAD adherence, the addition of rescue medication for hyperglycemia, the occurrence of any hypoglycemia event, and SMBG levels (as outlined in Section 6.10 and section 6.11). For subjects who had been on SU medications prior to the DMR/Sham procedure, a review of dietary as well as glycemic and medication history will be performed to assess adequacy of their current SU dose and to provide further dosing recommendations, as needed until patient resumes to the pre-procedue SU dose based on investigator clinical judgment.

5.5.3 Concomitant Medication

As outlined in Section 6.12, all concurrent medication reported by the subject is recorded. Any changes in medication are recorded on the medication log.

5.5.4 Adverse Events (AEs)

As outlined in Section 7.8, any AEs reported by or elicited from the subject, or dictated by blood tests or office evaluation, will be recorded in the eCRF.

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

The following evaluations will be completed at the Week 4 Visit:

5.6.1 Body Weight, Blood Pressure & Targeted Physical Exam

As outlined in Section 6.2, weight and blood pressure will be measured in all subjects. A symptom-directed physical examination will be conducted if new signs or symptoms are reported by a subject. Abnormal findings noted at the previous physical exam will be reevaluated and any abnormal findings recorded.

5.6.2 Blood Analysis

As outlined in Section 6.3, subjects will have sufficient blood drawn to complete the standard blood analysis and forwarded to a central laboratory for analysis.

5.6.3 Lifestyle Counseling

As outlined in Section 6.5, a member of the nutrition staff will query the subjects regarding their adherence to a healthy lifestyle regimen, and provide them with advice about improving their diet and exercise regimen, if needed. Subjects will be reminded of the importance of a healthy lifestyle to blood glucose control.

5.6.4 OAD and Rescue Medication Use, SMBG, and Glycemia Diary Review

The subject's Glycemia Diary will be reviewed by the study site personnel for OAD adherence, the addition of rescue medication for hyperglycemia, the occurrence of any hypoglycemia event, and SMBG levels.

5.6.5 Management of Glycemia and Antidiabetic Medication

As outlined in Section 6.11, subjects will continue to take antidiabetic medication without any changes to the regimen unless rescue criteria are met.

5.6.6 Concomitant Medication

As outlined in Section 6.12, all concurrent medication reported by the subject will be recorded. Any changes in medication will be recorded on the medication log.

5.6.7 Adverse Events (AEs)

As outlined in Section 7.8, any AEs reported by or elicited from the subject, or dictated by blood tests or office evaluation, will be recorded in the eCRF.

5.6.8 Blinding Assessment

The subject will be asked about treatment assignment and the response will be recorded in the eCRF.

5.7 Visit 7: Week 8 (Day 56) Telephone Call (+/- 2 days)

At Week 8 post-procedure, the subject will be contacted via telephone; no office/clinic visit will be required. The following reminders will be given and information collected during the call:

5.7.1 OAD and Rescue Medication Use, SMBG, and Glycemia Diary Review

The subject's Glycemia Diary will be reviewed by the study site personnel for OAD adherence, the addition of rescue medication for hyperglycemia, the occurrence of any hypoglycemia event, and SMBG levels.

5.7.2 Management of Glycemia and Antidiabetic Medication

As outlined in Section 6.11, subjects will continue to take antidiabetic medication without any changes to the regimen unless rescue criteria are met.

5.7.3 Lifestyle Counseling

As outlined in Section 6.7, a member of the nutrition staff will query the subjects regarding their adherence to a healthy lifestyle regimen, and provide them with advice about improving their diet and exercise regimen, if needed. Subjects will be reminded of the importance of a healthy lifestyle to blood glucose control.

5.7.4 Concomitant Medication

As outlined in Section 6.12, all concurrent medication reported by the subject will be recorded. Any changes in medication will be recorded on the medication log.

5.7.5 Adverse Events (AEs)

As outlined in Section 7.8 any AEs reported by or elicited from the subject, or dictated by blood tests or office evaluation, will be recorded in the eCRF.

5.8 Visit 8: Week 12 (Day 84) Clinic Visit (+/- 7 days)

The following evaluations will be completed at the Week 12 Visit:

5.8.1 Body Weight, Blood Pressure & Targeted Physical Exam

As outlined in Section 6.2, weight and blood pressure will be measured in all subjects. A symptom-directed physical examination will be conducted if new signs or symptoms are reported by a subject. Abnormal findings noted at the previous physical exam will be reevaluated and any abnormal findings recorded

5.8.2 Blood Analysis

As outlined in Section 6.3, subjects will have sufficient blood drawn to complete the standard blood analysis and forwarded to a central laboratory for analysis.

5.8.3 Renal Function

As outlined in Section 6.5, urinary albumin and creatinine levels will be analyzed to determine the UACR for evaluation of kidney function. A urine sample will be collected (at the same time as the fasting blood sample) from the subject and forwarded to a central laboratory for analysis.

5.8.4 MRE

As outlined in Section 6.7, subjects will undergo a MRE.

5.8.5 Lifestyle Counseling

As outlined in Section 6.7, a member of the nutrition staff will query the subjects regarding their adherence to a healthy lifestyle regimen, and provide them with advice about improving their diet and exercise regimen, if needed. Subjects will be reminded of the importance of a healthy lifestyle to blood glucose control.

5.8.6 SF-36 Quality of Life Questionnaire

As outlined in Section 6.8, subjects will complete the SF-36 for a health status and QOL assessment.

5.8.7 PROMIS® Patient Reported Outcomes

As outlined in Section 6.9, subjects complete PROMIS® questionnaires to evaluate physical health.

5.8.8 OAD and Rescue Medication Use, SMBG, and Glycemia Diary Review

The subject's Glycemia Diary will be reviewed by the study site personnel for OAD adherence, the addition of rescue medication for hyperglycemia, the occurrence of any hypoglycemia event, and SMBG levels.

5.8.9 Management of Glycemia and Antidiabetic Medication

As outlined in Section 6.11, subjects will continue to take antidiabetic medication without any changes to the regimen unless rescue criteria are met.

5.8.10 Concomitant Medication

As outlined in Section 6.12, all concurrent medication reported by the subject will be recorded. Any changes in medication will be recorded on the medication log.

5.8.11 Adverse Events (AEs)

As outlined in Section 7.8, any AEs reported by or elicited from the subject, or dictated by blood tests or office evaluation, will be recorded in the eCRF.

5.8.12 Blinding Assessment

The subject will be asked about treatment assignment and the response will be recorded in the eCRF.

5.9 Visit 9: Week 15 (Day 105) Telephone Call (+/- 2 days)

At Week 15 post-procedure, the subject will be contacted via telephone; no office/clinic visit will be required. The following reminders will be given and information collected during the call:

5.9.1 OAD and Rescue Medication Use, SMBG, and Glycemia Diary Review

The subject's Glycemia Diary will be reviewed by the study site personnel for OAD adherence, the addition of rescue medication for hyperglycemia, the occurrence of any hypoglycemia event, and SMBG levels.

5.9.2 Management of Glycemia and Antidiabetic Medication

As outlined in Section 6.11, subjects will continue to take oral antidiabetic medication without any changes to the regimen unless rescue criteria are met.

5.9.3 Lifestyle Counseling

As outlined in Section 6.7, a member of the nutrition staff will query the subjects regarding their adherence to a healthy lifestyle regimen, and provide them with advice about improving their diet and exercise regimen, if needed. Subjects will be reminded of the importance of a healthy lifestyle to blood glucose control.

5.9.4 Concomitant Medication

As outlined in Section 6.12, all concurrent medication reported by the subject will be recorded. Any changes in medication will be recorded on the medication log.

5.9.5 Adverse Events (AEs)

As outlined in Section 7.8, any AEs reported by or elicited from the subject, or dictated by blood tests or office evaluation, will be recorded in the eCRF.

5.10 Visit 10: Week 18 (Day 126) Clinic Visit (+/- 7 days)

The following evaluations will be completed at the Week 18 Visit:

5.10.1 Body Weight, Blood Pressure & Targeted Physical Exam

As outlined in Section 6.2, weight and blood pressure will be measured in all subjects. A symptom-directed physical examination will be conducted if new signs or symptoms are reported by a subject. Abnormal findings noted at the previous physical exam will be reevaluated and any abnormal findings recorded.

5.10.2 Blood Analysis

As outlined in Section 6.3, subjects will have sufficient blood drawn to complete the standard blood analysis and forwarded to a central laboratory for analysis.

5.10.3 Lifestyle Counseling

As outlined in Section 6.7 a member of the nutrition staff will query the subjects regarding their adherence to a healthy lifestyle regimen, and provide them with advice about improving their diet and exercise regimen, if needed. Subjects will be reminded of the importance of a healthy lifestyle to blood glucose control.

5.10.4 OAD and Rescue Medication Use, SMBG, and Glycemia Diary Review

The subject's Glycemia Diary will be reviewed by the study site personnel for OAD adherence, the addition of rescue medication for hyperglycemia, the occurrence of any hypoglycemia event, and SMBG levels.

5.10.5 Management of Glycemia and Antidiabetic Medication

As outlined in Section 6.11, subjects will continue to take oral antidiabetic medication without any changes to the regimen unless rescue criteria are met.

5.10.6 Concomitant Medication

As outlined in Section 6.12, all concurrent medication reported by the subject will be recorded. Any changes in medication will be recorded on the medication log.

5.10.7 Adverse Events (AEs)

As outlined in Section 7.8, any AEs reported by or elicited from the subject, or dictated by blood tests or office evaluation, will be recorded in the eCRF.

5.11 Visit 11: Week 21 (Day 147) Telephone Call (+/- 2 days)

At Week 21 post-procedure, the subject will be contacted via telephone; no office/clinic visit will be required. The following reminders will be given and information collected during the call:

5.11.1 OAD and Rescue Medication Use, SMBG, and Glycemia Diary Review

The subject's Glycemia Diary will be reviewed by the study site personnel for OAD adherence, the addition of rescue medication for hyperglycemia, the occurrence of any hypoglycemia event, and SMBG levels.

5.11.2 Management of Glycemia and Antidiabetic Medication

As outlined in Section 6.11, subjects will continue to take oral antidiabetic medication without any changes to the regimen unless rescue criteria are met.

5.11.3 Lifestyle Counseling

As outlined in Section 6.7, a member of the nutrition staff will query the subjects regarding their adherence to a healthy lifestyle regimen, and provide them with advice about improving their diet and exercise regimen, if needed. Subjects will be reminded of the importance of a healthy lifestyle to blood glucose control.

5.11.4 Concomitant Medication

As outlined in Section 6.12, all concurrent medication reported by the subject will be recorded. Any changes in medication will be recorded on the medication log.

5.11.5 Adverse Events (AEs)

As outlined in Section 7.8, any AEs reported by or elicited from the subject, or dictated by blood tests or office evaluation, will be recorded in the eCRF.

5.12 Visit 12: Week 24 (Day 168) Clinic Visit (+/- 7days)

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

The following evaluations will be completed at the Week 24 Visit (with the exception of Endoscopic Assessment which can be completed within 7 days of the Week 24 Visit):

5.12.1 Body Weight, Blood Pressure & Targeted Physical Exam

As outlined in Section 6.2, weight and blood pressure will be measured in all subjects. A symptom-directed physical examination will be conducted if new signs or symptoms are reported by a subject. Abnormal findings noted at the previous physical exam will be reevaluated and any abnormal findings recorded

5.12.2 Blood Analysis

As outlined in Section 6.3, subjects will have sufficient blood drawn to complete the standard blood analysis and forwarded to a central laboratory for analysis.

5.12.3 ECG

As outlined in Section 6.4, a 12-lead ECG will be performed.

5.12.4 Renal Function

As outlined in Section 6.5, urinary albumin and creatinine levels will be analyzed to determine the UACR for evaluation of kidney function. A urine sample will be collected (at the same time as the fasting blood sample) from the subject and forwarded to a central laboratory for analysis.

5.12.5 Lifestyle Counseling

As outlined in Section 6.7 a member of the nutrition staff will query the subjects regarding their adherence to a healthy lifestyle regimen, and provide them with advice about improving their diet and exercise regimen, if needed. Subjects will be reminded of the importance of a healthy lifestyle to blood glucose control.

5.12.6 SF-36 Quality of Life Questionnaire

As outlined in Section 6.8, subjects will complete the SF-36 for a health status and QOL assessment.

5.12.7 PROMIS® Patient Reported Outcomes

As outlined in Section 6.9, subjects complete PROMIS® questionnaires to evaluate physical health.

5.12.8 OAD and Rescue Medication Use, SMBG, and Glycemia Diary Review

The subject's Glycemia Diary will be reviewed by the study site personnel for OAD adherence, the addition of rescue medication for hyperglycemia, the occurrence of any hypoglycemia event, and SMBG levels.

5.12.9 Management of Glycemia and Antidiabetic Medication

As outlined in Section 6.11, subjects continue to take all antidiabetic medication without any changes to the regimen unless rescue criteria are met. Subjects in the Sham treatment arm on SUs who are unblinded, and are offered and accept to undergo the DMR procedure, will be provided with specific peri-procedural instructions regarding their SU dosing (see Section 5.12.13).

5.12.10 Concomitant Medication

As outlined in Section 6.12, all concurrent medication reported by the subject will be recorded. Any changes in medication will be recorded on the medication log.

5.12.11 Adverse Events (AEs)

As outlined in Section 7.8, any AEs reported by or elicited from the subject, or dictated by blood tests or office evaluation, will be recorded in the eCRF. Subjects with an ongoing possibly and probably device and procedure related AEs reported at week 24 follow up visit will be followed until resolution. This will also also include AEs (signs and symptoms) reported during 24 week follow up period but without a definitive diagnosis and/or attribution of the cause at this visit.

5.12.12 For Subjects Treated with the DMR Procedure Only Endoscopy and Endoscopic Evaluation

A follow up endoscopic evaluation to visually examine the treatment site and adjacent tissues will be conducted after all Week 24 Visit assessments are complete and within 7 days of visit 12 / week 24. A video of the procedure will be obtained, as well as any Investigator notes detailing their observations.

Biopsy
During the 24 week follow-up endoscopy, ablation site biopsies will be taken to evaluate the mucosal tissue that has regrown post DMR procedure.

During the index DMR procedure, the endoscopist approximated the distance in centimeters from the papilla to the proximal edge of the first completed ablation. This distance was documented at the time of the procedure and will be available to the endoscopist during the follow-up endoscopy. Biopsies will be taken from within the first ablation zone whose length is defined as the proximal edge, as determined above, to a distance of 2.0 cm distal which corresponds to the length of the Revita™ Catheter ablation balloon. This technique will ensure biopsies are taken from a location that was previously ablated.

A total of 4 biopsies will be taken from the ablation zone, with one biopsy taken from each circumferential quadrant on the lumen. A single biopsy from the un-ablated tissue proximal to the papilla will serve as a control.
In addition, the Investigator will take biopsies in any ablated area where the tissue appears abnormal under endoscopic visualization.

Biopsies will be taken using large capacity, radial jaw forceps and placed in 10% formalin containers labeled with subject ID and sample location.

Samples will be embedded in paraffin, and thin samples of each biopsy will be stained (hematoxylin and eosin; trichrome) to assess mucosal regrowth, inflammation and fibrosis using a 0-4 ordinal scoring system. The following assessments will be made comparing the ablated biopsies to the control:

- Villous Formation
- Acute Inflammation
- Chronic Inflammation
- Fibrosis

The biopsy specimen will be analyzed at a central pathology laboratory in accordance with Good Laboratory Practice Regulations under the direction of a Board Certified Pathologist.

5.12.13 For Subjects Treated with the Sham Procedure

At the Week 24 Visit, all subjects initially treated with the Sham Procedure will have the same evaluations as the subjects in the DMR treatment group listed above, **except** for the 24 Week Follow-up endoscopy, endoscopic evaluation and biopsy. For subjects who accept the offer to crossover, the Endoscopy / DMR procedure will be scheduled within 21 days of this Week 24 Visit. During the time between the Week 24 Visit and the crossover to DMR (Visit 3C), medications should be held stable. Prior to the procedure, subjects who are on SU medication will be instructed by the site regarding specific pre- and post-procedure SU management. They will be asked to take half their regular dose of SUs the day before the procedure, and omit taking any SU the day of the procedure.

Note: Subjects that choose not to crossover from sham to DMR will be discontinued (withdrawn) from the study and the End of Study eCRFs will be completed.

5.13 Visit 3C: Crossover to DMR Visit (+21 days from Visit 12)

This visit is for Sham subjects only. The endoscopy and the DMR procedure will be completed at this visit. A video of the procedure will be obtained, as well as any Investigator notes detailing their observations.

Once a Sham subject is treated with the DMR procedure, these subjects complete follow-up study Visits 4 (Day 7) through 12 (Week 24) as described in the protocol in Sections 5.4 through 5.12 (which are referred to as Visits 4C – 12C for the Sham crossover group). These visits after the crossover to DMR include the exact same assessments as the initial visits and these crossover subjects will now be following the same visit schedule as a subject that was initially randomized to DMR.

Note: Subjects randomized to Sham who crossover to DMR but do not receive any ablations during the DMR procedure will have all clinical findings documented, and will be followed through the 4 week post crossover visit and then discontinued from the study.

5.14 COVID-19 Exceptions

Due to the COVID-19 pandemic, in-clinic assessments, follow up endoscopic evaluations, biopsies and crossover procedures may not be offered to subjects unless the following criteria are met:

- It is safe for subjects, site staff, and Sponsor Proctor (for crossover visits only) to travel to the study site during the given window
- The study site allows on-site clinical research activities and elective procedures

If both of these criteria are not met and subjects are unable to be seen on site, the study team will contact subjects via telephone to collect adverse events and concomitant medication changes through Week 24.

5.15 Unscheduled Visits

An unscheduled visit can occur at any time during the study. All unscheduled visits will be documented in the source documentation and in the eCRF.

5.16 Subject Withdrawal & Early Termination

All subjects initially randomized to the DMR procedure will be followed for 24 weeks post-procedure. All subjects initially randomized to the Sham procedure will be followed for 24 weeks, crossover to DMR and be followed for 24 weeks post crossover. 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 will be made by the investigational site to obtain a final data set from the subject, corresponding to data captured at Visit 12. 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. If an AE or SAE occurs that could affect the subject's safety or well-being, this should be documented in the eCRF as a reason for a subject's study participation discontinuation.
- Lost to Follow-Up: Unable to locate the subject despite documented attempts to notify via telephone, email or mail.
- 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, making all effort to obtain information about possible underlying AEs leading to the decision to withdraw from study participation).
- 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 documented in the eCRF. All AEs ongoing at time of study end will be followed up until resolution or deemed to be chronic or stable. Withdrawn subjects will not be replaced.

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 HCP may be asked to provide medical records about the subject's medical history. Specific parameters to be captured include:

- Demographic information, including date of birth, sex, race, and ethnicity
- Diabetes history, including duration, prior therapy, current therapy
- History of macrovascular complications: coronary heart disease, cerebrovascular disease, and peripheral arterial disease
- Microvascular complications: retinopathy, nephropathy, and neuropathy
- Concurrent health conditions
- Previous surgeries/treatments
- Physical exam findings with a focus specifically for T2D, including:
  - Vital signs: pulse, blood pressure

- Height, weight
- Fundoscopic exam
- Thyroid palpation
- Abdominal exam
- Heart and lung auscultation
- Deep tendon reflex and sensation (vibration, pinprick) assessment in distal lower extremities
- Skin examination

6.2 Body Weight, Blood Pressure & Targeted Physical Exam

Weight and blood pressure will be obtained in all subjects.

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

- Blood pressure will be measured in a sitting position in duplicate (in same arm) after 15 min of rest. Note: For Eligibility assessment, use the mean of 3 separate blood pressure measurements >180 mmHg (systolic) or >100 mmHg (diastolic).

A symptom-directed physical examination will be conducted if new signs or symptoms are reported by the subject. Abnormal findings noted at the previous physical exam will be reevaluated and any abnormal findings recorded.

6.3 Blood Analysis

Subjects will have sufficient fasting blood drawn to complete the following tests in a schedule as outlined in Appendix 1 & 2. As indicated in the table below, the test name will have the associated specific evaluations included.

All blood drawn for analysis should be performed after at least an 8-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	ALT

	AST Total Bilirubin Alkaline Phosphatase Ferritin
Pancreatic Enzymes	Amylase Lipase
Thyroid Stimulating Hormone (TSH)	Same
Fasting Lipid Panel	Total Cholesterol High Density Lipoprotein (HDL) Low Density Lipoprotein (LDL) Triglycerides
Fasting Plasma Glucose	Same
Glycosylated hemoglobin (A1c)	Same
Fasting C-Peptide	Same
Fasting Insulin	Same
H.pylori *(Screening Visit Only)*	Same

At the Screening visit, subjects with test results outside acceptable ranges that are indicative of an underlying condition that would compromise their participation in the study, based on protocol-specified Exclusion Criteria or the Investigator's expertise, will be excluded from the study and considered to be Screen Failures. All out-of-range laboratory values obtained during the course of the study will be deemed as clinically significant or not clinically significant by the investigator. Clinically significant values will be considered AEs and recorded as such on the eCRFs, as described in Section 7.8.

Blood samples will be analyzed at a central laboratory.

6.4 Electrocardiogram

A 12-lead ECG will be performed in a schedule as outlined in Appendix 1 & 2. Clinically relevant abnormal findings will be reported as AEs, if they are newly discovered after inclusion in the study.

6.5 Renal Function

Urinary albumin and creatinine levels will be obtained to evaluate renal function. A urine sample will be collected (at the same time as the fasting blood sample) from the subject and forwarded to a central laboratory for analysis. Analyses will include albumin, creatinine and albumin/creatinine ratio.

6.6 MRE

Subjects will undergo MRE as outlined in Appendix 1 & 2 at the Baseline (Visit 2) to evaluate the duodenum and at Week 12 (Visit 8) to assess the entire 10 cm length of treated duodenum for thermal injury. Clinically-relevant abnormal

findings will be reported as AEs, if they are newly discovered after inclusion in the study.

6.7 Lifestyle Counseling

Subjects will be provided with standard diabetic nutrition, healthy lifestyle and exercise guidance that is consistent with ADA standards at Screening, and from Baseline (Visit 2) up to Week 24 (Visit 12) to educate them on the importance of diet in relation to blood glucose control. Compliance with diet and lifestyle recommendations will be discussed with the subject throughout the study and specifically in the case of insufficient glycemic control. The details are provided in the Study Reference Manual.

6.8 SF-36 Quality of Life Questionnaire

Subjects will complete an assessment of health status and quality of life, the SF-36 Questionnaire, at Baseline, and Weeks 12 and 24. These measures rely upon patient self-reporting. The SF-36 asks 36 questions to measure functional health and well-being from the patient's point of view. It is a practical, reliable and valid measure of physical and mental health that can be completed in five to ten minutes.

6.9 PROMIS® (Patient-Reported Outcomes Measurement Information System)

Subjects will complete the PROMIS® at Baseline, 12 and 24 Week Visits. PROMIS® is a set of person-centered measures that will be used to evaluate and monitor physical health in subjects. For the purposes of this study, the gastrointestinal symptom domains were chosen including nausea/vomiting, gas/bloating, diarrhea and belly pain.

6.10 Subject Self-Monitoring of Blood Glucose (SMBG) and Glycemia Diary

Subjects will be provided with a Glycemia Diary, a home blood glucose meter and supplies for use at home during the study, and will be instructed in correct SMBG technique. Subjects will measure blood glucoses according to a pre-specified schedule, presented below, and record them in their Glycemia Diary.

- Except as indicated for the Post-Procedure Intensive Monitoring Phase (Days 0-14), all subjects will be required to test a fasting (pre-breakfast) and a pre-dinner blood glucose level using SMBG daily. In addition, they will perform more intensive monitoring of blood glucose, 4 times per day (once pre-breakfast [fasting] AND once before lunch, once before dinner, and once before bed), on at least 3 days on the week before each clinic visit and each telephone visit.

- On Days 0-14 following the DMR procedure (the Post-Procedure Intensive Monitoring Phase), subjects will be required to perform more intensive monitoring of blood glucose, 4 times per day (once pre-breakfast [fasting] AND once before lunch, once before dinner, and once before bed), every single day during this period.

- Subjects will be requested to monitor blood glucose levels with increased frequency whenever they experience any illnesses (eg, cold, flu), or have symptoms of hyper- or hypoglycemia.

Subjects will be instructed to bring their Glycemia Diary to the clinic at every study visit, and to scan/fax 7-day records to the site prior to each telephone visit.

While symptoms of hyper- or hypoglycemia can be variable across patients with diabetes, the symptoms outline below may typically be associated with abnormal blood glucose levels, and should prompt subjects to perform SMBG more frequently:

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

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

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

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

6.11 Management of Glycemia and Antidiabetic Medication

While the subjects are in the study, they will continue seeing their HCPs per their customary schedule, or as needed, for all non-glucose related medical issues. The management of the subjects' glycemic control will be carried out by the investigator at the study site, who will be guided by the hyperglycemia and hypoglycemia management guidelines as outlined in the protocol (Section 6.11.2). The investigator will keep the subjects' HCPs apprised of any diabetes medication changes, and may seek their input if needed. At the completion of the study, the subjects' HCPs will resume full management of their diabetes.

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

- Antidiabetic medication use
- SMBG values as recorded in the Glycemia Diary
- A1c levels
- Occurrence of hypoglycemia
- Symptomatic severe hyperglycemia

All study Investigators and study site personnel will be instructed in the importance of SMBG, Glycemia Diary review, and meticulous diabetes management with lifestyle counseling at the study visits, especially for subjects whose glucose values exceed accepted thresholds (i.e., >180 mg/dL [10.0 mmol/L]). The Investigator will be instructed to probe for factors that may contribute to inadequate glycemic control, such as:

- Compliance with concurrent diabetes therapies
- Compliance with diet and exercise guidelines
- Intercurrent disease

Subjects will fax/scan their Glycemia Diary results prior to the telephone contacts, and bring their Glycemia Diaries to every study visit. During these telephone and on-site visits, the SMBG levels recorded in the Glycemia Diary will be reviewed, and compliance with concurrent diabetes therapies and diet and exercise guidelines will be assessed. Additional lifestyle and nutritional counseling will be provided to educate subjects on the importance of diet and exercise in relation to blood glucose control.

Antidiabetic medication regime established during the Run-In Period will be continued through the index procedure without change, except for SU use, until the Week 24 visit (Visit 12), unless subjects meet the Study Exclusion criteria as outlined in Section 4.1.2, at the Baseline Visit (Post Medication Run-In, Visit 2) or unless they meet the on-treatment rescue therapy criteria as outlined below. Subjects on SU medications at study entry who qualify for the DMR/Sham procedure will be instructed to take half their usual dose of SUs the day before the DMR/Sham procedure, and no SU intake the day of the procedure. Following the procedure, subjects on SU medications will be instructed to restart their medicines in an incremental fashion (step-wise increase to pre-procedure dose) guided by how well their dietary intake is progressing (eg, tolerability of full soft diet, calorie intake), by their blood glucose levels as noted during their intense glucose monitoring efforts and investigator clinical judgment.

6.11.1 **Hyperglycemia Management**

If any 2 consecutive FPG values as determined by SMBG exceed the threshold limits outlined below, the subject will be called for an unscheduled visit as soon as possible.

The threshold values for rescue treatment will be defined as follows:

- Baseline up to Week 12: FPG > 220 mg/dL (12.2 mmol/L)
- Week 12 up to Week 24: FPG >200 mg/dL (11.1 mmol/L) or no improvement in A1c from Baseline
  - A confirmatory FPG is to be obtained by the local or central laboratory. If the confirmatory FPG exceeds the threshold value, the investigator will perform an assessment for rescue using the factors listed below:
  - Blood glucose absolute value compared to rescue threshold
  - Overall trajectory of FPG relative to run-in and baseline
  - Isolated incident vs a persistent elevation in blood sugar
  - Presence or absence of hyperglycemic symptoms
  - Presence or absence of an assignable cause of high blood sugar (e.g. intercurrent infection)

At Week 24, subjects who were in the sham-treated group and who accept the offer to crossover to the DMR procedure will be assessed by the investigator for rescue therapy based on the criteria above if they meet the threshold value.

The DMR-treated subjects will be offered rescue therapy at Week 24 if they have an HbA1c >8% or no improvement in A1c from baseline, and subsequently will be offered treatment escalation at 12-week intervals if their HbA1c levels exceed 8%.

At the beginning of their study participation, randomized subjects will be on 2 or 3 oral antidiabetic medications (OADs), one of which must be metformin. Protocol-specified guidance on escalation of treatment based on the above glycemic criteria, occurring at 12-week intervals, is outlined in following Table:

Hyperglycemia Rescue Therapy Guidelines:

On-Study Regimen	Dose Adequacy[1]	Rescue Regimen
Metformin + other OAD(s)	Submaximal metformin only	↑ metformin dose if tolerated
	Submaximal other OAD only[2]	↑ other OAD dose if tolerated
	Submaximal both	↑ metformin dose if tolerated; if not, ↑ other OAD dose if tolerated[2]
Metformin + other OAD(s)	Maximally tolerated	Add Liraglutide 1.2[3] mg subcutaneous (sc) daily[4]
Metformin, other OAD(s), Liraglutide 1.2 mg	Maximally tolerated OADs	↑Liraglutide to 1.8 mg sc daily

Refer to Appendix 3 Table 8.3 of the American Diabetes Association (ADA) Standard of Medical Care in Diabetes 2018 for the maximum approved daily dose of non-insulin glucose lowering agents.

[2] *If a subject is on submaximal SU dose, that dose can be maintained.*

[3] *The choice of Liraglutide as a rescue agent was made to ensure homogeneity for the treatment population and ensure maximum efficacy for patients failing two to three OADs.*

[4] *Investigators are advised to follow the package insert for Liraglutide, namely to start at 0.6mg sc daily for two weeks and then escalate to 1.2mg sc daily thereafter, if tolerated, to reduce the risk of GI side effects.*

Prior to starting Liraglutide rescue therapy, a careful GI history should be obtained and the presence of nausea, vomiting or diarrhea be recorded prior to the initiation of liraglutide treatment. Subjects who are not felt to be candidates for Liraglutide therapy based on the Investigator's judgement, or who do not tolerate the drug, may have an OAD that the subject is not taking (TZD or DPP-4 inhibitor or SGLT2 inhibitor or SU) added to their regimen, and prescribed as per labeled instructions. For rescue therapy with SUs, only glipizide or glimepiride use is allowed.

For subjects who may require more intensive diabetes management, investigators will be counseled to consider initiating insulin therapy if blood glucose is ≥300 mg/dL (16.7 mmol/L) or HbA1C 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. If subjects remain poorly controlled despite intensification therapy with insulin, they will be discontinued from the study.

6.11.2 **Hypoglycemia Management**

Hypoglycemia is the major limiting factor in the glycemic management of both T1D and T2D. Subjects entering the Screening Phase of the study will be identified as having T2D without 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). During study conduct, however, subjects may be at risk of experiencing hypoglycemia due to the combination of background antidiabetic medication use and procedure effects.

The International Hypoglycaemia Study Group (2017) has classified hypoglycemia as outlined in following Table:

Hypoglycemia Definition and Treatment Guidelines:

	Hypoglycemia 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

During the Run-in Phase (Screening through Procedure), hypoglycemia meeting the criteria outlined below will be exclusionary.

Hypoglycemia Criteria	Outcome
• Any severe hypoglycemic event, defined as hypoglycemia requiring third-party assistance; or • Any clinically significant hypoglycemic event, defined as self-monitored or laboratory plasma glucose level < 54 mg/dL (3.0 mmol/L); or • ≥ 2 glucose alert values ≤70 mg/dL (3.9 mmol/L) unless a clear correctable precipitating factor can be identified	• Immediate treatment of hypoglycemia • Subject exclusion from study

Hypoglycemia that occurs following randomization, whether noted with SMBG or due to symptoms, must be recorded in the Glycemia Diary and treated. 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 treatment, if SMBG shows continued hypoglycemia, the treatment should be repeated. Once SMBG-obtained value 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), such that it is available should it be needed.
Patients are instructed to contact the Investigative site as soon as possible for review of Glycemia Diary data and to assess if a change in glycemic therapy is required in case one of the following occurs:

1. any severe hypoglycemic episode
2. 2 or more previously unreported episodes of blood glucose ≤70 mg/dl

If a subject has symptoms suggestive of hypoglycemia, the subject should perform SMBG, and treat if indicated, as discussed regarding hypoglycemia management above (6.11.2). However, if it is not possible to obtain a confirmatory SMBG value in the setting of symptoms suggestive of hypoglycemia, the subject should assume the symptoms were due to hypoglycemia and should be treated. 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. Information on hypoglycemia will be transcribed from the diary onto the hypoglycemia eCRF page by the site. Because the analysis for hypoglycemia will be based on data recorded on the Hypoglycemia Reporting eCRF page and not the AE eCRF page, it is requested that the Investigator not report the hypoglycemic events on the AE eCRF page unless the hypoglycemia episode meets the criteria of an SAE. However, the Investigator is not prohibited from characterizing hypoglycemia as an AE. Any event of hypoglycemia reported as an AE will be cross-checked to ensure that the event is also reported on the Hypoglycemia Reporting eCRF page.

In the case of symptomatic hypoglycemia or severe hypoglycemia appropriate adjustment of antidiabetic therapy, such as a dose reduction / discontinuation of ongoing rescue medication or existing background therapy can be initiated. Reduction or discontinuation of ongoing rescue medication should be considered before a reduction in the dose of existing background therapy.

6.12 Concomitant Medications

All concomitant medications will be recorded at the Screening Visit. The use of ongoing and any new medications will then be noted at each following study visit. All medication use will be captured in the source documents and on the appropriate eCRF page. The following information will be 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; 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) Review

IRB approval is required for each institution participating in this clinical investigation. Investigators are responsible for obtaining and maintaining

approval of the study, including the subject consent forms and recruitment materials, by their institution's IRB. The IRB approved Informed Consent Form must be retained at the investigational site and made available for inspection.

The clinical site's IRB must meet all relevant regulatory requirements. The study protocol and ICFs will be reviewed by the IRB, and written approval from the committee must be received by Fractyl prior to enrolling subjects into the study. The protocol must be re-approved by the IRB upon receipt of amendments and annually, as local regulatory requirements require.

The Investigator is responsible for submitting all protocol changes and SAE reports to the IRB according to local procedures. At a minimum, all SAEs requiring an investigational device exemption safety report must be immediately reported.

In accordance with applicable local regulatory requirements, the Investigator may be obligated to provide periodic safety updates on the conduct of the study at his or her site and notification of study closure to the IRB. Such periodic safety updates and notifications are the responsibility of the Investigator and not of the Sponsor.

All relevant correspondence from the IRB will be forwarded by the respective study site to the Sponsor in a timely fashion.

7.3 Study Records

All information and data sent to Fractyl or their authorized representatives concerning subjects or their participation in this study are considered confidential. All data used in the analysis and reporting of this evaluation will be 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 Roster
- IRB approval letter(s) and approved informed consent(s) (including any revisions)
- Approved advertisements for subject recruitment (if applicable)
- Correspondence with the IRB
- 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.)

- IFU
- 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
- eCRF 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 eCRFs
- 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 subjects in compliance with GCP standards and all applicable federal, state, and local laws, rules and regulations related to the conduct of a clinical study. Investigator files containing all records and reports of the investigation should be retained for a minimum of two years or longer after approval of a marketing application, two years after records are no longer required to support marketing application, or at least 2 years have elapsed since the formal discontinuation of clinical development of the DMR procedure. 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. Notice of transfer should be submitted to the FDA not later than 10 working days after the Sponsor has been notified of the 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 (as required)	Within 24 hours of knowledge
Device Malfunction	Fractyl	Within 24 hours of knowledge
Subject death during the investigation	Fractyl and IRB	Within 24 hours of knowledge
Unanticipated Adverse Device Effect	Fractyl, IRB (as required)	Within 24 hours of knowledge
Subject withdrawal	Fractyl	Within 7 days of knowledge
Withdrawal of IRB/EC approval	Fractyl	Within 24 hours of knowledge
Deviation from investigational protocol	Fractyl, IRB (as required)	Within 7 days of knowledge
Informed consent not obtained from subject	Fractyl and IRB	Within 24 hours of knowledge
Annual Progress report	Fractyl and IRB	Within 1 month of annual IRB/Approval date
Final summary report	Fractyl, IRB (as required)	Within 3 months of study completion
Other information as requested by Fractyl, IRB	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, 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 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 consumable devices and all pieces of capital equipment 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 (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, 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 eCRFs
- Failure to obtain Informed Consent
- Failure to report SAEs within 24 hours of knowledge
- Loss of or unaccounted for device inventory
- Repeated protocol deviations
- Failure to enroll an adequate number of subjects

7.8 Adverse Event Reporting

7.8.1 **Adverse Events (AEs)**

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

- This definition includes adverse events related to the medical device of this investigation.
- This definition includes adverse events related to the procedures involved (any procedures in the clinical investigational plan)
- For adverse events involving “users or other persons”, this definition is restricted to adverse events related to the medical device of this investigation.

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Adverse events are classified and tabulated by relationship to procedure or device, severity, and body system. Serious Adverse Events (SAEs), deaths and Unanticipated Adverse Device Effects (UADEs) will be listed separately.

The following should not be recorded as AEs:

- Pre-planned procedure unless the condition for which the procedure was planned has worsened from the first study-related activity after the subject has signed the informed consent form.
- Pre-existing conditions found as a result of screening procedures. These should be recorded as medical history/concomitant illness.

Out-of-range laboratory values that are deemed clinically significant by the Investigator will be considered AEs and recorded as such on the eCRFs,

Adverse Event information will be recorded in the eCRF Adverse Event Form. AEs, SAEs and UADEs will be coded using MedDRA.

Adverse events are graded on a 3-point scale and reported as indicated on the eCRF. 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 IRB and FDA 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 starting after informed consent has been signed.

AEs that may result from the DMR System include those commonly associated with gastrointestinal endoscopy procedures, as well as device-related AEs: potential acute and chronic adverse consequences of the device-induced duodenal ablation treatment, or those resulting from device malfunction, device user error, selected materials, device design or device construction. Some AEs may be associated with both the procedure and the device. In addition, device malfunctions may occur which may or may not result in a device-related AE.

Potential AEs associated with the endoscopic procedure and sedation include the following:

- Abdominal cramps, discomfort, or pain
- Allergic or adverse reaction to sedation or anesthesia
- Abdominal bloating
- Cardiac or respiratory arrest
- Death
- Delayed gastric emptying
- Dental injury
- Difficulty swallowing
- Digestive tract injury or perforation
- Fever
- Gastrointestinal bleeding
- Headache
- Hyperglycemia
- Hypoglycemia
- Hypotension
- Hypoxia
- Impaired judgment or reactions
- Indigestion
- Infection
- Injury to esophagus
- Laryngospasm
- Mucosal injury to GI tract
- Nausea
- Pancreatitis

- Perforation
- Pneumoperitoneum
- Pulmonary aspiration
- Sore or irritated throat
- Vomiting

Potential AEs associated with the device include the following:

- Abcess formation
- Abdominal cramps, discomfort, or pain
- Allergic reaction to the device materials or methylene blue
- Death
- Delayed gastric emptying
- Diarrhea
- Digestive tract injury
- Duodenal stenosis
- Fever
- Gastric dumping syndrome
- Gastritis
- Gastrointestinal bleeding
- Hyperglycemia
- Hypoglycemia
- Infection
- Mucosal injury to GI tract
- Nausea
- Nutritional malabsorption
- Pancreatitis
- Perforation
- Stomach or duodenal obstruction
- Stricture
- Structural damage to the GI tract
- Thermal damage to the duodenum wall or surrounding structures
- Ulcer
- Vomiting

Device malfunctions that lead to device-related AEs include:

- Console delivers incorrect ablation time and temperature profile resulting in GI tract injury or perforation
- Hole in hot fluid catheter balloon resulting in leakage of hot fluid that results in GI tract injury or perforation
- Lost catheter component in the GI tract or wall that results in GI tract injury or perforation

Device malfunctions that may or may not result in device-related AEs include:

- Component degradation
- Device breakage
- Device disarticulation

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

The determination of whether an adverse event is classified as a SAE or UADE is based on the definitions contained in sections 7.8.2 and 7.8.3, taking into account the clinical judgment of the investigator.

7.8.2 **Serious Adverse Events (SAEs)**

A SAE is any untoward medical occurrence that:

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

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

This definition includes device deficiencies that might have led to a SAE if a) suitable action had not been taken or b) intervention had not been made or c) if circumstances had been less fortunate. These are handled under the SAE reporting system.

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

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

7.8.3 **Unanticipated Adverse Device Effect (UADE)**

An 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.

7.8.4 **Adverse Events of Special Interest**

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

As stated in Section 6.11.2, hypoglycemia, unless the hypoglycemia episode meets the criteria of an SAE, will not be recorded as an adverse event, but will be captured on the Hypoglycemia Reporting eCRF page. However, the Investigator is not prohibited from characterizing hypoglycemia as an AE. Any event of hypoglycemia reported as an AE will be cross-checked to ensure that the event is also reported on the Hypoglycemia Reporting eCRF page.

Prior to starting Liraglutide rescue therapy, a careful GI history should be obtained and the presence of nausea, vomiting or diarrhea be recorded prior to the initiation of liraglutide treatment. For episodes of diarrhea, time from the DMR (or Sham) procedure, as well as duration of episode, will be recorded. Characteristics of diarrhea (bloody, steatorrhea), and other clinical symptoms associated with diarrhea (eg, fever, abdominal pain) will also be recorded.

All episodes of abdominal pain, or nausea, or vomiting will be reported as separate AEs. If a subject experiences combined symptoms of pain, nausea and vomiting, each will be reported as a separate AE unless a clear medical diagnosis is determined, eg, viral gastroenteritis, and time from the DMR (or Sham) procedure, as well as duration of episode, will be recorded. The Investigator needs to assess the clinical state of the subject to ensure that potential obstruction or stenosis/stricture of the GI tract is not present. Three SAEs of duodenal stricture were reported early in the DMR clinical program, but there have been no occurrences after procedural and device modifications were implemented. Nevertheless, if symptoms persist (e.g. two weeks for mild symptoms, three days for moderate symptoms and 48 hours for severe

symptoms) or progress, an endoscopic evaluation is recommended but left to the discretion of the investigator.

For any episodes of gastrointestinal bleeding, time from the DMR (or Sham) procedure, as well as duration of episode, will be recorded. All episodes will be followed carefully to resolution. Additional laboratory tests or diagnostic tests should be done according to medical judgment depending on the clinical course.

If a subject experiences a fever (> 38° C) that occurs within 2 weeks of the DMR/Sham procedure, and persists for several days, efforts should be made to identify a cause for the fever, if possible. All additional symptoms associated with the fever (eg, rigors, abdominal pain, diarrhea) should be recorded.

7.8.5 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 Adverse Event Form and reported to the Sponsor.

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

Investigator Safety Reporting Requirements

SAEs 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. Information not available at the time of the initial report must be documented in the Adverse Event Form within 24 hours of receipt of the new information. Substantiating data such as relevant hospital or medical records and diagnostic test reports should also be submitted by scan/fax to the Sponsor.

An Investigator shall submit to the Sponsor and to the reviewing IRB a report of any UADE occurring during an investigation as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect.

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

Sponsor Safety Reporting Requirements

SAEs and UADEs will be reported to the FDA, in accordance with 21 CFR Part 812.

In the event of a UADE, Sponsor will immediately conduct an evaluation of a UADE, and report the results of such evaluation to FDA and to all reviewing IRB’s and participating investigators within 10 working days after the Sponsor first receives notice of the effect. Thereafter the Sponsor shall submit such additional reports concerning the effect as FDA requests.

All possibly and probably device and procedure related AEs (including SAEs/UADEs/AESIs) reported during 24 weeks follow up will be followed until resolution. This will also also include resolution of all AEs (signs and symptoms) reported upto 24 weeks for which there is not yet a definitive diagnosis and/or attribution of cause by the 24 weeks follow up visit.

7.9 Data Monitoring Committee (DMC)

A DMC will be convened for the study and assembled prior to subject enrollment. The group will be multidisciplinary and membership will include individuals not participating in the clinical study. The DMC members will act independently from both the Sponsor and the study investigators. The group will consist of an endoscopist, endocrinologist and a biostatistician. Full DMC details including structure, roles and responsibilities are included in the DMC Charter.

General responsibilities of the DMC include:

- Review and finalization of the DMC Charter
- Review of data during the trial regarding safety and regarding quality of trial conduct, including participant risk versus benefit, and other factors potentially affecting patient safety
- Monitoring of the quality of the treatment provided at individual sites by reviewing the occurrence of peri-procedural complications and major protocol violations
- Providing recommendations to the Sponsor about modifications in the protocol and/or continuation of the trial necessary to maintain the safety of the subjects

To maintain continuous blinding and study integrity, the safety analysis will be conducted by an independent statistician, and measures will be taken to ensure the validity of the data and integrity of the study's conduct. As part of the DMC Charter, the DMC will agree upon a set of stopping rules for the study, consistent with principles outlined in Section 7.9.1. A fundamental responsibility of a DMC is to make recommendations to the Sponsor concerning the continuation of the study: whether to continue the study as designed; other recommendations that might be made include study termination, study continuation with major or minor modifications, or temporary suspension of enrollment and/or study intervention until some uncertainty is resolved. The DMC will document its recommendations, and the rationale for such recommendations, in a form that can be reviewed by the Sponsor and then circulated, if and as appropriate, to IRBs, FDA, and/or other interested parties. In almost all cases, a DMC is advisory to the Sponsor; the Sponsor decides whether to accept recommendations to discontinue a trial.

7.9.1 **Stopping Rules**

The DMC may recommend termination or suspension of the study if any of the following predefined conditions are met:

- The DMC may terminate or suspend the study if an SAE resulting in death is possibly, probably, or definitely related to the investigational device and/or procedure
- The DMC may recommend termination of the study if an SAE that is probably or definitely related to the investigational device or the investigational procedure occurs at a true rate as determined by the lower 95% confidence bound of SAEs resulting in serious injury, permanent impairment of a body function or permanent damage to a body structure that is greater than 1%
- In addition, termination or suspension may be recommended for any other perceived safety concern based on clinical judgment, including but not limited to a higher than anticipated rate for device failures resulting in adverse events, or unexpected SAEs
- Treatment of the subjects will be paused if 6 subjects require escalation of their baseline antidiabetic medications or addition of another antidiabetic medication at any time following DMR treatment or sham procedure, while the DMC evaluates the data to consider whether treatments should continue

7.10 Clinical Events Committee (Adjudication Committee)

A clinical events committee (CEC) will be established to review important safety adverse events reported by trial investigators to determine whether the adjudication of severity and relatedness meets protocol-specified criteria.

The CEC will be composed of members covering necessary medical specialties (eg, gastroenterology, endocrinology) and device clinical trial experts. CEC members must disclose any potential conflicts of interest and must be independent of the Sponsor.

Information reviewed on each death, SAE, UADE, or AE of Special Interest may include laboratory, pathology and/or imaging data, autopsy reports, physical descriptions, and any other data deemed relevant. The CEC will be masked to the assigned study arm when performing their assessments. The importance of the CEC is in assessing Investigator attribution of causality to the randomized treatment (DMR or Sham) in instances when severity or causality assessments may be deemed subjective and/or require the application of a complex definition.

In their assessments, the CEC will be guided by the adverse events depicted in Section 7.8.1 as potential adverse events associated with sedation, endoscopy or the DMR procedure, or device-related adverse events associated with the DMR catheter and console, including device-related adverse events from the materials selected, device design or construction. While the CEC will use their judgment in adjudicating causality, general guidelines can be stated:

- If the adverse event is associated with sedation, it should be ascribed to the procedure
- If the adverse event is one that has been described with endoscopic procedures, it should be ascribed to both the device and the procedure
- If the adverse event is one that is rarely, if at all, associated with non-invasive endoscopic procedures, it should be ascribed to the device
- If the adverse event is one that has been identified in the protocol as a potential device-related adverse event, it should be ascribed to the device

The relationship of an adverse event to the device and to the procedure is to be assessed by the Investigator utilizing the criteria outlined in Section 7.8.1, Study Procedure and Device Relationship. The CEC will review each causality assessment to ensure that the causality meets these protocol-specified criteria.

Only events that have been adjudicated will be used in the DMC safety assessments to guide the DMC decision regarding study continuation. The CEC will work in accordance with written guidelines included in the CEC Charter describing in details the composition, tasks, responsibilities and work processes of the Committee.

The CEC will not share responsibility with DMC for evaluating interim comparisons; however, their assessments (performed at frequent intervals throughout the trial with results incorporated into the database in a timely manner) will help to ensure that the data reviewed by DMC are as accurate and free of bias as possible.

8 Data Management and Statistical Considerations

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 eCRF completion is the responsibility of Fractyl. To ensure uniform data collection and protocol compliance, Fractyl-appointed clinical monitors will review the clinical protocol, techniques for the identification of eligible subjects, and instructions on in-hospital/office visit data collection with the study site research coordinators. This will be completed before or in conjunction with site initiation.

8.1.2 Electronic Case Report Forms (eCRFs)

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 will provide his/her electronic signature on the appropriate eCRFs in compliance with local regulations. A written signature on printed eCRFs will also be 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.

eCRFs must be 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 eCRFs 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 laws 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 will be verified by a Fractyl appointed monitor at the site at regular intervals throughout the study. To this end, the investigator must permit inspection of the study files, subject eCRFs, and subject medical records by Fractyl-appointed monitors and authorized government agencies, as indicated.

The study will be monitored according to applicable provisions of Fractyl or designee's Monitoring Procedures, and in conformance with Good Clinical Practices. Study monitors must be qualified by training and experience.

Monitoring will include 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 will be monitored to ensure that potential adverse trends are quickly identified allowing immediate corrective action. The monitor's duties will include: on-site visits, observation of treatment with the study devices and review of study documents and results.

The study monitor will review/verify IRB approvals, Informed Consent documents, source documents and eCRFs. Visual and/or electronic data review will be performed by the study monitor to identify possible data discrepancies. The study monitor(s) will verify the data entered into the eCRFs against hospital records, medical history, or other source documents to ensure accuracy and

completeness of the data. Manually generated and/or automatic queries will be created in the EDC system and issued to the site for appropriate response. Site staff will be responsible for resolving all queries in the database.

8.2 Statistical Considerations

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

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

8.2.1 General Considerations

While this protocol does specify primary and safety endpoints, these are not meant to define subject and study success. Instead, the results of this evaluation will be used to establish the safety and efficacy profile of the DMR procedure and to evaluate the effect size for powering future clinical investigations.

Nominal and ordinal variables for each time period will be presented using frequencies and percent of patients in each category. Interval and ratio continuous variables for each time period will be presented using means and standard deviations, median, quartiles, and minimum and maximum. For variables collected at multiple follow-up time periods, tables which include change from baseline (where baseline is defined as last measurement prior to attempted treatment with DMR) will be presented at each follow-up visit.

Distributions of each continuous variable will be assessed prior to analysis and examined for normality. Data with interval or ratio scales to be analyzed that are not normally distributed will be analyzed using non-parametric statistics. Statistical tests will be performed using two-sided significance levels of 5% unless otherwise specified.

The primary analysis phase is the first 24 weeks of the randomized treatment phase. Descriptive statistics on variables collected during the Medication Run-In phase will also be presented for completeness.

8.2.2 Determination of Sample Size

Up to 6 study sites will randomize a maximum of 9 subjects in a 2:1 randomization scheme (DMR:Sham). Sample size determination is based on the nature of this pilot study and not statistical considerations. The study is not powered to show statisticial significance.

8.2.3 Analysis Populations

Study Population: The study population includes all subjects consented at the site. Within this population there are Screened, Medication Run In, Intent-to-Treat, As-Treated and Safety populations.

Intent-to-Treat (ITT): The ITT population includes all subjects who were randomized after the Medication Run-In phase. This is the secondary analysis population for efficacy (no imputation will be made for missing data, given the nature of the study; i.e., analysis on this population will be performed using only available data). Subjects will be analyzed under the treatment to which they were randomized.

As-Treated (AT): The subset of ITT subjects who received at least one ablation or undergo the randomized sham procedure. This is the primary population for efficacy. No imputation will be made for missing data. Subjects will be analyzed under the treatment received.

Week 24 Per Protocol Population: The PP population includes all subjects in the AT population who did not have any major protocol deviations that could affect the assessment of efficacy and had their Week 24 study visit within the protocol-specified window. Subjects will be analyzed under the treatment received.

Safety: This population includes all subjects in whom sham or DMR was attempted. Subjects will be analyzed according to the treatment received.

8.2.4Demographic and Baseline Characteristics

Demographic and baseline data will be summarized using summary statistics of sample size, mean, standard deviation, median, quartiles, min and max for continuous variables and proportions and frequency of patients for categorical values. Demographics will be presented for the following analysis populations:

3. The Medication Run-In
4. ITT overall and by-randomized treatment group
5. AT overall and by-actual treatment group

8.2.5 Safety Analysis

All safety data will be displayed and analysed using descriptive statistical methods. No formal inferential analysis is planned for safety comparisons. The primary safety endpoint is proportion of subjects experiencing device or procedure related SAEs or UADEs through 24 Weeks following start of DMR or sham treatment. These will be presented overall and by system organ class and preferred term (PT). This will be conducted on the Safety analysis set overall and by actual treatment group. Subjects who experience more than one event in a given System Organ Class (SOC) and PT will be counted once within that SOC

and PT. The total number of events and the number and percentage of subjects with each event will be reported.

The remaining safety analyses discussed below will be carried out for the following sets within the Safety analysis population:

1. Safety population through 24 weeks post-randomization, by treatment group received at start of study (DMR or sham, depending on the treatment the patient actually received) and overall.
2. Safety population through 24 weeks post-DMR combined populations; this will include the first 24 weeks of the study for patients receiving DMR from the start of the study, and weeks 24-48 post crossover for patients switching from sham-to-DMR. Results will be presented separately for patients originally receiving DMR, for patients originally receiving Sham and receiving DMR at week 24, and for all patients combined receiving DMR at start of the study or at Week 24.

Clinical Laboratory Tests and Vital Signs: Descriptive statistics (sample size, mean, standard deviation, median, quartiles, minimum and maximum) of observed measurement at each visit and of the change from baseline (baseline is defined as the last measurement prior to DMR procedure) to each visit will be presented for each vital sign and laboratory variable. Listings of abnormal and/or clinically significant findings/values will be presented for each laboratory and vital sign variable.

Duodenal biopsy sample assessment of histological evidence of mucosal regrowth, inflammation and fibrosis will be summarized descriptively. Occurrence of severe fibrosis or inflammation from ablated area duodenal biopsy will be compared to non-ablated control sample.

Adverse Events: AEs, SAEs and UADEs will be coded using MedDRA. Treatment Emergent AEs, SAEs and UADEs are defined as events starting or worsening after start of DMR (or sham, if applicable). The number and percent of patients with Treatment Emergent AEs, SAEs and UADEs will be summarized overall and by primary SOC and preferred term (PT). Subjects who experience more than one event in a given SOC and PT will be counted once within that SOC and PT. Detailed listings of subjects that experience AEs and SAEs will be provided.

The number and percent of subjects with treatment emergent AEs, UADEs and SAEs will be further presented by severity and by relationship to the device or procedure. In tabulating the severity of AEs on a per subject basis, the greatest severity will be assigned to a subject should there be more than one occurrence of the same AE with different reported severities. Relationship will be categorized as unrelated, possibly, probably and definitely related. The highest level of

association will be reported for subjects with different relationships for the same AE.

The Hypoglycemia Reporting eCRF page will collect time of event, blood glucose value, symptoms if present, treatment, and duration. The incidence and event rates of hypoglycemia will be assessed based on the severity of the hypoglycemia: severe hypoglycemic event, defined as hypoglycemia requiring third-party assistance; or any clinically significant hypoglycemic event, defined as self-monitored or laboratory plasma glucose level < 54 mg/dL (3.0 mmol/L); or glucose alert values ≤70 mg/dL (3.9 mmol/L).

Episodes of diarrhea will be recorded both as events, and as incidence.

8.2.6 Effectiveness Analysis

Primary Efficacy Endpoint:
The primary efficacy endpoint is change in A1c at 24 Weeks. The analyses will be carried out on the AT analysis population (primary) ,the ITT analysis population, and the Week 24 PP (per-protocol) population. Descriptive statistics (mean, standard deviation, median, quartiles, minimum and maximum, and two-sided 95% confidence interval of the mean) of change in A1c will be presented by randomized treatment group (DMR vs. sham) for the ITT population and by actual treatment group for the AT and PP populations. Significance testing and statistical modeling will be omitted due to the small sample size.

Secondary Efficacy Endpoints:
(i) A1c change from baseline to Week 24 by visit over time, DMR vs. Sham
(ii) Fasting plasma glucose (FPG) change from baseline to Week 24, DMR vs. Sham
(iii) FPG change from baseline to Week 24 by visit over time, DMR vs. Sham
(iv) Urine Albumin Creatinine Ratio (UACR) change from baseline to Week 24, DMR vs. Sham
(v) Alanine Aminotransferase (ALT) and Aspartate Aminotransferase (AST) change from baseline to Week 24, DMR vs. Sham

The above secondary endpoints will be analyzed on the same analysis populations and the same manner as the primary efficacy endpoint.

Additional Endpoints of Interest:
The following are the additional endpoints of interest. They will be analyzed for (a) the ITT, AT, and PP subjects randomized to receiving DMR; (b) for the ITT, AT, and PP subjects switching from Sham to DMR at Week 24; and for (c) ITT, AT, amd PP subjects in (a) and (b) combined. Baseline is defined as the last measurement taken prior to the DMR procedure.

(i) A1c change from Week 24 (pre-DMR) in Sham cross-over group to Week 48

(ii) FPG change from Week 24 (pre-DMR) in Sham cross-over group to Week 48
(iii) Short Form (36) Health Survey Version 2 (SF-36) change from baseline at Week 24 (pre- assessments and endoscopy) vs Sham
(iv) Patient-Reported Outcomes Measurement Information System (PROMIS®) change from baseline at Week 24 (pre- assessments and endoscopy) vs Sham

For each endpoint, descriptive statistics (mean, standard deviation, median, quartiles, minimum and maximum, and two-sided 95% confidence interval of the mean) will be presented.

8.2.7 Handling of Missing Data

Missing data within this subject cohort is expected to occur at a low rate. All efforts will be made to prevent the occurrence of missing data. Site training and regular monitoring will help to minimize missing data. Due to the sample size and nature of this pilot study, there will be no imputation of missing data. In other words, analyses will be based only on available data.

In the clinical study report, the number and proportion of ITT subjects who were in compliance through Week 24 at each follow-up visit will be presented. The number and percent of ITT subjects who prematurely withdraw from the study will be tabulated overall and by reason for withdrawal. This will be performed by randomized treatment group and overall.

8.2.8 Analyses on Medication Run In Phase

The number and percent of patients with adverse events occurring during the Run-In phase will be presented overall and by SOC and PT. Descriptive statistics of end-of-run-in-phase A1c for all Medication Run-In subjects will be presented.

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Appendix 1: Schedule of Assessments – DMR Cases

Visit #	Visit	*Visit Window / Intervention*	Informed Consent	History & Full PE	Body Weight & Targeted PE	Pregnancy Test (if applicable)	Blood Analysis	H.pylori Test	ECG	Renal Function	MRE	Endoscopic Evaluation	Subject Randomization & Enrollment	DMR Procedure	Biopsy	Blinding Assessment	Lifestyle Counseling	SF-36 Questionnaire	PROMIS® Patient Reported Outcome	Self-Monitoring Blood Glucose/ Glycemia Diary	Adverse Events	Medication Use@
1	Screening (Pre Run-In)		X	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@
3	Procedure (DMR)	*Max is 21 days from Baseline Visit*										X	X	X			¥				X	X@
4	Day 7 Call	*+/- 2 days*															**			X	X	X@
5	Day 14 Call	*+/- 2 days*															**			X	X	X@
6	Week 4 (28 Day)	*+/- 7 days*			X		X									X	X			X	X	X
7	Week 8 Call (56 Day)	*+/- 2 days*															X			X	X	X
8	Week 12 (84 Day)	*+/- 7 days*			X		X			X	X					X	X	X	X	X	X	X
9	Week 15 Call (105 Day)	*+/- 2 days*															X			X	X	X
10	Week 18 (126 Day)	*+/- 7 days*			X		X										X			X	X	X
11	Week 21 Call (147 Day)	*+/- 2 days*															X			X	X	X
12	Week 24 (168 Day)	*+/- 7 days*			X		X		X	X		X#			X		X	X	X	X	X	X

& for the purpose of eligibility, Mean of 3 separate blood pressure measurements >180 mmHg (systolic) or >100 mmHg (diastolic), for other Blood Pressure assessments it will be measured in a sitting position in duplicate (in same arm) after 15 min of rest
**Provide diary & glucose meter to the subject*

@Patients using SU will be asked to adjust their SU intake based on section 5.3.1

#A follow up endoscopic evaluation to visually examine the treatment site and adjacent tissues will be conducted after unblinding and within 7 days of visit 12 / week 24

¥The 14-day post procedure diet reviewed with the subject

***Lifestyle Counseling discussions during phone calls at Day 7 & 14are conducted by the study coordinator in the form of reminders for the subjects and do not need to be conducted by a member of the nutrition staff*

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

Appendix 2: Schedule of Assessments – Sham Cases

Visit #	Visit	*Visit Window / Intervention*	Informed Consent	History & Full PE	Body Weight & Targeted PE	Pregnancy Test (if applicable)	Blood Analysis	H.pylori Test	ECG	Renal Function	MRE	Endoscopic Evaluation	Subject Randomization & Enrollment	Sham / Crossover DMR Procedure	Biopsy	Blinding Assessment	Lifestyle Counseling	SF-36 Quality of Life Questionnaire	PROMIS® Patient Reported Outcome	Self-Monitoring Blood Glucose/ Glycemia Diary	Adverse Events	Medication Use@
1	Screening (Pre Run-In)		X	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@
3	Procedure (DMR)	*Max is 21 days from Baseline Visit*										X	X	X			¥				X	X@
4	Day 7 Call	*+/- 2 days*															**			X	X	X@
5	14 Day Call	*+/- 2 days*															**			X	X	X@
6	Week 4 (28 Day)	*+/- 7 days*			X		X									X	X			X	X	X
7	Week 8 Call (56 Day)	*+/- 2 days*															X			X	X	X
8	Week 12 (84 Day)	*+/- 7 days*			X		X			X	X					X	X	X	X	X	X	X
9	Week 15 Call (105 Day)	*+/- 2 days*															X			X	X	X
10	Week 18 (126 Day)	*+/- 7 days*			X		X										X			X	X	X
11	Week 21 Call (147 Day)	*+/- 2 days*															X			X	X	X
12	Week 24 (168 Day)	*+/- 7 days*			X		X		X	X							X	X	X	X	X	X
3C	Crossover to DMR	*Within 21 days from Week 24*										X		X			¥				X	X
4C	Crossover Day 7 Call	*+/- 2 days*															**			X	X	X
5C	Crossover Day 14 Call	*+/- 2 days*															**			X	X	X
6C	Crossover Week 4 (28 Day)	*+/- 7 days*			X		X										X			X	X	X
7C	Crossover Week 8 Call	*+/- 2 days*															X			X	X	X

Visit #	Visit	*Visit Window / Intervention*	Informed Consent	History & Full PE	Body Weight & Targeted PE	Pregnancy Test (if applicable)	Blood Analysis	H.pylori Test	ECG	Renal Function	MRE	Endoscopic Evaluation	Subject Randomization & Enrollment	Sham / Crossover DMR Procedure	Biopsy	Blinding Assessment	Lifestyle Counseling	SF-36 Quality of Life Questionnaire	PROMIS® Patient Reported Outcome	Self-Monitoring Blood Glucose/ Glycemia Diary	Adverse Events	Medication Use@
	(56 Day)																					
8C	**Crossover Week 12 (84 Day)**	*+/- 7 days*			X		X			X	X						X	X	X	X	X	X
9C	**Crossover Week 15 Call (105 Day)**	*+/- 2 days*															X			X	X	X
10C	**Crossover Week 18 (126 Day)**	*+/- 7 days*			X		X										X			X	X	X
11C	**Crossover Week 21 Call (147 Day)**	*+/- 2 days*															X			X	X	X
12C	**Crossover Week 24 (168 Day)**	*+/- 7 days*			X		X		X	X								X	X	X	X	X

& for the purpose of eligibility, Mean of 3 separate blood pressure measurements >180 mmHg (systolic) or >100 mmHg (diastolic), for other Blood Pressure assessments it will be measured in a sitting position in duplicate (in same arm) after 15 min of rest

**Provide diary & glucose meter to the subject*

@Patients using SU will be asked to adjust their SU intake based on section 5.3.1

¥The 14-day post procedure diet reviewed with the subject

***Lifestyle Intervention discussionsduring phone calls at Day 7 & 14 are conducted by the study coordinator in the form of reminders for the subjects and do not need to be conducted by a member of the nutrition staff*

Note: Subjects randomized to Sham who crossover to DMR but do not receive any ablations during the DMR procedure will be followed through the 4 week post crossover visit and then discontinued from the study.

Note: Subjects that choose not to crossover from sham to DMR will be discontinued from the study and the End of Study CRFs will be completed.

Appendix 3: Maximum Approved Daily Dose of Non-Insulin Glucose Lowering Agents

ADA Standards of Medical Care in Diabetes 2018[43]

Table 8.3—Median monthly cost of maximum approved daily dose of noninsulin glucose-lowering agents in the U.S.

Class	Compound(s)	Dosage strength/product (if applicable)	Median AWP (min, max)†	Median NADAC (min, max)†	Maximum approved daily dose*
Biguanides	• Metformin	500 mg (IR)	$84 ($4, $93)	$2	2,000 mg
		850 mg (IR)	$108 ($6, $109)	$3	2,550 mg
		1,000 mg (IR)	$87 ($4, $88)	$2	2,000 mg
		500 mg (ER)	$89 ($82, $6,671)	$5 ($5, $3,630)	2,000 mg
		750 mg (ER)	$72 ($65, $92)	$5	1,500 mg
		1,000 mg (ER)	$1,028 ($1,028, $7,214)	$539 ($539, $5,189)	2,000 mg
Sulfonylureas (2nd generation)	• Glyburide	5 mg	$93 ($63, $103)	$17	20 mg
		6 mg (micronized)	$50 ($48, $71)	$12	12 mg (micronized)
	• Glipizide	10 mg (IR)	$75 ($67, $97)	$4	40 mg (IR)
		10 mg (XL)	$48	$16	20 mg (XL)
	• Glimepiride	4 mg	$71 ($71, $198)	$7	8 mg
Meglitinides (glinides)	• Repaglinide	2 mg	$659 ($122, $673)	$40	16 mg
	• Nateglinide	120 mg	$155	$56	360 mg
Thiazolidinediones	• Pioglitazone	45 mg	$348 ($283, $349)	$5	45 mg
	• Rosiglitazone	4 mg	$387	$314	8 mg
α-Glucosidase inhibitors	• Acarbose	100 mg	$104 ($104, $106)	$25	300 mg
	• Miglitol	100 mg	$241	N/A††	300 mg
DPP-4 inhibitors	• Sitagliptin	100 mg	$477	$382	100 mg
	• Saxagliptin	5 mg	$462	$370	5 mg
	• Linagliptin	5 mg	$457	$367	5 mg
	• Alogliptin	25 mg	$449	$357	25 mg
Bile acid sequestrants	• Colesevelam	625 mg tabs	$713	$570	3.75 g
		1.875 g suspension	$1,426	$572	3.75 g
Dopamine-2 agonists	• Bromocriptine	0.8 mg	$784	$629	4.8 mg
SGLT2 inhibitors	• Canagliflozin	300 mg	$512	$411	300 mg
	• Dapagliflozin	10 mg	$517	$413	10 mg
	• Empagliflozin	25 mg	$517	$415	25 mg
GLP-1 receptor agonists	• Exenatide	10 μg pen	$802	$642	20 μg
	• Lixisenatide	20 μg pen	$669	N/A††	20 μg
	• Liraglutide	18 mg/3 mL pen	$968	$775	1.8 mg
	• Exenatide (extended release)	2 mg powder for suspension or pen	$747	$600	2 mg**
	• Albiglutide	50 mg pen	$626	$500	50 mg**
	• Dulaglutide	1.5/0.5 mL pen	$811	$648	1.5 mg**
Amylin mimetics	• Pramlintide	120 μg pen	$2,336	N/A††	120 μg/injection†††

ER and XL, extended release; IR, immediate release. †Calculated for 30-day supply (AWP or NADAC unit price × number of doses required to provide maximum approved daily dose × 30 days); median AWP or NADAC listed alone when only one product and/or price. *Utilized to calculate median AWP and NADAC (min, max); generic prices used, if available commercially. ††Not applicable; data not available. **Administered once weekly. †††AWP and NADAC calculated based on 120 μg three times daily.