Safety and efficacy of hydrothermal duodenal mucosal resurfacing in patients with type 2 diabetes: the randomised, double-blind, sham-controlled, multicentre REVITA-2 feasibility trial

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Supplementary Material

Supplemental Methods

Trial design and oversight

A study monitor reviewed data collection forms as they were received from the study sites to assure there were no missing or incorrect data. Missing or incorrect data were queried and corrected in the database. Site re-training took place as required to ensure compliance with the protocol.

The study employed a data monitoring committee (DMC) to evaluate serious adverse events as well as to establish stopping rules to ensure continued safety monitoring. Employing an independent body to oversee evaluation of device and procedure adverse event relatedness provided added validity to the assessment of study safety endpoints and reduced the potential bias a sponsor might have completing the adjudication process on their own.

Post-procedure management

Patients who met preliminary eligibility criteria completed a minimum 4-week oral anti-diabetic medication run-in period to establish stable baseline glycaemia and participated in medication compliance and nutritional counselling. These patients then underwent an endoscopic evaluation under general anaesthesia or conscious sedation to confirm the absence of anatomical abnormalities or pathological oesophageal-gastric-duodenal alterations preventing their eligibility to participate in the trial (see protocol).

Following hospital discharge after DMR or sham procedure, patients were provided with continued nutritional counselling on the importance of diet in blood glucose regulation and were prescribed a progressive diet for 2 weeks (clear liquids on days 1–3, pureed foods on days 4–6, and soft foods on days 7–14) prior to resuming their normal diet. Patients were instructed to

record hypoglycaemic and hyperglycaemic events in a glycaemia diary. Patients were instructed to continue taking their prescribed oral diabetic medications from the start of the run-in period through week 24; however, if a patient experienced a hypoglycaemic or hyperglycaemic event, then changes in their antidiabetic medications were considered. Patients in the DMR group were followed up per protocol for 48 weeks; whereas patients in the sham group were followed up for 24 weeks and then offered the opportunity to cross over to undergo the DMR procedure. Crossover patients were followed up for an additional 24 weeks post-DMR.

Statistical Analysis

Sample Size Calculation

Assumptions of effect size for the primary efficacy endpoint of change from baseline at 24 weeks in HbA1c in the treatment arm are derived from the REVITA-1 study (see protocol in supplementary appendix). The treated subjects saw a mean change difference in HbA1c of –1.0 at 24 weeks with a standard deviation of 1.0. Based on previous experience, the estimated mean (± SD) sham effect at 24 weeks is –0.3 ± 1.0. To derive assumptions of effect size for the primary efficacy endpoint of absolute change from baseline at 12 weeks for MRI-PDFF in patients with baseline MRI-PDFF > 5%, we assumed the effect of DMR would be less pronounced than that of very low calorie diet[30] since we did not have previous experience with MRI-PDFF. Therefore, we assumed a difference between treatment and sham MRI-PDFF means of 4·0% and a standard deviation assumption of 6·5% per treatment group and this was further confirmed by the effect size on MRI-PDFF in the DRM arm sees in the Revita-2 training case set. Under (a) the assumption of a difference in mean change in HbA1c between treatment and control of 0·7 at 24 weeks with equal variance in both groups (standard deviation of 1·0) of the REVITA-2 study; (b) the assumption of a difference in mean change in MRI-PDFF between treatment and control of 4·0 at 12 weeks and a standard deviation of 6·5 per treatment group;

(c) approximately 3% of randomized subjects will not be evaluable for HbA1c and approximately 70% of randomized subjects will have baseline MRI-PDFF >5% and be evaluable for 12-week MRI-PDFF; and (d) the correlation between the two primary endpoints is 0 or very small, then 90 randomized subjects (45 per group) provides at least 90% power that the benefit of treatment over sham will be found for at least one primary endpoint using the Hochberg procedure controlling the experiment wise significance level at a one-sided 0·05 value.[21]

Intention-to-treat and per-protocol analyses

The primary analysis for each endpoint used an ANCOVA model and adjusted for the baseline value of the outcome, and the difference between the screening and baseline value of the outcome for only the HbA1c endpoint. Secondary continuous endpoints measured at a given time point in the randomisation phase were tested comparatively using an ANCOVA model and adjusted for the baseline value of the outcome, and the difference between the screening value and baseline value of the outcome (for endpoints where the screening value is available).

Missing data were imputed using multiple imputation for primary outcomes and last rank carried forward for secondary outcomes. Missing data were not imputed for exploratory endpoints. Values post-rescue medication use were set to missing for primary and secondary endpoints. If the baseline value was missing for a given variable and patient, the screening value was used in its place prior to calculating the descriptive statistics. Differences in baseline demographics were assessed between treatment groups using two-sided p values based on the Mann-Whitney U test for continuous variables to address non-normality and chi-squared test (or Fisher's exact test, when appropriate) for categorical variables. Treatment differences were assessed using one-sided p value based on an analysis of covariance model (at a one-sided 0.05 significance level).

For the analyses that are compared between treatments over time (i.e., the treatment comparison is not just at one time point such as 24 weeks, but where the treatments are compared at all visit time points simultaneously), a mixed-model repeated measures approach was used to compare treatments regarding the median outcome over time (the patient was treated as a random effect), region (the baseline value of the outcome measure), and the difference between the screening and baseline value of the outcome was used as a covariate. An unstructured, within-patient covariance structure was assumed; if the model did not converge, a compound symmetry within-patient covariance structure was assumed.

Assessments of normality and homogeneity

A normality assessment was prespecified in the statistical analysis plan (SAP) for primary and secondary endpoints to assess whether each variable was normally distributed. Normality was assessed by testing whether the residuals of the outcome for both primary and secondary endpoints, after adjusting for baseline variables, was normally distributed or not. All endpoints except for magnetic resonance imaging proton density fat fraction (MRI-PDFF) were also adjusted for the change from screening to baseline values. A residual was defined as the difference between an observed value and the predicted value. The normality assessment was done both visually by looking at Q-Q plots and histograms of the residuals and through a formal hypothesis test—the Shapiro-Wilk test ($p<0.05$ indicates variables are not normally distributed). No imputation was done to test for normality. If either visual inspection or the Shapiro-Wilk test indicated that variables were not normally distributed, missing data were imputed by multiple imputation on the rank values (modified ridit scores) for primary endpoints using SAS PROC MIANALYZE and last rank carried forward for secondary endpoints.

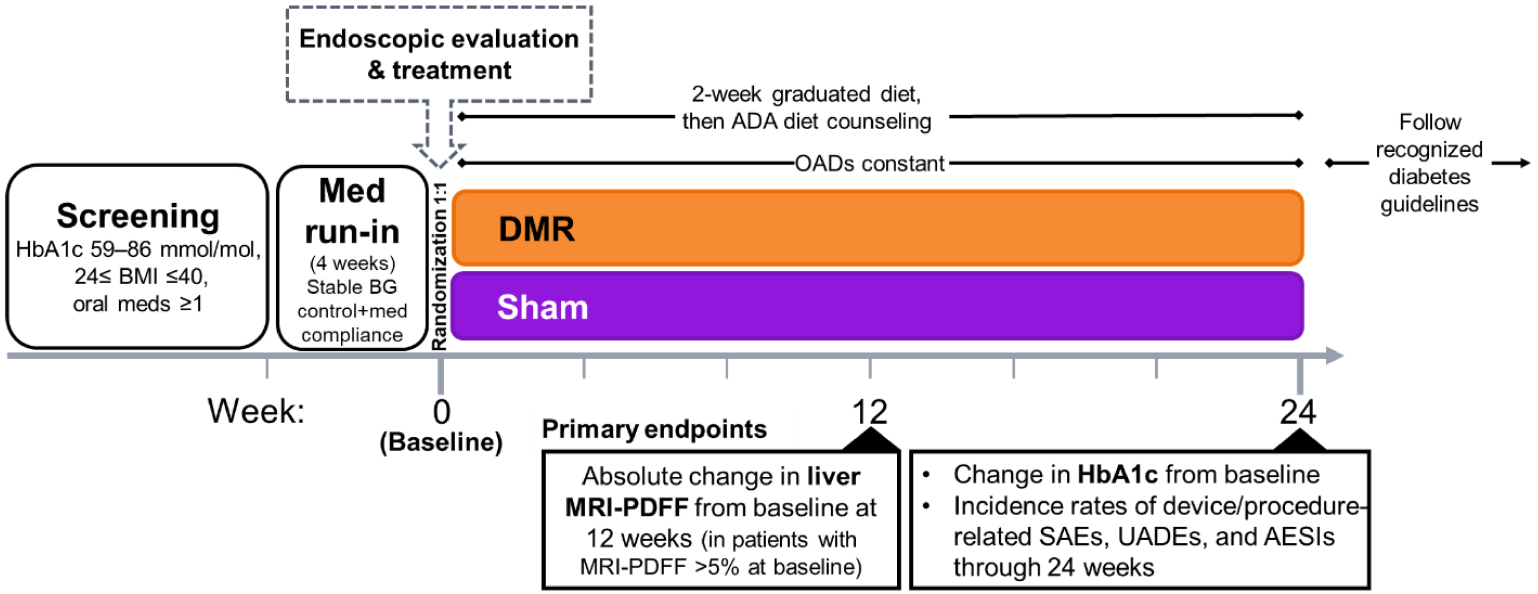
Prespecified assessments of homogeneity across regions evaluated consistency in treatment effect across geographic regions (Belgium, Brazil, Italy, Netherlands, and United Kingdom) for each of the two primary endpoints in the modified intent-to-treat analysis population using multiply imputed data and a treatment-by-region interaction test. Treatment-by-region significance was assessed using analysis of covariance with effects for treatment, region, baseline value of outcome, the difference between screening and baseline HbA1c outcome, and treatment-by-region interaction. If the treatment-by-region interaction p value was <0.10, then further analyses were performed to assess poolability of regions.

An exploratory analysis using partial least-squares–discriminant analysis (PLS-DA) was performed to further understand and assess the homogeneity in the prespecified study population regions. Variables in the X data matrix included available baseline and visit variables (weeks 0, 4, 12, 18, and 24) that were part of the primary and secondary endpoints (FPG, HbA1c, triglycerides, low-density lipoprotein, high-density lipoprotein, alanine transaminase, and aspartate transaminase levels, and MRI-PDFF). Only patients who had complete data for these variables and an MRI-PDFF >5% at baseline were included in the analysis. The groups in the Y data matrix were the two regions that showed a significant p value in the interaction test for homogeneity. PLS–DA aimed to maximize the covariance between the independent variables X (continuous variables) and the dependent variable Y (region groups) by finding a linear space comprised of the X variables. This allowed for the prediction of the Y variable on a reduced number of factors derived from the explanatory variables (X), which are known as PLS components. The PLS components describe the behaviour of the regions (Y) in the existing dataset. A ROC curve was plotted to show the performance of the PLS-DA classification model. This analysis was done in the following groups: all individuals, regardless of treatment groups; DMR-treated patients only; and sham-treated patients only.

Study withdrawal

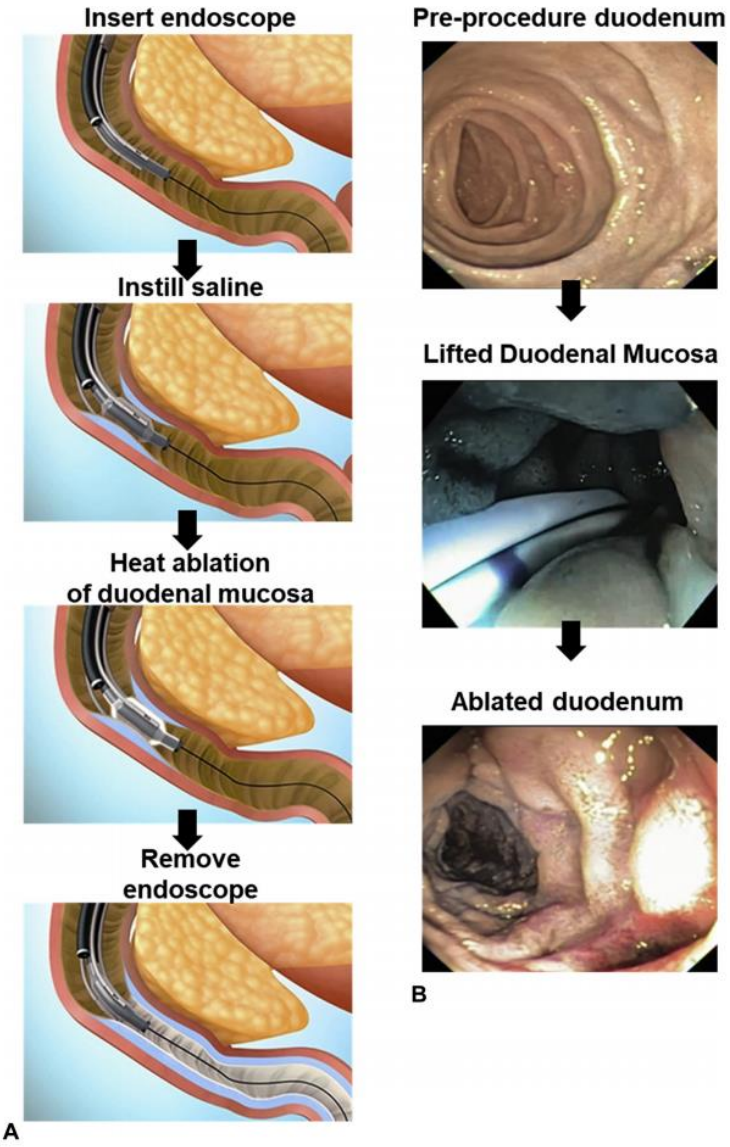
Only one patient in the sham group in Brazil did not attend subsequent appointments and was ultimately lost to follow-up. Two patients in the European cohorts withdrew consent (1 in the DMR and 1 in the sham group at 1 and 5 months, respectively). One patient in the sham group in Europe discontinued the study because of investigator's decision due to non-adherence. The 24-week follow-up was completed by 96.3% (104/108) of the patients enrolled in the trial.

Supplementary Figure 1



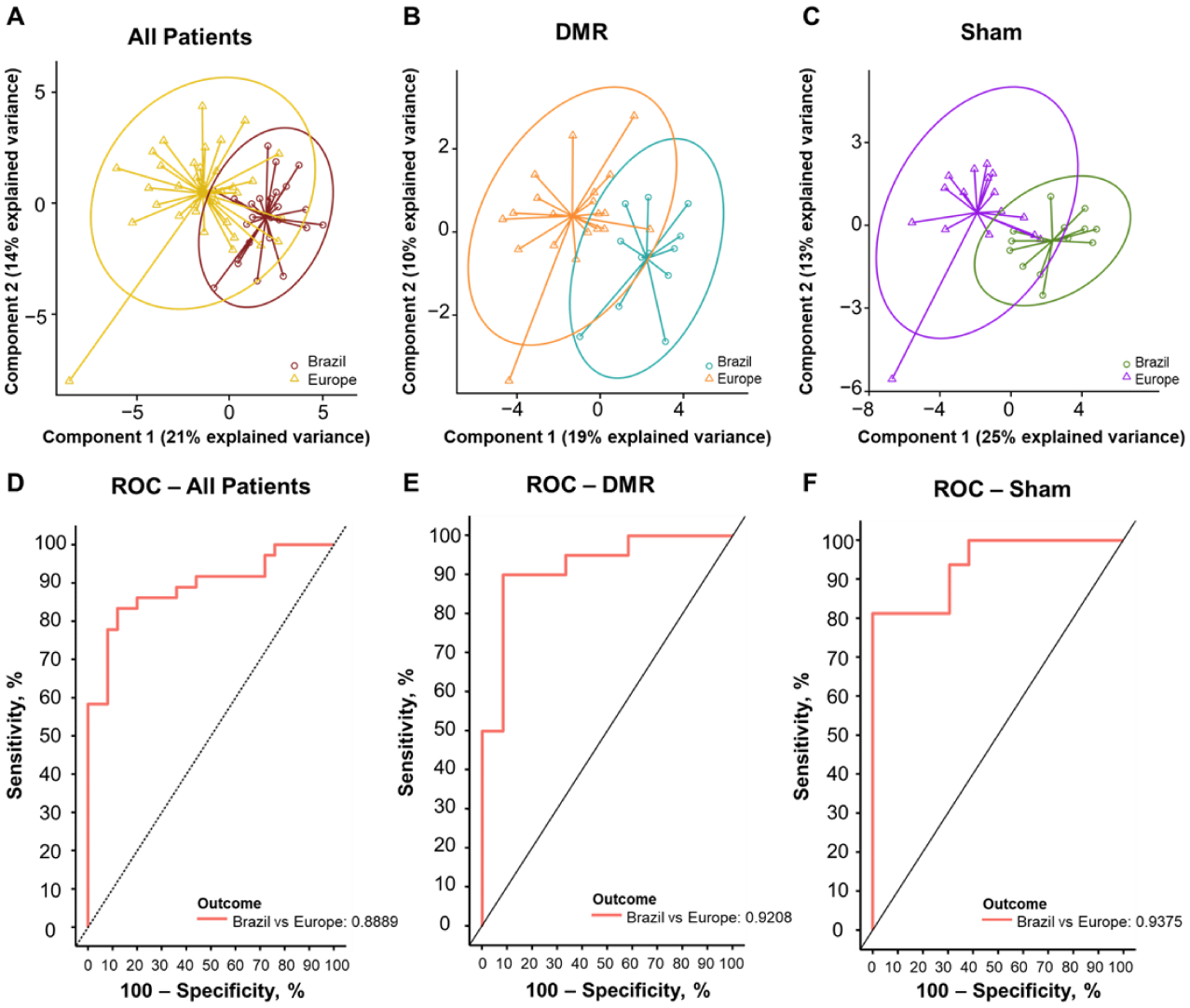
Supplementary Figure 1: Study design schematic ADA, American Diabetes Association; AESI, adverse event of special interest; BG, blood glucose; BMI, body mass index; DMR, duodenal mucosal resurfacing; HbA1c, haemoglobin A1; MRI-PDFF, magnetic resonance imaging proton density fat fraction; OAD, oral antidiabetic medication; SAE, serious adverse event; UADE, unanticipated adverse device effect.

Supplementary Figure 2



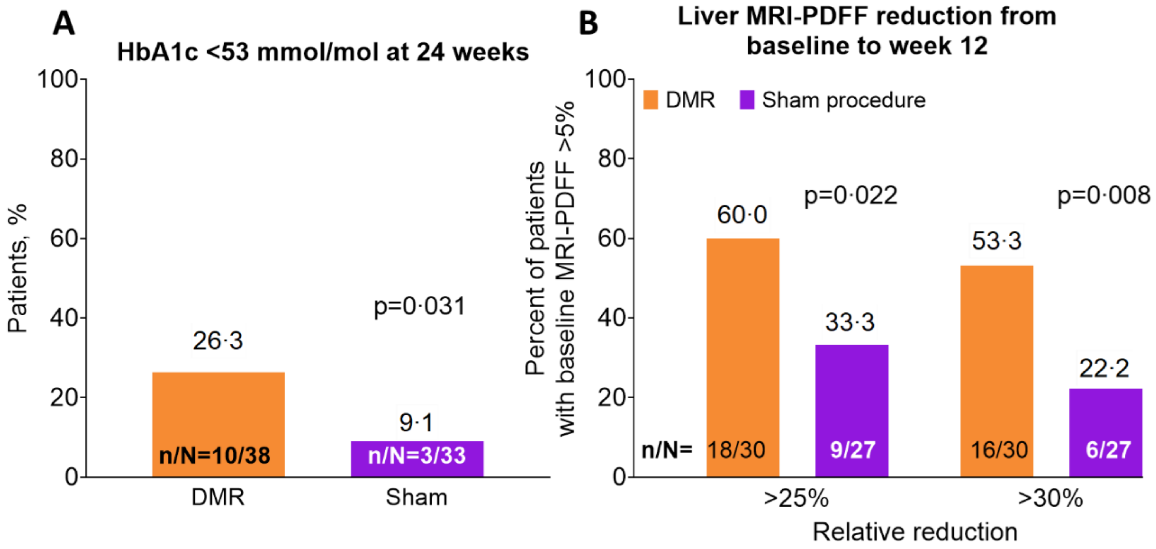
Supplementary Figure 2*:* Duodenal mucosal resurfacing procedure (A) Animation snapshots. (B) Endoscopic snapshots. Reprinted from Gastrointestinal Endoscopy, volume 90(4), Haidry RJ et al., Duodenal mucosal resurfacing: proof-of-concept, procedural development, and initial implementation in the clinical setting, 673-681, 2019, with permission from Elsevier.

Supplementary Figure 3



Supplementary Figure 3: Post-hoc PLS-DA to determine variance/covariance structures. The analysis including all patients, regardless of treatment group, showed that the first two components explained 35% of the variance that contributed to the separation of the European and Brazilian populations and showed an area under the curve of 0.89. PLS-DA in all patients (A), DMR-treated patients (B), and sham-treated patients (C). ROC curves for component one for all patients (D), DMR-treated patients (E), and sham-treated patients (F). Data for continuous variables are on non-imputed unadjusted descriptive statistics based on patients with non-missing values. DMR, duodenal mucosal resurfacing; PLS-DA, partial lease squares discriminant analysis.

Supplementary Figure 4



Supplementary Figure 4*:* Post-hoc HbA1c levels and MRI-PDFF responder analyses (European mITT population). (A) Percent of patients (DMR *vs* sham procedure) with HbA1c levels <83 mmol/mol at 24 weeks post-DMR. (B) Percent of patients (DMR *vs* sham procedure) with baseline liver MRI-PDFF >5% achieving relative MRI-PDFF reduction ≥25% or >30% from baseline to week 12. Treatment comparison (DMR *vs* sham procedure) one-sided p value from chi-square test with no imputation of missing data and values post-rescue medication are set to missing. DMR, duodenal mucosal resurfacing; HbA1c, haemoglobin A1c; mITT, modified intent to treat; MRI-PDFF, magnetic resonance imaging proton density fat fraction.

Supplementary Table 1. Eligibility criteria

Inclusion	
1	Aged 28–75 years
2	Diagnosed with T2D and evidence of preserved insulin secretion. Fasting insulin >7.0 µU/mL
3	HbA1c levels of 7.5–10.0% (59–86 mmol/mol)
4	Body mass index ≥24 and ≤40 kg/m^2
5	Currently taking one or more oral glucose-lowering medications, of which one must be metformin, with no changes in medication in the previous 12 weeks prior to study entry
6	Able to comply with study requirements and understand and sign the informed consent
Exclusion	
Screening visit (premedication run-in)	
1	Diagnosed with type 1 diabetes or with a history of ketoacidosis
2	Current use of insulin
3	Current use of glucagon-like peptide-1 analogues
4	Hypoglycaemia unawareness or a history of severe hypoglycaemia (more than one severe hypoglycaemic event, as defined by need for third-party assistance, in the last year)
5	Known autoimmune disease, as evidenced by a positive anti-glutamic acid decarboxylase test, including celiac disease, or preexisting symptoms of systemic lupus erythematosus, scleroderma, or other autoimmune connective tissue disorder
6	Active *Helicobacter pylori* infection (participants with active *H pylori* could continue with the screening process if they were treated via medication)
7	Previous gastrointestinal surgery (eg, Bilroth 2, Roux-en-Y gastric bypass, or other similar procedures or conditions) that could affect the ability to treat the duodenum
8	History of chronic or acute pancreatitis
9	Known active hepatitis or active liver disease
10	Symptomatic gallstones or kidney stones, acute cholecystitis, or history of duodenal inflammatory diseases, including Crohn's disease and celiac disease
11	History of coagulopathy, upper gastrointestinal bleeding conditions such as ulcers, gastric varices, strictures, or congenital or acquired intestinal telangiectasia
12	Use of anticoagulation therapy (such as warfarin), which cannot be discontinued for 7 days before and 14 days after the procedure
13	Use of P2Y12 inhibitors (clopidogrel, prasugrel, ticagrelor), which cannot be discontinued for 14 days before and 14 days after the procedure. Use of aspirin is allowed
14	Unable to discontinue non-steroidal anti-inflammatory drugs during treatment through 4 weeks post-procedure phase
15	Taking corticosteroids or drugs known to affect gastrointestinal motility (eg, metoclopramide)
16	Receiving weight loss medications such as Meridia, Orlistat, or over-the-counter weight-loss medications
17	Persistent anemia, defined as haemoglobin levels <10 g/dL
18	Estimated glomerular filtration rate or MDRD <30 mL/min/1.73 m^2
19	Active systemic infection
20	Active malignancy within the last 5 years

21	Not a potential candidate for surgery or general anaesthesia
22	Active illicit substance abuse or alcoholism
23	Participating in another ongoing clinical trial of an investigational drug or device
24	Any other mental or physical condition that, in the opinion of the Investigator, makes the patient a poor candidate for clinical trial participation
Baseline visit (post-medication run-in)	
1	HbA1c levels post run-in phase <7·5% (59 mmol/mol) or >10·0% (86 mmol/mol)
2	One or more clinically significant hypoglycaemic event defined as self-monitored or laboratory plasma glucose level of <54 mg/dL (3·0 mmol/L), or at least two such events if a clear correctable precipitating factor can be identified; or a severe hypoglycaemic event, as defined as hypoglycaemia requiring third-party assistance, since the screening visit
3	Hyperglycaemic event defined as three self-monitored finger sticks in 1 day during the run-in period with fasting blood glucose measurements >15 mmol/L (270 mg/dL) or non-fasting blood glucose measurements >20 mmol/L (360 mg/dL) or any combination of the two. Fasting glucose hyperglycaemia is not an exclusion if measured at the actual baseline visit (visit 2) blood analysis test
4	Those who are pregnant, nursing, or expect to become pregnant over the course of the study
Procedure	
1	Active and uncontrolled gastroesophageal reflux disease defined as grade III or greater esophagitis
2	Abnormalities of the gastrointestinal tract (including tortuous anatomy) preventing endoscopic access to the duodenum
3	Anatomic abnormalities in the duodenum that would preclude the completion of the DMR procedure
4	Malignancy newly diagnosed by endoscopy
5	Upper gastrointestinal conditions such as ulcers, polyps, gastric varices, strictures, and congenital or acquired intestinal telangiectasia

DMR, duodenal mucosal resurfacing; HbA1c, haemoglobin A1c; T2D, type 2 diabetes mellitus.

Supplementary Table 2. Classes of Oral Antidiabetic Medications by Cohort

European Cohort				
	mITT		**PP**	
	DMR (n=39)	**Sham** (n=36)	**DMR** (N=32)	**Sham** (N=34)
	N (%)	N (%)	N (%)	N (%)
Alpha glucosidase inhibitors	1 (2.6)	0 (0)	-	-
Biguanides	39 (100)	36 (100)	32 (100)	34 (100)
Dipeptidyl peptidase-4 inhibitors	10 (25.6)	8 (22.2)	8 (25.0)	8 (23.5)
Meglitinides	1 (2.6)	2 (5.6)	1 (3.1)	2 (5.9)
Sodium-glucose cotransporter-2 inhibitors	9 (23.1)	7 (19.4)	8 (25.0)	7 (20.6)
Sulfonylureas	21 (53.8)	20 (55.6)	17 (53.1)	19 (55.9)
Thiazolidinediones	2 (5.1)	1 (2.8)	1 (3.1)	1 (2.9)
Brazilian Cohort				
	mITT		**PP**	
	DMR (n=17)	**Sham** (n=16)	**DMR** (N=13)	**Sham** (N=12)
	N (%)	N (%)	N (%)	N (%)
Alpha glucosidase inhibitors	0 (0)	1 (6.3)	-	-
Biguanides	17 (100)	16 (100)	13 (100)	12 (100)
Dipeptidyl peptidase-4 inhibitors	2 (11.8)	0 (0)	2 (15.4)	0 (0)
Sodium-glucose cotransporter-2 inhibitors	0 (0)	2 (12.5)	0 (0)	1 (8.3)
Sulfonylureas	13 (76.5)	10 (62.5)	9 (69.2)	7 (58.3)
Thiazolidinediones	0 (0)	1 (6.3)	-	-

Supplementary Table 3. Predefined Rescue Algorithm for Hypo- and Hyper Glycaemia

Study Phase	Rescue Criteria	Treatment
Hyperglycaemia Requiring Rescue		
Run-in (between screening and procedure)	3 self-monitored finger sticks in 1 day meeting criteria	• Call clinic, schedule visit to confirm elevated HbA1c • Patient exclusion from study • Diabetes management as per their physician
Primary endpoint (procedure through 12 weeks)	HbA1c >9.0% at 12 weeks	• Patient medications should be modified per rescue criteria
	3 self-monitored finger sticks in 1 day meeting criteria	• Patient to call clinic, schedule visit to confirm elevated HbA1c • Consider anti-diabetic medication change
Primary endpoint (12 through 24 weeks)	HbA1c >8.5% at 24 weeks	• Patient medications should be modified per rescue criteria
	3 self-monitored finger sticks in 1 day meeting criteria	• Patient to call clinic, schedule visit to confirm elevated HbA1c • Consider anti-diabetic medication change
Long-term glycaemic follow-up phase (after 24 weeks)	HbA1c >8.5% at 36 weeks	• Patient medications should be modified per rescue criteria
	3 self-monitored finger sticks in 1 day meeting criteria	• Patient to call clinic, schedule visit to confirm elevated HbA1c • Consider anti-diabetic medication change
Acute Hyperglycaemia Requiring Short-term Rescue		
All study phases	Hyperglycaemia symptoms	• Patient should call clinic schedule visit to review SMBG and measure HbA1c
	3 self-monitored finger sticks in 1 day meeting criteria (elevated SMBG x3)	• Patient should call clinic, schedule visit to review symptoms and measure HbA1c
	If 2 of these 3 are met: • Elevated SMBG x3 in 1 day • HbA1c ≥10% • Hyperglycaemia symptoms	• Patient should call clinic, schedule visit to assess hyperglycaemia • If significant hyperglycaemia confirmed, insulin rescue permitted

Current Regimen	Dose Adequacy	Rescue Regimen
Metformin only	Submaximal	↑ metformin dose if tolerated

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

DPP-4, dipeptidyl peptidase-4 inhibitor; GLP-1RA, glucagon-like peptide-1 receptor agonist; HbA1c, haemoglobin A1c; OAD, oral antidiabetic medication; SGLT2, sodium glucose co-transporter 2; SMBG, self-monitoring of blood glucose; SU, sulfonylurea; TZD, thiazolidinediones.

Supplementary Table 4. Change in oral antidiabetic medication from baseline at week 24 (mITT population*)

	Europe†		Brazil	
Parameter	**DMR N=38**	**Sham N=35**	**DMR N=17**	**Sham N=15**
Increase	0 (0)	1 (2.9)	1 (5.9)	0 (0)
Neutral	37 (97.4)	32 (91.4)	11 (64.7)	12 (80.0)
Decrease	1 (2.6)	2 (5.7)	5 (29.4)	3 (20.0)

Data from patients with 24 weeks of follow-up are presented here as n (%), unless otherwise noted.

*mITT population defined as all randomised patients in whom the study procedure (DMR or sham) is attempted and who have a baseline measurement for at least one primary endpoint.

†European countries included Italy, United Kingdom, Belgium, Netherlands.

DMR, duodenal mucosal resurfacing; mITT, modified intent to treat.