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Original research

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

Geltrude Mingrone ,[1,2] Annieke CG van Baar,[3] Jacques Devière,[4] David Hopkins,[5] Eduardo Moura,[6] Cintia Cercato,[7] Harith Rajagopalan,[8] Juan Carlos Lopez-Talavera,[8] Kelly White,[8] Vijeta Bhambhani,[8] Guido Costamagna,[9] Rehan Haidry,[10] Eduardo Grecco,[11] Manoel Galvao Neto,[11] Guruprasad Aithal ,[12] Alessandro Repici,[13,14] Bu'Hussain Hayee ,[10] Amyn Haji ,[15] A John Morris,[16] Raf Bisschops ,[17] Manil D Chouhan,[18] Naomi S Sakai,[18] Deepak L Bhatt,[19] Arun J Sanyal,[20] J J G H M Bergman ,[3] Investigators of the REVITA-2 Study

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For numbered affiliations see end of article.

Correspondence to
Professor Geltrude Mingrone, Universita Cattolica del Sacro Cuore, 20123 Milano, Italy; geltrude.mingrone@unicatt.it

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ABSTRACT

Objective Hydrothermal duodenal mucosal resurfacing (DMR) is a safe, outpatient endoscopic procedure. REVITA-2, a double-blind, superiority randomised controlled trial, investigates safety and efficacy of DMR using the single catheter Revita system (Revita DMR (catheter and system)), on glycaemic control and liver fat content in type 2 diabetes (T2D).

Design Eligible patients (haemoglobin A1c (HbA1c) 59–86 mmol/mol, body mass index≥24 and ≤40 kg/m^2, fasting insulin >48.6 pmol/L, ≥1 oral antidiabetic medication) enrolled in Europe and Brazil. Primary endpoints were safety, change from baseline in HbA1c at 24 weeks, and liver MRI proton-density fat fraction (MRI-PDFF) at 12 weeks.

Results Overall mITT (DMR n=56; sham n=52), 24 weeks post DMR, median (IQR) HbA1c change was −10.4 (18.6) mmol/mol in DMR group versus −7.1 (16.4) mmol/mol in sham group (p=0.147). In patients with baseline liver MRI-PDFF >5% (DMR n=48; sham n=43), 12-week post-DMR liver-fat change was −5.4 (5.6)% in DMR group versus −2.9 (6.2)% in sham group (p=0.096). Results from prespecified interaction testing and clinical parameter assessment showed heterogeneity between European (DMR n=39; sham n=37) and Brazilian (DMR n=17; sham n=16) populations (p=0.063); therefore, results were stratified by region. In European mITT, 24 weeks post DMR, median (IQR) HbA1c change was −6.6 mmol/mol (17.5 mmol/mol) versus −3.3 mmol/mol (10.9 mmol/mol) post-sham (p=0.033); 12-week post-DMR liver-fat change was −5.4% (6.1%) versus −2.2% (4.3%) post-sham (p=0.035). Brazilian mITT results trended towards DMR benefit in HbA1c, but not liver fat, in context of a large sham effect. In overall PP, patients with high baseline fasting plasma glucose ((FPG)≥10 mmol/L) had significantly greater reductions in HbA1c post-DMR versus sham (p=0.002). Most adverse events were mild and transient.

Conclusions DMR is safe and exerts beneficial disease-modifying metabolic effects in T2D with or without non-alcoholic liver disease, particularly in patients with high FPG.

Trial registration number NCT02879383

Significance of this study

What is already known about this subject?

⇒ More than half of patients with type 2 diabetes mellitus are unable to sustain adequate glycaemic control with the current standard of care.

⇒ Current approaches do not adequately target underlying disease pathophysiology (ie, insulin resistance (IR) and hyperinsulinaemia).

⇒ Bariatric surgeries that bypass nutrient contact from the duodenum (eg, Roux-en-Y gastric bypass) improve glycaemic control and insulin sensitivity.

⇒ Duodenal mucosal resurfacing is a minimally invasive, outpatient endoscopic procedure that targets duodenal pathology to treat insulin-resistance–related metabolic disease, including type 2 diabetes mellitus. Published data from earlier open-label studies have shown statistically significant improvements in haemoglobin A1c (HbA1c), alanine transaminase, aspartate transaminase, weight and homeostatic model assessment of IR through 12-month follow-up.

What are the new findings?

⇒ In this first prospective, double-blind, sham-controlled study of Revita duodenal mucosal resurfacing, a single duodenal mucosal resurfacing procedure was well tolerated, safe, and elicits clinically and statistically significant improvements in HbA1c levels and liver fat content in European patients with poorly controlled type 2 diabetes mellitus.

⇒ These results confirm that the duodenal mucosa is a therapeutic target for type 2 diabetes with or without non-alcoholic fatty liver disease/non-alcoholic steatohepatitis.

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Significance of this study

How might it impact on clinical practice in the foreseeable future?

⇒ These data provide insight into a potential therapeutic opportunity for duodenal mucosal resurfacing to favourably impact both type 2 diabetes and non-alcoholic fatty liver disease/non-alcoholic steatohepatitis in a manner that can modify the natural history of these chronic and progressive diseases.

INTRODUCTION

The global prevalence of type 2 diabetes mellitus (T2D) and non-alcoholic fatty liver disease, due in part to the widespread adoption of diets with high sugar and fat content, is increasing at an alarming rate.[1–3] Insulin resistance (IR) and hyperinsulinemia play an important role in the pathological progression and decompensation of multiple organ systems in these conditions.[3 4] Despite the fact that over 50 unique pharmacological agents are currently approved to treat T2D, and the benefits of dietary interventions are well established, most patients with T2D are unable to sustain adequate glycaemic control (recommended haemoglobin A1c (HbA1c) levels≤53 mmol/mol).[5 6] Poor adherence and persistence to prescribed therapies, drug-to-drug interactions, side effects, and patient dissatisfaction are fundamental barriers to the real-world effectiveness of current approaches to manage T2D.[7 8]

Bariatric/metabolic surgeries that bypass nutrient contact from the duodenum, such as Roux-en-Y gastric bypass and biliopancreatic diversion, originally intended to aid weight loss, have demonstrated compelling evidence to provide sustainable improvements in patients with T2D.[9–11] Bariatric/metabolic surgery is safe with a low mortality rate (0.1%–0.5%), similar to that observed after cholecystectomy or hysterectomy.[12] Nevertheless, only 1% of eligible patients undergo this type of surgery.[13 14] Endoscopic procedures are emerging as an effective and minimally invasive approach to treat obesity and/or T2D, closing the gap between pharmacological therapy and bariatric/metabolic surgery.

Duodenal mucosal resurfacing (DMR) is a minimally invasive endoscopic procedure performing circumferential mucosal lift and hydrothermal ablation of the duodenal mucosa.[15] The first-in-human safety trial showed that DMR is safe and able to improve glycaemic control in proportion to the length of the ablated duodenal mucosal segment.[16 17] The following multicentre, open-label REVITA-1 trial in 46 patients with poorly controlled T2D showed a significant reduction of baseline HbA1c at 24 weeks after DMR of −10±2 mmol/mol (−0.9%±0.2%; p<0.001).[18]

Herein, we report the results of the first double-blind, multicentre, randomised controlled trial with a single DMR procedure, which assessed the efficacy and safety of DMR in patients with T2D with or without NAFLD versus a sham endoscopic procedure.

METHODS

Additional protocols and complete procedures are described in the online supplemental material and methods section.

Trial design and oversight

REVITA-2 was a randomised, double-blind (patient and endocrinologist), sham-controlled trial conducted across 11 sites (nine in Europe (Italy, UK, Belgium and Netherlands) and two in Brazil) from 11 September 2017 to 15 December 2018 (online supplemental figure 1).

A data monitoring committee oversaw this study (see online supplemental methods for details).

Randomisation and masking

Patients (see online supplemental table 1 for complete eligibility criteria) were randomised (1:1) to undergo the DMR or sham procedure by using a central web-based random allocation system (see online supplemental methods for details). Endocrinologists and patients were unaware of the treatment assignment until the 24-week follow-up visit.

Procedures

DMR was performed with the single catheter Revitasystem (Revita DMR(catheter and system), Fractyl Laboratories, Lexington, Massachusetts, USA) as previously described (online supplemental figure 2).[16–18] A full DMR procedure was defined as five sequential ablations of 2 axial centimetres each, starting within 3 centimetres distal to the Ampulla of Vater towards the Ligament of Treitz, totalling 10 axial centimetres of circumferentially ablated tissue in the duodenum during a single endoscopic session. The sham procedure consisted of placing the DMR catheter over the guidewire into the stomach and leaving it in place for 30 min prior to removing it from the patient.

Study endpoints and assessments

The two primary efficacy endpoints were the absolute change from baseline at 24 weeks in HbA1c in all patients and absolute change from baseline at 12 weeks in liver MRI proton density fat fraction (MRI-PDFF), specifically in those patients with NAFLD at baseline (liver MRI-PDFF >5%). The primary safety endpoints assessed were the incidence of device-related and procedure-related serious adverse events (SAEs), unanticipated adverse device events (UADEs), and AEs of special interest (AESIs), including hypoglycaemic events, through 24 weeks. Adverse events were recorded from the time the informed consent document was signed. The prespecified safety analysis tabulated the difference in the proportion of patients who experienced ≥1 major complication (DMR vs sham).

Secondary endpoints assessed were the relative change in liver MRI-PDFF from baseline at week 12 in patients with baseline liver MRI-PDFF >5% and absolute change from baseline at 24 weeks in fasting plasma glucose (FPG) levels, weight, and homeostatic model assessment of IR (HOMA-IR).

Exploratory endpoints assessed were absolute change from baseline at 24 weeks in triglycerides, low-density lipoprotein cholesterol, high-density lipoprotein, alanine transaminase (ALT), and aspartate transaminase levels, and change in oral antidiabetic medication from baseline at week 24. In addition, the percentage of patients achieving HbA1c levels<53 mmol/mol or liver fat content reduction >30% at the end of the study as well as the number of antihyperglycaemic drugs during the trial were assessed (see online supplemental table 2).

Rescue medications: persistent hyperglycaemia was a criterion to receive rescue medication, which was prescribed, per protocol (PP), with increasing doses of oral medications and/or insulin according to clinical practice guidelines (see online supplemental table 3).[19 20] Patients continued in the trial after receiving rescue medication.

Statistical analysis

The primary efficacy endpoints were planned to be tested for superiority of DMR versus sham with adjustment for multiple endpoints using the Hochberg procedure.[21] Under this procedure, DMR was considered beneficial over sham for both primary endpoints if the one-sided p value for each endpoint was <0.05; and/or, if the one-sided treatment comparison p value was<0.025 for one endpoint,

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then DMR was considered beneficial over sham for that given endpoint.

Intention-to-treat and PP analyses

The primary analysis population for primary and secondary endpoints was the modified intention-to-treat (mITT) population, defined as all randomised patients in whom the study procedure was attempted and who had a baseline measurement for ≥1 primary endpoint. The PP population was defined as the subset of mITT patients who received the treatment to which they were randomised and strictly adhered to the protocol.

Safety analyses were completed in all patients in whom the treatment (DMR or sham) was initiated and included all AEs revealed during the follow-up, independent of duration. AEs and SAEs are presented as the number and percent of patients; overall counts were compared using the two-sided Clopper-Pearson 95% CI of the incidence rates.

The following additional analyses were conducted: (1) proportion of all patients who achieved an HbA1c level <53 mmol/mol at 24 weeks post procedure; (2) proportion of patients with baseline MRI-PDFF >5% who achieved a relative liver MRI-PDFF reduction >30% from baseline at week 12; (3) stratification of end-study HbA1c by baseline FPG levels. The change in oral antidiabetic medication from baseline at week 24 (increase, neutral, or decrease) was assessed in patients with 24 weeks of follow-up.

Statistical analyses were performed using Statistical Analysis Software V.9.4 or later (SAS Institute) or R V.3.3.2 or later. See supplemental material for additional analyses details and powering assumptions.

Analysis of normality and homogeneity in the study populations

Assessments of normality and homogeneity were performed as specified in the statistical analysis plan. The normality tests assessed whether each variable was normally distributed. Assessments of homogeneity evaluated consistency in treatment effect across geographic regions (Belgium, Brazil, Italy, Netherlands and UK) with a prespecified treatment-by-region interaction p value of<0.10 (see online supplemental methods for details).

An exploratory analysis using partial least-squares-discriminant analysis (PLS-DA) was performed to further understand and assess the interaction by regions in the prespecified study populations. PLS-DA is a useful exploratory analysis showing patterns related to a treatment effect without testing a formal hypothesis; in other words, it provides a comparative and clear visual of different patterns in two samples (see online supplemental methods for details).

HOMA-IR and Matsuda Index Calculation

Fasting IR was measured based on the HOMA-IR calculated as (FPG * fasting insulin)/135, where FPG level was measured in mmol/L and fasting insulin was measured in pmol/L.[22]

The Matsuda Index was calculated as $10000/(G_0 \cdot I_0 \cdot G_m \cdot I_m)^{0.5}$, where G_0 and I_0 are premeal values for glucose and insulin and G_m and I_m are mean post-meal values during the first 120 min of the liquid meal tolerance test with glucose and insulin values in mmol/L and mU/L, as validated for a meal test.[23 24] Since the square root of the denominator takes into account the correction of nonlinear values distribution, these values are reported as mean±SD.

Role of the funding source

The funder of the study participated in study design, data collection, data analysis, data interpretation and writing of the report. The corresponding author (GM) had full access to all the data in the study and had final responsibility for the decision to submit the manuscript for publication.

Patient and public involvement

Patients were not directly involved in the design, recruitment or conduct of the study.

RESULTS

Patient baseline characteristics

Between 11 September 2017 and 15 December 2018, 359 patients were screened and 250 were excluded from the study (figure 1). 109 patients were randomised (although one did not receive treatment due to oesophageal varices) 1:1 either to DMR (n=56) or to sham procedure (n=52); 75 in Europe (39 DMR, 36 sham procedure) and 33 in Brazil (17 DMR, 16 sham procedure).

Overall, 71 patients (65.7%) were white, 7 (6.5%) were black, 2 (1.8%) were Asian, 3 (2.8%) belonged to other races and 25 (23.1%) preferred not to disclose their race.

Patient demographics and baseline characteristics were well balanced between the DMR and sham procedure groups (table 1). Men accounted for 69.4% of the patients. At baseline, the median body mass index was 31.5 (4.7) kg/m^2 in the DMR group and 30.7 (5.7) kg/m^2 in the sham group. The median baseline HbA1c levels were 65.6 (8.7) mmol/mol in the DMR group and 66.1 (10.4) mmol/mol in the sham group. The median duration of diabetes was 10.0 (6.0) years and 9.1 (8.8) years among patients who underwent DMR or sham procedure, respectively. Most patients (85.5% in the DMR group and 82.7% in the sham group) had more than 5% fat accumulation in the liver as detected at baseline by MRI-PDFF.

mITT analysis and post-hoc analyses

In the overall mITT population (DMR n=56; sham n=52), the median change in HbA1c from baseline at 24 weeks post procedure was −10.4 (18.6) mmol/mol in the DMR group compared with −7.1 (16.4) mmol/mol in the sham group (p=0.147; treatment difference −3.3 mmol/mol). In patients with baseline liver MRI-PDFF >5% (DMR n=48; sham n=43), the median absolute change in liver MRI-PDFF from baseline at 12 weeks was −5.4 (5.6)% in the DMR group compared with −2.9 (6.2)% in the sham group (p=0.096; treatment difference −2.5%).

A post-hoc analysis of pooled data from the overall PP population stratified by baseline FPG levels demonstrated that in patients with FPG ≥10 mmol/L, the median (IQR) reduction in HbA1c at week 24 post procedure was −14.2 (17.5) mmol/mol post DMR compared with −4.4 (15.3) mmol/mol in the sham group (p=0.002); whereas, in patients with FPG <10 mmol/L, the median reductions in HbA1c were similar between groups (p=0.148; figure 2A). In patients with baseline liver MRI-PDFF >5% and FPG ≥10 mmol/L, the median absolute change in liver MRI-PDFF was significantly greater in the DMR group compared with patients who underwent the sham procedure (p=0.001; figure 2B). Similar results were observed in the European PP population for both HbA1c and liver fat content changes (figure 2C,D) and in the Brazilian PP population, but only for liver fat content (figure 2E,F).

PRIMARY AND SECONDARY ENDPOINTS BY REGION

Demographics and baseline characteristics were similar (table 1), but prespecified interaction testing by region showed heterogeneity between patients in Europe (DMR N=39; sham N=36) and patients in Brazil (DMR N=17; sham N=16) for the HbA1c outcome (p=0.063). As such, European and Brazilian regions were analysed separately for all clinical outcomes. A post-hoc PLS-DA confirmed these regions were separate groups with different

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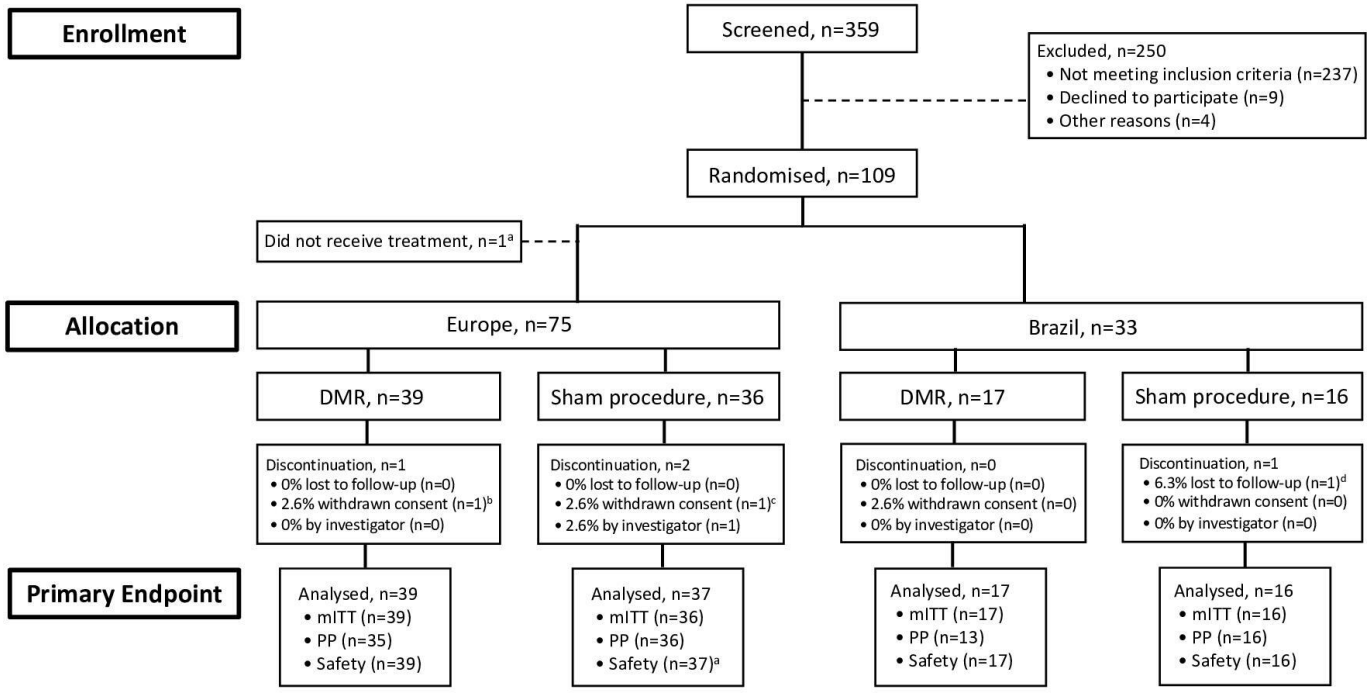

Figure 1 Patient disposition. Between 1 March 2017, and 15 December 2018, 109 of 359 patients assessed for eligibility were randomised. One patient at a European study site did not receive treatment due to oesophageal varices[a]; therefore, the modified intention-to-treat (mITT) population included 108 patients—75 in Europe (39 to duodenal mucosal resurfacing (DMR) and 36 to sham) and 33 in Brazil (17 to DMR and 16 to sham). Prespecified assessments of normality and homogeneity (see the Methods section for details) revealed that the European and Brazilian populations were not poolable. Therefore, all efficacy analyses were stratified into two populations (Europe and Brazil). [a]The one patient who withdrew and did not receive treatment was followed for safety, but not efficacy. Last completed visit was at week 4[a], week 21 (phone call)[b], and day 7 (phone call)[d]. PP, per protocol.

variance/covariance structures (online supplemental figure 3). The primary endpoints were found to be not normally distributed and are therefore presented as median (IQR).

PLS-DA is a linear classification model that is able to predict the class of new samples. We used PLS-DA as a post-hoc analysis that confirmed the European and Brazilian populations were separate groups with different variance/covariance structures (figure 3). This analysis including all patients, regardless of treatment group, showed that the first two components of PLS-DA explained 35% of the variance that contributed to the separation of the European and Brazilian populations. The general predictive performance of the PLS-DA model in correctly classifying the patients as belonging to the European or to the Brazilian groups was very good as shown by the area under the curve of 0.89. Therefore, due to heterogeneity demonstrated by multiple statistical methods and the unexpected differences seen between Europe and Brazil in the sham arms (table 2), analyses were stratified by region.

In the European mITT population, the median change in HbA1c from baseline at 24 weeks post procedure was –6.6 (17.5) mmol/mol in the DMR group compared with –3.3 (10.9) mmol/mol in the sham procedure group (p=0.033; treatment difference –3.3 mmol/mol; figure 3A). In patients with baseline liver MRI-PDFF >5%, the median absolute change in liver MRI-PDFF from baseline at 12 weeks revealed a reduction of liver fat content by 5.4 (6.1)% in the DMR group compared with 2.2 (4.3)% in the sham procedure group (p=0.035; treatment difference –3.2%; figure 3B). Similar results were observed in the European PP population and using a prespecified mixed-model repeated measures analysis (MMRM) (described within the online supplemental material).

In the Brazilian mITT population, change from baseline in HbA1c levels (figure 3C) was not significantly different in DMR compared with sham in the primary analysis, but was significantly lower in the prespecified sensitivity MMRM analysis (p=0.104 and p=0.034, respectively). In Brazil, there was no significant difference between treatment groups in liver MRI-PDFF (figure 3D).

In the European mITT population, the median reduction in weight 24 weeks post procedure was significantly greater in the DMR group (–2.4 (2.8) kg) than in the sham group (–1.4 (2.4) kg; p=0.012; treatment difference –1.0 kg; figure 4A). At 12 weeks post procedure, European patients with baseline liver MRI-PDFF >5% had a significantly greater reduction of the median relative liver MRI-PDFF from baseline in the DMR group compared with the sham group (–32.1% (20.6%) vs –17.9% (25.6%); p=0.020; treatment difference –14.2%; figure 4B). Median reduction in FPG levels from baseline at 24 weeks post procedure was numerically lower in the DMR group compared with sham procedure group (–1.5 mmol/L (4.6 mmol/L) vs –0.9 mmol/L (3.0 mmol/L); p=0.217; treatment difference –0.6 mmol/L; figure 4C), and median reduction in HOMA-IR was numerically lower in the DMR group compared with the sham group (–1.3 (2.5) vs –0.4 (1.5); p=0.060; treatment difference –0.9; figure 4D). Sensitivity analysis of HOMA-IR reached statistical significance in non-imputed complete case analysis for missing secondary endpoint data (p=0.028), indicating an insulin-sensitising mechanism of DMR. The mean (SD) increase in Matsuda Index, a post-hoc analysis of insulin sensitivity (higher numbers denoting better insulin sensitivity), was greater in the DMR group compared with the sham group (1.2±2.7 *vs* 0.2±1.5; p=0.035; treatment difference 1.0).

The mITT analysis of the relative changes in weight, liver fat content (MRI-PDFF), FPG and HOMA-IR in the Brazilian population did not show any significant difference between DMR and sham groups (figure 4E–H, respectively).

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Table 1 Baseline characteristics and demographics and change from baseline (modified intention-to-treat population*)

	Overall			Europe†			Brazil		
Parameter	DMR N=56	Sham N=52	P value	DMR N=39	Sham N=36	P value	DMR N=17	Sham N=16	P value
Age, years	58.0 (13.5)	58.5 (14.0)	0.747	59.0 (13.0)	56.5 (14.0)	0.627	56.0 (13.0)	59.5 (11.5)	0.164
Sex, n (%)			0.963			0.93			0.866
Female	17 (30.4)	16 (30.8)		9 (23.1)	8 (22.2)		8 (41.7)	8 (50.0)	
Male	39 (69.6)	36 (69.2)		30 (76.9)	28 (77.8)		9 (52.7)	8 (50.0)	
Race, n (%)			0.974			0.658			0.562
White	37 (66.1)	34 (65.4)		25 (64.1)	21 (58.3)		12 (70.6)	13 (81.3)	
Black	4 (7.1)	3 (5.8)		0	0		4 (23.5)	3 (18.8)	
Asian	1 (1.8)	1 (1.9)		0	1 (2.8)		1 (5.9)	0	
Other	1 (1.8)	2 (3.8)		1 (2.6)	2 (5.6)		0	0	
Undisclosed	13 (23.2)	12 (23.1)		13 (33.3)	12 (33.3)		0	0	
Weight, kg									
Baseline	93.0 (15.9)	92.6 (26.4)	0.438	93.1 (16.5)	94.5 (24.6)	0.644	89.0 (15.6)	87.8 (19.8)	0.627
Week 24	90.0 (17.5)	87.4 (26.0)	0.707	91.0 (17.5)	92.6 (27.0)	0.937	86.8 (19.7)	83.2 (22.6)	0.678
Change from baseline (week 24)									
Absolute	−2.5 (4.5)	−1.5 (3.3)	0.021	−2.4 (2.8)	−1.4 (2.4)	0.012	−4.1 (5.6)	−2.1 (5.7)	0.285
Relative (%)	−2.8 (4.5)	−1.8 (3.5)	0.037	−2.6 (3.4)	−1.5 (2.9)	0.013	−4.5 (5.7)	−2.8 (5.6)	0.403
BMI, kg/m^2									
Baseline	31.5 (4.7)	30.7 (5.7)	0.206	31.4 (4.5)	30.4 (6.1)	0.16	32.3 (4.7)	31.6 (6.2)	0.928
Week 24	30.6 (5.2)	29.9 (5.5)	0.563	30.6 (5.0)	29.7 (6.3)	0.376	30.6 (5.6)	30.8 (5.9)	0.828
Change from baseline (week 24)									
Absolute	−0.9 (1.5)	−0.5 (1.1)	0.025	−0.8 (1.2)	−0.5 (0.9)	0.011	−1.4 (1.9)	−0.8 (1.9)	0.28
Relative (%)	−2.8 (4.5)	−1.8 (3.5)	0.042	−2.6 (3.4)	−1.5 (2.9)	0.013	−4.5 (5.7)	−2.8 (5.6)	0.365
HbA1c levels, mmol/mol									
Baseline	65.6 (8.7)	66.1 (10.4)	0.839	65.0 (7.6)	66.1 (9.3)	0.45	70.5 (9.8)	65.6 (14.2)	0.213
Week 24	55.2 (16.4)	61.2 (18.0)	0.436	59.6 (16.4)	63.9 (14.2)	0.132	51.9 (5.5)	48.6 (8.7)	0.104
Change from baseline (week 24)									
Absolute	−10.4 (18.6)	−7.1 (16.4)	0.147	−6.6 (17.5)	−3.3 (10.9)	0.033	−20.2 (14.2)	−17.5 (9.8)	0.104
Relative (%)	−16.7 (28.6)	−10.6 (23.3)	0.184	−9.6 (27.1)	−3.8 (18.3)	0.034	−27.6 (14.9)	−25.6 (12.9)	0.105

DMR, duodenal mucosal resurfacing; HbA1c, haemoglobin A1c.

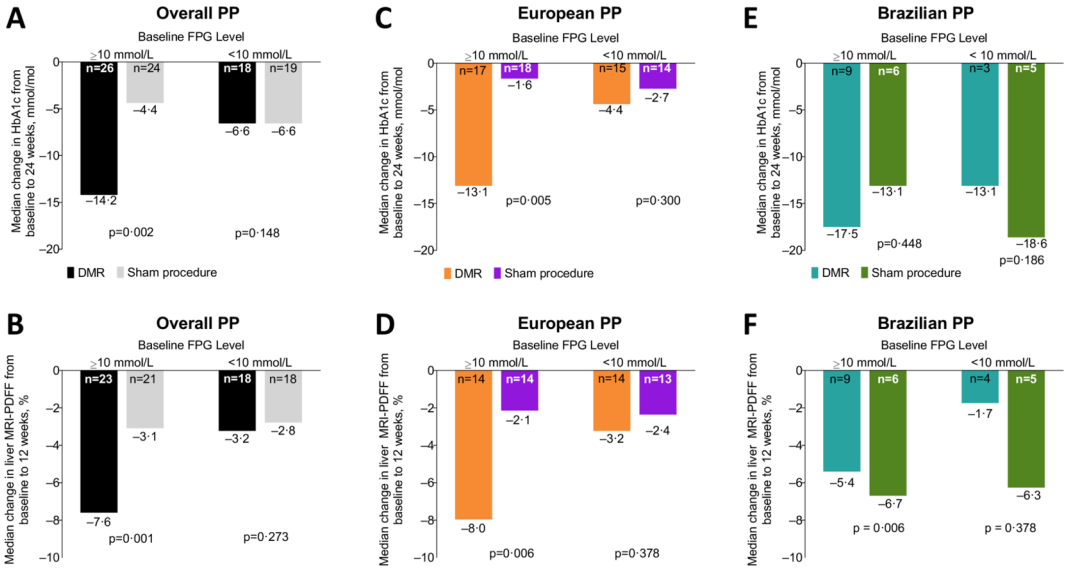

Figure 2 Post-hoc analysis of change in haemoglobin A1c (HbA1c) levels and liver MRI proton density fat fraction (MRI-PDFF) stratified by baseline fasting plasma glucose (FPG) level status (per-protocol (PP) populations). Median HbA1c per cent change from baseline to 24 weeks (duodenal mucosal resurfacing (DMR) versus sham procedure) in the overall (A), European (C) and Brazilian (E) PP patients with baseline FPG ≥10 mmol/L compared with patients with baseline FPG <10 mmol/L. In patients with baseline liver MRI-PDFF >5%, median liver MRI-PDFF per cent change from baseline to 12 weeks (DMR vs sham procedure) in the overall (B), European (D), and Brazilian (F) PP patients with baseline FPG ≥10 mmol/L compared with FPG <10 mmol/L. Treatment comparison of one-sided p value based on analysis of covariance model with multiple imputation on the rank values (modified ridit scores). Via multiple imputation, analysis is based on all patients in the population of interest. The overall PP population includes patients from both European and Brazilian study sites. The European PP population consists of patients from Italy, UK, Belgium and Netherlands.

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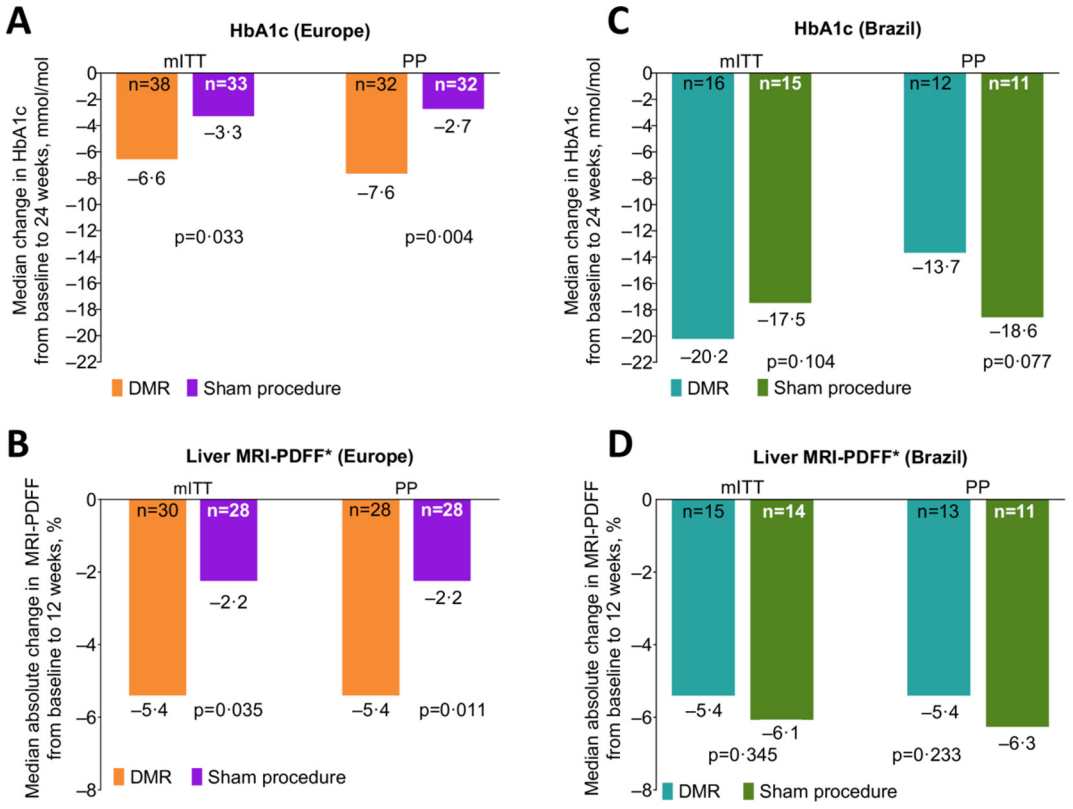

Figure 3 Haemoglobin A1c (HbA1c) levels and liver MRI proton density fat fraction (MRI-PDFF) at 24 weeks post duodenal mucosal resurfacing (DMR) (primary endpoint). Median per cent change in HbA1c levels (DMR vs sham procedure) from baseline to 24 weeks in the European (A) and Brazilian (B) modified intention-to-treat (mITT) and per-protocol (PP) populations. Median absolute per cent change in liver MRI-PDFF (DMR vs sham procedure) from baseline to 24 weeks in patients with baseline MRI-PDFF >5% (*) in the European (C) and Brazilian (D) mITT and PP populations. Treatment comparison one-sided p value based on analysis of covariance model with multiple imputation on the rank values (modified ridit scores). Via multiple imputation, analysis is based on all patients in the population of interest where post rescue values are first set to missing. Data for continuous variables are on non-imputed unadjusted descriptive statistics based on patients with non-missing values.

In the European mITT population, the DMR group had significantly more patients achieving HbA1c levels<53 mmol/mol at 24 weeks compared with the sham group (26.3% vs 9.1%; p=0.031; online supplemental figure 4A). Similarly, 53% of patients in the DMR group with baseline MRI-PDFF >5% achieved a relative liver MRI-PDFF reduction >30% from baseline at week 12, compared with 22% in the sham procedure group (p=0.008; online supplemental figure 4B).

Finally, most patients experienced no change or had an increased use in oral antidiabetic medication from baseline at week 24 in both the European and Brazilian mITT populations (online supplemental table 4).

Table 2 Change from baseline in haemoglobin A1c (HbA1c) levels, liver MRI proton density fat fraction (MRI-PDFF) and weight (sham-treated modified intention-to-treat population)

Parameter	Europe N=37	Brazil N=16
HbA1c levels at 24 weeks, mmol/mol	n=33	n=15
	−3.3 (10.9)	−17.5 (9.8)
Liver MRI-PDFF >5% at baseline, n (%)	28 (75.7)	14 (87.5)
Absolute change in liver MRI-PDFF at 12 weeks, %	−2.2 (4.3)	−6.1 (7.8)
Weight at 24 weeks, kg	n=34	n=15
	−1.4 (2.4)	−2.1 (5.7)

Data are presented as median (IQR), unless otherwise indicated.

TIME OF PROCEDURE

The median total catheter indwelling time in the entire sample was 56·.0 min (26·.0 min).

SAFETY ANALYSIS

All patients were included in the safety analysis, 76 in Europe (DMR n=39; sham n=37) and 33 in Brazil (DMR n=17; sham n=16). Most AEs were mild and transient; the most common were abdominal pain, diarrhoea, hyperglycaemia, hypoglycaemia, nasopharyngitis and headache. In the European population, no device-related or procedure-related SAEs or UADEs were reported through 24 weeks post procedure (table 3). Approximately 33% of patients in the DMR group (n=13) experienced a device-related or procedure-related AESI, compared with 27% of patients (n=10) in the sham procedure group. The most common (occurring in ≥5% of patients) device-related or procedure-related AESIs occurring ≤30 days post procedure were abdominal pain and hypoglycaemia. Similar number of events and percentage of patients with events of hypoglycaemia (related to procedure) were found in both groups (4 events; 7.7% (3/39) patients with event in DMR group and 8 events; 10.8% (4/37 patients with events in the sham group)). There was an absence of pancreatitis, infection and thermal injury. Follow-up endoscopy was performed (n=32); overall, the duodenum appeared normal with complete healing.

In the Brazilian population, 11.8% of patients (n=2) in the DMR group experienced SAEs related to the procedure (table 3). One

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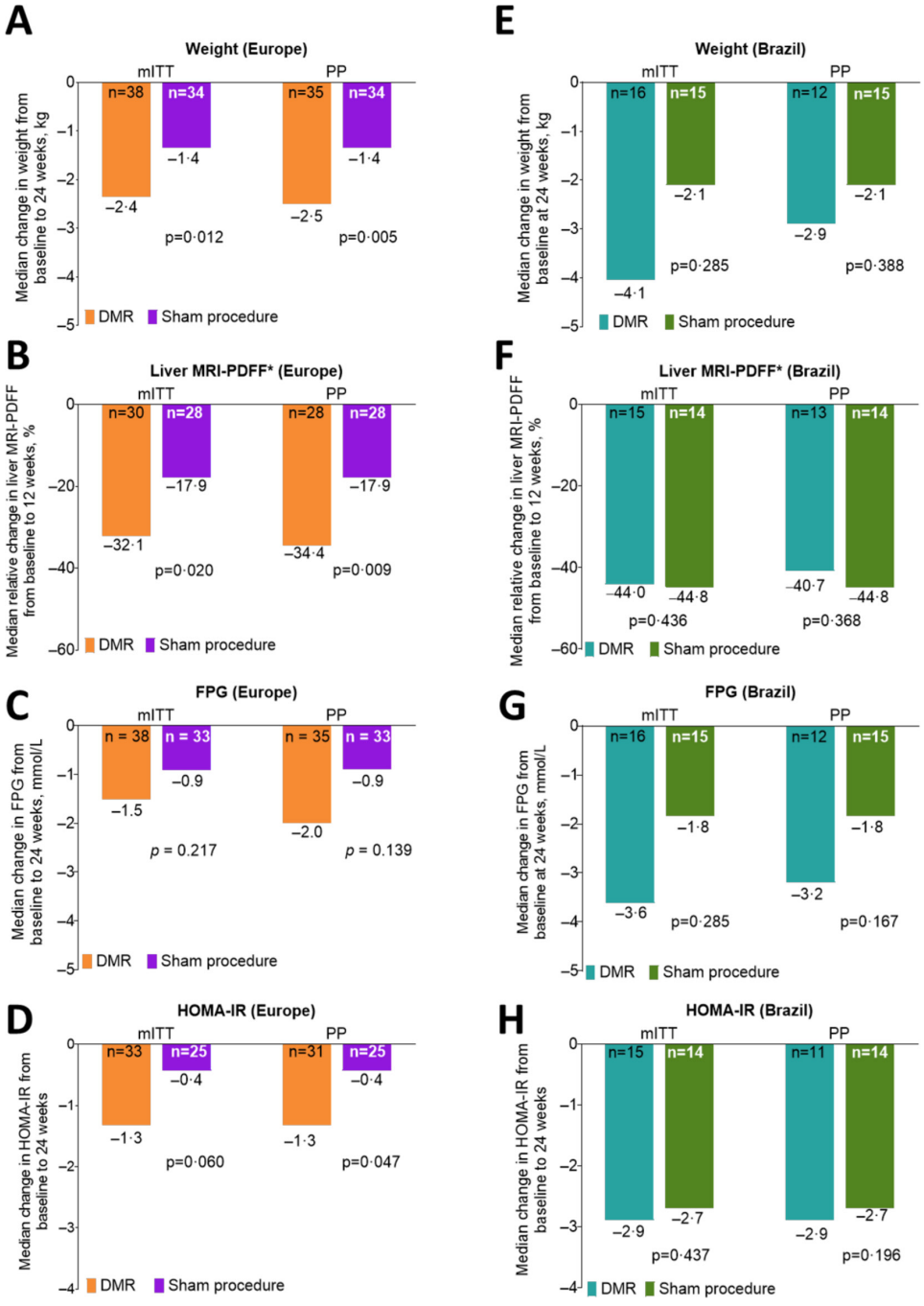

Figure 4 Clinically meaningful reductions in weight, liver fat and homeostatic model assessment of insulin resistance (HOMA-IR) with duodenal mucosal resurfacing (DMR). Median weight (kg) change from baseline to 24 weeks (DMR vs sham procedure) in the European (A) and Brazilian (B) modified intention-to-treat (mITT) and per-protocol (PP) populations. Median relative liver MRI proton density fat fraction (MRI-PDFF) per cent change from baseline to 12 weeks in patients with baseline MRI-PDFF >5% (*) in the European (C) and Brazilian (D) mITT and PP populations. Median fasting plasma glucose (FPG; millimoles per litre) change from baseline to 24 weeks (DMR vs sham procedure) in the European (E) and Brazilian (F) mITT and PP populations. Median HOMA-IR change from baseline to 12 weeks (DMR vs sham procedure) in the European (G) and Brazilian (H) mITT and PP populations. Data for continuous variables are on non-imputed unadjusted descriptive statistics based on patients with non-missing values. Treatment comparison one-sided p value based on analysis of covariance model on ranks (modified ridit scores) where post rescue values are first set to missing. Last rank carried forward on ranks was used for missing data for FPG levels, weight and HOMA-IR endpoints. HOMA-IR was determined as (FPG * fasting insulin)/135, where FPG levels were measured in millimoles per litre and fasting insulin is measured in picomoles per litre.

SAE was a precautionary hospitalisation for evaluation for a patient who noted mild haematochezia 8 days after a DMR procedure. The haematochezia was ascribed to a visible external haemorrhoid; however, the investigator adjudicated it as possibly related to procedure. The other SAE was a jejunal perforation caused by manipulation of the endoscope used in the procedure during the performance of an upper endoscopy, requiring surgical repair with no further sequelae. Hypoglycaemia (related to procedure) was reported in 47% (8/17) of patients in the DMR group and 56% (n=9/16) in the sham group with 64 and 74 events in each arm, DMR versus sham, respectively. Follow-up endoscopy was performed (n=17); overall, the duodenum appeared normal with complete healing.

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Table 3 Device-related/procedure-related adverse events through 24 weeks post procedure (safety population)

	Europe						Brazil					
	DMR N=39			Sham N=37			DMR N=17			Sham N=16		
	# of events	n (%)	95% CI‡	# of events	n (%)	95% CI‡	# of events	n (%)	95% CI‡	# of events	n (%)	95% CI‡
Summary (through 24 weeks post-treatment)												
SAE	0	0	(0.0 to 9.0)	0	0	(0.0 to 9.5)	3	2 (11.8)	(1.5 to 36.4)	0	0	(0.0 to 20.6)
UADE	0	0	(0.0 to 9.0)	0	0	(0.0 to 9.5)	0	0	(0·0 to 19.5)	0	0	(0.0 to 20.6)
AESI	19	13 (33.3)	(19.1 to 50.2)	16	10 (27.0)	(13.8 to 44.1)	74	12 (70.6)	(44.0 to 89.7)	76	10 (62.5)	(35.4 to 84.8)
Most common (≥5%) AESIs by preferred term (≤30 days post-treatment)												
Abdominal pain	9	7 (17.9)	(7.5 to 33.5)	2	2 (5.4)	(0.7 to 18.2)	6	5 (29.4)	(10.3 to 56.0)	2	2 (12.5)	(1.6 to 38.4)
Diarrhoea	1	1 (2.6)	(0.1 to 13.5)	2	2 (5.4)	(0.7 to 18.2)	1	1 (5.9)	(0.2 to 28.7)	1	1 (6.3)	(0.2 to 30.2)
Nausea	1	1 (2.6)	(0.1 to 13.5)	0	0	(0.0 to 9.5)	2	2 (11.8)	(1.5 to 36.4)	0	0	(0·0 to 20·6)
Vomiting	1	1 (2.6)	(0.1 to 13.5)	0	0	(0.0 to 9.5)	1	1 (5.9)	(0.2 to 28.7)	0	0	(0·0 to 20·6)
Hypoglycaemia	3	3 (7.7)	(1.62 to 20.9)	3	2 (5.4)	(0.7 to 18.2)	11	6 (35.3)	(14.2 to 61.7)	21	7 (43.8)	(19.8 to 70.1)
Most common (≥5%) AESIs by preferred term (>30 days post-treatment)												
Abdominal pain	1	1 (2.6)	(0.1 to 13.5)	2	2 (5·4)	(0.7 to 18.2)	0	0	(0.0 to 19.5)	0	0	(0.0 to 20.6)
Hypoglycaemia	1	1 (2.6)	(0.1 to 13.5)	4	2 (5·4)	(0.7 to 18.2)	53	5 (29.4)	(10.3 to 56.0)	52	8 (50.0)	(24.7 to 75.4)

Data are presented as n (%), with n as the number of patients with an event.
*The primary safety analysis population was defined as all patients in whom the treatment (DMR or sham) was initiated.
†European safety population included patients from Italy, UK, Belgium and Netherlands.
‡Two-sided Clopper-Pearson 95% CI of the incidence rates.
AESI, adverse event of special interest; DMR, duodenal mucosal resurfacing; SAE, serious adverse event; UADE, unanticipated adverse device effect.

DISCUSSION

In REVITA-2, a randomised, double-blind, sham-controlled, multicentre trial in patients with poorly controlled T2D with or without NAFLD, a single DMR procedure was well tolerated. Due to the regional heterogeneity revealed by interaction testing, the European and Brazilian populations were analysed separately. Though there was less power to detect a statistical difference between DMR and sham arms, in the European population DMR elicited a greater improvement than sham procedure in both primary endpoints (HbA1c and liver fat content via MRI-PDFF), as well as in secondary measures of insulin sensitivity and body weight. Significant differences in weight loss, HbA1c and hypoglycaemic events were found between the two European and Brazilian populations after unblinding, including in the sham arms. The fact that HbA1c in the sham group was reduced by 3.3 mmol/mol in the European population (consistent with prestudy assumptions), but by 17.5 mmol/mol in the Brazilian population (much greater than prestudy assumptions or even the magnitude of benefit from more potent anti-diabetic drugs) suggest these patients had a more intensive approach in their treatment of diabetes on study enrolment than the European ones, which led to the clinical and statistical differences observed between these populations. This is also true for dieting, since the weight loss was almost double in the Brazilian population as compared with the European population, which may explain the differences in observed treatment effect on MRI-PDFF in the European versus Brazilian populations. Despite the large sham effect size and smaller sample size, Brazilian patients treated with DMR also trended towards evidence of glycaemic efficacy. In Brazil, improvements in HbA1c levels compared with sham-treated patients were not significant in the primary statistical analysis of the cohort but were statistically significant on the mixed-model repeated measures sensitivity analyses.

Overall, we can affirm that in patients with marked hepatic IR (FPG ≥10 mmol/L and who represent up to 65% of patients with T2D),[25] DMR demonstrates meaningful improvements in both HbA1c and liver MRI-PDFF compared with the sham procedure. The post-hoc results in the overall population stratified by baseline FPG ≥10 mmol/L or <10 mmol/L are remarkable due to the magnitude of the effect size relative to sham in the high baseline FPG population: difference of –9.8 mmol/mol (3.0%) in HbA1c and –4.5% liver fat content between DMR and sham. This striking difference was also seen in the European population with high baseline FPG, with HbA1c reduction of −13.1 mmol/mol in DMR versus −1.6 mmol/mol in sham (p=0.005) at 24 weeks and MRI-PDFF reductions of −8.0% vs −2.1% (p=0.006) at 12 weeks. Consistent with this, DMR demonstrated statistically significant benefits on markers of IR in the European population, including HOMA-IR and Matsuda Index. Future studies enriching for patients with greater degrees of IR, such as high-baseline FPG patients, may result in a more-pronounced treatment effect of DMR on glycaemic and hepatic parameters.

Unlike for T2D, there are no proven pharmacological therapies available to treat patients with NAFLD. Meanwhile, the downstream consequences of NAFLD are now becoming more apparent with accelerated incidence rates of non-alcoholic steatohepatitis (NASH), cirrhosis, liver transplant and hepatocellular carcinoma being reported in patients with T2D.[26 27] We wanted to understand the extent of fatty liver in our patient population at baseline and throughout the study, therefore performed MRI-PDFF on patients at baseline and at week 12. Although the REVITA-2 study did not require a NAFLD diagnosis in patients at baseline, approximately 85% of patients had fatty liver, confirming prior evidence of the growing epidemiological overlap with T2D. Altogether, the prevalence of fatty liver in the overall REVITA-2 study population supports the concept and emphasises further the need for a call for action to implement effective screening programmes and methods to detect presymptomatic stages of NAFLD/NASH and liver fibrosis in patients with T2D. This approach could completely change the paradigm of how the epidemic of NAFLD/NASH is addressed today.[28] In REVITA-2, patients with NAFLD (liver MRI-PDFF >5%)[29] at baseline in the European cohort or in those patients with FPG ≥10 mmol/L showed a large magnitude and a clinically meaningful reduction in liver fat content at week 12, confirming earlier findings of non-invasive measurements (including reductions in ALT levels through 2 years).[24–26] Additionally, the European cohort has statistically significant differences between the DMR and sham arms with regards to the number of patients that had a decline of 30% or more in MRI-PDFF from baseline at week 12. Emerging data over the recent years have suggested that a 30% relative reduction in liver fat content as assessed by MRI-PDFF may be associated with histological improvement in NASH. Most recently, a multicentre study validated

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this association.[30] Liver biopsies were not performed in REVITA-2 as it was not our objective to confirm NASH in our patient population. These data provide insight into a potential therapeutic opportunity for DMR, at least in a selected population, to favourably treat both T2D and NAFLD/NASH in a manner that can modify the natural history of these chronic and progressive diseases.

Results from REVITA-2 confirm that DMR has a favourable safety profile. No UADEs were reported through 24 weeks post treatment, and there were no clinical or laboratory signs of AEs related to malabsorption, anaemia, pancreatitis, biliary complications or infection. Two SAEs were seen in the Brazilian safety population. During the study, a significantly larger number of asymptomatic events of hypoglycaemia were observed in Brazil than in Europe. After unmasking, it became clear that this is most likely due to the overall lower levels of ambient glycaemia in the Brazilian population relative to the European patients and also raises important considerations of the use of DMR in conjunction with antihyperglycaemic agents that have a known risk of causing hypoglycaemia (ie, sulfonylureas). Further assessment of the long-term (48 week) safety and efficacy of DMR is underway.

Limitations of this feasibility study include the relatively small patient population and heterogeneity between European and Brazilian populations. Moreover, the trial was not stratified for baseline characteristics relative to the secondary outcomes; therefore, differences in baseline insulin concentrations, length of time with T2D and number of baseline medications were found, and this may be contributing to differences in outcomes. Next, while full type-1 error was incorporated for the two primary endpoints, we acknowledge that there is a lack of control for false discovery rate in this study for our secondary and exploratory endpoints; therefore, those results should be interpreted with appropriate context. In relation to the differences in statistical and clinical results seen between the European and Brazilian populations, it is important to acknowledge that adherence to previously prescribed medications could not be objectively assessed in this study and race was not collected in the majority of the patient population in Europe. In a follow-up study, it will also be important to confirm the MRI-PDFF results with additional non-invasive tests such as fibroscan to evaluate Revita DMR's potential to additionally improve liver fibrosis. Lastly, this short-term study concluded at 48 weeks. Follow-up data on the 48 week DMR results are forthcoming, as well as plans for a pivotal study (Revita T2Di; NCT04419779) in T2D insulin-treated patients. This will be important research to confirm the metabolic benefits seen thus far in patients with T2D with or without NAFLD, provide long-term follow-up (including biopsies of the duodenal mucosa to further understand the long-term morphological changes), and provide the opportunity to understand the biological mechanisms likely behind the benefit of DMR on the treatment of these pathological conditions.

In conclusion, DMR is a safe procedure that significantly improved glycaemic control and reduced liver fat content in the European population compared with the sham procedure. In addition, a post-hoc analysis in the overall population showed that patients with high baseline FPG levels (≥10 mmol/L) had significantly greater reductions in HbA1c post-DMR, versus sham.

Author affiliations
[1]Division of Obesity and Metabolic Diseases, Fondazione Policlinico Universitario A. Gemelli IRCCS-Università Cattolica del Sacro Cuore, Rome, Italy
[2]Department of Diabetes, School of Life Course Sciences, King's College London, London, UK
[3]Departments of Gastroenterology and Hepatology, Academic Medical Center Amsterdam, Amsterdam, The Netherlands
[4]Department of Gastroenterology, Erasme University Hospital, Brussels, Belgium
[5]Institute of Diabetes, Endocrinology and Obesity, King's Health Partners, London, UK
[6]Department of Gastroenterology, Universidade de Sao Paulo Medical School, Sao Paulo, Brazil
[7]Obesity Unit, Department of Endocrinology, Hospital das Clínicas, University of Sao Paulo, Sao Paulo, Brazil
[8]Research and Development, Fractyl Laboratories, Inc, Lexington, Massachusetts, USA
[9]Digestive Endoscopy Unit, Fondazione Policlinico Universitario A. Gemelli IRCCS-Università Cattolica del Sacro Cuore, Rome, Italy
[10]Department of Gastroenterology, King's College Hospital, London, UK
[11]Department of Surgery, ABC University, Medical School, São Paulo, Brazil
[12]NIHR Nottingham Biomedical Research Centre, Ottingham University Hospitals NHS Trust and the University of Nottingham, Nottingham, UK
[13]Humanitas Clinical and Research Center – IRCCS, Rozzano, Italy
[14]Humanitas University, Department of Biomedical Sciences, Milan, Italy
[15]King's Institute of Therapeutic Endoscopy, King's College Hospital, London, UK
[16]Department of Gastroenterology, Glasgow Royal Infirmary, Glasgow, UK
[17]Gastroenterology Department, University of Leuven, Leuven, Belgium
[18]Division of Medicine, University College London Center for Medical Imaging, London, UK
[19]Division of Cardiovascular Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts, USA
[20]Division of Gastroenterology, Hepatology and Nutrition, Department of Internal Medicine, Virginia Commonwealth University School of Medicine, Richmond, Virginia, USA

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Collaborators Investigators of the REVITA-2 Study: Eduardo Grecco, Ana Teresa Santomauro (ABC Hospital, Sao Paulo, Brazil); Jacques Bergman, Max Nieuwdorp (Academic Medical Center Amsterdam, Amsterdam, Netherlands); John Morris, Russell Drummond, David Carty (Glasgow Royal Infirmary, Glasgow, UK); Jacques Devière, Laurent Crenier (Hopital Erasme, Brussels, Belgium); Eduardo Moura, Cintia Cercato (Hospital Das Clinical, Sao Paulo, Brazil); Alessandro Repici, Andrea Lania, Nazerena Betella (Humanitas Research Hospital, Milano, Italy); David Hopkins, Bu Hayee, Amyn Haji (King's College London, London, UK); Krish Ragunath, Iskander Idris, Carolyn Chee (Queen's Medical Centre, Nottingham, Nottingham, UK); Geltrude Mingrone, Guido Costamagna, Caterina Guidone (Università Cattolica del Sacro Cuore, Rome, Italy); Rehan Haidry, Rachel Batterham (University College Hospital, London, London, UK); Raf Bisschops, Ann Mertens (UZ Leuven, Leuven, Belgium).

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ORCID iDs
Geltrude Mingrone http://orcid.org/0000-0003-2021-528X
Guruprasad Aithal http://orcid.org/0000-0003-3924-4830
Bu'Hussain Hayee http://orcid.org/0000-0003-1670-8815
Amyn Haji http://orcid.org/0000-0002-6508-6488
Raf Bisschops http://orcid.org/0000-0002-9994-8226
J J G H M Bergman http://orcid.org/0000-0001-7548-6955

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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

Geltrude Mingrone, Annieke CG van Baar, Jacques Devière, David Hopkins, Eduardo GH de Moura, Cintia Cercato, Harith Rajagopalan, Juan Carlos Lopez-Talavera, Kelly White, Vijeta Bhambhani, Guido Costamagna, Rehan Haidry, Eduardo Grecco, Manoel Galvão Neto, Guruprasad P Aithal, Alessandro Repici, Bu Hayee, Amyn Haji, A John Morris, Raf Bisschops, Manil D Chouhan, Naomi S Sakai, Deepak L Bhatt, Arun J Sanyal, Jacques JGHM Bergman

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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.

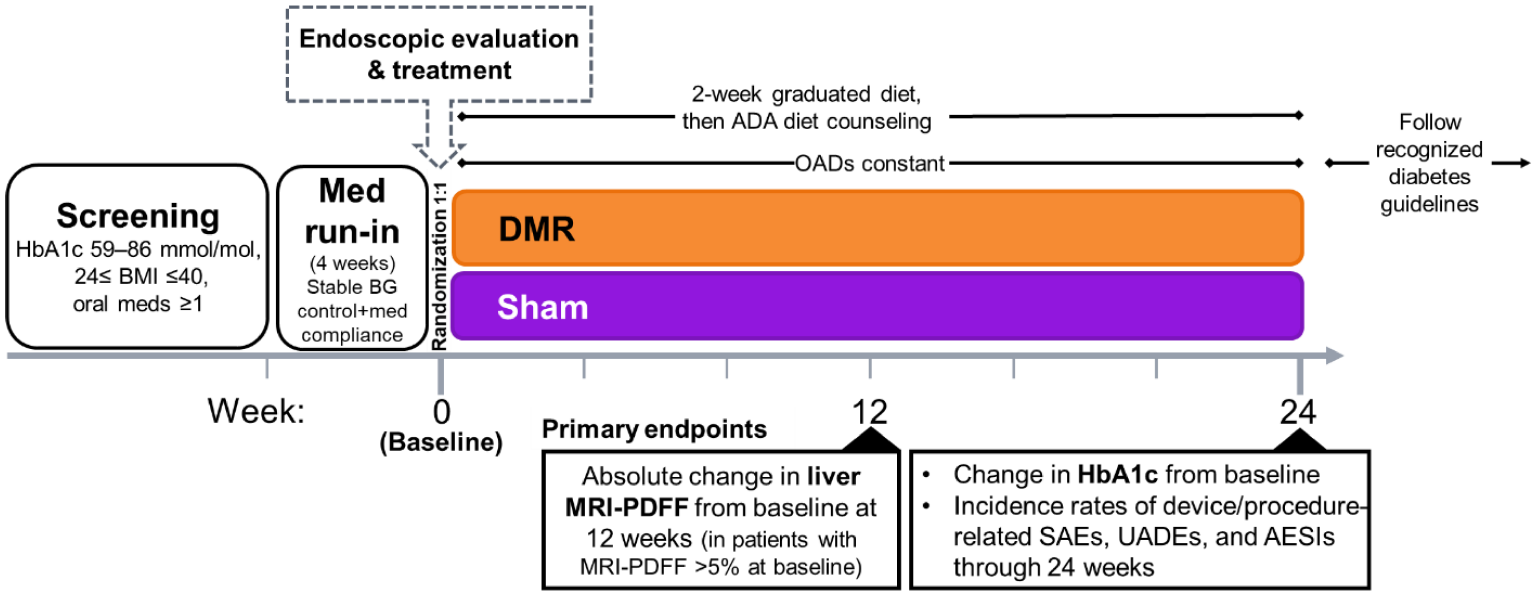
Prespecified assessments of homogeneity across regions evaluated consistency in treatment effect across geographic regions (Belgium, Brazil, Italy, Netherlands, and United Kingdom) for each of the two primary endpoints in the modified intent-to-treat analysis population using multiply imputed data and 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

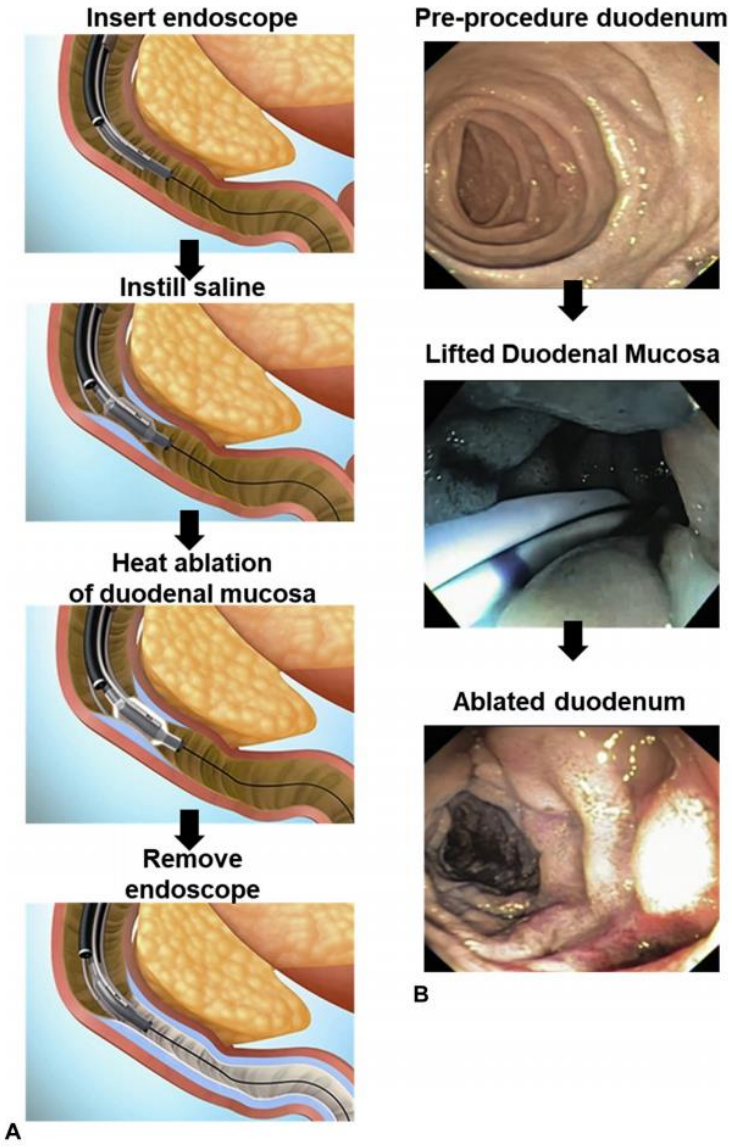
Only one patient in the sham group in Brazil did not attend subsequent appointments and was ultimately lost to follow-up. Two patients in the European cohorts withdrew consent (1 in the DMR and 1 in the sham group at 1 and 5 months, respectively). One patient in the sham group in Europe discontinued 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



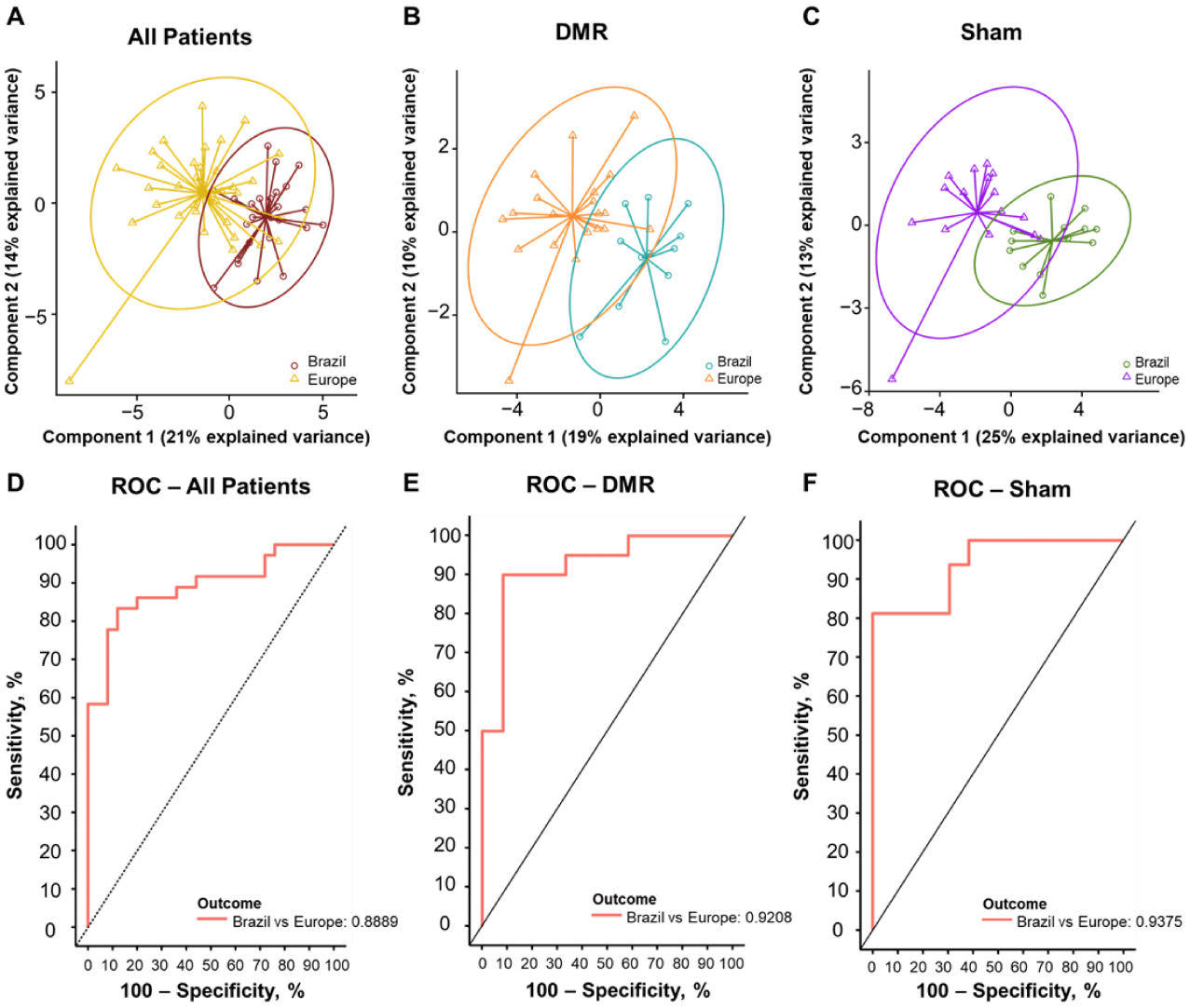
Supplementary Figure 1: Study design schematic ADA, American Diabetes Association; AESI, adverse event of special interest; BG, blood glucose; BMI, body mass index; DMR, duodenal mucosal resurfacing; HbA1c, haemoglobin A1; MRI-PDFF, magnetic resonance imaging proton density fat fraction; OAD, oral antidiabetic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

Supplementary Figure 2



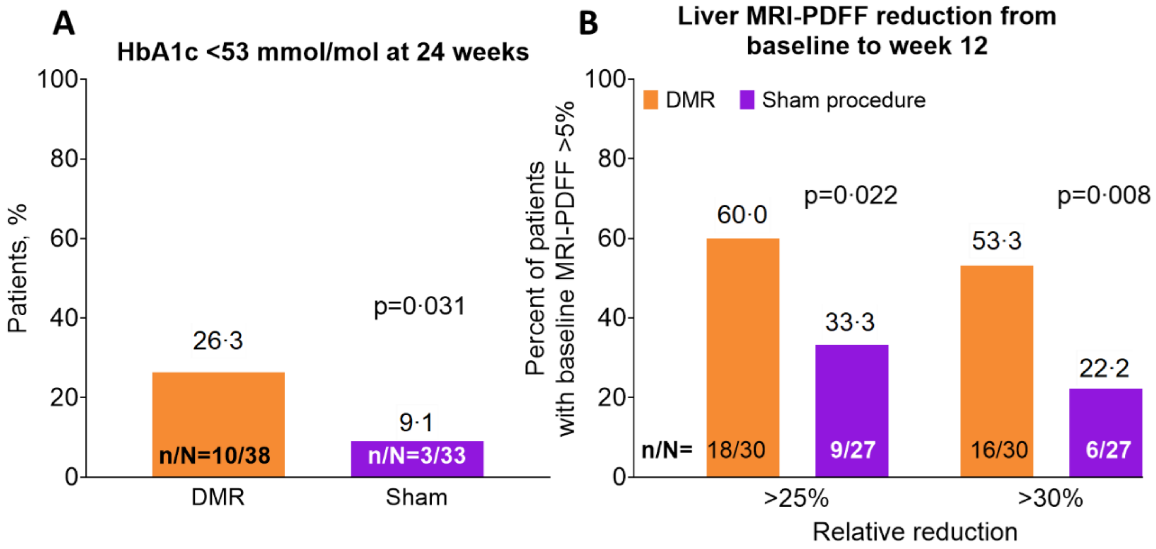
Supplementary Figure 2*:* Duodenal mucosal resurfacing procedure (A) Animation snapshots. (B) Endoscopic snapshots. Reprinted from Gastrointestinal Endoscopy, volume 90(4), Haidry RJ et al., Duodenal mucosal resurfacing: proof-of-concept, procedural development, and initial implementation in the clinical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

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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.

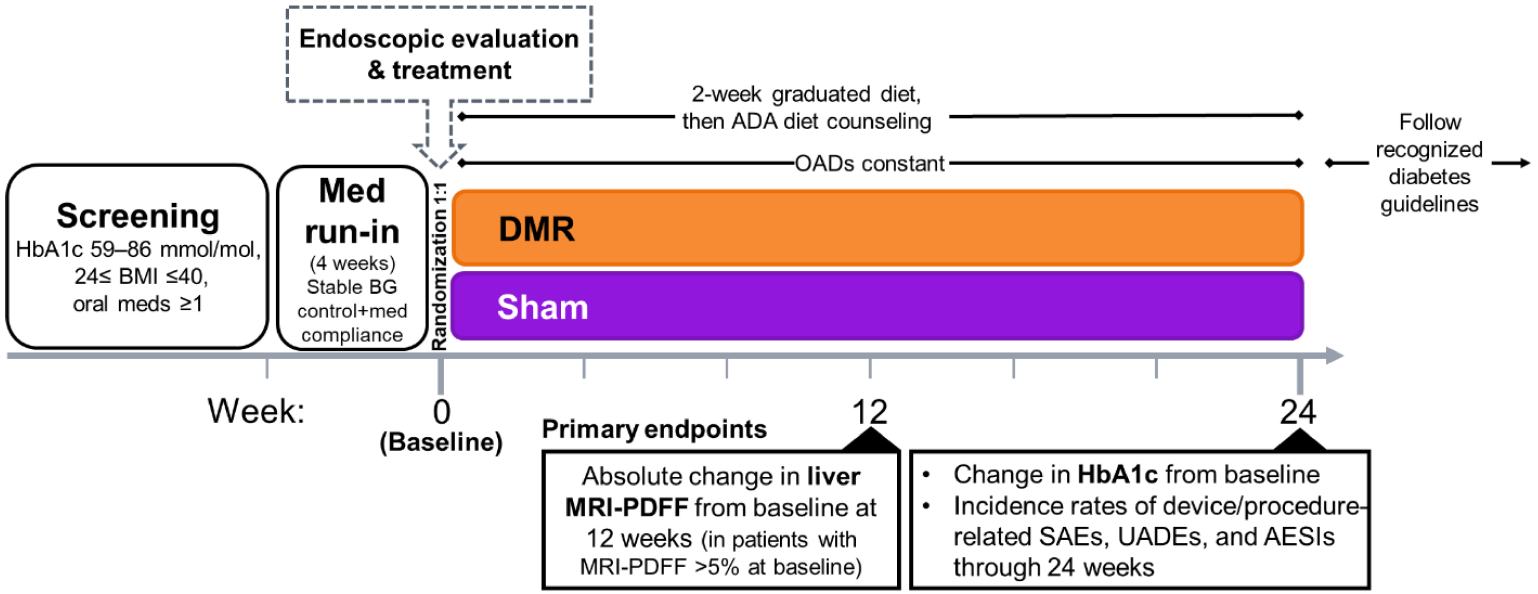
Prespecified assessments of homogeneity across regions evaluated consistency in treatment effect across geographic regions (Belgium, Brazil, Italy, Netherlands, and United Kingdom) for each of the two primary endpoints in the modified intent-to-treat analysis population using multiply imputed data and 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

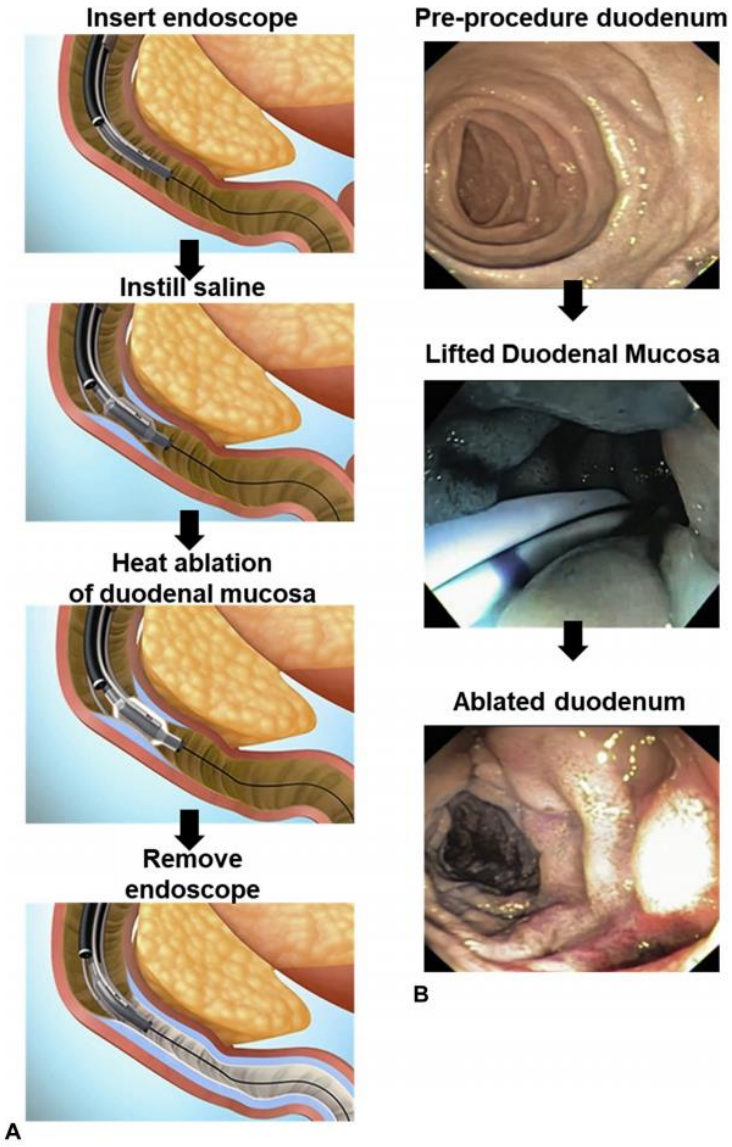
Only one patient in the sham group in Brazil did not attend subsequent appointments and was ultimately lost to follow-up. Two patients in the European cohorts withdrew consent (1 in the DMR and 1 in the sham group at 1 and 5 months, respectively). One patient in the sham group in Europe discontinued 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



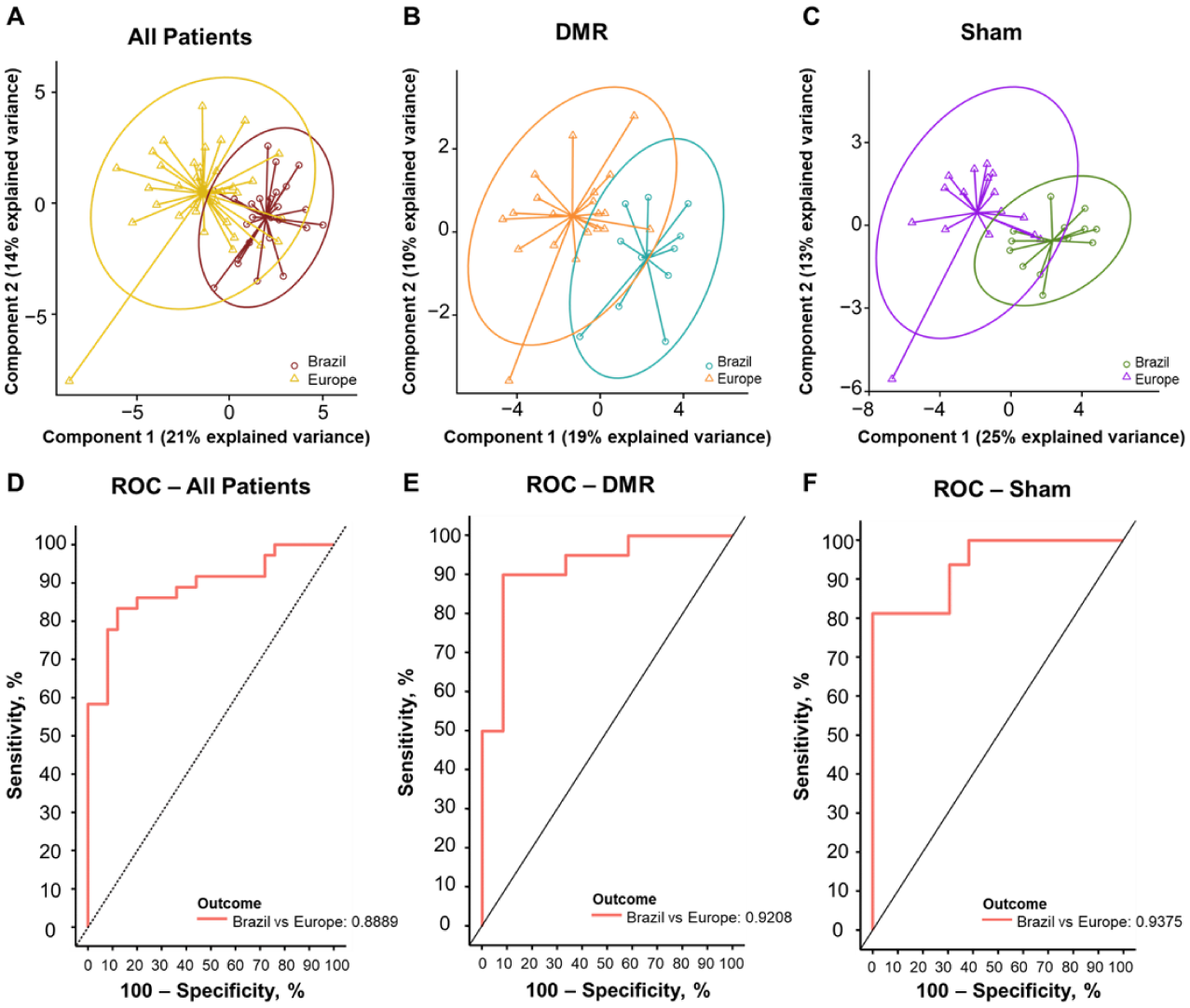
Supplementary Figure 1: Study design schematic ADA, American Diabetes Association; AESI, adverse event of special interest; BG, blood glucose; BMI, body mass index; DMR, duodenal mucosal resurfacing; HbA1c, haemoglobin A1; MRI-PDFF, magnetic resonance imaging proton density fat fraction; OAD, oral antidiabetic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

Supplementary Figure 2



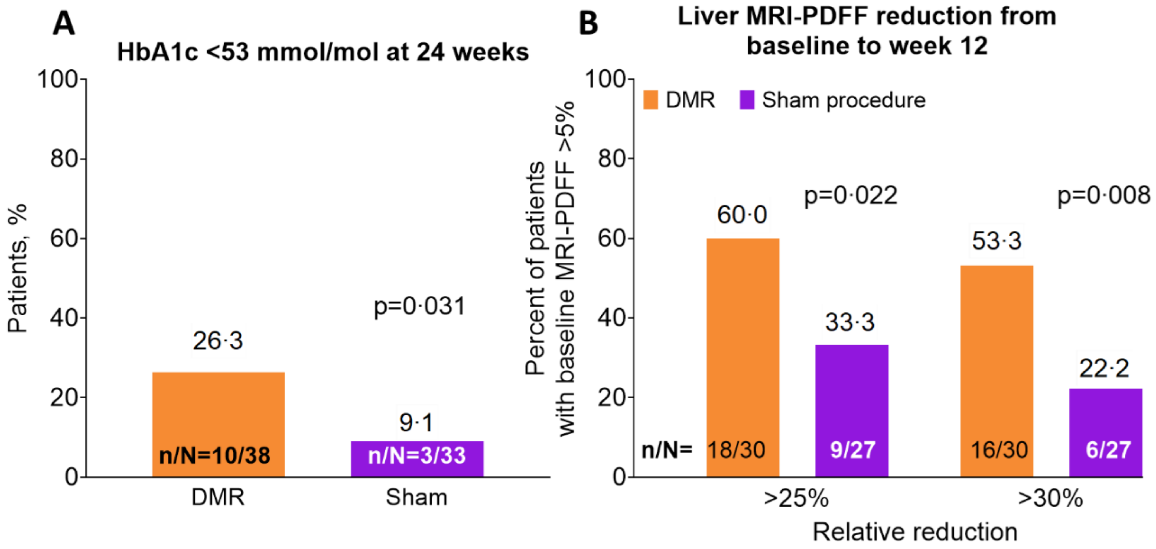
Supplementary Figure 2*:* Duodenal mucosal resurfacing procedure (A) Animation snapshots. (B) Endoscopic snapshots. Reprinted from Gastrointestinal Endoscopy, volume 90(4), Haidry RJ et al., Duodenal mucosal resurfacing: proof-of-concept, procedural development, and initial implementation in the clinical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