Durable Glycemic Improvements After Duodenal Mucosal Resurfacing (DMR) in Patients with Type 2 Diabetes (T2D): 48-week Results From the REVITA-2 European Cohort

T21-LB

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Background

- The duodenum is a metabolic signaling center and key regulator of metabolic homeostasis[1]
  - High-fat/sugar diet–induced hyperplasia of the duodenal lining alters hormonal signaling and nutrient absorption from the duodenum and is thought to be a root cause of insulin resistance, hyperinsulinemia, and impaired glucose metabolism[1,2]
  - Gastric bypass of the duodenum reverses metabolic disease in patients with type 2 diabetes mellitus (T2D)[3–5]
- Duodenal mucosal resurfacing (DMR) is a minimally invasive endoscopic procedure designed to treat insulin resistance–related metabolic diseases via hydrothermal rejuvenation of duodenal mucosa, leading to improvement in insulin sensitivity[6,7]
  - DMR is a well-tolerated procedure with few self-limited side effects[2,8,9]
  - Results from the multicenter, international, open-label, prospective REVITA-1 study showed a single DMR procedure durably improves glycemic and hepatic parameters through 2 years in patients with T2D, indicating potential benefit in T2D[8,10]
- Primary (24 week) results from REVITA-2, the first randomized, sham-controlled, double-blind, prospective, multicenter study, demonstrated that a single DMR procedure safely elicits noteworthy improvements in glycemic and hepatic parameters in patients with suboptimally controlled T2D and reduced liver fat content indicating potential benefit in T2D with concomitant nonalcoholic fatty liver disease/nonalcoholic steatohepatitis (NAFLD/NASH)[11]

Objective

- To evaluate the durability of glycemic results through 48 weeks posttreatment in patients participating in REVITA-2 at 9 European study centers

Methods

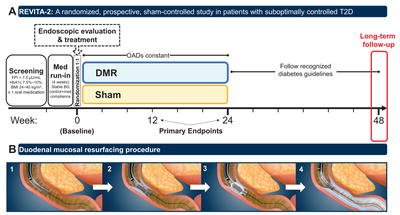
Patients

- Key inclusion criteria:
  - Aged 28–75 years
  - T2D with evidence of preserved insulin secretion (fasting insulin > 7.0 µU/mL)
  - Hemoglobin A1c (HbA1c) levels 7.5%–10.0% (59–86 mmol/mol)
  - Body mass index of 24–40 kg/m^2
  - Taking ≥ 1 oral antidiabetic drug, 1 must be metformin
  - No antidiabetic medication or dose changes 12 weeks prior to study entry
  - Ability to comply with study requirements and understand/sign informed consent document
- Exclusion criteria:
  - Current use of insulin or glucagon-like peptide-1
  - History of severe hypoglycemia (≥ 1 severe hypoglycemic event, as defined by need for third-party assistance, in the last year)
  - Known autoimmune disease
  - Active *Helicobacter pylori* infection
  - Previous gastrointestinal surgery (including bariatric)
  - Participation in another ongoing clinical trial of an investigational drug or device

REVITA-2 Study Design and DMR Procedure

- REVITA-2 was a randomized, prospective, double-blind (patient and endocrinologist), sham-controlled, multi-center, international study of DMR efficacy and safety in patients with sub-optimally controlled T2D (NCT02879383) **(Figure 1)**
- The primary results at 12 and 24 weeks were previously reported[11]
- Here, long-term follow-up results are presented through 48 weeks post-DMR

Figure 1. REVITA-2 Study Design and DMR Procedure



(A) REVITA-2 study design schematic. (B) DMR procedure schematic. DMR was performed as previously described.[7,8] Briefly, under general anesthesia or conscious sedation, the Revita® catheter was placed in the proximal duodenum distal to the papilla using a guidewire (Step 1). Then, the balloon was inflated, and the vacuum drew the intestinal mucosal tissue onto the ports on the balloon; the console delivered saline into the submucosa through the needles within the lumens of the catheter to create a complete circumferential lift of the mucosa (Step 2). The ablation cycle was started, and hot water (~90°C) was circulated into the balloon to ablate the previously expanded tissue (Step 3). The balloon was deflated, and the process of expansion, ablation, and repositioning was repeated distally until the needed length of duodenum was treated. Finally, the catheter and endoscope were removed (Step 4). BG = blood glucose; BMI = body mass index; DMR = duodenal mucosal resurfacing; FPI = fasting plasma insulin; HbA1c = hemoglobin A1c; OAD = oral antidiabetic drug; T2D = type 2 diabetes.

Assessments

Efficacy

- Median change from baseline in HbA1c, homeostatic model assessment of insulin resistance (HOMA-IR), and weight through 48 weeks
- Proportion of patients with an improvement in HbA1c or HOMA-IR from baseline to 24 weeks who maintained an improvement from baseline through 48 weeks
- Percent of patients achieving HbA1c < 7%

Safety

- Incidence rate of serious adverse events (SAEs), unanticipated adverse device effects, procedure- and device-related SAEs and unanticipated adverse device effects, and number of clinically significant hypoglycemic events (blood glucose levels < 54 mg/dL)

Statistical Analysis

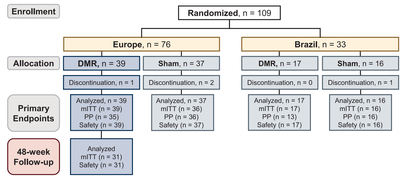
- The modified intent-to-treat (mITT) population included randomized patients in whom a procedure was attempted and who had a baseline measurement for at least 1 primary endpoint
- The per-protocol population included the subset of mITT patients who received the treatment to which they were randomized, excluding any patients with major protocol deviations
- Analyses were based on all patients in the mITT population where patients lost to follow-up were excluded, and data obtained post-rescue medication were set to missing
- Because of non-normality of the data, significance at the 0.05 level was determined using a 2-sided Wilcoxon signed-rank test
- Treatment responder for HbA1c or HOMA-IR was defined as any patient who experienced a reduction from baseline

Results

Patients

- 31 of 39 patients randomized to DMR (European mITT) were followed to 48 weeks, 8 patients were lost to follow-up **(Figure 2)**
- Most patients were white and male **(Table 1)**
- Baseline HbA1c was 8.1% and HOMA-IR was 4.8

Figure 2. Patient Disposition



109 of 359 patients assessed for eligibility were randomized. One patient did not receive treatment because of esophageal varices; therefore, the mITT population included 108 patients—75 in Europe (39 to DMR and 36 to sham) and 33 in Brazil (17 to DMR and 16 to sham). Prespecified assessments of normality and homogeneity revealed that the European and Brazilian populations could not be pooled. Therefore, all efficacy and safety analyses were stratified into 2 populations (Europe and Brazil), and here we report only the results relative to the European population.
DMR = duodenal mucosal resurfacing; mITT = modified intent to treat; PP = per protocol.

Table 1. Demographics and Baseline Characteristics (European mITT Population[a])

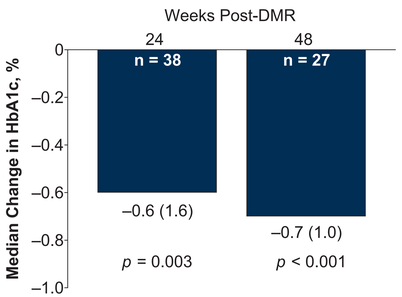
Parameter	DMR (N = 39)
Sex, n (%)	
Female	9 (23.1)
Male	30 (76.9)
Age, years	59.0 (13.0)
Race, n (%)	
White	25 (64.1)
Black	0
Asian	0
Other	1 (2.6)
Undisclosed	13 (33.3)
Weight, kg	93.1 (16.5)
BMI, kg/m^2	31.4 (4.5)
HbA1c	
%	8.1 (0.7)
mmol/mol	65.0 (7.0)
Fasting insulin, pmol/L	68.1 (5.6)
HOMA-IR	4.8 (3.9)
Fasting glucose, mmol/L	10.6 (4.3)
Duration of T2D at screening, years	10.3 (8.7)
Antidiabetic medications, n (%)	
1	8 (20.5)
2	18 (46.2)
3	12 (30.8)
> 3	1 (2.6)
Diabetes medication use at screening, years	8.2 (7.1)

Data for continuous variables are presented as median (IQR), unless otherwise noted.
[a]mITT population was defined as all randomized patients in whom the study procedure (DMR or sham) was attempted and who had a baseline measurement for at least 1 primary endpoint. European countries included Italy, United Kingdom, Belgium, and Netherlands.
BMI = body mass index; DMR = duodenal mucosal resurfacing; HbA1c = hemoglobin A1c; HOMA-IR = homeostatic model assessment of insulin resistance; IQR = interquartile range; mITT = modified intent to treat; T2D = type 2 diabetes mellitus.

Efficacy Results

- Median change from baseline HbA1c was –0.6% at 24 weeks (n = 38, p = 0.003) and –0.7% at 48 weeks (n = 27, p < 0.001) **(Figure 3)**
- 68% of patients achieved a reduction in HbA1c from baseline at 24 weeks (median HbA1c change, –1.1%) and were defined as responders **(Table 2)**
- Most responders (84%) maintained a durable response through 48 weeks (median interquartile range HbA1c change, –1.0% [2.0]) without an increase in antidiabetic medication **(data on file)**
- 33% of patients (9/27) had an HbA1c < 7% at 48 weeks

Figure 3. HbA1c Was Significantly Reduced at 24 Weeks and at 48 Weeks Post-DMR (European mITT Population)



Median (IQR) percent change in HbA1c from baseline at 24 and 48 weeks.
DMR = duodenal mucosal resurfacing; HbA1c = hemoglobin A1c; IQR = interquartile range; mITT = modified intent to treat.

Table 2. Durability of Response to DMR in Patients with HbA1c Improvement (mITT Population)

	Magnitude of improvement from baseline (N = 39)	
	n (%)	Median (IQR)
Patients with HbA1c improvement from baseline		
24 weeks	26/38 (68.4)	–1.1 (1.0)
Maintained at 48 weeks	17/19 (89.5)	–1.1 (0.8)
Patients with no improvement in HbA1c from baseline		
24 weeks	12/38 (31.6)	0.7 (0.9)
Improvement at 48 weeks	5/8 (62.5)	–0.7 (0.2)

DMR = duodenal mucosal resurfacing; HbA1c = hemoglobin A1c; IQR = interquartile range; mITT = modified intent to treat.

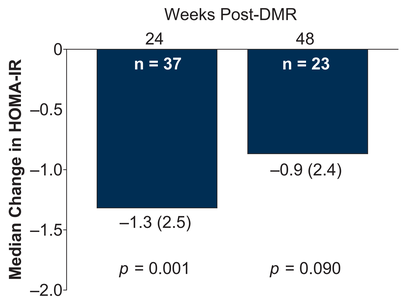
Table 3. Change in Oral Antidiabetic Medication From Baseline to Week 48 (mITT Population)

OAD medication change from baseline	DMR N = 31
Increase	4 (12.9)
Neutral	25 (80.6)
Decrease	2 (6.5)

Data are presented as n (%).
DMR = duodenal mucosal resurfacing; mITT = modified intent to treat; OAD = oral antidiabetic.

- Median raw change from baseline in HOMA-IR was –1.3 at 24 weeks (n = 37, p = 0.001) and –0.9 at 48 weeks (n = 23, p = 0.090) **(Figure 4)**
- 82% of patients achieved a reduction in HOMA-IR from baseline at 24 weeks (median HOMA-IR change, –1.7%) and were defined as responders **(Table 4)**
- Most responders (73%) maintained a durable response through 48 weeks (median HOMA-IR change, –1.6)

Figure 4. HOMA-IR Was Significantly Reduced at 24 Weeks Post-DMR and Remained Below Baseline at 48 Weeks (European mITT Population)



Median (IQR) percent change in HOMA-IR from baseline at 24 and 48 weeks.
DMR = duodenal mucosal resurfacing; HOMA-IR = homeostatic model assessment of insulin resistance; IQR = interquartile range; mITT = modified intent to treat.

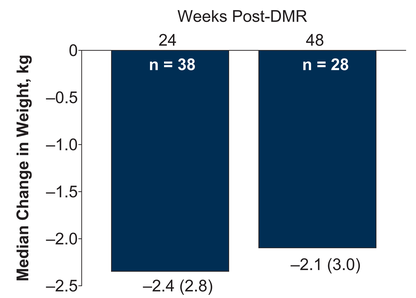
Table 4. Durability of Response to DMR in Patients with Improvement in HOMA-IR (mITT Population)

	Magnitude of improvement from baseline (N = 39)	
	n (%)	Median (IQR)
Patients with HOMA-IR improvement from baseline		
24 weeks	27/33 (81.8)	–1.7 (2.9)
Maintained at 48 weeks	11/15 (73.3)	–1.6 (4.0)
Patients with no improvement in HOMA-IR from baseline		
24 weeks	6/33 (18.2)	2.2 (5.1)
Improvement at 48 weeks	2/3 (66.7)	–0.2 (0.5)

DMR = duodenal mucosal resurfacing; HOMA-IR = homeostatic model assessment of insulin resistance; IQR = interquartile range; mITT = modified intent to treat.

- Median weight change was –2.4 kg at 24 weeks (n = 38, p < 0.001) and –2.1 kg at 48 weeks (n = 28, p = 0.003) **(Figure 5)**

Figure 5. Body Weight Was Significantly Reduced at 24 Weeks and Reduction Was Maintained 48 Weeks Post-DMR (European mITT Population)



Median (IQR) percent change in weight from baseline at 24 and 48 weeks.
DMR = duodenal mucosal resurfacing; IQR = interquartile range; mITT = modified intent to treat.

Safety Results

- No device- or procedure-related adverse events or unanticipated adverse device effects were noted between 24- and 48-weeks post-DMR

Conclusions

- A single DMR procedure safely elicits durable, clinically significant glycemic improvements through 48 weeks post-treatment in patients with suboptimally controlled T2D
  - Most patients who respond at 24 weeks maintain the beneficial effects at 48 weeks without needing additional medication

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DISCLOSURES

D Hopkins has received honorarium for consultancy and/or speaker fees from Novo Nordisk, Sanofi, AstraZeneca, Roche, Sunovion, and Fractyl Laboratories Inc. **G Mingrone** has received funding/grant support from Novo Nordisk, Fractyl Laboratories Inc, and Metacure, Keyron Ltd, and honorarium for consultancy from Johnson & Johnson, Novo Nordisk, and Fractyl Laboratories Inc. **GP Aithal** has served as a consultant and an advisory board member for Agios Pharmaceuticals Inc, Amryt Pharma, AstraZeneca, GlaxoSmithKline, and Pfizer. **G Costamagna** has received research grant support from Boston Scientific and Apollo and is on the advisory board for Cook Medical, Olympus, and Ethicon. **L Crenier** has received honorarium for consultancy and/or speaker fees from Novo Nordisk, Sanofi, AstraZeneca, Boehringer Ingelheim, and Eli Lilly. **J Devière** has received research support from Fractyl Laboratories Inc, Boston Scientific, and Olympus for IRB-approved studies. **R Drummond** has received honorarium for consultancy and/or speaker fees from Novo Nordisk, Sanofi, AstraZeneca, Napp, and Boehringer Ingelheim. **R Haidry** has received funding/grant support/honorarium for consultancy services from Cook Endoscopy, Pentax Europe, Medtronic, CJ Therapeutics, and Fractyl Laboratories Inc to support research infrastructure. **I Idris** has received a research grant from Eli Lilly and speaker fees from Eli Lilly, Sanofi, MSD, Napp, AstraZeneca, Novo Nordisk, and Boehringer Ingelheim. **A Lania** has received funding/grant support from Ipsen and Pfizer and honorarium for consultancy services from Ipsen. **C Magee** has no conflicts of interest to disclose. **M Nieuwdorp** has received research support from Eli Lilly, Novo Nordisk, and Boehringer Ingelheim, and has received an unrestricted grant from AstraZeneca. **JC Lopez-Talavera, H Rajagopalan, V Bhambhani, JHS Huang,** and **K White** are full-time employees of Fractyl Laboratories Inc and may hold Fractyl stock and/or stock options. **JJGHM Bergman** received research support from Fractyl for IRB-based studies and received a consultancy fee from Fractyl for a single advisory board meeting in September 2019.

ACKNOWLEDGMENTS

Fractyl Laboratories Inc participated in the study design; study research; collection, analysis, and interpretation of data; and writing, reviewing, and approving this poster. All authors had access to the data; participated in the development, review, and approval of this poster for presentation at the 80th Scientific Sessions of the American Diabetes Association. Fractyl funded the research for this study and provided writing support for this poster. Medical writing assistance, funded by Fractyl, was provided by Caroline Casares, PhD, of JB Ashtin.

Presented at the 80th Scientific Sessions of the American Diabetes Association | June 12–16, 2020 | Chicago, IL

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