Mixed-meal tolerance test (MMTT) results from REVITA-2, the first randomized, sham-controlled, double-blind, prospective, multicenter study of duodenal mucosal resurfacing (DMR) safety and efficacy in patients with suboptimally controlled type 2 diabetes (T2D)

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Disclosures

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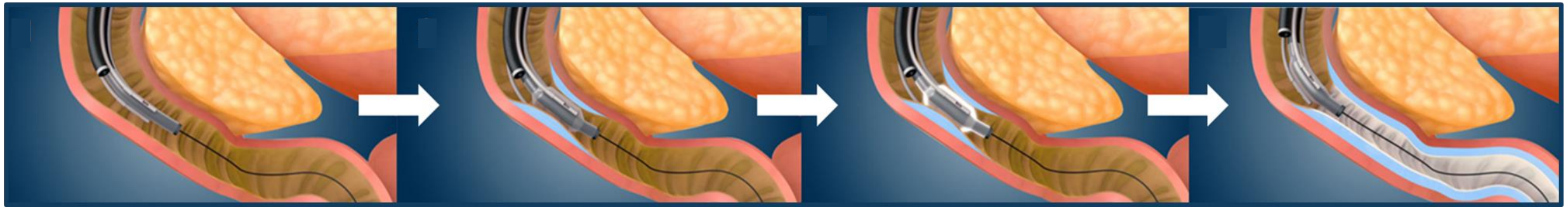
Introduction

- Novel, disease-modifying approaches are needed to treat and improve clinical outcomes in T2D
- The **duodenum** is a key regulator of metabolic homeostasis[1]
  - Diet-induced hyperplasia of duodenal mucosa alters hormonal signaling and nutrient absorption from duodenum, which has been proposed to be the root cause of insulin resistance and hyperinsulinemia[2]
  - Duodenal bypass surgery (eg, RYGB) reverses metabolic disease[3] in patients with T2D[4,5] and/or NAFLD/NASH,[6] which often co-exist in same patient
- Targeting duodenal mucosal hyperplasia is a potential therapeutic option for T2D[1]

1.Van Baar et al, *Gastroenterology*. 2018;154:773. 2. Cherrington et al, *Gastrointest Endosc Clin N Am*. 2017;27:299-311. 3. Cummings et al, SOARD. 2007;3:109-115. 4. Mingrone et al, *NEJM*. 2012;366:1577. 5. Schauer et al, *NEJM*. 2012;366:1567. 6. Lassailly et al, *Gastroenterology*. 2015;149:379.

RYGB = roux-en-Y gastric bypass; NAFLD = nonalcoholic fatty liver disease; NASH = nonalcoholic steatohepatitis; T2D = type 2 diabetes.

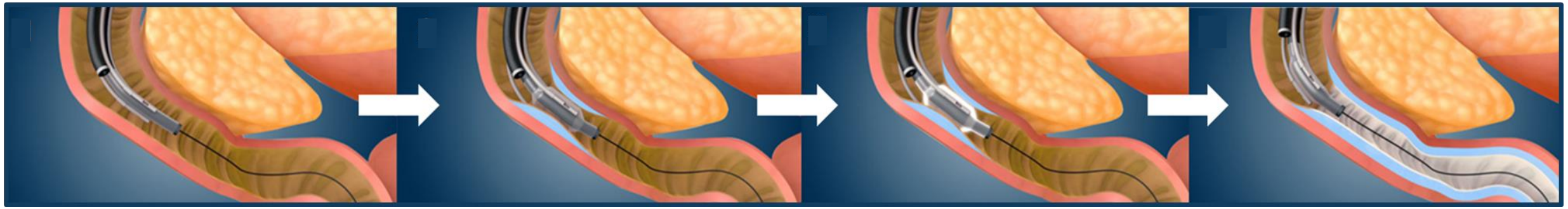
DMR: A novel, minimally invasive, outpatient, upper endoscopic procedure



- Revita® DMR catheter is designed to perform submucosal lift and hydrothermal ablation of hyperplastic duodenal mucosa, promote healthy epithelial regrowth within 12 weeks, and reduce insulin resistance and hyperinsulinemia[1,2]

1. Hadefi A et al, *Dig Dis*. 2018;36:322-324. 2. Rajagopalan H et al, *Diabetes Care*. 2016;39:2254-2261.
DMR = duodenal mucosal resurfacing.

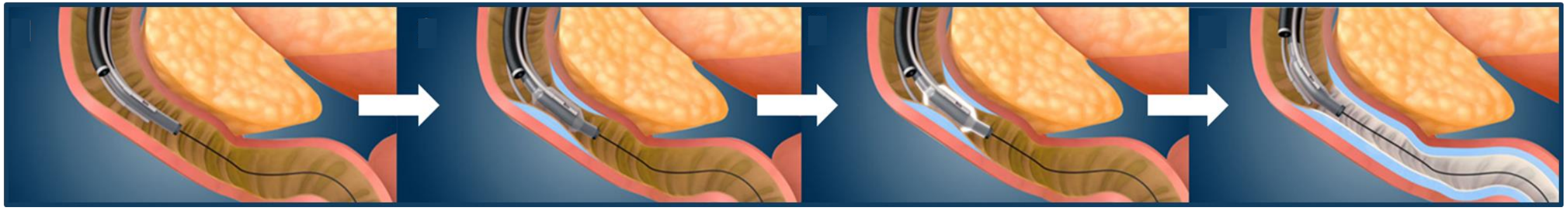
DMR: A novel, minimally invasive, outpatient, upper endoscopic procedure



- DMR is a well-tolerated procedure with few, self-limited side effects[1-3]

1. Cherrington A et al, *Gastrointest Endoscopy Clin N Am*. 2017;27:299-311. 2. Van Baar A et al, *Gut*. 2019; pii: gutjnl-2019-318349. 3. Haidry R et al, *GIE*. 2019; 673-681.e2.
DMR = duodenal mucosal resurfacing.

DMR: A novel, minimally invasive, outpatient, upper endoscopic procedure



- DMR is a well-tolerated procedure with few, self-limited side effects[1-3]
- Prior studies (eg, REVITA-1) showed a single DMR procedure durably improves glycemic and hepatic parameters through 2 years in patients with T2D, indicating potential benefit in T2D with concomitant NAFLD/NASH[3-4]

1. Cherrington A et al, *Gastrointest Endoscopy Clin N Am*. 2017;27:299-311. 2. Van Baar A et al, *Gut*. 2019; pii: gutjnl-2019-318349. 3. Haidry R et al, *GIE*. 2019; 673-681.e2. 4. van Baar ACG et al, Poster presented at Diabetes Technology Meeting: November 2019 Bethesda, MD.

DMR = duodenal mucosal resurfacing; NAFLD = nonalcoholic fatty liver disease; NASH = nonalcoholic steatohepatitis; T2D = type 2 diabetes.

REVITA-2: Prospective, sham-controlled study of DMR's effect on glycemic parameters in patients with T2D

Objective

Demonstrate DMR efficacy and safety compared with sham for the treatment of suboptimally controlled T2D

Key Inclusion Criteria

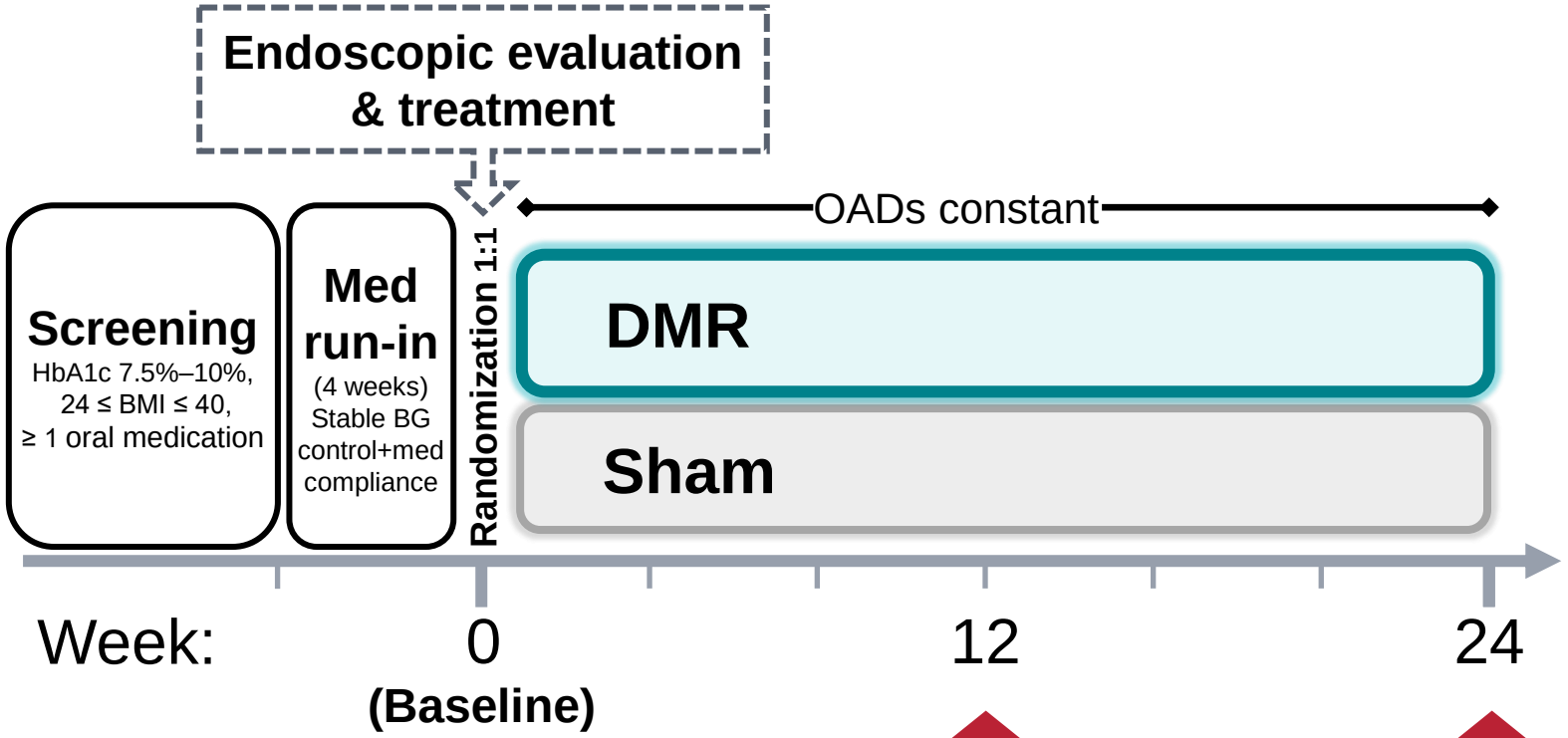
- Aged 28 – 75 years
- T2D with evidence of preserved insulin secretion (fasting insulin > 7.0 µU/ mL)
- HbA1c 7.5 – 10%
- BMI ≥ 24 and ≤ 40 kg/m^2
- Taking ≥ 1 oral antidiabetic medication (1 must be metformin)
- No medication or dose changes 12 weeks prior to study entry
- Able to comply with study and understand/sign informed consent

Key Exclusion Criteria

- Current use of insulin or GLP-1
- History of severe hypoglycemia
- Known autoimmune disease
- Active *Helicobacter pylori* infection
- Previous GI surgery (including bariatric)
- Participating in another ongoing clinical trial of an investigational drug or device

Data on File, Fractyl Laboratories Inc.
BMI = body mass index; GI = gastrointestinal; GLP-1 = glucagon-like peptide-1; HbA1c = hemoglobin A1c; T2D = type 2 diabetes.

REVITA-2: Study design



Analysis populations

Modified intent to treat (mITT): Randomized patients in whom the procedure was attempted and who had a baseline measurement for ≥ 1 primary endpoint (primary analysis population)

Per-protocol (PP): Subset of mITT patients who received the treatment to which they were randomized, excluding patients with major protocol deviations

Primary endpoints

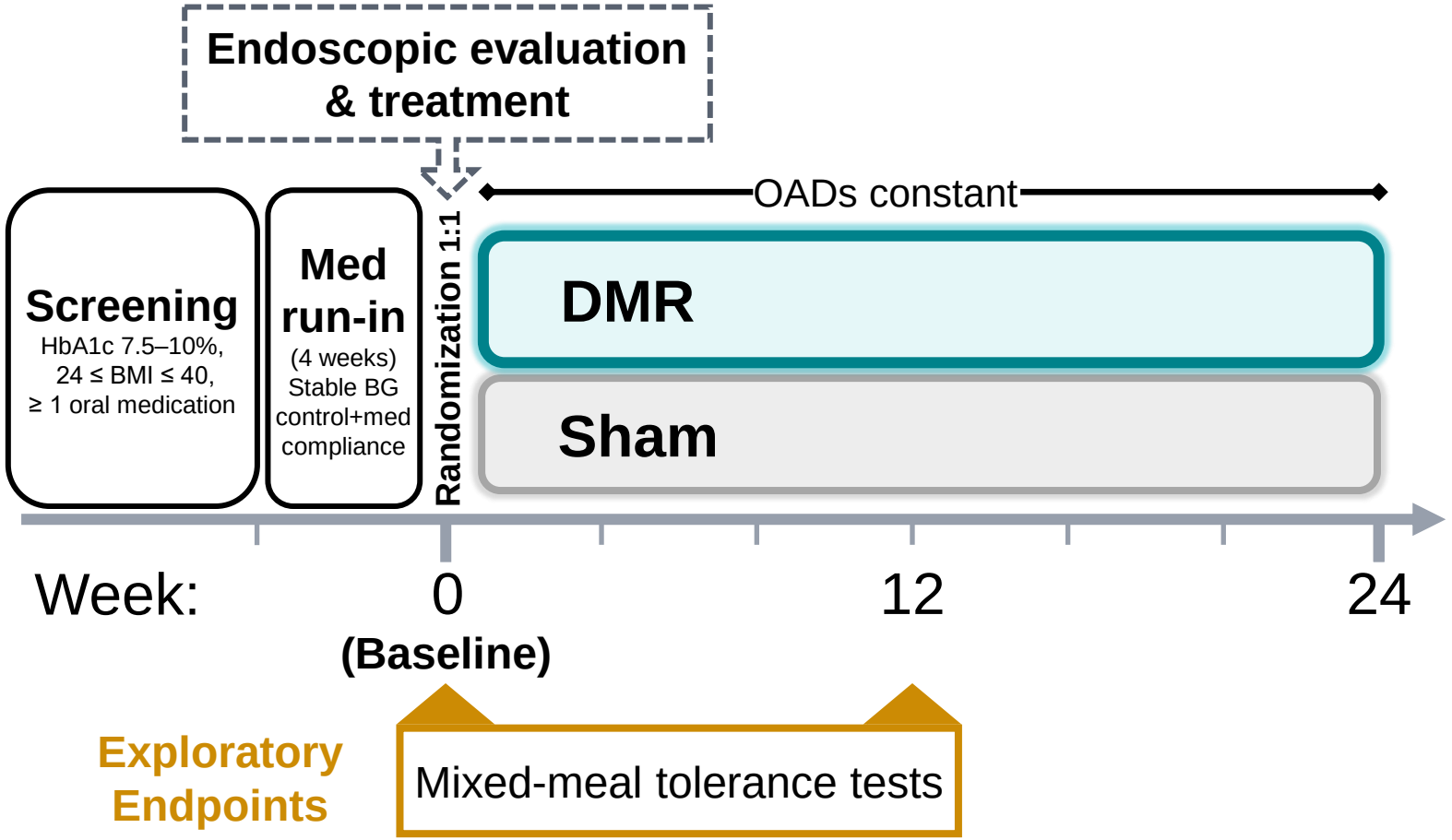
- Absolute change in **liver MRI-PDFF** from baseline (in patients with MRI-PDFF > 5% at baseline)

- **HbA1c** change from baseline
- Device/procedure-related SAE, UADE, and AESI incidence

Data on File, Fractyl Laboratories Inc.

AESI = adverse event of special interest; BG = blood glucose; BMI = body mass index; DMR = duodenal mucosal resurfacing; HbA1c = hemoglobin A1c; MRI-PDFF = magnetic resonance imaging-proton density fat fraction; OAD = oral antidiabetic medication; SAE = serious adverse event; UADE = unanticipated adverse device effects.

REVITA-2: Study design



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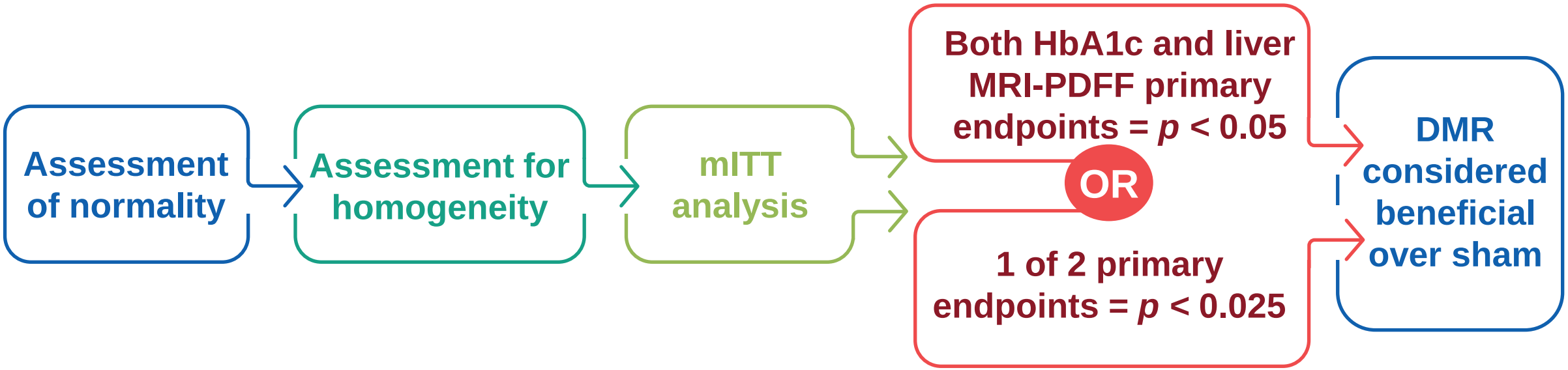
Data on File, Fractyl Laboratories Inc.
BG = blood glucose; BMI = body mass index; DMR = duodenal mucosal resurfacing; OAD = oral antidiabetic medication.

REVITA-2 statistical methods: How success was defined in SAP



Prespecified interaction statistical test **assessed homogeneity** across geographic regions

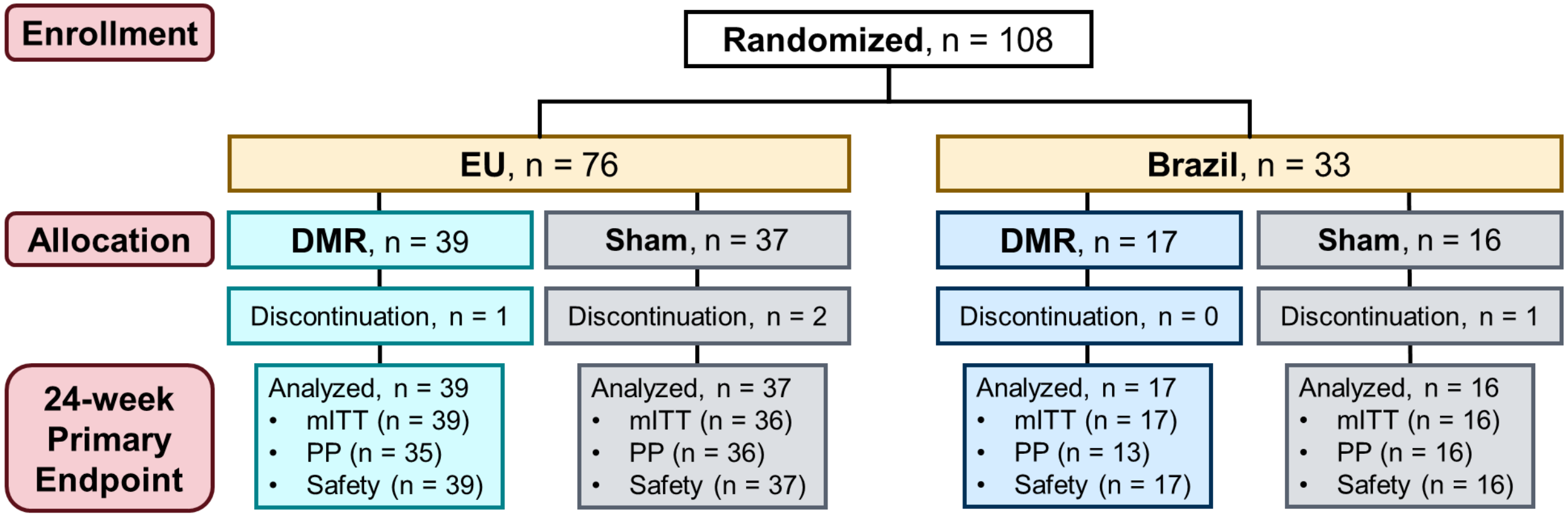
Brazil not homogeneous to European countries in hepatic and glycemic endpoints, regardless of treatment group

Brazilian and European populations not poolable, analyses were stratified, and **mITT results separated by region**

Data on File, Fractyl Laboratories Inc.

DMR = duodenal mucosal resurfacing; mITT = modified intent to treat; MRI-PDFF = magnetic resonance imaging-proton density fat fraction; SAP = statistical analysis plan.

REVITA-2: Patient disposition



Data on File, Fractyl Laboratories Inc.
DMR = duodenal mucosal resurfacing; EU = European Union; mITT = modified intent to treat; PP = per-protocol.

MMTT: An evaluation of hormone responses to nutrients to further elucidate the mechanism by which DMR improves glycemic control (European mITT population)[1,2]

At selected study sites, MMTT was performed at baseline and 12 weeks post procedure[3]

After a 10-hour overnight fast, patients ingested a liquid meal of Ensure (200 ccl) or equivalent within 10 minutes[3]

Blood samples were drawn at 0 minutes (fasting) and at 15, 30, 45, 60, 90, 120, and 180 minutes following start of meal[3]

- Change from baseline assessed at 12 weeks[3]:
  - MMTT glucose AUC through 2 hours
  - Measures of insulin secretion and insulin resistance
- Data from the **European mITT population** is presented here[3]
  - Complete case analysis was used, n's varied depending on mITT parameter being analyzed

1. Rajagopalan H et al., *Diabetes Care*. 2016;39:2254-2261; 2. Van Baar A et al., *Gut*. 2019; pii: gutjnl-2019-318349; 3. Data on File, Fractyl Laboratories Inc.
AUC = area under the curve; DMR = duodenal mucosal resurfacing; mITT = modified intent to treat; MMTT = mixed-meal tolerance test; PP = per-protocol.

REVITA-2: Patient demographics and baseline characteristics

Characteristic	European mITT Population[a]		
	DMR (N = 39)	Sham (N = 36)	*p* value[b]
Age, years	59.0 (40.0, 72.0)	56.5 (35.0, 75.0)	0.62
Male, n (%)	30 (76.9)	28 (77.8)	0.93
Race, n (%)			0.60
White	25 (64.1)	21 (58.3)	
Other	1 (2.6)	3 (8.3)	
Undisclosed	13 (33.3)	12 (33.3)	
Weight, kg	93.1 (64.8, 155.0)	94.5 (66.6, 113.4)	0.66
BMI, kg/m^2	31.4 (23.6, 39.5)	30.4 (24.2, 39.6)	0.16
Liver MRI-PDFF, %	16.5 (5.5, 33.0)	16.1 (5.6, 33.8)	0.50
> 5% at baseline, n (%)	33 (85)	27 (75)	0.25
ALT, U/L	31.0 (11.0, 76.0)	29.0 (12.0, 162.0)	0.65
AST, U/L	21.0 (11.0, 44.0)	19.5 (10.0, 131.0)	0.31
Fasting glucose, mg/dL	191.0 (122.0, 313.0)	185.5 (110.0, 344.0)	0.68
HbA1c, %	8.1 (7.5, 10.0)	8.2 (7.5, 10.0)	0.45
C-peptide, ng/mL	2.5 (0.7, 4.9)	2.3 (1.5, 5.0)	0.48
Fasting insulin, mU/L	9.8 (2.4, 22.6)	8.4 (3.9, 17.6)	0.08

Sanyal A et al, Oral presentation at AASLD: November 2019 Boston, MA.

Data for continuous variables are presented as median (minimum, maximum), unless otherwise noted.

[a]mITT population defined as all randomized patient in whom the study procedure (DMR or sham) is attempted and who have a baseline measurement for at least 1 primary endpoint and includes patients from European study sites.

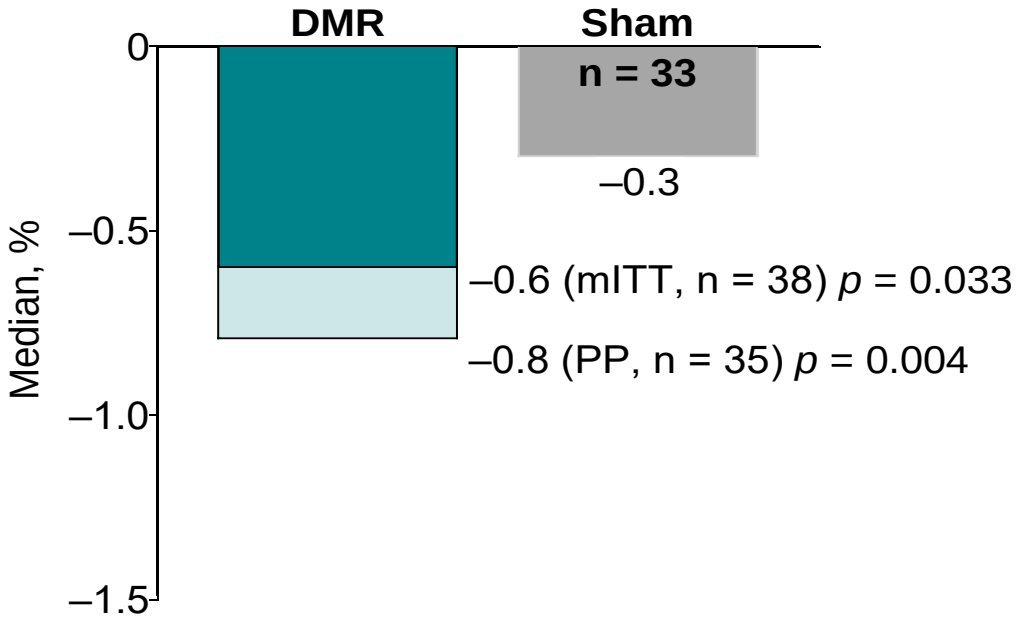
[b]*p* values are from Mann-Whitney U test for continuous variables due to non-normality and chi-squared test (or Fisher's exact test when appropriate) for categorical variables, unless otherwise specified. If the baseline value was missing for a given variable and patients, the screening value was used in its place prior to calculating the descriptive statistics. All *p* values are 2-sided.

ALT = alanine aminotransferase; AST = aspartate aminotransferase; BMI = body mass index; DMR = duodenal mucosal resurfacing; HbA1c = hemoglobin A1c; mITT = modified intent-to-treat; MRI-PDFF = magnetic resonance imaging-proton density fat fraction.

REVITA-2: Primary outcomes show DMR significantly improves glycemic control and liver fat content

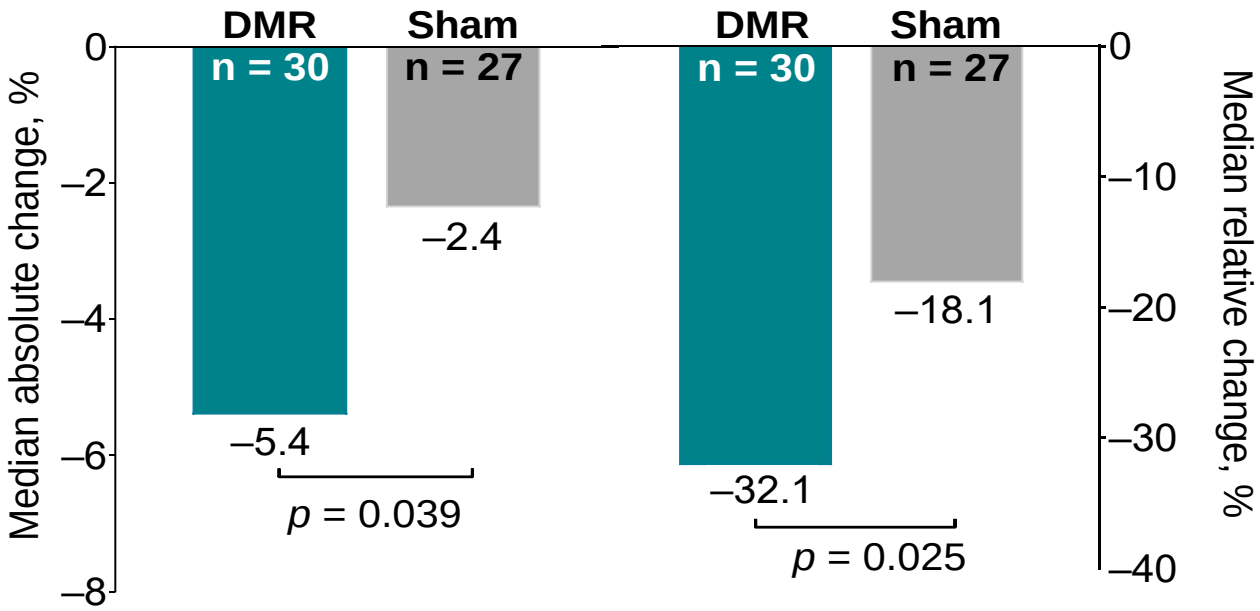
Change in HbA1c from baseline to 24 weeks

Baseline median (min, max) HbA1c: 8.1 (7.5, 10.0)



Changes in liver MRI-PDFF from baseline to 12 weeks in patients with > 5% liver fat content at baseline

Baseline median (min, max) liver MRI-PDFF: 16.1 (5.5, 35.8)



Sanyal A et al, Oral presentation at AASLD: November 2019 Boston, MA.

Treatment comparisons: 1-sided *p* value based on ANCOVA model with multiple imputation on the rank values (modified ridit scores). HbA1c analysis is based on all patients in the population of interest and additionally adjusts for screening to baseline change as well in the ANCOVA model. MRI-PDFF analysis is based on all patients in the population of interest where post-rescue values are first set to missing.

ANCOVA = analysis of covariance; DMR = duodenal mucosal resurfacing; max = maximum; min = minimum; mITT = modified intent to treat; MRI-PDFF = magnetic resonance imaging-proton density fat fraction; PP = per-protocol.

REVITA-2: Favorable safety profile 24 weeks post DMR

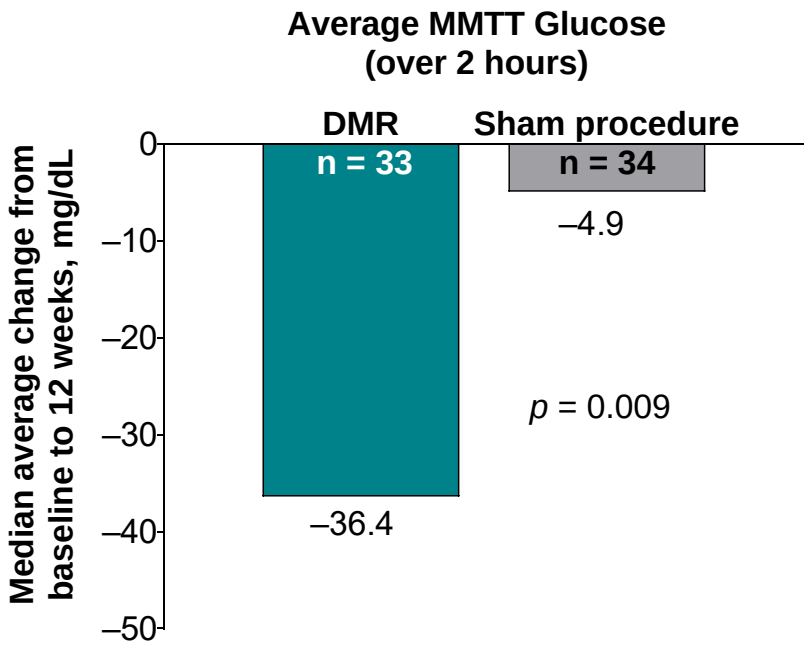
European safety population	DMR (N = 39)	Sham (N = 36)
Summary of device-/procedure-related		
SAE, n (%)	0	0
UADE, n (%)	0	0
AESI, n (%)	13 (33.3)	10 (27.0)
Most common (≥ 5%) device-/procedure-related AESI		
Gastrointestinal disorders	11 (28.2)	8 (21.6)
Abdominal pain	6 (15.4)	2 (5.4)
Abdominal pain upper	3 (7.7)	2 (5.4)
Diarrhea	1 (2.6)	3 (8.1)
Vomiting	2 (5.1)	0
Metabolism and nutrition disorders	3 (7.7)	3 (8.1)
Hypoglycemia	3 (7.7)	3 (8.1)

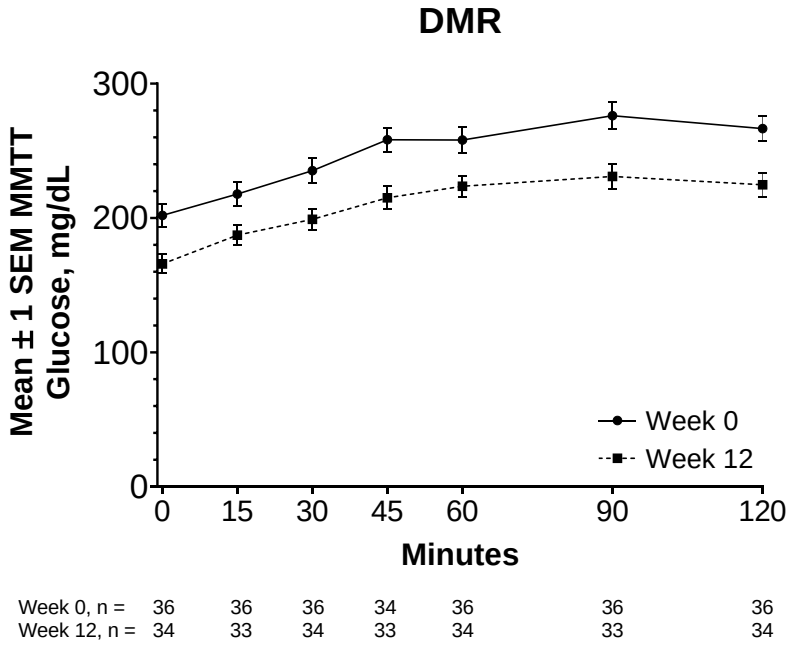
Data are presented as n (%), with n as the number of patients with an event.
Data are from the European safety population.
AE = adverse event; AESI = adverse event of special interest; DMR = duodenal mucosal resurfacing; SAE = serious adverse event; UADE = unanticipated adverse device effects.

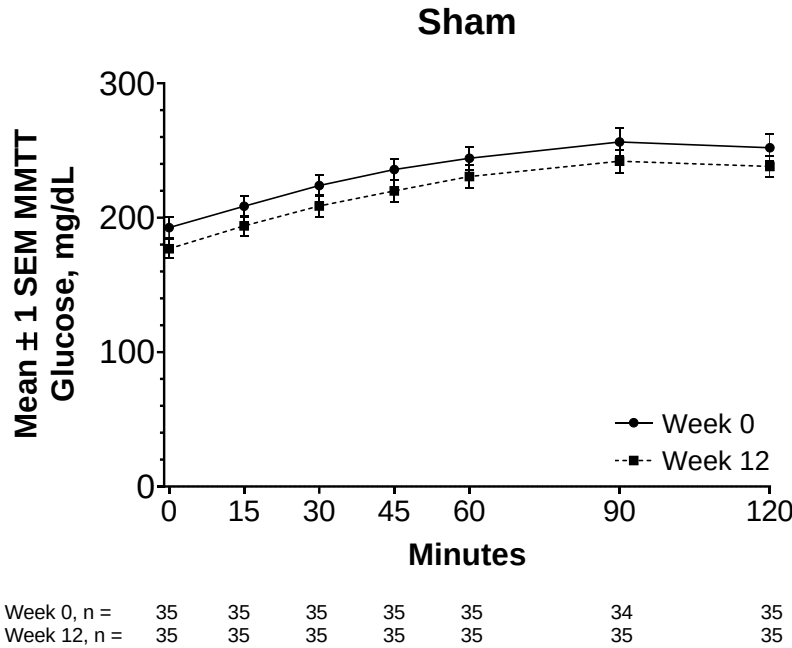
- No device-/procedure-related SAEs or UADEs reported through 24 weeks
- No clinical or laboratory signs of AEs related to malabsorption, anemia, pancreatitis, biliary complications, or infection
- Similar rates of hypoglycemia between DMR and sham groups
- 2 patients (11.8%) in the Brazilian safety population experienced an SAE
  - 1 was a precautionary hospitalization for diagnostic evaluation for a patient who noted mild hematochezia 11 days after a DMR procedure.
  - 1 was a jejunal perforation caused by endoscopic complication, not specific to DMR catheter or technique

Sanyal A et al, Oral presentation at AASLD: November 2019 Boston, MA.
mITT = modified intent to treat.

REVITA-2: MMTT AUC glucose was significantly reduced post DMR, indicating efficacy in improving glucose metabolism

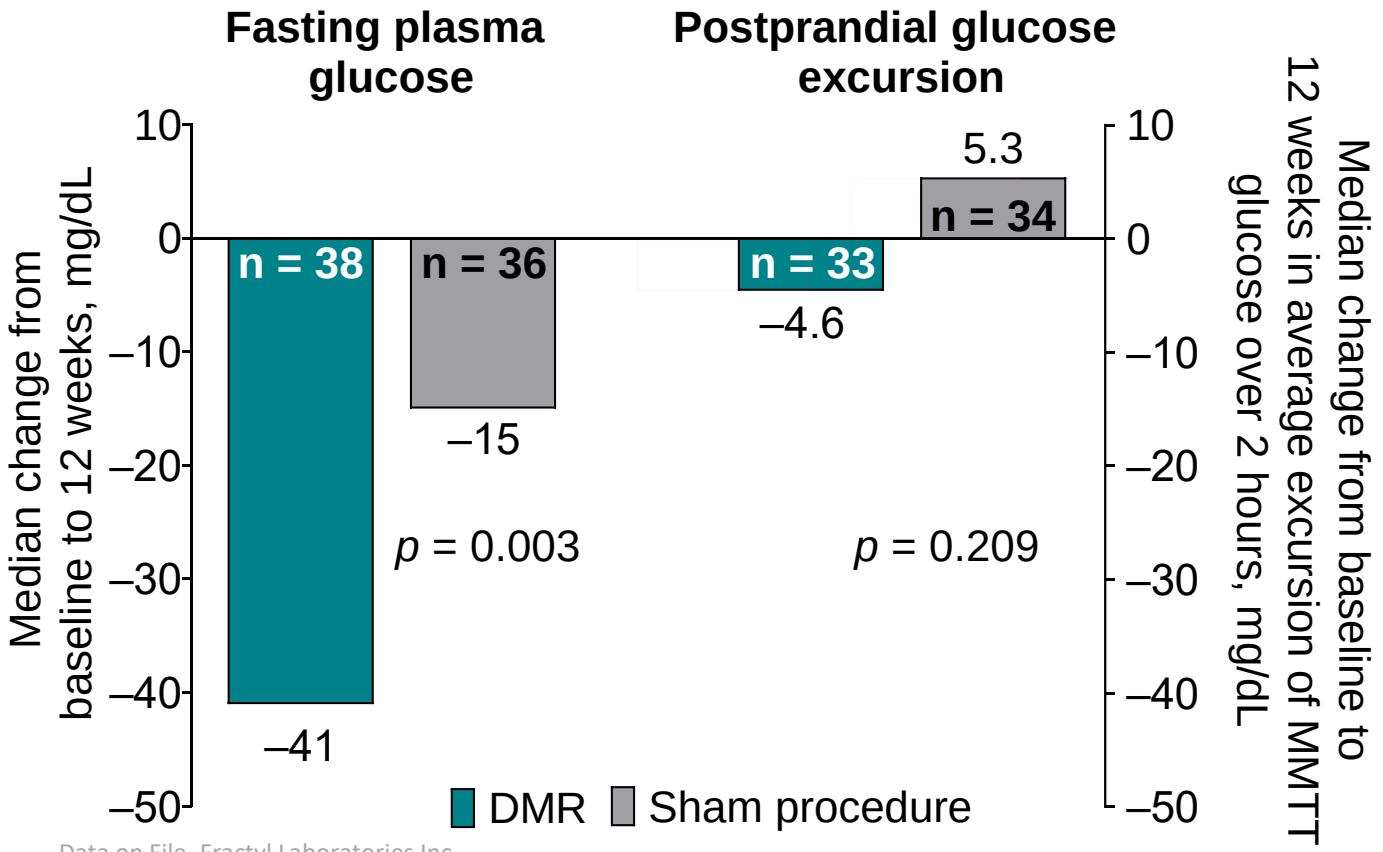






Data on File, Fractyl Laboratories Inc.
Treatment comparison: 1-sided *p* value based on ANCOVA model on ranks without imputation (at 0.05 significance level).
ANCOVA = analysis of covariance; AUC = area under the curve; DMR = duodenal mucosal resurfacing; mITT = modified intent to treat; MMTT = mixed-meal tolerance test; SEM = standard error of the mean.

REVITA-2: Improved glycemic control post DMR driven by FPG improvements, not postprandial glucose changes



- Glucose metabolism improvements mainly driven by reductions in fasting glucose rather than postprandial glucose excursion or absorption
- Implies improvement in hepatic glucose metabolism that could be due to a lessening of hepatic insulin resistance

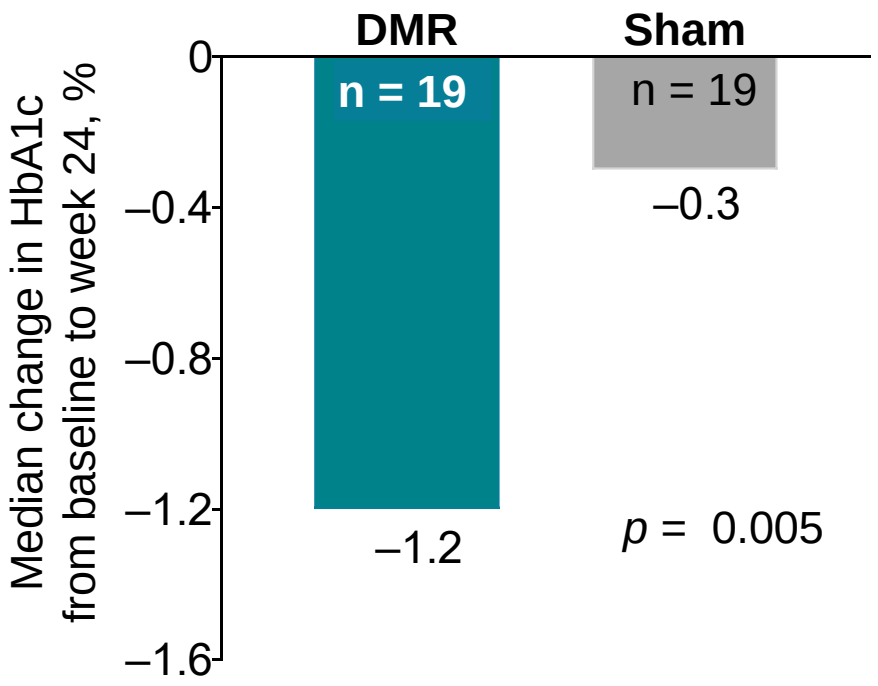
Data on File, Fractyl Laboratories Inc.

Treatment comparisons: 1-sided *p* value based on ANCOVA model on ranks without imputation (0.05 significance level). FPG ANCOVA models adjusted for baseline FPG and change in FPG from screening to baseline. Postprandial glucose excursion analysis is based on AUC through 2 hours calculated using the trapezoidal rule. Models adjusted for {AUC_t/t at baseline} as a covariate in the ANCOVA model, where t = 2 hours.

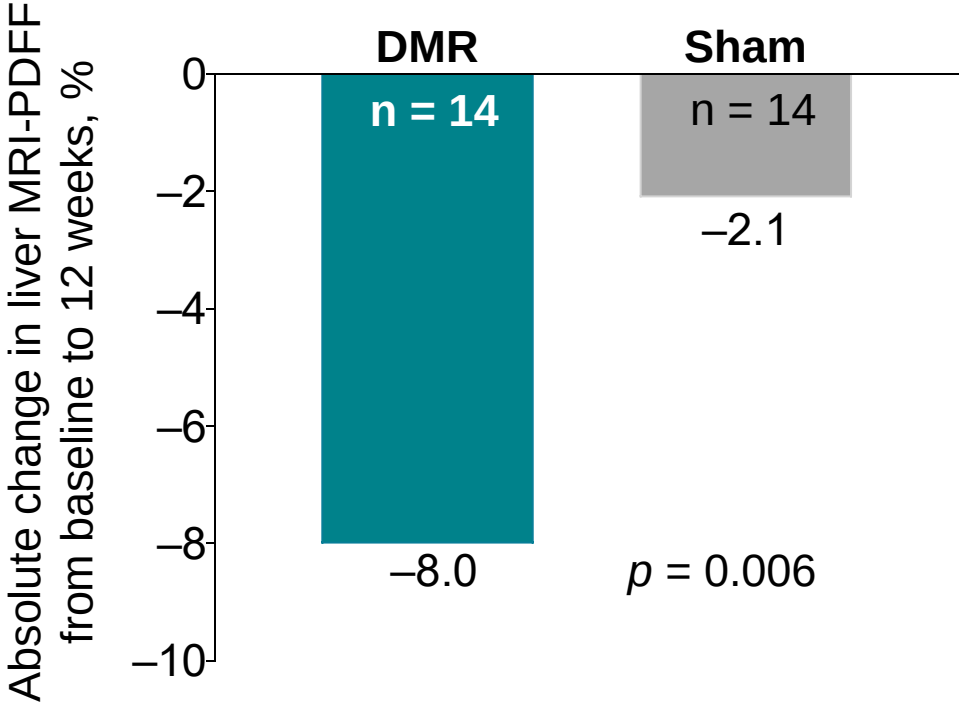
ANCOVA = analysis of covariance; AUC = area under the curve; DMR = duodenal mucosal resurfacing; FPG = fasting plasma glucose; mITT = modified intent to treat.

REVITA-2: Significantly greater reductions in liver MRI-PDFF and HbA1c in patients with baseline FPG ≥ 180 mg/dL

Baseline median (min, max) HbA1c: 8.5 (7.7, 10.0)[1]



Baseline median (min, max) liver MRI-PDFF: 20.3 (8.0, 35.8)[1]



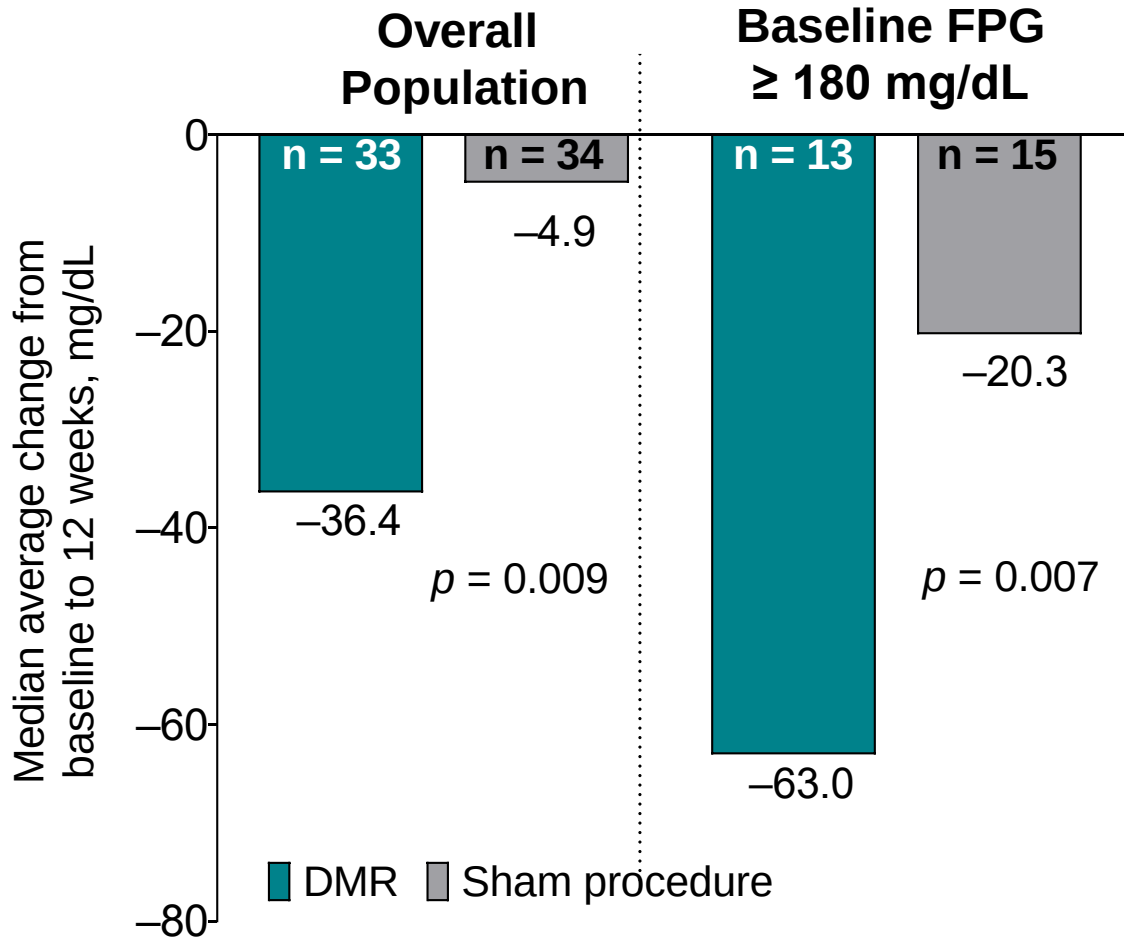
Greater benefit in patients (PP) with higher FPG at baseline[2] supports the role of hepatic IR in NAFLD/NASH and T2D

1. Sanyal A et al, Oral presentation at AASLD: November 2019 Boston, MA. 2. Rajagopalan H, et al., *Diabetes Care*. 2016;39:2254. Treatment comparison (DMR vs SHAM) 1-sided *p* value from ANCOVA on ranks (modified ridit scores) model with no imputation of missing data and values post rescue medication are set to missing with baseline value and the change from screening to baseline value as covariates in the model. Analyses presented were in complete casers.

DMR = duodenal mucosal resurfacing; FPG = fasting plasma glucose; max = maximum; min = minimum; MRI-PDFF = magnetic resonance imaging-proton density fat fraction; NAFLD = nonalcoholic fatty liver disease; NASH = nonalcoholic steatohepatitis; T2D = type 2 diabetes; PP = per-protocol.

REVITA-2: Average MMTT glucose (over 2 hours) reductions are more pronounced in patients with fasting hyperglycemia

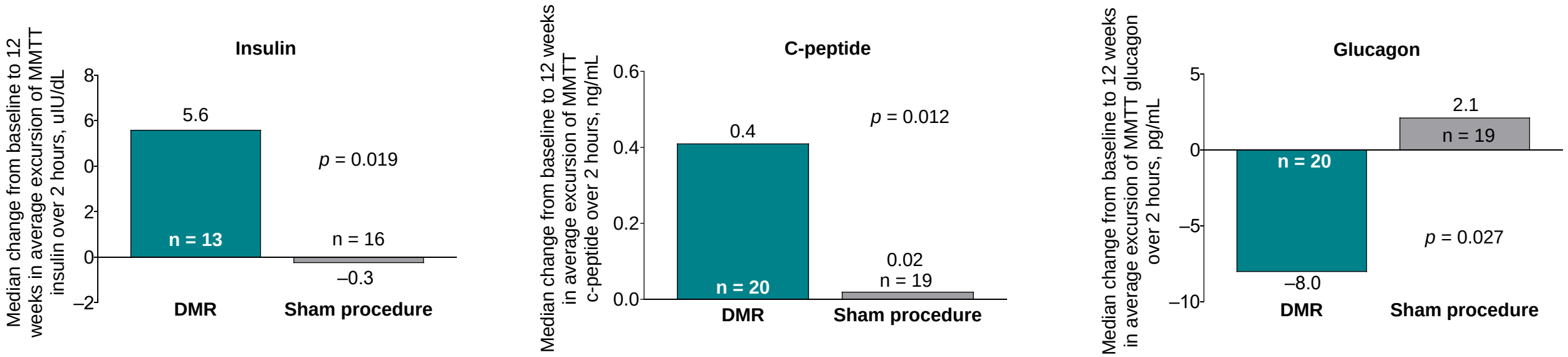
- Patients (mITT) with fasting hyperglycemia at baseline experienced much greater reductions in glucose than patients with lower baseline fasting glucose



Data on File, Fractyl Laboratories Inc.
For this post hoc analysis, treatments were compared using a 1-sided *p* value based on ANCOVA model on ranks without imputation (at 0.05 significance level).
Analysis is based on area under the curve (AUC) through 2 hours calculated using the trapezoidal rule.
Models adjust for (AUC_t/t at baseline) as a covariate in the ANCOVA model, where t = 2 hours.
AUC = area under the curve; ANCOVA = analysis of covariance; DMR = duodenal mucosal resurfacing; FPG = fasting plasma glucose; mITT = modified intent to treat; MMTT = mixed-meal tolerance test.

REVITA-2: Change from baseline to 12 weeks post-treatment in insulin, C-peptide, and glucagon indicate improvements in β cell function and hepatic insulin resistance

Postprandial excursion in patients with FPG ≥ 180 mg/dL at baseline



Data on File, Fractyl Laboratories Inc.

For this post hoc analysis, treatments were compared using a 1-sided p-value based on ANCOVA model on ranks without imputation (at 0.05 significance level). Analysis is based on AUC through 2 hours calculated using the trapezoidal rule. Models adjust for {AUC_t/t at baseline – MMTT outcome at baseline, hour 0} as a covariate in the ANCOVA model, where t = 2 hours.

ANCOVA = analysis of covariance; AUC = area under the curve; DMR = duodenal mucosal resurfacing; mITT = modified intent to treat.

Conclusions

- DMR improves glycemia throughout the day; this improvement is primarily driven by a decrease in FPG, suggesting a primary effect on hepatic glucose metabolism
- This improvement is primarily driven by a decrease in FPG, suggesting a primary effect on hepatic glucose metabolism
- DMR benefit most pronounced in patients with significant fasting hyperglycemia at baseline
- C-peptide, glucagon, and insulin changes with DMR in the FPG ≥ 180 mg/dL at baseline are consistent with improvements in β cell function
- These data help establish the putative role of the duodenum as both an endocrine organ that is responsible for impaired metabolic signaling and a therapeutic target for patients with T2D
- Many mechanistic questions regarding the role of the duodenum remain
- Future studies will include patients with higher baseline FPG who represent a subset of T2D with increased hepatic insulin resistance where DMR may exert greater benefit

DMR = duodenal mucosal resurfacing; FPG = fasting plasma glucose; T2D = type 2 diabetes.