# Duodenal Mucosal Resurfacing (DMR) for the Treatment of Type 2 Diabetes

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Session 11: Live Demonstrations
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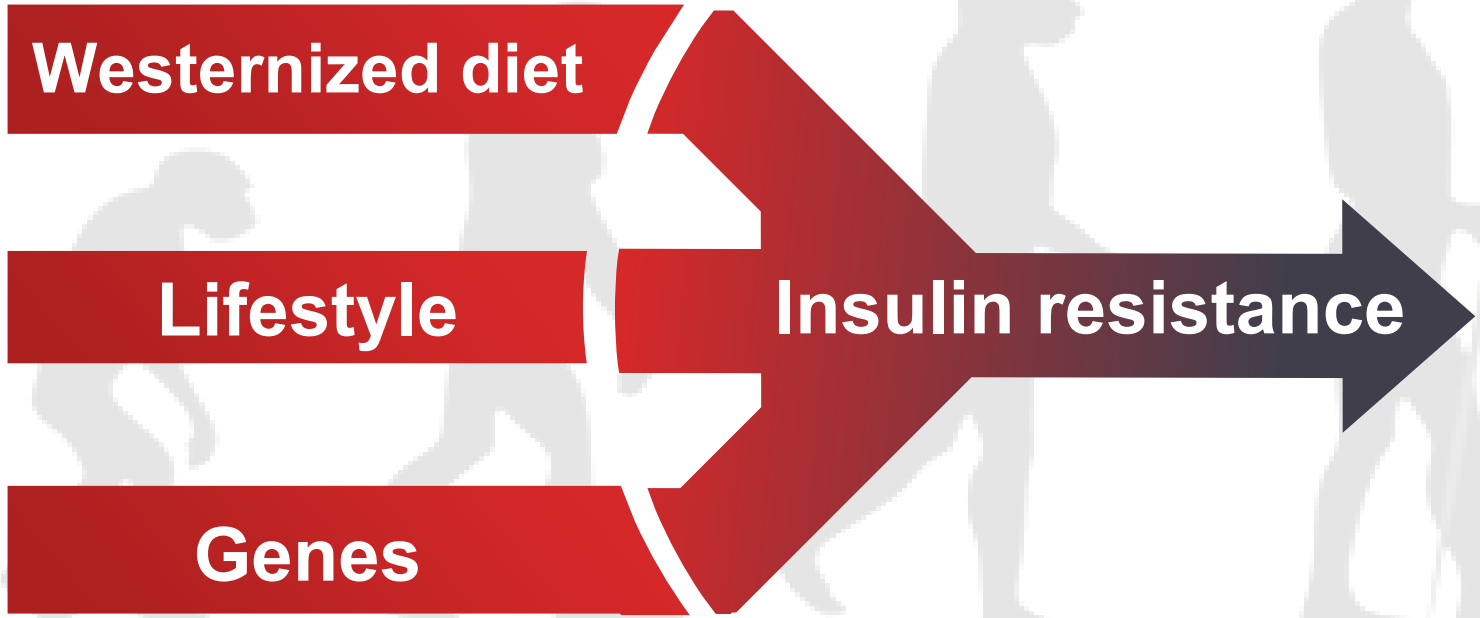
# Insulin resistance and hyperinsulinemia underlie metabolic diseases




**Metabolic diseases**[1-3]

- T2D
- NAFLD/NASH
- PCOS

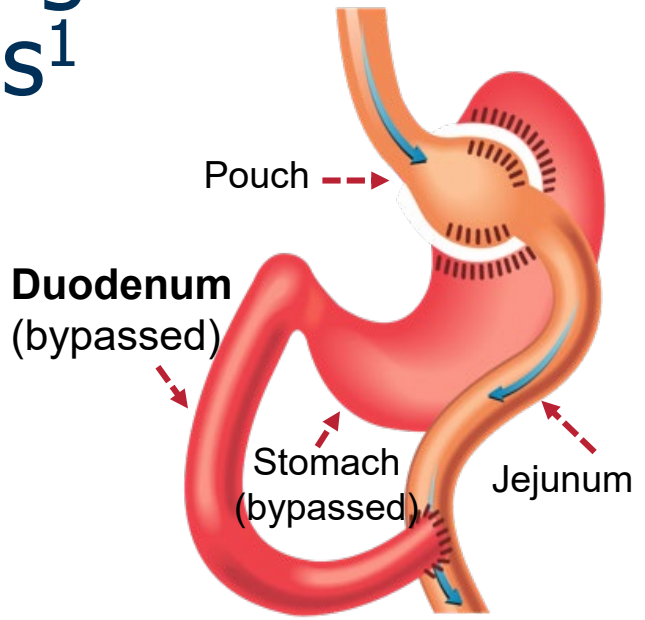
Current pharmacotherapies for T2D do not adequately address pathophysiologic defects underlying insulin resistance.[4-6] Novel, disease-modifying approaches are needed.

1. WHO. 2016 Global Report on Diabetes; 2. CDC. National Diabetes Statistics Report, 2017; 3. ADA. *Diabetes Care*. 2018;41(Suppl 1): S3-S3; 4. Resnick et al. *Diabetes Care*. 2006;29:531–537; 5. Davies et al. *Diabetologia*. 2018;61:2461–2498; 6. Ismail-Beigi. *N Engl J Med*. 2012;366:1319–1327.

NAFLD = nonalcoholic fatty liver disease; NASH = nonalcoholic steatohepatitis; PCOS = polycystic ovary syndrome; T2D = type 2 diabetes.

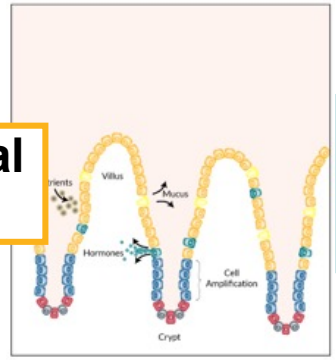
# The duodenum is a key metabolic signaling center and critical regulator of metabolic homeostasis[1]

Duodenal bypass surgery (eg, RYGB) reverses metabolic disease (T2D[2,3], NAFLD/NASH[4], PCOS[5,6]) independent of weight loss[7]



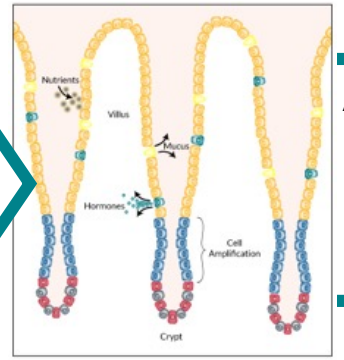

**Duodenal mucosa**

**Normal**




**High-fat and sugar diets**

**Hyperplastic**



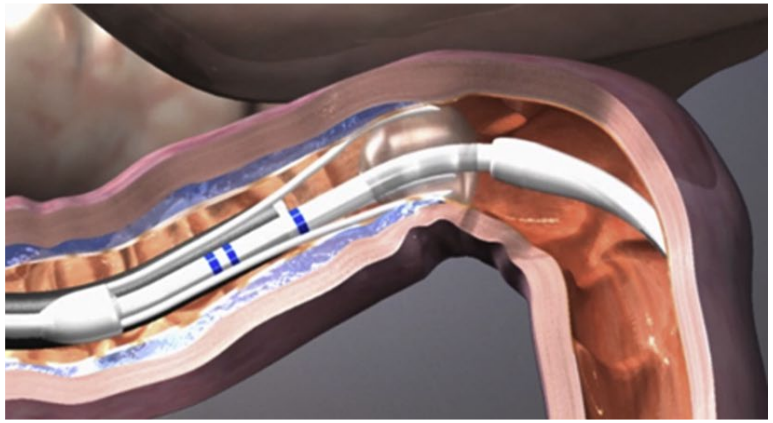

**Altered hormonal signaling and nutrient absorption:** abdominal obesity, insulin resistance, impaired glucose metabolism, hyperinsulinemia, dyslipidemia, and high blood pressure[8,9]

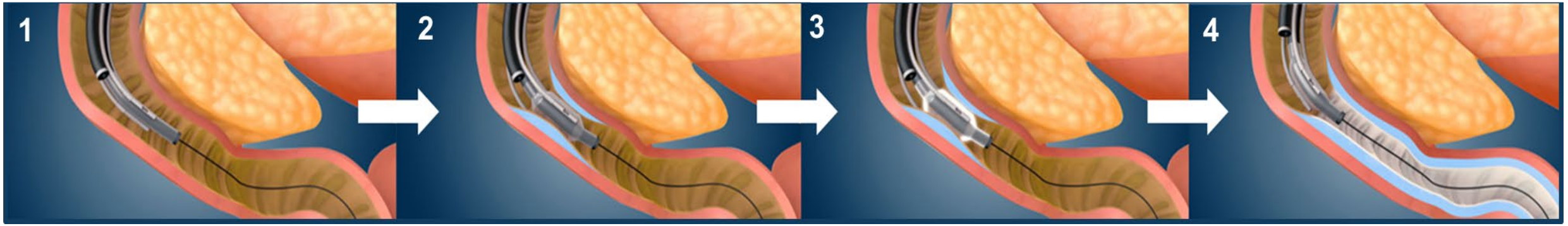
1. Van Baar et al. *Gastroenterology*. 2018;154:773; 2. Lassailly et al. *Gastroenterology*. 2015;149:379; 3. Mingrone et al. *NEJM*. 2012;366:1577; 4. Schauer et al. *NEJM*. 2012;366:1567; 5. Jamal et al. *Surg Obes Relat Dis*.2012;8:440–4; 6. Skubleny et al. *Obes Surg*. 2016;26:169; 7. Cummings et al. SOARD. 2007;3:109–115; 8. Cherrington et al. *Gastrointest Endosc Clin N Am*. 2017;27:299–311; 9. van Baar et al. *Gastroenterology*. 2018;154:773–777.

RYGB = Roux-en-Y gastric bypass; NAFLD = nonalcoholic fatty liver disease; NASH = nonalcoholic steatohepatitis; PCOS = polycystic ovary syndrome; T2D = type 2 diabetes.

# Revita DMR®: A novel, minimally invasive, outpatient, endoscopic procedure

- Submucosal lift and hydrothermal ablation of hyperplastic duodenal mucosa to promote epithelial regrowth and restore insulin sensitivity in patients with T2D[1,2]






1. Rajagopalan et al. *Diabetes Care*. 2016;39:2254–2261; 2. Haidry et al. *Gastrointest Endosc*. 2019;90:673–681.
DMR = duodenal mucosal resurfacing; T2D = type 2 diabetes.

# Revita DMR®: Fractyl-sponsored studies

## First in Human (FIH)

- **Completed**
- N = 57
- Single center (Chile)
- Single arm, uncontrolled; OAD-treated T2D patients
- Initial testing in humans; initial safe procedural implementation; initial efficacy/safety; double-catheter system

## REVITA-1

- **Completed**
- N = 46
- Multicenter (EU)
- Single arm, uncontrolled; OAD treated T2D; new single-catheter testing
- Further safe procedural implementation at multiple sites; further description of efficacy/safety; single-catheter system

## REVITA-2

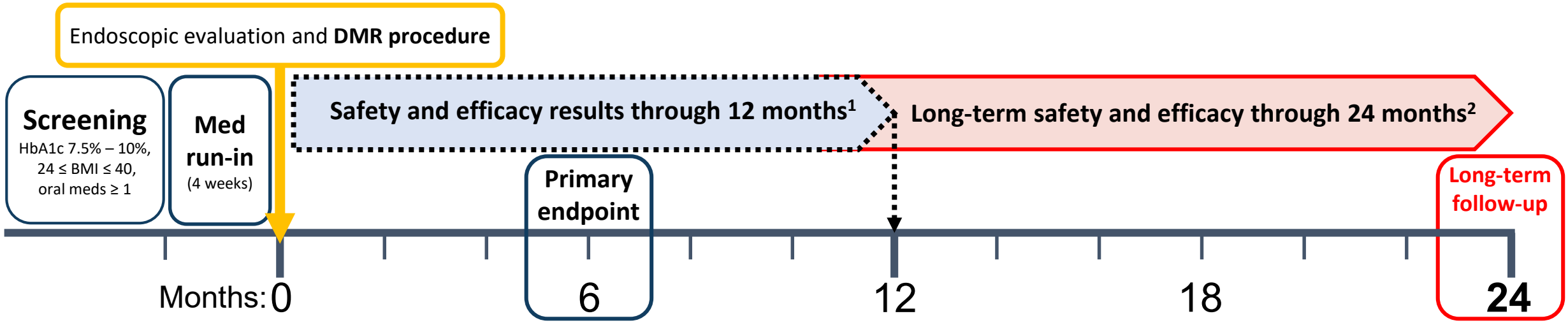
- **Active – Follow up** (enrollment complete)
- N = 31 open-label cases; N = 108 randomized-sham controlled
- Multicenter (EU, Brazil)
- Randomized, sham-controlled 1:1 design in OAD-treated T2D
- Randomized controlled data; comparative efficacy and safety; MOA liver (MRI-PDFF), gut hormones; single-catheter system

## US Pilot

- **Active (enrolling)**
- N = 5
- Multicenter (US)
- Randomized, sham-controlled 2:1 design in OAD-treated T2D
- Randomized controlled data; efficacy and safety; duodenal biopsy; single-catheter system

FIH: NCT01927562; REVITA-1: NCT02413567; REVITA-2: NCT02879383; US Pilot: NCT03653091. DMR = duodenal mucosal resurfacing; EU = European Union; MOA = mechanism of action; MRI-PDFF = magnetic resonance imaging proton density fat fraction; OAD = oral anti-diabetic; T2D = type 2 diabetes.

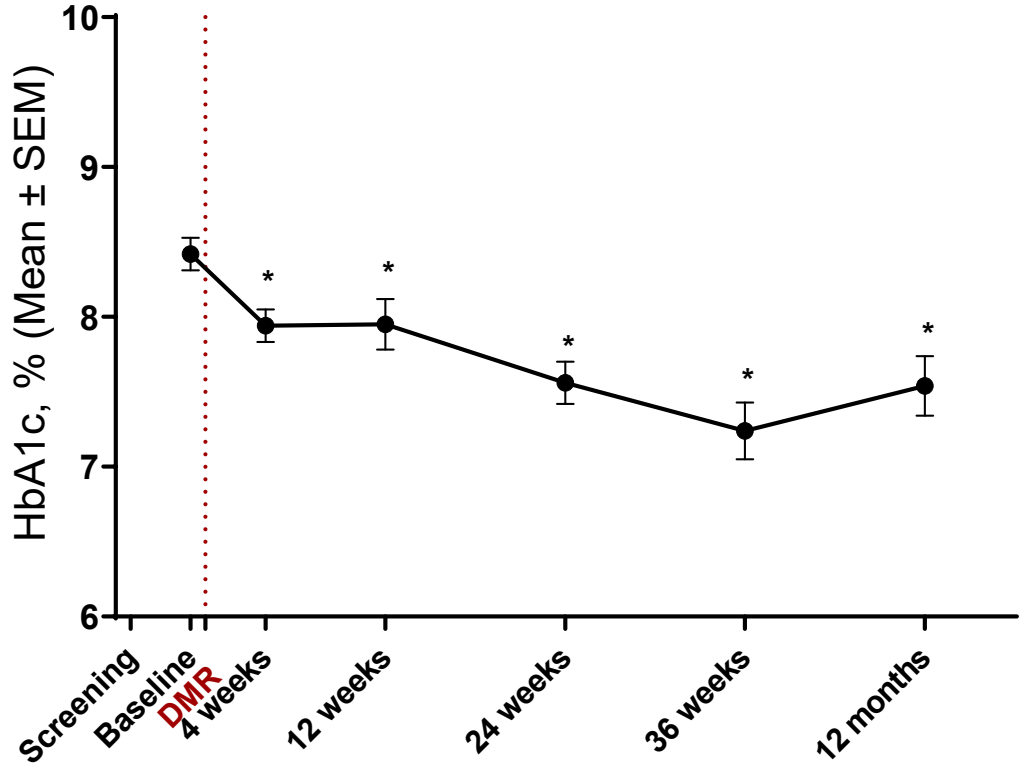
# **REVITA-1:** An open-label, prospective, multicenter study in patients with suboptimally controlled T2D on ≥ 1 OAD




- Glucose-lowering medication kept stable for ≥ 6 months post-DMR[1]
- **Assessments:** HbA1c, FPG, weight, hepatic transaminases, HOMA-IR, adverse events, and treatment satisfaction[1]
- **Analysis:** Repeated-measures ANOVA with Bonferroni correction[1]

1. van Baar et al. *Gut*. 2019. doi: 10.1136/gutjnl-2019-318349; 2. van Baar et al. Poster VAN 19122D presented at DTM; 15 Nov 2019.
ANOVA = analysis of variance; DMR = duodenal mucosal resurfacing; FPG = fasting plasma glucose; HbA1c = hemoglobin A1c; HOMA-IR = homeostatic model assessment insulin resistance; Med = medicine; OAD = oral anti-diabetic medication; T2D = type 2 diabetes.

# **REVITA-1:** DMR is feasible, safe, and effective in patients with suboptimally controlled T2D using OAD medication




- Sustained significant improvements in HbA1c ($p < 0.01$) despite net medication reductions

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HbA1c = hemoglobin A1c; DMR = duodenal mucosal resurfacing; OAD = oral anti-diabetic; SEM = standard error of the mean; T2D = type 2 diabetes.

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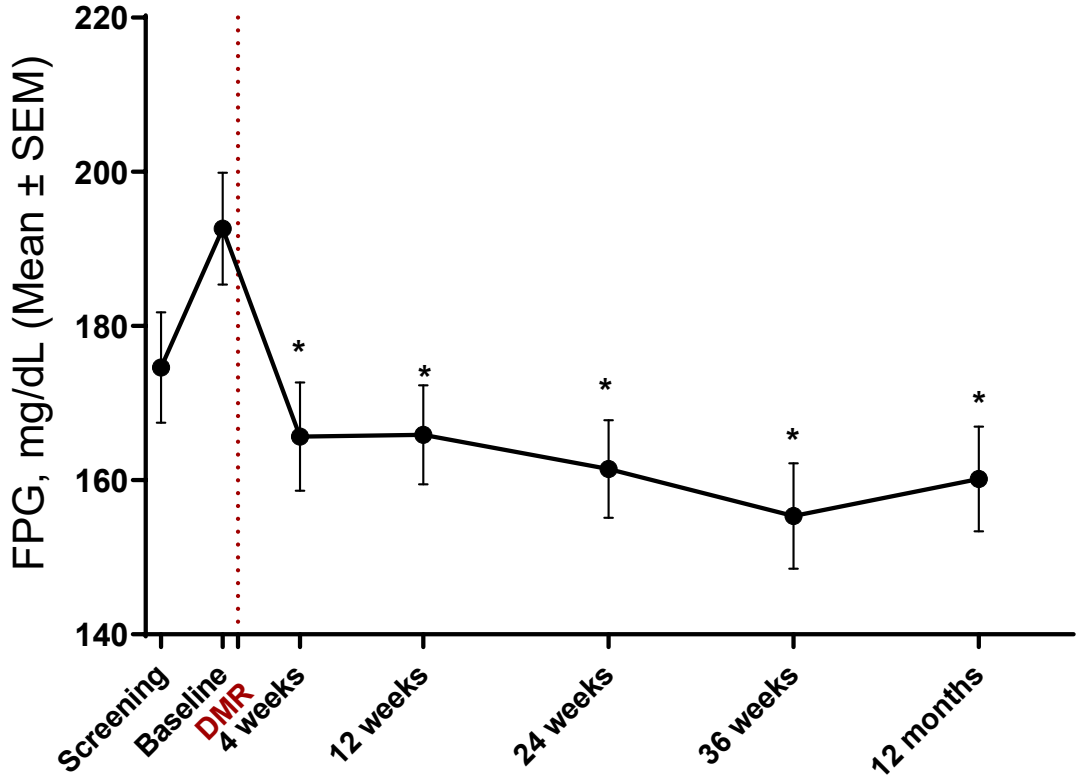


- Sustained significant improvements in HbA1c ($p < 0.01$) despite net medication reductions
- Substantial and clinically significant improvement in FPG

van Baar et al. *Gut*. 2019 Jul 22. doi: 10.1136/gutjnl-2019-318349.

HbA1c = hemoglobin A1c; HOMA-IR = homeostatic model assessment insulin resistance; DMR = duodenal mucosal resurfacing; FPG = fasting plasma glucose; OAD = oral anti-diabetic; SEM = standard error of the mean; T2D = type 2 diabetes.

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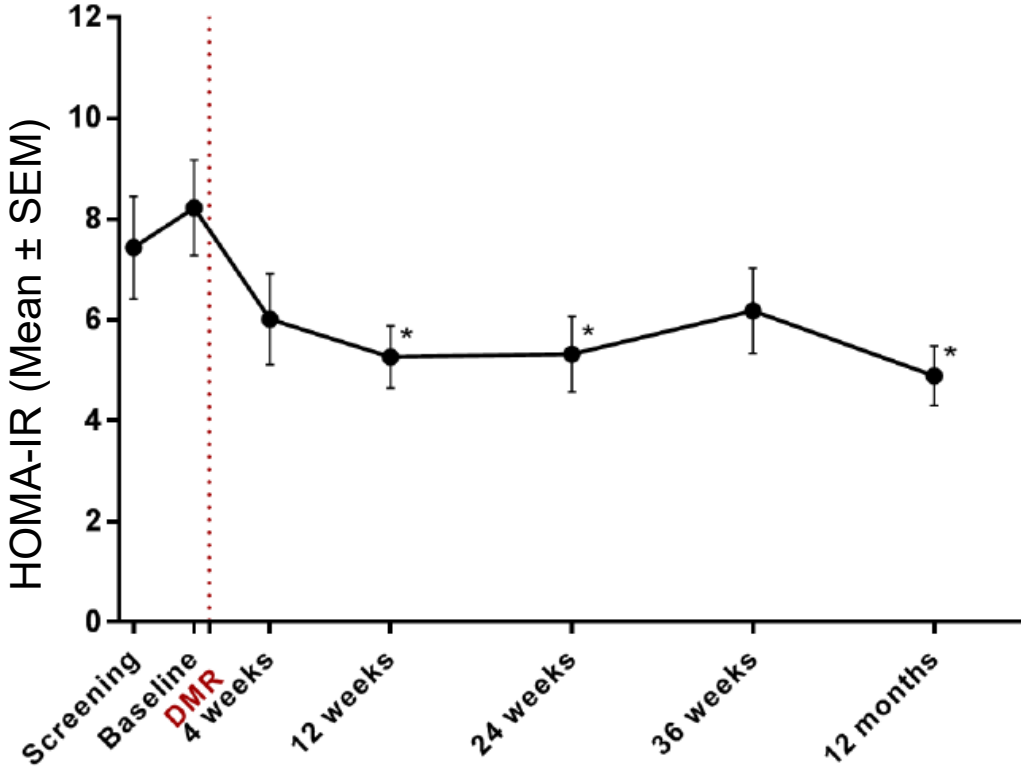


- Sustained significant improvements in HbA1c ($p < 0.01$) despite net medication reductions
- Substantial and clinically significant improvement in HOMA-IR

van Baar et al. *Gut*. 2019. doi: 10.1136/gutjnl-2019-318349.
HbA1c = hemoglobin A1c; HOMA-IR = homeostatic model assessment insulin resistance; DMR = duodenal mucosal resurfacing; OAD = oral anti-diabetic; SEM = standard error of the mean; T2D = type 2 diabetes.

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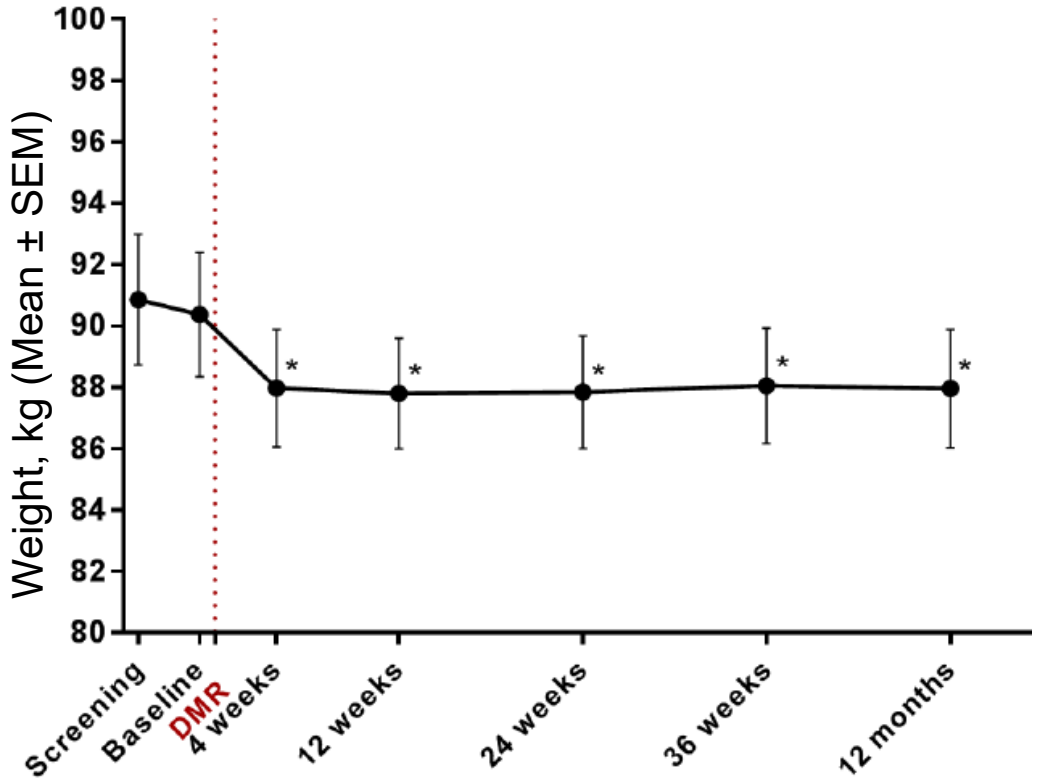


- Sustained significant improvements in HbA1c ($p < 0.01$) despite net medication reductions
- Substantial and clinically significant improvement in weight

van Baar et al. *Gut*. 2019. doi: 10.1136/gutjnl-2019-318349.

HbA1c = hemoglobin A1c; HOMA-IR = homeostatic model assessment insulin resistance; DMR = duodenal mucosal resurfacing; OAD = oral anti-diabetic; SEM = standard error of the mean; T2D = type 2 diabetes.

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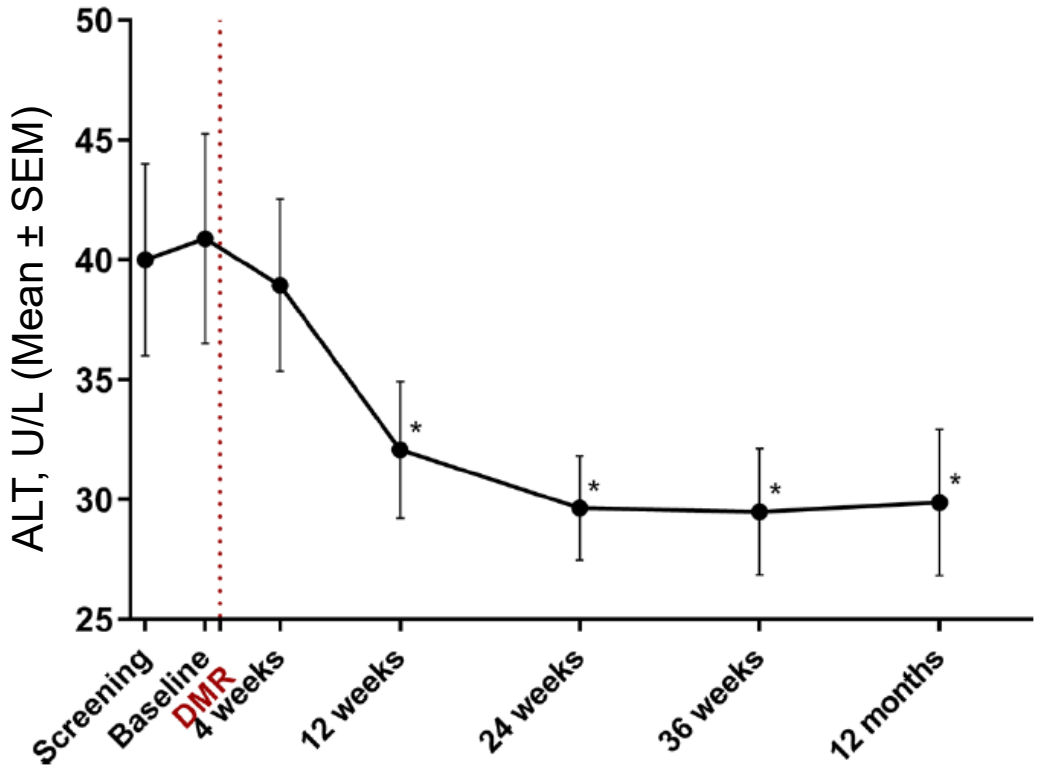


- Sustained significant improvements in HbA1c ($p < 0.01$) despite net medication reductions
- Substantial and clinically significant improvement in ALT

van Baar et al. *Gut*. 2019. doi: 10.1136/gutjnl-2019-318349.
ALT = alanine aminotransferase; HbA1c = hemoglobin A1c; HOMA-IR = homeostatic model assessment insulin resistance; DMR = duodenal mucosal resurfacing; OAD = oral anti-diabetic; SEM = standard error of the mean; T2D = type 2 diabetes.

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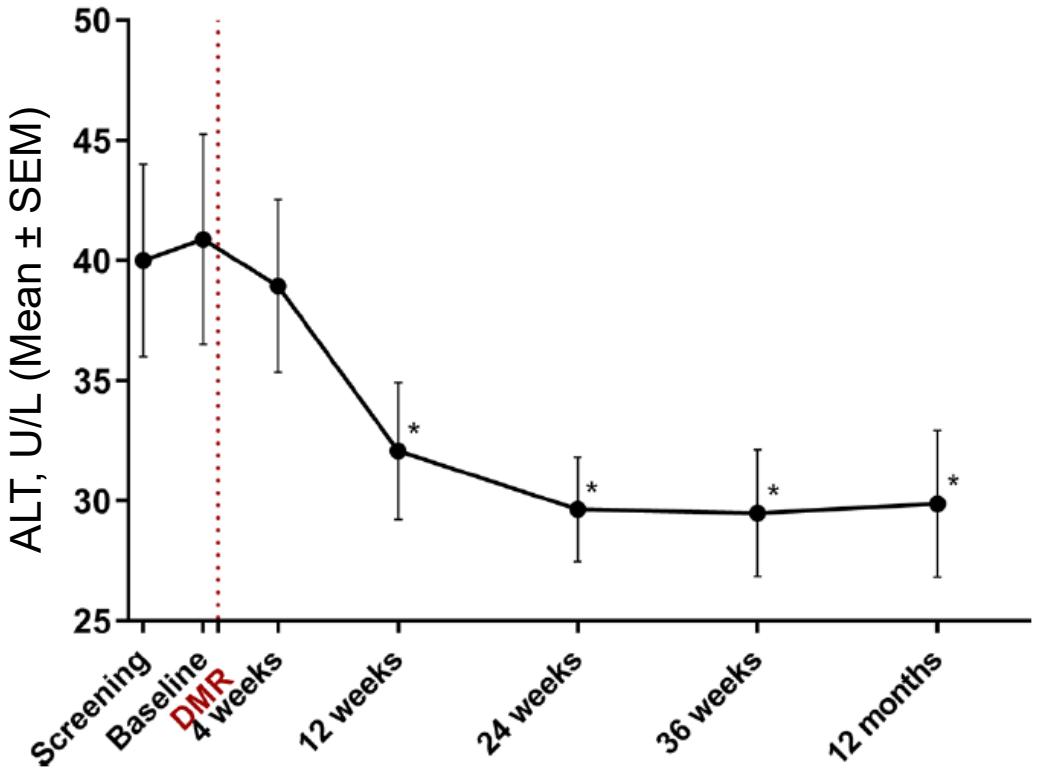


- Sustained significant improvements in HbA1c ($p < 0.01$) despite net medication reductions
- Substantial and clinically significant improvement in glycemia parameters (FPG and HOMA-IR)
- 24 (52%) patients had ≥ 1 AE related to DMR. Of these, 81% were mild.

van Baar et al. *Gut*. 2019. doi: 10.1136/gutjnl-2019-318349.

AE = adverse event; HbA1c = hemoglobin A1c; HOMA-IR = homeostatic model assessment insulin resistance; DMR = duodenal mucosal resurfacing; FPG = fasting plasma glucose; OAD = oral anti-diabetic; SEM = standard error of the mean; T2D = type 2 diabetes.

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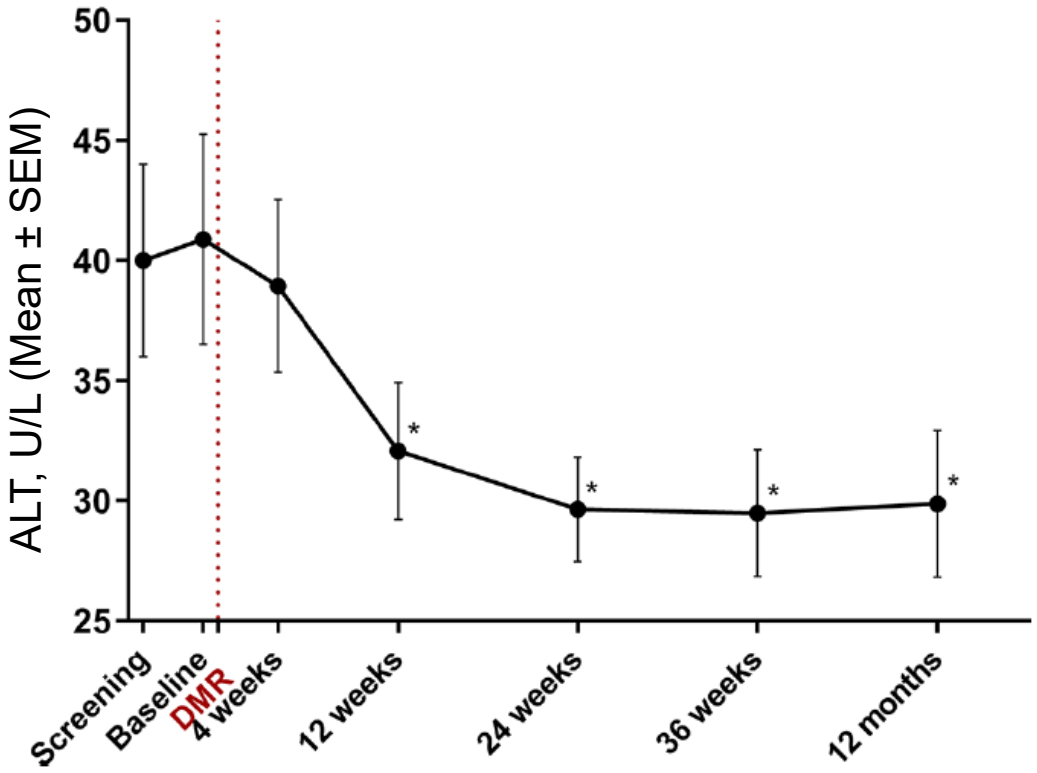


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HbA1c = hemoglobin A1c; DTSQ = diabetes treatment satisfaction questionnaires; HOMA-IR = homeostatic model assessment insulin resistance; DMR = duodenal mucosal resurfacing; FPG = fasting plasma glucose; OAD = oral anti-diabetic; SAE = serious adverse events; SEM = standard error of the mean; T2D = type 2 diabetes; UADE = unanticipated adverse device effects.

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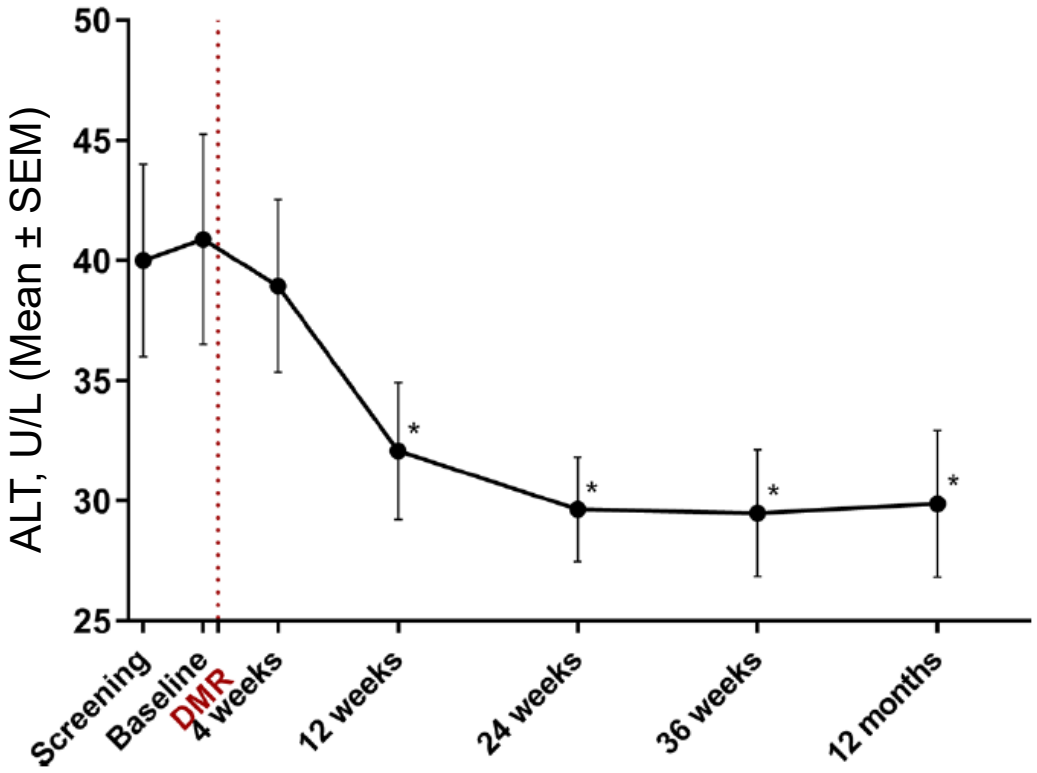


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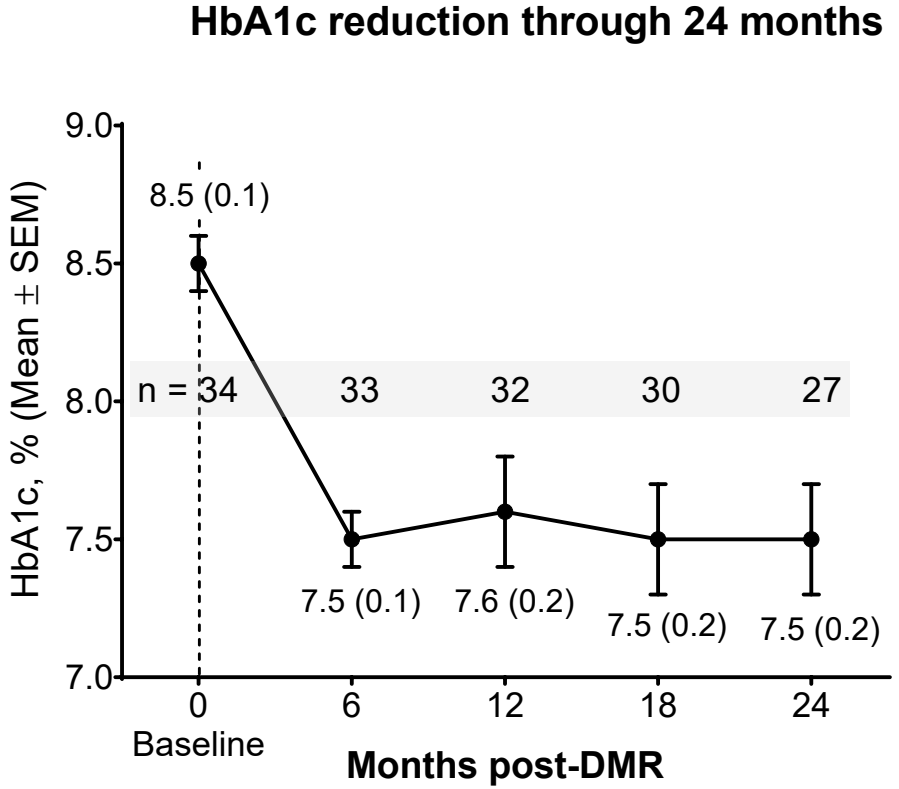
- Substantial and clinically significant improvement in glycemia parameters (FPG and HOMA-IR)
- 24 (52%) patients had ≥ 1 AE related to DMR. Of these, 81% were mild.
- No UADEs or unanticipated SAEs reported
- Associated with improved patient treatment satisfaction (DSTQ status and change)

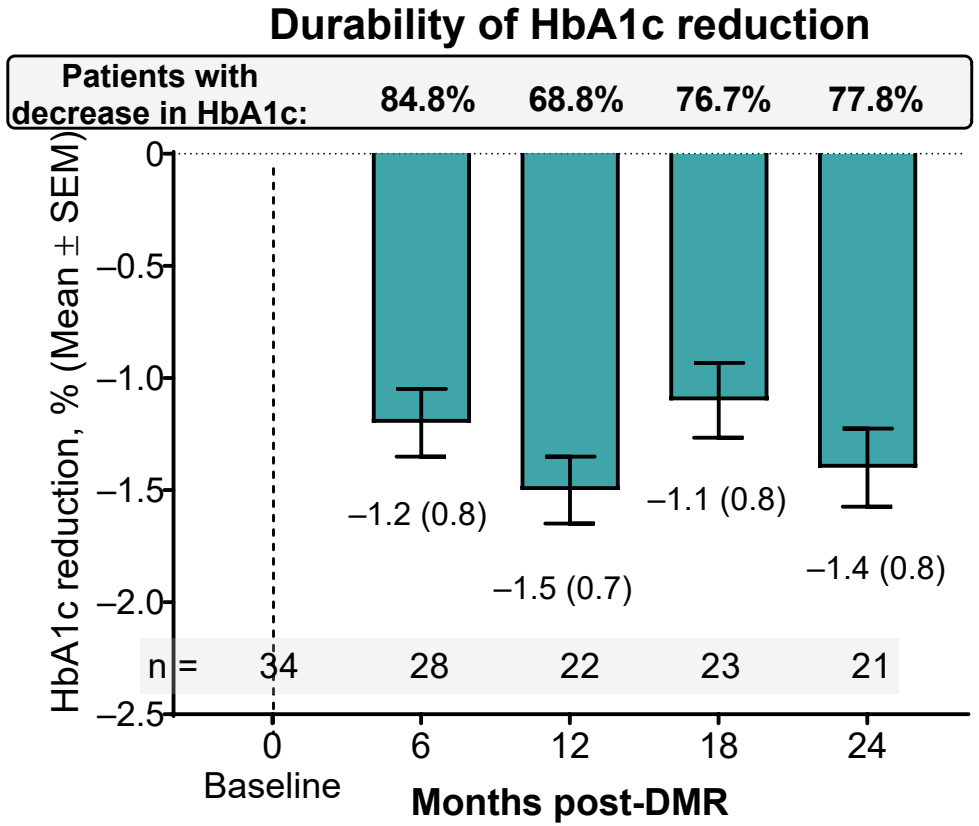
van Baar et al. *Gut*. 2019 Jul 22. doi: 10.1136/gutjnl-2019-318349.

HbA1c = hemoglobin A1c; DTSQ = diabetes treatment satisfaction questionnaires; HOMA-IR = homeostatic model assessment insulin resistance; DMR = duodenal mucosal resurfacing; FPG = fasting plasma glucose; OAD = oral anti-diabetic; SAE = serious adverse events; SEM = standard error of the mean; T2D = type 2 diabetes; UADE = unanticipated adverse device effects.

# **REVITA-1:** A single DMR procedure results in durable glycemic improvements through 24 months in T2D patients

No device- or procedure-related AEs or UADEs between 12 and 24 months post-DMR



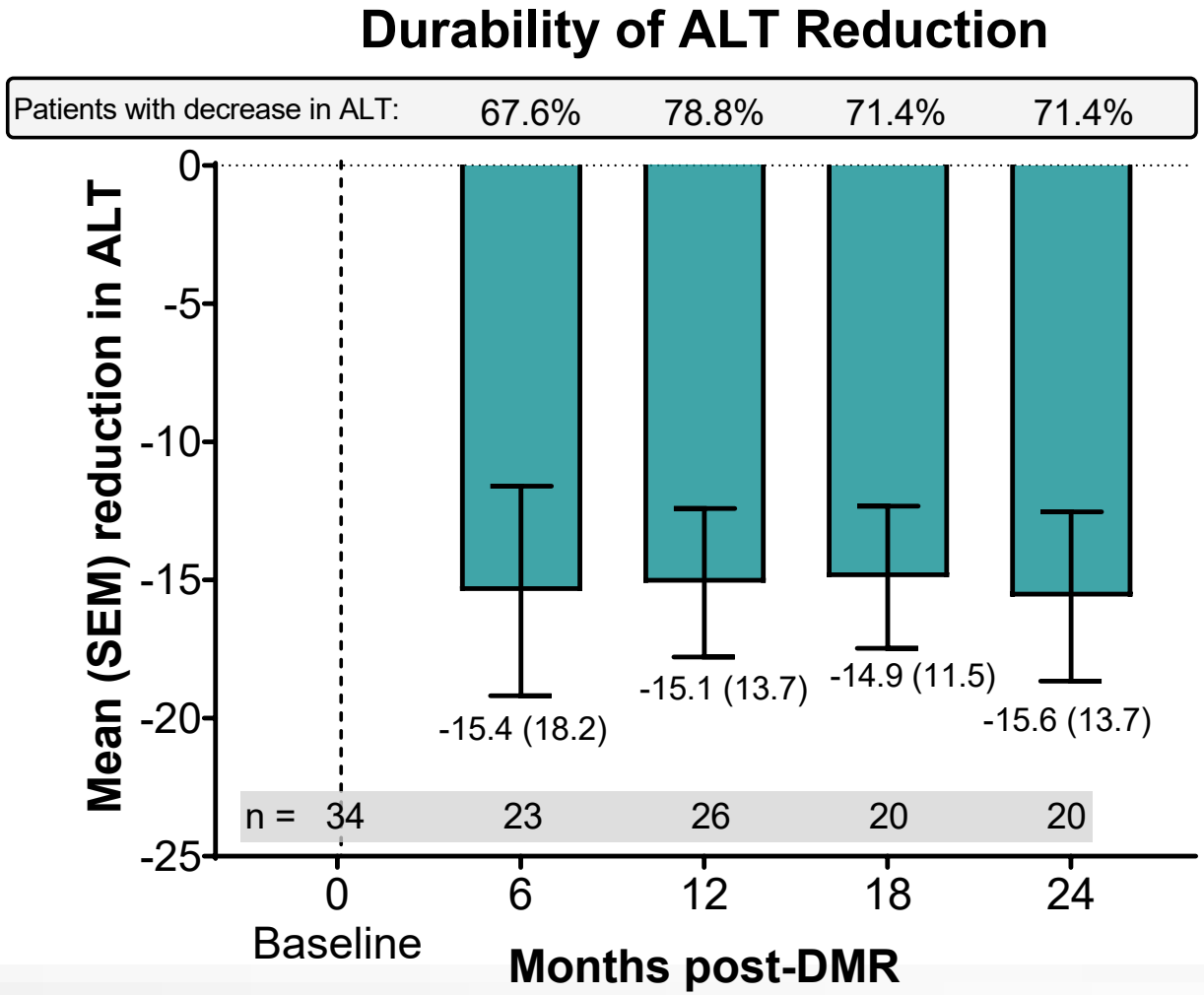




van Baar et al. Poster VAN 19122D presented at DTM; 15 Nov 2019.

Responders were defined as patients with any improvement from baseline in HbA1c levels at any given time point.

AE = adverse event; DMR = duodenal mucosal resurfacing; HbA1c = hemoglobin A1c; SEM = standard error of the mean; UADE = unanticipated adverse device effects; T2D = type 2 diabetes.

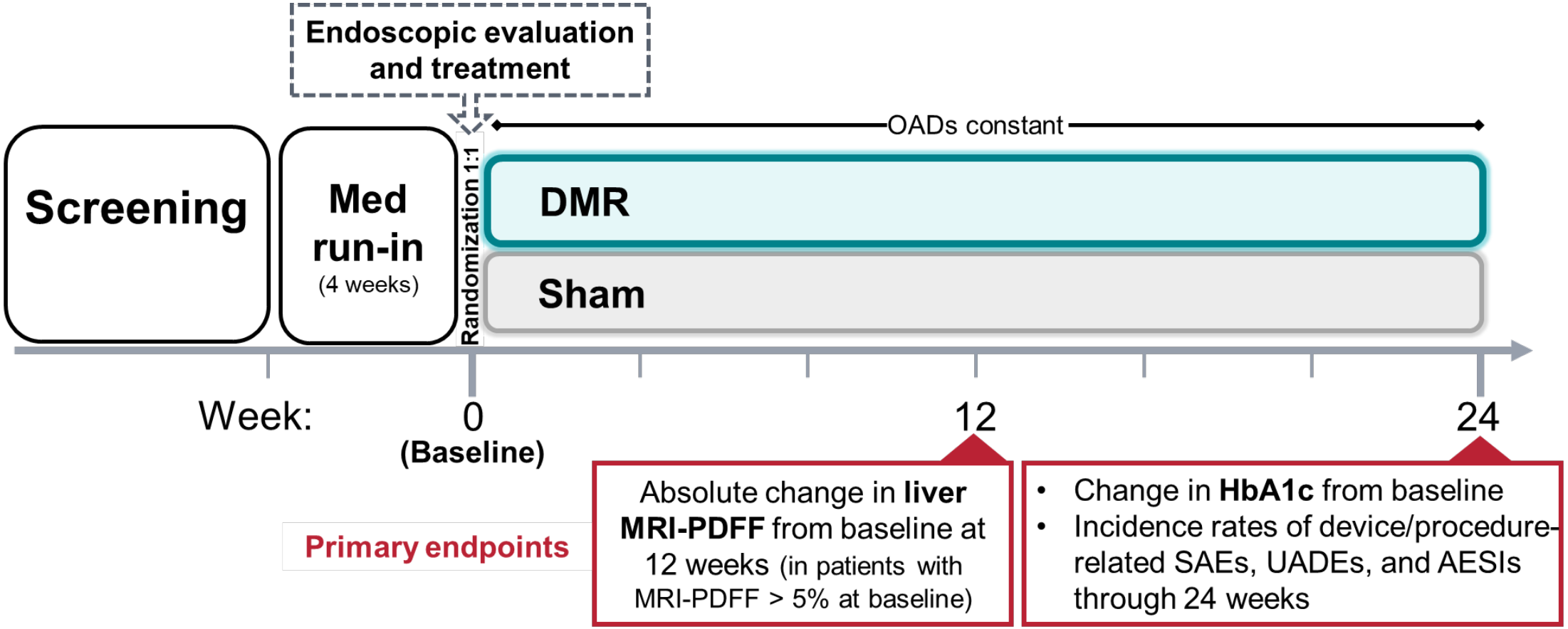
# **REVITA-1:** A single DMR procedure results in durable hepatic improvements through 24 months in T2D patients




- Persistent reductions in ALT in treatment responders suggest:
  - Sustained and meaningful reduction in liver injury and inflammation
  - Additional benefit of DMR on biomarkers of NAFLD

van Baar et al. Poster VAN 19122D presented at DTM; 15 Nov 2019.
Responders were defined as patients with any improvement from baseline in ALT levels at any given time point. Roughly 33% of patients entered the study with "normal" ALT levels. ALT = alanine aminotransferase; DMR = duodenal mucosal resurfacing; NAFLD = nonalcoholic fatty liver disease; SEM = standard error of the mean; T2D = type 2 diabetes.

# **REVITA-2:** First sham-controlled study of DMR in patients with suboptimally controlled T2D



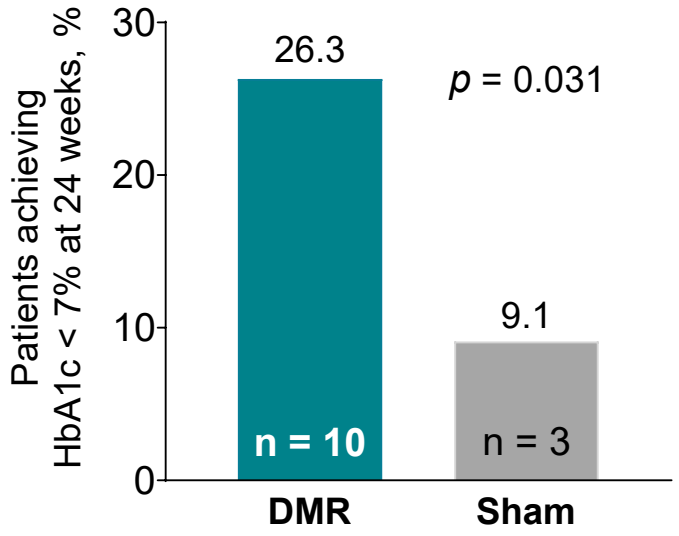

Bergman et al. oral presentation at AASLD; 11 Nov 2019; Boston, MA.

AESI = adverse event of special interest; BG = blood glucose; DMR = duodenal mucosal resurfacing; Med = medication; MRI-PDFF = magnetic resonance imaging proton density fat fraction; OAD = oral antidiabetic medication; SAE = serious adverse event; T2D = type 2 diabetes; UADE = unanticipated adverse device effects.

# **REVITA-2:** DMR positively impacts glucose metabolism

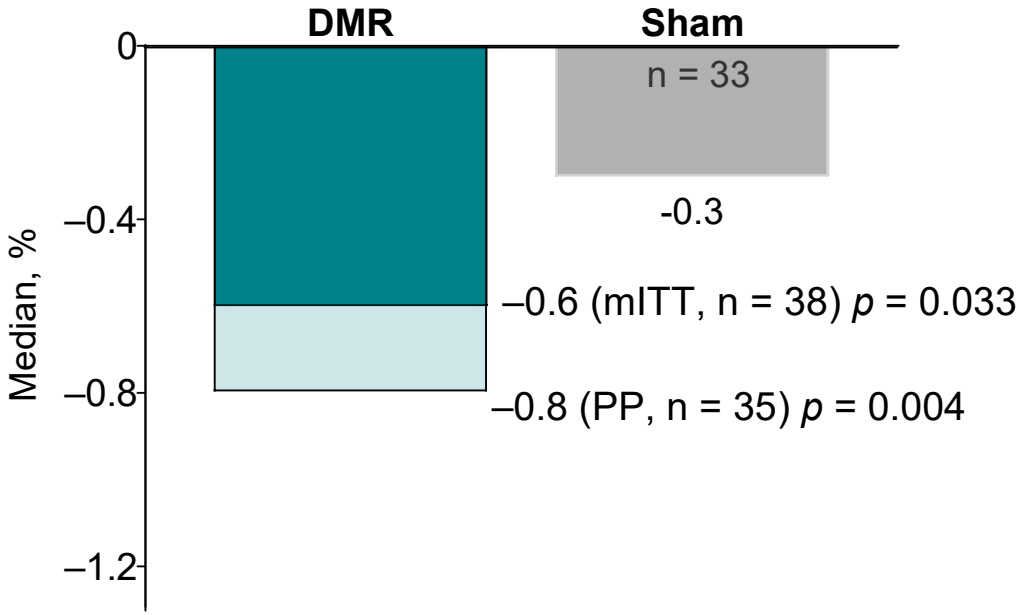
**A**

**HbA1c < 7% at 24 weeks**



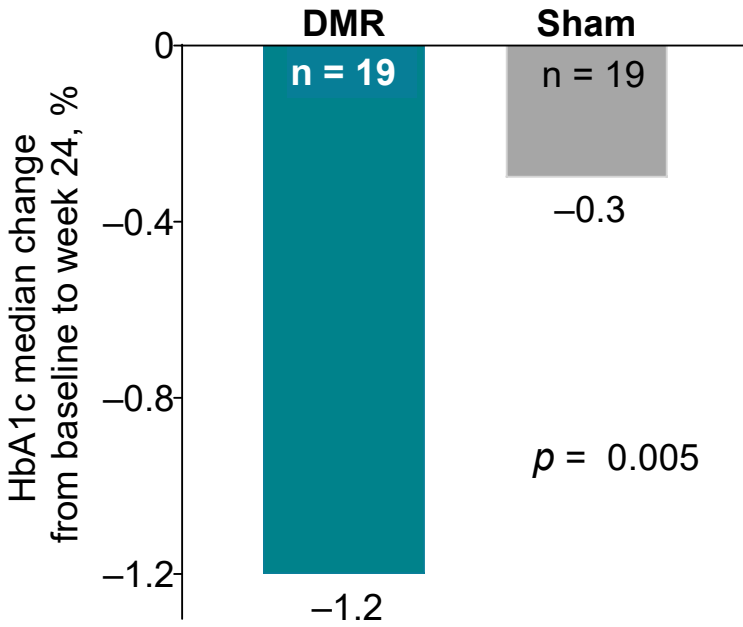

**B**

**Change in HbA1c from baseline to 24 weeks**




**C**

**More clinically significant reductions in HbA1c in patients with baseline FPG ≥ 180 mg/dL**




Bergman et al. oral presentation at AASLD; 11 Nov 2019; Boston, MA.

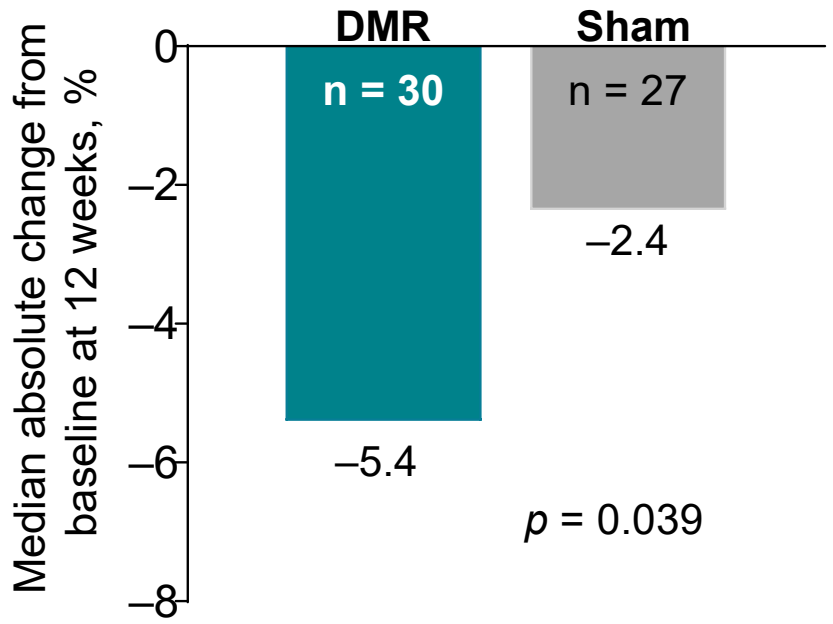
(A) Treatment comparison (DMR vs. SHAM) one-sided *p* value from chi-square test with no imputation of missing data and values post-rescue medication are set to missing. Two people missing HbA1c at week 24; One person set to missing post-rescue medication. 72 people in sample out of 75 Europeans (PP). Four patients in mITT group excluded from PP population. (B) Treatment comparison one-sided *p* value based on ANCOVA 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. (C) Treatment comparison (DMR vs. SHAM) one-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.

ANCOVA = analysis of covariance; DMR = duodenal mucosal resurfacing; FPG = fasting plasma glucose; HbA1c = hemoglobin A1c; mITT = modified intent-to-treat population defined as all randomized patients in whom the procedure was attempted and who had a baseline measurement for ≥ 1 primary endpoint (primary analysis population); PP = per-protocol.

# **REVITA-2:** DMR significantly improves liver fat content

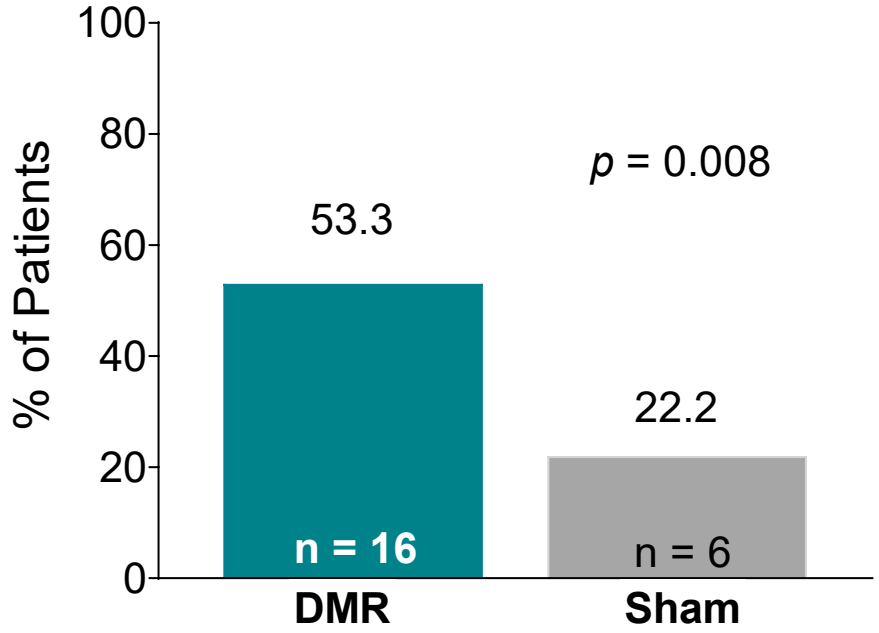
**A**

**Change in liver MRI-PDFF in patients with >5% liver MRI-PDFF at baseline (mITT)**




**B**

**Responder analysis: >30% reduction in relative liver MRI-PDFF from baseline to week 12 (mITT)**



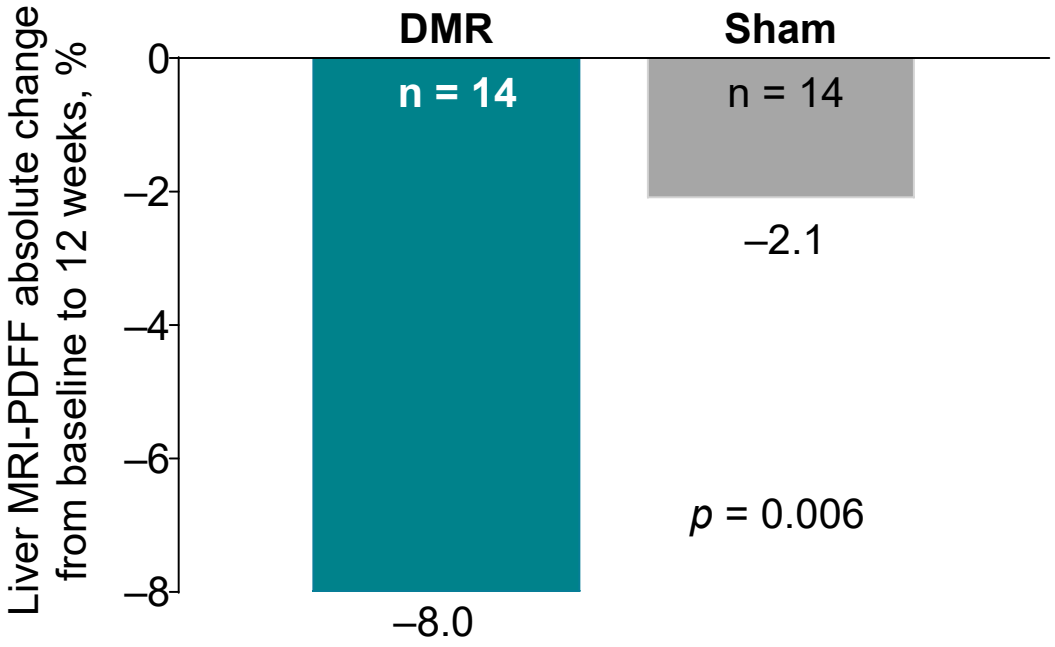

Bergman et al. oral presentation at AASLD; 11 Nov 2019; Boston, MA.

Treatment comparison one-sided *p* value based on ANCOVA model with multiple imputation on the rank values (modified ridit scores). 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; FPG = fasting plasma glucose; mITT = modified intent to treat; MRI-PDFF = magnetic resonance imaging proton density fat fraction.

# **REVITA-2:** DMR significantly improves liver fat content

**Change in liver MRI-PDFF in patients with FPG ≥ 180 mg/dL at baseline (mITT)**




**Change in hepatic transaminases from baseline at 12 weeks**

| Parameter | DMR N = 39 | Sham N = 36 | *p* value |
|---|---|---|---|
| **ALT**, U/L | n = 36<br>–4.5 (–37.0, 13.0) | n = 36<br>–2.0 (–36.0, 43.0) | 0.143 |
| **AST**, U/L | n = 32<br>–1.5 (–18.0, 9.0) | n = 31<br>–1.0 (–37.0, 12.0) | 0.117 |

Data are presented as median (min, max). One-sided *p* value based on ANCOVA model on the rank values (modified ridit scores) in mITT population for change from baseline to 12 weeks DMR vs. sham.

Bergman et al. oral presentation at AASLD; 11 Nov 2019; Boston, MA.

Treatment comparison one-sided *p* value based on ANCOVA 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. ALT = alanine aminotransferase; ANCOVA = analysis of covariance; AST = aspartate aminotransferase; DMR = duodenal mucosal resurfacing; FPG = fasting plasma glucose; mITT = modified intent to treat; MRI-PDFF = magnetic resonance imaging proton density fat fraction.

# **REVITA-2:** Favorable safety profile 24 weeks post-DMR (mITT 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) |

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

Bergman et al. oral presentation at AASLD; 11 Nov 2019; Boston, MA.

*Modified intent-to-treat population: Includes all randomized subjects in whom the study procedure (DMR or sham) is attempted and who have a baseline measurement for at least 1 primary endpoint. The mITT population is the primary analysis population for both the primary and secondary efficacy endpoints.

# Conclusions

- **DMR** is a novel, intestinal-targeted therapy for T2D
  - **REVITA-1** demonstrated durable glycemic and hepatic improvements through 2 years[1]
  - **REVITA-2** (first sham-controlled study): A single DMR procedure safely elicits favorable metabolic effects with improvements in glycemic and hepatic parameters through 6 months in patients with suboptimally controlled T2D[2]
    - Validates duodenum is a key therapeutic target for the treatment of insulin resistance underlying T2D and often overlapping NAFLD/NASH
    - Greater benefit in patients with baseline FPG ≥ 180 mg/dL highlights the important role of hepatic insulin resistance in pathophysiology of T2D and NALFD/NASH

1. van Baar et al. Gut. 2019. doi: 10.1136/gutjnl-2019-318349; 2. Bergman et al. oral presentation at AASLD; 11 Nov 2019; Boston, MA.
DMR = duodenal mucosal resurfacing; FPG = fasting plasma glucose; NAFLD = nonalcoholic fatty liver disease; NASH = nonalcoholic steatohepatitis; T2D = type 2 diabetes.

FRACTYL