Treatment of type 2 DIABETES and NAFLD

Can you disrupt the progression of type 2 diabetes (T2D) with a single endoscopic procedure?

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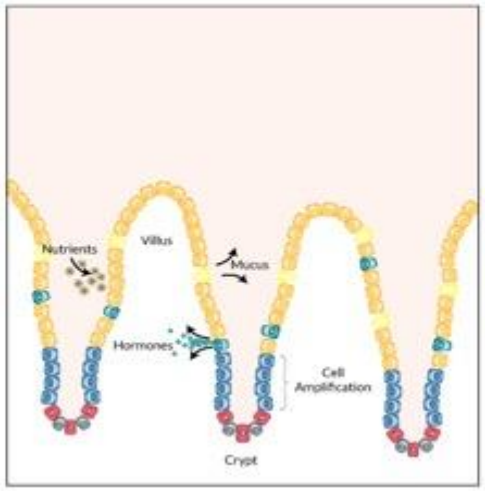
Medical Consultant Fractyl

Indication for Use

Duodenal mucosal resurfacing (Revita) is intended to improve glycaemic control in patients with Type 2 Diabetes who have preserved pancreatic function and whose diabetes is poorly controlled with oral glucose lowering medications.

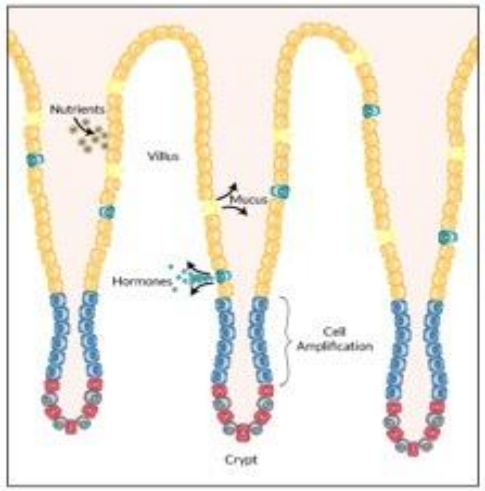
Duodenal mucosal hyperplasia as a driver of insulin resistance

Normal Duodenal Lining



Epithelial proliferation due to high fat & high sugar diets[1,4]

Duodenal Lining Overgrowth[2-4]



Duodenal hormone hyperactivity[2,5]

Insulin Resistance

Revita targets the overgrowth of the duodenal lining with hydrothermal ablation to promote healthy epithelial regrowth and improve insulin sensitivity, a disease-modifying approach to T2D

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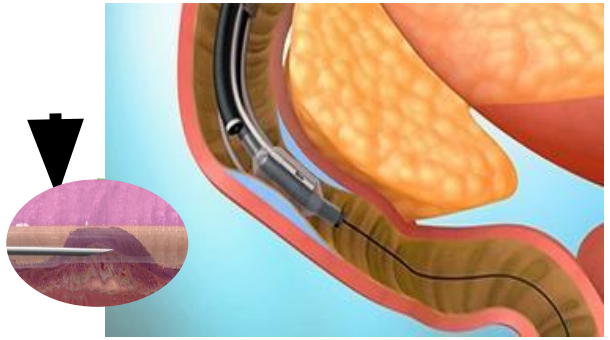
[1] O"Brien et al. Cell. 2012 Oct;147(3):603-614 [2] Gniuli et al. Diabetologia. 2010 Oct;53(10):2233-40. [3] Theodorakis et al. Am J Physiol Endocrinol Metab. 2006 Mar;290(3):E550-9. [4] Theodorakis et al. Diabetes Care. 2004 Jul;27(7):1692-8. [5] Adapted from: Ghosh S, et al. 78th ADA Scientific Sessions, June 2018, Orlando, FL 2018, Abstract 1900-P.

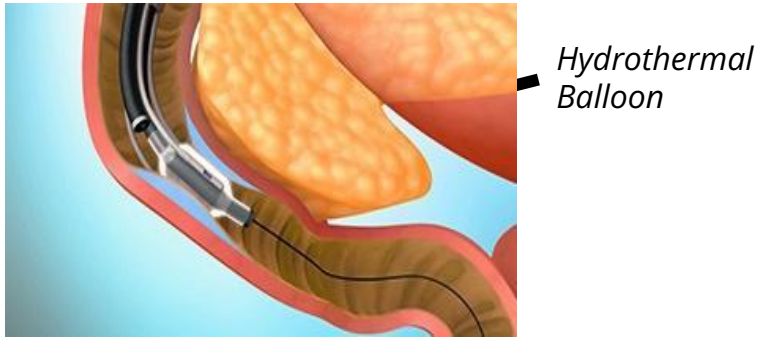
Duodenal Mucosal Resurfacing (Revita)

- 2-Step endoscopic ablation procedure performed in less than one hour in a day-case setting[1]
- No indwelling implant or surgical incision[1]
- A single treatment with durability up to 12 months or more[2]
- Performed by an interventional therapeutic endoscopist, ongoing care of patient remains with original T2D consultant
- Post-Revita, patient transitions from liquid to solid diet over 10-14 days[1]
- Leads to healthy epithelial regrowth within 4-6 weeks
- CE mark enables its use in EU as an endoscopic therapeutic approach for the treatment of complications derived from insulin resistance: T2D, NAFLD, PCOS

Targets duodenal mucosa between Ampulla of Vater and Ligament of Treitz

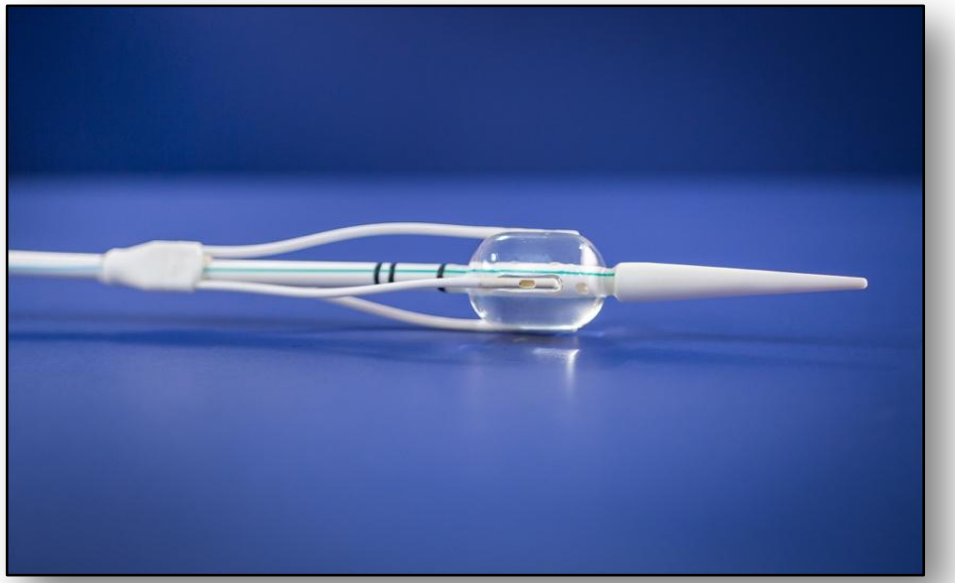


Step 1: Circumferential saline injection for a precise lift every time



Hydrothermal Balloon

Step 2: Hydrothermal ablation cycling cooled and heated water for maximum tissue protection



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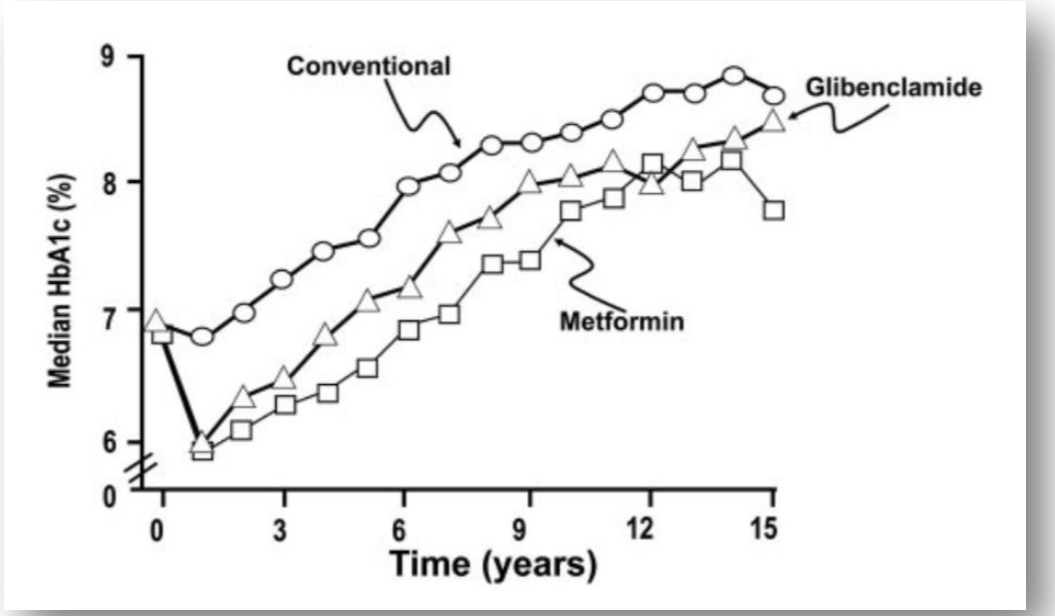
[1] Cherrington AD, Rajagopalan H, Maggs D, Devière J. Hydrothermal duodenal mucosal resurfacing: role in the treatment of metabolic disease. Gastrointest Endosc Clin N Am. 2017;27:299–311. [2] van Baar ACG, Holleman F, Crenier L, et al Endoscopic duodenal mucosal resurfacing for the treatment of type 2 diabetes mellitus: one year results from the first international, open-label, prospective, multicentre study Gut Published Online First: 22 July 2019. doi: 10.1136/gutjnl-2019-318349

T2D IS A PROGRESSIVE DISEASE; OPTIMAL GLYCAEMIC CONTROL IS CHALLENGING

T2D is characterized by insulin resistance, high blood sugar, and the chronic deterioration of beta cell function

Even with optimal adherence to Oral Anti-diabetic Medications (OADs), over time the progressive rise in HbA1c and deterioration in beta cell function may be observed, requiring medication intensification[1]



The effect of sulfonylurea (glibenclamide = glyburide) and metformin therapy on the plasma A1C concentration in newly diagnosed type 2 diabetic subjects.[1]

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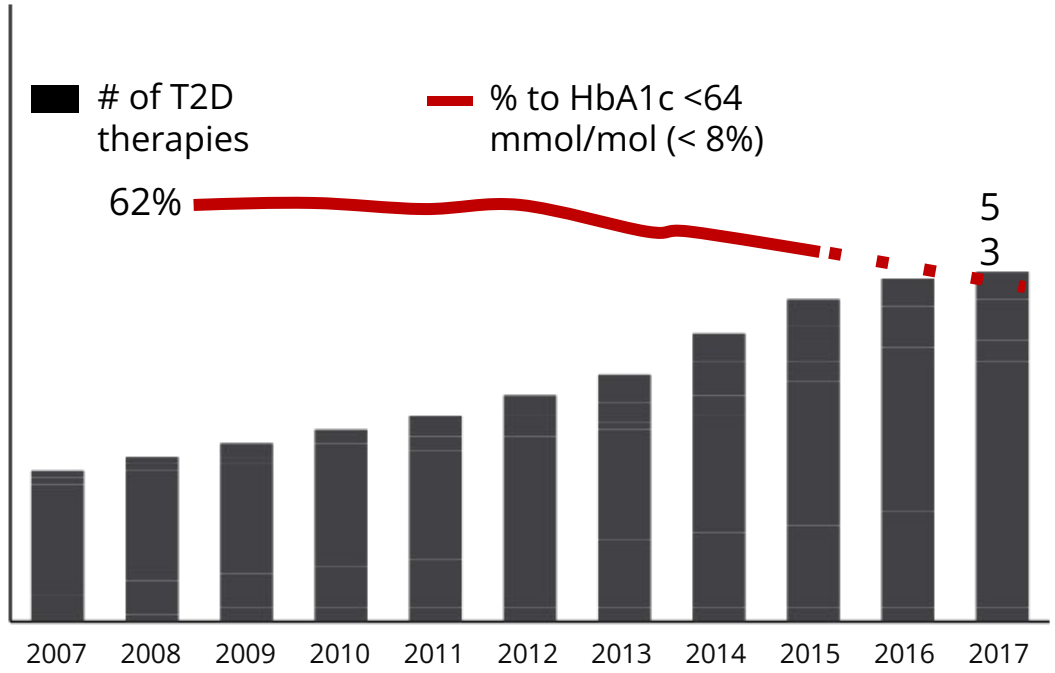
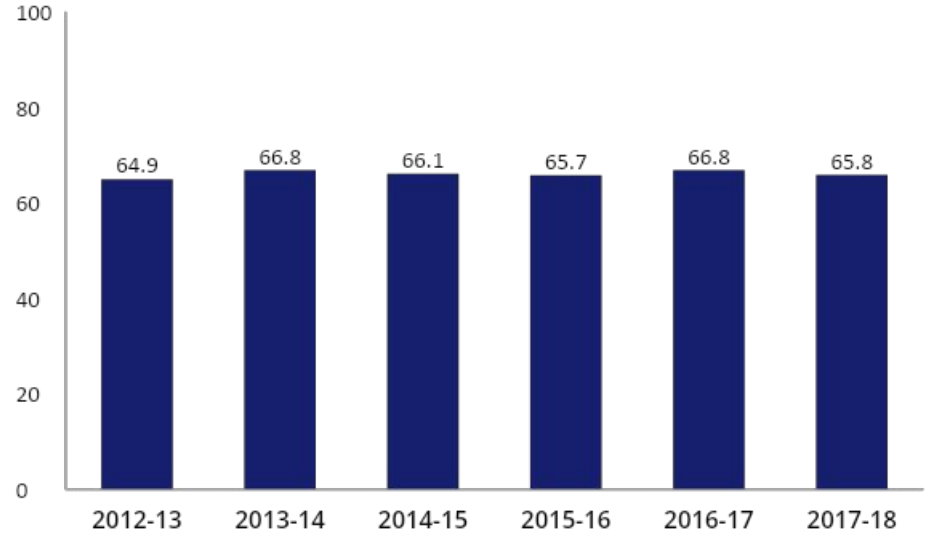
[1] Defronzo RA. Banting Lecture. From the triumvirate to the ominous octet: a new paradigm for the treatment of type 2 diabetes mellitus. Diabetes. 2009;58(4):773–795. doi:10.2337/db09-9028

DESPITE ADVANCES IN PHARMACOLOGICAL TREATMENTS, PATIENTS STILL STRUGGLE TO REACH HBA1C TARGETS

Although the Number Available Diabetes Medicines has Increased, Glucose Control is Not Improving[1-2]



National Diabetes Audit (England & Wales) Percentage Achieving Treatment Targets HbA1c <58 mmol/mol (<7.5%)[3]



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[1] Adapted from NCQA 2019 State of Health Care Quality Report Card, , https://www.ncqa.org/hedis/measures/comprehensive-diabetes-care/[2] FDA-Approved Diabetes Medicines fda.gov, 02/02/2018 [3] Adapted from National Diabetes Audit, 2017-18, Published on 8th November 2018; Accessed on 10/16/2019

INSULIN NAÏVE PATIENTS MAY DELAY INTENSIFICATION, EXTENDING GLYCAEMIC BURDEN[1]

Therapeutic Inertia Plays A Key Role in Hyper-Glycaemia[1]

- UK research showed ~50% of patients that fail ≥ 2 OADs (≥ 8.0% HbA1c) delay insulin initiation for almost 5 years after their first oral glucose-lowering agent (OGLA) failure[1]

Patient Barriers to Insulin Initiation[2]

- Quality of Life perceptions
- Fear of side effects (weight gain, hypoglycaemia, injection site pain)

Clinical Barriers to Insulin Initiation[2]

- Concerns about side-effects, i.e. hypoglycaemia
- Complicated patient-type, high comorbidities
- Insulin requires specialist training and more patient education

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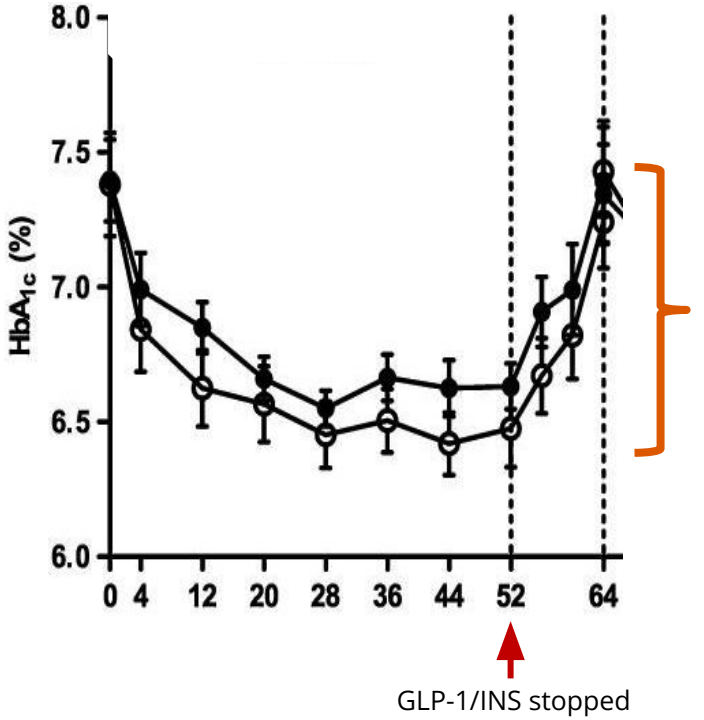
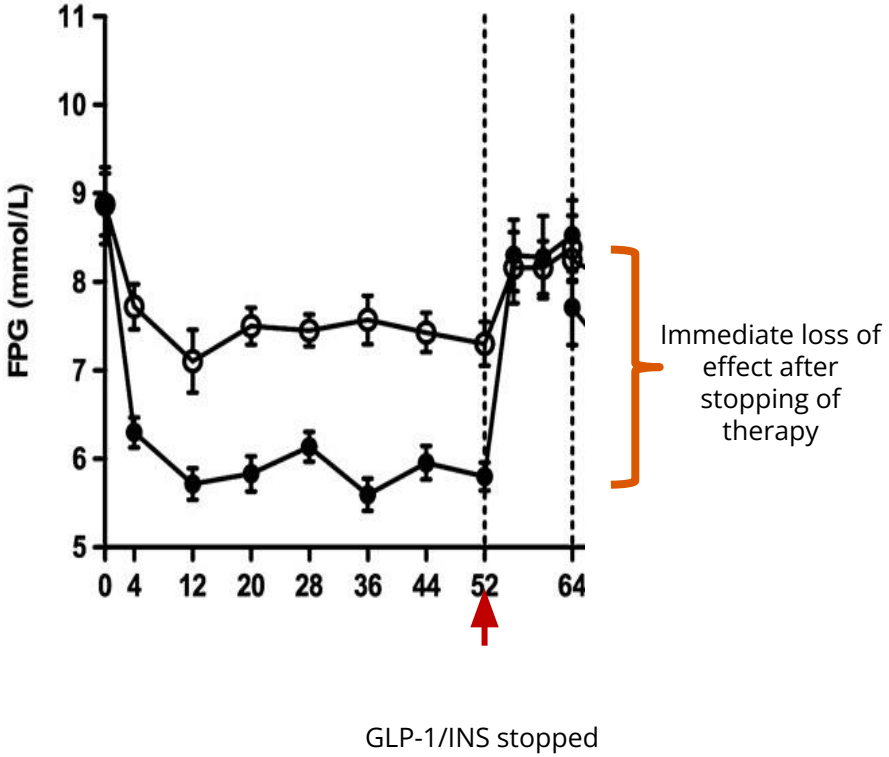
[1] Rubino, A & McQuay, Lisa & Gough, S & Kvasz, M & Tennis, P. (2008). Delayed initiation of subcutaneous insulin therapy after failure of oral glucose-lowering agents in patients with Type 2 diabetes: A population-based analysis in the UK. Diabetic medicine : a journal of the British Diabetic Association. 24. 1412-8. 10.1111/j.1464-5491.2007.02279.x. [2] Khunti K, Wolden ML, Thorsted BL, Andersen M, Davies MJ. Clinical inertia in people with type 2 diabetes: a retrospective cohort study of more than 80,000 people. Diabetes Care. 2013;36(11):3411–3417. doi:10.2337/dc13-0331

WITHOUT ONGOING INJECTABLE ADMINISTRATION & ADHERENCE, BENEFICIAL EFFECTS ARE NOT SUSTAINED[1]

HbA1c & Fasting Plasma Glucose Worsens After Ceasing GLP-1 and Insulin Therapy





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[1] Adapted from: Bunck MC, Cornér A, Eliasson B, et al. Effects of exenatide on measures of β-cell function after 3 years in metformin-treated patients with type 2 diabetes. Diabetes Care. 2011;34(9):2041–2047. doi:10.2337/dc11-0291

REVITA PATIENT PROFILE

CLINICAL

- Currently on multiple OAD medications
- HbA1c remains uncontrolled over multiple follow-up visits *OR*
- HbA1c has slipped from target and intensification is necessary
- High Fasting Plasma Glucose (FPG)
- Elevated liver enzymes, at risk for NAFLD/NASH
- High TG/HDL ratio
- BMI <40; weight loss is secondary to metabolic concerns
- Potentially on multiple medications for concomitant conditions (e.g. CV)
- Has received prior lifestyle/nutritional counseling

Professor

Advertising Executive

BEHAVIORAL

- Resistant/fear of intensification to injectable therapies and their side-effects (e.g. weight gain, hypoglycaemia, nausea)
- Frustrated by uncontrolled HbA1c despite already being on multiple anti-diabetic medications
- Concerned about the growing number of daily medications and their management
- Open and inquisitive about other treatment options

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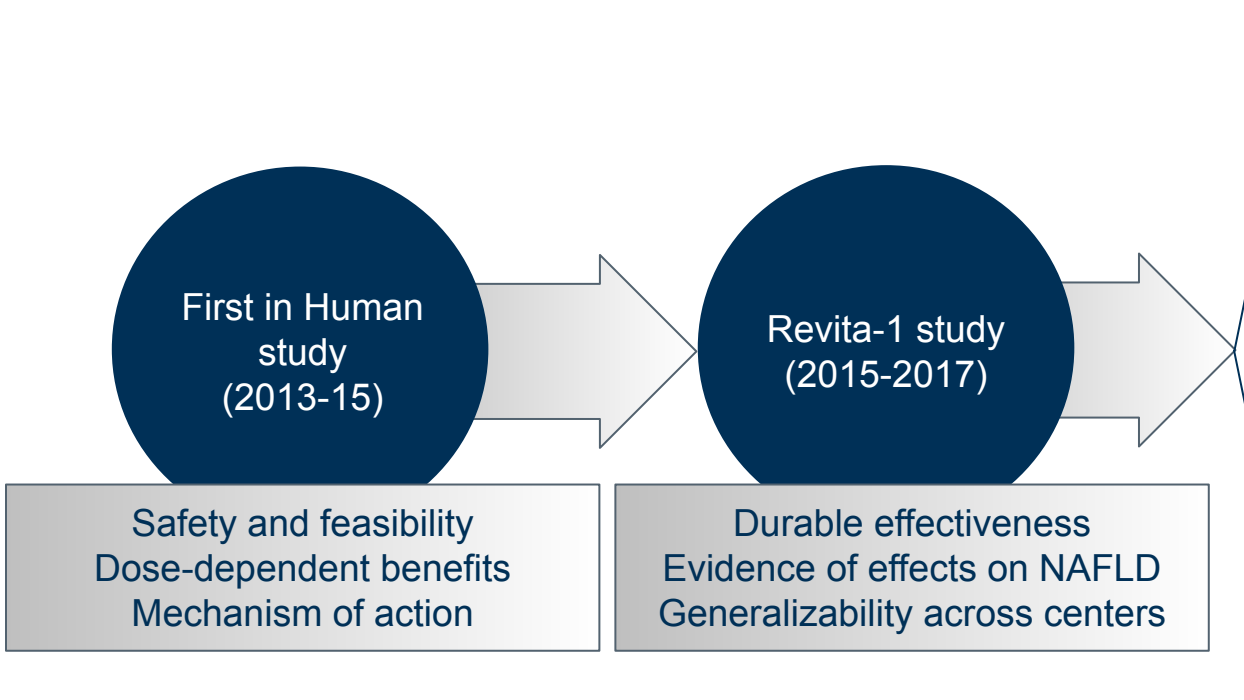
*Pictures For illustrative purposes only

Key DMR clinical trials



Revita-2 study
2017 - present

1st randomized + blinded study in T2D + NAFLD

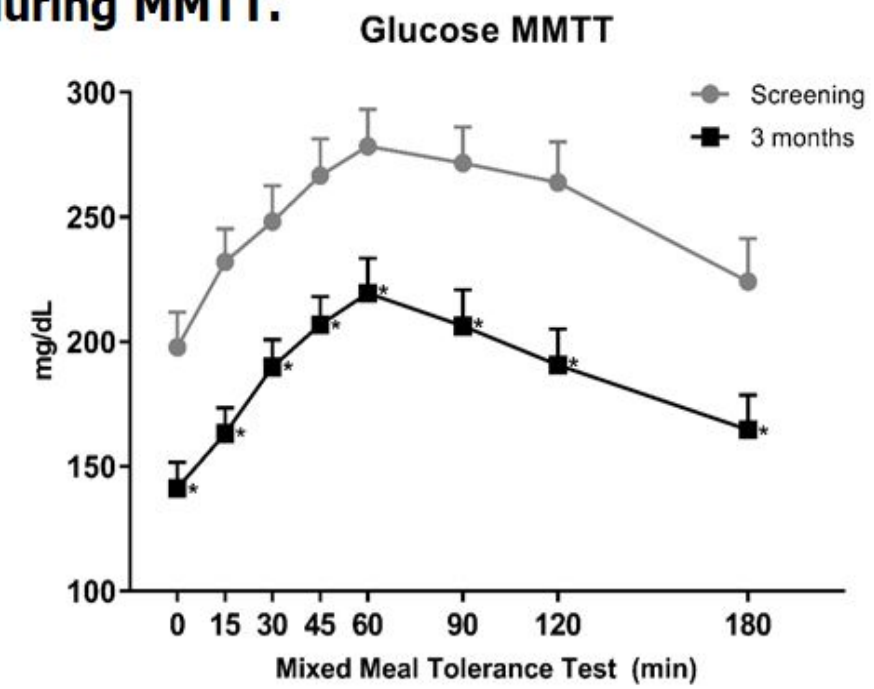
INSPIRE
2018 - present

Study of insulin withdrawal in T2D

First-in-Human Study (FIH) established feasibility and "dose-dependent" efficacy

- **Procedural implementation and safety**
- **DMR Efficacy**:
  - Lowered HbA1c, fasting glucose
    - 1.2% at 6 months in the full cohort (P < 0.001)
    - Dose-dependent glycemic improvement
      - LS : -1.4% at 6 months
      - SS : -0.7% at 6 months
  - Broad Metabolomic Benefit
    - ↓ Hepatic Insulin Resistance
    - ↓Oxidative Stress and Inflammation
    - ↑ Increased markers of improved mitochondrial function, lipid oxidation and Krebs cycle

Postprandial glucose levels measured during MMTT.

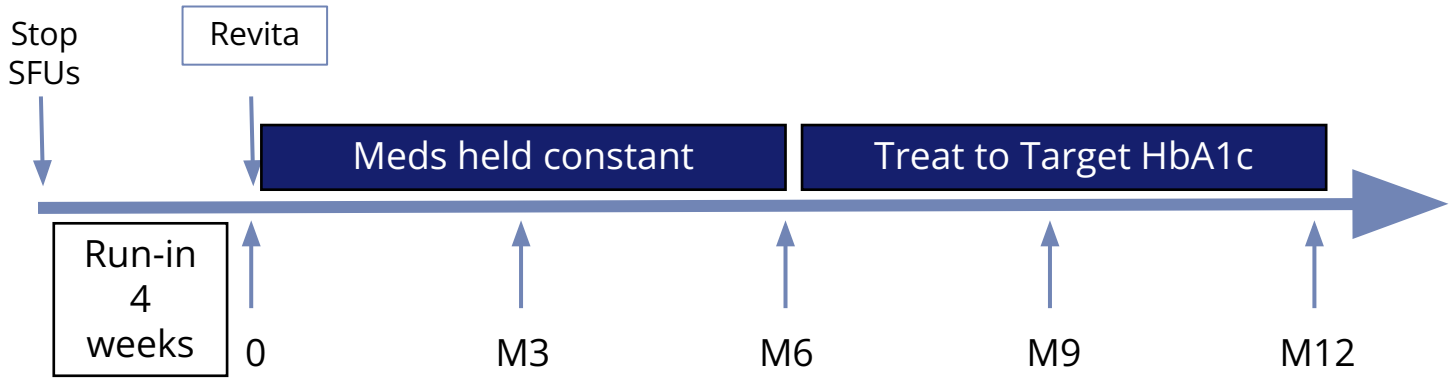


**Indicates a significant (p <0.05) change compared to the corresponding time point at screening (paired students t-test).*
Metabolomics analysis subcohort (n=14).

LS = long duodenal segment ablated (LS ~9.3 cm treated)
SS = Short duodenal segment ablated (SS ~3.4 cm treated)

Adapted from: Rajagopalan, H. et al. Diabetes Care. 2016 Dec; 39(12): 2254-2261
DMR = duodenal mucosal resurfacing; HbA1c = hemoglobin A1c; MMTT; Mixed-Meal Tolerance Test:

REVITA-1 STUDY DESIGN & PATIENT CHARACTERISTICS



- Multicenter center, single arm study
- Designed to evaluate efficacy and safety of DMR in T2D patients
- 7 participating sites in Europe and Chile
- Entry: HbA1c 7.5-10% on oral anti-diabetic medication
- Sulfonylureas withdrawn at -4 weeks prior to Revita procedure
- Concomitant meds constant through 24 weeks
- Patients followed for 2 years (current data available at 12 months)

Patient characteristics	N=46
Age, years (range)	55 (31-69)
Duration of type 2 diabetes, years (range)	6 (0.1-12)
Weight (kg)	90.3 (13.1)
BMI (kg/m^2)	31.6 (4.3)
HbA1c (mml/mol) (%)	70 (9) 8.6 (0.8)
FPG (mmol/L)	10.7 (2.7)
HOMA-IR Index	8.0 (5.7)

Clinical Characteristics at baseline. Values are mean (SD) unless other wise noted. BMI: Body Mass Index; HbA1c: Glycated Hemoglobin A1c; HOMA-IR: F-TGs: Fasting Plasma Glucose

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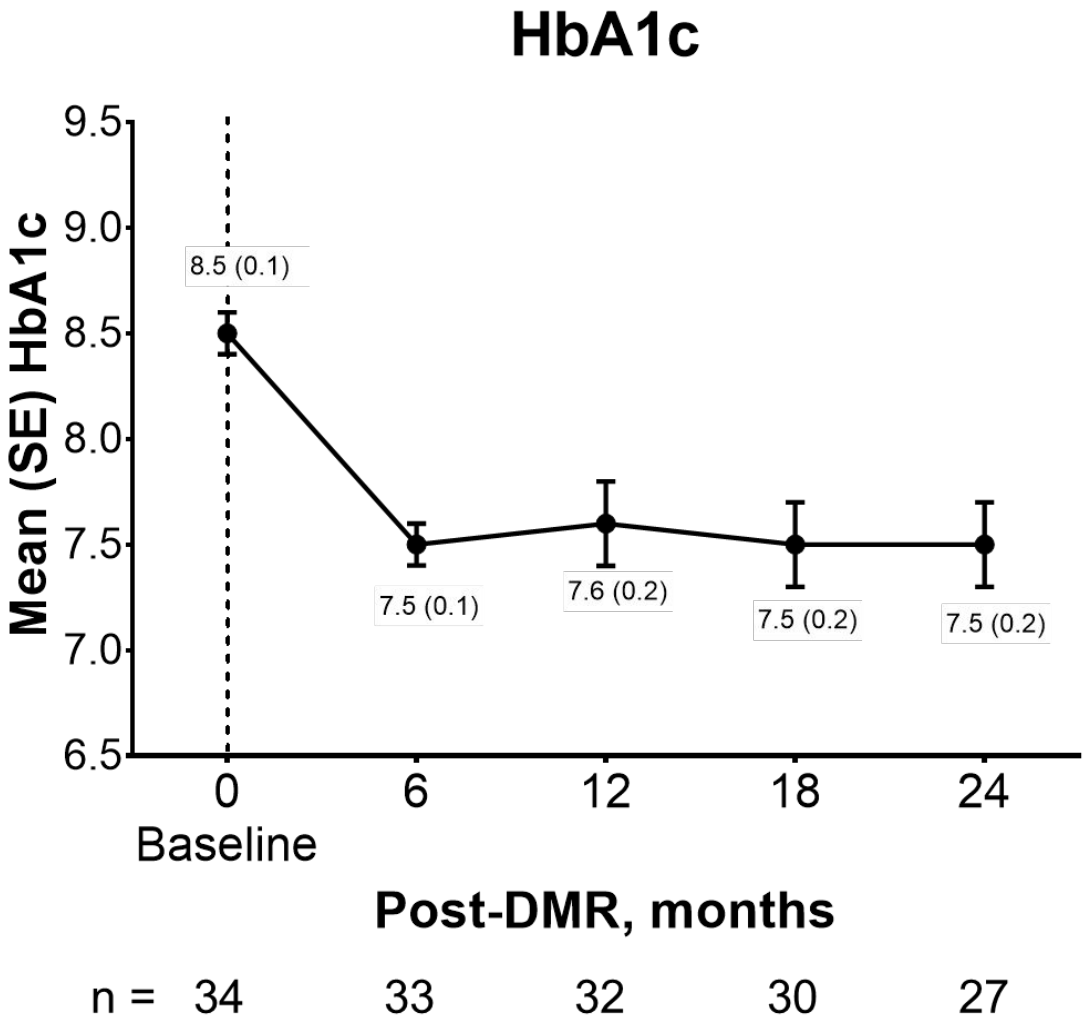
[1] Adapted from: van Baar ACG, Holleman F, Crenier L, et al Endoscopic duodenal mucosal resurfacing for the treatment of type 2 diabetes mellitus: one year results from the first international, open-label, prospective, multicentre study Gut Published Online First: 22 July 2019. doi: 10.1136/gutjnl-2019-318349 .

Significant and sustained improvements in HbA1c from a single procedure

Sustained HbA1c reductions through 24 months thus far

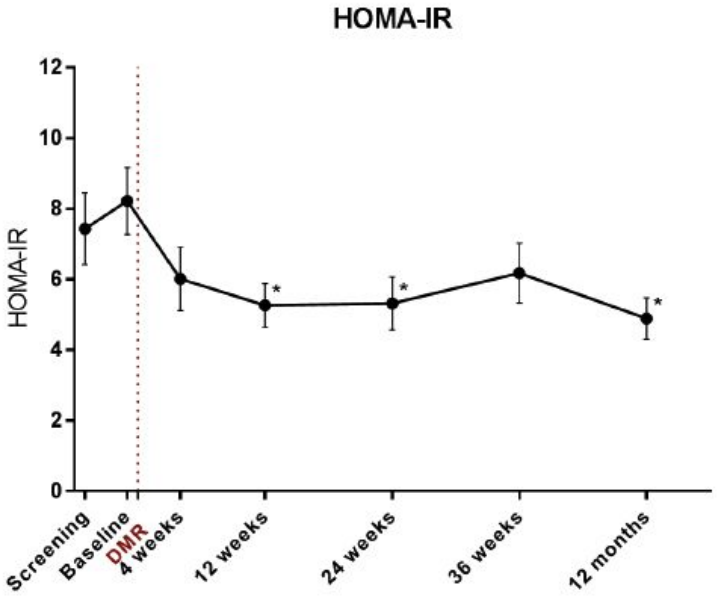
80% response rate with 1.4% HbA1c reduction at 24 months in responders

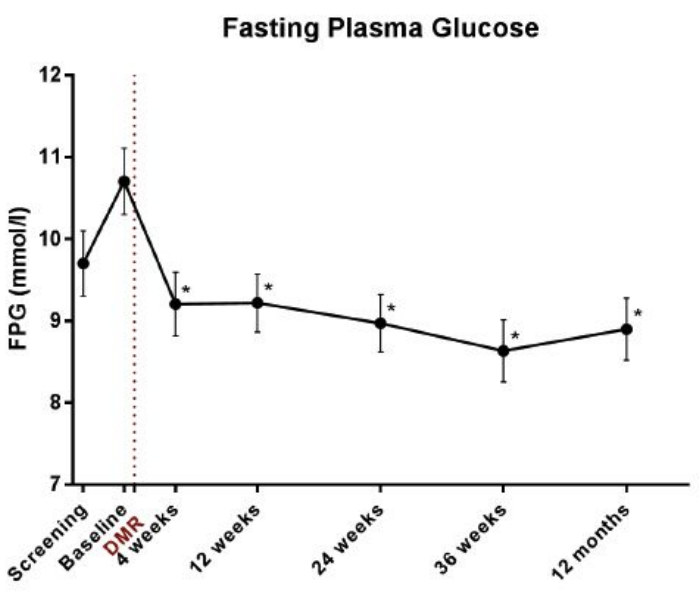
Significant and sustained improvement in quality of life

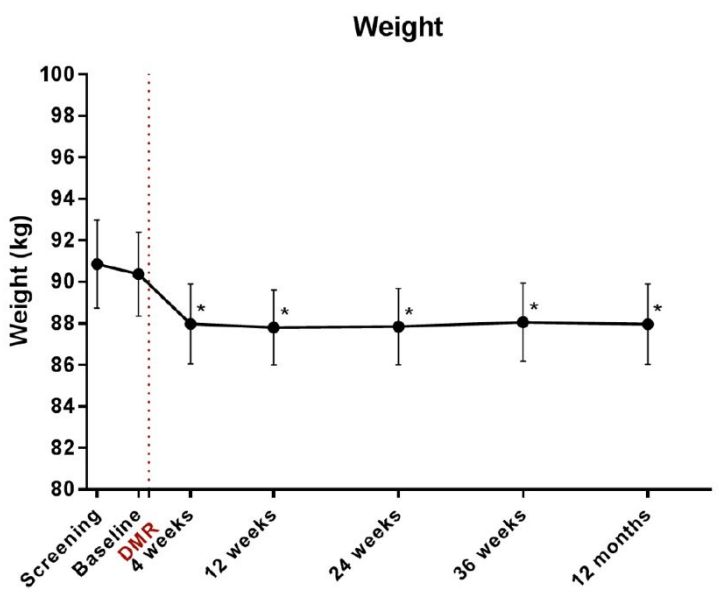


Van Baar et al Gut 2019 and DTM 2019

IMPROVED INSULIN SENSITIVITY AND LOWER FPG INDEPENDENT OF WEIGHT LOSS[1]







HOMA-IR was reduced by 2.9±1.1 at 24 weeks and by 3.3±0.9 at 12 months post DMR compared with baseline (p <.001)[1]

FPG reduced by 1.7±0.5 mmol/L (p <.001) and 1.8±0.5 mmol/L (p <.001) at 24 weeks and 12 months post DMR, compared with baseline[1]

A modest weight reduction was observed: −2.5±0.6 kg (p <.001) at 24 weeks and −2.4±0.7 kg (p <.001) at 12 months[1]

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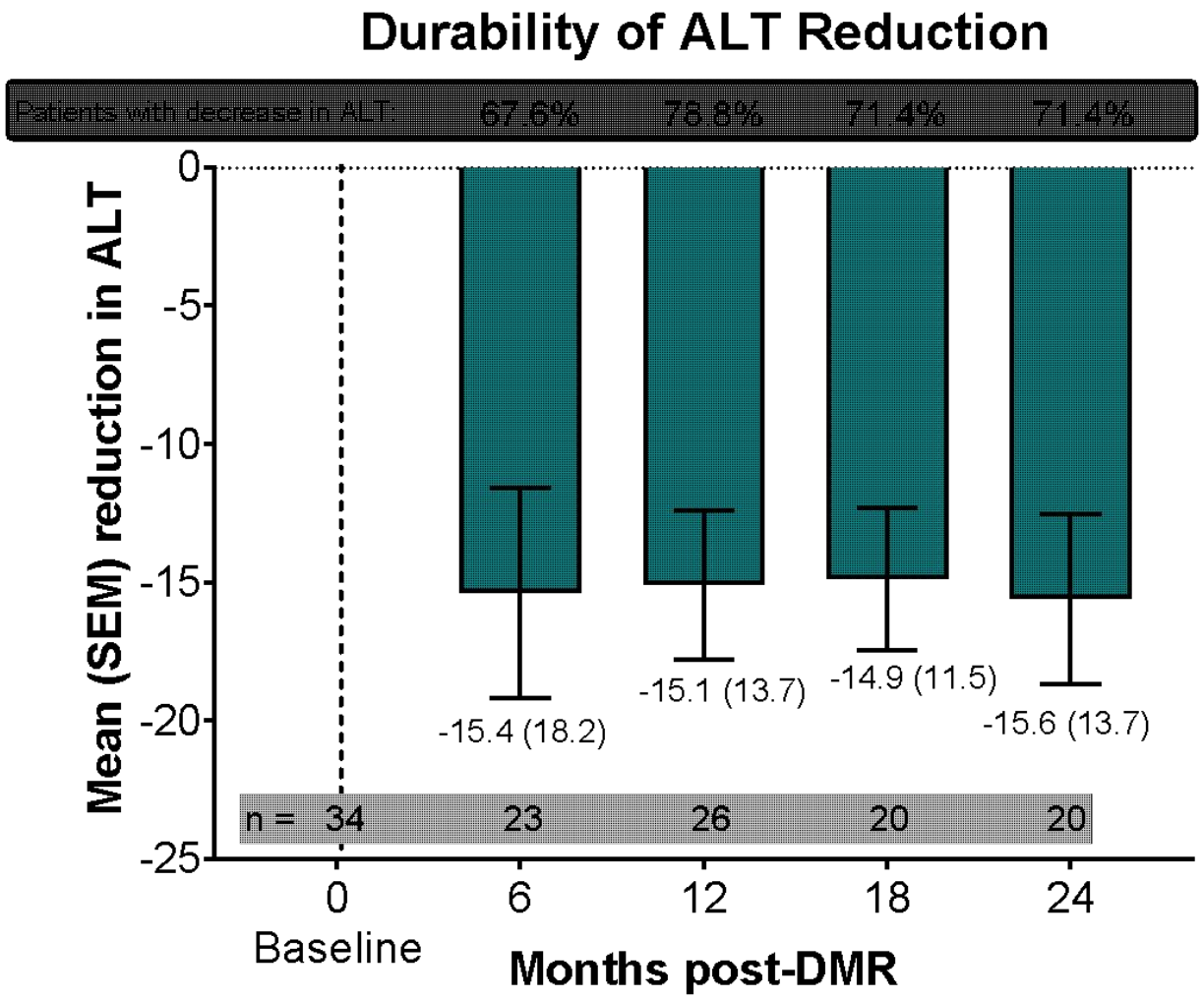
[1] van Baar ACG, Holleman F, Crenier L, *et al* Endoscopic duodenal mucosal resurfacing for the treatment of type 2 diabetes mellitus: one year results from the first international, open-label, prospective, multicentre study *Gut* Published Online First: 22 July 2019. doi: 10.1136/gutjnl-2019-318349

Durable improvements in LFTs



- 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.

IMPROVEMENT OF LIPID PARAMETERS & OTHER METABOLIC VALUES

Lipid parameters associated with cardiovascular risk improved with significant reductions in triglycerides and increases in fasting HDL[1]

Indices	Baseline	12 weeks	P value
Fasting C-peptide (ng/ml)	3.2 ± 0.3	2.7 ± 0.2	= 0.01
Fasting Triglycerides (mg/dl)	209.0 ± 32.0	150.0 ± 20.0	< 0.01
Fasting HDL (mg/dl)	45.7 ± 2.8	49.2 ± 3.2	< 0.05
Ferritin* (ng/ml)	90.8 ± 16.6	69.4 ± 15.5	< 0.01

Values are all mean (±SEM); n = 24 except where indicated; * n=23

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[1}] Adapted from Hopkins, et al. 4th World Congress on Interventional Therapies for Type 2 Diabetes (WCITD). New York City, NY, USA, April 2019

REVITA-2 study- safety and efficacy of DMR compared with a sham procedure

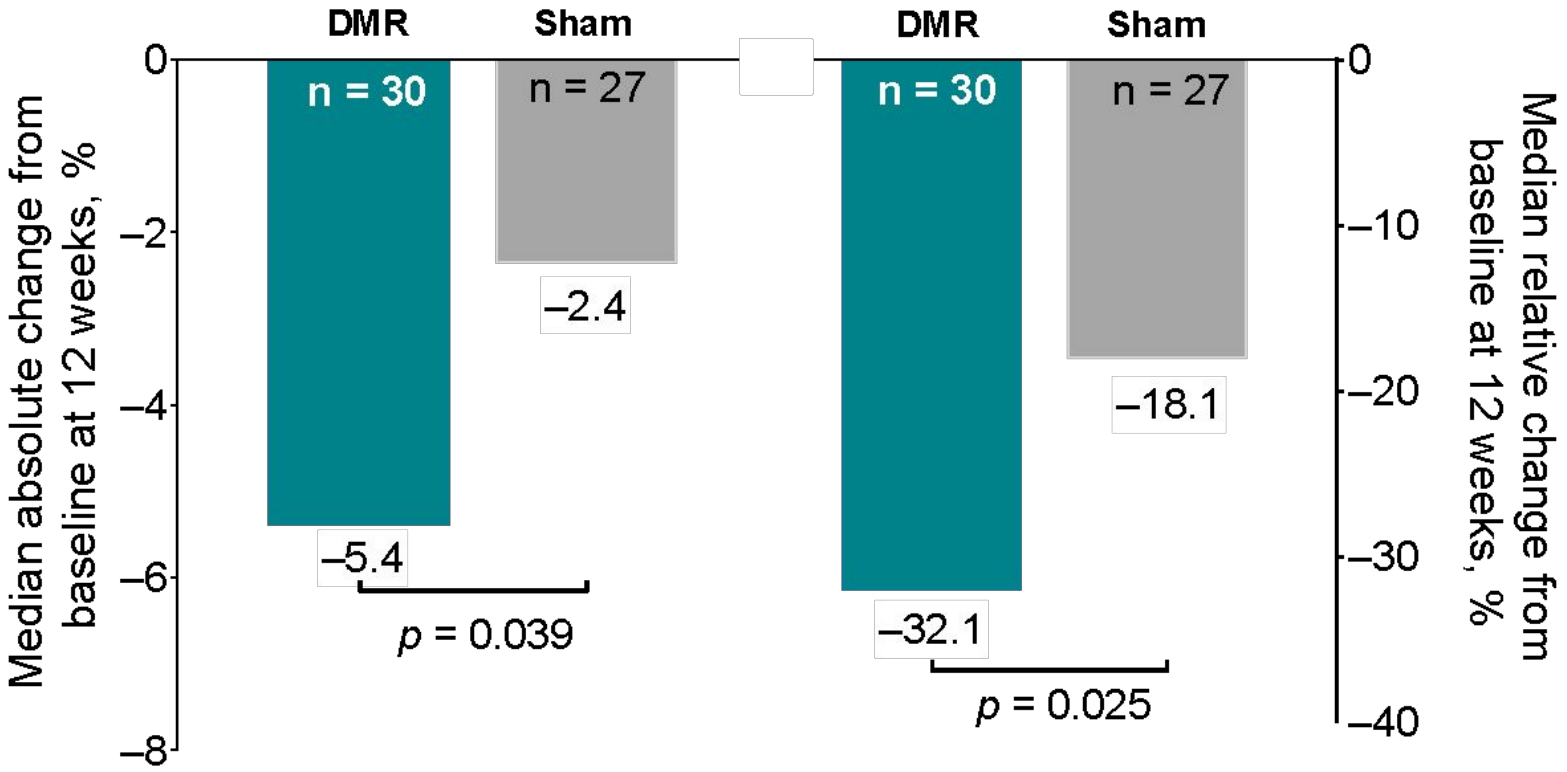
First sham-controlled study in T2D + NAFLD

Top-line positive results in both HbA1c and MRI-PDFF

First disease-modifying therapy for metabolic disease

Changes in Liver MRI-PDFF in Patients with > 5% Liver Fat Content at Baseline (mITT)

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

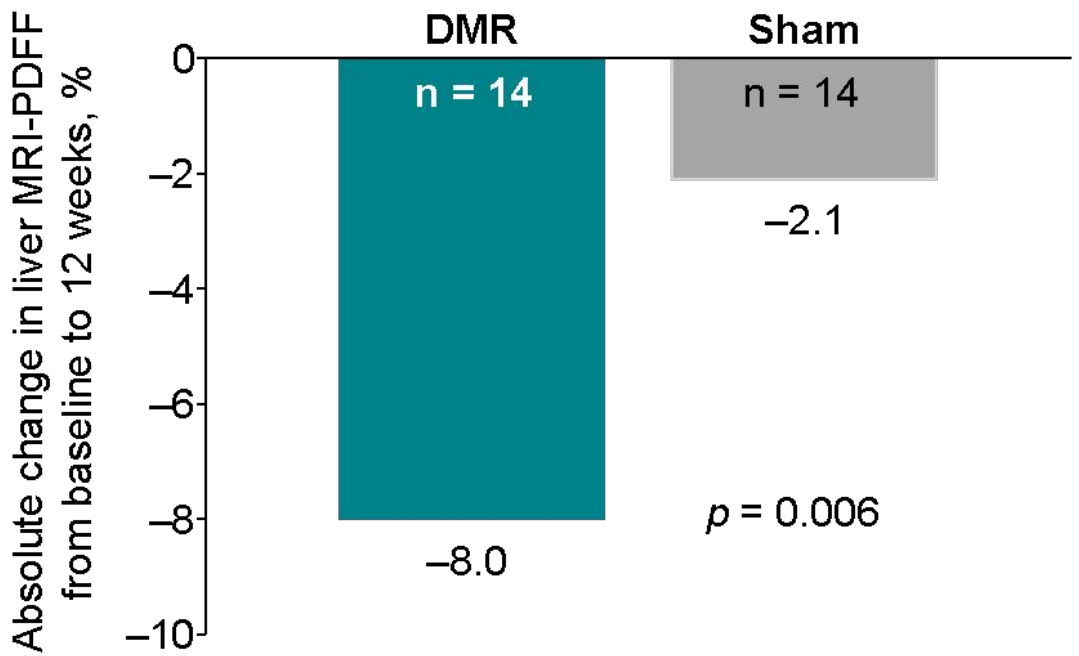


Data on File, Fractyl Laboratories Inc.

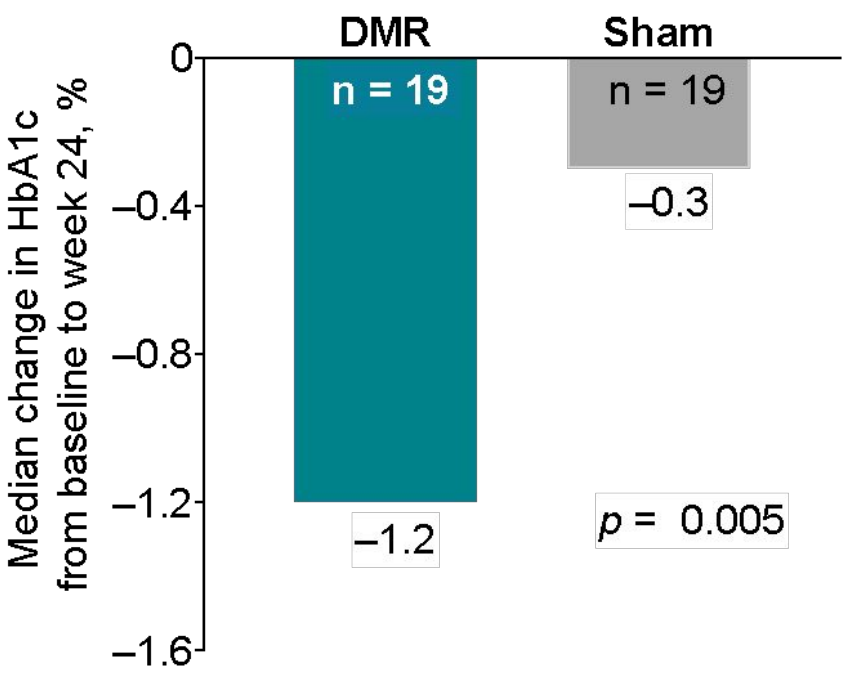
Treatment comparison one-sided *p* value based on ANCOVA model with Multiple Imputation on the rank values (modified ridit scores). Via multiple imputation, analysis is based on all patients in the population of interest where post-rescue values are first set to missing. ANCOVA = analysis of covariance; DMR = duodenal mucosal resurfacing; MRI-PDFF = magnetic resonance imaging proton density fat fraction.

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

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



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



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

1. Data on File, Fractyl Laboratories Inc. 2. Rajagopalan H, et al., *Diabetes Care*. 2016;39:2254. 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.

DMR = duodenal mucosal resurfacing; FPG = fasting plasma glucose; MRI-PDFF = magnetic resonance imaging proton density fat fraction; T2D = type 2 diabetes; PP = per-protocol.

INSPIRE study-can DMR eliminate the need for insulin in T2D?

INSPIRE study:

- Day 1: DMR procedure & stop insulin
- Day 14: Start liraglutide

Improved quality of life + metabolic health

Substantial (12% total body) weight loss

75% successfully discontinue insulin

True disease reversal

> 200 patient waiting list for DMR

Improvements seen in all parameters of metabolic health by 6 months			
	Baseline (n=16)	**6 months (n=16)**	***p*-value**
% free of insulin	0%	**75%**	
HbA1c (% pt)	7.5	7.0	NS
BMI (kg/m^2)	29.2	25.7	0.001
HOMA-IR	8.1	2.5	0.002

van Baar, A.C.G. et al. presented at UEGW 2019

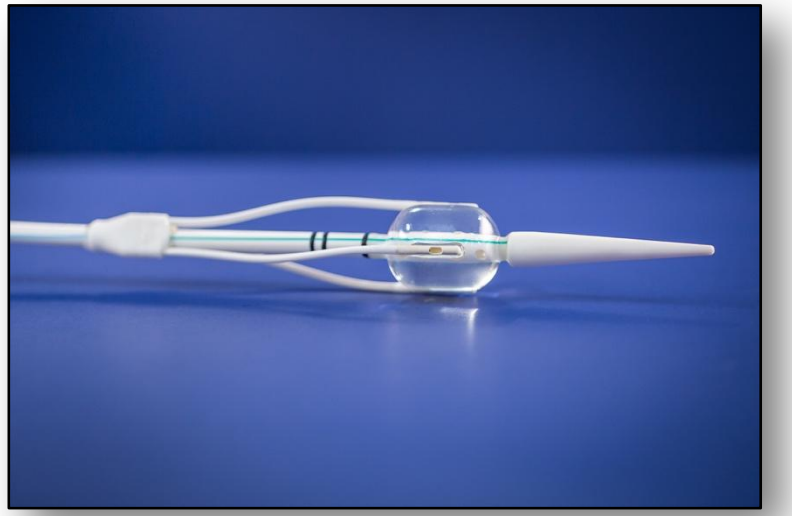
REVITA SAFETY & TOLERABILITY

DMR has an acceptable safety profile and is well-tolerated by patients

- Revita has been studied in close to 300 patients in clinical trials globally and within NHS hospitals in the UK
- No Unanticipated Adverse Device Effects (UADEs) reported
- No device or procedure related deaths reported
- No incidence of pancreatitis, gastro-intestinal bleeding or incidence of injury to surrounding organs
- No incidence of procedure-related infection (no systemic infection, no abscess)

Most commonly reported AEs were:

- Mostly mild
- Reported within the first month of the procedure
- Associated with the GI system post-endoscopic procedure effects
- Uncommon mild hypoglycaemia observed in the post-procedure period (2 weeks) in the presence of concomitant hypoglycemic agents



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Revita-1 Interim Clinical Study Report Oct 14 2019
van Baar, A.C.G. et al. Gastroenterology. 2017 Apr;152(5):S825.

IMPORTANT SAFETY INFORMATION

The Revita system is intended to improve glycaemic control in patients with Type 2 Diabetes who have preserved pancreatic function and whose diabetes is poorly controlled with oral glucose medications. In clinical trials, the most common device/procedure related adverse events reported were abdominal pain, constipation, diarrhoea, nausea, and throat pain, occurring in the first 30 days of treatment. Contraindications include: Type 1 Diabetes, history of ketoacidosis, probable insulin production failure, current use of insulin/GLP-1 analogues, hypoglycaemia unawareness, history of severe hypoglycaemia, known autoimmune disease, history of chronic or acute pancreatitis, known active hepatitis or active liver disease, symptomatic gallstones or kidney stones, and use of anticoagulation therapy, NSAIDS, corticosteroids, or weight loss medications which cannot be discontinued. Risk of complications include procedural risks that may lengthen hospital stay.

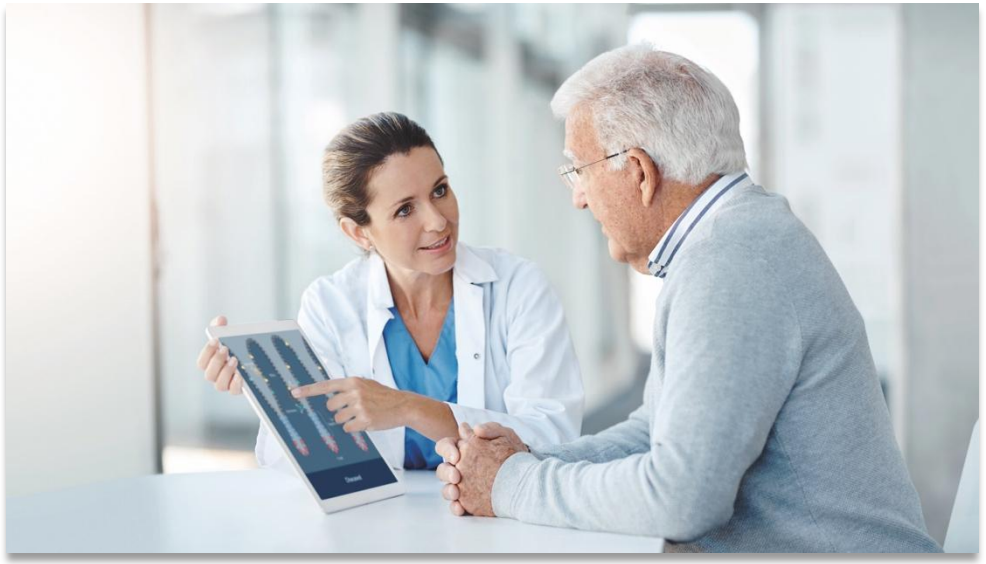
For a full list of indications, contraindications, and risks refer to the Revita system Instructions for Use

Summary

DMR procedure is targeting the progression of T2D with a single procedure, using minimally-invasive, therapeutic device

DMR procedure improves and sustain glycaemic and metabolic parameters without additional medication intensification and side effect burden[1]

- ✔ Improved glycemic parameters (HbA1c, FPG, and HOMA-IR) in as little as 4 weeks and sustained results for 24 months[1]
- ✔ Significant reductions in key hepatic parameters such as Alanine Aminotransferase (ALT) and absolute liver fat quantification (MRI-PDFF)[1-2]
- ✔ Benefits CV and lipid parameters[2]



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[1] van Baar ACG, Holleman F, Crenier L, et al Endoscopic duodenal mucosal resurfacing for the treatment of type 2 diabetes mellitus: one year results from the first international, open-label, prospective, multicentre study Gut Published Online First: 22 July 2019. doi: 10.1136/gutjnl-2019-318349 [2] [Hopkins, et al. 4th World Congress on Interventional Therapies for Type 2 Diabetes (WCITD). New York City, NY, USA, April 2019