

Endoscopic Duodenal Mucosal Resurfacing (DMR) Improves Metabolic Measures, Including Hepatic Transaminase Levels, in Patients with Type 2 Diabetes: Data from a First-in-Human Study

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Disclosures

➤ Financial Disclosures:

- *MGN*: Scientific advisor to and received research funding from Fractyl and GI Dynamics. Inc.
- *HR, JC*: employees of Fractyl and own shares in the company
- *LR, PB, PR, PV*: Research support from Fractyl

➤ Study funding:

- Fractyl Laboratories, Inc.

Background

- Bariatric surgeries that prevent nutrient contact with the duodenum improve measures of metabolism in type 2 diabetes (T2D), including indicators of fatty liver disease
- Revita™ duodenal mucosal resurfacing (DMR) may offer similar metabolic benefit

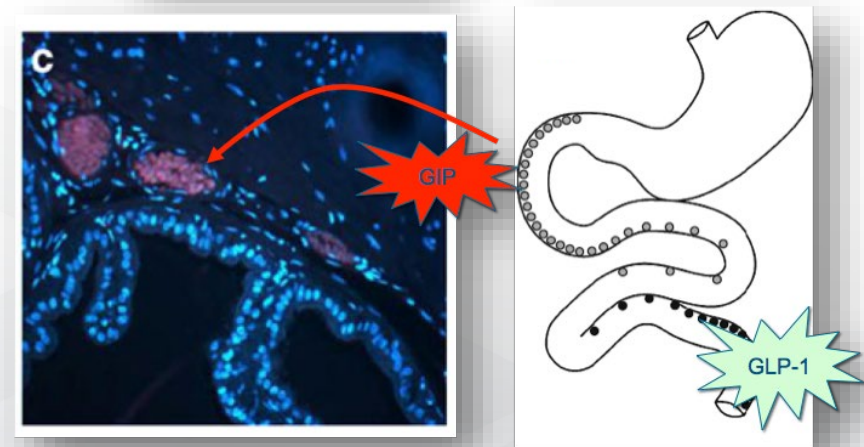
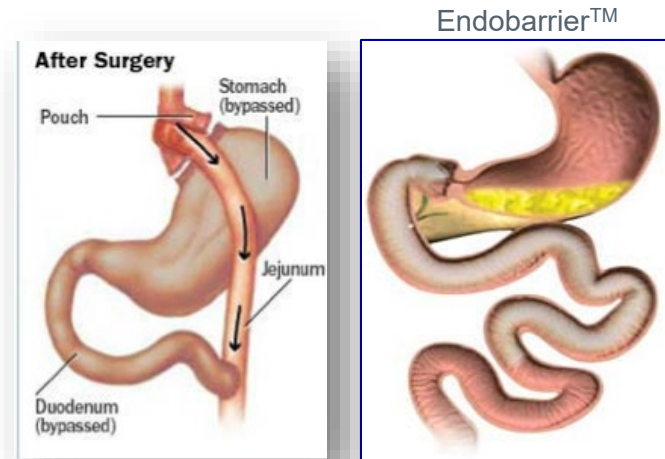
Aim

- To evaluate the effect of Revita DMR on metabolic parameters
- To assess procedural safety in patients with suboptimally controlled T2D (HbA1c > 7.5% on ≥ 1 anti-diabetic agent)

Revita DMR: Pathophysiologic Principle



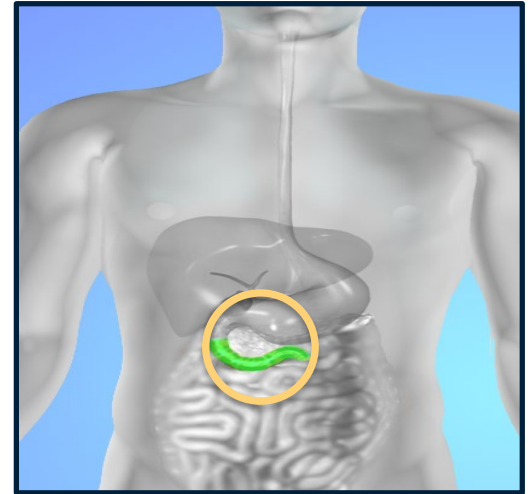
- Bypass of upper GI tract (surgery, sleeve) exerts potent effects on metabolism through insulin sensitizing pathways
- Nutrient re-exposure to the 'Roux' elicits return to hyperglycemia
- Abnormal hypertrophy of mucosa noted in diabetics' upper GI tract
- Abnormal entero-endocrine cell sub-population in upper GI mucosa of diabetic patients



Revita DMR Procedure



- Minimally invasive endoscopic therapy using an innovative balloon catheter
 - Targets duodenal mucosa between Ampulla of Vater and Ligament of Treitz
- Procedural Steps
 - Size duodenum
 - Lift sub-mucosal space with saline injection to create protective barrier
 - Circumferentially ablate superficial mucosa using a hydrothermal approach to stimulate regeneration
 - Procedure duration ~60 minutes



Methods

- Single center, single arm study (Santiago, Chile) using the Revita™ DMR System (Fractyl Laboratories, Waltham, MA, USA) in patients with suboptimally controlled T2D
- Thermal ablation performed on either a short (n=11; mean 3.4 cm) or long (n=28; mean: 9.3 cm) segment of duodenum
- Procedures performed by trained endoscopists with patients under anesthesia
- 2-week, low calorie, graduated diet for all patients post-procedure (liquids→soft→puree)
- No specific recommendation on post-procedure management of anti-diabetic medication
- Post-procedure endoscopies performed at 1 and 3 months

First-in-Human Study Enrollment



Patients enrolled between August 2013 and December 2014



- 5 patients excluded:
- 4 did not receive DMR
 - 2 failed screening endoscopy
 - 1 tortuous anatomy
 - 1 anticipated anesthesia duration
 - 1 patient anti-GAD + (treated and followed for safety but not efficacy)

Treated patients for efficacy analysis



“Long segment” ablation

“Long segment” ablation

“Short segment” ablation

“Short segment” ablation

Baseline HbA1c 7.5-10%

Baseline HbA1c >10-12%

Patient Characteristics



➤ Inclusion criteria

- Age 28-75
- BMI 24-40
- HbA1c 7.5-12%
- Disease diagnosed <10 years
- Fasting c-peptide >1 ng/ml
- ≥ 1 oral anti-diabetes medicine (Rx)

➤ Exclusion criteria

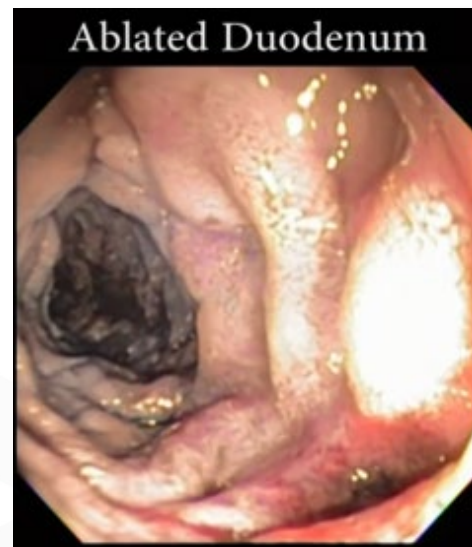
- Prior GI surgery that would preclude procedure
- Anatomical abnormalities
- Anti-GAD Ab+
- Injectable anti-diabetes Rx

Patient characteristics	Value (N=44)
Age, yrs (range)	53.3 +/- 7.5 (38-65)
Sex, n (%)	
Female	16 (36.4)
Male	28 (63.6)
Weight, kg	84.5 +/- 11.9
Height, cm	165.2 +/- 8.5
BMI, kg/m ²	30.9 +/- 3.5
Systolic BP, mmHg	122.1 +/- 14.4
Diastolic BP, mmHg	76.9 +/- 8.2
Duration T2D, yrs (range)	5.7 +/- 2.2 (1-9)
HbA1c, %	9.5 +/-1.3
FPG, mg/dL %	184 +/-58
Oral Anti-diabetic Rx	
Metformin, n (%)	44 (100)
Sulfonylurea, n(%)	20 (44)

Safety & Tolerability

- Procedure well tolerated with minimal GI symptoms
- 3 duodenal stenoses resolved with endoscopic balloon dilation
- No GI bleeds, perforation, pancreatitis, malabsorption or severe hypoglycemia
- Follow up endoscopy indicated full mucosal healing at 1 month

Post-Procedure Endoscopy



- Follow up endoscopies at 1 month document full mucosal healing

Efficacy

- More potent glycemic effect observed among long segment (LS) cohort
 - Modest weight effect noted, but no correlation between weight loss and glycemic improvement
- Robust reduction in hepatic transaminase levels also observed

Overview of Changes in Metabolic Parameters: LS Cohort



	Screening	1 Month	3 Month	6 Month	Normal Range*
HbA1c - %	9.6±1.4	7.9±1.1	7.1±0.9	8.2±1.6	4.0-6.0
Weight - kg	86±11	82±11	83±12	85±11	--
ALT - IU/L	40±23	32±17	27±14	27±12	≤ 38
AST - IU/L	32±17	27±11	23±8	22±6	≤ 40

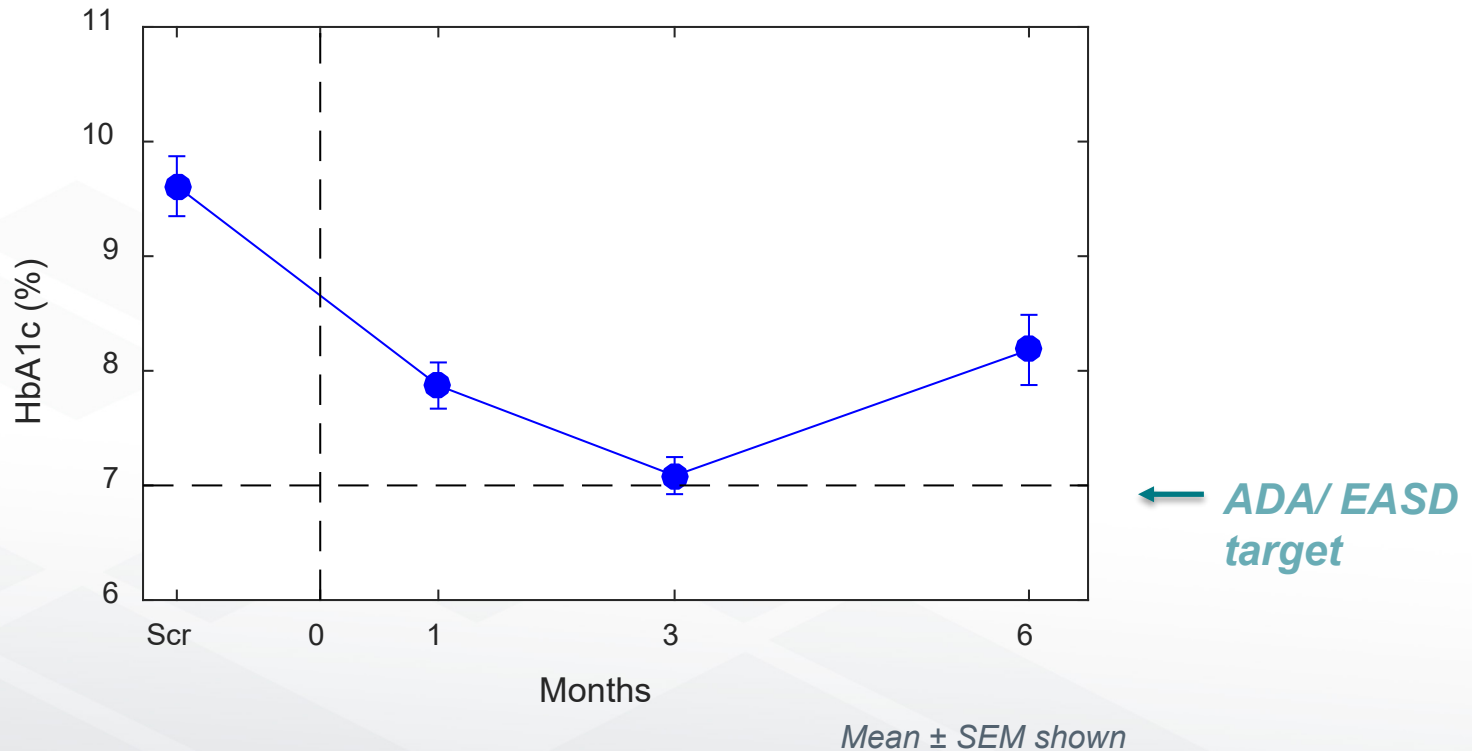
Abbreviations: HbA1c=glycated hemoglobin; ALT=alanine transaminase; AST=aspartate transaminase.

**Normal range based on ranges reported by lab that processed the samples. All numbers reported as mean ± SD.*

DMR Improves Glycemic Measures



**Average Change in HbA1c
LS Cohort (n=28)**

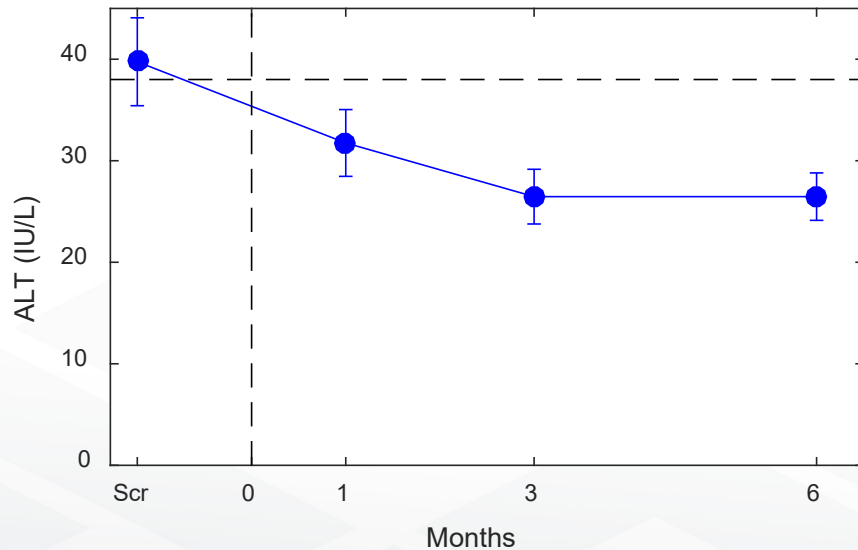


- ▶ Early and sustained improvement in both fasting glucose (data not shown) and HbA1c

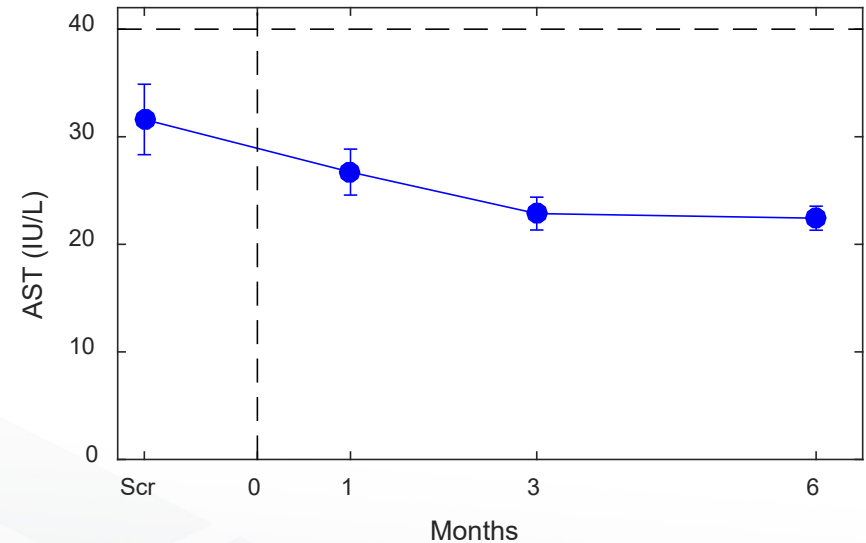
DMR Improves Hepatic Transaminase Levels



**Average Change in ALT
LS Cohort (n=28)**



**Average Change in AST
LS Cohort (n=28)**

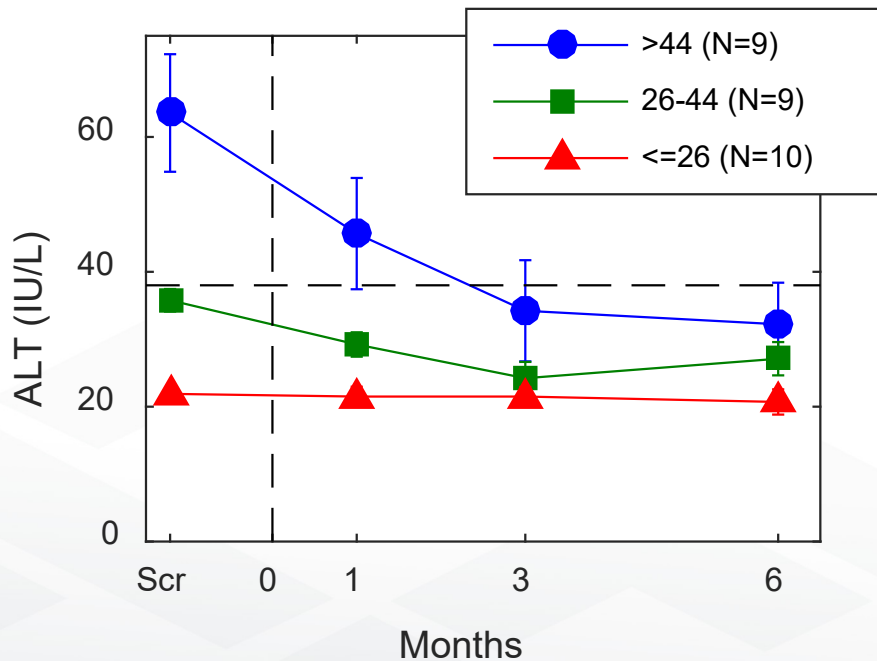


Mean ± SEM shown

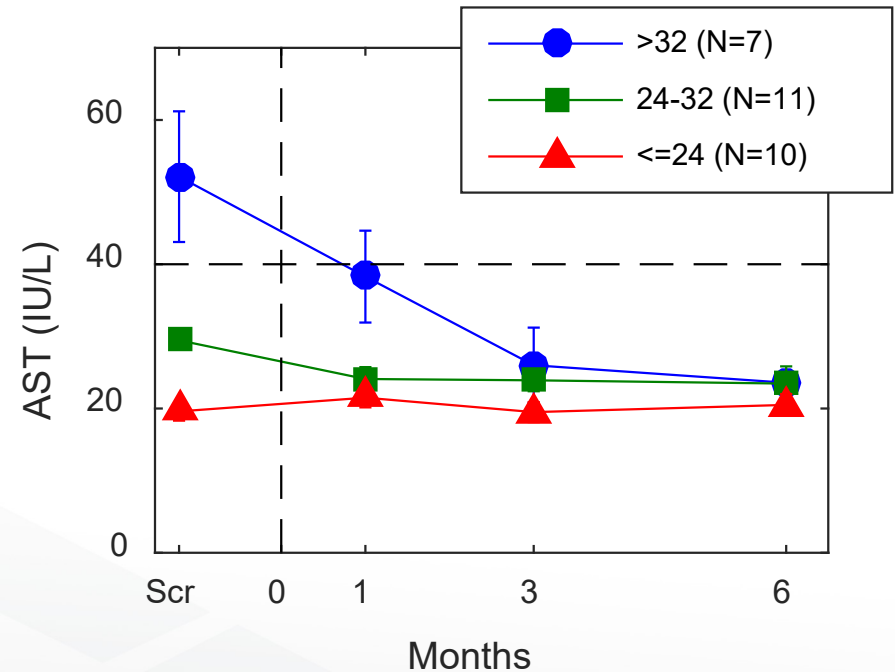
- Early and sustained improvement in ALT and AST

Hepatic Transaminase Changes by Tertile

ALT Tertiles
LS Cohort (n=28)



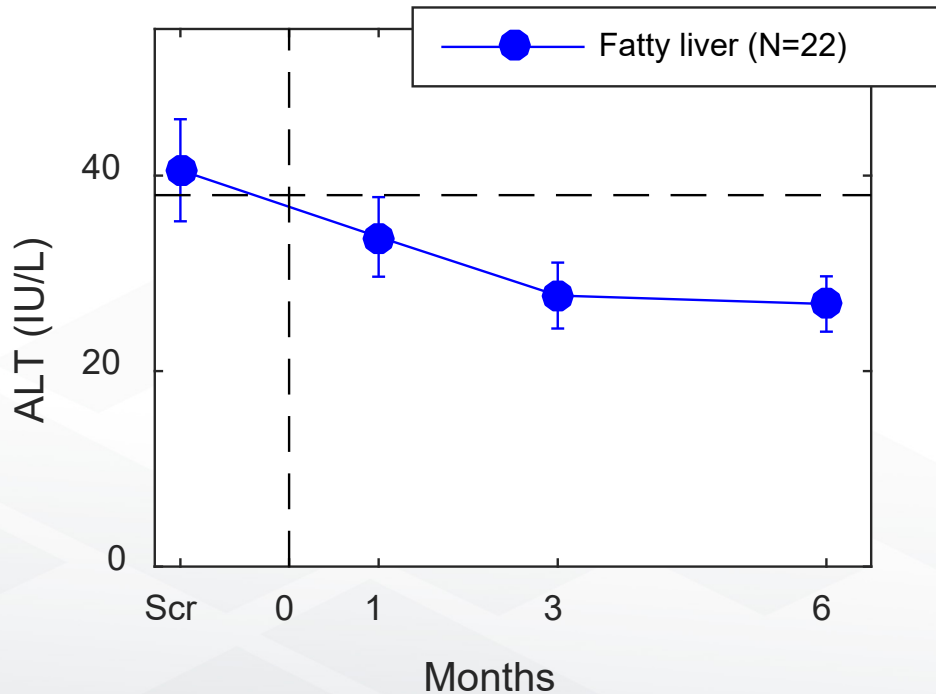
AST Tertiles
LS Cohort (n=28)



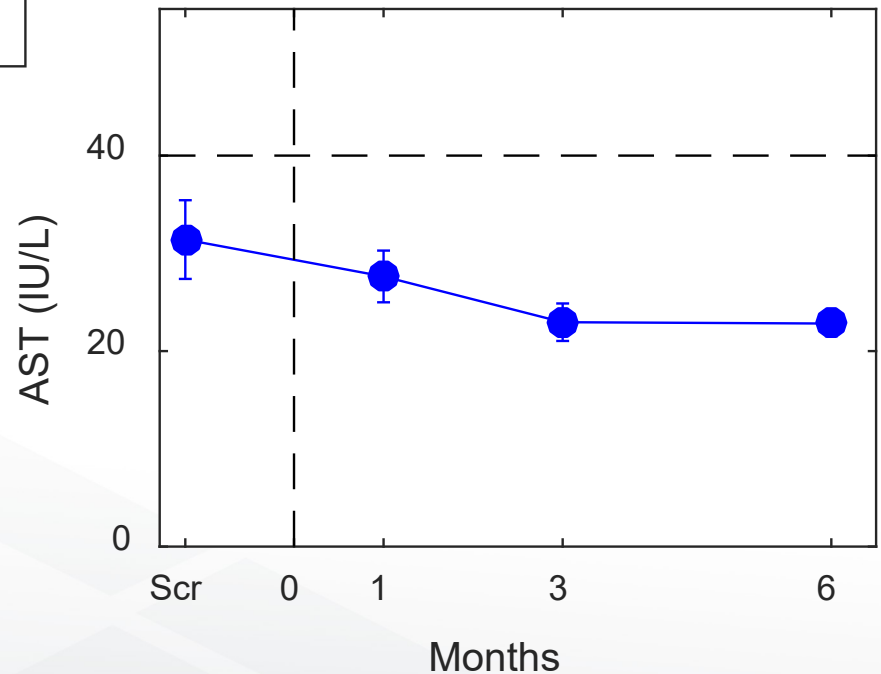
DMR Reduced ALT and AST in Patients with Fatty Liver



ALT in LS Subjects with Fatty Liver



AST in LS Subjects with Fatty Liver



- ▶ 22 subjects in LS DMR cohort had incidental finding of fatty liver on ultrasound

Conclusions



- DMR improves metabolic control in T2D patients, including a robust and sustained lowering of hepatic transaminase levels
- DMR offers the potential for a single-point intervention that improves both glycemia and fatty liver
- Further study in patients with fatty liver disease is warranted

Thank You!

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