Endoscopic Duodenal Mucosal Resurfacing (DMR) Improves Metabolic Measures in Type 2 Diabetes: First-in-Human Study 6-Month Data

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## Speaker Disclosures

Alan D. Cherrington, PhD, Vanderbilt University, reports the following financial relationships:

<table>
<thead>
<tr>
<th>Category</th>
<th>Relationships</th>
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<tr>
<td>Research Support</td>
<td>Eli Lilly &amp; Co, Merck &amp; Co, Metavention, Novo Nordisk, Silver Lake, Thermalin Diabetes</td>
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<tr>
<td>Equity/Stock Options</td>
<td>Fractyl Laboratories, Metavention, Sensulin, Thetis Pharmaceuticals, Zafgen</td>
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*Fractyl provided funding for the current study
Background

• Bariatric surgeries that prevent nutrient contact with the duodenum improve metabolic measures in type 2 diabetes (T2D)

• Revita™ duodenal mucosal resurfacing (DMR) may offer similar metabolic benefit
Aim

• To study the safety and efficacy of Revita DMR 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 upper endoscopic therapy using an innovative balloon catheter
- Targets duodenal mucosa between Ampulla of Vater and Ligament of Treitz
- Procedural Steps
  - Size duodenum and 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
- No implant, sutures or surgery
First-in-Human Study: Methods

- Single center, single arm study performed in Santiago, Chile, 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

- Procedure 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
Study Details

- **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

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>Value (N=44)</th>
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<tbody>
<tr>
<td>Age, yrs (range)</td>
<td>53.4 ± 7.5 (38-65)</td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>16 (36)</td>
</tr>
<tr>
<td>Male</td>
<td>28 (64)</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>84.4 ± 11.9</td>
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<tr>
<td>Height, cm</td>
<td>165.3 ± 8.4</td>
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<tr>
<td>BMI, kg/m²</td>
<td>30.8 ± 3.5</td>
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<tr>
<td>Systolic BP, mmHg</td>
<td>122.0 ± 14.2</td>
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<tr>
<td>Diastolic BP, mmHg</td>
<td>77.0 ± 8.1</td>
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<tr>
<td>Duration T2D, yrs (range)</td>
<td>5.7 ± 2.2 (0.2-9.7)</td>
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<tr>
<td>HbA1c, %</td>
<td>9.6 ± 1.4</td>
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<tr>
<td>FPG, mg/dL %</td>
<td>187 ± 58</td>
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<tr>
<td>Oral anti-diabetic Rx</td>
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<tr>
<td>Metformin, n (%)</td>
<td>42 (98)</td>
</tr>
<tr>
<td>Sulfonylurea, n(%)</td>
<td>16 (37)</td>
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Data are mean ± SD or n (%), unless otherwise indicated.
Safety & Tolerability

- Procedure well tolerated with minimal GI symptoms
- No difficulty tolerating oral diet in the days after the procedure
- AEs generally mild in severity & tended to occur in immediate post-procedure period
- Most common AE was transient abdominal pain due to air insufflation/endotracheal intubation (8/40 patients)
- Most significant AE was duodenal stenosis (3/40 patients)
  - All cases occurred within the first 6 weeks post-procedure
  - Non-emergent and resolved with endoscopic balloon dilation
  - No new cases after procedure and device improvements
- No GI bleeds, perforation, pancreatitis, malabsorption
- No severe hypoglycemia
Efficacy: DMR Ablation exhibits Dose-dependency
DMR Impact on Glycemic Indices

- ADD COMMENTS HERE

A

FPG
LS Cohort (n=28)

B

MMTT - PG
LS Cohort (n=28)

C

ΔAUC
LS Cohort (n=28)

D

LS cohort, change from screening
p<0.01 at 3-mo, p<0.05 at 6-mo

For PG(t=0): p<0.001 at 3-mo, p=0.07 at 6-mo
For PG AUC: p<0.001 at 3-mo, p<0.05 at 6-mo
DMR Effect on HbA1c

by Screening HbA1c and Post-Procedure Medication Use

A  Higher vs Lower Screening HbA1c
LS Cohort (n=28)

- Higher Pre-Treatment HbA1c
- Lower Pre-Treatment HbA1c

B  Reduced vs Stable Medications
LS Cohort with HbA1c ≤10% at Screening (n=18)

- Reduced Medications
- Stable Medications

LS cohort with lower pre-treatment HbA1c;
p=0.11 for stable vs. reduced medications at 6 months
DMR Impact on Broader Metabolic Indices

DMR in LS cohort exhibited the following changes:

- Minimal change in body weight
- Lowering of HOMA-IR

Metabolomic analysis also observed:

- Lowering of XX
- YY
- ZZ
Conclusions

• DMR improves metabolic control in T2D patients, including improvements in glycemic and broader metabolic indices indicative of likely insulin sensitizing mechanism

• Low rate and severity of adverse events during 6 months of follow-up

• DMR offers the potential for a single-point, endoscopic, duodenum-directed treatment for T2D

• Further examination of DMR efficacy, safety and clinical utility is needed