Successful Implementation Of Duodenal Mucosal Resurfacing Endoscopic Procedure Across Multiple Centers in Type 2 Diabetes Subjects

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Introduction
- Duodenal Mucosal Resurfacing (DMR) is currently being investigated as a treatment for metabolic diseases including Type 2 diabetes (T2D).
- Data from a previous multicenter, single-arm study in T2D patients (REbATE-D) showed improvement in fasting plasma glucose (FPG), homeostasis model assessment index (HOMA-IR) as well as a lowering of liver transaminase levels.

Objective
- The REVITA-2 is a clinical trial (NCT03781388) in a blinded, sham controlled study designed to examine the effects of DMR on glycemic and other metabolic parameters in patients with T2D.
- The trial includes an open label training phase whereby the sites familiarize themselves with the intervention procedure before beginning the randomized phase of the protocol. This allows for an open label case cohort distinct from the randomized cohort. All subjects enrolled in the open label cohort are treated with the DMR procedure and followed per protocol for 48 Weeks.

Methods
- REbATE-2 is an international, multi-center, randomized double-blind (subject and endoscopist) sham controlled trial. The study has been initiated and examined the effect of DMR in patients with T2D.

Key Inclusion criteria include:
- Age 28-75 years
- HbA1c 7.5-10.0%
- BMI 24-45 kg/m²
- Fasting insulin >7 μU/mL
- On oral anti-diabetic medication
- Known autoimmune disease, as evidenced by a positive ANA test
- Active H. pylori infection
- Previous GI surgery that could affect the ability to treat the duodenum
- History of chronic or acute pancreatitis
- Known active hepatitis or active liver disease

- Eligible patients participate in a 4 week oral anti-diabetic medication run-in period to establish stable baseline glycemia in conjunction with medication compliance and nutritional counseling. Oral diabetics medications are to be held constant from start of run-in to week 24 period following a predefined rescue algorithm for hypoglycemic or hyperglycemia.
- Patients undergo the DMR procedure which is conducted under deep sedation with the patient in a left lateral position.
- The catheter (followed with an endoscope for visualization) is inserted trans-orally of Treitz (Figure 1C).
- The duodenum is treated by performing circumferential mucosal lifting followed by hydrothermal ablation at five sequential locations between the papilla and ligament of Treitz (Figure 1B).
- Prior to initiation of the randomized cohort phase, each REbATE-2 study site is required to conduct up to 5 (open-label) training cases for a maximum of 50 total cases.
- The data from the training cases will not be included in the randomized primary cohort. All subjects enrolled in the open-label cohort are treated with the DMR procedure and followed per protocol for 48 Weeks.

Key Exclusion criteria include:
- Diagnosis with Type 1 Diabetes or with a history of ketonuria
- Current use of SU or GLP-1 analogues
- Hypoglycemia unawareness or a history of severe hypoglycemia
- Known autonomic neuropathy, as evidenced by a positive Valsalva test
- History of chronic or acute pancreatitis
- Known active hepatitis or active liver disease

Results
- Initial data from the open-label cohort are available for 24 patients through 3 months (12 weeks); data reported are as of 1 February 2018.
- Enrolled patients had a mean age of 58 years with a mean duration of T2D of 8 years. All but one patient was receiving metformin and a majority (63%) were taking a sulfonylurea.

Figure 1A. Second-generation REVITA™ Catheter

Figure 1B. Schematic of the DMR Procedure

Figure 1C. DMR Images

Figure 2. Changes Over 12 Weeks in HbA1c and Weight (mean ± SEM) Following Duodenal Mucosal Resurfacing

Efficacy
- Key procedural metrics including procedure time, defined as catheter in to catheter out duration, and number of ablations completed vs. intended are shown in Table 2.
- Compared to baseline, significant improvement in all parameters of glycemia and broader metabolic parameters was observed (Table 3).

Table 1. Patient Characteristics and Baseline Demographics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Baseline (n=24)</th>
</tr>
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<tbody>
<tr>
<td>Age, years</td>
<td>58 (50-65)</td>
</tr>
<tr>
<td>Gender</td>
<td>7 (29)</td>
</tr>
<tr>
<td>Duration of T2D, years (range)</td>
<td>8 (4-10)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>89.3 ± 13.0</td>
</tr>
<tr>
<td>Oral antidiabetic medications</td>
<td>Pioglitazone, n (%)</td>
</tr>
<tr>
<td>Meglitinide, n (%)</td>
<td>8 (33)</td>
</tr>
<tr>
<td>Amaryllidaceae, n (%)</td>
<td>3 (12)</td>
</tr>
<tr>
<td>SGLT2 inhibitors, n (%)</td>
<td>4 (17)</td>
</tr>
<tr>
<td>DPP-4 inhibitors, n (%)</td>
<td>9 (38)</td>
</tr>
<tr>
<td>Glucagon-like peptide</td>
<td>5 (21)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>31.4 ± 5.7</td>
</tr>
</tbody>
</table>

Table 2. Key Procedural Metrics

<table>
<thead>
<tr>
<th>Metric</th>
<th>Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of ablations completed/intended ablations*, n (%)</td>
<td>116/120 (97%)</td>
</tr>
</tbody>
</table>

Safety
- No unanticipated adverse device effects have been reported.
- No device or procedure related serious AEs have been reported.
- No unanticipated adverse device effects have been reported.

Conclusions
- In this international, multi-center study, initial observations from the open-label cohort suggest that DMR can be safely implemented in T2D subjects with a favorable safety and tolerability profile.
- Initial metabolic data in this open-label cohort (12 weeks post-procedure), also suggest DMR exerts a favorable metabolic effect with an improvement in glycosylated hemoglobin and other metabolic parameters.
- Further assessment of the open-label case cohort is necessary to examine longer term safety and efficacy, and the conduct of the randomized phase of study will generate safety and efficacy data under more controlled trial conditions.

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- S.M and A.V. are employees of Fractyl Laboratories, Inc. and have stock/ stock options in Fractyl Laboratories.

DISCLOSURES
- The authors have no financial interests or relationships to disclose.
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REFERENCES
- Available at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6214195/

Table 3. Baseline and Week 12 Values

<table>
<thead>
<tr>
<th>Indices</th>
<th>Baseline</th>
<th>12 weeks</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c (%)</td>
<td>8.4 ± 1.7</td>
<td>7.6 ± 0.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FPG (mg/dl)</td>
<td>184 ± 8</td>
<td>160 ± 10</td>
<td>&lt;0.001</td>
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<tr>
<td>F-TGE (mg/dl)</td>
<td>209 ± 22</td>
<td>150 ± 20</td>
<td>&lt;0.001</td>
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<tr>
<td>H-HDL (mg/dl)</td>
<td>40 ± 2.8</td>
<td>40 ± 2.8</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>DPP-4 inhibitor</td>
<td>12 ± 0.1</td>
<td>9.6 ± 0.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>F-G-polypeptide (nmol/L)</td>
<td>3.2 ± 2.8</td>
<td>2.0 ± 1.8</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>ALT (U/L)</td>
<td>25 ± 8.4</td>
<td>26 ± 8.4</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>ALP (U/L)</td>
<td>94 ± 10</td>
<td>73 ± 14</td>
<td>&lt;0.001</td>
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<tr>
<td>Body weight (kg)</td>
<td>69 ± 7.1</td>
<td>60 ± 2.3</td>
<td>&lt;0.001</td>
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