Successful Implementation Of Duodenal Mucosal Resurfacing Endoscopic Procedure Across Multiple Centers in a Study of 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).[1-4]
- Data from a previous multicenter, single-arm study in T2D patients (Revita-1) demonstrated sustained reductions to 12 months in HbA1c, fasting plasma glucose (FPG), and Homeostasis Model Assessment index (HOMA-IR) as well as a lowering of liver transaminase levels.[4]

Objective

- The Revita-2 clinical trial (NCT02879383) is 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 study 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

- Revita-2 is an international, multi-center, randomized double-blinded (subject and endocrinologist) sham controlled trial. The study has been initiated and examines the effect of DMR in patients with T2D.

Key Inclusion criteria include:

- Aged 28-75 years
- HbA1c 7.5-10.0%
- BMI 24-40 kg/m²
- Fasting insulin >7 µU/ mL
- Are sub-optimally controlled on at least 1 oral anti-diabetic medication

Key Exclusion criteria include:

- Diagnosed with Type 1 Diabetes or with a history of ketoacidosis
- Current use of Insulin or GLP-1 analogues
- Hypoglycemia unawareness or a history of severe hypoglycemia
- Known autoimmune disease, as evidenced by a positive AntiGAD 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 diabetic medications are to be held constant from start of run-in period through the 24 week endpoint following a predefined rescue algorithm for hypo- and hyper-glycemia".
- 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 over a stiff guidewire into the duodenum, to a location just distal to the papilla (Figure 1A and B).
  - 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 1C).
- Prior to initiation of the randomized cohort phase, each Revita 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 efficacy analysis and is presented here as an independent, preliminary report.

Figure 1A. Second-generation REVITA™ Catheter

Figure 1B. Schematic of the DMR Procedure

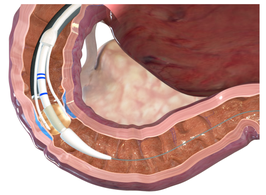
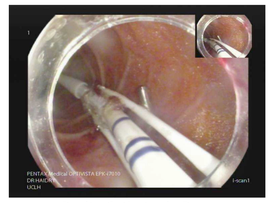
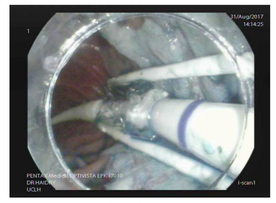


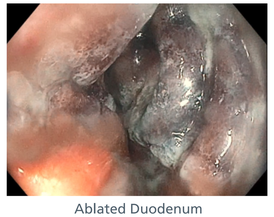
Figure 1C. DMR Images



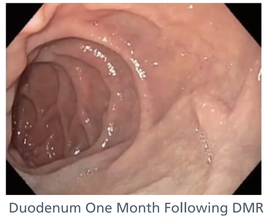
Revita Catheter in Place



Ablated Duodenum



Ablated Duodenum

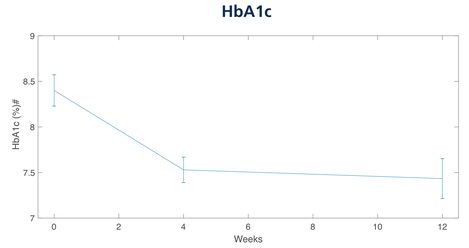


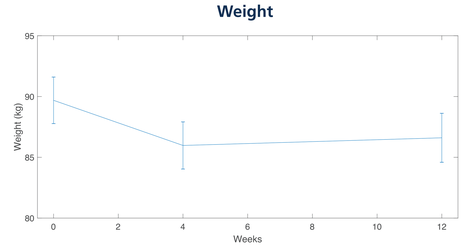
Duodenum One Month Following DMR

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 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 Demographics and Baseline Characteristics

Patient Characteristics	Baseline (n=24)
Age, years (range)	58 (43-69)
Gender, n (%)	
Female	7 (29)
Male	17 (71)
Duration of T2D, years (range)	8 (0.4 -17)
Weight (kg)	89.7 (1.9)
BMI (kg/m²)	31.6 (3.0)
Oral antidiabetic medications	
Metformin*, n (%)	23 (96)
Sulfonylurea, n (%)	15 (63)
Meglitinide, n (%)	0
DPP-4 inhibitor*, n (%)	9 (38)
SGLT-2 inhibitor, n (%)	5 (21)
Pioglitazone, n (%)	0

Values are mean (SD) unless otherwise noted. BMI: Body Mass Index; * includes combination agents counted in each category

Table 2. Key Procedural Metrics

Metric	Data
Median procedure time (Inter-quartile range), min	45 (18)
Number of ablations completed/intended ablations*, n (%)	116/120 (97%)

*Five intended ablations per protocol

DISCLOSURES

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Table 3. Baseline and Week 12 Values

Indices	Baseline	12 weeks	P value
HbA1C (%)	8.4±0.17	7.4±0.22	<0.001
FPG (mg/dl)	186±8	160±10	<0.002
F-TGs (mg/dl)	209±32	150±20	=0.008
F-HDL (mg/dl)	45.7±2.8	49.2±3.2	=0.02
FPI* (µU/ml)	13.6±1.8	9.8±1.1	=0.03
F-C-peptide (ng/ml)	3.22±0.29	2.63±0.17	=0.01
ALT (U/L)	35.8±4.1	26.8±2.4	<0.001
Ferritin** (ng/ml)	98.1±20.9	72.0±18.7	<0.001
Body weight (kg)	89.7±1.9	86.6±2.0	<0.001

Values are all mean (±SEM); n = 24 except where indicated; * n=22;** n=18; HbA1c: Glycated Hemoglobin A1c; FPG: Fasting Plasma Glucose; FPI: Fasting Plasma Insulin; HOMA-IR: F-TGs: Fasting Triglycerides; F-HDL: Fasting HDL; ALT: Alanine Aminotransferase

Safety

- Mild gastro-intestinal symptoms immediately post-procedure was the most commonly reported adverse event (AE) including abdominal pain, constipation, diarrhea, dyspepsia.
- 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 (to 12 weeks post-procedure), also suggest DMR exerts a favorable metabolic effect with an improvement in glycemic 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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