Duodenal Mucosal Resurfacing Stabilizes Weight Loss and Glycemic Control After Glucagon-Like Peptide-1 Receptor Agonist Withdrawal: REVEAL-1 - A Prospective Multicenter Open-Label Study

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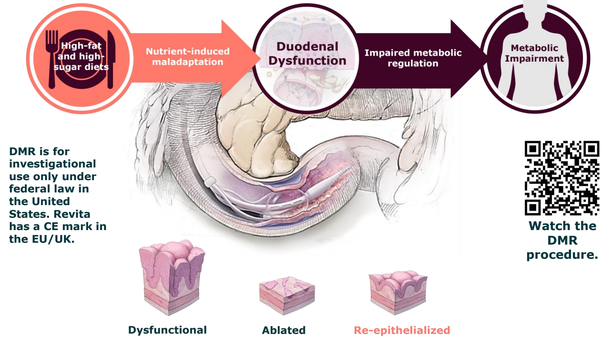
Introduction

- Glucagon-like peptide-1 receptor agonists (GLP-1s) have transformed obesity care by producing significant weight loss and metabolic improvement. However, real-world adherence is poor: ~50-70% of patients discontinue therapy within the first year, resulting in rapid reversal of benefits. In the SURMOUNT-4 (tirzepatide) and STEP-1 (semaglutide) trials, weight regain averaged ~10% and HbA1c rebounded ~0.4% within 6 months of stopping therapy[1,2].
- Duodenal mucosal resurfacing (DMR) is an investigational, minimally invasive, endoscopic procedure that uses hydrothermal ablation to restore duodenal metabolic function, known to be impaired in metabolic disease (Figure 1)[3-21].
- In a pooled clinical trial analysis in >100 patients with type 2 diabetes (62% with BMI >30 kg/m^2), DMR durably maintained body weight loss out to 48 weeks post-procedure.

Here, we share the 6-month findings from the open-label arm of the REMAIN-1 randomized, controlled, double-blind pivotal trial (NCT06484114), designed to evaluate the safety and efficacy of DMR in maintaining weight loss after GLP-1 discontinuation.

Figure 1. **Rationale for Targeting Duodenal Dysfunction with DMR.**



Study Overview

	REVEAL-1 Cohort n ~ 20	REMAIN-1 Midpoint Cohort n ~ 45	REMAIN-1 Pivotal Cohort n ~ 315
Rationale	Post-GLP-1 weight maintenance in a real-world setting	Randomized, controlled pilot study	Randomized, controlled pivotal study
Design	• Open-label	• Tirzepatide run-in phase • Double-blind DMR vs sham (2:1)	• Tirzepatide run-in phase • Double-blind DMR vs sham (2:1)
Participants	With obesity (BMI > 30 kg/m^2) prior to GLP-1 and ≥15% TBWL with GLP-1 drug	With obesity (BMI 30-45 kg/m^2) without T2D and GLP-1 drug naive	With obesity (BMI 30-45 kg/m^2) without T2D and GLP-1 drug naive

REVEAL-1 Study Design

Figure 2. **REVEAL-1 Study Design.** REVEAL-1 enrolled adults aged 21-70 years without diabetes who had a BMI of >30 kg/m^2 at GLP-1 initiation, achieved ≥15% TBWL on therapy, and wished to discontinue GLP-1s. GLP-1s were withdrawn ≥1 week prior to DMR. Participants received standardized lifestyle counseling throughout follow-up.

Results

Demographics/Characteristics	Baseline Post-GLP-1 (n=22)
Age, yrs, mean (SD)	**50 (12)**
Sex, no. (%)	
Male	3 (14)
Female	**19 (86)**
Prediabetes*, no. (%)	**3 (14)**
On Tirzepatide, no (%)	**21 (95)**
Time on GLP-1, yrs, mean (SD)	1.4 (1.1)
Body Weight Pre-GLP-1, kg, mean (SD)	105 (19)
Body Weight Post-GLP-1, kg, mean (SD)	80 (15)
TBW Change on GLP-1, %, mean (SD)	**-24 (7)**
BMI Post-GLP-1, kg/m^2, mean (SD)	29 (4)
HbA1c Post-GLP-1, %, mean (SD)	**5.1 (0.4)**

Table 1. **Demographics and Baseline Characteristics.** Twenty-two participants discontinued GLP-1 therapy and underwent DMR. Demographics and baseline characteristics are representative of the broad U.S. obesity population with mean age 50 years, 86% female, and 14% of participants with prediabetes. Participants achieved substantial weight loss on GLP-1s (mean 24% TBWL, >50lbs) with 95% on tirzepatide. Post-GLP-1 mean HbA1c was 5.1%. *Prediabetes in participant medical history or per protocol definition: HbA1c 5.7-6.5 and/or fasting plasma glucose 100-125 mg/dL at baseline.

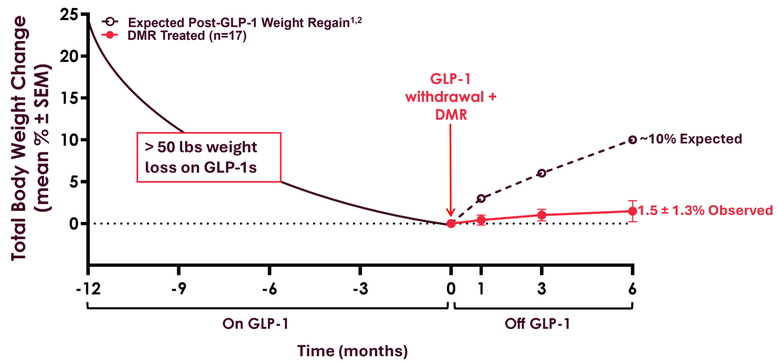
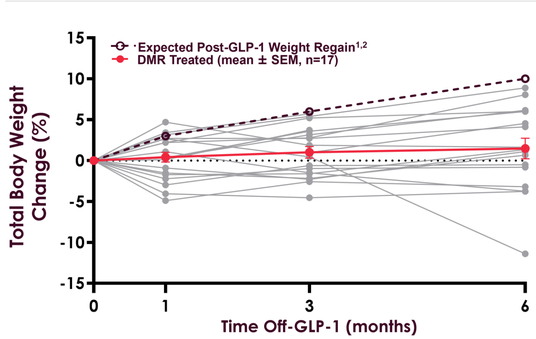


Figure 3. **DMR Maintained Weight Loss After GLP-1 Discontinuation.** Seventeen participants had evaluable 6-month outcomes (3 withdrew/were lost to follow-up; 2 restarted GLP-1s). At 6 months post-procedure, participants treated with DMR following GLP-1 discontinuation had a mean total body weight change of 1.5% compared with the ~10% regain reported after GLP-1 discontinuation[1,2]. GLP-1 weight loss from months -12 to 0 is illustrative and based on average weight loss and time on medication in REVEAL-1 subjects.

TEAEs (n=22)	Patients, n (%)	Duration (days)
Grade ≥III TEAEs	0 (0)	N/A
Grade II TEAEs	0 (0)	N/A
Grade I TEAEs	8 (36)	1-5
Sore throat	4 (18)	1-5
Bloating	2 (9)	2-3
Swollen, blistered lips	2 (9)	5
Nausea	2 (9)	1-4
Vomiting	1 (5)	1
Diarrhea	1 (5)	4
Abdominal pain and bloating	1 (5)	5
Inflammation to face lips and throat	1 (5)	5

Clavien-Dindo Classification: Standardized system for TEAE grading: Grade I: minor, any deviation from normal course without requiring treatment; Grade II: requiring treatment; Grade III: requiring surgical, endoscopic, radiologic intervention; Grade IV: Life-threatening, requiring ICU; Grade V: Death[22].

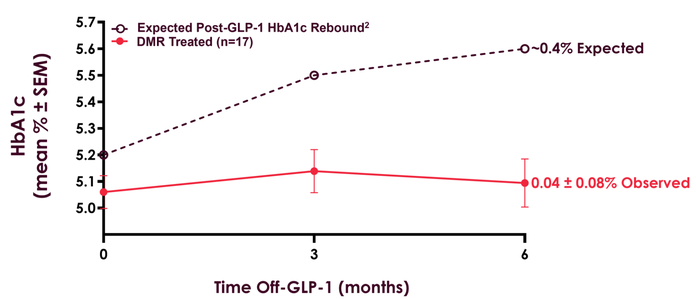
Table 3. **Safety Summary and Treatment-Emergent Adverse Events.** The DMR procedure was well tolerated with most patients experiencing no treatment-emergent adverse events (TEAEs) and none experiencing an event greater than Grade I (minor). Grade I TEAEs occurred in 8 patients (36%), were transient in nature (1-5 days), and were indistinguishable from those typically seen with a routine upper endoscopy.



6 Month Weight Regain Threshold Response	No. (%)
<10% Regain	17 (100)
<5% Regain	12 (71)
Incremental Weight Loss	6 (35)

Figure 4 and Table 2. **One-Hundred Percent of Participants Were Below Expected Post-GLP-1 Weight Regain After DMR Treatment.** At 6 months post-procedure, all 17 participants treated with DMR following GLP-1 discontinuation had regained less than 10% of their total body weight. Seventy-one percent of participants regained less than 5% of their total body weight while 35% lost additional weight following GLP-1 discontinuation and DMR treatment.

Figure 5. **DMR Sustained Glycemic Control After GLP-1 Discontinuation.** Mean HbA1c change was 0.04% after DMR treatment, compared with the ~0.4% increase historically reported after GLP-1 discontinuation alone.



Conclusions and Next Steps

DMR maintained post-GLP-1 weight loss and glycemic control through 6 months post-procedure in a real-world, hard-to-treat GLP-1 responder population

The DMR procedure was well tolerated, with only minor, transient TEAEs consistent with routine upper endoscopy

The REMAIN-1 Pivotal cohort has completed randomization with topline 6-month randomized data expected in early Q4 2026[23]

Publications and Presentations **Clinicaltrials.gov** **Poster Access**

Abbreviations: BMI=body mass index, DMR=duodenal mucosal resurfacing, GLP-1=glucagon-like peptide-1, HbA1c=hemoglobin A1c, SEM=standard error of the mean, SD=standard deviation, TBW=total body weight, TBWL=total body weight loss, TEAE=treatment-emergent adverse event, T2D=type 2 diabetes.

References: 1. Aronne et al. JAMA. 2024;331(1):38–44. doi:10.1001/jama.2023.24944. 2. Wilding et al. Diabetes Obes Metab. 2022 Aug;24(8):1553-1564. 3. Mah AT et al. Endocrinology. 2014;155:3302-334. 4. Baldassano S et al. J Endocrinol. 2013;217:11-4. 5. Mao J et al. Diabetes. 2013;62:3736-3744. 6. Alliaev A et al. Nat Metab. 2021;3:1202-124. 7. Dailey MJ. Physiol Behav. 2014;136:74-74. 8. Theodorakis MJ et al. Am J Physiol Endocrinol Metab. 2006;290:E550-554. 9. Verdam FJ et al. J Clin Endocrinol Metab. 2011;96:E379-E383. 10. Gniuli et al. Diabetologia. 2010;53:2233-40. 11. Fiorentino et al. Obesity (Silver Spring). 2023;31:724-731. 12. Dyer J et al. Am J Physiol Gastrointest Liver Physiol. 2002;282:G241–G244. 13. Fiorentino et al. J Clin Endocrinol Metab. 2017;102:3979–3989. 14. de Moura EGH et al. Endosc Int Open. 2019;7:E685-E690. 15. Haidry RJ, et al. Gastrointest Endosc. 2019;90:673-681.e2. 16. van Baar ACG, et al. Endosc Int Open. 2020;8:E1683-E1684. 17. Rajagopalan H, et al Diabetes Care. 2016;39(12):2254-2261. 18. van Baar ACG, et al. Gut. 2020;69:295-303. 19. Mingrone G, et al. Gut. 2022;71:254-264. 20. van Baar ACG, et al. Gastrointest Endosc. 2021;94:111-120.e3. 21. van Baar et al. Diabetes Res. Clin. Pract. 2022;184:109194. 22. Dindo et al. Annals of Surgery 240(2):p 205-213, August 2004. 23. These forward-looking statements are based on management's current estimates and expectations. Refer to the latest disclosures filed with the SEC for a discussion regarding Risk Factors to these and other estimates and expectations.

Data presented in this poster are preliminary and based on an ongoing study. The study database has not been locked, and the data are subject to further cleaning and validation.