Duodenal Mucosal Resurfacing Stabilizes Weight Loss After Glucagon-Like Peptide 1 Receptor Agonist Withdrawal

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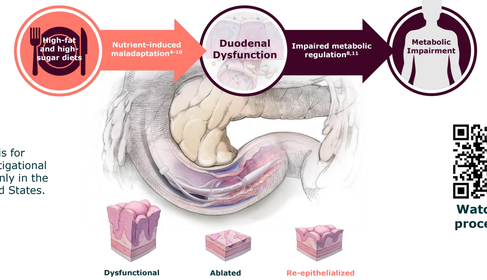
Introduction

- Glucagon-like peptide-1 receptor agonist therapies (GLP-1Rxs) are a cornerstone of obesity treatment; however, 50% of patients discontinue therapy[1], leading to rapid weight regain[2,3]. In GLP-1Rx clinical trials, mean weight regain after 1- and 3-month treatment cessation was ~3% and ~5-6% of total body weight, respectively[2,3].
- 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)[4-22].
- 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 initial 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-1Rx discontinuation

Figure 1. Rationale for Targeting Duodenal Dysfunction with DMR.



DMR is for investigational use only in the United States.

Watch the procedure.

Study Design

	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

Patients on GLP-1 Drugs Who Have Lost ≥ 15% TBW → Discontinue GLP-1 Drug → DMR Procedure → Weight at 6 months → Weight at 12 months

Results

Demographics/Characteristics	Baseline Post-GLP-1Rx (n=13)
Age, yrs, mean (IQR)	49 (24)
Sex, no. (%)	
Male	2 (15)
Female	11 (85)
Pre-diabetes, no. (%)	**2 (15)**
Body Weight Post-GLP-1Rx, kg, mean (IQR)	80.1 (12.5)
TBW Change on GLP-1Rx, %, mean (IQR)	**-23.0 (12.1)**
BMI Post-GLP-1Rx, kg/m^2, mean (IQR)	28.9 (5.4)
BMI Change on GLP-1Rx, kg/m^2, mean (IQR)	-8.8 (4.6)

Tables 1. Demographics and Baseline Characteristics. Patient demographics and baseline characteristics are representative of the broad U.S. obesity population (middle-aged, mostly female). Fifteen percent of patients had pre-diabetes. Heterogenous weight loss (-23.0% ± 12.1%) is reflective of the real-world patient population taking GLP-1Rxs.

Patient #	GLP-1Rx	Pre-GLP-1Rx Weight (kg)	Pre-GLP-1Rx BMI (kg/m^2)	Time On Drug (yrs)	Post-GLP-1Rx Weight (kg)	Post-GLP-1Rx TBW Change (%)	1-month Post-DMR TBW Change (%)**	3-months Post-DMR TBW Change (%)**
1	TZP	108.8	42.5	1.9	77.0	-29.2	**2.67**	**0.46**
2	TZP	103.0	38.2	0.7	85.4	-17.1	**0.33**	**3.15**
3	TZP	97.5	30.8	0.4	83.2	-14.7	**-2.97**	**-0.62**
4	TZP	85.3	31.7	0.5	72.2	-15.4	**4.69**	**1.88**
5	TZP	104.3	39.5	2.3	64.8	-37.9	**2.21**	**2.76**
6	TZP	92.8	36.3	3.1	72.0	-22.4	**0.43**	**0.97**
7	TZP	93.4	35.8	1.0	64.3	-31.2	**1.07**	**-1.50**
8*	TZP	152.3	45.5*	1.1	106.0	-30.4	**3.41**	**5.71**
9	TZP	100.2	42.8	0.5	84.5	-15.7	**-0.90**	**-2.30**
10	TZP	83.1	30.5	2.6	65.7	-20.9	**0.12**	**3.73**
11	TZP	134.8	43.5	0.6	102.6	-23.9	**-2.23**	**-0.96**
12	TZP	105.2	35.8	1.2	84.4	-19.8	**-1.52**	**-2.19**
13	TZP	98.8	36.5	0.5	79.2	-19.8	**1.32**	**-0.20**
Mean	-	**104.6**	**37.7**	**1.3**	**80.1**	**-23.0**	**0.66**	**0.84**
Median		**100.2**	**36.5**	**1.0**	**79.2**	**-20.9**	**0.43**	**0.46**
IQR		**11.8**	**6.7**	**1.4**	**12.5**	**12.1**	**3.1**	**3.7**

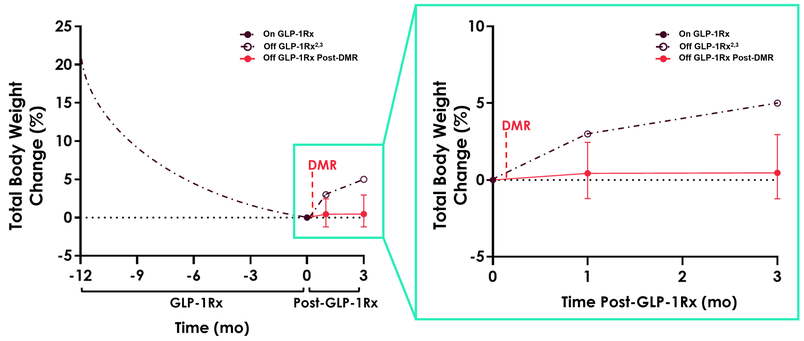
Table 2. Individual Patient Anthropometric Outcomes Pre- and Post-DMR. All participants had taken tirzepatide (TZP) for 5 months to 3 years and lost a mean of 23% total body weight prior to DMR. 12 of 13 patients maintained or lost weight at 3 months, with 6 of 13 losing additional weight after stopping GLP-1 therapy and undergoing the DMR procedure. Median weight remained stable (0.46%) through 3 months, compared to the ~5-6% regain expected after discontinuing GLP-1Rxs[2,3]. *Patient #8 would not have qualified for REMAIN-1 randomization based on BMI inclusion criteria. **TBW change calculated using pre-GLP-1Rx weight and weight at 1- and 3-months post-DMR.

n=13	Patients, n (%)	Duration (days)
Grade ≥III TEAEs	0 (0)	N/A
Grade II TEAEs	0 (0)	N/A
Grade I TEAEs	3 (23)	2-5
Nausea	0 (0)	N/A
Vomiting	0 (0)	N/A
Abdominal pain and bloating	1 (8)	5
Bloating	1 (8)	2
Diarrhea	1 (8)	4
Sore throat	1 (8)	2
Inflammation to face, lips, and throat	1 (8)	5

Clavien-Dindo Classification: Standardized FDA recommended 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[23].

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 3 patients (23%), were transient in nature (2-5 days), and were indistinguishable from those typically seen with a routine upper endoscopy.

Figure 2. DMR Maintained Weight Loss After GLP-1Rx Discontinuation. At 3 months post-procedure, patients treated with DMR following GLP-1Rx discontinuation had a median 0.46% weight change (~1 pound), compared with the ~5-6% regain (10-15 pounds) observed after GLP-1Rx discontinuation[2,3]. GLP-1Rx weight loss from months -12 to 0 is illustrative, based on average weight loss and time on medication in REVEAL-1 subjects. Data shown for DMR are median ± interquartile range.



Abbreviations: BMI=body mass index, DMR=duodenal mucosal resurfacing, GLP-1=glucagon-like peptide-1, GLP-1Rx=glucagon-like peptide-1 receptor agonist therapy, IQR=interquartile range, PMA=premarket approval, TBW=total body weight, TBWL=total body weight loss, TEAE=treatment-emergent adverse event, T2D=type 2 diabetes, TZP=tirzepatide.

References: 1. Blue Health Intelligence, Issue Brief May 2024 2. Aronne et al. JAMA. 2024;331(1):38-48. doi:10.1001/jama.2023.24945. 3. Wilding et al. Diabetes Obes Metab. 2022 Aug;24(8):1553-1564 4. Mah AT et al. Endocrinology. 2014;155:3302-3314. 5. Baldassano S et al. J Endocrinol. 2013;217:11-20. 6. Mao J et al. Diabetes. 2013;62:3736-3746. 7. Aliluev A et al. Nat Metab. 2021;3:1202-1216. 8. Dailey MJ. Physiol Behav. 2014;136:74-78. 9. Theodorakis MJ et al. Am J Physiol Endocrinol Metab. 2006;290:E550-559. 10. Verdam FJ et al. J Clin Endocrinol Metab. 2011;96:E379-E383. 11. Gniuli et al. Diabetologia. 2010;53:2233-40. 12. Fiorentino et al. Obesity (Silver Spring). 2023;31:724731. 13. Dyer J et al. Am J Physiol Gastrointest Liver Physiol. 2002;282:G241-G248. 14. Fiorentino et al. J Clin Endocrinol Metab. 2017;102:3979–3989 15. de Moura EGH et al. Endosc Int Open. 2019;7:E685-E690. 16. Haidry RJ, et al. Gastrointest Endosc. 2019;90:673-681.e2. 17. van Baar ACG, et al. Endosc Int Open. 2020;8:E1683-E1689. 18. Rajagopalan H, et al Diabetes Care. 2016;39(12):2254-2261. 19. van Baar ACG, et al. Gut. 2020;69:295-303. 20. Mingrone G, et al. Gut. 2022;71:254-264. 21. van Baar ACG, et al. Gastrointest Endosc. 2021;94;111-120.e3 22. van Baar et al. Diabetes Res. Clin. Pract. 2022;184:109194 23. Dindo et al. Annals of Surgery 240(2):p 205-213, August 2004. 24. 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.

Conclusions and Next Steps

DMR maintained weight loss after GLP-1Rx discontinuation, with nearly all REVEAL-1 patients sustaining or further reducing weight at 3 months post-procedure

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

Positive 3-month efficacy and safety data were reported for the first randomized REMAIN-1 cohort in September 2025

The REMAIN-1 Pivotal cohort has completed enrollment; randomization is anticipated in early 2026, with 6-month topline data and a potential Premarket Approval (PMA) filing expected in H2 2026[24]

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