Oral-083

GLY-200 (Oral Pharmacologic Duodenal Exclusion) Reduces Bodyweight and Glucose in Patients with T2D

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Background: GLY-200 is an oral non-absorbed polymer drug designed to bind to and enhance the barrier function of gastrointestinal mucus as a non-invasive alternative to metabolic surgery and duodenal exclusion devices. In healthy volunteers, GLY-200 lowered glucose and increased GLP-1, PYY, and bile acids, indicating pharmacologic effects in the proximal small intestine. This study evaluated the safety, tolerability, and pharmacodynamic effects of GLY-200 in patients with type 2 diabetes (T2D).

Methods: In this randomized, double-blind, placebo (PBO)-controlled study in patients with T2D washed off metformin, BMI 18–40, subjects ($N = 51$, BMI 31.3 ± 4.2 kg/m^2, baseline HbA1c 7.12 ± 0.57%) received 14 days of 0.5, 1.0, or 2.0 g GLY-200 or PBO, BID. Assessments included safety and tolerability, food intake, appetite visual analog scale, body weight (BW), glucose profiles following a standardized meal, and continuous glucose monitoring (CGM).

Results: GLY-200 appeared safe and well-tolerated. Glucose was reduced on Day 1 in the 2.0 g GLY-200 group and reductions improved over time in the lower doses. Day 14 iAUC was ↓27% ($p = 0.11$), ↓29% ($p = 0.13$), and ↓45% ($p = 0.01$) in the 0.5, 1.0, and 2.0 g GLY-200 groups, respectively, versus PBO. Treatment with 0.5 and 2.0 g GLY-200 significantly ($p < 0.05$) improved CGM % Time in Range versus PBO. Progressive reductions in BW were seen over the 14-day treatment period, with the largest reductions seen with 2.0 g GLY-200 (up to −1.8% change from baseline). Consistent with this, 2.0 g GLY-200 subjects had higher overall appetite suppression scores after standardized breakfasts (↑36.1% vs PBO immediately post meal, $p = 0.002$; ↑27.3% vs PBO 60 min post meal, $p = 0.022$) and significantly lower food intake at ad libitum dinners (↓16.7%, $p = 0.018$).

Conclusions: Data from this proof-of-concept study suggest that duodenal exclusion is possible with an oral polymer drug and support further development of GLY-200 for the treatment of T2D and obesity.

Oral-084

4-Year Setmelanotide Weight Outcomes of Patients With POMC and LEPR Deficiency Obesity

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Background: Patients with proopiomelanocortin (POMC; including variants in *POMC* or *PCSK1*) or leptin receptor (LEPR) deficiency due to biallelic gene variants have impaired melanocortin-4 receptor signaling that leads to hyperphagia and early-onset, severe obesity. Setmelanotide treatment in this population improved weight-related measures and hunger severity and was well tolerated. Reported here are long-term extension (LTE) outcomes after 4 years of setmelanotide treatment.

Methods: Patients with POMC or LEPR deficiency who achieved clinical benefit and acceptable safety in a prior trial of setmelanotide could enroll in the LTE (NTC03651765) and continue setmelanotide for ≥5 years or transition to a commercial product or other clinical trials. This analysis reports weight outcomes and adverse events at 4 years of setmelanotide treatment for patients who achieved a clinically meaningful, age-appropriate, 1-year index trial weight response defined as either ≥10% weight reduction (age ≥ 18 years at baseline) or reduction of ≥5 percentage points in percent of the 95th percentile for BMI (%BMI$_{95}$; age < 18 years at baseline).

Results: A total of 24 patients entered the LTE with clinically meaningful weight response; 12 patients had 4 years of measurements and were included in this analysis. Of the 12 patients excluded, 3 pediatric patients transitioned to adulthood between the index trial and this analysis, 5 transitioned to commercial therapy, and 4 discontinued treatment. Compared with index trial baseline, the mean (SD) change in body weight was −32.6 kg (36.7) for patients aged ≥18 years ($n = 8$) and −42.7 (22.44) percentage points in %BMI$_{95}$ for patients aged <18 years ($n = 4$). No new safety signals were observed between the index trial and the LTE.

Conclusions: Continuous setmelanotide treatment in patients with POMC or LEPR deficiency is supported by sustained meaningful benefit in weight-related measures with no new safety signals at 4 years of treatment in this population.

Oral-085

Effects of Tirzepatide on Eating Behavior: A Phase 1 Study in People Living with Obesity

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Background: The GIP/GLP-1 receptor agonist tirzepatide is under investigation for chronic weight management. We tested the effects of tirzepatide on energy intake and eating attitudes and behaviors.

Methods: In this Phase 1, multicentre, parallel arm study with a 6-week treatment period, participants with overweight/obesity ($N = 114$) were randomized 1:1:1 to once weekly blinded tirzepatide