CLOSER LOOK

MEMORANDUM

ATTAIN-MAINTAIN topline results show that Lilly's orforglipron oral GLP-1 RA helps maintain weight loss when switching from injectable to oral GLP-1 RAs – December 18, 2025

Only 1-6% body weight gain observed after switching from injectable semaglutide or tirzepatide to orforglipron over 52 weeks; safety and tolerability were consistent with previous studies

Lilly announced today positive topline results from the phase 3 ATTAIN-MAINTAIN trial (n=376) of orforglipron (once-daily oral small molecule GLP-1 RA) for weight maintenance after the use of injectable GLP-1 RAs. Participants were either overweight or had obesity (BMI >25.0 kg/m^2) and had multiple weight-related comorbidities.

Previously, orforglipron demonstrated up to 11% body weight loss without the need for refrigeration. Unlike Novo Nordisk's Rybelsus (oral semaglutide), which must be taken on an empty stomach and requires a 30-minute wait before eating or drinking, orforglipron does not come with restrictions on food or water. The formulation offers considerable ease of use compared to injectable GLP-1 RAs, which require refrigeration, and increases alternative options for individuals with injection hesitancy.

Table of Contents

Topline results demonstrate only 1-6% body weight gain after switching from injectable GLP-1 RAs to orforglipron over 52 weeks

Orforglipron demonstrated strong performance in maintaining weight; over a full year, more weight gain than 1-6% is often seen. For patients initiating semaglutide treatment at the start of the SURMOUNT-5 trial, the mean starting weight was 250 lbs, which dropped over 15% to 209 lbs over nearly a year and a half (72 weeks). After switching to orforglipron for 52 weeks, the mean weight was 211 lbs, reflecting just a 1% body weight gain. For patients who started tirzepatide in the SURMOUNT-5 trial, the mean weight was 255 lbs, dropping 22% to 200 lbs over 72 weeks. After 52 weeks on orforglipron, the mean weight was also 211 pounds, representing a 6% body weight gain.

Body weight loss totaled 16% after treatment with semaglutide followed by orforglipron, compared to 17% after treatment with tirzepatide followed by orforglipron. Ultimately, although those who started on Novo Nordisk's Wegovy experienced less weight gain (2 lbs versus 11 lbs) after switching to orforglipron, the total weight loss ultimately favored those who started on Lilly's injectable therapy by one percentage point.

Safety and tolerability were consistent with previous studies, with low rates of discontinuation compared to placebo

The reported overall safety and tolerability profile of orforglipron was consistent with that of previous phase 3 studies of

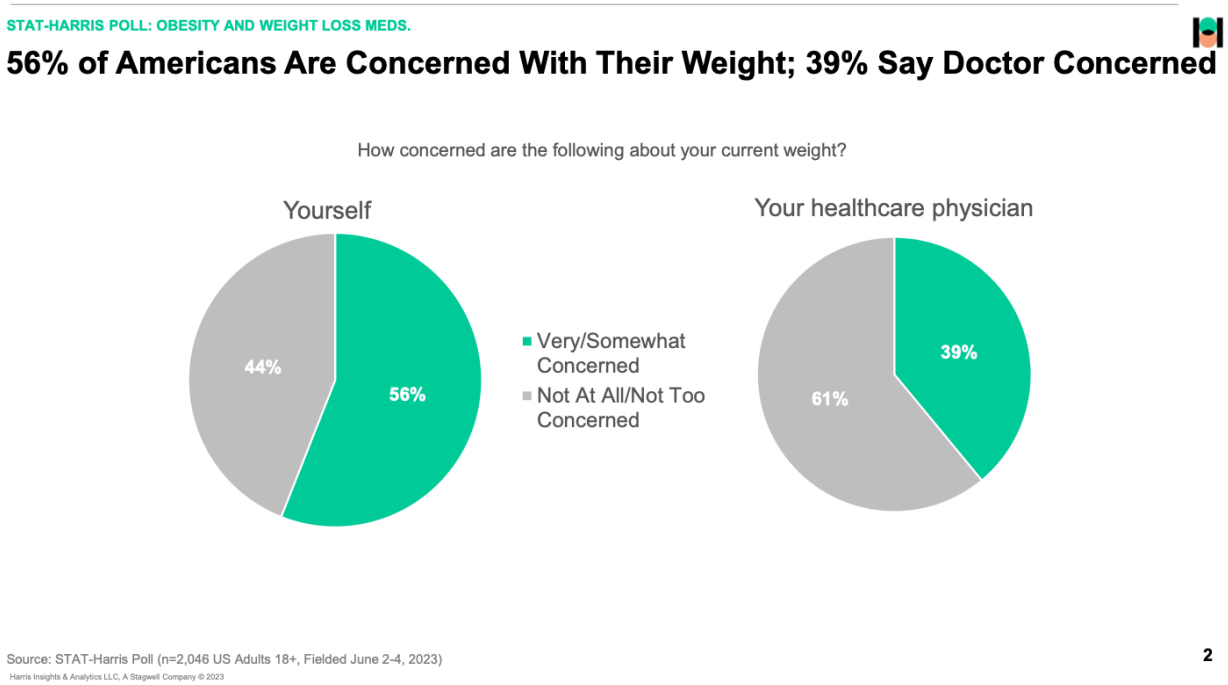
the treatment. For reference, in ATTAIN-2, the most common adverse events (AEs) were gastrointestinal, mild to moderate in severity, and occurred primarily during the dose escalation period. As expected, AEs were more frequent with orforglipron than placebo. The most common events included nausea (20-36% vs. 8% with placebo), diarrhea (21-27% vs. 15%), constipation (18-22% vs. 8%), and vomiting (13-23% vs. 4%). Given some controversy associated with placebo-controlled trials, we are curious about trial design in the future and how such trials might be designed.

In this study, discontinuation rates due to AEs for patients were 4.8% (randomized to orforglipron from semaglutide), 7.6% (randomized to placebo from semaglutide), 7.2% (randomized to orforglipron from tirzepatide), and 6.3% (randomized to placebo from tirzepatide). No concerns of liver damage were noted.

Orforglipron offers much-anticipated access benefits from clinical and patient perspectives

Orforglipron has attracted attention from clinicians far in advance of its potential approval or clinical availability. At ObesityWeek® 2025, Dr. Donna Ryan (Pennington Biomedical Research Center) discussed the therapy's manageable tolerability profile, the flexibility it provides without food or water restrictions, its storage thresholds that do not require refrigeration, and the environmental benefits of reducing the need for injection materials. Dr. Ryan also addressed pricing, emphasizing the scalability of orforglipron. She highlighted a 2023 Harris Poll (n>2,000), which showed that nearly half of US adults would pay $100/month for obesity medications, emphasizing the widespread demand for weight loss treatments regardless even of starting weight. It was interesting, as the graphic below shows, even for average Americans who don't necessarily have obesity or are overweight, there is much more concern among them than the average clinician surveyed. She said that orforglipron has the potential to fill a large unmet need in the obesity market, although she expects competition to be significant.

Proportion Americans and their physicians concerned with body weight



Source: STAT-Harris poll, Obesity and Weight Loss Meds.: Attitudes and Interest

At EASD 2025, Dr. Vanita Aroda (Brigham and Women's Hospital, Boston) further emphasized benefits for patients. She pointed out that previous trials of the therapy, including the ATTAIN-1 trial, enrolled a broadly representative population, with an average age in the 40s and diversity in terms of gender and race, benefits that were demonstrated across demographics.

Other studies in the ATTAIN and ACHIEVE programs demonstrate robust efficacy for both weight loss and glycemic management

Orforglipron has demonstrated efficacy for weight loss and A1c reduction as recently as last month. At ObesityWeek® 2025, full results of the phase 3 ATTAIN-2 trial (n=1,613) were presented by Drs. Deborah Horn (University of Texas McGovern Medical School) and Nasreen Alfaris (King Fahad Medical City, Saudi Arabia). Orforglipron 6 mg, 12 mg, and 36 mg resulted in 5%, 8%, and 11% weight loss from a baseline of 224 lbs, respectively; in comparison, the placebo group conferred just a 2% body weight loss. In addition, A1c reductions for the doses were 1.3%, 1.6%, and 1.8%, respectively (from a baseline mean of 8.1%). Notably, nearly 30% of participants on orforglipron 36 mg achieved an A1c <5.7%. The ATTAIN program also includes:

- **ATTAIN-1 (n=3,127), which** assessed orforglipron on weight management in adults with obesity or overweight with related conditions but not T2D. In 2Q25, orforglipron achieved up to 12% weight loss in people with obesity, with ~60% achieving ≥10% weight reduction and 40% achieving ≥15%. Full results were presented at EASD 2025.
- **ATTAIN-OSA (n=600)** is evaluating orforglipron in people with moderate-to-severe sleep apnea and who have obesity or are overweight. The trial is expected to complete in a little over a year in January 2027.
- **ATTAIN-HYPERTENSION (n=487)** is evaluating orforglipron for managing high blood pressure in adults with overweight or obesity. The trial is expected to complete in September 2027.

Orforglipron has also conferred positive results across the phase 3 ACHIEVE program in 3Q25, including the ACHIEVE-2, ACHIEVE-3, and ACHIEVE-5 trials. Additionally, full results of the ACHIEVE-1 trial were presented at ADA 2025 and simultaneously published in *NEJM (in June 2025)*.

- **ACHIEVE-1 (n=559)** compared orforglipron to AstraZeneca's SGLT-2 inhibitor (dapagliflozin) in adults with T2D with inadequate glycemic management using metformin. In the trial, orforglipron demonstrated an A1c reduction of 1.3%-1.6% from a baseline of 8.0% for the efficacy estimand.
- **ACHIEVE-2 (n=962)** compared once-daily orforglipron (3 mg, 12 mg, and 36 mg) to a maximum dose of dapagliflozin (10 mg) in adults with inadequately managed T2D on metformin. Orforglipron achieved the primary endpoint, demonstrating a superior A1c reduction from 1.3% to 1.7% across doses, compared to 0.8% with dapagliflozin (from a baseline A1c of 8.1%).
- **ACHIEVE-3 (n=1,698)** compared orforglipron (12 mg and 36 mg) to oral semaglutide (7 mg and 14 mg) on glycemic reduction and weight loss. Orforglipron conferred 9.2% weight loss, higher than 5.3% with oral semaglutide, a 74% relative improvement.
- **ACHIEVE-5(n=751)** was a phase 3 add-on trial for adults with inadequately managed T2D on titrated insulin glargine, with or without metformin and/or SGLT-2 inhibitors. Orforglipron was tested at the three doses (3 mg, 12 mg, and 36 mg) against placebo. Orforglipron achieved A1c reduction from 1.5% to 1.9% across doses, compared to 0.8% on placebo (from a baseline A1c of 8.5%).

The ACHIEVE-4 trial (n=2,749) is the last remaining trial in the ACHIEVE program awaiting results. Upcoming results are expected to lead to a regulatory submission of orforglipron for T2D by 1H26.

Close Concerns' Questions

1. How might the elevated discontinuation rate in those who were randomized to placebo from semaglutide be explained? How do these data inform thinking around the therapy?

2. What will influence significant demand from patients previously taking Rybelsus? What factors will most influence demand from patients and recommendations from clinicians?

3. How long might clinicians expect patients will take orforglipron for weight maintenance? Is this more likely to be on the scale of years or decades?

-- by Nour Khachemoune, Jeremy Alkire, Esther Min, and Kelly Close