CLOSER LOOK

MEMORANDUM

Lilly announces topline results of the phase 3 TRIUMPH-4 trial of once-weekly retatrutide (triple GLP-1/GIP/glucagon RA) in people with obesity or overweight and osteoarthritis – December 11, 2025

Retatrutide 12 mg achieved 28.7% weight loss and 75.8% WOMAC pain reduction in obesity and osteoarthritis, with 59% of participants achieving ≥25% weight loss on the 12 mg dose

Lilly announced today positive topline results from its phase 3 TRIUMPH-4 trial (n=405) of retatrutide (triple GLP-1/GIP/glucagon RA) in people with obesity or overweight and osteoarthritis of the knee. At Week 68, retatrutide 12 mg conferred a mean 28.7%weight reduction compared with 2.1% in the placebo group. Notably, this is compared with a mean weight loss of 22.5% on the highest dose of Lilly's Zepbound (tirzepatide) and 15% on the highest dose of Novo Nordisk's Wegovy. Given its magnitude of weight reduction, retatrutide may offer particular benefit to those with obesity-related complications requiring substantial weight loss. Retatrutide also demonstrated a 75.8% reduction in Western Ontario and McMaster Universities Arthritis Index (WOMAC)[1] pain subscale.

There are seven additional phase 3 trials ongoing. These results, expected in 2026, will help position retatrutide as a promising candidate for broad indications for obesity, diabetes, and related comorbidities. The full results of the TRIUMPH-4 trial will be presented at an upcoming medical meeting and subsequently published in a peer-reviewed journal.

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TRIUMPH-4 assesses the efficacy of retatrutide in adults with obesity or overweight and osteoarthritis

The TRIUMPH-4 trial (n=405) evaluated the efficacy of once-weekly retatrutide in adults with obesity or overweight (BMI ≥27 kg/m²) and osteoarthritis of the knee. The study compared retatrutide 9 mg and 12 mg with placebo. The trial's co-primary endpoints were: (i) the change in body weight from a mean baseline of 113 kg (~249 lbs) and a mean BMI of 40.4 kg/m²; and (ii) the WOMACpain subscale score, which presents an evaluation of hip and knee osteoarthritis. The WOMAC scores were normalized to a zero to 10 point scale, where higher values correlate with worse symptoms. At baseline, the mean WOMAC score was six points.

Retatrutide demonstrated 29% weight reduction and 76% reduction in WOMAC pain score

The trial met its primary endpoint, with once-weekly retatrutide achieving a mean weight reduction of 26.4% and 28.7% in participants in the 9 mg and 12 mg arms, respectively, compared to 2.1% with placebo. In addition to weight loss, retatrutide conferred a 4.5-point (75.8%) and 4.4-point (74.3%) reduction in WOMAC pain subscale scores in the 9 mg and 12 mg arms, respectively, compared to a 2.4-point reduction with placebo. In addition, 59% of participants achieved ≥25% weight loss on the 12 mg dose, along with 48% on the 9 mg dose. Furthermore, 18% and 24% of participants

achieved ≥35% weight loss in the 9 mg and 12 mg groups, respectively.

Safety findings demonstrated that discontinuation rates were highly correlated with higher BMI at baseline

Safety findings of retatrutide were consistent with other incretin-based therapies, with gastrointestinal side effects (i.e., nausea, diarrhea, constipation, and vomiting) as the most common outcomes. Nausea occurred in 38% and 43% of participants in the 9 mg and 12 mg groups, respectively, compared to 11% with placebo. Diarrhea was reported in 35% and 33%, constipation in 22% and 25%, and vomiting in 20% and 21% of participants in the 9 mg and 12 mg groups, respectively. In comparison, the rates were 13%, 9%, and 0% with placebo, for each side effect.

Unlike previous trials of retatrutide, however, Lilly reported dysesthesia in 8.8% and 20.9% of patients treated with 9 mg and 12 mg respectively. Dysesthesia is a tingling sensation that often occurs due to nerve damage. Despite the higher proportion of patients experiencing this safety signal, reports were generally mild and were not associated with discontinuation of the study drug.

Discontinuation due to adverse events occurred in 12% and 18% of participants in the 9 mg and 12 mg groups, respectively, compared to 4% with placebo. These rates were highly correlated with baseline BMI and included discontinuations for perceived excessive weight loss. Among participants with a baseline BMI ≥35 kg/m², the discontinuation rates due to adverse events were 9% and 12% for the 9 mg and 12 mg doses, respectively, compared to 5% with placebo.

The phase 3 TRIUMPH program includes eight phase 3 trials across diverse patient populations

Lilly's TRIUMPH program comprises eight phase 3 trials evaluating retatrutide across a spectrum of obesity-related comorbidities in multiple clinical settings. Retatrutide has been positioned as a way to serve individuals with very high BMI or obesity-related complications, and the diversity of TRIUMPH trials reflects this segmentation strategy.

Below are the seven remaining trials in the TRIUMPH program. Today's press release stated that results from the other seven trials are expected in 2026. We note that on Clinicaltrials.gov, two of the trials are expected to complete in 2027 and 2029, respectively.

- **TRIUMPH-1** (n=2,300) assesses retatrutide in people with obesity or overweight. It is expected to complete in May 2026.
- **TRIUMPH-2** (n=1,000) investigates retatrutide in people with T2D and overweight or obesity, and is expected to complete in May 2026.
- **TRIUMPH-3** (n=1,800) evaluates retatrutide in people with obesity and established CVD, with study completion expected in May 2026.
- **TRIUMPH-6** (n=643) evaluates retatrutide for weight maintenance in people with T2D and obesity or overweight, with study completion expected in May 2026.
- **TRIUMPH-7** (n=586) evaluates retatrutide for people with overweight or obesity and chronic low back pain, with study expected to complete in September 2027.
- **TRIUMPH-Outcomes** (n=10,000) trial will evaluate cardiorenal benefits and is expected to be completed in February 2029.

Close Concerns' Questions

1. Might Lilly incorporate CGM endpoints into its other phase 3 trials in the TRIUMPH program?
2. How does triple agonism (GLP-1/GIP/glucagon) contribute to pain reduction in osteoarthritis beyond weight loss?
3. How might Lilly prioritize indications across the TRIUMPH program? Will osteoarthritis, CVD, or T2D take precedence in regulatory strategy?
4. Are there any mechanisms that might explain the rates of dysesthesia?

--by Kayla Mathieu, Esther Min, Monica Oxenreiter, and Kelly Close

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[1] The WOMAC is a self-administered questionnaire, which includes 24 items divided into three subgroups: (i) pain; (ii) stiffness; and (iii) physical function.