CLOSER LOOK

MEMORANDUM

Lilly announces topline results of the phase 3 TRANSCEND-T2D-1 trial of once-weekly retatrutide (triple GLP-1/GIP/glucagon RA) in people with T2D – March 19, 2026

At the highest dose, retatrutide demonstrates up to 2% A1c reduction and 17% weight loss; a fourth of those in trial experienced GI side effects, like nausea and diarrhea

Lilly announced today positive topline results from TRANSCEND-T2D-1, the first phase 3 trial (n=537) of its highly-anticipated investigational triple GLP-1/GIP/glucagon RA retatrutide in adults with T2D inadequately managed with diet and exercise.

At Week 40, retatrutide conferred A1c reductions of 1.7-2.0% from the mean baseline of 7.9%. On the highest dose, participants lost an average of 17% of their body weight (36.6 lbs) from the baseline of 96.9 kg (214 lbs), with no plateau observed throughout the treatment period. Safety profile was consistent with incretin-based therapies, with gastrointestinal events occurring most frequently during dose escalation.

Table of Contents

Study design and baseline characteristics

TRANSCEND-T2D-1 was a 40-week, randomized, placebo-controlled trial evaluating retatrutide 4 mg, 9 mg, and 12 mg versus placebo in adults with T2D inadequately controlled with diet and exercise alone. The study randomized participants in a 1:1:1:1 ratio, with all retatrutide groups initiating therapy at 2 mg once-weekly and escalating every four weeks. The primary and secondary endpoints were reductions in A1c and body weight. CGM was not used in the trial; as usual, we think it would help significantly in contextualizing A1c if CGM were included as part of the tools for this trial. For more information and insight on this, see "Continuous glucose monitoring and metrics for clinical trials: an international consensus statement" in the Lancet by Prof. Tadej Battelino, Prof. Moshe Phillip, et al. This publication is based on a highly-regarded consensus meeting organized by The diaTribe Foundation in 2023 that has now resulted in nearly 750 citations for this strong and actionable publication.

In TRANSCEND-T2D-1, the diverse population of participants had average A1cs between 7.0% and 9.5%, a BMI ≥23 kg/m², and a mean diabetes duration of just 2.5 years. Mean baseline A1c was 7.9%, body weight was 96.9 kg (213.6 lbs), and BMI was 35.8 kg/m². Individuals were naïve to insulin therapy except for prior gestational diabetes. Dose escalation followed a structured step-wise schedule: one step for the 4 mg arm, three steps for the 9 mg arm, and four steps for the 12 mg arm.

Full results will be presented at ADA in June, with additional phase 3 readouts expected over the next year. We are very excited to see what we assume will be a quite valuable series of presentations!

Retatrutide demonstrated up to 2.0% reductions in A1c and nearly 17% in weight loss

Retatrutide demonstrated A1c reductions of 1.7-2.0% at 40 weeks from a baseline of 7.9%, compared to a reduction of 0.8% with placebo. Participants on the highest dose lost an average of 16.8% of their body weight (36.6 lbs) versus 2.5%

with placebo, with no plateau observed through the treatment period. Retatrutide also improved non-HDL cholesterol, triglycerides, and systolic blood pressure.

Primary Endpoint						
		Retatrutide 4 mg	**Retatrutide 9 mg**	**Retatrutide 12 mg**	**Placebo**	
Change in A1c from baseline of 7.9% at 40 weeks	Efficacy estimand	-1.7 %	-2.0 %	-1.9 %	-0.8 %	
	Treatment-regimen estimand	-1.7 %	-1.9 %	-1.9 %	-0.8 %	
Key Secondary Endpoint						
		Retatrutide 4 mg	**Retatrutide 9 mg**	**Retatrutide 12 mg**	**Placebo**	
Change in body weight at 40 weeks from a baseline of 96.9 kg (213.6 lbs; BMI of 35.8 kg/ m²)	Efficacy estimand	-11.5% (-11.1 kg; -24.5 lbs)	-15.5% (-15.1 kg; -33.3 lbs)	-16.8% (-16.6 kg; -36.6 lbs)	-2.5% (-2.8 kg; -6.2 lbs)	
	Treatment-regimen estimand	-11.5% (-11.1 kg; -24.5 lbs)	-13.9% (-13.5 kg; -29.8 lbs)	-15.3% (-15.1 kg; -33.3 lbs)	-2.6% (-2.7 kg; -6.0 lbs)	

Source: Lilly's press release

Retatrutide had high rates of GI-related events, with up to 27% experiencing nausea and 18% vomiting

The safety and tolerability profile was consistent with incretin-based therapies, with gastrointestinal events occurring most frequently during dose escalation.

Nausea ranged from 16.4-26.5% across doses 4-12 mg; diarrhea occurred in 18.7-26.3%; and vomiting was reported in 15.0-17.6%. Across all doses, these GI events were generally mild-to-moderate and tended to lessen as participants reached maintenance dosing.

Dysesthesia (painful sensations like burning or electric shocks) occurred in 4.5% at 4 mg, 2.3% at 9 mg, and 4.4% at 12 mg, and most cases resolved during treatment.

Discontinuation rates remained low, at 2.2%, 4.5%, and 5.1% across the 4 mg, 9 mg, and 12 mg doses, respectively, compared to none with placebo.

Retatrutide is also investigated in phase 3 trials

Retatrutide is evaluated in multiple phase 3 trials, including TRIUMPH and TRANSCEND programs.

- **The TRIUMPH program evaluates tirzepatide for the treatment of obesity and overweight, obstructive**

sleep apnea, and osteoarthritis.

- **TRIUMPH-1** (n=2,300) assesses retatrutide in people with obesity or overweight and 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-4** (n=405) evaluated retatrutide 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. In addition to weight loss, retatrutide conferred a 4.5-point (75.8%) and 4.4-point (74.3%) reduction in pain subscale scores in the 9 mg and 12 mg arms, respectively, compared to a 2.4-point reduction with placebo.

- **The TRANSCEND program is investigating retatrutide in people with T2D.**
  - **TRANSCEND-T2D-2** (n=1,250) evaluates retatrutide compared to semaglutide in people with T2D and inadequate glycemic control with metformin and with or without SGLT-2 inhibitors. The study is expected to complete in January 2027, with primary completion in August 2026.
  - **TRANSCEND-T2D** (n=320) investigates retatrutide in people with T2D and renal impairment with inadequate glycemic control on basal insulin with or without metformin and SGLT-2 inhibitor therapy. The study is expected to complete in October 2026.
- **Retatrutide is also in phase 3 trials for** high-risk metabolic dysfunction-associated steatotic liver disease (MASLD), chronic low back pain, and cardiovascular/renal outcomes.

Competitive landscape of incretin-based triple agonists continues to expand

The triple-agonist landscape continues to grow with numerous companies accelerating their pipeline candidates.

- Novo Nordisk and United Biotechnology are advancing triple GLP-1/GIP/glucagon RA, UBT251, which achieved 19.7% weight loss at 24 weeks in Chinese adults with obesity or overweight in a phase 2 trial (n=205), and is moving toward phase 3 development. The molecule is also being explored for T2D, CKD, and MASH.
- Ascletis is developing ASC37, a once-monthly triple agonist, which achieved a half-life 7-fold longer than retatrutide in non-human primate studies.
- Boehringer Ingelheim and Gubra found a favorable phase 1 profile of BI 3034701 for obesity.

Close Concerns' Questions

1. For which patient populations (early T2D, severe obesity, metabolic complications) will retatrutide be most beneficial?
2. How might Lilly guide clinicians to decide between retatrutide and other similarly performing drugs like tirzepatide?
3. How might retatrutide's cardiovascular and renal outcomes compare with GLP-1 RA and dual agonists?
4. Given the high GI event rates at 12 mg, how might Lilly recommend clinicians to improve tolerability in real-world practice?
5. What titration protocols are recommended for patients who might transition from other incretin-based therapies, like semaglutide and tirzepatide, to retatrutide and vice versa?

-- by Kayla Mathieu, Kat Moon, Monica Oxenreiter, and Kelly Close