CLOSER LOOK

MEMORANDUM

Roche and Zealand announce positive topline results of the phase 2 ZUPREME-1 trial of petrelintide in people with overweight or obesity – March 5, 2026

Petrelintide conferred 11% weight loss (vs. 2%) at Week 42 with a tolerability profile comparable to placebo

Roche and Zealand announced today positive topline results of the phase 2 ZUPREME-1 trial (n=493), which evaluated Zealand-partnered long-acting amylin analog petrelintide for people with overweight or obesity.

The trial met its primary endpoint, with all five petrelintide doses conferring significant weight loss at Week 28. At Week 42, petrelintide led to 10.7% weight loss vs. 1.7% with placebo. Importantly, petrelintide demonstrated a placebo-like tolerability profile even at the most efficacious doses.

Full results of the ZUPREME-1 trial, including nine-week follow-up data, will be presented at an undisclosed meeting and will shape the design of its phase 3 program, expected to launch in 2H26.

Table of Contents

At Week 42, petrelintide led to sustained weight loss up to 11% vs. 2% with placebo

While full baseline characteristics were not presented, the distribution of male and female participants was even, and the mean BMI was 37 kg/m².

At Week 42, petrelintide led to 10.7% weight loss (vs. 1.7% with placebo) in the efficacy estimand, assuming full treatment adherence. Because petrelintide had a favorable tolerability profile and high adherence rates, the treatment regimen estimand was similar to the efficacy estimand.

Interestingly, women lost significantly more weight than men, similar to the weight loss profile seen with GLP-1 RAs.

In 4Q25, Zealand cautioned that the ZUPREME-1 trial was not designed to optimize the headline weight loss percentage but to inform the phase 3 design. Zealand expects petrelintide to deliver 15-20% weight loss in phase 3 studies.

Petrelintide demonstrates an impressive safety profile; no reports of vomiting or GI-related discontinuation at the most efficacious dose

The safety and tolerability profile of petrelintide was comparable to that of placebo, with the most common adverse events being mild and GI-related.

- **Vomiting** was less common in the petrelintide arm than in the placebo. In fact, there were no reports of vomiting in the most effective dose group.
- **Nausea** improved from the phase 1b trial (n=54) of petrelintide, which had a faster dose-escalation scheme (every second week) than in this trial (every fourth week). Most did not experience nausea on the maintenance dose.

- **Diarrhea and constipation** were infrequent and consistent across treatment and placebo arms.
- **Discontinuation rates** due to adverse events were comparable across treatment (4.8%) and placebo (4.9%) groups. Discontinuation for any reason was more common in the placebo group (13.6% vs. 8.4% in the treatment arm).

Previously, Zealand emphasized that its goal is not to deliver the greatest weight loss possible but rather to offer another class of weight loss medication with a favorable tolerability profile.

Phase 2 ZUPREME-2 trial is ongoing for use in T2D; phase 3 for monotherapy and phase 2 for combination therapy to launch in 2026

Petrelintide is also evaluated in the 28-week phase 2 ZUPREME-2 trial (n=221) in people with overweight or obesity and T2D. It has completed enrollment as of November 2025, and topline results are expected in 2H26.

Based on the phase 2 results, Roche and Zealand also plan to initiate a phase 3a trial for petrelintide monotherapy in 2H26, with additional phase 3b trials for various comorbidities to follow. They also plan to conduct a phase 2 trial evaluating a combined therapy of petrelintide and Roche's dual GLP-1/GIP RA CT-388 later this year.

Other long-acting amylin agonists in development have demonstrated 10-20% weight loss

Given that long-acting amylin agonists offer an improved tolerability profile compared to GLP-1 RAs, many candidates are advancing across clinical development. These include:

- **Novo Nordisk's cagrilintide.** A post-hoc analysis of the phase 3 REDEFINE-1 trial (n=3,417) found that cagrilintide conferred 12% weight loss (vs. 2.3% with placebo) at Week 68.
- **Lilly's eloralintide.** In a 48-week phase 2 trial (n=263), all doses of eloralintide demonstrated statistically significant weight loss, ranging from 9.5% to 20.1%, compared to 0.4% with placebo and a favorable tolerability profile.

Close Concerns' Questions

1. How did petrelintide affect other cardiometabolic markers, such as A1c, lipid levels, blood pressure, and inflammation? How might these results inform Roche and Zealand to pursue additional indications?

2. What is the quality of weight loss caused by petrelintide? How might the changes in body composition differ between males and females?

3. Why does petrelintide lead to significantly greater weight loss among women?

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