Petrelintide Trades Some Weight Loss for a Lot Less Nausea

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> Up to three-quarters of patients quit injectable GLP-1 therapy within a year, and gastrointestinal side effects are the single most-cited reason why. Phase 2 results for the amylin analogue petrelintide, published in The Lancet Diabetes & Endocrinology, show a drug that delivers double-digit weight loss while keeping nausea rates closer to placebo than to incretin therapy.1

KEY TAKEAWAYS

- The Pivot: Petrelintide, an amylin analogue, delivers double-digit weight loss through a mechanism independent of the incretin pathway GLP-1 drugs use, with markedly better gastrointestinal tolerability.
- The Data: Weight loss reached 10.7% at 42 weeks versus 1.7% with placebo, while nausea affected 20% of participants versus 6% on placebo, a fraction of the gap seen in GLP-1 trials.
- The Action: Consider amylin-class therapy as a realistic option for patients who have discontinued or avoided GLP-1 drugs specifically because of gastrointestinal intolerance, pending phase 3 confirmation.

Amylin is a pancreatic hormone that regulates appetite through pathways that run largely independent of the incretin system GLP-1 drugs exploit. That distinction matters clinically: real-world data suggest roughly 37% of semaglutide discontinuations in a cardiovascular outcomes trial were driven by gastrointestinal adverse events alone, and stopping treatment tends to bring the weight back.1

Petrelintide is one of several long-acting amylin analogues now in development, alongside cagrilintide and eloralintide. The phase 2 trial behind this week's data enrolled 714 people across 32 sites in the United States, Poland and Romania between December 2024 and February 2025, randomizing 485 of them to once-weekly petrelintide at 1.0mg, 2.5mg, 5.0mg, 7.0mg or 9.0mg, or to placebo.1

The Numbers

By week 42, mean weight loss ranged from 8.7% at the lowest dose to 10.7% at 5.0mg, with the two higher doses landing close behind at 10.5% and 10.2%. Placebo produced 1.7% loss. Every active dose from 2.5mg upward converged in a tight band around 9-11%, a flatter dose-response curve than GLP-1 trials typically show.1

Tolerability is where petrelintide separates from the incretin class. Nausea affected 20% of participants on active treatment against 6% on placebo, a gap far narrower than the 20-to-40-point spreads reported for semaglutide and tirzepatide trials. Vomiting was actually less frequent with petrelintide, 3%, than with placebo, 6%. Diarrhoea matched

placebo at 7%, and constipation ran only slightly ahead, 7% versus 4%.

The discontinuation data reinforce the same pattern. Only 1.5% of participants permanently stopped petrelintide because of gastrointestinal adverse events, and 2.2% needed a dose reduction for that reason. Between 88% and 98% of participants successfully escalated to one of the three highest maintenance doses, all of which produced similar weight loss by week 42.

Petrelintide also improved blood pressure, LDL cholesterol, triglycerides and C-reactive protein, a marker of systemic inflammation, echoing the cardiometabolic benefits seen with GLP-1 therapy despite the different mechanism. Eighteen serious adverse events occurred across the trial, evenly split between petrelintide (3%) and placebo (4%), with no death reported and no dose-related pattern.

CLINICAL IMPLICATIONS

The headline weight-loss number for petrelintide, 10.7% at best, will read as modest next to the 15-20% routinely reported for tirzepatide and now retatrutide. That comparison misses the actual clinical question this trial answers: what happens to the roughly one in three to four patients who cannot tolerate an incretin drug long enough to reach those numbers in the first place. For that population, a drug that stays close to placebo on nausea and vomiting while still producing meaningful weight loss is not a consolation prize, it is the difference between a treatment a patient actually stays on and one they quietly stop filling.

Zealand Pharma funded the trial and will need phase 3 data before petrelintide reaches prescribers, so nothing here changes practice today. But the tolerability signal is specific and consistent enough, across nausea, vomiting, discontinuation and dose-escalation success, that it is worth flagging to patients now weighing whether to start or continue a GLP-1 drug: a materially different option is moving through the pipeline.

The linked commentary from Madsbad and Holst points toward where this likely goes next: combination therapy. Cagrilintide paired with semaglutide already exists in trials, and a unimolecular dual agonist hitting both the GLP-1 and amylin receptors, zenagamtide, is in development as both an injection and an oral formulation. Whether combining mechanisms compounds the side-effect burden or preserves petrelintide's tolerability advantage is, per the commentators' own admission, still an open question the cagrilintide-semaglutide data has not settled either way.

For now, amylin-class monotherapy reads as a plausible first-line option specifically for patients prioritising tolerability over maximum weight loss, not a replacement for incretin therapy across the board. The mechanism is different enough, and the safety data consistent enough, to earn that distinct place rather than being filed as simply a weaker GLP-1 alternative.
Phase 3 trials will need to confirm this tolerability advantage holds at scale and over a longer duration than 42 weeks, and regulators will want to see whether the flatter dose-response curve observed here means most patients can stay on a mid-range dose without chasing the marginal gains that push GLP-1 prescribing toward

> maximum tolerated doses. Until then, petrelintide belongs in the conversation as a genuine mechanism-distinct alternative, not yet a prescribing decision.

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REFERENCES

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