

GLP-1 intolerance: Petrelintide offers a new path to weight loss?

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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.

While the overall safety profile of petrelintide appears favorable, the study's relatively short duration of 42 weeks warrants consideration for long-term efficacy and safety. Obesity is a chronic condition requiring sustained management, and the durability of weight loss and cardiometabolic improvements beyond this timeframe remains to be fully elucidated. Furthermore, the trial excluded individuals with a history of bariatric surgery, severe cardiovascular disease, or uncontrolled diabetes, limiting the generalizability of these findings to these specific patient populations who often represent a significant portion of those seeking weight management interventions. Future studies will need to address these gaps to provide a more comprehensive understanding of petrelintide's role across the broader spectrum of patients with obesity and related comorbidities.

Clinical Implications and Future Directions

Petrelintide's distinct mechanism of action and favorable tolerability profile present a promising alternative for patients who experience significant gastrointestinal adverse events with GLP-1 receptor agonists, potentially expanding the therapeutic landscape for weight management. The observed weight loss, while slightly lower than the upper range reported for some GLP-1/GIP co-agonists, is clinically meaningful and achieved with significantly reduced rates of nausea and vomiting, which are primary drivers of GLP-1 discontinuation. This improved tolerability could translate into higher adherence rates in real-world settings, ultimately leading to more sustained weight loss and better long-term health outcomes for a subset of patients.

The convergence of weight loss across the higher petrelintide doses (2.5mg to 9.0mg) suggests a plateau effect, indicating that escalating beyond 5.0mg may not yield substantial additional weight reduction. This flat dose-response curve, contrasting with the more linear increases often seen with GLP-1s, could simplify dosing strategies and potentially minimize the risk of dose-related adverse events. Clinicians may find this particularly useful in titrating treatment, aiming for the lowest effective dose to maximize patient comfort and adherence without compromising efficacy. Further research into optimal dosing strategies and the potential for combination therapies, perhaps with lower-dose GLP-1s, could unlock even greater benefits.

While the cardiometabolic improvements observed with petrelintide mirror those seen with GLP-1 therapies, direct

head-to-head trials against established GLP-1 receptor agonists are crucial to definitively position petrelintide within the current treatment paradigm. Such comparative effectiveness research would provide invaluable data on relative efficacy, safety, and cost-effectiveness, guiding clinical decision-making. Additionally, exploring petrelintide's impact on hard cardiovascular outcomes in a dedicated trial, similar to those conducted for GLP-1s, would solidify its role in reducing cardiovascular morbidity and mortality in patients with obesity.

The development of petrelintide, alongside other amylin analogues like cagrilintide and eloralintide, signals a renewed focus on non-incretin pathways for weight management. This diversification of therapeutic targets is critical for addressing the heterogeneity of obesity and providing personalized treatment options. For healthcare professionals, petrelintide represents a potential new tool, particularly for patients struggling with GLP-1 intolerance, offering a path to achieve clinically significant weight loss with a more manageable side effect profile. Monitoring for long-term data and real-world evidence will be essential to fully understand its place in the evolving landscape of obesity pharmacotherapy.

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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