Petrelintide produces double-digit weight loss with fewer side effects

European Association for the Study of Diabetes

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Reviewed

New research to be presented at the Annual Meeting of The European Association for the Study of Diabetes (EASD) in Milan, Italy (Sept 28 – Oct 2) and published in *The Lancet Diabetes & Endocrinology* shows that weekly injections with the new amylin-based obesity drug petrelintide can enable those treated to lose more than 10% of their body weight – generally lower than existing incretin-based (GLP-1 RA) drugs, but also with far fewer side effects. The authors, including Professor Timothy Garvey, University of Alabama at Birmingham, Birmingham, AL, USA, say the new drug will offer a viable alternative to incretin therapies especially in those less tolerant of side effects.

Real-world data estimate that up to 75% of individuals discontinue injectable glucagon-like peptide receptor agonist (GLP-1 RA) therapy (which includes drugs such as semaglutide and tirzepatide) within 12 months, which can result in weight regain within the first year of stopping treatment and might lead to a worsening of weight-related complications, including a reversal of beneficial effects on cardiometabolic disease parameters. Gastrointestinal adverse events are frequently reported as a leading cause of treatment discontinuation of GLP-1 RAs, particularly during the first few months of therapy, with approximately 37% of discontinuations in a cardiovascular outcomes trial of semaglutide attributed to gastrointestinal side effects.

Given the high global burden and growing effect of obesity, these limitations highlight the need for novel effective therapies that target energy–balance pathways distinct from and additional to GLP-1 RAs, and that offer improved tolerability and the potential for more durable effects.

Amylin is a pancreatic hormone that helps regulate appetite via mechanisms partly independent of incretin pathways. Several long-acting amylin analogs are in development for obesity treatment. Available data indicate that these agents (which include cagrilintide, eloralintide, and petrelintide) could be important alternatives to incretin-based therapies for the treatment of obesity; as well as producing substantial and clinically meaningful weight loss, they appear to be

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associated with a low incidence of gastrointestinal adverse events. This phase 2 trial aimed to evaluate the efficacy and safety of once-weekly petrelintide versus placebo in individuals with obesity.

The trail took place across 32 sites in the USA, Poland and Romania. From Dec 9, 2024, to Feb 25, 2025, the researchers screened 714 participants, of whom 485 were randomly assigned and dosed with once-weekly subcutaneous injections of petrelintide or placebo. All participants received standardized lifestyle counselling throughout the trial, including dietary guidance targeting an energy deficit of approximately 500 kcal/day and recommendations for at least 150 minutes of moderate-intensity physical activity per week.

A total of 79 participants received at least one dose of treatment with petrelintide 1·0 mg, 81 with petrelintide 2·5 mg, 83 with petrelintide 5·0 mg, 79 with petrelintide 7·0 mg, 82 with petrelintide 9·0 mg, and 81 with placebo. 255 (53%) participants were female, 230 (47%) were male, mean age was 47 years, mean bodyweight 107·1 kg, mean BMI 36·7 kg/m², and 419 (86%) were White. Mean percentage change in bodyweight from baseline after 42 by dose was –8·7% for 1.0 mg petrelintide, –9·2% for 2.5 mg, –10·7% for 5.0 mg, –10·5% for 7.0 mg, and –10·2% for 9.0 mg. For the placebo group, mean weight loss was -1.7%.

In addition, petrelintide resulted in improvements in key cardiovascular risk factors, including reductions in blood pressure and levels of c-reactive protein (a marker of systemic inflammation and cardiovascular risk) and improvement in lipid parameters (blood cholesterol and triglycerides).

The most common adverse event with petrelintide was nausea (79 [20%] of 404 participants vs five [6%] of 81 participants with placebo). Vomiting was infrequent with petrelintide (12 [3%] participants vs five [6%] with placebo); active treatment and placebo had similarly low rates for diarrhoea (30 [7%] participants vs six [7%] with placebo) and constipation (28 [7%] vs three [4%] with placebo). Overall, 18 serious adverse events were reported during the trial, with similar incidences in the petrelintide group (14 [3%]) and placebo group (three [4%]) and with no apparent association with dose or treatment group. No deaths were reported.

The authors say: "The study showed that the vast majority of participants (88 to 98%) were able to successfully escalate to the three highest maintenance

doses evaluated, all of which produced similar weight loss at week 42. The tolerability profile of petrelintide was further supported by the low proportion of participants who permanently discontinued petrelintide due to gastrointestinal adverse events – 1·5% - as well as the small percentage who required dose reduction for this reason: 2·2%." (see p16-18 appendix)

They explain that the apparent difference in gastrointestinal tolerability between amylin analogs and incretin-based therapies might reflect differences in how different therapies affect signalling within the body's central nervous system - although both therapies activate pathways that regulate satiety or 'feelings of fullness', amylin analogues might result in less activation of nausea and sickness pathways at therapeutically effective doses.

The authors say: "These findings support both the effectiveness of this novel amylin agonist and add to the evidence that amylin-based therapies for obesity might substantially improve tolerability and overall patient experience and potentially drive greater treatment adherence."

They further explain: "The findings from this and other longer-term studies of amylin agonist monotherapy underscore the potential for a new class of non-incretin-based therapies as a well-tolerated and effective option for chronic obesity treatment. If reproduced in confirmatory phase 3 trials, this therapy could be suitable for many individuals seeking double-digit percentage weight loss without significant, treatment-limiting, gastrointestinal adverse events. The safety and tolerability profile of petrelintide supports continued phase 3 development and positions amylin agonist therapy as a potential first-line option for long-term weight management, either as an alternative to or in combination with incretin-based treatments."

In a linked comment published with the study, Dr Sten Madsbad, University of Copenhagen, Copenhagen, Denmark, and Dr Jens J Holst, Novo Nordisk Foundation Center for Basic Metabolic Research, University of Copenhagen, Copenhagen, Denmark and University of Copenhagen, Copenhagen, Denmark, say: "*The partly complementary mechanisms of amylin and GLP-1 receptor agonism also provide a rationale for combination therapy, in which the weight effects of the individual components seem to be additive. This concept is already exemplified by the combination of cagrilintide and semaglutide, and combinations with tirzepatide and zenagamtide (previously known as amycretin), a unimolecular dual agonist activating both the GLP-1 and amylin*

receptors, administered either as injection or in an oral formulation. The important open question is whether the side-effect profile of the combination therapies is improved compared with single GLP-1 agonist therapy, which was not evident in the cagrilintide and semaglutide trials. However, amylin-based therapies might have a future as individual as well as combination therapies."

Source:

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Garvey, W. T., *et al.* (2026). Petrelintide, a human amylin analogue for the treatment of obesity (ZUPREME 1): a randomised, double-blind, placebo-controlled, phase 2 trial. *The Lancet Diabetes & Endocrinology*. DOI: 10.1016/s2213-8587(26)00213-5. https://www.thelancet.com/journals/landia/article/PIIS2213-8587(26)00213-5/abstract