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Eloralintide: A selective alternative targeting the amylin receptor for obesity management

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The clinical success of incretin-based therapies, particularly glucagon-like peptide-1 (GLP-1) receptor agonists such as semaglutide, has transformed the landscape of pharmacological obesity treatment.[1] However, their use is limited by individual variation in efficacy (including suboptimal response or non-response in some patients) and adverse effects.[1] Alternative anti-obesity pathways, such as amylin signaling, have been explored. Amylin signaling regulates satiety and gastric emptying, yet amylin-based treatment faced difficulties, including a short half-life, modest efficacy, and off-target effects.[2] Encouragingly, a Phase 2 study of eloralintide, a highly selective, long-acting amylin receptor agonist, recently published in *the Lancet*, demonstrated an astonishing 20% maximum weight loss within 48 weeks.[3]

This was a 48-week, randomized, double-blind, placebo-controlled phase 2 trial, in which 263 individuals with obese or overweight (without type 2 diabetes) participated. Participants received once-weekly subcutaneous injections of placebo or eloralintide at fixed doses (1 mg, 3 mg, 6 mg, or 9 mg) or under dose-escalation regimens (6-9 mg or 3-9 mg) for 48 weeks. The therapeutic effect was impressive, with eloralintide producing significant, dose-dependent weight loss within 48 weeks: an average reduction of 9% (1 mg), 12% (3 mg), 18% (6 mg), and 20% (9 mg), compared with only 0.4% for placebo. Notably, the dose-escalation strategy (6-9 mg) achieved a 20% weight loss, matching the highest fixed dose (9 mg) while better balancing efficacy with tolerability during the treatment initiation phase.

When compared with the therapeutic effect of other pharmacotherapies for obesity, eloralintide's weight-loss efficacy matches that of leading GLP-1 receptor agonists over a comparable period,[1] and dual-energy X-ray absorptiometry confirms that this weight loss is predominantly from fat mass. Notably, its efficacy is better than that of both first-generation amylin receptor agonists (e.g., pramlintide, achieving 3-5% weight loss with multiple daily injections) and contemporary non-selective amylin receptor agonists still in clinical development (e.g., cagrilintide, achieving ~10% weight loss at 26 weeks).[2,4] This enhanced efficacy may be mechanistically linked to eloralintide's high selectivity for the amylin receptor subtype AMY1R, which is primarily involved in central appetite regulation.[5] AMY1R activation engages brainstem nuclei such as the area postrema and nucleus tractus solitarius, which relay satiety signals to the hypothalamus, thereby suppressing orexigenic neuronal populations and reinforcing appetite-suppressing pathways. By maximizing activation of appetite-suppressing pathways while avoiding the side effects associated with other amylin receptor subtypes, eloralintide could achieve greater therapeutic efficacy without the off-target signaling that can limit dosing and tolerability.

In addition to weight loss, eloralintide also improved several metabolic markers, such as triglycerides, low-density lipoprotein cholesterol, and high-sensitivity C-reactive protein, and led to modest improvements in glycaemia, despite the non-diabetic study population. The distinct effect of eloralintide on heart rate is particularly noteworthy. Eloralintide lowered resting heart rate, an effect consistent with that observed with other non-selective amylin receptor agonists such as cagrilintide, but diverging from the tachycardia induced by GLP-1 and GLP-1/GIP receptor agonists.[1] This difference likely reflects distinct engagement of central autonomic circuits. AMY1R is abundantly expressed in brainstem regions such as the area postrema and nucleus tractus solitarius, which link metabolic sensing to cardiovascular control, providing an anatomical basis for heart-rate reduction.[5] From a clinical perspective, this different profile suggests that eloralintide may offer a theoretical advantage for patients with obesity who also have heart failure, ischemic heart disease, or arrhythmias, conditions in which heart rate control is crucial, as well as for those intolerant to GLP-1-induced palpitations. However, one participant in the trial discontinued the medication due to asymptomatic bradycardia, suggesting that the reduction in heart rate may be a double-edged sword. For patients with underlying bradycardia or those taking medications such as beta-blockers, continuous heart rate monitoring or regular electrocardiograms should be considered upon initiation of treatment.

Beyond the noteworthy effects on heart rate, the gastrointestinal adverse events and fatigue associated with eloralintide deserve equal attention. Regarding gastrointestinal safety, the incidence of common symptoms such as nausea and vomiting in this trial was comparable to that observed with existing GLP-1-based and multi-agonist therapies. However, it is notable that no drug-related intestinal obstruction or pancreatitis, serious events that are monitored with GLP-1 receptor agonist therapy, was reported in this trial. This suggests that eloralintide has the potential to address the gap in treatment options for patients at risk of GLP-1–associated gastrointestinal complications. Given that eloralintide also delays gastric emptying, its impact on gastrointestinal motility disturbances, even the risk of gastroparesis, was not systematically assessed and the risk requires focused evaluation in future studies. Fatigue represents another notable tolerability challenge. It contributed to treatment discontinuation, weakening the compliance advantage of long-acting weekly medication. Although the mechanisms underlying eloralintide's high selectivity for AMY1R remain to be fully elucidated, fatigue is associated with the physiological state of rapid weight loss following eloralintide treatment. The sustained activation of AMY1R-associated brainstem circuits may not only suppress appetite but also reduce central arousal and motivational drive, particularly in the area postrema and nucleus tractus solitarius which integrate satiety and energy status.[5] Together with the systemic energy deficit resulting from rapid weight loss, these interrelated mechanisms could potentially converge to produce the clinical symptom of fatigue. The observation that dose escalation markedly reduced fatigue not only supports the view that fatigue represents an adaptive physiological response, but also offers a practical method to enhance tolerability in clinical practice.

In summary, this phase 2 clinical trial has established the unique position of eloralintide in the field of obesity treatment. Its remarkable weight loss efficacy (up to 20%) is comparable to that of currently available GLP-1 and GLP-1/GIP receptor agonists such as semaglutide and tirzepatide.[1] Crucially, its clinical profile is distinct. It lowers rather than raises heart rate and reduces the incidence of certain serious gastrointestinal adverse events associated with GLP-1 and GLP-1/GIP receptor agonists. Furthermore, when combined with dose escalation, it can mitigate the adverse effects such as fatigue. Therefore, eloralintide provides a potential alternative for the treatment of obesity, offering an important option for patients with obesity and insulin resistance, and represents a critical step towards a new era of multi-target personalized therapy.

When interpreting these inspiring results, several limitations of the clinical trial design should be considered. The allocation of participants across multiple dosing cohorts resulted in relatively small sample sizes within each group, limiting the ability to detect rare adverse events, particularly regarding potential long-term risks to the pancreas or cardiovascular system. The follow-up ten weeks after discontinuation of medication provided only a rough estimate of weight gain, and different dosing regimens may lead to different

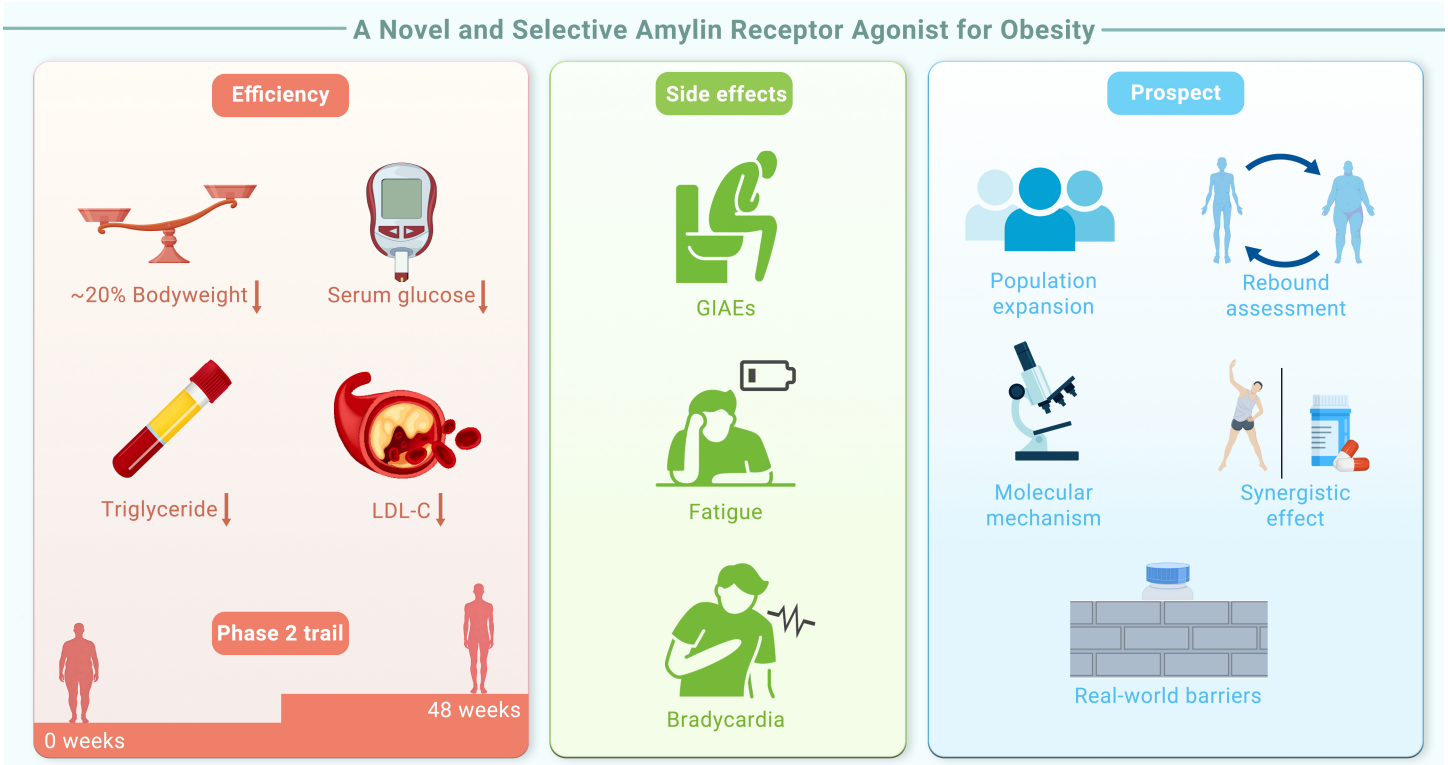

Figure 1. A Novel and Selective Amylin Receptor Agonist for Obesity Overview of a 48-week Phase 2 trial for eloralintide Treatment resulted in significant weight loss (~20%) and metabolic benefits, with gastrointestinal adverse events, fatigue and heart rate reduction as the most notable adverse events. Future research will focus on validation in broader populations, long-term weight rebound, molecular mechanism studies, real-world barriers and exploration of synergistic effects with GLP-1 agonists and lifestyle interventions. LDL-C, Low-Density Lipoprotein Cholesterol; GIAEs, Gastrointestinal Adverse Events.

patterns of weight regain, which is also an important part of long-term disease management. In addition, the exclusion of patients with type 2 diabetes may limit the generalizability of the conclusions to older adults with multiple comorbidities commonly occurred in clinical practice. Finally, the study did not evaluate the synergistic effect of eloralintide with structured lifestyle changes (diet and exercise), which has direct implications for real-world clinical effectiveness.

There are still several steps required to turn this proof-of-concept into a real-world long-term treatment. First, the results must be confirmed in larger and longer phase 3 trials to detect rare adverse events in broader populations and evaluate efficacy and safety in complex clinical subgroups such as patients with type 2 diabetes and other comorbidities. Moreover, the phase 3 trials should include a meaningful follow-up period to assess weight maintenance and rebound. At the same time, future studies should clarify the mechanisms of fatigue, evaluate the long-term effects of heart-rate reduction on cardiovascular risk, and assess the impact on gastrointestinal motility given eloralintide's delayed gastric emptying. Furthermore, a crucial direction for future research lies in the exploration of combination therapies. This approach combines agents with distinct mechanisms, such as eloralintide and GLP-1 receptor agonists, to engage multiple signaling pathways and potentially enhance efficacy. Their differing side effects also create an opportunity to design regimens with improved overall tolerability. Studying how such pharmacotherapies synergize with lifestyle changes (diet and exercise) will also be important for maximizing their clinical effectiveness. The last but often overlooked step involves real-world barriers. As a long-term injectable peptide therapy, considerations such as production costs and injection device design will critically influence patients' access and adherence to the treatment (Figure 1).

REFERENCES

1. Elmaleh-Sachs A., Schwartz J.L., Bramante C.T., et al. (2023). Obesity management in adults: A review. *JAMA* **330**:2000–2015. DOI:10.1001/jama.2023.19897
2. Walker C.S., Aitken J.F., Vazhoor Amarsingh G., et al. (2025). Amylin: Emergent therapeutic opportunities in overweight, obesity and diabetes mellitus. *Nat. Rev. Endocrinol.* **21**:482–494. DOI:10.1038/s41574-025-01125-9
3. Billings L.K., Hsia S., Bays H., et al. (2025). Eloralintide, a selective amylin receptor agonist for the treatment of obesity: A 48-week phase 2, multicentre, double-blind, randomised, placebo-controlled trial. *Lancet* **406**:2631–2643. DOI:10.1016/S0140-6736(25)02155-5
4. Lau D.C.W., Erichsen L., Francisco A.M., et al. (2021). Once-weekly cagrilintide for weight management in people with overweight and obesity: A multicentre, randomised, double-blind, placebo-controlled and active-controlled, dose-finding phase 2 trial. *Lancet* **398**:2160–2172. DOI:10.1016/S0140-6736(21)01751-7
5. Hay D.L., Chen S., Lutz T.A., et al. (2015). Amylin: Pharmacology, physiology, and clinical potential. *Pharmacol. Rev.* **67**:564–600. DOI:10.1124/pr.115.010629

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AUTHOR CONTRIBUTIONS

H.P. led the project, provided critical feedback, and revised the manuscript. A, Z-. Y. conducted the literature search, wrote the initial draft. Y. D. designed and created the figure. All authors contributed to and approved the manuscript.

DECLARATION OF INTERESTS

The authors declare no competing interests.