



Oral small-molecule GLP-1 receptor agonist for type 2 diabetes and obesity

See [Articles](#) page 2927

With the rising use of nutrient-stimulating hormone-based therapy for the treatment of obesity, developing oral alternatives could help address the limitations of injectable therapies, including needle phobia, injection site reaction, and storage concerns, and could ultimately improve patient acceptability. Peptide-based oral GLP-1 receptor agonists, such as oral semaglutide, are limited by the need for diet restriction, timing of administration, and low oral bioavailability.¹ Peptide-based GLP-1 receptor agonists are also more costly to manufacture and require refrigeration. Orforglipron is a new small-molecule, non-peptide GLP-1 receptor agonist designed for once-daily oral administration with an improved bioavailability of 79%. The efficacy and safety of orforglipron have previously been examined in people with obesity² and in people with type 2 diabetes on diet control,³ achieving a mean bodyweight reduction of 4.5–11% and significant glycated haemoglobin (HbA_{1c}) lowering, with an acceptable side-effect profile.

In *The Lancet*, Deborah B Horn and colleagues⁴ report the results of ATTAIn-2, a phase 3, double-blind, placebo-controlled trial investigating efficacy and safety of orforglipron in people with type 2 diabetes and obesity with a BMI of 27 kg/m² or higher and HbA_{1c} of 7–10%. Participants were randomly assigned 1:1:1:2 to oral orforglipron (6 mg, 12 mg, or 36 mg) or placebo for 72 weeks. The primary endpoint was the percentage

change in bodyweight. The study population consisted of 1613 participants with type 2 diabetes, of whom 757 (46.9%) were female and 1143 (70.9%) were White. Participants had a mean age of 56.8 years (SD 10.7), mean baseline BMI of 35.6 kg/m² (6.6), and mean baseline HbA_{1c} of 8.05% (0.75). All participants received lifestyle modification emphasising a healthy, balanced diet rather than caloric restriction. In ATTAIn-2, orforglipron demonstrated superior bodyweight reduction at all doses compared with placebo. The mean percentage change in bodyweight from baseline was dose-dependent, ranging from –5.1% (95% CI –6.0 to –4.2) with orforglipron 6 mg to –9.6% (–10.5 to –8.7) with orforglipron 36 mg. Participants receiving orforglipron also had greater dose-dependent reduction in HbA_{1c}, ranging from 1.22% with 6 mg to 1.66% with 36 mg, compared with 0.47% with placebo. These clinical benefits were further supported by patient-reported outcome assessments, which suggested improved patient acceptability for oral orforglipron, highlighting its role as an alternative to subcutaneous GLP-1 receptor agonists.

The changes in bodyweight reported in ATTAIn-2 appear similar to those reported for people with obesity and type 2 diabetes with peptide-based GLP-1 monoagonists,^{5,6} although weight loss was less than reported with dual GLP-1 and glucose-dependent insulinotropic polypeptide receptor agonists.⁷ However, differences in baseline characteristics and design might limit direct comparisons in the absence of head-to-head trials. Notably, the glycaemic improvement associated with orforglipron appears greater than some existing oral and subcutaneous peptide-based GLP-1 receptor agonists.^{6,8} A mean HbA_{1c} decline of 1.66% was observed with the top dose of orforglipron 36 mg daily and approximately one in four participants receiving orforglipron 36 mg daily reached normoglycaemia (HbA_{1c} less than 5.7%). In pharmacological studies, orforglipron displays partial agonism at the GLP-1 receptor, stimulating cAMP accumulation over β -arrestin recruitment⁹ and augmenting insulin secretion.¹⁰ The potential for orforglipron as a potent oral antihyperglycaemic agent makes it useful for people with type 2 diabetes in need of better glycaemic control and in diabetes prevention.



Nirat Termmee via Getty Images

Development of several small-molecule GLP-1 receptor agonists was discontinued due to concerns of hepatotoxicity.^{11,12} Although the exact mechanism for the observed liver injury is unknown, one hypothesis relates to impaired liver metabolism and drug transport in a subset of participants.¹¹ In contrast, there were no clinically significant hepatotoxic signals reported in ATTAIn-2. Three people receiving orforglipron experienced clinically significant elevations in liver enzymes secondary to gallbladder disease but, overall, the mean alanine aminotransferase and aspartate aminotransferase concentrations decreased across all orforglipron groups. Although the reasons for these differences are unclear, it would be prudent to monitor long-term liver safety of small-molecule GLP-1 receptor agonists in the real world.

In real-world settings, over half of people receiving GLP-1 receptor agonists discontinue treatment within the first year, with gastrointestinal side-effects being a common reason.¹³ In ATTAIn-2, treatment discontinuation due to adverse events (predominantly gastrointestinal) was observed with orforglipron (6.1–9.9% vs 4.1% with placebo), which was similar to previous trials of orforglipron (ranging from 4.4% to 10.3%).^{2,3} Although it is reassuring that gastrointestinal side-effects of orforglipron (diarrhoea, vomiting, nausea, constipation) were similar to other peptide-based GLP-1 receptor agonists, these were more common during the dose escalation period. Appropriate dose escalation strategies would be important in ensuring persistence and adherence.

While the efficacy and safety of orforglipron in ATTAIn-2 are promising, several important questions remain. The study did not report detailed body composition assessments, and the impact of small-molecule GLP-1 receptor agonists on excess adiposity, including visceral adiposity and muscle mass, is of relevance. The 36 mg orforglipron dose did result in an 8.3 cm mean decrease in waist circumference as well as improvements in lipid and inflammatory indices. There are scant clinical data on CNS penetration of small-molecule GLP-1 receptor agonists clinically and consequent effects on food intake and satiety. Moreover, although overall weight loss was greater with orforglipron compared with placebo, over 30% of participants lost less than 5% of their weight despite receiving the highest dose. The mechanisms behind the varying responses to GLP-1 receptor agonists are not fully understood. A

significant reduction of cardiorenal endpoints has been reported with peptide-based GLP-1 receptor agonists;^{14,15} however, whether a similar magnitude of protection can be achieved with orforglipron would need to be confirmed in dedicated cardiovascular outcome trials.

In summary, orforglipron represents another advance in the realm of GLP-1 receptor agonist therapies for people living with type 2 diabetes and obesity, achieving clinically meaningful weight and glucose reductions without the inconvenience of injections. Better bioavailability and lower transport and manufacturing costs have the potential to substantially improve access to GLP-1 receptor agonist treatments globally, including in low-income and middle-income countries. However, advancements in medical treatments for obesity should not undermine the role of prevention and environmental factors that foster an obesogenic cycle, especially in underserved communities. The next step calls for global implementation strategies that personalise incretin-based therapies based on clinical phenotype as well as patient preference and tolerability and combine affordable medical therapies with lifestyle changes to achieve meaningful and sustainable improvements in health.

EW-KC reports travel sponsorship by Boehringer Ingelheim and Novo Nordisk. EC reports speaker honoraria from Novo Nordisk, Medtronic, Roche, Sanofi, and Sinocare, and institutional research grant support from Medtronic Diabetes. All proceeds have been donated to the Chinese University of Hong Kong for research purposes.

Edith Wing-Kar Chow, *Elaine Chow
e.chow@cuhk.edu.hk

Department of Medicine and Therapeutics, Prince of Wales Hospital, The Chinese University of Hong Kong, Hong Kong Special Administrative Region, China (EW-KC, EC); Phase 1 Clinical Trial Centre, Prince of Wales Hospital, The Chinese University of Hong Kong, Hong Kong Special Administrative Region, China (EW-KC, EC); Li Ka Shing Institute of Health Sciences, Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong Special Administrative Region, China (EW-KC, EC); Hong Kong Institute of Diabetes and Obesity, The Chinese University of Hong Kong, Hong Kong Special Administrative Region, China (EC)

- 1 Buckley ST, Bækdal TA, Vegge A, et al. Transcellular stomach absorption of a derivatized glucagon-like peptide-1 receptor agonist. *Sci Transl Med* 2018; **10**: eaar7047.
- 2 Wharton S, Aronne LJ, Stefanski A, et al, and the ATTAIn-1 Trial Investigators. Orforglipron, an oral small-molecule GLP-1 receptor agonist for obesity treatment. *N Engl J Med* 2025; **393**: 1796–806.
- 3 Rosenstock J, Hsia S, Nevarez Ruiz L, et al, and the ACHIEVE-1 Trial Investigators. Orforglipron, an oral small-molecule GLP-1 receptor agonist, in early type 2 diabetes. *N Engl J Med* 2025; **393**: 1065–76.
- 4 Horn DB, Ryan DH, Kis SG, et al. Orforglipron, an oral small-molecule GLP-1 receptor agonist, for the treatment of obesity in people with type 2 diabetes (ATTAIn-2): a phase 3, double-blind, randomised, multicentre, placebo-controlled trial. *Lancet* 2025; **406**: 2927–44.
- 5 Davies M, Færch L, Jeppesen OK, et al, and the STEP 2 Study Group. Semaglutide 2.4 mg once a week in adults with overweight or obesity, and type 2 diabetes (STEP 2): a randomised, double-blind, double-dummy, placebo-controlled, phase 3 trial. *Lancet* 2021; **397**: 971–84.

- 6 Davies MJ, Bergenstal R, Bode B, et al, and the NN8022-1922 Study Group. Efficacy of liraglutide for weight loss among patients with type 2 diabetes: the SCALE diabetes randomized clinical trial. *JAMA* 2015; **314**: 687–99.
- 7 Chow E, Chan JCN. The emerging role of incretins and twincretins. *Nat Rev Endocrinol* 2022; **18**: 73–74.
- 8 Aroda VR, Rosenstock J, Terauchi Y, et al, and the PIONEER 1 Investigators. PIONEER 1: randomized clinical trial of the efficacy and safety of oral semaglutide monotherapy in comparison with placebo in patients with type 2 diabetes. *Diabetes Care* 2019; **42**: 1724–32.
- 9 Kawai T, Sun B, Yoshino H, et al. Structural basis for GLP-1 receptor activation by LY3502970, an orally active nonpeptide agonist. *Proc Natl Acad Sci USA* 2020; **117**: 29959–67.
- 10 Jones B, Buenaventura T, Kanda N, et al. Targeting GLP-1 receptor trafficking to improve agonist efficacy. *Nat Commun* 2018; **9**: 1602.
- 11 Buckeridge C, Tsamandouras N, Carvajal-Gonzalez S, Brown LS, Hernandez-Illas M, Saxena AR. Once-daily oral small-molecule glucagon-like peptide-1 receptor agonist lotiglipron (PF-07081532) for type 2 diabetes and obesity: two randomized, placebo-controlled, multiple-ascending-dose phase 1 studies. *Diabetes Obes Metab* 2024; **26**: 3155–66.
- 12 Buckeridge C, Cobain S, Bays HE, et al. Efficacy and safety of danuglipron (PF-06882961) in adults with obesity: a randomized, placebo-controlled, dose-ranging phase 2b study. *Diabetes Obes Metab* 2025; **27**: 4915–26.
- 13 Rodriguez PJ, Zhang V, Gratzl S, et al. Discontinuation and reinitiation of dual-labeled GLP-1 receptor agonists among US adults with overweight or obesity. *JAMA Netw Open* 2025; **8**: e2457349-e.
- 14 Sattar N, Lee MMY, Kristensen SL, et al. Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of randomised trials. *Lancet Diabetes Endocrinol* 2021; **9**: 653–62.
- 15 Ling J, Chow E. Glucagon-like peptide receptor-1 receptor agonists: the emerging fourth pillar in type 2 diabetes and chronic kidney disease? *Med (NY)* 2024; **5**: 845–47.



Neoadjuvant quadruplet chemotherapy PAXG for pancreatic cancer

Published Online
November 20, 2025
[https://doi.org/10.1016/S0140-6736\(25\)01864-1](https://doi.org/10.1016/S0140-6736(25)01864-1)
See [Articles](#) page 2945

Perioperative management of localised pancreatic ductal adenocarcinoma (PDAC) is informed by resectability criteria, which consider anatomy together with biological and clinical factors.¹ In patients with resectable PDAC, adjuvant mFOLFIRINOX (modified 5-fluorouracil, leucovorin, irinotecan, and oxaliplatin) is a standard of care;^{2,3} however, many are unable to receive this regimen due to inadequate performance status after surgery. Trials have evaluated various neoadjuvant chemotherapy regimens; notably, two randomised controlled trials did not confirm superiority of mFOLFIRINOX or FOLFIRINOX over gemcitabine–nab-paclitaxel (SWOG 1505)⁴ and gemcitabine with radiation (PREOPANC-2).⁵

The quadruplet regimen PAXG (cisplatin, nab-paclitaxel, capecitabine, and gemcitabine) was evaluated in a small randomised phase 2 trial (PACT-19) in advanced PDAC, showing a 6-month progression-free survival of 74% compared with 46% in patients receiving gemcitabine–nab-paclitaxel.⁶ Using multiagent regimens can overcome tumour heterogeneity and resistance, and switch approaches have further shown the efficacy of this approach.⁷

In *The Lancet*, Michele Reni and colleagues report the results of CASSANDRA⁸ to assess the superiority of PAXG over mFOLFIRINOX in patients with resectable and borderline resectable PDAC. This study was initially an open-label, randomised, phase 2 trial that became a phase 3 trial and used a 2 × 2 multifactorial design to compare the PAXG regimen with mFOLFIRINOX for patients with resectable and borderline resectable PDAC. The trial was designed first to test the superiority of PAXG and second to document the optimal duration of neoadjuvant chemotherapy. Following 4 months of neoadjuvant chemotherapy, patients underwent a second randomisation to either continue neoadjuvant chemotherapy for a further 2 months (totalling 6 months) followed by surgery or to proceed to surgery followed by a further 2 months of adjuvant treatment.

Of 260 patients enrolled, 134 (52%) were classified as borderline resectable PDAC, including patients with anatomically resectable PDAC and a carbohydrate antigen 19-9 (CA19-9) more than 500 IU/mL.



Krueger via Getty Images