New oral GLP-1 RA, orforglipron, achieves up to 11.2% mean weight loss

Orforglipron, an oral, small-molecule GLP-1 receptor agonist at a daily dose of 36 mg, achieved a mean 11.2% weight loss over 72 weeks compared to 2.1% with placebo, in the ATTAIN-1 study, presented at the 2025 EASD Annual Meeting and simultaneously published in the *New England Journal of Medicine*. In addition to weight loss, orforglipron improved cardiometabolic risk factors. More than one-third of those receiving the 36 mg top dose achieved weight loss of at least 15% and nearly one fifth achieved 20% or greater weight loss. Unlike oral semaglutide, orforglipron does not require any special dosing regimen to optimise absorption, suggesting it will be more convenient to use than oral semaglutide once it is licensed. As anticipated, the majority of side effects were gut-related, and no previously unrecognised side effects were identified during the study. Orforglipron is not yet licensed in the UK.

Pam Brown
GP in Swansea

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) are very effective drugs for weight management, but all the currently licensed drugs require subcutaneous injection, which is not acceptable for everyone. Injectable weight loss drugs can be administered once weekly; however, users require training in how to use the injector device, the drugs can cause discomfort or injection site reactions, there is a significant cost to scale up injector production and an environmental impact of the waste plastic generated, and the drugs need cold chain delivery and refrigeration for long-term storage, which may not be available in some countries.

Oral semaglutide is the only oral GLP-1 RA currently licensed in the UK, and only for management of type 2 diabetes. It must be taken exactly as directed to ensure absorption: first thing in the morning on an empty stomach, with a sip of tap water and no food, drink or other medications for at least 30 minutes afterwards. As a result, it is believed that many people get suboptimal benefit due to not taking the drug correctly. Higher 25 mg and 50 mg daily doses of this drug are in development for weight loss, with similar efficacy to the weekly injectable semaglutide 2.4 mg, but these are not yet licensed in the UK.

Orforglipron is the first oral, small-molecule, non-peptide GLP-1 receptor agonist to reach Phase 3 trials for obesity treatment. It is also in development for treatment of type 2 diabetes, hypertension, osteoarthritis and obstructive sleep apnoea. Recently, two other small-molecule GLP-1 RAs in development for obesity were discontinued due to liver problems in clinical trials, but there is a raft of other similar drugs in Phase 2 and 3 development.

The demand for GLP-1 RAs for weight management in the UK continues to expand rapidly, emphasising the need for effective, easy-to-dose, oral drugs.

The present study

ATTAIN-1 was a 72-week, Phase 3, randomised, double-blind, placebo-controlled trial examining the efficacy and safety of three doses of daily orforglipron (6 mg, 12 mg and 36 mg). The results were presented at the 61st European Association for the Study of Diabetes (EASD) Annual Meeting in Vienna and published simultaneously in the *New England Journal of Medicine* (Wharton et al, 2025a).

A total of 3127 adults without type 2 diabetes, with either a BMI ≥30 kg/m^2 or a BMI ≥27 kg/m^2 and at least one obesity-related comorbidity (hypertension, dyslipidaemia, cardiovascular disease or obstructive sleep apnoea), were enrolled. Orforglipron or placebo were used alongside individualised advice on a healthy diet (no caloric reduction) and physical activity. Orforglipron was initiated at 1 mg daily, escalated to 3 mg and then, depending

Citation: Brown P (2025) Diabetes Distilled: New oral GLP-1 RA, orforglipron, achieves up to 11.2% mean weight loss. *Diabetes & Primary Care* **27**: 167–9

Read more

NICE overweight and obesity guidelines – what's new?

The new NG246 guideline replaces several pre-existing NICE obesity guidelines. Sally Erskine reviews the key changes.

Diabetes & Primary Care **27**: 51–3

Click here to access

on randomisation, escalated to 6 mg, 12 mg or 36 mg.

Just under 34% of participants were male, a higher proportion than in most weight loss trials, and 9.2% of those randomised had a BMI <30 kg/m^2; 36% had prediabetes (HbA_{1c} >39 mmol/mol). Mean baseline weight was 103.2 kg, mean BMI 37 kg/m^2, mean age was 45 years, and 56.5% of participants were White, 28.6% Asian and 8.6% Black.

The primary endpoint was the percentage change in body weight from baseline to week 72. Secondary endpoints were the proportions of participants achieving 5%, 10%, 15% and 20% weight loss at 72 weeks, and changes in waist circumference, systolic blood pressure, non-HDL cholesterol and triglycerides. Dual-energy X-ray absorptiometry (DEXA) was used to assess changes in body composition in 171 participants in the active treatment groups.

Results

From baseline to week 72, the mean reduction in body weight in the four groups was as follows:

- Orforglipron 6 mg: 7.5%.
- Orforglipron 12 mg: 8.4%.
- Orforglipron 36 mg: 11.2%.
- Placebo: 2.1%.

At 72 weeks, 33%, 40% and 55% of participants achieved at least 10% weight loss in the orforglipron 6 mg, 12 mg and 36 mg groups, respectively. More than one-third of those on the 36 mg dose achieved weight loss of at least 15% and nearly one-fifth had a reduction of at least 20%.

Orforglipron treatment significantly improved the cardiometabolic risk factors which were secondary endpoints in the study and, although direct comparison is not possible, these were deemed to be similar to effects achieved with oral or injectable semaglutide in weight loss studies, despite the lower weight loss achieved with orforglipron. The lower mean weight loss in ATTAIN-1 may relate to the increased proportion of male participants, who are known to lose less weight than women during GLP-1 RA treatment.

In the pooled group of orforglipron recipients who underwent DEXA body composition measurement, mean fat loss was 13.8%, lean mass loss 4.5% and visceral fat mass loss 19%, compared with changes of –1.7%, 0.3% and 7.4%, respectively, in the placebo group.

As expected, the most common adverse effects were gastrointestinal, including nausea, constipation, diarrhoea, vomiting and dyspepsia, and these were evenly distributed across the groups; however, they caused discontinuation in 3.5–7.0% of orforglipron recipients versus 0.4% of placebo recipients.

Serious adverse reactions occurred in 3.8–5.5% of participants treated with orforglipron, and in 4.9% of the placebo group. These included five cases of mild pancreatitis, all in orforglipron recipients. No cases of medullary thyroid cancer were identified during the study.

Small-molecule drugs such as orforglipron can bind to other receptors, causing adverse effects, and liver reactions have halted development of other small-molecule GLP-1 RAs for weight loss. Despite careful scrutiny, however, there were no liver safety signals detected in this study.

Discussion

Just under 20% of recipients discontinued orforglipron during the course of the study but, interestingly, 30% stopped the placebo. Presenting the independent commentary at the EASD symposium where the findings were presented, Vanita Aroda (Director of Diabetes Clinical Research, Brigham and Women's Hospital, and Associate Professor, Harvard Medical School) sought to put the study withdrawals into context by reminding the audience of how difficult it is to participate in clinical trials. Those in the placebo group will realise early that there is no change in appetite, no weight loss and possibly even weight gain, suggesting that they are receiving the placebo, and they may choose to opt out and source a different active weight loss treatment rather than putting their weight loss journey on hold for 72 weeks. In the active treatment group, people are likely to experience some early gastrointestinal side effects during therapy titration and, although they may be happy to stay on a lower dose where side effects are minimal, they must follow protocol and increase doses until they achieve their maximal tolerated dose, which may be accompanied with greater side effects. Again, this may prompt them to leave the trial.

Limitations of the trial include lack of comparison with other weight management drugs, and use of BMI cut-offs developed in White populations as inclusion criteria. Strengths include the large, diverse patient population, from nine countries and four continents, and the significant number of men enrolled.

The OASIS 4 double-blind, randomised controlled trial of oral semaglutide 25 mg daily was published in the same issue of the *New England Journal of Medicine* (Wharton et al, 2025b). This demonstrated a mean weight loss of 13.6% from baseline to 64 weeks, compared to 2.2% weight loss with placebo, which was similar to the 15.1% weight loss achieved with semaglutide 50 mg daily in the OASIS 1 study (Knop et al, 2023).

Implications for practice

Demand for effective weight loss drugs continues to increase, and some people are unable to cope with injectable treatment. Daily oral semaglutide is not yet licensed for weight loss in the UK at any dose, although at lower doses it is comparably effective to subcutaneous semaglutide for management of hyperglycaemia in type 2 diabetes. The SOUL study of oral semaglutide confirms cardiovascular benefits in those with type 2 diabetes and established atherosclerotic cardiovascular disease at doses up to 14 mg (McGuire et al, 2025; see previous *Diabetes Distilled*).

Oral semaglutide must be taken exactly as directed to ensure absorption. A new formulation with improved absorption is being rolled out across the UK for management of type 2 diabetes, but we are reminded that this will still need similar careful guidance on administration if people are to gain the maximal effects.

If licensed and included in weight management options here in the UK, orforglipron, as a small-molecule, non-peptide GLP-1 RA, will be an easier-to-use medication with no dosing restrictions. These results from ATTAIN-1 suggest that orforglipron, when used as an adjunct to healthy diet and physical activity, offers at least 10% weight loss to half of people taking the drug over 72 weeks. This is significant weight loss from a simple daily pill, and we eagerly anticipate information on how this will be priced.

As with all currently available GLP-1 RA therapies for weight loss, primary care will have an important role in encouraging and supporting physical activity, particularly resistance exercise, and adequate protein intake, to reduce loss of lean body mass and muscle while using these drugs. ■

Knop FK, Aroda VR, do Vale RD et al; OASIS 1 investigators (2023) Oral semaglutide 50 mg taken once per day in adults with overweight or obesity (OASIS 1): A randomised, double-blind, placebo-controlled, Phase 3 trial. *Lancet* **402**: 705–19

McGuire DK, Marx N, Mulvagh SL et al; SOUL Study Group (2025) Oral semaglutide and cardiovascular outcomes in high-risk type 2 diabetes. *N Engl J Med* **392**: 2001–12

Wharton S, Aronne LJ, Stefanski A et al; ATTAIN-1 trial investigators (2025a) Orforglipron, an oral small-molecule GLP-1 receptor agonist for obesity treatment. *N Engl J Med* 16 Sep [Epub ahead of print]. https://doi.org/10.1056/NEJMoa2511774

Wharton S, Lingvay I, Bogdanski P et al; OASIS 4 Study Group (2025b) Oral semaglutide at a dose of 25 mg in adults with overweight or obesity. *N Engl J Med* **393**: 1077–87

Orforglipron, an oral small-molecule GLP-1 receptor agonist for obesity treatment

Read the article in full
(open access; free account required)

Read more

Interactive case study: GLP-1 and GIP/GLP-1 receptor agonists in type 2 diabetes

The practicalities of prescribing incretin-based therapies for the management of type 2 diabetes.

Diabetes & Primary Care **27**: 119

Click here to access