Greater reductions in HbA_{1c} ACHIEVEd with orforglipron versus oral semaglutide 14 mg

Orforglipron is a once-daily, small-molecule, non-peptide GLP-1 receptor agonist, which can be taken orally with no dosing restrictions on food or drink consumption. In this open-label, active-control, randomised study published in *The Lancet*, orforglipron 12 mg and 36 mg were superior to oral semaglutide 7 mg and 14 mg in lowering HbA_{1c} in people with type 2 diabetes inadequately controlled with metformin. At 52 weeks, HbA_{1c} reductions of 1.71% and 1.91% were achieved with orforglipron, compared to 1.23% and 1.47% with oral semaglutide. Weight reductions were also greater with orforglipron 36 mg than with either dose of semaglutide. The safety profile with both drugs was similar to that seen with other GLP-1 RAs, with greater adverse event rates in the orforglipron arms compared with semaglutide. Twice as many people treated discontinued treatment for gastroenterological adverse events with the two orforglipron doses (9% and 10%) compared with semaglutide (4% and 5%). Orforglipron has been submitted to the European and UK medical regulators but is not licensed in the UK at this time.

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Although once-weekly injectable GLP-1 receptor agonists effectively reduce HbA_{1c} and have cardiovascular and renal benefits in people with type 2 diabetes, some people do not want injectable therapy. Currently, semaglutide is the only oral GLP-1 RA licensed in the UK. Although it has a long half-life, poor absorption means it needs to be taken daily, on an empty stomach, first thing in the morning, with less than 120 mL of tap water, and with no other medication, food or drink for at least 30 minutes.

Orforglipron is a once-daily, small-molecule, non-peptide, partial GLP-1 RA, which can be administered orally without any special precautions in relation to food or drink. It is in development for both type 2 diabetes and weight management.

Previously, the ACHIEVE-1 study evaluated orforglipron monotherapy in people with early type 2 diabetes uncontrolled with lifestyle intervention, and demonstrated a 12 mmol/mol (1.1%) greater HbA_{1c} reduction and a 5.9% greater body weight reduction than placebo (Rosenstock et al, 2025).

The present study

ACHIEVE-3 was a 52-week, non-inferiority, open-label, active-control, randomised, phase 3 trial comparing orforglipron 12 mg or 36 mg versus oral semaglutide 7 mg or 14 mg (Rosenstock et al, 2026). Participants comprised people with type 2 diabetes inadequately controlled on metformin, with an HbA_{1c} of 53–91 mmol/mol (7.0–10.5%) and a BMI of at least 25 kg/m^2 at baseline.

The study was powered to assess non-inferiority and, if this was achieved, superiority of orforglipron 36 mg versus semaglutide 14 mg and of orforglipron 12 mg versus semaglutide 7 mg. The primary endpoint was change in HbA_{1c} over 52 weeks.

Secondary endpoints included achievement of HbA_{1c} levels <7.0%, <6.5% and <5.7%; changes in body weight, BMI and waist circumference; and various cardiometabolic parameters, including lipid levels and blood pressure.

Safety endpoints were evaluated in all those who received at least one dose of medication, and included:

- Number and incidence of serious adverse events.
- Treatment-emergent adverse events.
- Discontinuation due to adverse events.

The treatment estimand, based on data from all those enrolled in the study irrespective of discontinuation or additional treatments needed, was the main analysis, with results from the efficacy estimand (assuming all those recruited remained on treatment without any additions, throughout the 52 weeks) seen as supportive.

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Table 1. Treatment estimand results at 52 weeks (baseline average HbA_{1c} 8.3%, weight 90 kg).

	Orforglipron 12 mg	Orforglipron 36 mg	Semaglutide 7 mg	Semaglutide 14 mg
HbA_{1c} reduction (DCCT units – %)	1.71%	1.91%	1.23%	1.47%
Mean body weight reduction	6.1%	8.2%	3.9%	5.3%
Self-reported gastrointestinal adverse events	59%	58%	37%	45%
Discontinuations due to adverse events	8%	10%	4%	5%

DCCT=Diabetes Control and Complications Trial.

Results

A total of 1698 people were recruited and randomised to receive orforglipron 12 mg or 36 mg, or semaglutide 7 mg or 14 mg. Overall, 91% of participants completed the study. *Table 1* shows the key results of the treatment estimand analysis.

Both doses of orforglipron were non-inferior and superior to the two doses of semaglutide for reduction in HbA_{1c} in both the treatment and efficacy estimands, with differences emerging in the treatment estimand after 4 weeks. As expected, those with baseline HbA_{1c} >8.0% had greater reductions in HbA_{1c} with either drug compared to those with HbA_{1c} <8.0%.

Fewer people needed rescue therapy for hyperglycaemia in the orforglipron groups: 3% and 2% on 12 mg and 36 mg, respectively, compared to 12% and 6% in the 7 mg and 14 mg oral semaglutide groups.

Weight reductions were also greater in those treated with orforglipron, with differences emerging by 4 weeks. Weight reduction with orforglipron 36 mg was superior to that achieved with both doses of semaglutide. Although the weight loss with orforglipron 12 mg was superior to that achieved with semaglutide 7 mg, it was not significantly greater than with semaglutide 14 mg. Orforglipron 36 mg demonstrated the greatest mean reductions in BMI and waist circumference.

Adverse events were reported in 75% of each orforglipron group, compared to 71% and 72% in people receiving semaglutide 7 mg and 14 mg, respectively. Adverse events were mainly gastrointestinal, and these were more common with orforglipron than with semaglutide (*Table 1*). Twice as many participants discontinued orforglipron than semaglutide due to adverse events.

Serious adverse event rates were slightly higher with orforglipron 36 mg than in the other groups. Four cases of acute pancreatitis were reported: two with orforglipron 12 mg and two with semaglutide 14 mg. Two cases of papillary thyroid cancer were reported: one in each of the orforglipron 12 mg and semaglutide 14 mg groups. An increase in mean pulse rate of 3–4 bpm was seen with orforglipron, greater than the increase of 1 bpm seen with semaglutide.

Small reductions in mean eGFR were observed over the study period, with no differences between the drugs. However, albumin:creatinine ratio decreased in both groups, with greater reductions (31.4% and 32.5%) in the orforglipron groups compared with the semaglutide groups (14.5% and 23.8%).

Fourteen percent of participants had diabetic retinopathy at baseline (most mild non-proliferative), and the rates of retinopathy progression during the study were low (6% and 8% with orforglipron and 7% and 8% with semaglutide), with no significant difference between groups. There were also no significant differences in rates of retinopathy progression between groups in those with established retinopathy at baseline.

In an accompanying comment, Nauck and Horowitz (2026) highlight that this study should not be interpreted as demonstrating greater efficacy of orforglipron compared to semaglutide, since similar HbA_{1c} and weight reductions can be achieved with similar adverse event rates with the (not yet licensed in the UK) 25 mg and 50 mg doses of oral semaglutide (Aroda et al, 2023). Since many of the adverse events and discontinuations occurred before maintenance doses were achieved, Nauck and Horowitz suggest that the priority may be to find ways to improve tolerability of oral GLP-1 RAs, including by exploring dose-escalation regimens.

Limitations of ACHIEVE-3 include the open-label design, which was necessary to allow semaglutide to be dosed to facilitate absorption; the self-reporting of gastrointestinal side-effects,

which is common in studies; and the limiting of treatment duration to 52 weeks.

Oral semaglutide has previously been shown to reduce cardiovascular events in people with type 2 diabetes and pre-existing cardiovascular disease, chronic kidney disease or both in the SOUL trial (McGuire et al, 2025). A cardiovascular outcomes trial of orforglipron is ongoing.

Implications for practice

Despite the potential benefits of once-weekly subcutaneous GLP-1 RAs, some people remain unwilling to consider injectable therapies. The licensing of oral semaglutide provided a step forward in type 2 diabetes management for this group, and the publication of the SOUL study in 2025 reassured us that oral semaglutide could also offer cardiovascular benefit in those at highest risk. However, in my experience after many years of prescribing oral semaglutide, people have varying ability to fit the dosing regimen into their daily lives consistently. As a result, some are able to achieve glucose and weight reductions comparable to injectable semaglutide therapy, while others struggle with missed doses and dosing with other medications or food and drink, and thus suboptimal benefits.

With careful demonstration of the devices, and encouragement to use thigh injection sites rather than abdominal if preferred, many of these people are happy to convert to a once-weekly injectable GLP-1 RA for the convenience. The benefits of GLP-1 RAs make it important for us to tactfully explore oral adherence and dosing at each consultation, and to discuss a switch to injectable therapy if results seem suboptimal or administration is problematic.

This study compared doses of orforglipron used in clinical studies with the maintenance doses of oral semaglutide that are currently marketed in the UK. Even though higher doses of oral semaglutide (25 mg and 50 mg) can achieve similar HbA_{1c} and weight reductions to orforglipron, the convenience of unrestricted daily orforglipron dosing means this is likely to be more attractive to people requesting an oral drug, depending on whether cardiovascular benefits are observed in the outcomes study.

Around 50% of people discontinue GLP-1 RAs within the first year, yet these drugs offer significant benefits in both type 2 diabetes and obesity. Spending time helping people find the drug that best suits their needs and lifestyle, and providing regular support to help them continue therapy, will have long-term benefits. As primary care clinicians, we are in the ideal place to offer such support, as well as to share the benefits of orforglipron once it is licensed in the UK. ■

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Efficacy and safety of once-daily oral orforglipron compared with oral semaglutide in adults with type 2 diabetes (ACHIEVE-3)

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