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Metabolism and Target Organ Damage

Bernasconi *et al. Metab Target Organ Damage.* 2026;6:57 **DOI:**10.20517/mtod.2026.142

Orforglipron versus oral semaglutide in type 2 diabetes, clinical implications of the ACHIEVE-3 trial

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Citation: Bernasconi D, Lunati ME, Fiorina P. Orforglipron versus oral semaglutide in type 2 diabetes, clinical implications of the ACHIEVE-3 trial. *Metab Target Organ Damage.* 2026;6:57. https://dx.doi.org/10.20517/mtod.2026.142

Received: 6 Jul 2026 **First Decision:** 20 Jul 2026 **Revised:** 15 Sep 2026 **Accepted:** 17 Sep 2026 **Published:** 28 Sep 2026

Academic Editor: Amedeo Lonardo **Copy Editor:** Ting-Ting Hu **Production Editor:** Ting-Ting Hu

COMMENTARY

Over recent decades, the paradigm of diabetes treatment has shifted with the introduction of new agents, such as glucagon-like peptide-1 receptor agonists (GLP-1 RAs) and sodium-glucose cotransporter-2 inhibitors (SGLT-2i)[1]. With these drug classes, treatment goals have shifted beyond glycemic control to a broader metabolic perspective that includes cardiovascular and renal risk reduction, while mechanistic and imaging studies continue to explore immunomodulatory and vascular effects[2-5]. Semaglutide, one of the most widely used agents in this class, has been developed in both subcutaneous and oral formulations. Both formulations have demonstrated substantial efficacy in glucose and weight management, and cardiovascular protection in patients with type 2 diabetes[5]. The oral formulation avoids injections, but its administration remains specific: absorption depends on sodium N-(8-[2-hydroxybenzoyl] amino) caprylate (SNAC), and the tablet must be taken under fasting conditions with a limited amount of water, followed by a waiting period before food, beverages, or other oral medications[6]. In this context, ACHIEVE-3 (NCT06045221), sponsored by Eli Lilly and Company, is the first head-to-head phase 3 trial comparing two oral GLP-1 RAs: oral semaglutide and orforglipron, a non-peptide small-molecule GLP-1 RA[7-9]. Unlike oral semaglutide, orforglipron can be administered without specific restrictions related to food or fluid intake[6-9]. The trial has investigated how orforglipron, a next-generation oral, non-peptide GLP-1 RA, performs against the established oral comparator in the class.

This multinational, randomised, open-label phase 3 trial involving 1,698 adults with type 2 diabetes inadequately controlled on metformin, once-daily oral orforglipron at 12 and 36 mg was evaluated in prespecified dose-matched comparisons: orforglipron 12 mg *vs.* oral semaglutide 7 mg and orforglipron 36 mg *vs.* oral semaglutide 14 mg. The primary objective was non-inferiority for glycated hemoglobin (HbA1c) change at week 52, followed by prespecified hierarchical superiority testing. For the

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treatment-regimen estimand, the between-group differences were -0.48 percentage points [95% confidence interval (CI): -0.65 to -0.31] and -0.44 percentage points (95%CI: -0.62 to -0.26), respectively. Cross-dose comparisons were also statistically significant: -0.24 percentage points (95%CI: -0.41 to -0.072) for orforglipron 12 mg *vs*. semaglutide 14 mg and -0.68 percentage points (95%CI: -0.85 to -0.50) for orforglipron 36 mg *vs*. semaglutide 7 mg[9] [Figure 1A]. The weight-loss findings are equally consistent. At week 52, mean body weight reduction was 6.1% and 8.2% with orforglipron, *vs*. 3.9% and 5.3% with semaglutide [Figure 1B], and the higher orforglipron dose produced clearly greater proportions of participants achieving 5%, 10%, and even 15% weight reduction. Cross-dose comparison showed superiority for orforglipron 12 mg *vs*. semaglutide 7 mg (-2.3%, 95%CI: -3.2 to -1.3; $P < 0.0001$), for orforglipron 36 mg *vs*. semaglutide 7 mg (-4.3%, 95%CI: -5.3 to -3.3; $P < 0.0001$) and for orforglipron 36 mg *vs*. semaglutide 14 mg (-2.8%, 95%CI: -3.9 to -1.9; $P < 0.0001$), but not for orforglipron 12 mg *vs*. semaglutide 14 mg. These results establish statistical superiority for HbA1c and weight comparisons studied. However, other key factors must be considered to define clinical superiority: tolerability, treatment persistence, patient preference, and effects on clinically meaningful long-term outcomes are central in clinical decision-making. The comparator dose also matters. PIONEER PLUS showed greater HbA1c and body-weight reductions with oral semaglutide 25 and 50 mg than with 14 mg[10]. This is particularly relevant to the comparison of orforglipron 36 mg with semaglutide 14 mg: because oral semaglutide 25 mg produces larger HbA1c and body-weight reductions than 14 mg, the observed efficacy gap may be larger than it would have been against a contemporary higher-dose semaglutide comparator. ACHIEVE-3 should therefore be read as evidence of superiority over the oral semaglutide doses that were studied, rather than over the full efficacy range of oral semaglutide.

These efficacy gains were accompanied by a less favorable tolerability profile. Gastrointestinal adverse events were more frequent with orforglipron than with semaglutide, and discontinuations due to adverse events were roughly doubled in the orforglipron groups [Figure 1C]. This trade-off is clinically relevant because an efficacy advantage loses practical value when patients cannot sustain treatment. The study has several strengths. A large and geographically diverse population, the randomized design, the use of an active comparator, and the 52-week observation period are major strengths. Nevertheless, several limitations should temper interpretation. The open-label design introduces potential bias, although not all outcomes are equally susceptible. HbA1c and measured body weight are relatively objective, whereas gastrointestinal symptoms and treatment discontinuation are more vulnerable to expectations, symptom attribution, and knowledge of treatment assignment. Unblinding could influence reporting or attribution. In particular, positive expectations among participants receiving a novel, more efficacious agent and greater investigator tolerance of symptoms in the newer arm could both attenuate the observed tolerability gap, although the trial cannot quantify the magnitude of this effect. Furthermore, although 52 weeks is substantial for a phase 3 metabolic trial, it is still insufficient to define long-term durability, rare adverse effects, and cardiovascular and renal benefits. The trial was also funded, designed, monitored, and analyzed by the manufacturer, which does not invalidate the findings but warrants caution in interpretation and reinforces the value of independent and longer-term evidence. Comparator-dose selection was also part of the sponsor-controlled design; therefore, the use of semaglutide 14 mg as the highest comparator should be considered when interpreting the magnitude and generalizability of the reported superiority.

ACHIEVE-3 shows that a non-peptide small-molecule GLP-1 RA can achieve substantial glycemic and weight effects through a fully oral regimen, although its long-term clinical position remains to be established. Orforglipron is not simply another formulation of a peptide GLP-1 RA: its small-molecule, non-peptide chemistry allows oral administration without the absorption-enhancer and fasting requirements of oral semaglutide[6-9]. These characteristics may be particularly relevant for patients who want to avoid injections or find the fasting and water requirements of oral semaglutide difficult, provided gastrointestinal tolerability is acceptable. Conversely, oral semaglutide may remain preferable when established cardiovascular outcome

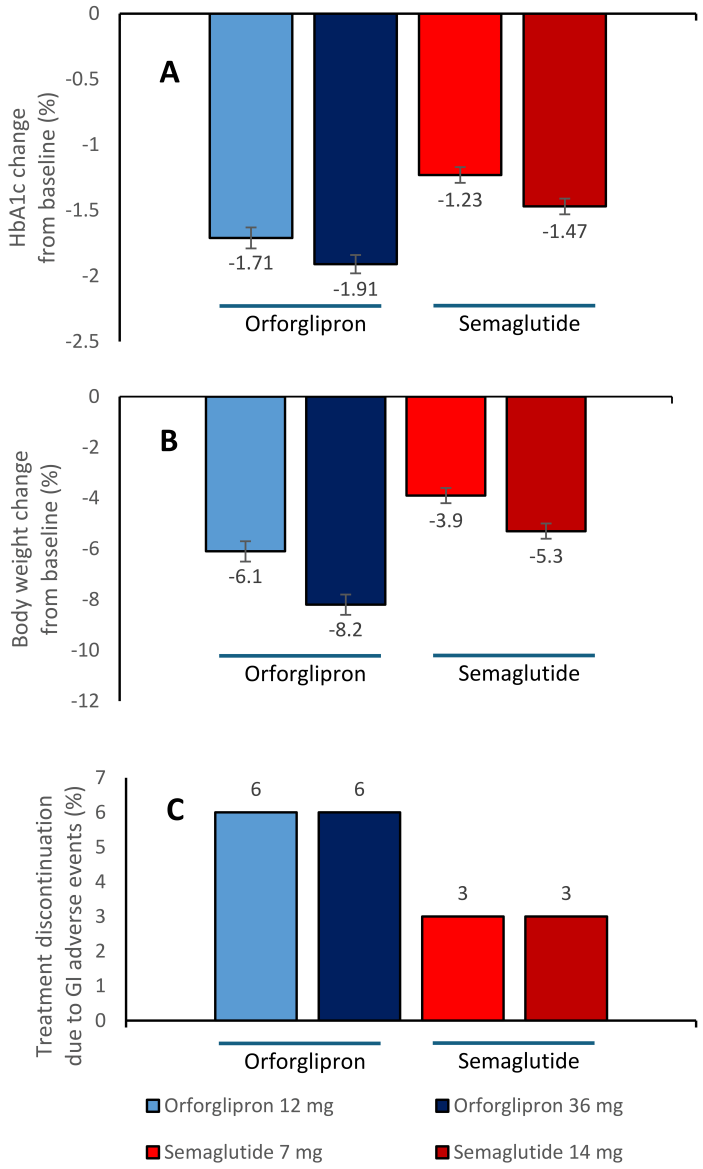

Figure 1. ACHIEVE-3 outcomes at week 52. (A) mean HbA1c change from baseline (%) with orforglipron 12 mg, orforglipron 36 mg, oral semaglutide 7 mg, and oral semaglutide 14 mg; (B) mean body-weight change from baseline (%) in the same treatment groups; (C) percentage of participants who discontinued study treatment because of GI adverse events. (A and B) show treatment-regimen estimand means. The prespecified HbA1c comparisons and 95%CIs are reported in the text. Figure created by the authors from numerical data reported by Rosenstock *et al.* in ACHIEVE-3[8,9]. Error bars in (A and B) represent SE. CI: Confidence interval; GI: gastrointestinal; HbA1c: glycated hemoglobin; SE: standard error.

evidence is a major treatment priority[5]. A history of gastrointestinal intolerance may also favor the better-tolerated option over the more efficacious dose. Orforglipron will enter a treatment landscape that also includes highly effective injectable agents such as tirzepatide and emerging dual or triple agonists, so oral convenience will be only one component of treatment selection. Its oral administration also eliminates injection-site reactions.

Regarding weight loss, body composition deserves a more precise discussion. Body weight, lean mass, skeletal muscle mass, and muscle function are related but not interchangeable outcomes. ACHIEVE-3 did not report dedicated body-composition or muscle-function measurements, so whether orforglipron has a distinctive effect on lean or skeletal muscle mass remains unknown. Across GLP-1-based therapies, a recent

meta-analysis estimated that lean-mass loss accounts for approximately one quarter of total weight loss (pooled mean differences *vs*. control: -3.55 kg for total body weight (95%CI: -4.81 to -2.29) and -0.86 kg for lean mass (95%CI: -1.30 to -0.42), although the clinical relevance of this change depends on baseline age, frailty, muscle mass, and muscle function[11,12].

Given current diabetes management objectives and the range of glucose-lowering medications, treatment regimens should be tailored to each patient's risk profile. The lack of evidence on orforglipron's potential role in reducing cardiovascular and renal risk will remain a central consideration in therapeutic decisions. One of orforglipron potential roles could already be defined. ATTAIN-MAINTAIN addresses a different clinical question than ACHIEVE-3, regarding treatment sequencing. In adults with obesity who had previously received injectable tirzepatide or semaglutide, switching to once-daily oral orforglipron preserved more of the previously achieved weight loss at 52 weeks than placebo (74.7% *vs*. 49.2% after tirzepatide and 79.3% *vs*. 37.6% after semaglutide)[13]. The study did not compare switching with continued injectable treatment, so these findings should be viewed as evidence for a possible oral maintenance strategy rather than as proof of therapeutic equivalence. Important questions remain: long-term tolerability and safety, cardiovascular and renal outcomes, body composition, treatment persistence, cost, and access will determine the place of orforglipron in diabetes care. ACHIEVE-3 provides strong evidence of metabolic efficacy against the oral semaglutide doses studied, but it does not yet establish broader clinical superiority. If future outcome and real-world studies confirm a favorable benefit-risk profile, orforglipron may become an important additional option in the treatment of type 2 diabetes.

DECLARATIONS

Authors' contributions

Conceptualization, literature review, writing - original draft, figure preparation: Bernasconi D
Conceptualization, critical revision, writing - review and editing: Lunati ME
Conceptualization, supervision, critical revision, writing - review and editing: Fiorina P
All authors read and approved the final manuscript.

Availability of data and materials

Not applicable.

AI and AI-assisted tools statement

Not applicable.

Financial support and sponsorship

None.

Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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