Lilly's oral GLP-1, orforglipron, superior to oral semaglutide in head-to-head trial

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For the primary endpoint, orforglipron lowered A1C by 2.2% vs. 1.4% with oral semaglutide at the highest doses

Participants taking the highest dose of orforglipron lost an average of 19.7 lbs (9.2%) vs. 11.0 lbs (5.3%) with oral semaglutide, a 73.6% relative improvement, in a key secondary endpoint

The safety and tolerability of orforglipron were consistent with previous trials

INDIANAPOLIS, Sept. 17, 2025 /PRNewswire/ -- Eli Lilly and Company (NYSE: LLY) today announced positive topline results from ACHIEVE-3, an open-label randomized Phase 3 clinical trial evaluating the safety and efficacy of orforglipron compared to oral semaglutide, administered according to approved label instructions, in 1,698 adults with type 2 diabetes inadequately controlled with metformin. The 52-week trial compared orforglipron (12 mg and 36 mg) to oral semaglutide (7 mg and 14 mg) across four active treatment arms to assess glycemic control and weight loss. At 52 weeks, orforglipron met the primary and all key secondary endpoints across each dose comparison vs. oral semaglutide, delivering greater improvements in A1C and weight.[1]

"Head-to-head trials are a gold standard for comparing potential treatments," said Kenneth Custer, Ph.D., executive vice president and president of Lilly Cardiometabolic Health. "In this type 2 diabetes trial, orforglipron, even at the lower dose, outperformed both doses of oral semaglutide in reducing A1C. At the highest dose, orforglipron helped nearly three times as many participants reach near-normal blood sugar versus the highest dose of oral semaglutide. These results, combined with orforglipron's once-daily oral dosing and broad scalability, reinforce its potential as a foundational treatment for type 2 diabetes."

In the ACHIEVE-3 trial, orforglipron met the primary endpoint and showed superiority vs. oral semaglutide, lowering A1C by an average of 1.9% (12 mg) and 2.2% (36 mg) compared to 1.1% (7 mg) and 1.4% (14 mg) with oral semaglutide at 52 weeks using the efficacy estimand.[2] In a secondary endpoint, 37.1% of participants taking the highest dose of orforglipron achieved an A1C <5.7% compared to 12.5% taking the highest dose of oral semaglutide.[3] In key secondary endpoints, orforglipron was also superior to oral semaglutide for weight loss, and participants taking orforglipron lost an average of 14.6 lbs (6.7%; 12 mg) and 19.7 lbs (9.2%; 36 mg) compared to 7.9 lbs (3.7%; 7 mg) and 11.0 lbs (5.3%; 14 mg) with oral semaglutide, a 73.6% greater relative weight loss at the highest dose comparison. Orforglipron also showed clinically meaningful improvements across key cardiovascular risk factors, including non-HDL cholesterol, systolic blood pressure and triglycerides.[4]

Efficacy Estimand Results				
	Orforglipron 12 mg	**Orforglipron 36 mg**	**Oral semaglutide 7 mg**	**Oral semaglutide 14 mg**
Primary Endpoint				
Change in A1C from baseline of 8.3% at week 52	-1.9%[i,ii]	-2.2%[i,ii]	-1.1 %	-1.4 %
Secondary Endpoints				
Change in weight from baseline of 97.0 kg (213.9 lbs) at week 52[iv]	-6.7%[i,iii] (-6.6 kg; -14.6 lbs)[i,ii]	-9.2%[i,ii] (-8.9 kg; -19.7 lbs)[i,ii]	-3.7 % (-3.6 kg; -7.9 lbs)	-5.3 % (-5.0 kg; -11.0 lbs)
Percentage of participants achieving A1C <5.7% at week 52[v]	25.4%[i,ii]	37.1%[i,ii]	7.8 %	12.5 %

[i] *p<0.001 vs. oral semaglutide 7 mg*

[ii] *p<0.001 vs. oral semaglutide 14 mg*

[iii] *p<0.01 vs. oral semaglutide 14 mg*

[iv] *Body weight for orforglipron 12 mg vs. oral semaglutide 14 mg was not controlled for family-wise type 1 error.*

[v] *Percentage of participants achieving A1C <5.7% was not controlled for family-wise type 1 error.*

For the treatment-regimen estimand, each dose of orforglipron led to statistically significant improvements across the primary and all key secondary endpoints, including:[1,5,6]

- Change in A1C: -1.7% (12 mg) and -1.9% (36 mg) with orforglipron vs. -1.2% (7 mg) and -1.5% (14 mg) with oral

semaglutide
- Percent change in weight: -6.1% (12 mg) and -8.2% (36 mg) with orforglipron vs. -3.9% (7 mg) and -5.3% (14 mg) with oral semaglutide
- Change in weight: -6.2 kg (-13.7 lbs; 12 mg) and -8.1 kg (-17.8 lbs; 36 mg) with orforglipron vs. -3.8 kg (-8.4 lbs; 7 mg) and -5.2 kg (-11.5 lbs; 14 mg) with oral semaglutide
- Percentage of participants achieving A1C <5.7%: 21.4% (12 mg) and 31.4% (36 mg) with orforglipron vs. 7.4% (7 mg) and 11.7% (14 mg) with oral semaglutide

The overall safety and tolerability profile of orforglipron in ACHIEVE-3 was consistent with previous trials. The most commonly reported adverse events were gastrointestinal-related and generally mild-to-moderate in severity. Treatment discontinuation rates due to adverse events were 8.7% (12 mg) and 9.7% (36 mg) for orforglipron vs. 4.5% (7 mg) and 4.9% (14 mg) for oral semaglutide. However, the study was not powered to compare the safety and tolerability of orforglipron and oral semaglutide. No hepatic safety signal was observed for orforglipron.

The detailed results of the ACHIEVE-3 trial will be presented at a future medical meeting and published in a peer-reviewed journal. Lilly expects to submit orforglipron for the treatment of type 2 diabetes to global regulatory agencies in 2026.

About orforglipron
Orforglipron (or-for-GLIP-ron) is an investigational, once-daily small molecule (non-peptide) oral glucagon-like peptide-1 receptor agonist that can be taken any time of the day without restrictions on food and water intake.[7] Orforglipron was discovered by Chugai Pharmaceutical Co., Ltd. and licensed by Lilly in 2018. Chugai and Lilly published the preclinical pharmacology data of this molecule together.[8] Lilly is running Phase 3 studies on orforglipron for the treatment of type 2 diabetes and for weight management in adults with obesity or overweight with at least one weight-related medical problem. It is also being studied as a potential treatment for obstructive sleep apnea (OSA) and hypertension in adults with obesity.

About ACHIEVE-3 and ACHIEVE clinical trial program
ACHIEVE-3 (NCT06045221) is a Phase 3, 52-week, randomized, open-label trial evaluating the efficacy and safety of orforglipron compared with oral semaglutide in adults with type 2 diabetes inadequately controlled with metformin. The trial randomized 1,698 participants across the U.S., Argentina, China, Japan, Mexico and Puerto Rico to receive either 12 mg or 36 mg orforglipron or 7 mg or 14 mg oral semaglutide in a 1:1:1:1 ratio. The primary objective of the study was to demonstrate that orforglipron is non-inferior in A1C reduction from baseline after 52 weeks compared to oral semaglutide when comparing the lower and higher doses. All participants in the orforglipron treatment arms started the study at a dose of orforglipron 1 mg once-daily and then increased the dose in a step-wise approach at four-week intervals until reaching their randomized maintenance dose of 12 mg (via steps at 1 mg, 3 mg and 6 mg) or 36 mg (via steps at 1 mg, 3 mg, 6 mg, 12 mg and 24 mg). All participants in the oral semaglutide treatment arms started the study at a dose of oral semaglutide 3 mg once-daily and then increased the dose in a step-wise approach at four-week intervals until reaching their final randomized maintenance dose of 7 mg (via a step at 3 mg) or 14 mg (via steps at 3 mg and 7 mg). If participants were unable to tolerate a dose of orforglipron or oral semaglutide, they were allowed, once during the study, to reduce to the previous dose, with a minimum dose of orforglipron 3 mg or oral semaglutide 7 mg.

The ACHIEVE Phase 3 global clinical development program for orforglipron has enrolled more than 6,000 people with type 2 diabetes across five global registration trials. The program began in 2023 with results anticipated later this year and into 2026.

Endnotes and References

1. Body weight for orforglipron 12 mg vs. oral semaglutide 14 mg was a prespecified secondary endpoint and showed nominal statistical significance using the efficacy estimand; however, it was not controlled for family-wise type 1 error for the efficacy estimand or treatment-regimen estimand.
2. The efficacy estimand represents efficacy had all randomized participants remained on study intervention (with possible dose interruptions and/or dose modifications) for 52 weeks without initiating additional antihyperglycemic medications (>14 days of use).
3. American Diabetes Association. Standards of Care in Diabetes—2020 Abridged for Primary Care Providers. Clinical Diabetes 2020; 38(1):10–38. https://doi.org/10.2337/cd20-as01
4. Not controlled for family-wise type 1 error.
5. The treatment-regimen estimand represents the estimated average treatment effect regardless of adherence to study intervention or initiation of additional antihyperglycemic medications.
6. Percentage of participants achieving A1C <5.7% was not controlled for family-wise type 1 error.
7. Ma X, Liu R, Pratt EJ, Benson CT, Bhattachar SN, Sloop KW. Effect of Food Consumption on the Pharmacokinetics, Safety, and Tolerability of Once-Daily Orally Administered Orforglipron (LY3502970), a Non-peptide GLP-1 Receptor Agonist. Diabetes Ther. 2024 Apr;15(4):819-832. https://doi.org/10.1007/s13300-024-01554-1. Epub 2024 Feb 24. PMID: 38402332; PMCID: PMC10951152.
8. Kawai T, Sun B, Yoshino H, Feng D, Suzuki Y, Fukazawa M, Nagao S, Wainscott DB, Showalter AD, Droz BA, Kobilka TS, Coghlan MP, Willard FS, Kawabe Y, Kobilka BK, & Sloop KW, Structural basis for GLP-1 receptor activation by LY3502970, an orally active nonpeptide agonist, Proc. Natl. Acad. Sci. U.S.A. 117 (47) 29959-29967, https://doi.org/10.1073/pnas.2014879117 (2020).

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This press release contains forward-looking statements (as that term is defined in the Private Securities Litigation Reform Act of 1995) about orforglipron as a potential treatment for adults with type 2 diabetes, Lilly's ability to supply orforglipron, if approved, and the timeline for regulatory submissions, future readouts, presentations, and other milestones relating to orforglipron and its clinical trials and reflects Lilly's current beliefs and expectations. However, as with any pharmaceutical product, there are substantial risks and uncertainties in the process of drug research, development, and commercialization. Among other things, there is no guarantee that planned or ongoing studies will be completed as planned, that future study results will be consistent with study results to date, that orforglipron will prove to be a safe and effective treatment for type 2 diabetes, that orforglipron will receive regulatory approval, or that Lilly will execute its strategy as expected. For further discussion of these and other risks and uncertainties that could cause actual results to differ from Lilly's expectations, see Lilly's Form 10-K and Form 10-Q filings with the United States Securities and Exchange Commission. Except as required by law, Lilly undertakes no duty to update forward-looking statements to reflect events after the date of this release.

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