Lilly's oral GLP-1, orforglipron, delivered superior blood sugar control and weight loss compared to oral semaglutide in head-to-head type 2 diabetes trial published in The Lancet

February 26, 2026

For the primary endpoint, orforglipron 36 mg lowered A1C by 2.2% vs. 1.4% with oral semaglutide 14 mg in ACHIEVE-3

In a key secondary endpoint, participants on orforglipron 36 mg lost 19.7 lbs (9.2%) compared to 11.0 lbs (5.3%) with oral semaglutide 14 mg, representing a 73.6% greater relative weight loss

Lilly has submitted orforglipron to regulators in over 40 countries, with potential U.S. action for obesity in Q2 2026

INDIANAPOLIS, Feb. 26, 2026 /PRNewswire/ -- Eli Lilly and Company (NYSE: LLY) today announced detailed results from ACHIEVE-3, the first head-to-head Phase 3 trial evaluating the safety and efficacy of orforglipron, a small molecule oral GLP-1 without food or water restrictions, compared with oral semaglutide in adults with type 2 diabetes inadequately controlled with metformin. The 52-week trial enrolled 1,698 participants across four treatment arms: orforglipron 12 mg and 36 mg, and oral semaglutide 7 mg and 14 mg. In ACHIEVE-3, orforglipron outperformed oral semaglutide across the primary and all key secondary endpoints, delivering significantly greater improvements in A1C and weight.[1,2] The results were published today in *The Lancet.*

"ACHIEVE-3 gives us the first head-to-head comparison between two oral GLP-1 receptor agonist therapies in adults with type 2 diabetes, and the differences were clinically meaningful," said Dr. Julio Rosenstock, clinical professor of medicine at the University of Texas Southwestern Medical Center and lead investigator. "Orforglipron 12 mg and 36 mg doses outperformed oral semaglutide 7 mg and 14 mg diabetes-related doses on every key endpoint we measured, including A1C and weight loss, with improvements appearing as early as four weeks and sustained throughout the study."

ACHIEVE-3 Full Results

		Oral Semaglutide 7 mg	**Oral Semaglutide 14 mg**	**Orforglipron 12 mg**	**Orforglipron 36 mg**
Primary Endpoint					
Change in A1C from baseline of 8.3% at week 52	Efficacy estimand[2]	-1.1 %	-1.4 %	-1.9%[i,ii]	-2.2%[i,ii]
	Treatment-regimen estimand[3]	-1.2 %	-1.5 %	-1.7%[i,iii]	-1.9%[i,ii]
Secondary Endpoints					
Change in weight from baseline of 97.0 kg (213.9 lbs) at week 52[iv]	Efficacy estimand	-3.7% (-3.6 kg; -7.9 lbs)	-5.3% (-5.0 kg; -11.0 lbs)	-6.7%[i,iii] (-6.6 kg; -14.6 lbs)	-9.2%[i,ii] (-8.9 kg; -19.7 lbs)
	Treatment-regimen estimand	-3.9% (-3.8 kg; -8.4 lbs)	-5.3% (-5.2 kg; -11.5 lbs)	-6.1%[i] (-6.2 kg; -13.7 lbs)	-8.2%[i,ii] (-8.1 kg; -17.8 lbs)
Percentage of participants achieving A1C <7% at week 52	Efficacy estimand	54.6 %	66.1 %	80.0% [i,ii]	85.4% [i,ii]
	Treatment-regimen estimand	53.9 %	63.8 %	72.2% [i,iii]	75.8% [i,ii]
Percentage of participants achieving A1C ≤6.5% at week 52	Efficacy estimand	40.9 %	50.9 %	71.8%[i,ii]	76.8%[i,ii]
	Treatment-regimen estimand	38.4 %	48.3 %	62.7%[i,ii]	67.7%[i,ii]
Percentage of participants achieving A1C <5.7% at week 52[iv]	Efficacy estimand	7.8 %	12.5 %	25.4%[i,ii]	37.1%[i,ii]
	Treatment-regimen estimand	7.4 %	11.7 %	21.4%[i,ii]	31.4%[i,ii]

[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 and percentage of participants achieving A1C <5.7% were not controlled for family-wise type 1 error.*[1]

Orforglipron also showed clinically meaningful improvements from baseline across key cardiovascular risk factors, including non-HDL cholesterol, HDL cholesterol, VLDL cholesterol, total cholesterol, systolic blood pressure and triglycerides.[4]

"The results of ACHIEVE-3 highlight the potential advantages of orforglipron over oral semaglutide for type 2 diabetes: greater A1C reduction, more weight loss, and the ability to take it without food or water timing restrictions — that's a combination that could matter significantly to people managing their disease day in and day out," said Kenneth Custer, Ph.D., executive vice president and president of Lilly Cardiometabolic Health. "With global submissions underway and FDA action on obesity expected next quarter, we're focused on making this option available as quickly as possible."

The overall safety and tolerability profile of orforglipron in ACHIEVE-3 was consistent with previous trials. For orforglipron and oral semaglutide, the most common adverse events were nausea, diarrhea, vomiting, dyspepsia and decreased appetite. 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.

Lilly has submitted orforglipron to regulators in over 40 countries, with submission for type 2 diabetes in the U.S. planned later this year.

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.[5] 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.[6] 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 with 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 detailed results from the three remaining registrational trials anticipated later this year.

Endnotes and References

1. All measures except for body weight for orforglipron 12 mg vs. oral semaglutide 14 mg and percentage of participants achieving A1C <5.7% were controlled for family-wise type 1 error using the efficacy estimand and treatment-regimen estimand. Body weight for orforglipron 12 mg vs. oral semaglutide 14 mg and percentage of participants achieving A1C <5.7% were prespecified secondary endpoints and showed nominal statistical significance using the efficacy 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. The treatment-regimen estimand represents the estimated average treatment effect regardless of adherence to study intervention or initiation of additional antihyperglycemic medications.
4. Not controlled for family-wise type 1 error.
5. 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.
6. 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).

About Lilly
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diseases. With each step toward a healthier world, we're motivated by one thing: making life better for millions more people. That includes delivering innovative clinical trials that reflect the diversity of our world and working to ensure our medicines are accessible and affordable. To learn more, visit Lilly.com and Lilly.com/news, or follow us on Facebook, Instagram and LinkedIn. P-LLY

Cautionary Statement Regarding Forward-Looking Statements
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, and the timeline for regulatory submissions and actions, 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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