Lilly's oral GLP-1, orforglipron, showed compelling efficacy and a safety profile consistent with injectable GLP-1 medicines, in complete Phase 3 results published in The New England Journal of Medicine

June 21, 2025

The investigational once-daily pill lowered A1C by an average of 1.3% to 1.6% across doses, with improvements seen as early as four weeks, in adults with type 2 diabetes

In ACHIEVE-1, orforglipron also led to an average weight loss of 16.0 lbs (7.9%) at the highest dose by week 40 in a key secondary endpoint

The safety profile of orforglipron was consistent with the established GLP-1 class

INDIANAPOLIS, June 21, 2025 /PRNewswire/ -- Eli Lilly and Company (NYSE: LLY) today announced detailed results from ACHIEVE-1, a Phase 3 trial evaluating the safety and efficacy of orforglipron compared to placebo in adults with type 2 diabetes and inadequate glycemic control with diet and exercise alone. Orforglipron is the first oral small molecule (non-peptide) glucagon-like peptide-1 (GLP-1) receptor agonist, taken without food and water restrictions, to successfully complete a Phase 3 trial. At 40 weeks, all three doses (3 mg, 12 mg, 36 mg) of orforglipron achieved the primary endpoint of superior A1C reduction. In addition, the 12 mg and 36 mg doses showed clinically meaningful and statistically significant reductions in body weight vs. placebo. In the study, orforglipron had a safety profile similar to the established GLP-1 class, and the most frequently reported adverse events were gastrointestinal-related. The results were presented at the American Diabetes Association (ADA) 85th Scientific Sessions 2025 and simultaneously published in *The New England Journal of Medicine.*

In the study, orforglipron met the primary endpoint of superior A1C reduction compared to placebo at 40 weeks, lowering A1C by 1.3% to 1.6% from a baseline of 8.0%, for the efficacy estimand.[1] In key secondary endpoints, up to 76.2% of participants taking orforglipron achieved the ADA treatment target A1C of <7%, 66.0% achieved an A1C of ≤6.5%, and 25.8% achieved <5.7%, defined as a normal A1C value.[2,3] Improvements in A1C were observed as early as four weeks and were accompanied by similar reductions in fasting serum glucose. In another key secondary endpoint, participants taking the highest dose of orforglipron lost an average of 16.0 lbs (7.9%). While participants in ACHIEVE-1 did not appear to reach a weight plateau, longer-duration trials, such as the ATTAIN trials, will provide a comprehensive evaluation of the safety and efficacy of orforglipron for the treatment of obesity.

"The ACHIEVE-1 trial demonstrated that orforglipron, a novel oral small-molecule GLP-1, achieved clinically meaningful reductions in A1C and body weight over 40 weeks in adults with type 2 diabetes," said Dr. Julio Rosenstock, senior scientific advisor for Velocity Clinical Research at Medical City Dallas, clinical professor of medicine, University of Texas Southwestern Medical Center, and lead trial investigator. "The early onset of glycemic improvement, observed as soon as four weeks, reinforces the therapeutic potential of orforglipron as an effective, oral GLP-1 therapy for early type 2 diabetes treatment. These findings support further investigation in broader populations and longer-duration studies."

Full Results					
		Orforglipron 3 mg	**Orforglipron 12 mg**	**Orforglipron 36 mg**	**Placebo**
Primary Endpoint					
A1C reduction from baseline of 8.0 %[i]	Efficacy estimand	1.3 %	1.6 %	1.5 %	0.1 %
	Treatment-regimen estimand[4]	1.2 %	1.5 %	1.5 %	0.4 %
Key Secondary Endpoints[ii]					
Percent weight reduction from baseline of 90.2 kg (198.9 lbs)[i,iii]	Efficacy estimand	4.7 %	6.1 %	7.9 %	1.6 %
	Treatment-regimen estimand	4.5 %	5.8 %	7.6 %	1.7 %
Weight reduction from baseline of 90.2 kg (198.9 lbs)[i,iii]	Efficacy estimand	4.4 kg (9.7 lbs)	5.5 kg (12.2 lbs)	7.3 kg (16.0 lbs)	1.3 kg (2.9 lbs)
	Treatment-regimen estimand	4.2 kg (9.3 lbs)	5.2 kg (11.5 lbs)	7.2 kg (15.8 lbs)	1.5 kg (3.4 lbs)
Percent of participants achieving A1C <7 %[i]	Efficacy estimand	72.9 %	76.2 %	74.9 %	28.0 %
	Treatment-regimen estimand	68.1 %	72.9 %	72.7 %	33.0 %
Percent of participants achieving A1C ≤6.5 %[i,ii]	Efficacy estimand	61.5 %	62.3 %	66.0 %	13.5 %
	Treatment-regimen estimand	56.9 %	58.1 %	61.9 %	14.9 %
Percent of participants achieving A1C <5.7 %[iii]	Efficacy estimand	17.7 %	25.8 %	23.9 %	3.8 %
	Treatment-regimen estimand	16.8 %	23.9 %	21.5 %	3.8 %

Fasting serum glucose reduction from baseline of 147.5 mg/dL[i]	Efficacy estimand	30.6 mg/dL	37.4 mg/dL	37.8 mg/dL	1.1 mg/dL
	Treatment-regimen estimand	30.7 mg/dL	36.5 mg/dL	34.7 mg/dL	10.8 mg/dL

[i]Superiority test was adjusted for multiplicity.

[ii]Data from the full list of key secondary endpoints are available in the publication.

[iii]Percent of participants achieving A1C <5.7% across all orforglipron doses and body weight for orforglipron 3 mg were not controlled for Type 1 error.

"This convenient once-daily pill with no restrictions on food and water intake could be an option for millions of people with type 2 diabetes who prefer oral medications over injectables," said Jeff Emmick, M.D., Ph.D., senior vice president of product development at Lilly. "The positive ACHIEVE-1 results position orforglipron as a potential treatment option with meaningful A1C and weight reduction, and a safety profile similar to injectable GLP-1 therapies. We look forward to the four remaining global readouts from the ACHIEVE program, as well as results of the ATTAIN program in obesity, and working with regulators to bring this once-daily oral GLP-1 to people around the world."

The overall safety profile of orforglipron in ACHIEVE-1 was consistent with the established GLP-1 class. The most common adverse events for participants treated with orforglipron (3 mg, 12 mg and 36 mg, respectively) were diarrhea (19%, 21% and 26%) vs. 9% with placebo, nausea (13%, 18% and 16%) vs. 2% with placebo, dyspepsia (11%, 20% and 15%) vs. 7% with placebo, constipation (8%, 17% and 14%) vs. 4% with placebo, and vomiting (5%, 7% and 14%) vs. 1% with placebo. These gastrointestinal-related adverse events were generally mild-to-moderate in severity and occurred primarily during dose escalation. Overall treatment discontinuation rates due to adverse events were 6% (3 mg), 4% (12 mg) and 8% (36 mg) for orforglipron vs. 1% with placebo. No hepatic safety signal was observed.

Later this year, Lilly expects to share topline results from ACHIEVE-2, evaluating orforglipron compared with dapagliflozin, and ACHIEVE-3, evaluating orforglipron compared to oral semaglutide, both in adults with type 2 diabetes inadequately controlled with metformin. ATTAIN-1 and ATTAIN-2, evaluating orforglipron for weight management, will also be shared in the third quarter of this year. Lilly remains on track to submit orforglipron for weight management to global regulatory agencies by the end of this year and for the treatment of type 2 diabetes 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.[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 and hypertension in adults with obesity.

About ACHIEVE-1 and the ACHIEVE clinical trial program

ACHIEVE-1 (NCT05971940) is a Phase 3, 40-week, randomized, double-blind, placebo-controlled trial comparing the efficacy and safety of orforglipron 3 mg, 12 mg and 36 mg as monotherapy to placebo in adults with type 2 diabetes and inadequate glycemic control with diet and exercise alone. The trial randomized 559 participants across the U.S., China, India, Japan and Mexico in 1:1:1:1 ratio to receive either 3 mg, 12 mg or 36 mg orforglipron or placebo. The primary objective of the study was to demonstrate that orforglipron (3 mg, 12 mg, 36 mg) is superior in A1C reduction from baseline after 40 weeks, compared to placebo, in people with type 2 diabetes who have not taken any anti-diabetic medications for at least 90 days prior to visit 1, and are naïve to insulin therapy. Study participants had a HbA1c between ≥7.0% and ≤9.5% and a BMI of ≥23 kg/m^2. 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 to their final randomized maintenance dose of 3 mg (via a 1 mg step), 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). Flexible dosing was not permitted.

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.

About Lilly

Lilly is a medicine company turning science into healing to make life better for people around the world. We've been pioneering life-changing discoveries for nearly 150 years, and today our medicines help tens of millions of people across the globe. Harnessing the power of biotechnology, chemistry and genetic medicine, our scientists are urgently advancing new discoveries to solve some of the world's most significant health challenges: redefining diabetes care; treating obesity and curtailing its most devastating long-term effects; advancing the fight against Alzheimer's disease; providing solutions to some of the most debilitating immune system disorders; and transforming the most difficult-to-treat cancers into manageable 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

1. The efficacy estimand represents the treatment effect had on all participants who adhered to the study drug (with possible dose interruptions) for 40 weeks without initiating additional antihyperglycemic medications (>14 days of use).
2. American Diabetes Association. Standards of Care in Diabetes—2020 Abridged forPrimary Care Providers. Clinical Diabetes 2020; 38(1):10–38. https://doi.org/10.2337/cd20-as01
3. Percent of participants achieving A1C <5.7% across all doses was not controlled for Type 1 error.
4. The treatment-regimen estimand represents the estimated average treatment effect regardless of treatment discontinuation or initiation of additional antihyperglycemic medications.
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. T. Kawai, B. Sun, H. Yoshino, D. Feng, Y. Suzuki, M. Fukazawa, S. Nagao, D.B. Wainscott, A.D. Showalter, B.A. Droz, T.S. Kobilka, M.P. Coghlan, F.S. Willard, Y. Kawabe, B.K. Kobilka, & K.W. Sloop, 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).

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 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.

Trademarks and Trade Names

Refer to: Brooke Frost; brooke.frost@lilly.com; 317-432-9145 (Media)
Michael Czapar; czapar_michael_c@lilly.com; 317-617-0983 (Investors)

View original content to download multimedia:https://www.prnewswire.com/news-releases/lillys-oral-glp-1-orforglipron-showed-compelling-efficacy-and-a-safety-profile-consistent-with-injectable-glp-1-medicines-in-complete-phase-3-results-published-in-the-new-england-journal-of-medicine-302487392.html

SOURCE Eli Lilly and Company