Lilly's oral GLP-1, orforglipron, demonstrated superior glycemic control in two successful Phase 3 trials, reconfirming its potential as a foundational treatment in type 2 diabetes

In ACHIEVE-2, orforglipron lowered A1C by up to 1.7% compared to 0.8% with dapagliflozin, meeting the primary endpoint

In ACHIEVE-5, orforglipron lowered A1C by an additional 2.1% when taken with insulin glargine, meeting the primary endpoint

INDIANAPOLIS, Oct. 15, 2025 /PRNewswire/ -- Eli Lilly and Company (NYSE: LLY) today announced positive topline results from the Phase 3 ACHIEVE-2 and ACHIEVE-5 trials. ACHIEVE-2, the second head-to-head trial in the program, evaluated orforglipron versus dapagliflozin, an SGLT-2 inhibitor, in adults with type 2 diabetes inadequately controlled on metformin. Separately, ACHIEVE-5 assessed orforglipron versus placebo in adults with type 2 diabetes and inadequate glycemic control with titrated insulin glargine, with or without metformin and/or SGLT-2 inhibitors. In both trials, orforglipron (3 mg, 12 mg, 36 mg) met the primary and all key secondary endpoints at 40 weeks for both the efficacy and treatment-regimen estimands, delivering significant A1C reduction and weight loss as well as improvements in multiple cardiovascular risk factors, all consistent with previously disclosed studies in type 2 diabetes.[1,2,3]

"Orforglipron has now demonstrated superiority over two active comparators in clinical trials for type 2 diabetes," said Jeff Emmick, M.D., Ph.D., senior vice president of product development, Lilly Cardiometabolic Health. "In ACHIEVE-2, orforglipron outperformed dapagliflozin, a commonly used SGLT-2 therapy, and in ACHIEVE-3, showed greater efficacy than oral semaglutide. The findings from ACHIEVE-5 add to this momentum, showing significant A1C reduction and weight loss when used in combination with titrated basal insulin. Together, these results reinforce orforglipron's potential to become a new standard of care for people living with type 2 diabetes."

ACHIEVE-2 and ACHIEVE-5 Results

ACHIEVE-2 Primary Endpoint					
		Orforglipron 3 mg	**Orforglipron 12 mg**	**Orforglipron 36 mg**	**Dapagliflozin 10 mg**
Change in A1C from baseline of 8.1% at week 40[i]	Efficacy estimand	-1.3 %	-1.7 %	-1.7 %	-0.8 %
	Treatment-regimen estimand	-1.2 %	-1.5 %	-1.6 %	-0.8 %
ACHIEVE-5 Primary Endpoint					
		Orforglipron 3 mg	**Orforglipron 12 mg**	**Orforglipron 36 mg**	**Placebo**
Change in A1C from baseline of 8.5% at week 40 with titrated insulin glargine[i,ii]	Efficacy estimand	-1.5 %	-2.1 %	-1.9 %	-0.8 %
	Treatment-regimen estimand	-1.6 %	-1.9 %	-1.8 %	-0.8 %

[i] *All doses of orforglipron achieved statistical significance vs. the comparator, with p<0.001 under both the efficacy and treatment-regimen estimands.*

[ii] *Insulin glargine doses were adjusted per a treat-to-target algorithm with no restriction from week four to week 40.*

In both trials, the overall safety and tolerability profile of orforglipron, as well as treatment discontinuation rates, were consistent with previous studies. The most common adverse events were gastrointestinal-related and generally mild-to-moderate in severity. No hepatic safety signal was observed.

The detailed results of these trials will be presented at a future medical meeting and published in a peer-reviewed journal. Results are expected in the first quarter of 2026 for ACHIEVE-4, the final global registration trial in the ACHIEVE program. Lilly plans to submit orforglipron for the treatment of type 2 diabetes to global regulatory agencies in 2026, while submission for the treatment of obesity is on track to occur by the end of 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.[4] 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.[5] 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, hypertension and osteoarthritis pain in adults with obesity.

About ACHIEVE-2, ACHIEVE-5 and the ACHIEVE clinical trial program

ACHIEVE-2 (NCT06192108) is a Phase 3, 40-week, randomized, active-controlled, open-label study comparing the efficacy and safety of orforglipron 3 mg, 12 mg and 36 mg to dapagliflozin 10 mg in participants with type 2 diabetes and inadequate glycemic control with metformin. The study randomized 962 participants in a 1:1:1:1 ratio to receive either orforglipron 3 mg, 12 mg or 36 mg, or dapagliflozin 10 mg once daily, in addition to background metformin therapy. The objective of the study was to demonstrate that orforglipron is non-inferior in A1C reduction from baseline after 40 weeks, compared to dapagliflozin. Study participants had an A1C between ≥7.0% and ≤10.5% and a BMI of ≥23 kg/m^2. Participants randomized to orforglipron initiated treatment with 1 mg once daily and increased the dose every four weeks until reaching the randomized dose of 3 mg, 12 mg or 36 mg.

ACHIEVE-5 (NCT06109311) is a Phase 3, 40-week, randomized, double-blind, placebo-controlled study assessing the efficacy and safety of orforglipron 3 mg, 12 mg and 36 mg in participants with type 2 diabetes and inadequate glycemic control with insulin glargine, with or without metformin and/or SGLT-2 inhibitors. The study randomized 546 participants in a 1:1:1:1 ratio to receive either orforglipron 3 mg, 12 mg or 36 mg, or placebo with background therapy of titrated insulin glargine alone or in combination with metformin and/or SGLT-2 inhibitors. The objective of the study was to demonstrate that orforglipron is superior in A1C reduction from baseline after 40 weeks, compared to placebo. Study participants had an A1C between ≥7.0% and ≤10.5% and a BMI of ≥23 kg/m^2. Participants randomized to orforglipron initiated treatment with

1 mg once daily and increased the dose every four weeks until reaching the randomized dose of 3 mg, 12 mg or 36 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, and additional results are anticipated in early 2026.

Endnotes and References

1. The efficacy estimand represents efficacy had all randomized participants remained on study intervention (with possible dose interruptions) without initiating additional antihyperglycemic medications (>14 days of use).
2. The treatment-regimen estimand represents the estimated average treatment effect regardless of adherence to study intervention or initiation of additional antihyperglycemic medications.
3. Body weight for orforglipron 3 mg vs. dapagliflozin 10 mg was not a primary or key secondary endpoint in ACHIEVE-2.
4. 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.
5. 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).

About Lilly

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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 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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