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Head-to-head trial pitting Eli Lilly's oral GLP-1 against oral semaglutide underscores efficacy of weight-loss pills

A new trial found that Eli Lilly's GLP-1 pill resulted in greater reductions in blood sugar levels and weight than oral semaglutide did, but fewer people stayed on it

BY LAUREN J. YOUNG EDITED BY CLAIRE CAMERON



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A [clinical trial for diabetes](#) that pit orforglipron, a diabetes and weight-loss pill developed by Eli Lilly, against oral semaglutide, made by Novo Nordisk, suggests the former pill may have the edge in reducing blood sugar and weight.

The results, which were published in the *Lancet* on Thursday, are “very encouraging” for the safety and efficacy of orforglipron in people with type 2 diabetes, says Daniel Drucker, an endocrinologist at the University of Toronto, adding that he is awaiting further clinical trial results of the drug in people with obesity. Drucker has previously consulted for Novo Nordisk, Eli Lilly and other companies that have been developing weight-loss medications.

“More options for people with these challenging diseases will be very helpful, particularly if the new oral tablet medicines are priced reasonably,” he says.

Orforglipron is a once-a-day pill that acts on glucagonlike peptide 1 (GLP-1) receptors. The injectable GLP-1 drugs [Zepbound and Mounjaro](#) are also made by Eli Lilly.

Oral semaglutide has been on the market to treat type 2 diabetes since 2019. That version of the drug has been sold as the once-daily pill Rybelsus by Novo Nordisk, which also makes the GLP-1 drugs Ozempic and Wegovy. In December 2025 the company's [Wegovy pill](#) became the [first oral GLP-1 medication to be approved by the U.S. Food and Drug Administration to treat obesity](#). Now orforglipron is inching closer to becoming the next oral option to be approved in the U.S.

The new trial of 1,698 people compared the effects of taking 12-milligram and 36-mg doses of orforglipron with taking 7 mg and 14 mg of oral semaglutide. After 52 weeks, participants who took 36 milligrams of orforglipron saw a key blood sugar marker reduce by nearly 2 percent, while those who received 14 milligrams of oral semaglutide saw levels drop by nearly 1.5 percent.

“I’m hoping that for people with type 2 diabetes, this could really help them be less reliant on insulin,” says Rozalina McCoy, an endocrinologist and internist at the University of Maryland School of Medicine. “With insulin, there is risk of weight gain, for hypoglycemia, and there’s more treatment burden and need for glucose monitoring.”

GLP-1 drugs have also been shown to have [cardiovascular benefits](#), she adds, though further clinical trials are needed to assess orforglipron’s effects on heart health.

Orforglipron also surpassed oral semaglutide in terms of weight loss: 36-milligram doses of Eli Lilly’s drug resulted in an average of 8 percent body-weight reduction (nearly 20 pounds) compared with 5 percent weight loss (11 pounds) in participants who took 14 mg of oral semaglutide.

Importantly, this trial compared orforgliprin with oral semaglutide doses that were based on those that are currently available for Rybelsus, but the maximum effective dose offered for the recently approved Wegovy pill for obesity is 25 mg.

“We know that oral semaglutide can be taken in much higher doses as currently approved for obesity,” McCoy says. It’s hard to know if those higher doses of oral semaglutide would show different performance, she says.

A spokesperson for Eli Lilly told *Scientific American* that the trial used 7 mg and 14 mg doses of oral semaglutide because “they were the only approved doses for type 2 diabetes at the time this trial was designed and executed,” adding that the “results should be interpreted within the context of the doses studied.”

If approved by the FDA, orforglipron will be available in six doses—1 mg, 3 mg, 6 mg, 12 mg, 24 mg and 36 mg—the spokesperson said.

Orforglipron showed higher rates of adverse side effects such as nausea, vomiting and other gastrointestinal issues compared with semaglutide. More people discontinued orforglipron during the trial than those who stopped taking semaglutide, too.

“We can’t fully divorce side effects from effectiveness,” McCoy says. “It’s not that one drug is worse than the others. I think it emphasizes the importance of [matching] treatment to the right patient and making sure that we, as clinicians, really counsel patients about what to expect and how to reduce their risk of having those side effects.”

Both pills target GLP-1 receptors in the body to increase insulin secretion and satiety levels. Oral versions of these drugs need to be given in much higher doses than injectable versions to withstand digestion. At the same time, how the active protein, or peptide, in GLP-1 drugs such as oral semaglutide are absorbed through the gut can vary among people—causing differences in effectiveness and tolerability, McCoy says.

Orforglipron’s active ingredient is a nonpeptide small molecule that absorbs more readily in the gut without breaking down in the stomach.

“It’s always been the dream to have a small molecule version of a GLP-1 drug because not only can it now be taken orally, but also, small molecules are a lot

easier to produce,” McCoy says. “The hope is that when they’re easier to produce, they will be more much more affordable.”

Eli Lilly expects U.S. federal regulators to make a decision on whether to approve orforglipron for obesity as soon as this spring. The company also has plans to submit the drug for review for type 2 diabetes later this year.

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LAUREN J. YOUNG is associate editor for health and medicine at *Scientific American*. She has edited and written stories that tackle a wide range of subjects, including the COVID pandemic, emerging diseases, evolutionary biology and health inequities. Young has nearly a decade of newsroom and science journalism experience. Before joining *Scientific American* in 2023, she was an associate editor at *Popular Science* and a digital producer at public radio’s *Science Friday*. She has appeared as a guest on radio shows, podcasts and stage events. Young has also spoken on panels for the Asian American Journalists Association, American Library Association, NOVA Science Studio and the New York Botanical Garden. Her work has appeared in *Scholastic MATH*, *School Library Journal*, *IEEE Spectrum*, *Atlas Obscura* and *Smithsonian Magazine*. Young studied biology at California Polytechnic State University, San Luis Obispo, before pursuing a master’s at New York University’s Science, Health & Environmental Reporting Program.

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