New competitor to Wegovy shows promise in clinical trials

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An experimental drug appears to outperform the trendy medications

Wegovy and Ozempic for both weight loss and diabetes control, a pair of early clinical trials shows.

Retatrutide helped people with obesity drop about one-quarter of their starting weight, on average, during 48 weeks taking the drug, according to phase 2 trial results published online June 26 in the New England Journal of Medicine.

"What is clear is that 24% weight loss from a single drug has not been seen before," said co-researcher Dr. Lee Kaplan, an associate professor with Harvard Medical School. "And the subjects in the trial were still losing weight at the end."

The best comparable results come from last year's clinical trial results for the diabetes drug Mounjaro (tirzepatide), which after 72 weeks had produced an average weight loss of more than 22%, Kaplan said.

Retatrutide also helped patients establish better control over their blood sugar levels, according to a second phase 2 trial published online June 26 in The Lancet.

Retatrutide works by targeting three different gut hormones that are stimulated by food intake, explained Dr. Ania Jastreboff, director of the Yale Obesity Research Center, in New Haven, Conn. Jastreboff led the obesity trial and was a co-author for the diabetes management trial.

The hormones include one targeted by Ozempic and two targeted by Mounjaro, Jastreboff and Kaplan said.

"These are all involved in the regulation of metabolism," Kaplan said. "They're complex, they work together to coordinate the body's response to eating, the body's response to the need for sugar management, and the like. They're involved in appetite. They're involved in energy

expenditure. This is a complicated system, and the three in normal life tend to collaborate in various ways."

In the obesity trial, researchers tested retatrutide in 338 obese people, randomly assigning them to different weekly doses of the injectable drug or a placebo.

People on the highest dose of retatrutide dropped more than 17% of their body weight, on average, after 24 weeks, and progressed to an average 24% weight loss by the end of 48 weeks, the researchers found.

"That translated to an average absolute weight reduction of 58 pounds, so nearly 60 pounds in the 11 months of the study," Jastreboff said.

The drug worked even better for some. "Two-thirds lost at least 20%, nearly half lost 25% or more, and a quarter lost 30% or more," Jastreboff said.

By comparison, there was only about 2% average weight loss in the placebo group.

The diabetes trial found that retatrutide produced clinically meaningful improvements in blood sugar control, as well as robust reductions in body weight.

That trial tested retatrutide against either placebo or the diabetes drug Trulicity (dulaglutide) in 281 patients with type 2 diabetes and obesity.

The most prominent side effects in both trials were nausea, diarrhea and vomiting, the researchers found.

"In general, it was the same as what you see with other drugs in the category, the ones that activate one or two of those receptors," Kaplan

said.

The researchers were concerned that retatrutide might cause blood sugar to plummet in some, but there were no reports of severe hypoglycemia during the study.

Retatrutide will now advance to phase 3 clinical trials that will gather evidence supporting the drug's approval in the United States. Those trials will take at least a couple of years, Kaplan said.

The approach taken by retatrutide to target multiple gut hormones makes sense, said Dr. Katherine Saunders, an internal medicine specialist with Weill Cornell Medicine in New York City.

"Because diabetes and obesity aren't simple conditions, it's more effective to target several pathways at the same time," Saunders said. "So instead of one simple target, targeting two or three different receptors can lead to either additive or synergistic weight loss and diabetes control ."

It's not yet clear all the levels at which these weight-loss drugs work, but appetite and satiety are definitely two, Jastreboff and Saunders said.

Participants in the retatrutide trials "report decreased appetite or increased satiety," Jastreboff said. "For those of us who are in the field, we think this is part of how these medications are working."

The drugs also appear to alter what is referred to as the body's "defended fat mass set point," Jastreboff said.

"The brain determines how much fat or energy storage we should have, and we call that the defended fat mass set point," Jastreboff said. "These medications are treating obesity by potentially regulating, or resetting or

decreasing, that defended mass set point."

People do tend to regain weight after they stop taking these drugs. "What we think is going on is when you stop therapy, that defended fat mass set point goes back up," Jastreboff explained.

In that respect, Jastreboff compares treating obesity with the new weight-loss drugs to treating high blood pressure.

"Obesity is a chronic treatable disease and we need to treat it as we treat other chronic, treatable diseases, with therapies that target disease mechanisms. And I think these new highly effective medications do that," Jastreboff said.

"There's the question of, well, when therapy is stopped, the weight returns," she continued. "But if you think about it, if you have someone who has high blood pressure and you stop the medication, what happens? Your blood pressure goes back up."

The two clinical trials were funded by Eli Lilly and Co., the developer of retatrutide.

More information: Ania M. Jastreboff et al, Triple–Hormone-Receptor Agonist Retatrutide for Obesity—A Phase 2 Trial, *New England Journal of Medicine* (2023). DOI: 10.1056/NEJMoa2301972

Julio Rosenstock et al, Retatrutide, a GIP, GLP-1 and glucagon receptor agonist, for people with type 2 diabetes: a randomised, double-blind, placebo and active-controlled, parallel-group, phase 2 trial conducted in the USA, *The Lancet* (2023). DOI: 10.1016/S0140-6736(23)01053-X