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Clinical Trial Report

Tirzepatide for the win in the weight loss wars?

Tirzepatide, the latest weapon in the war on obesity, is more effective than semaglutide for weight loss. The difference was significant.

The SURMOUNT-5 Trial, published in the New England Journal of Medicine, was a phase 3b controlled clinical trial that pitted newcomer tirzepatide against the reigning weight-loss champion semaglutide (1).

The goal was simple - was the new dual-action therapy better than the older single-drug intervention?

So, what is tirzepatide, and why could it be more effective than semaglutide? Tirzepatide (Mounjaro®, Zepbound®), developed by Eli Lilly and Company, differs from previous weight-loss medications by targeting two gut hormone receptors. Its bioactive components mimic glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), potentially enhancing its effects on fat metabolism.

In contrast, semaglutide (Ozempic®, Wegovy®) by Novo Nordisk acts exclusively on

the GLP-1 receptor. Tirzepatide's dual mechanism allows it to pull a one-two punch on two obesity factors rather than just one. How good is it?

The details ...

Participants in the SURMOUNT-5 Trial had obesity, were female (64%), and over half had pre-diabetes (57%), but not full-blown

diabetes. Seven hundred fifty-one participants (n=751) were randomized 1:1 between the tirzepatide and semaglutide arms.

Tirzepatide treatment began at 2.5 mg/week, and the dose escalated by 2.5 mg at 4-weekly intervals to the maximum tolerated dose of 15 mg/week. Semaglutide treatment began at 0.25 mg/week, with the dose increasing by 0.25 mg every 4 weeks to the maximum tolerated dose of 2.4 mg/week.

The primary outcome of the trial was the percentage change in body weight at 72 weeks. Secondary outcomes were body weight reduction targets of 10%, 15%, 20%, and 25% and reductions in waist circumference over the same period.

The downside ...

Adherence rates were similar in both arms (85%), as were reported adverse events (76%). These were mild or moderate in severity and gastrointestinal in nature—nausea (44%), constipation (27%), or diarrhoea (15%). As with earlier GLP1-RA trials, they were more common in the days after a dose escalation. In such cases, the dosage was reduced for four weeks before the escalation continued. Ninety per cent of all participants received at least one maximum dose of the respective drug in the 72-week period.

And the winner is ...

The results were clear. Tirzepatide was the more effective therapy for both primary and secondary endpoints by a statistically significant margin. Participants in the tirzepatide arm lost an average of 20.2 % body weight and 18.4 cm in waist circumference in the 72 weeks. Semaglutide participants lost 13.7% and 13 cm, respectively.

Weight loss thresholds showed similar benefits in the tirzepatide arm. Weight loss among participants ranged from 10% of bodyweight (81.6% vs 60.5%) up to 25% of bodyweight (31.6% vs 16.1%) in the tirzepatide and semaglutide arms, respectively. Most participants started with a BMI (body mass index) of 39.4 ± 7.4 kg/m^2- those whose BMI fell to 22 kg/m^2 had their dosage reduced and were advised to increase their caloric intake to maintain weight at that level.

This was an open-label trial- participants and investigators knew which drug the participant was receiving. However, the results aligned closely with previous trials that had been blinded, suggesting that the trial design introduced negligible bias into the results.

Other key takeaways from SURMOUNT-5 include the broad ethnic and genetic diversity of the participants, primarily from the USA and Puerto Rico, suggesting that these findings will apply to other populations.

A clinical benefit of the SURMOUNT-5 trial was determining the upper limits of tolerability of both drugs and how dose-cycling can increase tolerance to the GLP1-RA therapy in general.

Obesity is a multifactorial disease and a contributory risk factor for other chronic diseases, such as diabetes and some cancers. Therefore, it is no surprise that the next generation of weight loss therapeutics might target more than one of the gut hormones that control metabolism in general and satiety in particular.

Tirzepatide might be the first dual incretin therapy to wage war on weight, but it will not be the last.

Fact Box

GLP1-RAs - in brief

Glucagon-like peptide receptor agonists (GLP1-RA) are a broad family of incretin mimetics proven safe and effective for diabetes management and weight loss. The modern GLP1-RAs have been engineered to be long-acting mimics of the human hormones GLP1 and GIP. They boost insulin, reduce glucagon, and improve blood sugar control. Furthermore, they slow gastric emptying, which may explain their effects on satiety and weight loss in humans. The current generation of GLP1-RAs need to be injected once a week, a considerable improvement from the twice-daily injections of the original GLP1-RA, exendin-4, isolated in 2005 from the saliva of a Gila Monster in the southwestern USA.

References

1. Aronne LJ, Horn DB, le Roux CW, et al. Tirzepatide as Compared with Semaglutide for the Treatment of Obesity. *N Engl J Med*. Published online May 11, 2025. doi:10.1056/NEJMoa2416394

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