Tirzepatide Weight Loss Consistent Regardless of BMI

Becky McCall

March 15, 2024

Tirzepatide (Zepbound for weight loss; Mounjaro for type 2 diabetes; Eli Lilly) consistently reduced body weight regardless of pretreatment body mass index (BMI) and reduced body weight and waist circumference regardless of duration of overweight or obesity.

The analyses — firstly of the impact of baseline BMI and secondly investigating the impact of the duration of overweight/obesity — are drawn from combined findings from the SURMOUNT 1-4 studies that examined the efficacy and safety of tirzepatide vs placebo. They are scheduled to be presented at May's European Congress on Obesity (ECO) by Carel Le Roux, MD, University College Dublin, Ireland, and Giovanna Muscogiuri, MD, endocrinologist from the University of Naples Federico II, Naples, Italy, respectively.

The first analysis of tirzepatide, a dual glucose-dependent insulinotropic polypeptide and glucagon-like peptide 1 receptor agonist, aimed to analyze the impact of baseline BMI category on weight reduction across the series of phase 3 trials.

More participants on tirzepatide than on placebo achieved the body weight reduction targets of 5%, 10%, and 15%. "Across the SURMOUNT 1-4 trials, treatment with tirzepatide, along with a reduced-calorie diet and increased physical activity, consistently resulted in clinically significant weight reductions of 5% or more, 10% or more, or 15% or more, as compared to placebo, regardless of baseline BMI subgroup, in adults with obesity or overweight (BMI of 27 and above)," said obesity specialist, Louis J. Aronne, MD, from the Comprehensive Weight Control Center, Weill Cornell Medicine, New York City, and coauthor of the BMI-related analysis.

Muscogiuri, who is first author of the second analysis that looked at the impact of duration of adiposity, and her coauthors concluded that, "Tirzepatide consistently reduced body weight and waist circumference in people living with obesity or overweight with weight-related comorbidities regardless of the duration of disease. These results are consistent with the overall findings from each study in the SURMOUNT program."

Weight Loss Consistent Regardless of BMI

The SURMOUNT series of trials involved people with a BMI of 30 kg/m^2 and above, or 27 kg/m^2 with at least one weight-related comorbidity without type 2 diabetes (SURMOUNT-1, 72 weeks), with type 2 diabetes (SURMOUNT-2, 72 weeks), and without type 2 diabetes after a 12-week intensive lifestyle intervention (SURMOUNT-3, 72 weeks from randomization) or after an 88 week intervention (SURMOUNT-4, 36-week open label tirzepatide lead-in and 52 weeks following randomization).

BMI subgroups were defined by 27-30 (overweight), 30-35 (obesity class I), 35-40 (obesity class II), and 40 kg/m^2 and above (obesity class III). Percentage change in body weight from randomization to week 72 (SURMOUNT-1, -2, and -3) or to week 52 (SURMOUNT-4) was determined, as well as the proportions of participants achieving the weight reduction targets of 5%, 10%, and 15%. The per protocol analyses included all participants who received at least one dose of tirzepatide or placebo.

Across these BMI levels, up to 100% of tirzepatide-treated participants achieved weight reduction of 5% or more compared with 30% on placebo in SURMOUNT-1, up to 93% vs 43% in SURMOUNT-2, and up to 97% vs 15%, respectively, in SURMOUNT-3.

At least 10% weight reduction was achieved by up to 93% vs 16%, respectively, in SURMOUNT-1, up to 76% vs 14% in SURMOUNT-2, and up to 92% vs 8% in SURMOUNT-3.

Weight reduction of 15% was achieved by up to 85% compared with 7% of patients on tirzepatide and placebo, respectively, in SURMOUNT-1; up to 60% vs 3%, respectively, in SURMOUNT-2; and up to 78% vs 4% in SURMOUNT-3.

In SURMOUNT-4, during the 36-week open-label tirzepatide treatment, the mean body weight % or more reduction was 21%. Following this lead-in period, further weight reductions of 5% or more, 10%, and 15% or more were achieved by up to 70%, 39%, and 22%, respectively, of participants treated with tirzepatide compared with 2%, 2%, and 0% of patients on placebo.

Body Weight and Waist Circumference Reduced Regardless of Disease Duration

In this second presentation, participants were categorized based on duration with overweight/obesity at baseline (10 years or less, between 10 and 20 years, and above 20 years). Percentage body weight change; the proportions achieving weight loss targets of 5%, 10%, 15%, 20%, and 25%; and the change in waist circumference were analyzed.

Greater weight reductions were found in participants who took tirzepatide than in those who took placebo across the SURMOUNT 1-4 study endpoints, including weight reduction targets of 5%, 10%, 15%, 20%, and 25% compared with placebo-treated participants, regardless of disease duration, reported the authors in an early press release from ECO. The magnitude of weight reductions was generally similar across the disease duration categories.

For example, in the SURMOUNT-1 trial, for patients given 10-mg dose of tirzepatide, those with disease duration under 10 years lost 21% of their weight after 72 weeks compared with 20% body weight loss for those with 10-20 years disease duration and 23% for those with over 20 years disease duration.

In the SURMOUNT-2 trial (where all participants were also living with type 2 diabetes), for patients given the 10-mg dose of tirzepatide, those with disease duration under 10 years lost 12.6% of their body weight, while those with disease duration of 10-20 years lost 12.5%; in people living with overweight or obesity for over 20 years, 14.4% of body weight was lost.

Waist circumference also reduced to a greater extent than placebo for each disease duration category across the four studies, and again, these reductions were consistent across disease duration subgroups.

A difference between patients with and without type 2 diabetes was evident and requires further analysis to explore and understand why patients with type 2 diabetes have less weight loss in these trials than those without type 2 diabetes.

Asked to comment on the findings, Jens Juul Holst, MD, from the Department of Biomedical Sciences and Novo Nordisk Foundation Center for Basic Metabolic Research, University of Copenhagen, Copenhagen, Denmark, said that the results were as expected.

"The first abstract is said to show that there is the same effect regardless of the baseline BMI, but this is the expected outcome — nothing exciting there," he told *Medscape Medical News*. "The second deals with the effects in people with different duration of adiposity. Again, it was equally effective in all groups and that was also the expected outcome, although important."

"One question is whether one should treat people with BMI < 30 at all, and that depends on preexisting comorbidities — in particular metabolic syndrome, where treatment could be lifesaving and prevent complications," added Holst.

Medscape Medical News also asked Jason Halford, ECO president, for his view on the findings. He remarked that with these weight loss drugs overall, "Usually weight loss tends to be proportional and actually greater in the lower BMI categories. This is partly because dosing is not done by body weight, and everyone gets the same doses irrespective of how they weigh. There is an argument that doses should be adjusted. The data suggests these drugs are so potent this does not occur for some reason."

Holst added that, "In principle, for a given reduction in food intake, one would expect a similar reduction in body mass, and these agents should be dosed according to the size of the individual — since energy expenditure depends linearly on body weight, this is probably a reasonable measure. But what actually happens is dosing is according to the occurrence of side effects, which is a good pragmatic principle."

Holst pointed out that the interesting question here is whether the very obese would somehow be resistant to the GLP-1 RAs (like leptin) — "they are not," he noted.

He added that to his knowledge, the question around the role played by duration of the adiposity had not been explicitly looked at before. "However, the many individuals with obesity studied after GLP-1 RA treatment have varied widely with respect to duration and weight loss has not previously been known to depend on this, but there is no known physiological mechanism underpinning this."

Tirzepatide (Mounjaro) was approved by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for the treatment of type 2 diabetes in 2022. In November 2023, the FDA approved tirzepatide (Zepbound) for chronic weight management in adults with BMI $\geq$ 30 kg/m^2 or BMI $\geq$ 27 kg/m^2 with at least one weight-related comorbidity. Also in November 2023, the EMA Committee for Medicinal Products for Human Use offered a positive opinion on extension of the Mounjaro label to include weight management in adults with BMI $\geq$ 30 kg/m^2 or BMI $\geq$ 27 kg/m^2 and at least one weight-related comorbid condition.

Holst had no conflicting interest with Eli Lilly but is a member of advisory boards for Novo Nordisk. This work (abstract 014) was funded by Eli Lilly and Company. Le Roux reported grants from the Irish Research Council, Science Foundation Ireland, Anabio, and the Health Research Board. He served on advisory boards and speaker panels of Novo Nordisk, Herbalife, GI Dynamics, Eli Lilly, Johnson & Johnson, Glia, Irish Life Health, Boehringer Ingelheim, Currax, Zealand Pharma, and Rhythm Pharma. CIR is a member of the Irish Society for Nutrition and Metabolism outside the area of work commented on here. He was the chief medical officer and director of the Medical Device Division of Keyron in 2021. Both of these are unremunerated positions. CIR was a previous investor in Keyron, which develops endoscopically implantable medical devices intended to mimic the surgical procedures of sleeve gastrectomy and gastric bypass. No patients have been included in any of Keyron's studies, and they are not listed on the stock market. CIR was gifted stock holdings in September 2021 and divested all stock holdings in Keyron in September 2021. He continues to provide scientific advice to Keyron for no remuneration. CIR provides obesity clinical care in the Beyond BMI clinic and is a shareholder in the clinic. LA reported receiving grants or personal fees from Altimmune, AstraZeneca, Boehringer Ingelheim, Eli Lilly, ERX, Gelesis, Intellihealth, Jamieson Wellness, Janssen, Novo Nordisk, Optum, Pfizer, Senda Biosciences, and Versanis and being a shareholder of Allurion, ERX Pharmaceuticals, Gelesis, Intellihealth, and Jamieson Wellness. FJ, TF, MM, LG, and LN are employees and shareholders of Eli Lilly and Company.

More from the Center of Excellence
OBESITY

Does Telemedicine in Obesity Care Reduce Weight Bias?

Medscape Diabetes | Mon Jan 08 2024

Do-It-Yourself Medications: Self-Injected Drugs on the Rise

WebMD Health News | Thu Jul 13 2023

Solving Obesity: New Drugs Can't Change How Little We Know

WebMD Health News | Wed Jul 05 2023