Lilly's Zepbound™ (tirzepatide) achieved additional 6.7% weight loss following a 36-week open-label lead-in period, for a total mean weight loss of 26.0% from study entry over 88 weeks

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People who were randomized to placebo following the lead-in period experienced mean weight regain of 14.8% at 88 weeks, indicating Zepbound led to sustained weight loss compared to placebo

Full results from the SURMOUNT-4 study were published in The Journal of the American Medical Association

INDIANAPOLIS, Dec. 11, 2023 /PRNewswire/ -- Detailed results from SURMOUNT-4, which showed Zepbound™ (tirzepatide) injection achieved superior mean percent change in body weight compared to placebo in adults with obesity or overweight with weight-related comorbidities, excluding type 2 diabetes, were published in *The Journal of the American Medical Association (JAMA)*. Zepbound met the primary endpoint of mean percent change in body weight, and all key secondary endpoints for both estimands[i,ii], compared to placebo 52 weeks after randomization.

Study Design

SURMOUNT-4, a phase 3 study evaluating the safety and efficacy of Zepbound compared to placebo, had two periods.

- Lead-in period: 36-week open-label period during which participants took Zepbound at the maximum tolerated dose.
- Double-blind treatment period: 52-week treatment period during which participants were randomized to either continue on Zepbound or switch to placebo.

SURMOUNT-4 utilized a maximum tolerated dose of 10 mg or 15 mg once-weekly. The starting dose of 2.5 mg Zepbound was increased by 2.5 mg every four weeks until maximum tolerated dose was achieved. Participants who tolerated 15 mg continued on 15 mg as their maximum tolerated dose. Participants who tolerated 10 mg but did not tolerate 15 mg continued on 10 mg as their maximum tolerated dose.

"Patients, providers and the public do not always understand obesity is a chronic disease that often requires ongoing treatment, which can mean that treatment is stopped once weight goals are met," said Jeff Emmick, MD, Ph.D., senior vice president, product development, Lilly. "However, studies like SURMOUNT-4 show that continued therapy can help people living with obesity maintain their weight loss."

Detailed Results

After 36 weeks of open-label Zepbound, participants, who would then go on to be randomized to Zepbound or placebo in the double-blind period, experienced a mean weight reduction of 20.9% from mean body weight of 236.6 lb. (107.3 kg) at study entry. Primary and key secondary endpoints assessed efficacy during the double-blind period (week 36 to week 88) and over the course of the entire treatment period (week 0 to week 88). For both estimands, Zepbound met the primary endpoint and all key secondary endpoints, including:

	Efficacy Estimand Results at 88 Weeks		**Treatment-Regimen Estimand Results at 88 Weeks**	
	Zepbound	**Placebo**	**Zepbound**	**Placebo**
Primary Endpoint				
Mean percent change in weight from week 36 (randomization) to week 88*	-6.7 %	14.8 %	-5.5 %	14.0 %
Key Secondary Endpoints				
The mean change in body weight from week 36*	-5.7 kg	11.9 kg	-4.7 kg	11.1 kg
Percentage of participants who maintained ≥80% of weight lost during the lead-in period*	93.4 %	13.5 %	89.5 %	16.6 %
The mean change in waist circumference from week 36*	-4.6 cm	8.3 cm	-4.3 cm	7.8 cm
Percentage of participants who achieved ≥20% weight reduction from week 0*	72.6 %	11.6 %	69.5 %	12.6 %
Additional Secondary and Exploratory Endpoints				
Percent change in body weight from week 0	-26.0 %	-9.5 %	-25.3 %	-9.9 %
Percentage of participants who achieved ≥25% weight reduction from week 0	56.6 %	4.0 %	54.5 %	5.0 %

**Tested for superiority, controlled for type 1 error.*

Additional secondary endpoints showed that Zepbound was also associated with improvements in BMI, fasting insulin, lipids, blood pressure, and health-related quality of life.

The overall safety profile of tirzepatide in SURMOUNT-4 was similar to previously reported SURMOUNT and SURPASS trials. The most commonly reported adverse events in SURMOUNT-4 were gastrointestinal-related and generally mild to moderate in severity. During the Zepbound lead-in treatment period, the most frequent adverse events were nausea (35.5%), diarrhea (21.1%), constipation (20.7%) and vomiting (16.3%). During the double-blind period, the most frequent adverse events for Zepbound and placebo, respectively, were diarrhea (10.7% vs 4.8%), nausea (8.1% vs 2.7%), vomiting (5.7% vs 1.2%), COVID-19 (14.0% vs 14.9%) and upper respiratory infection (2.4% vs 5.4%). Treatment discontinuation due to an adverse event occurred in 7.0% of enrolled participants during the 36-week open-label lead-in treatment period, mainly due to gastrointestinal events. After the open-label lead-in period, treatment discontinuation rates due to adverse events were 1.8% (Zepbound) and 0.9% (placebo).

About SURMOUNT-4 and the SURMOUNT clinical trial program[1]

SURMOUNT-4 (NCT04660643) was a multi-center, randomized, double-blind, parallel, placebo-controlled trial comparing the efficacy and safety of tirzepatide to placebo in adults with obesity or overweight with weight-related comorbidities, excluding type 2 diabetes. The trial had two periods in which treatment was given as an adjunct to a reduced calorie diet and increased physical activity: a 36-week open-label lead-in period in which all participants took tirzepatide, and a subsequent 52-week double-blind treatment period in which participants were randomized to either continue on tirzepatide or switch to placebo, in addition to increased physical activity and reduced-calorie diet. The trial enrolled 783 participants across the U.S., including Puerto Rico, Argentina, Brazil and Taiwan into the open-label lead-in period and 670 participants were randomized in a 1:1 ratio in the 52-week double-blind treatment period to receive tirzepatide or placebo. The primary objective of the study was to demonstrate that tirzepatide is superior in percent change in body weight from randomization at 36 weeks to 88 weeks compared to placebo.

The SURMOUNT phase 3 global clinical development program for tirzepatide in chronic weight management began in late 2019 and has enrolled more than 5,000 people with obesity or overweight across six registration studies, four of which are global studies. SURMOUNT-1 and SURMOUNT-2 were submitted to the FDA and demonstrated tirzepatide significantly reduced body weight compared with placebo in people living with obesity or overweight, with or without type 2 diabetes through 72 weeks.

Topline data for SURMOUNT-3 and SURMOUNT-4 were announced on July 27, 2023; results for SURMOUNT-3 were presented in October at ObesityWeek 2023 and simultaneously published in *Nature Medicine*.

About Zepbound ™(tirzepatide) injection[2]
Zepbound™ (tirzepatide) injection is FDA-approved as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adults with obesity (BMI ≥ 30 kg/m^2), or overweight (BMI ≥ 27 kg/m^2) with at least one weight-related comorbid condition. Zepbound is the first and only FDA-approved obesity treatment that activates both GIP (glucose-dependent insulinotropic polypeptide) and GLP-1 (glucagon-like peptide-1) hormone receptors.

INDICATION AND SAFETY SUMMARY WITH WARNINGS

Zepbound™ (ZEHP-bownd) is an injectable prescription medicine that may help adults with obesity, or with excess weight (overweight) who also have weight-related medical problems, lose weight and keep it off. It should be used with a reduced-calorie diet and increased physical activity.

- Zepbound contains tirzepatide and should not be used with other tirzepatide-containing products or any GLP-1 receptor agonist medicines. It is not known if Zepbound is safe and effective when taken with other prescription, over-the-counter, or herbal weight loss products. It is not known if Zepbound can be used in people who have had pancreatitis. It is not known if Zepbound is safe and effective for use in children under 18 years of age.

Warnings - Zepbound may cause tumors in the thyroid, including thyroid cancer. Watch for possible symptoms, such as a lump or swelling in the neck, hoarseness, trouble swallowing, or shortness of breath. If you have any of these symptoms, tell your healthcare provider.

- Do not use Zepbound if you or any of your family have ever had a type of thyroid cancer called medullary thyroid carcinoma (MTC).
- Do not use Zepbound if you have Multiple Endocrine Neoplasia syndrome type 2 (MEN 2).
- Do not use Zepbound if you have had a serious allergic reaction to tirzepatide or any of the ingredients in Zepbound.

Zepbound may cause serious side effects, including:

Severe stomach problems. Stomach problems, sometimes severe, have been reported in people who use Zepbound. Tell your healthcare provider if you have stomach problems that are severe or will not go away.

Kidney problems (kidney failure). Diarrhea, nausea, and vomiting may cause a loss of fluids (dehydration), which may cause kidney problems. It is important for you to drink fluids to help reduce your chance of dehydration.

Gallbladder problems. Gallbladder problems have happened in some people who use Zepbound. Tell your healthcare provider right away if you get symptoms of gallbladder problems, which may include pain in your upper stomach (abdomen), fever, yellowing of skin or eyes (jaundice), or clay-colored stools.

Inflammation of the pancreas (pancreatitis). Stop using Zepbound and call your healthcare provider right away if you have severe pain in your stomach area (abdomen) that will not go away, with or without vomiting. You may feel the pain from your abdomen to your back.

Serious allergic reactions. Stop using Zepbound and get medical help right away if you have any symptoms of a serious allergic reaction, including

swelling of your face, lips, tongue or throat, problems breathing or swallowing, severe rash or itching, fainting or feeling dizzy, or very rapid heartbeat.

Low blood sugar (hypoglycemia). Your risk for getting low blood sugar may be higher if you use Zepbound with medicines that can cause low blood sugar, such as a sulfonylurea or insulin. **Signs and symptoms of low blood sugar may include** dizziness or light-headedness, sweating, confusion or drowsiness, headache, blurred vision, slurred speech, shakiness, fast heartbeat, anxiety, irritability, mood changes, hunger, weakness or feeling jittery.

Changes in vision in patients with type 2 diabetes. Tell your healthcare provider if you have changes in vision during treatment with Zepbound.

Depression or thoughts of suicide. You should pay attention to changes in your mood, behaviors, feelings or thoughts. Call your healthcare provider right away if you have any mental changes that are new, worse, or worry you.

Common side effects

The most common side effects of Zepbound include nausea, diarrhea, vomiting, constipation, stomach (abdominal) pain, indigestion, injection site reactions, feeling tired, allergic reactions, belching, hair loss, and heartburn. These are not all the possible side effects of Zepbound. Talk to your healthcare provider about any side effect that bothers you or doesn't go away.

Tell your healthcare provider if you have any side effects. **You can report side effects at 1-800-FDA-1088 or** www.fda.gov/medwatch.

Before using Zepbound

- **Your healthcare provider should show you how to use Zepbound before you use it for the first time.**
- **Tell your healthcare provider if you are taking medicines to treat diabetes including insulin or sulfonylureas which could increase your risk of low blood sugar. Talk to your healthcare provider about low blood sugar levels and how to manage them.**
- **If you take birth control pills by mouth, talk to your healthcare provider before you use Zepbound. Birth control pills may not work as well while using Zepbound.** Your healthcare provider may recommend another type of birth control for 4 weeks after you start Zepbound and for 4 weeks after each increase in your dose of Zepbound.

Review these questions with your healthcare provider:

Do you have other medical conditions, including problems with your pancreas or kidneys, or severe problems with your stomach, such as slowed emptying of your stomach (gastroparesis) or problems digesting food?

Do you take diabetes medicines, such as insulin or sulfonylureas?

Do you have a history of diabetic retinopathy?

Do you take any other prescription medicines or over-the-counter drugs, vitamins, or herbal supplements?

Are you pregnant, plan to become pregnant, breastfeeding, or plan to breastfeed? Zepbound may harm your unborn baby. Tell your healthcare provider if you become pregnant while using Zepbound. It is not known if Zepbound passes into your breast milk. You should talk with your healthcare provider about the best way to feed your baby while using Zepbound.

- **Pregnancy Exposure Registry:** There will be a pregnancy exposure registry for women who have taken Zepbound during pregnancy. The purpose of this registry is to collect information about the health of you and your baby. Talk to your healthcare provider about how you can take part in this registry.

How to take

- Read the **Instructions for Use** that come with Zepbound.
- Use Zepbound exactly as your healthcare provider says.
- Zepbound is injected under the skin (subcutaneously) of your stomach (abdomen), thigh, or upper arm.
- **Use Zepbound 1 time each week, at any time of the day.**
- Change (rotate) your injection site with each weekly injection. **Do not** use the same site for each injection.
- If you take too much Zepbound, call your healthcare provider, seek medical advice promptly, or contact a Poison Center expert right away at 1-800-222-1222.

Learn more

Zepbound is a prescription medicine. For more information, go to www.zepbound.lilly.com.

This summary provides basic information about Zepbound but does not include all information known about this medicine. Read the information that comes with your prescription each time your prescription is filled. This information does not take the place of talking with your healthcare provider. Be sure to talk to your healthcare provider about Zepbound and how to take it. Your healthcare provider is the best person to help you decide if Zepbound is right for you.

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About Lilly

Lilly unites caring with discovery to create medicines that make life better for people around the world. We've been pioneering life-changing discoveries for nearly 150 years, and today our medicines help more than 51 million people across the globe. Harnessing the power of biotechnology, chemistry and genetic medicine, our scientists are urgently advancing new discoveries to solve some of the world's most significant health challenges, redefining diabetes care, treating obesity and curtailing its most devastating long-term effects, advancing the fight against Alzheimer's disease, providing solutions to some of the most debilitating immune system disorders, and transforming the most difficult-to-treat cancers into manageable diseases. With each step toward a healthier world, we're motivated by one thing: making life better for millions more people. That includes delivering innovative clinical trials that reflect the diversity of our world and working to ensure our medicines are accessible and affordable. To learn more, visit Lilly.com and Lilly.com/newsroom or follow us on Facebook, Instagram, Twitter and LinkedIn. P-LLY

[i] The efficacy estimand represents efficacy prior to discontinuation of study drug.
ii The treatment-regimen estimand represents the estimated average treatment effect regardless of treatment discontinuation.

Lilly Cautionary Statement Regarding Forward-Looking Statements
This press release contains forward-looking statements (as that term is defined in the Private Securities Litigation Reform Act of 1995) about Zepbound (tirzepatide) as a treatment for adults with obesity or overweight and reflects Lilly's current belief 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 can be no guarantee that planned or ongoing studies will be completed as planned, that future study results will be consistent with the results to date, that Zepbound will receive additional regulatory approvals, that Zepbound will be commercially successful or that we will meet anticipated timelines for its commercialization. For further discussion of these and other risks and uncertainties, see Lilly's most recent 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.

References

1. le Roux, C., Zhang, S., Aronne, L. et. al. Tirzepatide for the Treatment of Obesity: Rationale and Design of the SURMOUNT Clinical Development Program 2022 Obesity doi: 10.1002/oby.23612
2. Zepbound. Prescribing Information. Lilly USA, LLC.

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