Lilly's tirzepatide successful in phase 3 study showing benefit in adults with heart failure with preserved ejection fraction and obesity

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Tirzepatide reduced the risk of heart failure outcomes – heart failure urgent visit or hospitalization, oral diuretic intensification or cardiovascular death – by 38% compared to placebo

Tirzepatide significantly improved heart failure symptoms and physical limitations

Tirzepatide led to 15.7% weight loss in a combined population of people with and without type 2 diabetes

INDIANAPOLIS, Aug. 1, 2024 /PRNewswire/ -- Eli Lilly and Company (NYSE: LLY) announced today positive topline results from the SUMMIT phase 3 clinical trial evaluating the safety and efficacy of tirzepatide injection (5 mg, 10 mg or 15 mg) in adults with heart failure with preserved ejection fraction (HFpEF) and obesity. Tirzepatide demonstrated statistically significant improvements in both primary endpoints with a reduction in the risk of heart failure outcomes, assessed as a composite endpoint, and improvements in heart failure symptoms and physical limitations, as measured by the Kansas City Cardiomyopathy Questionnaire (KCCQ) Clinical Summary Score (CSS),[i] compared with placebo.

All key secondary endpoints were also met, including improvement in exercise capacity as measured by the 6-Minute Walk-Test Distance (6MWD), reduction in the inflammation marker high-sensitivity C-reactive protein (hsCRP), and mean body weight reduction from baseline at 52 weeks. For the efficacy estimand,[ii] tirzepatide led to a 15.7% body weight reduction compared to 2.2% for placebo. For the treatment-regimen estimand,[iii] tirzepatide led to a 13.9% body weight reduction compared to 2.2% for placebo.

"HFpEF accounts for nearly half of all heart failure cases, and in the U.S. almost 60% of those impacted also live with obesity.[1,2] Despite a continuing increase in the number of people with both HFpEF and obesity, treatment options remain limited,[1]" said Jeff Emmick, MD, PhD, senior vice president, product development, Lilly. "Previous incretin studies in this population focused on symptoms and physical limitations. In a first-of-its-kind trial, tirzepatide reduced severity of symptoms and improved heart failure outcomes in people with HFpEF and obesity."

Topline Primary Endpoint Results

Relative risk reduction of time-to-first occurrence of heart failure outcomes (median follow up of 104 weeks)		-38% Hazard Ratio=0.62 95% CI 0.41 to 0.95; P=0.026	
		Efficacy Estimand	**Treatment-Regimen Estimand**
Improvements in heart failure symptoms and physical limitations from baseline as measured by the mean change from baseline of KCCQ-CSS	**Tirzepatide MTD**	24.8 points	19.5 points
	Placebo	15.0 points	12.7 points

HFpEF is a condition in which the heart's left pumping chamber becomes stiff and unable to fill properly. It is associated with a high burden of symptoms and physical limitations affecting daily life, including fatigue, shortness of breath, reduced ability to exercise and swelling of extremities.

The overall safety profile of tirzepatide in the SUMMIT trial was consistent with previously reported tirzepatide studies, including SURMOUNT and SURPASS. The most frequently reported adverse events in SUMMIT were primarily gastrointestinal in nature and generally mild to moderate in severity. The most common adverse events for patients treated with tirzepatide were diarrhea, nausea, constipation and vomiting.

Lilly will continue to evaluate the SUMMIT results, which will be presented at an upcoming medical meeting and submitted to a peer-reviewed journal. Lilly plans to submit the SUMMIT study results to the U.S. Food and Drug Administration (FDA) and other regulatory agencies starting later this year.

About SUMMIT

SUMMIT (NCT04847557) was a multi-center, randomized, double-blind, parallel, placebo-controlled phase 3 study comparing the efficacy and safety of tirzepatide to placebo in adults living with heart failure with preserved ejection fraction (HFpEF) and obesity, with or without type 2 diabetes. The trial randomized 731 participants across the U.S., Argentina, Brazil, China, India, Israel, Mexico, Puerto Rico, Russia and Taiwan in a 1:1 ratio to receive tirzepatide maximum tolerated dose (MTD) 5 mg, 10 mg or 15 mg or placebo. The two primary objectives were to reduce the risk of the composite endpoint of time-to-first occurrence of urgent heart failure visit, heart failure hospitalization, oral diuretic intensification and cardiovascular death to study completion (median follow up of 104 weeks), and change in the Kansas City Cardiomyopathy Questionnaire Clinical Summary Score (KCCQ-CSS) from baseline to week 52.

SUMMIT utilized MTD of 5 mg, 10 mg or 15 mg once weekly. The starting dose of 2.5 mg tirzepatide was increased by 2.5 mg every four weeks until MTD was achieved. Participants who tolerated 15 mg continued on 15 mg as their MTD. Participants who tolerated 10 mg but did not tolerate 15 mg continued on 10 mg as their MTD, and participants who tolerated 5 mg but did not tolerate 10 mg continued on 5 mg as their MTD.

About tirzepatide

Tirzepatide is a once-weekly GIP (glucose-dependent insulinotropic polypeptide) receptor and GLP-1 (glucagon-like peptide-1) receptor agonist. Tirzepatide is a single molecule that activates the body's receptors for GIP and GLP-1, which are natural incretin hormones. Both GIP and GLP-1 receptors are found in areas of the human brain important for appetite regulation. Tirzepatide has been shown to decrease food intake and modulate fat utilization. Studies of tirzepatide in chronic kidney disease (CKD) and in morbidity/mortality in obesity (MMO) are also ongoing. Lilly submitted data for tirzepatide in moderate-to-severe obstructive sleep apnea (OSA) and obesity to the U.S. Food and Drug Administration (FDA) and other global regulatory agencies earlier this year.

Tirzepatide was approved by the FDA as Mounjaro® for adults with type 2 diabetes to improve glycemic control on May 13, 2022, and as Zepbound® for adults with obesity (a BMI of 30 kg/m^2 or greater) or those who are overweight (a BMI of 27 kg/m^2 or greater) who also have a weight-related comorbid condition on November 8, 2023. Both Mounjaro and Zepbound should be used as an adjunct to diet and exercise.

INDICATION AND SAFETY SUMMARY WITH WARNINGS

Mounjaro® (mown-JAHR-OH) is an injectable medicine for adults with type 2 diabetes used along with diet and exercise to improve blood sugar (glucose).

- It is not known if Mounjaro can be used in people who have had inflammation of the pancreas (pancreatitis). Mounjaro is not for use in people with type 1 diabetes. It is not known if Mounjaro is safe and effective for use in children under 18 years of age.

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

Mounjaro may cause serious side effects, including:

Inflammation of the pancreas (pancreatitis). Stop using Mounjaro 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.

Low blood sugar (hypoglycemia). Your risk for getting low blood sugar may be higher if you use Mounjaro with another medicine 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, or mood changes, hunger, weakness and feeling jittery.

Serious allergic reactions. Stop using Mounjaro 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, and very rapid heartbeat.

Kidney problems (kidney failure). In people who have kidney problems, diarrhea, nausea, and vomiting may cause a loss of fluids (dehydration), which may cause kidney problems to get worse. It is important for you to drink fluids to help reduce your chance of dehydration.

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

Changes in vision. Tell your healthcare provider if you have changes in vision during treatment with Mounjaro.

Gallbladder problems. Gallbladder problems have happened in some people who use Mounjaro. 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), and clay-colored stools.

Common side effects

The most common side effects of Mounjaro include nausea, diarrhea, decreased appetite, vomiting, constipation, indigestion, and stomach (abdominal) pain. These are not all the possible side effects of Mounjaro. 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 Mounjaro

- **Your healthcare provider should show you how to use Mounjaro before you use it for the first time.**
- **Talk to your healthcare provider about low blood sugar and how to manage it.**
- **If you take birth control pills by mouth, talk to your healthcare provider before you use Mounjaro. Birth control pills may not work as well while using Mounjaro.** Your healthcare provider may recommend another type of birth control for 4 weeks after you start Mounjaro and for 4 weeks after each increase in your dose of Mounjaro.

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 other diabetes medicines, such as insulin or sulfonylureas?
❑ Do you have a history of diabetic retinopathy?
❑ Are you pregnant, plan to become pregnant, breastfeeding, or plan to breastfeed? It is not known if Mounjaro will harm your unborn baby or pass into your breast milk.
❑ Do you take any other prescription medicines or over-the-counter drugs, vitamins, or herbal supplements?

How to take

- Read the **Instructions for Use** that come with Mounjaro.
- Use Mounjaro exactly as your healthcare provider says.
- Mounjaro is injected under the skin (subcutaneously) of your stomach (abdomen), thigh, or upper arm.
- **Use Mounjaro 1 time each week, at any time of the day.**
- **Do not** mix insulin and Mounjaro together in the same injection.
- You may give an injection of Mounjaro and insulin in the same body area (such as your stomach area), but not right next to each other.
    - Change (rotate) your injection site with each weekly injection. **Do not** use the same site for each injection.
- If you take too much Mounjaro, call your healthcare provider or seek medical advice promptly.

Learn more

Mounjaro is a prescription medicine. For more information, call 1-833-807-MJRO (833-807-6576) or go to **www.mounjaro.com.**

This summary provides basic information about Mounjaro 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 Mounjaro and how to take it. Your healthcare provider is the best person to help you decide if Mounjaro is right for you.

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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, or you may contact Lilly at 1-800-LillyRx (1-800-545-5979).

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, call 1-800-LillyRx (1-800-545-5979) or 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 is a medicine company turning science into healing to 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/news, or follow us on Facebook, Instagram and LinkedIn. P-LLY

[i] The Kansas City Cardiomyopathy Questionnaire Clinical Summary Score (KCCQ-CSS) is a patient-reported outcome instrument that uses a 1-100 point scale to assess heart failure symptoms and physical limitations. Higher KCCQ-CSS values indicate better symptom management and reduced physical limitations in people with heart failure.

[ii] The efficacy estimand represents efficacy prior to discontinuation of study drug.

[iii] The treatment-regimen estimand represents the estimated average treatment effect regardless of treatment discontinuation.

References

1. Borlaug BA, Jensen MD, Kitzman DW, Lam CSP, Obokata M, Rider OJ. Obesity and heart failure with preserved ejection fraction: new insights and pathophysiological targets. Cardiovasc Res. 2023;118(18):3434-3450. doi:10.1093/cvr/cvac120
2. Allen LA, Tang F, Jones P, Breeding T, Ponirakis A, Turner SJ. Signs, symptoms, and treatment patterns across serial ambulatory cardiology visits in patients with heart failure: insights from the NCDR PINNACLE® registry. BMC Cardiovasc Disord. 2018 May 3;18(1):80. doi: 10.1186/s12872-018-0808-2. PMID: 29724164; PMCID: PMC5934811.

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 tirzepatide as a potential treatment for people with heart failure with preserved ejection fraction (HFpEF) and obesity and the timeline for future readouts, presentations, and other milestones relating to tirzepatide and its clinical trials, and reflects Lilly's current beliefs 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 is no guarantee that planned or ongoing studies will be completed as planned, that future study results will be consistent with study results to date, that tirzepatide will prove to be a safe and effective treatment for HFpEF and obesity, that tirzepatide will receive additional regulatory approvals, or that Lilly will execute its strategy as expected. For further discussion of these and other risks and uncertainties that could cause actual results to differ from Lilly's expectations, see Lilly's 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.

Refer to: Kristiane Silva Bello: bello_kristiane@lilly.com, 317-315-9052 (Media)
Joe Fletcher: jfletcher@lilly.com, 317-296-2884 (Investors)

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