Lilly's tirzepatide was superior to placebo for MASH resolution, and more than half of patients achieved improvement in fibrosis at 52 weeks

June 8, 2024

SYNERGY-NASH results were presented at the European Association for the Study of the Liver Congress 2024 and simultaneously published in The New England Journal of Medicine

INDIANAPOLIS, June 8, 2024 /PRNewswire/ -- Eli Lilly and Company (NYSE: LLY) announced detailed results from SYNERGY-NASH, a phase 2 study of 190 patients, with or without type 2 diabetes, to evaluate the investigational use of tirzepatide in adults with biopsy-proven metabolic dysfunction-associated steatohepatitis (MASH) with stage 2 or 3 fibrosis. The efficacy estimand[i] showed 51.8%, 62.8% and 73.3% of participants taking 5 mg, 10 mg and 15 mg, respectively, achieved an absence of MASH with no worsening of fibrosis on liver histology compared to 13.2% of participants on placebo at 52 weeks of treatment, meeting the study's primary endpoint. The data were presented at the European Association for the Study of the Liver (EASL) Congress 2024 and simultaneously published in *The New England Journal of Medicine (NEJM)*.

In a secondary endpoint, the efficacy estimand showed 59.1%, 53.3% and 54.2% of participants taking 5 mg, 10 mg and 15 mg, respectively, achieved a 1-stage or greater fibrosis improvement without worsening of MASH compared to 32.8% of participants on placebo. Evaluation of additional secondary endpoints showed tirzepatide was associated with improvements in body weight, blood markers of liver injury, and biomarkers of liver fat, inflammation and fibrosis. While the phase 2 study was not designed to prove that tirzepatide improves fibrosis, the study results showed the potential for a clinically meaningful treatment effect across all doses.

"MASH is the second most common contributor to liver transplantation in the U.S., highlighting the need for novel therapies[1]," said Rohit Loomba, MD, MHSc, chief of the division of gastroenterology and hepatology at University of California San Diego School of Medicine. "The study is significant, given the urgent need for treatment options that are capable of slowing the progression of the disease and potentially reducing serious health complications."

Results of the treatment-regimen estimand[ii] analysis (below) were consistent with those observed with the efficacy estimand:

	Tirzepatide 5 mg	Tirzepatide 10 mg	Tirzepatide 15 mg	Placebo
Primary Endpoint				
MASH resolution without worsening of fibrosis (defined as no increase in fibrosis stage) at week 52	43.6 % (p<0.001)	55.5 % (p<0.001)	62.4 % (p<0.001)	9.8 %
Secondary Endpoint				
>1 stage decrease in fibrosis stage without worsening of MASH (defined as no increase in the NAS score[iii])*	54.9 % (p=0.016)	51.3 % (p=0.039)	51.0 % (p=0.043)	29.7 %

*p values for the secondary endpoint are nominal and not adjusted for multiple comparisons.

The overall safety profile of tirzepatide in SYNERGY-NASH was similar to that observed in the previously reported SURMOUNT and SURPASS trials. The most commonly reported adverse events in SYNERGY-NASH were gastrointestinal-related (nausea, diarrhea, decreased appetite, constipation and weight loss) and generally mild to moderate in severity.

"Lilly is very pleased with the degree of MASH resolution observed in the SYNERGY-NASH study, and we are encouraged by the improvement of fibrosis observed," said Jeff Emmick, MD, PhD, senior vice president, product development, Lilly. "MASH is expected to impact more than 19 million adults in the U.S. by 2039[2] and based on the study results, we believe tirzepatide may have the potential to help people living with this disease."

Lilly is engaged with regulatory authorities on the next steps for tirzepatide for the treatment of MASH.

About SYNERGY-NASH

SYNERGY-NASH was a multicenter, double-blind, randomized, placebo-controlled phase 2 study evaluating the efficacy and safety of tirzepatide at various doses in adults with biopsy-confirmed metabolic dysfunction-associated steatohepatitis (MASH), previously referred to as nonalcoholic steatohepatitis (NASH), with stage 2 or 3 fibrosis. The trial randomized 190 participants to receive tirzepatide 5 mg, 10 mg, 15 mg or placebo, administered subcutaneously once weekly for 52 weeks. The primary endpoint was MASH resolution without worsening of fibrosis at 52 weeks. Secondary endpoints included fibrosis improvement without worsening of MASH.

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. Tirzepatide is being studied as a potential treatment for people with obesity and/or overweight with heart failure with preserved ejection fraction (HFpEF), obstructive sleep apnea (OSA) and metabolic dysfunction-associated steatohepatitis (MASH). Studies of tirzepatide in chronic kidney disease (CKD) and in morbidity/mortality in obesity (MMO) are also ongoing.

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

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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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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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 efficacy estimand represents efficacy prior to study treatment discontinuation.

[ii] The treatment-regimen estimand represents the efficacy for randomized participants regardless of treatment discontinuation.

[iii] The NAFLD Activity Score (NAS) is a histological score that assesses the severity of disease activity for metabolic dysfunction-associated steatotic liver disease (MASLD), formerly called non-alcoholic fatty liver disease (NAFLD).

References

1. Paklar N, Mijic M, Filipec-Kanizaj T. The Outcomes of Liver Transplantation in Severe Metabolic Dysfunction-Associated Steatotic Liver Disease Patients. Biomedicines. 2023;11(11):3096. doi:10.3390/biomedicines11113096
2. Younossi Z, Paik J, Henry L, Yang J, Fernades G, Stepanova M, Nader F. The Growing Economic and Clinical Burden of Nonalcoholic Steatohepatitis (NASH) in the United States. Journal of Clinical and Experimental Hepatology, 2022;13,3(454 – 467). Doi:10.1016/j.jceh.2022.12.005

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 metabolic dysfunction-associated steatohepatitis (MASH) 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 receive regulatory approval and prove to be a safe and effective treatment for MASH, 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.

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