New analyses of Mounjaro™ (tirzepatide) injection for the treatment of adults with type 2 diabetes presented at the American Diabetes Association's® 82nd Scientific Sessions®

June 6, 2022

Mounjaro led to significantly greater fat mass reductions compared to placebo and to injectable semaglutide 1 mg in adults with type 2 diabetes in mechanism of action study

Exploratory analysis showed that Mounjaro achieved A1C and weight targets in less time than injectable semaglutide 1 mg or titrated insulin degludec

INDIANAPOLIS, June 6, 2022 /PRNewswire/ -- New data from a mechanism of action study and new analyses of the global registration program for Eli Lilly and Company's (NYSE: LLY) Mounjaro™ (tirzepatide) injection were presented at the American Diabetes Association's® (ADA) 82nd Scientific Sessions®, adding to the robust body of data about Mounjaro for the treatment of adults with type 2 diabetes. More than 20 presentations on Mounjaro were accepted for disclosure at the ADA's Scientific Sessions.

"Lilly is proud to present new mechanism of action data and new analyses of the results that Mounjaro delivered throughout the SURPASS program at the ADA's Scientific Sessions, helping us further evaluate how Mounjaro can help adults living with type 2 diabetes manage key aspects of their disease," said Laura Fernández Landó, MD, associate vice president, Medical, Lilly Diabetes. "Exploring factors such as how quickly Mounjaro can help lower A1C and weight, or the relationship between those two measures throughout the SURPASS program, is important as we begin to bring Mounjaro to people living with type 2 diabetes."

Mounjaro Mechanism of Action Study
Additional results of a phase 1 mechanism of action study were presented in an oral presentation on Monday, June 6 during the "Incretin Based Therapies" session. This study was a 28-week, randomized, double-blind, parallel study to evaluate the effect of Mounjaro 15 mg compared to placebo and to injectable semaglutide 1 mg. The primary endpoint, previously disclosed, compared the effect of Mounjaro 15 mg versus placebo on total clamp disposition index at 28 weeks. The secondary objectives presented today at ADA compared the effects of Mounjaro 15 mg to placebo and to injectable semaglutide 1 mg on energy intake, appetite and body composition in adults with type 2 diabetes as measured by change from baseline.

At 28 weeks, participants taking Mounjaro (N=45) had significantly greater reductions in weight and in fat mass compared to those taking injectable semaglutide 1 mg (N=44) and placebo (N=28):

- Weight reduction: 11.2 kg (24.7 lb., Mounjaro 15 mg), 6.9 kg (15.2 lb., injectable semaglutide 1 mg) and 0 kg (placebo), p<0.001
- Fat mass reduction: 9.7 kg (21.4 lb., Mounjaro 15 mg) and 5.9 kg (13.0 lb., injectable semaglutide 1 mg), p=0.002

Further, treatment with Mounjaro 15 mg and injectable semaglutide 1 mg resulted in significant reductions from baseline in energy intake (-348.4 kcal and -284.1 kcal, respectively, p=0.187) as well as reductions in appetite ratings.

Relationship Between Body Weight Change and Glycemic Control with Mounjaro
Results from this post-hoc analysis of all five studies within the SURPASS global registration program were presented in a poster session. This analysis assessed the relationship between A1C and body weight reductions with Mounjaro treatment (5 mg, 10 mg or 15 mg) across the SURPASS-1 through -5 clinical trials. Results showed that between 87% and 97% of participants taking Mounjaro experienced both A1C and weight reductions.

Time to Reach Glycemic and Weight Targets with Tirzepatide Compared to Injectable Semaglutide 1 mg and Titrated Insulin Degludec
Results from this exploratory analysis of SURPASS-2 and SURPASS-3 were shared in a poster session, evaluating the median time taken to achieve certain glycemic targets (i.e., median time to A1C <7% and ≤6.5%) and the median time taken to achieve at least 5% weight loss. The analysis compared the time to reach the A1C targets from baseline among participants treated with Mounjaro (5 mg, 10 mg and 15 mg) versus those treated with injectable semaglutide 1 mg (SURPASS-2) or those treated with titrated insulin degludec (SURPASS-3), and the time to reach the weight target among participants treated with Mounjaro or injectable semaglutide 1 mg. Participants taking all three doses of Mounjaro reached these A1C targets about four weeks sooner than those taking injectable semaglutide 1 mg, and between four weeks and 12 weeks sooner than those taking titrated insulin degludec.

Specifically, results showed:

- Median time to achieve A1C <7%: 8 weeks (Mounjaro), 12 weeks (injectable semaglutide 1 mg), 12 weeks (titrated insulin degludec)
- Median time to achieve A1C ≤6.5%: 12 weeks (Mounjaro), 16 weeks (injectable semaglutide 1 mg), 24 weeks (titrated insulin degludec)
- Median time to achieve ≥5% weight reduction: 12 weeks (Mounjaro 10 mg and 15 mg), 16 weeks (Mounjaro 5 mg), 24 weeks (injectable semaglutide 1 mg)

About Mounjaro™ (tirzepatide) injection
Mounjaro™ (tirzepatide) injection is FDA-approved as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. As the first and only FDA-approved GIP and GLP-1 receptor agonist, Mounjaro is a single molecule that activates the body's receptors for

GIP (glucose-dependent insulinotropic polypeptide) and GLP-1 (glucagon-like peptide-1). Mounjaro is available in six doses (2.5 mg, 5 mg, 7.5 mg, 10 mg, 12.5 mg, 15 mg) and comes in Lilly's well-established auto-injector pen with a pre-attached, hidden needle that patients do not need to handle or see.

Limitations of Use:

- Has not been studied in patients with a history of pancreatitis
- Is not indicated for use in patients with type 1 diabetes mellitus

Important Safety Information for Mounjaro™ (tirzepatide)

WARNING: RISK OF THYROID C-CELL TUMORS

In both male and female rats, tirzepatide causes dose-dependent and treatment-duration-dependent thyroid C-cell tumors at clinically relevant exposures. It is unknown whether Mounjaro causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans as human relevance of tirzepatide-induced rodent thyroid C-cell tumors has not been determined.

Mounjaro is contraindicated in patients with a personal or family history of MTC or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). Counsel patients regarding the potential risk for MTC with the use of Mounjaro and inform them of symptoms of thyroid tumors (e.g., a mass in the neck, dysphagia, dyspnea, persistent hoarseness). Routine monitoring of serum calcitonin or using thyroid ultrasound is of uncertain value for early detection of MTC in patients treated with Mounjaro.

Mounjaro is contraindicated in patients with a personal or family history of MTC or in patients with MEN 2, and in patients with known serious hypersensitivity to tirzepatide or any of the excipients in Mounjaro.

Risk of Thyroid C-cell Tumors: Counsel patients regarding the potential risk for MTC with the use of Mounjaro and inform them of symptoms of thyroid tumors (e.g., a mass in the neck, dysphagia, dyspnea, persistent hoarseness). Routine monitoring of serum calcitonin or using thyroid ultrasound is of uncertain value for early detection of MTC in patients treated with Mounjaro. Such monitoring may increase the risk of unnecessary procedures, due to the low test specificity for serum calcitonin and a high background incidence of thyroid disease. Significantly elevated serum calcitonin values may indicate MTC and patients with MTC usually have calcitonin values >50 ng/L. If serum calcitonin is measured and found to be elevated, the patient should be further evaluated. Patients with thyroid nodules noted on physical examination or neck imaging should also be further evaluated.

Pancreatitis: Acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis, has been observed in patients treated with GLP-1 receptor agonists. Pancreatitis has been reported in Mounjaro clinical trials. Mounjaro has not been studied in patients with a prior history of pancreatitis. It is unknown if patients with a history of pancreatitis are at higher risk for development of pancreatitis on Mounjaro. Observe patients for signs and symptoms, including persistent severe abdominal pain sometimes radiating to the back, which may or may not be accompanied by vomiting. If pancreatitis is suspected, discontinue Mounjaro and initiate appropriate management.

Hypoglycemia with Concomitant Use of Insulin Secretagogues or Insulin: Concomitant use with an insulin secretagogue (e.g., sulfonylurea) or insulin may increase the risk of hypoglycemia, including severe hypoglycemia. The risk of hypoglycemia may be lowered by reducing the dose of sulfonylurea (or other concomitantly administered insulin secretagogue) or insulin. Inform patients using these concomitant medications of the risk of hypoglycemia and educate them on the signs and symptoms of hypoglycemia.

Hypersensitivity Reactions: Hypersensitivity reactions, sometimes severe, have been reported with Mounjaro in clinical trials. If hypersensitivity reactions occur, discontinue use of Mounjaro; treat promptly per standard of care, and monitor until signs and symptoms resolve. Do not use in patients with a previous serious hypersensitivity to Mounjaro. Use caution in patients with a history of angioedema or anaphylaxis with a GLP-1 receptor agonist because it is unknown if such patients will be predisposed to these reactions with Mounjaro.

Acute Kidney Injury: Mounjaro has been associated with gastrointestinal adverse reactions, which include nausea, vomiting, and diarrhea. These events may lead to dehydration, which if severe could cause acute kidney injury. In patients treated with GLP-1 receptor agonists, there have been postmarketing reports of acute kidney injury and worsening of chronic renal failure, sometimes requiring hemodialysis. Some of these events have been reported in patients without known underlying renal disease. A majority of reported events occurred in patients who had experienced nausea, vomiting, diarrhea, or dehydration. Monitor renal function when initiating or escalating doses of Mounjaro in patients with renal impairment reporting severe adverse gastrointestinal reactions.

Severe Gastrointestinal Disease: Use of Mounjaro has been associated with gastrointestinal adverse reactions, sometimes severe. Mounjaro has not been studied in patients with severe gastrointestinal disease, including severe gastroparesis, and is therefore not recommended in these patients.

Diabetic Retinopathy Complications in Patients with a History of Diabetic Retinopathy: Rapid improvement in glucose control has been associated with a temporary worsening of diabetic retinopathy. Mounjaro has not been studied in patients with non-proliferative diabetic retinopathy requiring acute therapy, proliferative diabetic retinopathy, or diabetic macular edema. Patients with a history of diabetic retinopathy should be monitored for progression of diabetic retinopathy.

Acute Gallbladder Disease: In clinical trials, acute gallbladder disease was reported by 0.6% of Mounjaro-treated patients and 0% of placebo-treated patients. If cholelithiasis is suspected, gallbladder diagnostic studies and appropriate clinical follow-up are indicated.

The most common adverse reactions reported in ≥5% of Mounjaro-treated patients in placebo-controlled trials were nausea, diarrhea, decreased appetite, vomiting, constipation, dyspepsia, and abdominal pain.

Drug Interactions: When initiating Mounjaro, consider reducing the dose of concomitantly administered insulin secretagogues (such as sulfonylureas) or insulin to reduce the risk of hypoglycemia. Mounjaro delays gastric emptying, and thereby has the potential to impact the absorption of concomitantly administered oral medications, so caution should be exercised.

Pregnancy: Limited data on Mounjaro use in pregnant women are available to inform on drug-associated risk for major birth defects, miscarriage, or

other adverse maternal or fetal outcomes. Based on animal reproduction studies, there may be risks to the fetus from exposure to tirzepatide. Use only if potential benefit justifies the potential risk to the fetus.

Lactation: There are no data on the presence of tirzepatide in human milk, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Mounjaro and any potential adverse effects on the breastfed infant from Mounjaro or from the underlying maternal condition.

Females of Reproductive Potential: Advise females using oral hormonal contraceptives to switch to a non-oral contraceptive method, or add a barrier method of contraception for 4 weeks after initiation and for 4 weeks after each dose escalation.

Pediatric Use: Safety and effectiveness of Mounjaro have not been established and use is not recommended in patients less than 18 years of age.

Please click to access Prescribing Information**, including Boxed Warning about possible thyroid tumors, including thyroid cancer, and** Medication Guide**.**
Please see Instructions for Use **included with the pen.**

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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 47 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

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 Mounjaro™ (tirzepatide) injection for the treatment of adults with type 2 diabetes 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 findings to date, that Mounjaro will receive additional regulatory approvals, or that Mounjaro will be commercially successful. 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.

[1] Pedersen, SD, et al. Relationship between body weight change and glycemic control with tirzepatide treatment in people with type 2 diabetes. Abstract 729-P. Presented at the American Diabetes Association's® (ADA) 82nd Scientific Sessions®; June 3–7, 2022.
[2] Pantalone, K, et al. Patients with Type 2 Diabetes Reach Glycemic Targets Faster with Tirzepatide Compared to Semaglutide and Titrated Insulin Degludec. Abstract 732-P. Presented at the American Diabetes Association's® (ADA) 82nd Scientific Sessions®; June 3–7, 2022.
[3] Heise, T, et al. Tirzepatide reduces appetite, energy intake and fat mass in people with T2D. Abstract 338-OR. Presented at the American Diabetes Association's® (ADA) 82nd Scientific Sessions®; June 3–7, 2022.
[4] Mounjaro™ (tirzepatide) injection Prescribing InformationEli Lilly & Company; May 2022.

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