Lilly's SURMOUNT-1 results published in The New England Journal of Medicine show tirzepatide achieved between 16.0% and 22.5% weight loss in adults with obesity or overweight

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Detailed results from Lilly's first phase 3 trial in obesity or overweight presented at the American Diabetes Association's® 82nd Scientific Sessions® and simultaneously published in NEJM

INDIANAPOLIS, June 4, 2022 /PRNewswire/ -- Detailed results from Eli Lilly and Company's (NYSE: LLY) phase 3 SURMOUNT-1 clinical trial evaluating tirzepatide for the treatment of obesity or overweight were simultaneously published today in *The New England Journal of Medicine* (NEJM) and presented in a symposium sponsored by the American Diabetes Association® (ADA) during the ADA's 82nd Scientific Sessions®. Tirzepatide met both co-primary endpoints of superior mean percent change in body weight from baseline and greater percentage of participants achieving body weight reductions of at least 5% compared to placebo for both estimands[i].

For the efficacy estimand[ii], participants taking tirzepatide achieved average weight reductions of 16.0% (35 lb. or 16 kg on 5 mg), 21.4% (49 lb. or 22 kg on 10 mg) and 22.5% (52 lb. or 24 kg on 15 mg), compared to placebo (2.4%, 5 lb. or 2 kg). Additionally, 89% (5 mg) and 96% (10 mg and 15 mg) of people taking tirzepatide achieved at least 5% body weight reductions compared to 28% of those taking placebo.

All three doses of tirzepatide achieved all key secondary endpoints at 72 weeks of treatment for the efficacy estimand, including:

- Percentage of participants achieving at least 10% body weight reductions: 73% (5 mg, not controlled for type 1 error), 86% (10 mg) and 90% (15 mg) compared to 14% with placebo.
- Percentage of participants achieving at least 15% body weight reductions: 50% (5 mg, not controlled for type 1 error), 74% (10 mg) and 78% (15 mg) compared to 6.0% with placebo.
- Percentage of participants achieving at least 20% body weight reductions: 32% (5 mg, not controlled for type 1 error), 55% (10 mg) and 63% (15 mg) compared to 1.3% with placebo.
- Change in waist circumference from baseline: -14.6 cm (5 mg, not controlled for type 1 error), -19.4 cm (10 mg) and -19.9 cm (15 mg) compared to -3.4 cm with placebo.

All three doses of tirzepatide achieved an additional secondary endpoint at 72 weeks of treatment, measuring the percentage of participants achieving at least 25% body weight reductions (not controlled for type 1 error): 16.5% (5 mg), 35% (10 mg) and 39.7% (15 mg) compared to 0.3% with placebo.

Participants taking tirzepatide also achieved an approximately three times greater percent reduction in fat mass versus lean mass (33.9% fat mass reduction compared to a 10.9% lean mass reduction).

"Obesity is a chronic, treatable disease, and individuals living with obesity deserve effective and safe treatment options that can help restore their weight to levels that support optimal health," said Ania Jastreboff, MD, Ph.D., Associate Professor of Medicine & Pediatrics, Endocrinology & Metabolism, at Yale School of Medicine; Director, Weight Management & Obesity Prevention at the Yale Stress Center; and co-Director of the Yale Center for Weight Management. "In SURMOUNT-1, participants taking tirzepatide on average lost up to one fifth of their body weight – and notably, about nine out of ten participants taking tirzepatide lost weight. These results are significantly higher than the placebo arm and underscore the importance of this study."

Tirzepatide also met the co-primary and all key secondary endpoints for the treatment-regimen estimand[iii], including:

- Average body weight reductions: 15.0% (5 mg), 19.5% (10 mg) and 20.9% (15 mg) compared to 3.1% with placebo.
- Percentage of participants achieving body weight reductions of ≥5%: 85% (5 mg), 89% (10 mg) and 91% (15 mg) compared to 35% with placebo.
- Percentage of participants achieving ≥10% body weight reductions: 69% (5 mg, not controlled for type 1 error), 78% (10 mg) and 84% (15 mg) compared to 19% with placebo.
- Percentage of participants achieving ≥15% body weight reductions: 48% (5 mg, not controlled for type 1 error), 67% (10 mg) and 71% (15 mg) compared to 9% with placebo.
- Percentage of participants achieving body weight reductions of ≥20%: 30% (5 mg, not controlled for type 1 error), 50% (10 mg), and 57% (15 mg) compared to 3.1% with placebo.
- Change in waist circumference from baseline: -14.0 cm (5 mg, not controlled for type 1 error), -17.7 cm (10 mg) and -18.5 cm (15 mg) compared to -4.0 cm with placebo.
- Percentage of participants taking tirzepatide achieving ≥25% body weight reductions (not controlled for type 1 error): 15.3% (5 mg), 32.3% (10 mg) and 36.2% (15 mg) compared to 1.5% with placebo.

"Lilly is proud to share the detailed results from SURMOUNT-1, which reinforce our confidence in the potential of tirzepatide as a treatment for obesity, as participants lost between an average of 35 and 52 pounds throughout the trial," said Mike Mason, president, Lilly Diabetes. "Lilly aims to transform

how diseases like obesity are understood and treated, and today's simultaneous publication and presentation of these results mark an important milestone in our mission."

The overall safety and tolerability profile of tirzepatide was similar to other incretin-based therapies approved for the treatment of obesity. The most commonly reported adverse events were gastrointestinal-related and generally mild to moderate in severity, usually occurring during the dose escalation period. For those treated with tirzepatide (5 mg, 10 mg and 15 mg, respectively), nausea (24.6%, 33.3%, 31.0%), diarrhea (18.7%, 21.2%, 23.0%), constipation (16.8%, 17.1%, 11.7%), and vomiting (8.3%, 10.7%, 12.2%) were more frequently experienced compared to placebo (9.5% [nausea], 7.3% [diarrhea], 5.8% [constipation], 1.7% [vomiting]).

Treatment discontinuation rates due to adverse events were 4.3% (5 mg), 7.1% (10 mg), 6.2% (15 mg) and 2.6% (placebo). The overall treatment discontinuation rates were 14.3% (5 mg), 16.4% (10 mg), 15.1% (15 mg) and 26.4% (placebo). The overall trial completion rates were 89% (5 mg), 88% (10 mg), 90% (15 mg) and 77% (placebo).

About SURMOUNT-1 and the SURMOUNT clinical trial program
SURMOUNT-1 (NCT04184622) is a multi-center, randomized, double-blind, parallel, placebo-controlled trial comparing the efficacy and safety of tirzepatide 5 mg, 10 mg and 15 mg to placebo as an adjunct to a reduced-calorie diet and increased physical activity in adults without type 2 diabetes who have obesity, or overweight with at least one of the following comorbidities: hypertension, dyslipidemia, obstructive sleep apnea or cardiovascular disease. The trial randomized 2,539 participants across the U.S., Argentina, Brazil, China, India, Japan, Mexico, Russia and Taiwan in a 1:1:1:1 ratio to receive either tirzepatide 5 mg, 10 mg or 15 mg or placebo. The co-primary objectives of the study were to demonstrate that tirzepatide 10 mg and/or 15 mg is superior in percentage of body weight reductions from baseline and percentage of participants achieving ≥5% body weight reduction at 72 weeks compared to placebo. Participants who had pre-diabetes at study commencement will remain enrolled in SURMOUNT-1 for an additional 104 weeks of treatment following the initial 72-week completion date to evaluate the impact on body weight and potential differences in progression to type 2 diabetes at three years of treatment with tirzepatide compared to placebo.

All participants in the tirzepatide treatment arms started the study at a dose of tirzepatide 2.5 mg once-weekly and then increased the dose in a step-wise approach at four-week intervals to their final randomized maintenance dose of 5 mg (via a 2.5 mg step), 10 mg (via steps at 2.5 mg, 5 mg and 7.5 mg) or 15 mg (via steps at 2.5 mg, 5 mg, 7.5 mg, 10 mg and 12.5 mg).

The SURMOUNT phase 3 global clinical development program for tirzepatide began in late 2019 and has enrolled more than 5,000 people with obesity or overweight across six clinical trials, four of which are global studies. Results from SURMOUNT-2, -3, and -4 are anticipated in 2023.

Ania Jastreboff, MD, PhD conducts multi-center trials with Eli Lilly, Novo Nordisk, and Rhythm Pharmaceuticals; serves on scientific advisory boards for Eli Lilly, Intellihealth, Novo Nordisk, Pfizer, Rhythm Pharmaceuticals, and WW (formerly WeightWatchers); and consults for Boehringer Ingelheim and Scholar Rock.

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 novel molecule that activates the body's receptors for GIP and GLP-1, which are natural incretin hormones. GIP is a hormone that may complement the effects of GLP-1 receptor agonists. In preclinical models, GIP has been shown to decrease food intake and increase energy expenditure therefore resulting in weight reductions, and when combined with GLP-1 receptor agonism, may result in greater effects on markers of metabolic dysregulation such as body weight, glucose and lipids. Tirzepatide is in phase 3 development for adults with obesity or overweight with weight-related comorbidity and is under regulatory review in Europe, Japan and several additional countries for the treatment of type 2 diabetes. It is also being studied as a potential treatment for non-alcoholic steatohepatitis (NASH) and heart failure with preserved ejection fraction (HFpEF). Studies of tirzepatide in obstructive sleep apnea (OSA), in chronic kidney disease and in morbidity/mortality in obesity are planned as well.

Tirzepatide was approved as Mounjaro™ (tirzepatide) by the FDA on May 13, 2022. MOUNJARO™ is a glucose-dependent insulinotropic polypeptide (GIP) receptor and glucagon-like peptide-1 (GLP-1) receptor agonist indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

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

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

Mounjaro™ (tirzepatide) injection for the treatment of adults with type 2 diabetes, tirzepatide as a potential treatment for adults with obesity or overweight and the timeline for future readouts, presentations and other milestones relating to tirzepatide and its clinical trials, and reflects Lilly's current belief and expectations. However, as with any pharmaceutical product, there are substantial risks and uncertainties in the process of 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 tirzepatide will receive additional regulatory approvals, or that Mounjaro will be commercially successful. 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.

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[i] Treatment differences for two estimands – efficacy and treatment-regimen – were evaluated for three tirzepatide doses (5 mg, 10 mg and 15 mg) compared to placebo.

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

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

Refer to:
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