Lilly's SURPASS-1 results published in The Lancet show tirzepatide's superior A1C and body weight reductions versus placebo in adults with type 2 diabetes

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Data presented at ADA's 81st Scientific Sessions® show the highest dose of tirzepatide (15 mg) reduced A1C by 2.07 percent and weight by 9.5 kg (20.9 lb., 11.0 percent)

Majority of study population was treatment-naïve; lowest dose of tirzepatide (5 mg) led to A1C and body weight reductions of 1.87 percent and 7.0 kg (15.4 lb., 7.9 percent)

INDIANAPOLIS, June 26, 2021 /PRNewswire/ -- Tirzepatide led to superior A1C and body weight reductions from baseline across all three doses in adults with type 2 diabetes after 40 weeks of treatment in Eli Lilly and Company's (NYSE: LLY) SURPASS-1 monotherapy clinical trial evaluating the efficacy and safety of tirzepatide compared to placebo. Detailed SURPASS-1 results were presented today in an oral presentation during the American Diabetes Association's® (ADA) 81st Scientific Sessions®, were simultaneously published in *The Lancet* and will be featured during an ADA-sponsored symposium on Tuesday, June 29.

Study participants in SURPASS-1, 54.2 percent of whom were treatment-naïve, had a relatively short mean duration of diabetes of 4.7 years, a baseline A1C of 7.9 percent and a baseline weight of 85.9 kg. For the efficacy estimand[i], tirzepatide reduced A1C by up to 2.07 percent and body weight by up to 9.5 kg (20.9 lb., 11.0 percent) compared to placebo (+0.04 A1C change and body weight change of -0.7 kg [1.5 lb., 0.9 percent]). Up to 52 percent of participants achieved an A1C less than 5.7 percent – the level seen in people without diabetes. Tirzepatide also led to improvements in the change in fasting serum glucose from baseline. In an additional secondary endpoint, tirzepatide led to improvements in the change in two-hour post-meal glucose values from baseline from self-monitored blood glucose data.[1,2]

The overall safety profile of tirzepatide was similar to the well-established glucagon-like peptide-1 (GLP-1) receptor agonist class, with gastrointestinal side effects being the most commonly reported adverse events. Treatment discontinuation rates due to adverse events were less than 7 percent in each tirzepatide treatment arm.[1]

"Type 2 diabetes is a progressive disease, and many people with the condition have trouble reaching their A1C goals through diet and exercise. This monotherapy clinical trial was designed to assess the impact of tirzepatide alone on several important diabetes treatment targets, including glycemic control and weight loss," said Julio Rosenstock, M.D., Director of the Dallas Diabetes Research Center at Medical City and Principal Investigator of SURPASS-1. "In the SURPASS-1 results, tirzepatide led to significant improvements across all primary and key secondary endpoints with clinically meaningful A1C reductions and robust weight loss among study participants, who had a relatively short duration of type 2 diabetes."

Tirzepatide is a novel investigational once-weekly dual glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 receptor agonist that integrates the actions of the GIP and GLP-1 incretins into a single molecule, representing a new class of medicines being studied for the treatment of type 2 diabetes.

For both estimands[ii], all three tirzepatide doses reached statistical significance in A1C and body weight reductions from baseline and in the percentage of participants who achieved an A1C of less than 7 percent (the American Diabetes Association's recommended target for people with diabetes) or less than 5.7 percent.[1]

At 40 weeks, tirzepatide led to a significant decrease in fasting serum glucose (FSG) compared to placebo. In an additional secondary endpoint, the mean two-hour post-meal glucose values for tirzepatide across all three doses were under 140 mg/dL (considered normal values in individuals without diabetes).[2]

Specifically, the efficacy estimand results showed:

- A1C change: -1.87% (5 mg), -1.89% (10 mg), -2.07% (15 mg), +0.04% (placebo)
- Weight reduction: -7.0 kg (-7.9%, 5 mg), -7.8 kg (-9.3%, 10 mg), -9.5 kg (-11.0%, 15 mg), -0.7 kg (-0.9%, placebo)
- Percent of participants achieving A1C <7%: 87% (5 mg), 92% (10 mg), 88% (15 mg), 20% (placebo)
- Percent of participants achieving A1C <5.7%: 34% (5 mg), 31% (10 mg), 52% (15 mg), 1% (placebo)
- Change in FSG: -43.6 mg/dL (5 mg), -45.9 mg/dL (10 mg), -49.3 mg/dL (15 mg), +12.9 mg/dL (placebo)

The treatment-regimen estimand[iii] results showed:

- A1C reduction: -1.75% (5 mg), -1.71% (10 mg), -1.69% (15 mg), -0.09% (placebo)
- Weight reduction: -6.3 kg (5 mg), -7.0 kg (10 mg), -7.8 kg (15 mg), -1.0 kg (placebo)
- Percent of participants achieving A1C <7%: 82% (5 mg), 85% (10 mg), 78% (15 mg), 23% (placebo)
- Percent of participants achieving A1C <5.7%: 31% (5 mg), 27% (10 mg), 38% (15 mg), 1% (placebo)
- Change in FSG: -39.6 mg/dL (5 mg), -39.8 mg/dL (10 mg), -38.6 mg/dL (15 mg), +3.7 mg/dL (placebo)

No events of severe hypoglycemia or hypoglycemia less than 54 mg/dL were observed in the tirzepatide treatment arms.[1,2]

In an additional exploratory endpoint, all three doses of tirzepatide led to favorable changes from baseline in fasting lipids. Specifically, at the highest dose of tirzepatide (15 mg): total cholesterol was reduced by 8.4 percent, triglycerides were reduced by 21.0 percent, low-density lipoprotein (LDL) cholesterol was reduced by 12.4 percent, very low-density lipoprotein (VLDL) cholesterol was reduced by 19.8 percent, and high-density lipoprotein (HDL) cholesterol was increased by 7.5 percent.[2]

The most commonly reported adverse events for tirzepatide were gastrointestinal-related and mostly mild to moderate in severity, usually occurring during the dose escalation period. For study participants treated with tirzepatide (5 mg, 10 mg and 15 mg, respectively), nausea (11.6 percent, 13.2 percent, 18.2 percent, respectively), diarrhea (11.6 percent, 14.0 percent, 11.6 percent, respectively), vomiting (3.3 percent, 2.5 percent, 5.8 percent, respectively) and constipation (5.8 percent, 5.0 percent, 6.6 percent, respectively) were more frequently experienced compared to placebo (6.1 percent [nausea], 7.8 percent [diarrhea], 1.7 percent [vomiting], 0.9 percent [constipation]). The overall treatment discontinuation rates were 9.1 percent (tirzepatide 5 mg), 9.9 percent (tirzepatide 10 mg) and 21.5 percent (tirzepatide 15 mg), compared to 14.8 percent (placebo). The majority of the discontinuations in the 15 mg and placebo arms were due to reasons other than adverse events (such as concerns due to the coronavirus pandemic and family or work reasons).[2]

SURPASS-1 is the first of five global registration studies for tirzepatide in type 2 diabetes, all of which have been completed. Lilly intends to submit the full registration package to regulatory authorities by the end of 2021.

About tirzepatide
Tirzepatide is a once-weekly dual glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) receptor agonist that integrates the actions of both incretins into a single novel molecule. GIP is a hormone that may complement the effects of GLP-1. In preclinical models, GIP has been shown to decrease food intake and increase energy expenditure therefore resulting in weight reductions, and when combined with a GLP-1 receptor agonist, may result in greater effects on glucose and body weight. Tirzepatide is in phase 3 development for blood glucose management in adults with type 2 diabetes and for chronic weight management. It is also being studied as a potential treatment for non-alcoholic steatohepatitis (NASH) and heart failure with preserved ejection fraction (HFpEF).

About SURPASS-1 and the SURPASS clinical trial program
SURPASS-1 (NCT03954834) is a 40-week, multi-center, randomized, double-blind, parallel, placebo-controlled trial comparing the efficacy and safety of tirzepatide 5 mg, 10 mg and 15 mg as monotherapy to placebo in adults with type 2 diabetes inadequately controlled with diet and exercise alone. The trial randomized 478 study participants across the U.S., Mexico, India and Japan in 1:1:1:1 ratio to receive either tirzepatide 5 mg, 10 mg or 15 mg or placebo. The objective of the study was to demonstrate that tirzepatide (5 mg, 10 mg or 15 mg) is superior in A1C reduction from baseline after 40 weeks in people with type 2 diabetes naïve to injectable therapy who haven't used any oral antidiabetic medicines within three months compared to placebo. Study participants had a mean A1C between 7 percent and 9.5 percent and a BMI greater than or equal to 23 kg/m^2. 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 SURPASS phase 3 global clinical development program for tirzepatide has enrolled more than 19,000 people with type 2 diabetes across 10 clinical trials, five of which are global registration studies. The program began in late 2018, and all five global registration trials have been completed.

About Diabetes
Approximately 34 million Americans[3] (just over 1 in 10) and an estimated 463 million adults worldwide[4] have diabetes. Type 2 diabetes is the most common type internationally, accounting for an estimated 90 to 95 percent of all diabetes cases in the United States alone[3]. Diabetes is a chronic disease that occurs when the body does not properly produce or use the hormone insulin.

About Lilly Diabetes
Lilly has been a global leader in diabetes care since 1923, when we introduced the world's first commercial insulin. Today we are building upon this heritage by working to meet the diverse needs of people with diabetes and those who care for them. Through research, collaboration and quality manufacturing we strive to make life better for people affected by diabetes and related conditions. We work to deliver breakthrough outcomes through innovative solutions—from medicines and technologies to support programs and more. For the latest updates, visithttp://www.lillydiabetes.com/ or follow us on Twitter: @LillyDiabetes and Facebook: LillyDiabetesUS.

About Eli Lilly and Company
Lilly is a global healthcare leader that unites caring with discovery to make life better for people around the world. We were founded more than a century ago by a man committed to creating high-quality medicines that meet real needs, and today we remain true to that mission in all our work. Across the globe, Lilly employees work to discover and bring life-changing medicines to those who need them, improve the understanding and management of disease, and give back to communities through philanthropy and volunteerism. To learn more about Lilly, please visit us at lilly.com and lilly.com/newsroom. 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 tirzepatide as a potential treatment for people with type 2 diabetes 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 the studies will be completed as planned, that future study results will be consistent with the results to date or that tirzepatide will receive regulatory approvals. 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.

[1] Rosenstock, J, et. al. Efficacy and Safety of Once Weekly Tirzepatide, a Dual GIP/GLP-1 Receptor Agonist Versus Placebo as Monotherapy in People with Type 2 Diabetes (SURPASS-1). Abstract 100-OR. Presented virtually at the American Diabetes Association's 81st Scientific Sessions; June 25-29.
[2] Rosenstock, J, et. al. (2021). Efficacy and Safety of Once Weekly Dual GIP/GLP-1 Receptor agonist Tirzepatide Versus Placebo in People with Type

2 Diabetes Inadequately Controlled with Diet and Exercise (SURPASS-1): A Double-blind, Randomised Controlled Trial. *The Lancet*, https://doi.org/10.1016/S0140-6736(21)01324-6.

[3] Centers for Disease Control and Prevention. National Diabetes Statistics Report, 2020. Atlanta, GA: Centers for Disease Control and Prevention, U.S. Dept. of Health and Human Services; 2020.

[4] International Diabetes Federation. IDF Diabetes Atlas, 9th edn. Brussels, Belgium: International Diabetes Federation, 2019. Available at: http://diabetesatlas.org.

[i] Efficacy estimand represents efficacy prior to discontinuation of study drug or initiating rescue therapy for persistent severe hyperglycemia.

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

[iii] Treatment-regimen estimand represents the efficacy irrespective of adherence to the investigational medicine or introduction of rescue therapy for persistent severe hyperglycemia.

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