Tirzepatide significantly reduced A1C and body weight in people with type 2 diabetes in two phase 3 trials from Lilly's SURPASS program

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In the 52-week SURPASS-3 study - the longest in the program to date - the highest dose of tirzepatide reduced A1C by 2.37 percent and body weight by 12.9 kg (28.4 lb., 13.9 percent)

INDIANAPOLIS, Feb. 17, 2021 /PRNewswire/ -- Tirzepatide led to significant A1C and body weight reductions from baseline in adults with type 2 diabetes in Eli Lilly and Company's (NYSE: LLY) SURPASS-3 and SURPASS-5 phase 3 clinical trials after 52 weeks and 40 weeks, respectively. In topline results, the primary and all key secondary endpoints were met for both estimands[i] in SURPASS-3, which compared tirzepatide to titrated insulin degludec, and in SURPASS-5, which compared tirzepatide to placebo, both as an add-on to titrated insulin glargine.

Using the efficacy estimand[ii], the highest dose of tirzepatide (15 mg) reduced A1C by 2.37 percent and body weight by 12.9 kg (13.9 percent) in SURPASS-3, and reduced A1C by 2.59 percent and body weight by 10.9 kg (11.6 percent) in SURPASS-5. At the highest dose, 62.4 percent of SURPASS-5 participants – who had a mean duration of diabetes of 13.3 years – achieved an A1C of less than 5.7 percent, the level seen in people without diabetes. In both studies, the overall safety profile of tirzepatide was similar to that of the well-established glucagon-like peptide-1 (GLP-1) receptor agonist class, with gastrointestinal side effects being the most commonly reported adverse events and decreasing with continued dosing.

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

"Tirzepatide delivered impressive A1C and body weight reductions in both studies and continued to achieve consistent efficacy and safety results in people living with type 2 diabetes, regardless of how long they have had the condition," said Mike Mason, president, Lilly Diabetes. "Significantly lowering A1C levels and weight are high priorities throughout the type 2 diabetes treatment journey, and the results we have seen from three SURPASS studies to date fuel our belief in tirzepatide's ability to meet those needs."

SURPASS-3

SURPASS-3 was a 52-week randomized, open-label trial comparing the efficacy and safety of three doses of tirzepatide (5 mg, 10 mg and 15 mg) to titrated insulin degludec in adults with type 2 diabetes who have inadequate glycemic control on stable doses of metformin with or without an SGLT-2 inhibitor. Study participants were insulin-naïve and had a mean duration of diabetes of 8.4 years, a baseline A1C of 8.17 percent and a baseline weight of 94.3 kg.

The study met its primary and key secondary endpoints across both the efficacy and treatment-regimen[iii] estimands. All three tirzepatide doses (5 mg, 10 mg and 15 mg) led to superior A1C and body weight reductions compared to titrated insulin degludec (mean dose at 52 weeks was 48.8 units per day[iv]). Across the three doses, up to 92.6 percent of participants on tirzepatide achieved an A1C of less than 7 percent (the American Diabetes Association's recommended target for people with diabetes). Further, in an additional secondary endpoint, up to 48.4 percent of participants treated with tirzepatide achieved an A1C of less than 5.7 percent.

SURPASS-3 Efficacy Estimand Results				
	Tirzepatide 5 mg	**Tirzepatide 10 mg**	**Tirzepatide 15 mg**	**Insulin Degludec[iv]**
A1C reduction from baseline of 8.17%	-1.93%*	-2.20%*	-2.37%*	-1.34%
Weight change from baseline of 94.3 kg	-7.5 kg* (-8.1%)	-10.7 kg* (-11.4%)	-12.9 kg* (-13.9%)	+2.3 kg (+2.7%)
Percent of participants achieving A1C <7%	82.4%*	89.7%*	92.6%*	61.3%
Percent of participants achieving A1C <5.7%†	25.8%†	38.6%†	48.4%†	5.4%

**Denotes statistical significance compared to insulin degludec*

†Not controlled for type I error

In the treatment-regimen estimand, each of the tirzepatide doses led to statistically significant A1C and body weight reductions versus titrated insulin degludec:

- A1C reduction: -1.85% (5 mg), -2.01% (10 mg), -2.14% (15 mg), -1.25% (insulin degludec)
- Weight change: -7.0 kg (5 mg), -9.6 kg (10 mg), -11.3 kg (15 mg), +1.9 kg (insulin degludec)
- Percent of participants achieving A1C <7%: 79.2% (5 mg), 81.5% (10 mg), 83.5% (15 mg), 58.0% (insulin degludec)

Hypoglycemia less than 54 mg/dL (level two) was reported in 1.4 percent (5 mg), 1.1 percent (10 mg) and 2.2 percent (15 mg) of participants in the tirzepatide arms and in 7.3 percent of participants in the insulin degludec arm.

The most commonly reported adverse events in the tirzepatide arms were gastrointestinal-related and generally mild to moderate in severity, usually occurring during the dose escalation period and decreasing with continued dosing. For study participants treated with tirzepatide (5 mg, 10 mg and 15 mg, respectively), nausea (11.5 percent, 22.5 percent, 23.7 percent), diarrhea (15.4 percent, 16.7 percent, 15.6 percent) and vomiting (5.9 percent, 9.4 percent, 10.0 percent) were more frequently experienced compared to titrated insulin degludec (1.7 percent [nausea], 3.9 percent [diarrhea], 1.1 percent [vomiting]). Treatment discontinuation rates due to adverse events were 7.2 percent (tirzepatide 5 mg), 9.7 percent (tirzepatide 10 mg) and 10.9 percent (tirzepatide 15 mg), compared to 1.4 percent (insulin degludec).

"For people with type 2 diabetes who are at the point in their treatment journey where they would progress to an injectable therapy, these positive results emphasize tirzepatide's potential to deliver a meaningful impact in lowering their A1C and weight," said Bernhard Ludvik, M.D., Associate Professor of Medicine, Landstrasse Clinic, Vienna, and Principal Investigator of SURPASS-3. "Throughout the year-long study, tirzepatide provided sustained A1C reduction and progressive weight loss with low occurrence of level two hypoglycemia, an important consideration for people with diabetes and their clinicians."

SURPASS-5

SURPASS-5 was a 40-week randomized, double-blind trial comparing the efficacy and safety of three doses of tirzepatide (5 mg, 10 mg and 15 mg) compared to placebo, both as an add-on to titrated insulin glargine with or without metformin in adults with type 2 diabetes. Study participants had a mean duration of diabetes of 13.3 years, a baseline A1C of 8.31 percent, a baseline weight of 95.2 kg and a baseline insulin glargine dose of 37.6 units per day[v].

The study met its primary and key secondary endpoints across both the efficacy and treatment-regimen estimands. All three doses of tirzepatide demonstrated superior A1C reductions and weight reductions from baseline compared to placebo. Across the three doses, up to 97.4 percent of participants on tirzepatide achieved an A1C of less than 7 percent. Further, 62.4 percent of participants treated with the highest dose of tirzepatide achieved an A1C of less than 5.7 percent. The mean insulin glargine dose at 40 weeks was lower in all of the tirzepatide arms than in placebo and was 37.6 units per day (5 mg), 35.7 units per day (10 mg), 29.4 units per day (15 mg) and 58.8 units per day (placebo).

SURPASS-5 Efficacy Estimand Results				
	Tirzepatide 5 mg	**Tirzepatide 10 mg**	**Tirzepatide 15 mg**	**Placebo**
A1C reduction from baseline of 8.31%	-2.23%*	-2.59%*	-2.59%*	-0.93%
Weight change from baseline of 95.2 kg	-6.2 kg* (-6.6%)	-8.2 kg* (-8.9%)	-10.9 kg* (-11.6%)	+1.7 kg (+1.7%)
Percent of participants achieving A1C <7%	93.0%*	97.4%*	94.0%*	33.9%
Percent of participants achieving A1C <5.7%	26.1%†	47.8%*	62.4%*	2.5%

**Denotes statistical significance compared to placebo*
†Not controlled for type I error

In the treatment-regimen estimand, each of the tirzepatide doses led to statistically significant A1C and body weight reductions versus placebo:

- A1C reduction: -2.11% (5 mg), -2.40% (10 mg), -2.34% (15 mg), -0.86% (placebo)
- Weight reduction: -5.4 kg (5 mg), -7.5 kg (10 mg), -8.8 kg (15 mg), +1.6 kg (placebo)
- Percent of participants achieving A1C <7%: 87.3% (5 mg), 89.6% (10 mg), 84.7% (15 mg), 34.5% (placebo)

Hypoglycemia less than 54 mg/dL was reported in 15.5 percent (5 mg), 19.3 percent (10 mg) and 14.2 percent (15 mg) of participants in the tirzepatide arms and in 12.5 percent of participants in the placebo arm.

The most commonly reported adverse events in the tirzepatide arms were gastrointestinal-related and generally mild to moderate in severity, usually occurring during the dose escalation period and decreasing with continued dosing. For study participants treated with tirzepatide (5 mg, 10 mg and 15 mg, respectively), nausea (12.9 percent, 17.6 percent, 18.3 percent), diarrhea (12.1 percent, 12.6 percent, 20.8 percent), vomiting (6.9 percent, 7.6 percent, 12.5 percent) and constipation (6.0 percent, 6.7 percent, 6.7 percent) were more frequently experienced compared to placebo (2.5 percent [nausea], 10.0 percent [diarrhea], 2.5 percent [vomiting], 1.7 percent [constipation]). Treatment discontinuation rates due to adverse events were 6.0 percent (tirzepatide 5 mg), 8.4 percent (tirzepatide 10 mg) and 10.8 percent (tirzepatide 15 mg), compared to 2.5 percent (placebo).

The complete SURPASS-3 and SURPASS-5 data have not yet been evaluated but will be presented at the American Diabetes Association's® 81st Scientific Sessions® and published in a peer-reviewed publication in 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 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 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).

About SURPASS-3, SURPASS-5 and the SURPASS Clinical Trial Program

SURPASS-3 (NCT03882970) is a 52-week, multi-center, randomized, open-label trial evaluating the efficacy of tirzepatide 5 mg, 10 mg and 15 mg compared to titrated insulin degludec on glycemic control in adults with type 2 diabetes treated with metformin with or without an SGLT-2 inhibitor. The trial randomized 1,444 participants in a 1:1:1:1 ratio to receive either tirzepatide 5 mg, 10 mg or 15 mg or titrated insulin degludec. The primary endpoint was to evaluate A1C reduction from baseline after 52 weeks for two doses (10 mg and 15 mg). Study participants had an A1C between 7 percent and 10.5 percent and a BMI greater than or equal to 25 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). All participants in the titrated insulin degludec treatment arm started with a baseline dose of 10 units per day and followed a treat-to-target algorithm to reach a fasting blood glucose below 90 mg/dL.

SURPASS-5 (NCT04039503) is a 40-week, multi-center, randomized, double-blind trial evaluating the efficacy and safety of tirzepatide compared to placebo in adults with inadequately controlled type 2 diabetes already being treated with insulin glargine, with or without metformin. The trial randomized 475 participants in a 1:1:1:1 ratio to receive either tirzepatide 5 mg, 10 mg or 15 mg or placebo in addition to insulin glargine with or without metformin. The primary endpoint was to evaluate A1C reduction from baseline after 40 weeks. Study participants had an A1C between 7.0 percent and 10.5 percent and a BMI greater than or equal to 23 kg/m^2. Insulin glargine was titrated in all arms following a treat-to-target algorithm with the goal of fasting blood glucose below 100 mg/dL.

The SURPASS phase 3 global clinical development program for tirzepatide has enrolled more than 13,000 people with type 2 diabetes across 10 clinical trials, five of which are global registration studies. The program began in late 2018 with full results from the registration studies anticipated in 2021.

About Diabetes

Approximately 34 million Americans[1] (just over 1 in 10) and an estimated 463 million adults worldwide[2] 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[1]. 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] 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.

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

[i] Treatment differences for two estimands – efficacy and treatment-regimen – were evaluated for three tirzepatide doses (5 mg, 10 mg and 15 mg) versus the respective comparators for SURPASS-3 and SURPASS-5.

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

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

[iv] The mean starting dose of insulin degludec was 10 units per day. The insulin dose was titrated following a treat-to-target algorithm with the goal of fasting blood glucose below 90 mg/dL.

[v] Insulin glargine was titrated in all arms following a treat-to-target algorithm with the goal of fasting blood glucose below 100 mg/dL.

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in-people-with-type-2-diabetes-in-two-phase-3-trials-from-lillys-surpass-program-301229506.html

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