Tirzepatide results published in The Lancet show superior A1C and body weight reductions compared to insulin glargine in adults with type 2 diabetes with increased cardiovascular risk

October 19, 2021

Newly published data show that participants maintained A1C and weight control up to two years in SURPASS-4, the largest and longest SURPASS trial completed to date

No increased cardiovascular risk identified with tirzepatide; hazard ratio of 0.74 observed for MACE-4 events

INDIANAPOLIS, Oct. 19, 2021 /PRNewswire/ -- Adults with type 2 diabetes with increased cardiovascular (CV) risk experienced superior A1C and body weight reductions from baseline across all three doses of tirzepatide compared to titrated insulin glargine in detailed results from Eli Lilly and Company's (NYSE: LLY) SURPASS-4 clinical trial, which were published today in *The Lancet*. At 52 weeks, the highest dose of tirzepatide led to an A1C reduction of 2.58 percent and reduced body weight by 11.7 kg (-25.8 lb., -13.0 percent) compared to results for those treated with insulin glargine (A1C reduction of 1.44 percent and weight gain of 1.9 kg [+4.2 lb., +2.2 percent]) for the efficacy estimand.[i,1]

SURPASS-4 is the largest and longest clinical trial completed to date of the phase 3 program studying tirzepatide as a potential treatment for type 2 diabetes. The primary endpoint was measured at 52 weeks, with participants continuing treatment up to 104 weeks or until study completion. The completion of the study was triggered by the accrual of major adverse cardiovascular events (MACE) to assess CV risk. In newly published data from the treatment period after 52 weeks, participants taking tirzepatide maintained A1C and weight control for up to two years.

The overall safety profile of tirzepatide, assessed over the full study period, was consistent with the safety results measured at 52 weeks, with no new findings up to 104 weeks. Gastrointestinal side effects were the most commonly reported adverse events, usually occurring during the escalation period and then decreasing over time.

"We are encouraged by the continued A1C and weight control that participants experienced past the initial 52 week treatment period and up to two years as we continue to explore the potential impact of tirzepatide for the treatment of type 2 diabetes," said John Doupis, M.D., Ph.D., Director, Diabetes Division and Clinical Research Center, Iatriko Paleou Falirou Medical Center, Athens, Greece and Senior Investigator for SURPASS-4.

Tirzepatide is a novel investigational 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 molecule, representing a new class of medicines being studied for the treatment of type 2 diabetes.

SURPASS-4 was an open-label global trial comparing the safety and efficacy of three tirzepatide doses (5 mg, 10 mg and 15 mg) to titrated insulin glargine in 2,002 adults with type 2 diabetes with increased CV risk who were treated with between one and three oral antihyperglycemic medicines (metformin, a sulfonylurea or an SGLT-2 inhibitor). Of the total participants randomized, 1,819 (91%) completed the primary 52-week visit and 1,706 (85%) completed the study on treatment. The median study duration was 85 weeks and 202 participants (10%) completed two years.

Study participants had a mean duration of diabetes of 11.8 years, a baseline A1C of 8.52 percent and a baseline weight of 90.3 kg. More than 85 percent of participants had a history of cardiovascular events. In the insulin glargine arm, the insulin dose was titrated following a treat-to-target algorithm with the goal of fasting blood glucose below 100 mg/dL. The starting dose of insulin glargine was 10 units per day, and the mean dose of insulin glargine at 52 weeks was 43.5 units per day.

SURPASS-4 achieved each of its primary and key secondary endpoints. All three doses of tirzepatide (5 mg, 10 mg and 15 mg) led to statistically significant and superior A1C and body weight reductions compared to insulin glargine for both estimands[ii] at 52 weeks (the primary endpoint). Specifically, the efficacy estimand results showed:

- A1C reduction: -2.24% (5 mg), -2.43% (10 mg), -2.58% (15 mg), -1.44% (insulin glargine)
- Weight change: -7.1 kg (-8.1%, 5 mg), -9.5 kg (-10.7%, 10 mg), -11.7 kg (-13.0%, 15 mg), +1.9 kg (+2.2%, insulin glargine)
- Percent of participants achieving A1C <7%: 81% (5 mg), 88% (10 mg), 91% (15 mg), 51% (insulin glargine)
- Percent of participants achieving A1C <5.7% (not controlled for type 1 error): 23% (5 mg), 33% (10 mg), 43% (15 mg), 3% (insulin glargine)

For the treatment-regimen estimand[iii], all three doses of tirzepatide led to superior A1C and weight reductions at 52 weeks. Specifically, results showed:

- A1C reduction: -2.11% (5 mg), -2.30% (10 mg), -2.41% (15 mg), -1.39% (insulin glargine)
- Weight change: -6.4 kg (5 mg), -8.9 kg (10 mg), -10.6 kg (15 mg), +1.7 kg (insulin glargine)
- Percent of participants achieving A1C <7%: 75% (5 mg), 83% (10 mg), 85% (15 mg), 49% (insulin glargine)

Participants taking tirzepatide maintained A1C and weight control for up to two years in exploratory analyses.

- The mean A1C values at 52 and 104 weeks were:
  - At 52 weeks (N=1,750): 6.3% (5 mg), 6.1% (10 mg), 6.0% (15 mg), 7.1% (insulin glargine)
  - At 104 weeks (N=199): 6.4% (5 mg), 6.1% (10 mg), 6.1% (15 mg), 7.5% (insulin glargine)

- The changes in body weight at 52 and 104 weeks were:
  - At 52 weeks (N=1,755): -7.1 kg (-8.1%, 5 mg), -9.5 kg (-10.7%, 10 mg), -11.7 kg (-13.0%, 15 mg), +1.9 kg (+2.2%, insulin glargine)
  - At 104 weeks (N=202): -5.8 kg (-8.6%, 5 mg), -10.4 kg (-10.8%, 10 mg), -11.1 kg (-12.8%, 15 mg), +2.3 kg (+2.3%, insulin glargine)

Hypoglycemia less than 54 mg/dL was reported in 8.8 percent (5 mg), 6.1 percent (10 mg) and 8.0 percent (15 mg) of participants in the tirzepatide arms and in 19.1 percent of participants in the insulin glargine arm over the full study period. Episodes of hypoglycemia were seen more often in participants who had a background therapy of a sulfonylurea.

In an additional exploratory endpoint, all three doses of tirzepatide led to favorable changes from baseline in fasting lipids at 52 weeks. Specifically, at the highest dose of tirzepatide (15 mg): total cholesterol was reduced by 5.6 percent, triglycerides were reduced by 22.5 percent, low-density lipoprotein (LDL) cholesterol was reduced by 7.9 percent, very low-density lipoprotein (VLDL) cholesterol was reduced by 21.8 percent, and high-density lipoprotein (HDL) cholesterol was increased by 10.8 percent.

The most commonly reported adverse events over the full study period in the tirzepatide arms were gastrointestinal-related and generally mild to moderate in severity. For study participants treated with tirzepatide (5 mg, 10 mg and 15 mg, respectively), nausea (12 percent, 16 percent, 23 percent), diarrhea (13 percent, 20 percent, 22 percent) and vomiting (5 percent, 8 percent, 9 percent) were more frequently experienced compared to insulin glargine (2 percent [nausea], 4 percent [diarrhea], 2 percent [vomiting]). Treatment discontinuation rates due to adverse events over the full study period were 7.3 percent (tirzepatide 5 mg), 7.9 percent (tirzepatide 10 mg) and 8.9 percent (tirzepatide 15 mg), compared to 1.9 percent (insulin glargine).

A safety analysis evaluated adjudicated MACE-4, a composite endpoint of death from cardiovascular causes, myocardial infarction, stroke and hospitalization for unstable angina. Within SURPASS-4, comparing pooled tirzepatide to insulin glargine, no increased cardiovascular risk was identified with tirzepatide; a hazard ratio of 0.74 (95% confidence interval, 0.51 to 1.08) was observed.

"Given the progressive nature of type 2 diabetes, evaluating the positive efficacy results we have seen with tirzepatide over longer periods of time is important. Throughout the length of SURPASS-4, tirzepatide delivered robust improvements in blood glucose levels, significant weight loss and consistent safety results in adults with type 2 diabetes and increased cardiovascular risk," said Jeff Emmick, M.D., Ph.D., vice president, Product Development.

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, for chronic weight management and heart failure with preserved ejection fraction (HFpEF). It is also being studied as a potential treatment for non-alcoholic steatohepatitis (NASH).

About SURPASS-4 and the SURPASS clinical trial program
SURPASS-4 (NCT03730662) is a randomized, parallel, open-label trial comparing the efficacy and safety of tirzepatide 5 mg, 10 mg and 15 mg to insulin glargine in adults with type 2 diabetes inadequately controlled with at least one and up to three oral antihyperglycemic medications (metformin, sulfonylureas or SGLT-2 inhibitors), who have increased cardiovascular (CV) risk. The trial randomized 2,002 study participants in a 1:1:1:3 ratio to receive either tirzepatide 5 mg, 10 mg or 15 mg or insulin glargine. Participants were located in the European Union, North America (Canada and the United States), Australia, Israel, Taiwan and Latin America (Brazil, Argentina and Mexico). The primary objective of the study was to demonstrate that tirzepatide (10 mg and/or 15 mg) is non-inferior to insulin glargine for change from baseline A1C at 52 weeks in people with type 2 diabetes and increased CV risk. The primary and key secondary endpoints were measured at 52 weeks, with participants continuing treatment up to 104 weeks or until study completion. The completion of the study was triggered by the accrual of major adverse cardiovascular events (MACE). Study participants enrolled had to have a mean baseline A1C between 7.5 percent and 10.5 percent and a BMI greater than or equal to 25 kg/m^2 at baseline. 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 glargine treatment arm started with a baseline dose of 10 units per day and titrated following a treat-to-target algorithm to reach a fasting blood glucose below 100 mg/dL.

The SURPASS phase 3 global clinical development program for tirzepatide has enrolled more than 20,000 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[2] (just over 1 in 10) and an estimated 463 million adults worldwide[3] 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[2]. 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 drug 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] Del Prato, S, et. al. (2021). Tirzepatide versus insulin glargine in type 2 diabetes and increased cardiovascular risk (SURPASS-4): a randomised, open-label, parallel-group, multicentre, phase 3 trial. *The Lancet*, https://doi.org/10.1016/S0140-6736(21)02188-7.

[2] 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.

[3] 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 three tirzepatide doses (5 mg, 10 mg and 15 mg) compared to insulin glargine.

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

Refer to:Maggie Pfeiffer; monson_maggie@lilly.com; 317-650-5939 (Media)
Kevin Hern; hern_kevin_r@lilly.com; 317-277-1838 (Investors)

View original content to download multimedia:https://www.prnewswire.com/news-releases/tirzepatide-results-published-in-the-lancet-show-superior-a1c-and-body-weight-reductions-compared-to-insulin-glargine-in-adults-with-type-2-diabetes-with-increased-cardiovascular-risk-301402843.html

SOURCE Eli Lilly and Company