Lilly's tirzepatide led to greater improvements in liver fat content compared to insulin degludec in adults with type 2 diabetes in SURPASS-3 MRI sub-study

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Participants taking tirzepatide 15 mg experienced 47.11% relative reduction in liver fat content compared to 11.17% for insulin degludec

Volume of abdominal adipose tissue decreased with tirzepatide, compared to an increase with insulin degludec

INDIANAPOLIS, Sept. 30, 2021 /PRNewswire/ -- Tirzepatide led to greater improvements in liver fat content and abdominal adipose tissue compared to titrated insulin degludec in adults with type 2 diabetes in an MRI sub-study of Eli Lilly and Company's (NYSE: LLY) phase 3 SURPASS-3 clinical trial.[1] The results were presented today at the 57th European Association for the Study of Diabetes (EASD) Annual Meeting in an EASD-sponsored symposium.

The MRI (magnetic resonance imaging) sub-study achieved its primary and secondary endpoints. As evaluated by MRI scans, the sub-study showed all three doses of tirzepatide (5 mg, 10 mg, 15 mg) led to greater reductions in liver fat content compared to insulin degludec and reductions in volume of visceral adipose tissue and abdominal subcutaneous adipose tissue compared to increases in volume of both measurements with insulin degludec at 52 weeks.

"Increased ectopic fat – such as liver fat or visceral adipose tissue – is commonly seen in adults with type 2 diabetes and is associated with an inflammatory response and increased cardiometabolic risk," said Amalia Gastaldelli, Ph.D., Research Director of Cardiometabolic Risk Unit, Institute of Clinical Physiology, CNR, Pisa Italy. "We are encouraged by the robust reductions in liver fat content and abdominal adipose tissue observed with all three doses of tirzepatide in this population of adults with type 2 diabetes and elevated liver fat content."

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-3 was a 52-week, multi-center, randomized, phase 3, open-label trial evaluating the efficacy and safety of tirzepatide compared to titrated insulin degludec[i] 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 SURPASS-3 MRI sub-study compared the effect of tirzepatide to titrated insulin degludec on liver fat content (LFC), volume of visceral adipose tissue (VAT) and abdominal subcutaneous adipose tissue (ASAT) in 296 participants as evaluated by MRI scans at baseline and at 52 weeks. The subpopulation of adults with type 2 diabetes who participated in this sub-study had an overall baseline LFC of 15.7 percent.

Results among participants taking tirzepatide at 52 weeks showed:

- Greater absolute reduction from baseline in LFC for pooled 10 mg and 15 mg arms (-8.09% from 15.67% at baseline) compared to insulin degludec (-3.38% from 16.58% at baseline), the primary endpoint.
- Greater relative reduction from baseline in LFC (29.78%-47.11% across the three doses) compared to 11.17% for insulin degludec.
- The majority of participants taking tirzepatide achieved at least a 30% reduction in LFC from baseline (66.9%-81.4% across the three doses) compared to a third of those taking insulin degludec (32.12%).
- Up to -1.65 liter (L) reduction from baseline of 6.81 L in VAT (15 mg) and -2.25 L reduction from baseline of 10.21 L in ASAT (10 mg) compared to an increase with insulin degludec (+0.38 L from 6.34 L baseline and +0.63 L from 10.04 L baseline respectively).

The overall safety profile of tirzepatide in SURPASS-3 was similar to the well-established GLP-1 receptor agonist class. Gastrointestinal side effects were the most commonly reported adverse events and decreased with continued dosing.

"In this study, we found that more than twice as many participants taking tirzepatide experienced greater than 30 percent reduction in liver fat content compared to those taking insulin degludec," said Laura Fernández Landó, M.D., senior medical director, Lilly Diabetes. "The results provide us with a deeper understanding of the potential metabolic benefits of tirzepatide in adults with type 2 diabetes and we look forward to continuing to study the effects of tirzepatide beyond glucose and weight control alone."

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 the SURPASS-3 sub-studies and the SURPASS clinical trial program
Lilly developed two sub-studies in order to assess additional glycemic control measures and the effect on liver fat content and abdominal adipose tissue in SURPASS-3, a 52-week randomized, phase 3, open-label trial evaluating the efficacy and safety of tirzepatide compared 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. In SURPASS-3, 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.

The SURPASS-3 MRI sub-study compared the effect of tirzepatide to titrated insulin degludec on liver fat content (LFC), volume of visceral adipose tissue (VAT) and abdominal subcutaneous adipose tissue (ASAT) as evaluated by MRI scans in a subpopulation of SURPASS-3 trial participants. The subpopulation were adults with type 2 diabetes that had a higher risk of elevated LFC as measured by having a Fatty Liver Index ≥60. A total of 296 participants were enrolled in this sub-study and randomized to receive either tirzepatide doses of 5 mg, 10 mg or 15 mg or insulin degludec. The primary objective was to compare the effect of tirzepatide (pooled 10 mg and 15 mg) on change from baseline in the percentage of LFC compared to insulin degludec as measured by MRI scans at baseline and at 52 weeks. The secondary objectives included comparing tirzepatide 5 mg, 10 mg and 15 mg versus insulin degludec in the proportion of participants achieving LFC ≤10%; the proportion of participants with a relative decrease from baseline in LFC ≥30%; the volume of abdominal visceral and subcutaneous adipose tissue and the change from baseline.

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
An estimated 463 million adults worldwide[2] have diabetes. Type 2 diabetes is the most common type, accounting for an estimated 90 to 95 percent of all diabetes cases[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] Cusi, K. The effects of tirzepatide on liver fat content and abdominal adipose tissue in patients with type 2 diabetes (SURPASS-3 MRI). Session S42a. Presented virtually at the 57th European Association for the Study of Diabetes Annual Meeting; September 27- October 1.
[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] 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.

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