Summary of Key Published Data Regarding Tirzepatide

Tirzepatide, a novel, once-weekly injectable dual glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 receptor agonist (GLP-1 RA), is approved for type 2 diabetes (T2D) and is under development for obesity and nonalcoholic steatohepatitis. It has been approved to be used as an adjunct to diet and exercise to improve glycemic control in adults with T2D. The integrated potency and signaling properties of tirzepatide provide a unique pharmacologic profile tailored for improving broad metabolic control. Tirzepatide has shown a greater degree of engagement for the GIP receptor than the GLP-1 receptor.[1]

The approval of tirzepatide was based on results from SURPASS phase 3 global clinical development program, which assessed tirzepatide as an add-on to various standard-of-care medications including the selective GLP-1 RA once-weekly injectable semaglutide 1 mg, insulin glargine, and insulin degludec for T2D.

In each study, tirzepatide achieved its primary and key secondary endpoints for the efficacy estimand and delivered consistent safety and efficacy with sustained A1C reduction and progressive weight loss among people with T2D. All participants in the tirzepatide treatment arms started the study at a dose of 2.5 mg once-weekly and then increased the dose in a step-wise approach at 4-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). In each study, tirzepatide doses of 5, 10, and 15 mg consistently demonstrated A1C reductions across multiple stages of patients' T2D journeys. Average A1C reductions between 1.8% and 2.1% for tirzepatide 5 mg and between 1.7% and 2.4% for both tirzepatide 10 mg and 15 mg were observed. While not indicated for weight loss, reduction in weight was a key secondary endpoint, and tirzepatide demonstrated average weight reductions between 12 lb (5 mg) and 25 lb (15 mg).

In SURPASS-1[2], a 40-week study, tirzepatide (5 mg, 10 mg, or 15 mg) as a monotherapy was compared to placebo in adults with T2D inadequately controlled with diet and exercise alone.
- 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 T2D naïve to injectable therapy who haven't used any oral antidiabetic medicines within 3 months compared to placebo.
- Tirzepatide demonstrated statistically significant and clinically meaningful improvements in A1C reductions compared to placebo.
- From a baseline A1C of 7.9%, tirzepatide reduced participants' A1C by a mean of 1.8% (5 mg) and 1.7% (10 mg and 15 mg) compared to 0.1% in placebo.
- In a key secondary endpoint, from a baseline weight of 189 lb, tirzepatide reduced participants' weight by mean of 14 lb (5 mg), 15 lb (10 mg), and 17 lb (15 mg) compared to 2 lb for placebo.

In SURPASS-2[3], a 40-week study, tirzepatide (5 mg, 10 mg, or 15 mg) was compared to injectable semaglutide 1 mg in adults with T2D inadequately controlled with ≥1500mg/day metformin alone.
- The primary objective of SURPASS-2 was to demonstrate that the two higher doses of tirzepatide (10 mg and/ or 15 mg) led to non-inferior A1C reductions from baseline compared to semaglutide after 40 weeks in people with T2D.
- Participants in the semaglutide treatment arm started the study at a dose of semaglutide 0.25 mg once weekly for 4 weeks, then increased the dose to 0.5 mg for 4 weeks and then reached the final dose of 1 mg.
- From a baseline A1C of 8.3%, tirzepatide reduced participants' A1C by a mean of 2% (5mg), 2.2% (10 mg), and 2.3% (15 mg) compared to 1.9% with semaglutide.
- From a baseline weight of 207 lb, tirzepatide reduced participants' weight by mean of 17 lb (5 mg), 21 lb (10mg), and 25 lb (15mg) compared to 13 lb for semaglutide.

In SURPASS-3[4], a 52-week study, tirzepatide (5 mg, 10 mg, or 15 mg) was compared to insulin degludec in adults with T2D treated with metformin with or without an sodium-glucose co-transporter 2 (SGLT-2) inhibitor.
- The primary endpoint was A1C reduction from baseline after 52 weeks for two doses (10 mg and 15 mg).
- 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.
- From a baseline A1C of 8.2%, tirzepatide reduced participants' A1C by a mean of 1.9% (5 mg), 2.0% (10 mg), and 2.1% (15 mg) compared to 1.3% for insulin degludec.
- From a baseline weight of 208 lb, tirzepatide reduced participants' weight by a mean of 15 lb (5 mg), 21lb (10 mg), and 25 lb (15 mg) compared to an increase of 4 lb for insulin degludec.

SURPASS-3 CGM[5]:
- A subset of SURPASS-3 study patients with a normal wake-sleep cycle were enrolled into SURPASS-3 continuous glucose monitoring (CGM) sub study, and interstitial glucose values were collected by CGM for approximately 7 days at baseline, 24 weeks, and 52 weeks.
- The primary endpoint was the proportion of time that CGM values were in the tight target range (71–140 mg/dL) at 52 weeks, assessed in all randomly assigned participants who received at least one dose of study drug and had an evaluable CGM session at either baseline or after baseline. Participants were assigned to 10 mg and 15 mg tirzepatide versus insulin degludec.
- The secondary outcomes were to compare tirzepatide (5 mg, 10 mg, and 15 mg) versus insulin degludec for the proportion and duration of time in tight target range at 24 and 52 weeks.
- Participants assigned to tirzepatide spent significantly more time in tight target range at 52 weeks compared with those assigned to insulin degludec (5 mg, 12%; 10 mg, 24%; and 15 mg, 25%).
- Participants assigned to tirzepatide 10 mg and 15 mg, but not to tirzepatide 5 mg, spent significantly more time in tight target range at 24 weeks compared with insulin degludec (10 mg, 19% and 15 mg, 21%).

SURPASS-3 MRI[6]:
- A subset of SURPASS-3 study patients with fatty liver index of at least 60 were enrolled into SURPASS-3 MRI sub study. Reduction in liver fat content (LFC) and visceral adipose tissue (VAT) and abdominal subcutaneous adipose tissue (ASAT) volumes in tirzepatide-treated patients were compared with those of participants treated with insulin degludec using MRI scans.
- The primary endpoint was the change from baseline in LFC (as measured by MRI-proton density fat fraction [MRI-PDFF]) at week 52 using pooled data from the tirzepatide 10 mg and 15 mg groups versus insulin degludec.
- From an overall mean baseline LFC of 15.71%, the absolute reduction in LFC at week 52 was significantly greater for the pooled tirzepatide 10 mg and 15 mg groups (-8.09%) versus the insulin degludec group (−3.38%). The estimated treatment difference versus insulin degludec was −4·71%. The reduction in LFC was significantly correlated with baseline LFC, reductions in VAT, reductions in ASAT, and reductions in body weight in the tirzepatide groups.

In SURPASS-4[7], a 104-week study, tirzepatide (5 mg, 10 mg, or 15 mg) was compared to insulin glargine in adults with T2D 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 primary endpoint was measured at 52 weeks, with participants continuing treatment up to 104 weeks or until study completion.
- 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.
- From a baseline A1C of 8.5%, tirzepatide reduced participants' A1C by a mean of 2.1% (5 mg), 2.3% (10 mg), and 2.4% (15 mg) compared to 1.4% for insulin glargine.
- From a baseline weight of 199 lb, tirzepatide reduced participants' weight by a mean of 14 lb (5 mg), 20 lb (10 mg), and 23 lb (15 mg) compared to an increase of 4 lb for insulin glargine.

- A safety analysis evaluated adjudicated major adverse CV events (MACE-4), a composite endpoint of death from CV causes, myocardial infarction, stroke, and hospitalization for unstable angina. No increased CV risk was identified with tirzepatide.

In SURPASS-5[8], a 40-week study, tirzepatide (5 mg, 10 mg, or 15 mg) was compared to placebo in adults with inadequately controlled T2D already being treated with insulin glargine, with or without metformin.
- The primary endpoint was A1C reduction from baseline after 40 weeks.
- Insulin glargine was titrated in all arms following a treat-to-target algorithm with the goal of fasting blood glucose below 100 mg/dL.
- From a baseline A1C of 8.3%, tirzepatide reduced participants' A1C by a mean of 2.1% (5 mg), 2.4% (10 mg), and 2.3% (15 mg) compared to 0.9% for placebo.
- From a baseline weight of 210 lb, tirzepatide reduced participants' weight by a mean of 12 lb (5 mg), 17 lb (10 mg), and 19 lb (15 mg) compared to an increase of 4 lb for placebo.

References

1. Willard FS, Douros JD, Gabe MB, et al. Tirzepatide is an imbalanced and biased dual GIP and GLP-1 receptor agonist. *JCI Insight*. 2020 Sep 3;5(17):e140532. https://pubmed.ncbi.nlm.nih.gov/32730231/

- Tirzepatide (LY3298176) is a dual GIP and GLP-1 receptor agonist under development for the treatment of type 2 diabetes mellitus (T2DM), obesity, and nonalcoholic steatohepatitis. Early phase trials in T2DM indicate that tirzepatide improves clinical outcomes beyond those achieved by a selective GLP-1 receptor agonist. Therefore, we hypothesized that the integrated potency and signaling properties of tirzepatide provide a unique pharmacological profile tailored for improving broad metabolic control. Here, we establish methodology for calculating occupancy of each receptor for clinically efficacious doses of the drug. This analysis reveals a greater degree of engagement of tirzepatide for the GIP receptor than the GLP-1 receptor, corroborating an imbalanced mechanism of action. Pharmacologically, signaling studies demonstrate that tirzepatide mimics the actions of native GIP at the GIP receptor but shows bias at the GLP-1 receptor to favor cAMP generation over β-arrestin recruitment, coincident with a weaker ability to drive GLP-1 receptor internalization compared with GLP-1. Experiments in primary islets reveal β-arrestin1 limits the insulin response to GLP-1, but not GIP or tirzepatide, suggesting that the biased agonism of tirzepatide enhances insulin ecretio. Imbalance toward GIP receptor, combined with distinct signaling properties at the GLP-1 receptor, together may account for the promising efficacy of this investigational agent.

2. Rosenstock J, Wysham C, Frías JP, et al. Efficacy and safety of a novel dual GIP and GLP-1 receptor agonist tirzepatide in patients with type 2 diabetes (SURPASS-1): a double-blind, randomized, phase 3 trial. *Lancet*. 2021 Jul 10;398(10295): 143-155. https://pubmed.ncbi.nlm.nih.gov/34186022/

- **Background:** Despite advancements in care, many people with type 2 diabetes do not meet treatment goals; thus, development of new therapies is needed. We aimed to assess efficacy, safety, and tolerability of novel dual glucose-dependent insulinotropic polypeptide and GLP-1 receptor agonist tirzepatide monotherapy versus placebo in people with type 2 diabetes inadequately controlled by diet and exercise alone.
- **Methods:** We did a 40-week, double-blind, randomised, placebo-controlled, phase 3 trial (SURPASS-1), at 52 medical research centers and hospitals in India, Japan, Mexico, and the USA. Adult participants (≥18 years) were included if they had type 2 diabetes inadequately controlled by diet and exercise alone and if they were naive to injectable diabetes therapy. Participants were randomly assigned (1:1:1:1) via computer-generated random sequence to once a week tirzepatide (5, 10, or 15 mg), or placebo. All participants, investigators, and the sponsor were masked to treatment assignment. The primary endpoint was the mean change in glycated hemoglobin (HbA1c) from baseline at 40 weeks. This study is registered with ClinicalTrials.gov, NCT03954834.

- **Findings:** From June 3, 2019, to Oct 28, 2020, of 705 individuals assessed for eligibility, 478 (mean baseline HbA1c 7·9% [63 mmol/mol], age 54·1 years [SD 11·9], 231 [48%] women, diabetes duration 4·7 years, and body-mass index 31·9 kg/m2) were randomly assigned to tirzepatide 5 mg (n=121 [25%]), tirzepatide 10 mg (n=121 [25%]), tirzepatide 15 mg (n=121 [25%]), or placebo (n=115 [24%]). 66 (14%) participants discontinued the study drug and 50 (10%) discontinued the study prematurely. At 40 weeks, all tirzepatide doses were superior to placebo for changes from baseline in HbA1c, fasting serum glucose, bodyweight, and HbA1c targets of less than 7·0% (<53 mmol/mol) and less than 5·7% (<39 mmol/mol). Mean HbA1c decreased from baseline by 1·87% (20 mmol/mol) with tirzepatide 5 mg, 1·89% (21 mmol/mol) with tirzepatide 10 mg, and 2·07% (23 mmol/mol) with tirzepatide 15 mg versus +0·04% with placebo (+0·4 mmol/mol), resulting in estimated treatment differences versus placebo of -1·91% (-21 mmol/mol) with tirzepatide 5 mg, -1·93% (-21 mmol/mol) with tirzepatide 10 mg, and -2·11% (-23 mmol/mol) with tirzepatide 15 mg (all p<0·0001). More participants on tirzepatide than on placebo met HbA1c targets of less than 7·0% (<53 mmol/mol; 87-92% vs 20%) and 6·5% or less (≤48 mmol/mol; 81-86% vs 10%) and 31-52% of patients on tirzepatide versus 1% on placebo reached an HbA1c of less than 5·7% (<39 mmol/mol). Tirzepatide induced a dose-dependent bodyweight loss ranging from 7·0 to 9·5 kg. The most frequent adverse events with tirzepatide were mild to moderate and transient gastrointestinal events, including nausea (12-18% vs 6%), diarrhea (12-14% vs 8%), and vomiting (2-6% vs 2%). No clinically significant (<54 mg/dL [<3 mmol/L]) or severe hypoglycemia were reported with tirzepatide. One death occurred in the placebo group.
- **Interpretation:** Tirzepatide showed robust improvements in glycemic control and bodyweight, without increased risk of hypoglycemia. The safety profile was consistent with GLP-1 receptor agonists, indicating a potential monotherapy use of tirzepatide for type 2 diabetes treatment.

3. Frias JP, Davies MJ, Rosenstock J, et al. Tirzepatide versus semaglutide once weekly in patients with type 2 diabetes. *N Engl J Med.* 2021 Aug 5; 385:503-515. https://pubmed.ncbi.nlm.nih.gov/34170647/

- **Background:** Tirzepatide is a dual glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1 (GLP-1) receptor agonist that is under development for the treatment of type 2 diabetes. The efficacy and safety of once-weekly tirzepatide as compared with semaglutide, a selective GLP-1 receptor agonist, are unknown.
- **Methods:** In an open-label, 40-week, phase 3 trial, we randomly assigned 1879 patients, in a 1:1:1:1 ratio, to receive tirzepatide at a dose of 5 mg, 10 mg, or 15 mg or semaglutide at a dose of 1 mg. At baseline, the mean glycated hemoglobin level was 8.28%, the mean age 56.6 years, and the mean weight 93.7 kg. The primary end point was the change in the glycated hemoglobin level from baseline to 40 weeks.
- **Results:** The estimated mean change from baseline in the glycated hemoglobin level was -2.01 percentage points, -2.24 percentage points, and -2.30 percentage points with 5 mg, 10 mg, and 15 mg of tirzepatide, respectively, and -1.86 percentage points with semaglutide; the estimated differences between the 5-mg, 10-mg, and 15-mg tirzepatide groups and the semaglutide group were -0.15 percentage points (95% confidence interval [CI], -0.28 to -0.03; P = 0.02), -0.39 percentage points (95% CI, -0.51 to -0.26; P<0.001), and -0.45 percentage points (95% CI, -0.57 to -0.32; P<0.001), respectively. Tirzepatide at all doses was noninferior and superior to semaglutide. Reductions in body weight were greater with tirzepatide than with semaglutide (least-squares mean estimated treatment difference, -1.9 kg, -3.6 kg, and -5.5 kg, respectively; P<0.001 for all comparisons). The most common adverse events were gastrointestinal and were primarily mild to moderate in severity in the tirzepatide and semaglutide groups (nausea, 17 to 22% and 18%; diarrhea, 13 to 16% and 12%; and vomiting, 6 to 10% and 8%, respectively). Of the patients who received tirzepatide, hypoglycemia (blood glucose level, <54 mg per deciliter) was reported in 0.6% (5-mg group), 0.2% (10-mg group), and 1.7% (15-mg group); hypoglycemia was reported in 0.4% of those who received semaglutide. Serious adverse events were reported in 5 to 7% of the patients who received tirzepatide and in 3% of those who received semaglutide.
- **Conclusions:** In patients with type 2 diabetes, tirzepatide was noninferior and superior to semaglutide with respect to the mean change in the glycated hemoglobin level from baseline to 40 weeks.

4. Ludvik B, Giorgino F, Jódar E, et al. Once-weekly tirzepatide versus once-daily insulin degludec as add-on to metformin with or without SGLT2 inhibitors in patients with type 2 diabetes (SURPASS-3): a randomized, open-label, parallel-group, phase 3 trial. *Lancet.* 2021 Aug 14; 398(10300): 583-598. https://pubmed.ncbi.nlm.nih.gov/34370970/

- **Background:** Tirzepatide is a novel dual glucose-dependent insulinotropic polypeptide and GLP-1 receptor agonist under development for the treatment of type 2 diabetes. We aimed to assess the efficacy and safety of tirzepatide versus titrated insulin degludec in people with type 2 diabetes inadequately controlled by metformin with or without SGLT2 inhibitors.
- **Methods:** In this open-label, parallel-group, multicenter (122 sites), multinational (13 countries), phase 3 study, eligible participants (aged ≥18 years) had a baseline glycated hemoglobin (HbA1c) of 7·0-10·5%, body-mass index of at least 25 kg/m2, stable weight, and were insulin-naive and treated with metformin alone or in combination with an SGLT2 inhibitor for at least 3 months before screening. Participants were randomly assigned (1:1:1:1), using an interactive web-response system, to once-weekly subcutaneous injection of tirzepatide (5, 10, or 15 mg) or once-daily subcutaneous injection of titrated insulin degludec, and were stratified by country, HbA1c, and concomitant use of oral antihyperglycemic medications. Tirzepatide was initially given at 2·5 mg and the dose was escalated by 2·5 mg every 4 weeks until the assigned dose was reached. Insulin degludec was initially given at 10 U per day and was titrated once weekly to a fasting self-monitored blood glucose of less than 5·0 mmol/L (<90 mg/dL), following a treat-to-target algorithm, for 52 weeks. The primary efficacy endpoint was non-inferiority of tirzepatide 10 mg or 15 mg, or both, versus insulin degludec in mean change from baseline in HbA1c at week 52. Key secondary efficacy endpoints were non-inferiority of tirzepatide 5 mg versus insulin degludec in mean change from baseline in HbA1c at week 52, superiority of all doses of tirzepatide versus insulin degludec in mean change from baseline in HbA1c and bodyweight, and the proportion of participants achieving HbA1c of less than 7·0% (<53 mmol/mol) at week 52. We used a boundary of 0·3% to establish non-inferiority in HbA1c difference between treatments. Efficacy and safety analyses were assessed in the modified intention-to-treat population (all participants who received at least one dose of study drug). This trial is registered with ClinicalTrials.gov, number NCT03882970, and is complete.
- **Findings:** Between April 1 and Nov 15, 2019, we assessed 1947 participants for eligibility, 1444 of whom were randomly assigned to treatment. The modified intention-to-treat population was 1437 participants from the tirzepatide 5 mg (n=358), tirzepatide 10 mg (n=360), tirzepatide 15 mg (n=359), and insulin degludec (n=360) groups. From a mean baseline HbA1c of 8·17% (SD 0·91), the reductions in HbA1c at week 52 were 1·93% (SE 0·05) for tirzepatide 5 mg, 2·20% (0·05) for tirzepatide 10 mg, and 2·37% (0·05) for tirzepatide 15 mg, and 1·34% (0·05) for insulin degludec. The non-inferiority margin of 0·3% was met. The estimated treatment difference (ETD) versus insulin degludec ranged from -0·59% to -1·04% for tirzepatide (p<0·0001 for all tirzepatide doses). The proportion of participants achieving a HbA1c of less than 7·0% (<53 mmol/mol) at week 52 was greater (p<0·0001) in all three tirzepatide groups (82%-93%) versus insulin degludec (61%). At week 52, from a baseline of 94·3 kg (SD 20·1), all three tirzepatide doses decreased bodyweight (-7·5 kg to -12·9 kg), whereas insulin degludec increased bodyweight by 2·3 kg. The ETD versus insulin degludec ranged from -9·8 kg to -15·2 kg for tirzepatide (p<0·0001 for all tirzepatide doses). The most common adverse events in tirzepatide-treated participants were mild to moderate gastrointestinal events that decreased over time. A higher incidence of nausea (12-24%), diarrhea (15-17%), decreased appetite (6-12%), and vomiting (6-10%) was reported in participants treated with tirzepatide than in those treated with insulin degludec (2%, 4%, 1%, and 1%, respectively). Hypoglycemia (<54 mg/dL or severe) was reported in five (1%), four (1%), and eight (2%) participants on tirzepatide 5, 10, and 15 mg, respectively, versus 26 (7%) on insulin degludec. Treatment discontinuation due to an adverse event was more common in the tirzepatide groups than in the insulin degludec group. Five participants died during the study; none of the deaths were considered by the investigators to be related to the study treatment.
- **Interpretation:** In patients with type 2 diabetes, tirzepatide (5, 10, and 15 mg) was superior to titrated insulin degludec, with greater reductions in HbA1c and bodyweight at week 52 and a lower risk of hypoglycemia. Tirzepatide showed a similar safety profile to that of GLP-1 receptor agonists.

5. Battelino T, Bergenstal RM, Rodrigues A, et al. Efficacy of once-weekly tirzepatide versus once-daily insulin degludec on glycaemic control measured by continuous glucose monitoring in adults with type 2 diabetes (SURPASS-3 CGM): a substudy of the randomised, open-label, parallel-group, phase 3 SURPASS-3 trial. *Lancet.* 2022 Apr 22; online first. https://www.thelancet.com/journals/landia/article/PIIS2213-8587(22)00077-8/fulltext

- **Background:** Tirzepatide is a novel dual glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 receptor agonist under development for the treatment of type 2 diabetes. In this study, we used continuous glucose monitoring (CGM) to compare the 24 h glucose profile for participants given tirzepatide compared with those given insulin degludec.
- **Methods:** This substudy of the open-label, parallel-group, phase 3 SURPASS-3 trial, was done at 45 sites across six countries (Hungary, Poland, Romania, Spain, Ukraine, and the USA). Eligible participants in the main study were adults with type 2 diabetes, a baseline HbA1c of 7·0–10·5% (53–91 mmol/mol), and a BMI of 25 kg/m2 or more, who were insulin-naive, and treated with metformin alone or in combination with a SGLT2 inhibitor for at least 3 months before screening. Participants in the main study were randomly assigned (1:1:1:1) to receive once-weekly subcutaneous injection of tirzepatide 5 mg, 10 mg, or 15 mg, or once-daily subcutaneous injection of titrated insulin degludec (100 U/mL), using an interactive web-response system. Participants were stratified by country, HbA1c concentration, and concomitant oral antihyperglycaemic medication. A subset of these patients with a normal wake–sleep cycle were enrolled into this substudy, and interstitial glucose values were collected by CGM for approximately 7 days at baseline, 24 weeks, and 52 weeks. The primary outcome was to compare pooled participants assigned to 10 mg and 15 mg tirzepatide versus insulin degludec for the proportion of time that CGM values were in the tight target range (71–140 mg/dL) at 52 weeks, assessed in all randomly assigned participants who received at least one dose of study drug and had an evaluable CGM session at either baseline or after baseline. The secondary outcomes were to compare tirzepatide (5 mg, 10 mg, and 15 mg) versus insulin degludec for the proportion and duration of time in tight target range at 24 and 52 weeks. This was a substudy of the trial registered with ClinicalTrials.gov, NCT03882970, and is complete.
- **Findings:** From April 1 to Nov 27, 2019, 313 participants were screened for eligibility, 243 of whom were enrolled in CGM substudy (tirzepatide 5 mg, n=64; tirzepatide 10 mg, n=51; tirzepatide 15 mg, n=73; and insulin degludec, n=55). Patients given once-weekly tirzepatide (pooled 10 mg and 15 mg groups) had a greater proportion of time in tight target range compared with patients given insulin degludec (estimated treatment difference 25% [95% CI 16–33]; p<0·0001). Participants assigned to tirzepatide spent significantly more time in tight target range at 52 weeks compared with those assigned to insulin degludec (5 mg 12% [1–22], p=0·031; 10 mg 24% [13–35], p<0·0001; and 15 mg 25% [14–35], p<0·0001). Participants assigned to tirzepatide 10 mg and 15 mg, but not to tirzepatide 5 mg, spent significantly more time in tight target range at 24 weeks compared with insulin degludec (10 mg 19% [8–30], p=0·0008; 15 mg 21% [11–31], p<0·0001).
- **Interpretation:** Once-weekly treatment with tirzepatide showed superior glycemic control measured using CGM compared with insulin degludec in participants with type 2 diabetes on metformin, with or without a SGLT2 inhibitor. These new data provide additional evidence to the effect of tirzepatide and potential for achieving glycemic targets without increase of hypoglycemic risk compared with a basal insulin.

6. Gastaldelli A, Cusi K, Lando LF, et al. Effect of tirzepatide versus insulin degludec on liver fat content and abdominal adipose tissue in people with type 2 diabetes (SURPASS-3 MRI): a substudy of the randomised, open-label, parallel-group, phase 3 SURPASS-3 trial. *Lancet*. 2022 Apr 22; online first. https://www.thelancet.com/journals/landia/article/PIIS2213-8587(22)00070-5/fulltext

- **Background:** Tirzepatide is a novel dual glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 receptor agonist under development for the treatment of type 2 diabetes. The aim of this substudy was to characterize the changes in liver fat content (LFC), volume of visceral adipose tissue (VAT), and abdominal subcutaneous adipose tissue (ASAT) in response to tirzepatide or insulin degludec in a subpopulation of the SURPASS-3 study.

- **Methods:** This substudy of the randomised, open-label, parallel-group, phase 3 SURPASS-3 trial was done at 45 medical research centers and hospitals across eight countries (Argentina, Austria, Greece, Hungary, Italy, Romania, Spain, and the USA). Eligible participants were adults with type 2 diabetes, a baseline HbA1c 7·0–10·5% (53–91 mmol/mol), a BMI of at least 25 kg/m2, stable weight, were insulin-naive, and on treatment with metformin alone or in combination with a SGLT2 inhibitor for at least 3 months before screening. In addition to the main study inclusion criteria, substudy participants had a fatty liver index of at least 60. Participants had an MRI scan and were randomised (1:1:1:1) in the main study to subcutaneous injection once per week of tirzepatide 5 mg, 10 mg, or 15 mg, or subcutaneous injection once per day of titrated insulin degludec, using an interactive web-response system, and were stratified by country, HbA1c, and concomitant oral anti-hyperglycemic medication. The primary efficacy endpoint was the change from baseline in LFC (as measured by MRI-proton density fat fraction [MRI-PDFF]) at week 52 using pooled data from the tirzepatide 10 mg and 15 mg groups versus insulin degludec. Analyses were assessed in the enrolled MRI population, which consisted of participants in the modified intention-to-treat population of the main study who also had a valid MRI at either baseline or after baseline. This is a substudy of the trial registered with ClinicalTrials.gov, number NCT03882970, and is complete.
- **Findings:** From April 1, 2019, to Nov 15, 2019, 502 participants were assessed for eligibility to participate in this substudy, 296 (59%) of whom were included in the enrolled MRI population and randomly assigned to treatment (tirzepatide 5 mg, n=71; tirzepatide 10 mg, n=79; tirzepatide 15 mg, n=72; and insulin degludec, n=74). Baseline demographics and clinical characteristics were similar across all treatment groups. From an overall mean baseline LFC of 15·71% (SD 8·93), the absolute reduction in LFC at week 52 was significantly greater for the pooled tirzepatide 10 mg and 15 mg groups (−8·09%, SE 0·57) versus the insulin degludec group (−3·38%, 0·83). The estimated treatment difference versus insulin degludec was −4·71% (95% CI −6·72 to −2·70; p<0·0001). The reduction in LFC was significantly correlated (p≤0·0006) with baseline LFC (ρ=−0·71), reductions in VAT (ρ=0·29), reductions in ASAT (ρ=0·33), and reductions in body weight (ρ=0·34) in the tirzepatide groups.
- **Interpretation:** Tirzepatide showed a significant reduction in LFC and VAT and ASAT volumes compared with insulin degludec in this subpopulation of patients with type 2 diabetes in the SURPASS-3 study. These data provide additional evidence on the metabolic effects of this novel dual GIP and GLP-1 receptor agonist.

7. Del Prato S, Kahn SE, Pavo I, Weerakkody GJ, et al. Tirzepatide versus insulin glargine in type 2 diabetes and increased cardiovascular risk (SURPASS-4): a randomized, open-label, parallel-group, multicenter, phase 3 trial. *Lancet.* 2021 Nov 13;398(10313):1811-1824. https://pubmed.ncbi.nlm.nih.gov/34672967/

- **Background:** We aimed to assess efficacy and safety, with a special focus on cardiovascular safety, of the novel dual GIP and GLP-1 receptor agonist tirzepatide versus insulin glargine in adults with type 2 diabetes and high cardiovascular risk inadequately controlled on oral glucose-lowering medications.
- **Methods:** This open-label, parallel-group, phase 3 study was done in 187 sites in 14 countries on five continents. Eligible participants, aged 18 years or older, had type 2 diabetes treated with any combination of metformin, sulfonylurea, or sodium-glucose co-transporter-2 inhibitor, a baseline glycated hemoglobin (HbA1c) of 7·5-10·5% (58-91 mmol/mol), body-mass index of 25 kg/m2 or greater, and established cardiovascular disease or a high risk of cardiovascular events. Participants were randomly assigned (1:1:1:3) via an interactive web-response system to sub cutaneous injection of either once-per-week tirzepatide (5 mg, 10 mg, or 15 mg) or glargine (100 U/mL), titrated to reach fasting blood glucose of less than 100 mg/dL. The primary endpoint was non-inferiority (0·3% non-inferiority boundary) of tirzepatide 10 mg or 15 mg, or both, versus glargine in HbA1c change from baseline to 52 weeks. All participants were treated for at least 52 weeks, with treatment continued for a maximum of 104 weeks or until study completion to collect and adjudicate major adverse cardiovascular events (MACE). Safety measures were assessed over the full study period. This study was registered with ClinicalTrials.gov, NCT03730662.
- **Findings**: Patients were recruited between Nov 20, 2018, and Dec 30, 2019. 3045 participants were screened, with 2002 participants randomly assigned to tirzepatide or glargine. 1995 received at least one dose of tirzepatide 5 mg

(n=329, 17%), 10 mg (n=328, 16%), or 15 mg (n=338, 17%), or glargine (n=1000, 50%), and were included in the modified intention-to-treat population. At 52 weeks, mean HbA1c changes with tirzepatide were -2·43% (SD 0·05) with 10 mg and -2·58% (0·05) with 15 mg, versus -1·44% (0·03) with glargine. The estimated treatment difference versus glargine was -0·99% (multiplicity adjusted 97·5% CI -1·13 to -0·86) for tirzepatide 10 mg and -1·14% (-1·28 to -1·00) for 15 mg, and the non-inferiority margin of 0·3% was met for both doses. Nausea (12-23%), diarrhea (13-22%), decreased appetite (9-11%), and vomiting (5-9%) were more frequent with tirzepatide than glargine (nausea 2%, diarrhea 4%, decreased appetite <1%, and vomiting 2%, respectively); most cases were mild to moderate and occurred during the dose-escalation phase. The percentage of participants with hypoglycemia (glucose <54 mg/dL or severe) was lower with tirzepatide (6-9%) versus glargine (19%), particularly in participants not on sulfonylureas (tirzepatide 1-3% vs glargine 16%). Adjudicated MACE-4 events (cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina) occurred in 109 participants and were not increased on tirzepatide compared with glargine (hazard ratio 0·74, 95% CI 0·51-1·08). 60 deaths (n=25 [3%] tirzepatide; n=35 [4%] glargine) occurred during the study.

- **Interpretation:** In people with type 2 diabetes and elevated cardiovascular risk, tirzepatide, compared with glargine, demonstrated greater and clinically meaningful HbA1c reduction with a lower incidence of hypoglycemia at week 52. Tirzepatide treatment was not associated with excess cardiovascular risk.

8. Dahl D, Onishi Y, Norwood P, et al. Effect of subcutaneous tirzepatide vs placebo added to titrated insulin glargine on glycemic control in patients with type 2 diabetes: The SURPASS-5 randomized clinical trial. *J Amer Med Assoc.* 2022;327:534-545. https://pubmed.ncbi.nlm.nih.gov/35133415/

- **Importance:** The effects of tirzepatide, a dual glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1 receptor agonist, as an addition to insulin glargine for treatment of type 2 diabetes have not been described.
- **Objective:** To assess the efficacy and safety of tirzepatide added to insulin glargine in patients with type 2 diabetes with inadequate glycemic control.
- **Design, setting, and participants:** Randomized phase 3 clinical trial conducted at 45 medical research centers and hospitals in 8 countries (enrollment from August 30, 2019, to March 20, 2020; follow-up completed January 13, 2021) in 475 adults with type 2 diabetes and inadequate glycemic control while treated with once-daily insulin glargine with or without metformin.
- **Interventions:** Patients were randomized in a 1:1:1:1 ratio to receive once-weekly subcutaneous injections of 5-mg (n = 116), 10-mg (n = 119), or 15-mg (n = 120) tirzepatide or volume-matched placebo (n = 120) over 40 weeks. Tirzepatide was initiated at 2.5 mg/week and escalated by 2.5 mg every 4 weeks until the assigned dose was achieved.
- **Main outcomes and measures:** The primary end point was mean change from baseline in glycated hemoglobin A1c (HbA1c) at week 40. The 5 key secondary end points included mean change in body weight and percentage of patients achieving prespecified HbA1c levels.
- **Results:** Among 475 randomized participants (211 [44%] women; mean [SD] age, 60.6 [9.9] years; mean [SD] HbA1c, 8.31% [0.85%]), 451 (94.9%) completed the trial. Treatment was prematurely discontinued by 10% of participants in the 5-mg tirzepatide group, 12% in the 10-mg tirzepatide group, 18% in the 15-mg tirzepatide group, and 3% in the placebo group. At week 40, mean HbA1c change from baseline was -2.40% with 10-mg tirzepatide and -2.34% with 15-mg tirzepatide vs -0.86% with placebo (10 mg: difference vs placebo, -1.53% [97.5% CI, -1.80% to -1.27%]; 15 mg: difference vs placebo, -1.47% [97.5% CI, -1.75% to -1.20%]; P < .001 for both). Mean HbA1c change from baseline was -2.11% with 5-mg tirzepatide (difference vs placebo, -1.24% [95% CI, -1.48% to -1.01%]; P < .001]). Mean body weight change from baseline was -5.4 kg with 5-mg tirzepatide, -7.5 kg with 10-mg tirzepatide, -8.8 kg with 15-mg tirzepatide and 1.6 kg with placebo (5 mg: difference, -7.1 kg [95% CI, -8.7 to -5.4]; 10 mg: difference, -9.1 kg [95% CI, -10.7 to -7.5]; 15 mg: difference, -10.5 kg [95% CI, -12.1 to -8.8]; P < .001 for all). Higher percentages of patients treated with tirzepatide vs those treated with placebo had HbA1c less than 7% (85%-90% vs 34%; P < .001 for all). The most common treatment-emergent adverse events in the tirzepatide groups vs placebo group were diarrhea (12%-21% vs 10%) and nausea (13%-18% vs 3%).
- **Conclusions and relevance:** Among patients with type 2 diabetes and inadequate glycemic control despite treatment with insulin glargine, the addition of subcutaneous tirzepatide, compared with placebo, to titrated insulin glargine resulted in statistically significant improvements in glycemic control after 40 weeks.