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A quick guide to the SURPASS and SURMOUNT trials

Phase 3 trials of tirzepatide in type 2 diabetes and obesity

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medwireNews: **Tirzepatide (formerly known as LY3298176) is a novel glucose-lowering medication that stimulates the receptors for both glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide (GLP)-1.**

Phase 2 findings published in *The Lancet* in 2018 were promising, with the medication showing dose-dependent effects on glucose levels and bodyweight. **It outperformed dulaglutide 1.5 mg/day at the highest doses, albeit in a small group of study participants.**

The phase 3 trials are testing the medication as monotherapy, as an add-on to other treatments, and against established glucose-lowering drugs in people with type 2 diabetes, as well as a weight-loss agent in people with diabetes and obesity.

All the trials are sponsored by tirzepatide's manufacturer, Eli Lilly. We provide a round-up of them below and will update this page with the results as they are released.

And click here for a linked commentary, in which Medicine Matters editorial board member John Wilding outlines the potential advantages of dual GIP-GLP-1 agonists as a treatment approach for people with type 2 diabetes.

See also:

- A quick guide to the STEP trials (semaglutide for obesity)
- A quick guide to the PIONEER trials (oral semaglutide)
- A quick guide to the SUSTAIN trials (semaglutide)
- A quick guide to the AWARD trials (dulaglutide)
- A quick guide to the GetGoal trials (lixisenatide)
- A quick guide to the LEAD trials (liraglutide)

- A quick guide to the DURATION trials (exenatide)

The SURPASS trials

SURPASS-1

Trial population: Drug-naïve people with type 2 diabetes	Comparator treatment: Placebo

NCT03954834; published

SURPASS-1 tested tirzepatide at doses of 5, 10, and 15 mg, administered as a weekly subcutaneous injection, in people with type 2 diabetes who had elevated glycated hemoglobin (HbA1c) levels despite diet and exercise interventions.

As reported in *The Lancet*, the placebo-adjusted HbA1c reductions during 40 weeks of treatment ranged from 1.91% to 2.11% (20.80–23.10 mmol/mol), depending on the tirzepatide dose, and weight reductions ranged from 6.3 to 8.8 kg.

Up to 92% of participants taking tirzepatide achieved HbA1c below 7.0% (53 mmol/mol), compared with 19% of those taking placebo, and up to 52% versus 1% achieved levels below 5.7% (39 mmol/mol).

Related news story: **SURPASS-1: Tirzepatide has 'potent' glucose-lowering and weight loss efficacy**

SURPASS-2

Trial population: People taking metformin monotherapy	Comparator treatment: Semaglutide

NCT03987919; published

In SURPASS-2, tirzepatide at the same three weekly doses (5, 10, and 15 mg) was tested against weekly injections of the GLP-1 receptor agonist semaglutide 1.0 mg.

The findings published in *The New England Journal of Medicine* revealed HbA1c reductions of up to 2.30 percentage points during 40 weeks of tirzepatide treatment, which were significantly greater than the 1.86 percentage point reduction achieved with semaglutide. Tirzepatide also resulted in significantly greater weight reductions, of up to 5.5 kg more than seen with semaglutide.

Related news stories: Tirzepatide has efficacy edge over semaglutide in SURPASS-2Mechanisms underlying tirzepatide efficacy revealed

SURPASS-3

Trial population: People taking metformin with/without an SGLT2 inhibitor	Comparator treatment: Insulin degludec

NCT03882970; published

In this trial, the investigators compared the efficacy of weekly tirzepatide (5, 10, and 15 mg) with daily insulin degludec in people with poorly controlled blood glucose despite stable treatment with metformin with or without an SGLT (sodium-glucose cotransporter)2 inhibitor.

They reported at the virtual ADA 81st Scientific Sessions that participants taking the highest tirzepatide dose achieved an average 2.37 percentage point reduction in HbA1c after 52 weeks of treatment, which was significantly more than the 1.34 percentage point reduction for those taking degludec.

The tirzepatide groups lost an average of 7.5, 10.7, and 12.9 kg, compared with an average 2.3 kg gain in the degludec group, and they were significantly less likely to experience hypoglycemia.

Related news stories: **SURPASS-3: Tirzepatide proves better option than degludec for type 2 diabetesTirzepatide reduces liver fat, improves time in range**

SURPASS-4

Trial population: People at increased cardiovascular risk taking metformin with/without a sulfonylurea or SGLT2 inhibitor	Comparator treatment: Insulin glargine

NCT03730662; published

As reported in *The Lancet*, all three tirzepatide doses resulted in significantly greater HbA1c reduction than insulin glargine, at 2.58% (28.2 mmol/mol) for the highest dose (15 mg/week), compared with 1.44% (15.7 mmol/mol). Tirzepatide treatment also resulted in significantly more weight loss and less hypoglycemia.

The trial enrolled people with increased cardiovascular risk, with 87% of participants having previous events. Over an extended follow-up of up to

104 weeks, major adverse cardiovascular event rates were similar for those taking tirzepatide and glargine, at 5% and 6%, respectively.

Related news story: **Tirzepatide preferable to glargine when OADs fail in SURPASS-4**

SURPASS-5

Trial population: People taking insulin glargine	Comparator treatment: Placebo

NCT04039503; published

The SURPASS-5 trial tested tirzepatide (5, 10, and 15 mg) in people taking insulin glargine for type 2 diabetes, with or without metformin.

As reported at the virtual ADA 81st Scientific Sessions and later published in *JAMA*, 40 weeks of treatment with glargine plus the highest tirzepatide dose resulted in an average 2.59% reduction in HbA1c, which was significantly greater than the 0.93% reduction seen for glargine and placebo.

Also, the tirzepatide group lost an average of 10.9 kg and reduced their insulin dose, whereas the placebo group gained 1.7 kg, on average, and their insulin dose rose by 75%.

Related news story: **SURPASS-5: Glycemic, weight benefits of tirzepatide in insulin-dependent type 2 diabetes**

SURPASS-6

Trial population: People taking insulin glargine, with or without metformin	Comparator treatment: Insulin lispro

NCT04537923; estimated study completion in November 2022

SURPASS-6 is assessing tirzepatide as an alternative to starting a prandial insulin in people already using a basal insulin to treat type 2 diabetes. The primary endpoint is change in HbA1c after 52 weeks of treatment.

SURPASS-CVOT

Trial population: People with type 2 diabetes, confirmed atherosclerotic cardiovascular disease, and overweight	Comparator treatment: Dulaglutide

NCT04255433; recruiting, estimated study completion in October 2024

For its cardiovascular outcomes trial, tirzepatide is up against dulaglutide 1.5 mg, which has a confirmed cardioprotective effect.

The investigators are assessing a three-point major adverse cardiovascular event endpoint (myocardial infarction, stroke, and cardiovascular death), over an estimated maximum of 54 months.

Trials for Japanese/Asian markets

SURPASS J-mono

Trial population: People who are drug-naïve or taking monotherapy (discontinued before baseline)	Comparator treatment: Dulaglutide

NCT03861052; published

This trial in Japanese people with type 2 diabetes compared weekly tirzepatide (5, 10, or 15 mg) against weekly dulaglutide 0.75 mg in people taking no other glucose-lowering medications during the study.

As reported in *The Lancet Diabetes & Endocrinology*, participants given tirzepatide 5, 10, or 15 mg experienced a significantly greater average reduction in HbA1c levels from baseline to week 52 compared with those given dulaglutide, at 2.4%, 2.6%, and 2.8%, respectively, versus 1.3%.

Related news story: **SURPASS J trials support tirzepatide use in Japanese people with type 2 diabetes**

SURPASS J-combo

Trial population: People taking antidiabetes medications other than incretin-based classes	Comparator treatment: None

NCT03861039; published

This safety study, published in *The Lancet Diabetes & Endocrinology*, was designed to monitor adverse events in Japanese people given tirzepatide (5, 10, or 15 mg/week) in addition to non-incretin-based antidiabetes medications over 52 weeks of treatment.

The investigators reported that add-on tirzepatide was well tolerated, with no new safety signals identified in the trial. A total of 77% of participants reported treatment-emergent adverse events, most commonly gastrointestinal.

They also observed dose-dependent reductions in HbA1c and bodyweight with tirzepatide treatment.

Related news story: **SURPASS J trials support tirzepatide use in Japanese people with type 2 diabetes**

SURPASS-AP-Combo

Trial population: People taking metformin with/without a sulfonylurea	Comparator treatment: Insulin glargine

NCT04093752; completed, not yet published

This trial is testing tirzepatide versus insulin glargine, over a 40-week period, in people taking metformin with or without a sulfonylurea of at least half the maximum dose.

It has recruited people from Australia, China, India, and the Republic of Korea.

SURMOUNT-J

Trial population: Japanese people with a BMI of ≥35 kg/m^2 and at least one related comorbidity or of 27–<35 kg/m^2 with two comorbidities	Comparator treatment: Placebo

NCT04844918; estimated study completion in June 2023

This trial in Japanese study locations will compare participants' weight loss during 72 weeks of treatment with one of two doses of tirzepatide versus placebo.

SURMOUNT-CN

Trial population: Chinese people with a BMI of 28 kg/m^2 or of 24 kg/m^2 with related comorbidities	Comparator treatment: Placebo

NCT05024032; estimated study completion in December 2022

This trial in Chinese people with obesity or overweight will compare weight loss during 52 weeks of treatment with one of two doses of tirzepatide versus placebo.

Trials of tirzepatide for obesity

SURMOUNT-1

Trial population: People with obesity or BMI 27 kg/m^2 and related comorbidities	Comparator treatment: Placebo

NCT04184622; published

The SURMOUNT-1 trial tested the ability of tirzepatide to produce weight loss in people with obesity who do not have diabetes.

During 72 weeks of treatment, people taking tirzepatide at doses of 5, 10, or 15 mg lost an average of 15.0%, 19.5%, and 20.9%, respectively, compared with just 3.1% in people taking placebo.

For the co-primary endpoint of the proportion of people attaining at least a 5% reduction in their baseline bodyweight, the corresponding values were 85%, 89%, and 91% versus 35%.

The trial is published in *The New England Journal of Medicine*.

Related news story: SURMOUNT-1 places tirzepatide weight loss efficacy within surgical range

SURMOUNT-2

Trial population: People with type 2 diabetes plus BMI ≥27 kg/m^2	Comparator treatment: Placebo

NCT04657003; estimated study completion in April 2023

SURMOUNT-2 has the same study design as SURMOUNT-1, but testing just the 10 and 15 mg tirzepatide doses in people who also have type 2 diabetes.

SURMOUNT-3

Trial population: People with obesity or BMI 27 kg/m^2 and related comorbidities	Comparator treatment: Placebo

NCT04657016; estimated study completion in May 2023

This trial in people who do not have diabetes, is testing whether tirzepatide can help people maintain, or even improve on, weight loss achieved during an intensive lifestyle intervention.

Again, it has the co-primary endpoints of percent change in bodyweight and the proportion of people attaining at least a 5% reduction in their baseline bodyweight by week 72.

SURMOUNT-4

Trial population: People with obesity or BMI 27 kg/m^2 and related comorbidities	Comparator treatment: Placebo

NCT04660643; estimated study completion in May 2023

After 36 weeks of treatment with tirzepatide, the SURMOUNT-3 participants will be randomly assigned to either continue with the treatment or switch to placebo.

At week 88, the investigators will assess whether the participants lost, maintained, or regained weight from the point of randomization.

A trial of tirzepatide for HFpEF

SUMMIT

Trial population: People with obesity plus HFpEF	Comparator treatment: Placebo

NCT04847557; estimated study completion in November 2023

In this trial, people with obesity plus HFpEF (heart failure with preserved ejection fraction) will take tirzepatide or placebo for 52 weeks.

The primary outcome is a hierarchical composite endpoint comprising mortality, heart failure events, exercise capacity, and heart failure symptoms.

A trial of tirzepatide in children

SURPASS-PEDS

Trial population: Children aged 10–17 years with type 2 diabetes taking metformin, insulin, or both	Comparator treatment: Placebo

NCT05260021; estimated study completion in December 2027

For this trial, children with poorly controlled type 2 diabetes will take one of two tirzepatide doses or placebo for 30 weeks. The primary outcome is change in HbA1c over this period.

There will then follow an open-label extension through week 52 during which the placebo-treated participants will switch to tirzepatide.