



Tirzepatide for maintenance of bodyweight reduction in people with obesity in the USA (SURMOUNT-MAINTAIN): a multicentre, double-blind, randomised, placebo-controlled trial

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Summary

Background Obesity treatment improves long-term health and quality of life outcomes. Weight reduction and its maintenance play an important role in achieving these goals. We evaluated the efficacy and safety of continuing tirzepatide at the maximum tolerated dose (MTD) or lowering the dose to 5 mg compared with switching to placebo on the maintenance of bodyweight reduction obtained with tirzepatide MTD in adults with obesity.

Methods This phase 3b, placebo-controlled, 112-week trial, including a 60-week open-label weight-loss period and a 52-week, double-blind weight maintenance period, was conducted across 20 sites in the USA. After completing the initial weight-loss period with once weekly subcutaneous tirzepatide at the MTD (10 mg or 15 mg), adults (aged ≥ 18 years) with a BMI of 30 kg/m² and above or 27 kg/m² and above with one or more weight-related comorbidities, and a history of at least one self-reported unsuccessful dietary effort to lose bodyweight were randomly assigned in a 3:3:2 ratio to continue tirzepatide MTD, reduce to tirzepatide 5 mg, or switch to placebo for an additional 52 weeks. Starting at week 84 (24 weeks after random allocation), participants could receive rescue tirzepatide if their weight regain exceeded 50%. The primary endpoint was the percentage change in bodyweight from baseline to week 112. The primary estimand was the modified treatment-regimen estimand, which assumed that participants who initiated rescue tirzepatide would not have gained further benefit from their assigned study treatment and included all randomly allocated participants, regardless of treatment discontinuation or initiation of prohibited medications. The efficacy estimand was supportive. Safety was assessed in all participants who received at least one dose of study drug. This completed trial was registered at ClinicalTrials.gov (NCT06047548).

Findings From Sept 20, 2023, to Jan 20, 2026, 441 patients were enrolled in and took at least one dose of study treatment during the weight-loss period, with 378 participants randomly allocated at week 60 (140 to tirzepatide MTD; 144 to dose-reduction to 5 mg tirzepatide; and 94 to placebo). 372 received at least one dose of study drug during the weight maintenance period (139 for tirzepatide MTD; 142 for 5 mg tirzepatide; and 91 for placebo). 345 (91%) of 378 participants completed the study. The majority of participants were White (67%); 288 (65%) participants were female and 153 (35%) were male; and the mean age was 46.6 years (SD 13.0). At baseline, participants had a mean bodyweight of 113.8 kg (SD 27.0), a BMI of 40.1 kg/m² (SD 8.1), and HbA_{1c} 5.64% (SD 0.4; 38.2 mmol/mol [SD 4.0]). The model-based estimate percent change in bodyweight from baseline to week 112 was -21.9% (95% CI -23.5 to -20.3) with MTD (estimated treatment difference [ETD] -12.0% [95% CI -13.8 to -10.1]), -16.6% (95% CI -18.0 to -15.1) with 5 mg tirzepatide (ETD -6.6 [95% CI -8.3 to -5.0]), versus -9.9% (95% CI -11.1 to -8.8) with placebo ($p < 0.0001$ for all comparisons). Among participants who regained at least 50% of lost bodyweight, observed means were 11 (8%) of 138, 35 (25%) of 142, and 60 (67%) of 90 participants received rescue therapy in the tirzepatide MTD, 5 mg tirzepatide, and placebo, respectively. The most common adverse events with tirzepatide were gastrointestinal events, which were mostly mild to moderate in severity and mostly occurred during dose escalation.

Interpretation In adults with obesity, long-term treatment is often necessary to maintain bodyweight reduction and its associated cardiometabolic benefits. In the SURMOUNT-MAINTAIN trial, continuing tirzepatide at MTD maintained bodyweight reduction and health-related benefits. Reducing to 5 mg tirzepatide might provide a valuable alternative to discontinuation, although individuals' treatment response might vary. Together, these findings support the importance of ongoing therapy for long-term obesity management and provide evidence to inform individualised, patient-centred obesity care.

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See [Comment](#) page 2269

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Research in context

Evidence before this study

Maintenance of bodyweight reduction is important in individuals living with obesity to sustain cardiometabolic benefits. This remains challenging for many patients. Incretin-based therapies for obesity have demonstrated efficacy in inducing clinically meaningful bodyweight reduction and improvement in clinical outcomes. In contrast, discontinuation of these therapies has been associated with weight regain and attenuated or reversal of these benefits. Tirzepatide is a once weekly injectable dual glucose-dependent insulinotropic polypeptide and GLP-1 receptor agonist that, across all studied doses in the phase 3 SURMOUNT clinical trial programme, produced significant bodyweight reduction and improvement in cardiometabolic risk factors in adults with obesity. On Jan 5, 2026, we searched PubMed using the search terms “GLP-1 receptor agonist” AND “obesity” AND “overweight” AND “weight maintenance” for any published articles, with no date or language restrictions. In SURMOUNT-4, participants who were switched from tirzepatide to placebo in a controlled, masked manner experienced significant weight regain.

Added value of this study

To our knowledge, SURMOUNT-MAINTAIN is the first obesity medication trial and first tirzepatide trial investigating the effect of reducing the dose of an effective obesity medication on the maintenance of bodyweight reduction. In this 112-week trial, adults with obesity (BMI ≥ 30 kg/m² or BMI ≥ 27 kg/m² with at least one obesity-related complication) received a 60-week open-label treatment with once weekly tirzepatide maximum tolerated dose (MTD) and then were randomly allocated to continue tirzepatide MTD, to reduce the dose to 5 mg, or to switch to placebo for a subsequent 52 weeks.

The two tirzepatide groups obtained superior and clinically meaningful overall reductions in bodyweight from baseline with tirzepatide MTD and 5 mg versus switching to placebo at week 112. Participants who continued tirzepatide (MTD or 5 mg) maintained most of the initial bodyweight reduction obtained with tirzepatide MTD, and participants who switched to placebo maintained less than half their bodyweight reduction at week 112. These data should be interpreted in context of rescue tirzepatide being provided to participants with 50% or more weight regain, a novel patient-centred approach in this trial. Continuing tirzepatide also resulted in significant and sustained improvements in cardiometabolic risk factors, including lipid profile, blood pressure, and glycaemia compared with placebo. Similar to other incretin-based therapies, the most frequent adverse events with tirzepatide were gastrointestinal events, which were mostly mild to moderate in severity, including nausea, diarrhoea, vomiting, and constipation.

Implications of all the available evidence

Together with previous evidence, these findings underscore the importance of continued therapy for the long-term management of obesity and demonstrate that staying on tirzepatide MTD resulted in superior maintenance of bodyweight reduction and associated cardiometabolic benefits versus placebo. In addition, this is the first incretin-based obesity medication trial of its kind providing data to elucidate clinical considerations associated with reducing treatment intensity such as dose lowering to maintain a majority of the bodyweight reduction and to provide evidence to inform individualised, patient-centred obesity care.

Introduction

In people living with obesity who have obtained bodyweight reduction through combined use of effective obesity medications and lifestyle interventions, maintaining bodyweight reduction long term remains a challenge and is usually difficult to manage with lifestyle interventions alone.^{1–3} Factors contributing to weight regain include the progressive and chronic course of the disease of obesity; the body's attempt to return to homeostasis at a higher adipocyte mass;^{3,4} and premature treatment discontinuation.^{5–8} Against this background, it remains unknown in the field of obesity whether the intensity of obesity treatment required to achieve the initial weight reduction versus maintenance of weight reduction is the same or different. Additionally, if reducing the treatment intensity is desired due to other reasons such as tolerability, patient preference, cost, etc, there is a lack of high-quality data such as randomised controlled trial data to inform on the expected changes in efficacy with such clinical decisions.

Tirzepatide is a once weekly dual glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 receptor

agonist (GIP–GLP-1) approved in adults for the treatment of obesity, obstructive sleep apnoea, and type 2 diabetes. In the SURMOUNT clinical trial programme, tirzepatide treatment demonstrated clinically significant bodyweight reductions of 13–26% and improved markers of weight-related cardiometabolic complications in adults with obesity, with and without type 2 diabetes.^{9–13} Furthermore, sustained bodyweight reductions of 15–23% were observed following over 3 years of tirzepatide treatment in adults with prediabetes and obesity,¹⁴ supporting long-term treatment of tirzepatide to maintain clinically meaningful bodyweight reduction.

The degree to which adults with obesity can maintain their bodyweight with a lower tirzepatide dose after achieving bodyweight reduction with the maximum tolerated dose ([MTD]; either 10 mg or 15 mg) remains unknown. SURMOUNT-MAINTAIN is the first clinical trial of its kind and first tirzepatide trial to assess whether continued tirzepatide treatment (MTD or dose reduced to 5 mg) can maintain the initial bodyweight reduction obtained with tirzepatide MTD compared with switching to placebo.

Methods

Study design and participants

Detailed methodology, eligibility, and key definitions have already been published,¹⁵ with amendments to the protocol available in appendix 1 and appendix 2 (p 9). Briefly, this phase 3b, multicentre, randomised, parallel-group, double-blinded, placebo-controlled, 112-week clinical trial was conducted in 20 sites in the USA. Clinical trial sites were selected based on their ability to enrol and retain eligible participants while maintaining high data quality and regulatory compliance. Selection considered previous clinical trial experience, access to appropriate patient populations, and operational capacity, informed by feasibility assessments and historical site performance. Key inclusion criteria included participants aged 18 years and older with a BMI of 30 kg/m² or above or 27 kg/m² or above with at least one weight-related comorbidity (eg, hypertension, dyslipidaemia, obstructive sleep apnoea, or cardiovascular disease), and a history of at least one self-reported unsuccessful dietary effort to lose bodyweight. Additionally, per the protocol, all study participants received lifestyle interventions throughout the trial, including dietary and physical activity counselling by a dietitian or nutritionist, or equivalently qualified delegate, according to local standards. Key exclusion criteria included a previous diagnosis of diabetes or people who had at least one laboratory value suggestive of diabetes during screening, a self-reported change in bodyweight greater than 5 kg within the 3 months before screening, and any use of a GLP-1 receptor agonist within 12 months of screening. A full list of eligibility criteria and study investigators is provided in appendix 2 (pp 5–8).

The protocol was approved by local institutional review boards (appendix 2 p 4), and this trial was conducted in accordance with the Declaration of Helsinki guidelines on good clinical practices. All participants provided written informed consent. The completed trial is registered on ClinicalTrials.gov (NCT06047548).

Randomisation and masking

After completing a 60-week, open-label weight-loss period, participants meeting randomisation criteria (ie, had lost $\geq 5\%$ bodyweight and tolerated at least 10 mg tirzepatide) were randomised in a 3:3:2 ratio to continue once weekly treatment with tirzepatide MTD (10 mg or 15 mg), reduce the dose to 5 mg, or switch to placebo. Assignment to treatment group was determined by a computer-generated random sequence using the Lilly interactive web-response system. Randomisation was stratified by achieving plateau at week 60 (yes or no), sex (female or male), and percentage of total bodyweight loss at week 60 ($<20\%$ vs $\geq 20\%$). Participants were considered to have obtained plateau if percent change in bodyweight from week 48 to week 60 was less than 5%. All participants, investigators, and the study sponsor were masked to treatment assignment.

Procedures

During the weight-loss period, all enrolled participants received once weekly subcutaneous injections of tirzepatide starting at 2.5 mg for 4 weeks and increased by 2.5 mg every 4 weeks until a MTD of 10 mg or 15 mg was reached. Participants who met the randomisation criteria at week 60 were then randomly allocated to continue once weekly treatment of tirzepatide MTD (10 mg or 15 mg), reduce the dose to 5 mg, or switch to placebo for an additional 52 weeks during the double-blind weight maintenance period, as described above (appendix 2 p 17). Dose modification was permitted for management of intolerable gastrointestinal symptoms or in case of reaching a BMI of 22 kg/m² or under, along with dietary modification. Only one cycle of dose de-escalation and re-escalation in response to persistent intolerance was permitted during the weight-loss period, but not during the weight maintenance period. Participants who did not tolerate at least 10 mg by visit 12 (week 48) were not eligible for randomisation and were discontinued from the study drug and from the study. All participants received lifestyle modification counselling consistent with current guidelines for weight management.¹⁶ Rescue tirzepatide was provided starting at week 84 (ie, 24 weeks after random allocation) in case of weight regain exceeding the prespecified threshold of 50%.¹⁷ Qualified participants from the placebo group were reinitiated on 5 mg tirzepatide, qualified participants from the 5 mg tirzepatide group had their dose increased to 7.5 mg, and qualified participants from the tirzepatide MTD group remained at their MTD of 10 mg or 15 mg. Rescue doses were escalated by 2.5 mg increments every 4 weeks until MTD was reached while keeping the random allocation masked to all participants, investigators, site staff, clinical monitors, and sponsor. Efficacy and safety assessments were collected at the fasting state throughout the trial, except for bodyweight at visits 6 and 10, and were evaluated at a central laboratory (appendix 1).

Outcomes

Figure 1A is a conceptual diagram illustrating bodyweight change and maintenance. The primary endpoint was the percent change from baseline (week 0) in bodyweight at week 112. All key secondary endpoints were controlled for multiplicity (appendix 1). The key secondary endpoints among all participants who reached a bodyweight plateau, defined as less than a 5% bodyweight change between week 48 and week 60, included percent maintenance of bodyweight reduction obtained during the weight-loss period at week 112 and a yes or no assessment of maintaining 80% or greater of the bodyweight reduction obtained during the weight-loss period. The key secondary endpoints among all participants included the absolute change (in kg) and percent change from random allocation (week 60) in bodyweight at week 112, the absolute change (kg) from

See Online for appendices 1 and 2

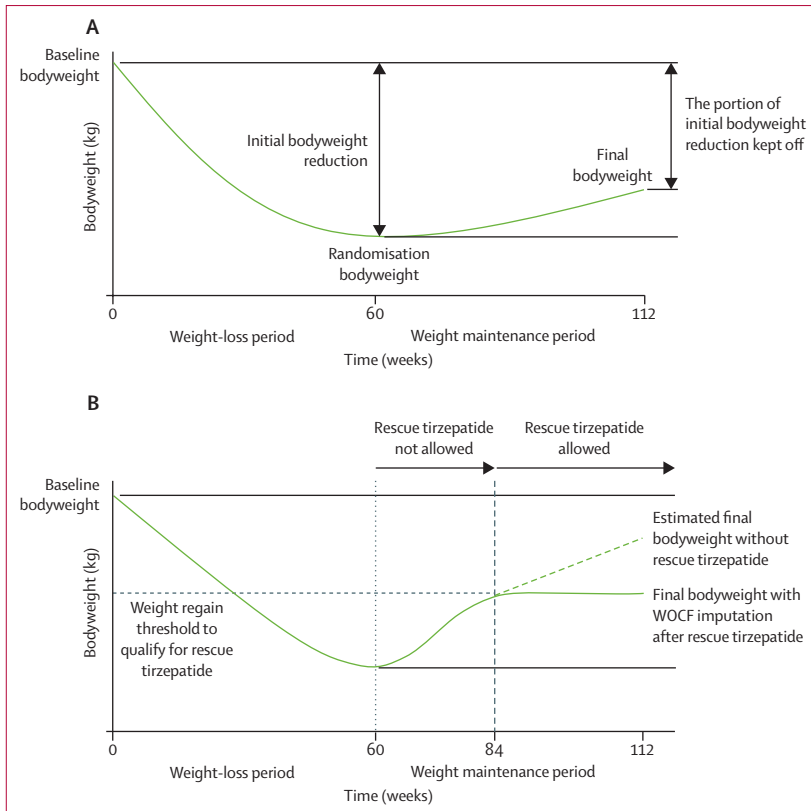


Figure 1: Conceptual diagram of bodyweight reduction and maintenance (A) and rescue tirzepatide and worse value imputation (B)

Change in weight—the difference between baseline weight (week 0) and final weight (week 112), expressed in kg. Percentage change in weight—the change in weight from week 0 to week 112, expressed as a percentage of baseline weight. Percentage maintenance—the portion of initial weight reduction kept off at week 112. WOCF=worst observation carried forward.

baseline in bodyweight at week 112, and the percent change from baseline in bodyweight at week 84 before rescue tirzepatide treatment was provided. Additional secondary endpoints among all participants included maintenance of 15% or more of the bodyweight reduction at week 112 among those who had already lost 15% or more of their bodyweight at random allocation, change in waist circumference from random allocation (in cm), and percentage maintenance of bodyweight reduction obtained during the weight-loss period at week 112. Among participants who reached a bodyweight plateau, percent maintenance of bodyweight reduction obtained during the weight-loss period was assessed at week 84.

Prespecified exploratory endpoints included changes from random allocation and changes from baseline in lipid profile (triglycerides, HDL cholesterol, VLDL cholesterol, and non-HDL cholesterol), systolic and diastolic blood pressure, glycaemic parameters (glycated haemoglobin [HbA1c], fasting serum glucose, and fasting insulin), BMI, and patient-reported outcomes including Power of Food Scale,^{18,19} Food Craving Questionnaire-trait-reduced; not reported,²⁰ and the Short Form-36 Health Survey Version 2,²¹ change from baseline in waist

circumference (in cm), use of rescue tirzepatide for weight regain at 50% or more of the bodyweight reduction obtained during the open-label weight-loss period, and maintenance of 20% or greater bodyweight reduction at week 112 among those who had already lost 20% or more of their bodyweight at random allocation.

Safety endpoints were treatment-emergent adverse events, serious adverse events, and study drug discontinuation due to adverse events. Deaths, major adverse cardiovascular events (myocardial infarction, hospitalisation due to unstable angina or heart failure, coronary revascularisation, and cerebrovascular events), and pancreatitis were adjudicated by an independent external adjudication committee (appendix 1).

Statistical analysis

The sample size of 120 (tirzepatide MTD), 120 (tirzepatide 5 mg), and 80 (placebo) was selected to provide approximately 90% power to detect a 5% difference in mean percentage change of bodyweight from week 0 at week 112 between tirzepatide MTD versus placebo or 5 mg tirzepatide versus placebo. This sample size is based on a common SD of 10% (based on previous data from phase 3 studies for tirzepatide, such as SURMOUNT-1),⁹ using a two-group *t*-test and a 0.025 two-sided significance α level. Assessment of superiority of tirzepatide MTD or 5 mg tirzepatide to placebo was conducted at an alpha level of 0.025 for each comparison to allow an overall 0.05 alpha level for the study. The detailed type 1 error control strategy is presented in appendix 1, and the graphical testing scheme is provided in appendix 2 (p 18).

The primary estimand for this study was the modified-treatment regimen estimand with the efficacy estimand used as supportive. The modified treatment-regimen estimand was evaluated using the full analysis set, which was based on the modified intent-to-treat (mITT) population, irrespective of study treatment adherence and initiation of other obesity medications (GLP-1 receptor agonists, GIP-GLP-1 receptor agonists, or dipeptidyl peptidase [DPP-4] inhibitors). Data obtained after rescue tirzepatide or having bariatric surgery or other weight-loss procedures were excluded and worst value observed before initiation of rescue or having bariatric surgery or other weight-loss procedures was carried forward (WOCF; figure 1B).

The primary endpoint and the key secondary endpoints were assessed using the mITT population for all randomly allocated participants who were exposed to at least one dose of the study drug (tirzepatide or placebo), and excluding participants who were inadvertently enrolled. Endpoints related to maintenance were evaluated in participants from the mITT population who obtained bodyweight plateau. Primary, secondary, and exploratory endpoints were also assessed under the efficacy estimand using the efficacy analysis set, defined by the mITT population and excluding data collected

after treatment discontinuation, initiation of other obesity medications (GLP-1 receptor agonists, GIP–GLP-1 receptor agonists, DPP-4 inhibitors, or rescue tirzepatide), or after bariatric surgery or other weight-loss procedures. Use of rescue tirzepatide in each treatment group was summarised in the mITT population. To prevent a high amount of missing data after rescue, WOCF after rescue occurred if 60% or more of participants in any treatment group received rescue. A prespecified sensitivity analysis was also conducted not using WOCF. Data are reported as model-based estimate (ie, estimates from a prespecified statistical model [such as ANCOVA or mixed model for repeated measures [MMRM], evaluated at defined covariate values and reflecting the expected outcome under the model assumptions, rather than a simple observed average) and 95% CIs, unless otherwise specified. Safety was assessed using the safety analysis set consisting of data obtained during the screening period, weight-loss period, and maintenance period, and excluding data obtained after rescue tirzepatide. Adverse events were coded by investigators using the Medical Dictionary for Regulatory

Activities (MedDRA) and subsequently evaluated for severity and relationship to study treatment. The frequency and proportion of participants' adverse events were summarised descriptively with categorical comparisons using Fisher's exact test and risk differences with 95% CIs. Some prespecified continuous measures were analysed using MMRM with relevant covariates. Additional statistical methodology is given in appendix 1 and appendix 2 (p 8). Change from baseline in waist-to-height ratio and proportion of participants with prediabetes at baseline achieving HbA1c less than 5.7% are post hoc exploratory endpoints. Results reported herein are from the modified treatment-regimen estimand, unless otherwise specified.

Role of the funding source

The study sponsor was involved in study design, data collection, review, analyses, and drafting of the report.

Results

The study was conducted between Sept 20, 2023, and Jan 20, 2026. A total of 441 participants were enrolled in

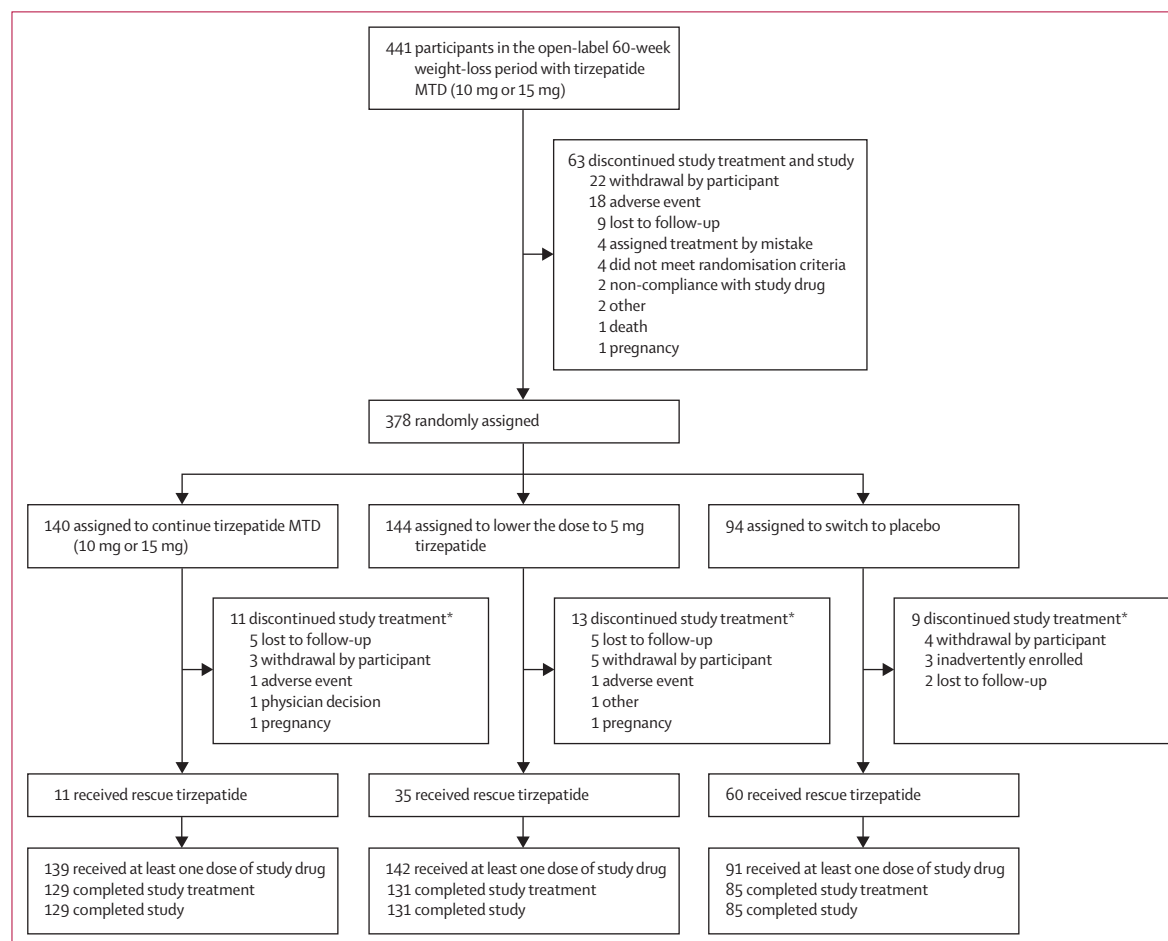


Figure 2: Trial profile

MTD=maximum tolerated dose. *All participants who discontinued study treatment also discontinued the study.

the weight-loss period with 378 participants randomly allocated at week 60 (140 to tirzepatide MTD; 144 to dose-reduction to 5 mg tirzepatide; and 94 to placebo) and 372 received at least one dose of study drug during the weight maintenance period (139 for tirzepatide MTD; 142 for 5 mg tirzepatide; and 91 for placebo; figure 2). Of participants who received at least one dose of the study

drug, 33 (9%) discontinued the study prematurely during the weight maintenance period (figure 2); 345 (91%) of 378 participants completed the study.

At baseline, the overall median duration of obesity was 12.8 years (IQR 5.8–21.9) with a mean bodyweight of 113.8 kg (SD 27.0), a BMI of 40.1 kg/m² (SD 8.1) and waist circumference of 119.4 cm (SD 17.5), and HbA1c of 5.64% (SD 0.4; 38.2 mmol/mol [SD 4.0]). The majority of participants were White (67%); 288 (65%) participants were female and 153 (35%) were male; and the mean age was 46.6 years (SD 13.0; table 1). At the time of random allocation, the group assigned to placebo had slightly higher bodyweight, and more participants older than 65 years, who were Black, and who were Hispanic or Latino ethnicity (table 1). Between week 48 and week 60, bodyweight plateau occurred in 118 (84%) of 140, 120 (83%) of 144, and 80 (85%) of 91 participants randomly allocated to continue tirzepatide MTD, reduce to tirzepatide 5 mg, or switch to placebo, respectively (table 1). Overall, 11 (8%) of 138, 35 (25%) of 142, and 60 (67%) of 90 received rescue therapy in the tirzepatide MTD, 5 mg tirzepatide, and placebo groups, respectively (table 2, appendix 2 p 19). Additional baseline information is provided in appendix 2 (pp 10–11).

At week 112, the mean model-based estimate percentage change from baseline in bodyweight was –21.9% (95% CI –23.5 to –20.3), equivalent to –24.6 kg (–26.6 to –22.6) with tirzepatide MTD; –16.6% (–18.0 to –15.1), equivalent to –18.8 kg (–20.5 to –17.2) with 5 mg tirzepatide; and –9.9% (–11.1 to –8.8), equivalent to –11.3 kg (–12.6 to –10.0) with placebo (figure 3A, C, table 2). Both tirzepatide doses were superior to placebo, with estimated treatment differences relative to placebo of –12.0% (95% CI –13.8 to –10.1) or –13.3 kg (–15.5 to –11.2) for tirzepatide MTD and –6.6% (–8.3 to –5.0) or –7.6 kg (–9.4 to –5.7) for 5 mg tirzepatide (p<0.0001 for all comparisons; figure 3B, D, table 2). For the efficacy estimand (appendix 2 pp 12, 20), the mean model-based estimate change in bodyweight was –22.4% (95% CI –23.8 to –21.1) or –25.2 kg (–26.8 to –23.5) with tirzepatide MTD, –17.0% (–18.2 to –15.8) or –19.2 kg (–20.6 to –17.8) with 5 mg tirzepatide, and –10.1% (–11.2 to –9.0) or –11.5 kg (–12.7 to –10.3) with placebo. Estimated treatment differences were –12.3% (95% CI –14.1 to –10.6) or –13.7 kg (–15.7 to –11.7) for tirzepatide MTD versus placebo, and –6.9 percentage points (–8.5 to –5.3) or –7.7 kg (–9.6 to –5.9) for 5 mg tirzepatide versus placebo (p<0.0001 for all comparisons).

At week 112, the model-based estimate percent change from random allocation in bodyweight was –0.2% (95% CI –1.5 to 1.0) or –0.2 kg (–1.3 to 0.9) with tirzepatide MTD, 7.0% (5.8 to 8.2) or 6.0 kg (5.0 to 7.0) with 5 mg tirzepatide, and 15.2% (13.6 to 16.8) or 12.8 kg (11.5 to 14.1) with placebo (table 2). Both tirzepatide doses were superior to placebo, with estimated treatment differences relative to placebo of –15.4%

| | Week 0* | Week 60 (random allocation) | | |
|---|---|---|------------------------------------|--------------------------|
| | Weight-loss period with tirzepatide MTD (n=441) | 10 mg or 15 mg tirzepatide, MTD (n=140) | Reduce to 5 mg tirzepatide (n=144) | Switch to placebo (n=94) |
| Age, years | 46.6 (13.0) | 48.5 (13.2) | 49.4 (12.3) | 46.4 (12.6) |
| <65 years | 391 (89%) | 119 (85%) | 121 (84%) | 86 (91%) |
| ≥65 years | 50 (11%) | 21 (15%) | 23 (16%) | 8 (9%) |
| Sex† | | | | |
| Male | 153 (35%) | 49 (35%) | 50 (35%) | 32 (34%) |
| Female | 288 (65%) | 91 (65%) | 94 (65%) | 62 (66%) |
| Race‡ | | | | |
| White | 295/438 (67%) | 89/139 (64%) | 101/144 (70%) | 57/92 (62%) |
| Black or African American | 107/438 (24%) | 35/139 (25%) | 34/144 (24%) | 29/92 (32%) |
| Asian | 20/438 (5%) | 8/139 (6%) | 5/144 (3%) | 4/92 (4%) |
| Multiple | 11/438 (3%) | 6/139 (4%) | 3/144 (2%) | 2/92 (2%) |
| American Indian or Alaska Native | 3/438 (1%) | 0 | 1/144 (1%) | 0 |
| Native Hawaiian or Other Pacific Islander | 2/438 (<1%) | 1/139 (1%) | 0 | 0 |
| Ethnicity† | | | | |
| Hispanic or Latino | 99 (22%) | 27 (19%) | 31 (22%) | 25 (27%) |
| Not Hispanic or Latino | 342 (78%) | 113 (81%) | 113 (78%) | 69 (73%) |
| Duration of obesity, years† | 12.8 (5.8–21.9) | 13.8 (5.8–23.8) | 11.4 (5.8–20.8) | 13.3 (6.8–23.8) |
| Bodyweight, kg | 113.8 (27.0) | 88.3 (22.3) | 88.7 (24.5) | 93.7 (27.5) |
| BMI, kg/m ² | 40.1 (8.1) | 30.8 (6.9) | 31.1 (7.2) | 33.4 (8.7) |
| BMI category | | | | |
| <30 | 20 (5%) | 72 (51%) | 76 (53%) | 34 (36%) |
| ≥30 to <35 | 111 (25%) | 33 (24%) | 36 (25%) | 29 (31%) |
| ≥35 to <40 | 122 (28%) | 21 (15%) | 14 (10%) | 11 (12%) |
| ≥40 | 188 (43%) | 14 (10%) | 18 (13%) | 20 (21%) |
| Bodyweight plateau | NA | 118 (84%) | 120 (83%) | 80 (85%) |
| Percent bodyweight reduction at week 60 | | | | |
| <20% | NA | 62 (44%) | 64 (44%) | 42 (45%) |
| ≥20% | NA | 78 (56%) | 80 (56%) | 52 (55%) |
| Waist circumference, cm | 119.4 (17.5) | 99.1 (17.2) | 100.0 (17.8) | 103.6 (19.9) |
| HbA1c | 5.64% (0.36) | 5.16% (0.31) | 5.13% (0.33) | 5.09% (0.34) |
| HbA1c, mmol/mol | 38.2 (4.0) | 32.9 (3.4) | 32.6 (3.6) | 32.1 (3.7) |
| Fasting serum glucose, mg/dL | 94.7 (11.8) | 82.1 (8.0) | 82.2 (7.7) | 80.5 (6.8) |
| Fasting serum glucose, mmol/L | 5.3 (0.7) | 4.6 (0.4) | 4.6 (0.4) | 4.5 (0.4) |
| Systolic blood pressure, mm Hg | 126.3 (12.8) | 116.3 (13.1) | 117.4 (14.3) | 119.1 (13.8) |
| Diastolic blood pressure, mm Hg | 81.3 (8.2) | 77.6 (9.8) | 77.9 (9.3) | 78.5 (8.4) |
| Pulse, bpm | 71.9 (9.8) | 74.9 (9.6) | 74.9 (8.4) | 75.2 (8.5) |

(Table 1 continues on next page)

(95% CI -17.5 to -13.4) or -13.0 kg (-14.7 to -11.3) for tirzepatide MTD and -8.2% (-10.1 to -6.2) or -6.8 kg (-8.4 to -5.2) for 5 mg tirzepatide ($p < 0.0001$, all comparisons; table 2). For the efficacy estimand, the percent change from random allocation in bodyweight was -0.9% (95% CI -2.0 to 0.2) or -0.8 kg (-1.8 to 0.2) with tirzepatide MTD, 6.5% (5.3 to 7.6) or 5.6 kg (4.6 to 6.6) with 5 mg tirzepatide, and 14.9% (13.4 to 16.4) or 12.6 kg (11.4 to 13.8) with placebo, with estimated treatment differences were -15.9% (95% CI -17.7 to -14.0) or -13.4 kg (-15.0 to -11.8) for tirzepatide MTD, and -8.5% (-10.3 to -6.6) or -7.0 kg (-8.5 to -5.4) for 5 mg tirzepatide versus placebo ($p < 0.0001$ for all comparisons; appendix 2 pp 12, 21).

At week 84, the mean model-based estimate percent change from baseline in bodyweight was -22.4% (95% CI -23.8 to -21.1) with tirzepatide MTD, -18.7% (-20.1 to -17.4) with 5 mg tirzepatide, and -12.3% (-13.7 to -10.9) with placebo; giving estimated treatment differences of -10.1% (95% CI -11.9 to -8.4) for tirzepatide MTD versus placebo, and -6.4% (-8.2 to -4.7) for 5 mg tirzepatide versus placebo ($p < 0.0001$ for all comparisons; table 2). For the efficacy estimand, percent change from baseline in bodyweight at week 84 was -22.4% (95% CI -23.6 to -21.3) with tirzepatide MTD, -18.8% (-19.9 to -17.7) with 5 mg tirzepatide, and -12.3% (-13.5 to -11.0) with placebo, with estimated treatment differences of -10.2% (95% CI -11.9 to -8.5) for tirzepatide MTD versus placebo, and -6.5% (-8.2 to -4.8) for 5 mg tirzepatide versus placebo ($p < 0.0001$ for all comparisons; appendix 2 p 12).

Among participants who reached a bodyweight plateau, those continuing tirzepatide MTD maintained 96.5% (95% CI 88.5 – 104.5) of bodyweight reduction obtained during the weight-loss period and those who reduced to the 5 mg tirzepatide dose maintained 67.9% (61.9 – 73.9), versus 42.8% (36.5 – 49.1) with placebo, with an estimated treatment difference relative to placebo of 53.7% (95% CI 43.6 – 63.8) with tirzepatide MTD and 25.1% (16.7 – 33.6) for 5 mg tirzepatide at week 112 ($p < 0.0001$ for all comparisons; table 2). For the efficacy estimand, those continuing tirzepatide MTD maintained 100.0% (95% CI 93.3 – 106.8) of bodyweight reduction and those who reduced to the 5 mg tirzepatide dose maintained 70.5% (65.9 – 75.1) versus 44.3% (38.5 – 50.1) with placebo at week 112, with an estimated treatment difference relative to placebo of 55.7% (95% CI 46.8 – 64.6) with tirzepatide MTD and 26.2% (18.8 – 33.6) for 5 mg tirzepatide ($p < 0.0001$ for all comparisons; figure 3E, appendix 2 pp 12, 22).

Among participants who reached a bodyweight plateau, 80% or greater of the bodyweight reduction obtained during the weight-loss period was maintained in 77.5% (SE 3.9) of participants treated with tirzepatide MTD (90 of 116), 42.4% (4.4) with 5 mg tirzepatide (50 of 118), and 10.4% (3.5) with placebo at week 112 (eight of 76), with a risk difference relative to placebo of 67.1% (95% CI

| | Week 0* | Week 60 (random allocation) | | |
|--|---|---|------------------------------------|--------------------------|
| | Weight-loss period with tirzepatide MTD (n=441) | 10 mg or 15 mg tirzepatide, MTD (n=140) | Reduce to 5 mg tirzepatide (n=144) | Switch to placebo (n=94) |
| (Continued from previous page) | | | | |
| Lipid parameters, mg/dL | | | | |
| Total cholesterol | 192.2 (37.0) | 182.0 (40.5) | 177.4 (34.6) | 184.7 (39.1) |
| HDL cholesterol | 50.7 (13.4) | 54.7 (15.0) | 54.9 (13.3) | 54.6 (14.1) |
| LDL cholesterol | 115.7 (31.1) | 110.1 (37.0) | 105.2 (29.5) | 112.3 (33.8) |
| VLDL cholesterol | 25.2 (11.8) | 17.2 (6.6) | 17.3 (8.4) | 18.1 (9.2) |
| Triglycerides | 128.7 (70.0) | 86.3 (33.0) | 86.6 (41.9) | 90.4 (45.9) |
| eGFR, mL/min per 1.73 m ² ‡ | 89.7 (19.5) | 94.5 (19.1) | 95.3 (18.4) | 95.8 (17.7) |
| Comorbidities | | | | |
| Prediabetes | 268 (61%) | 93 (66%) | 89 (62%) | 55 (59%) |

Data are mean (SD) or n (%), except duration of obesity, which is presented as median (IQR). A full list of comorbidities and number of comorbidities at baseline is provided in appendix 2 (p 10). Baseline SF-36v2 (norm-based) scores are provided in appendix 2 (p 11). bpm=beats per minute. eGFR=estimated glomerular filtration rate. HbA1c=glycated haemoglobin. MTD=maximum tolerated dose. NA=not applicable. SF-36v2=Short Form-36 Health Survey Version 2. *Start of 60-week open-label weight-loss period with tirzepatide MTD. †Sex, race, ethnicity, and duration of obesity were self-reported. The denominator for Race is based on number of participants with no missing data. ‡eGFR was calculated with the serum cystatin-C Chronic Kidney Disease Epidemiology Collaboration equation.

Table 1: Demographics and clinical characteristics at baseline and random allocation

56.7 – 77.5) with tirzepatide MTD and 32.0% (21.0 – 43.0) with 5 mg tirzepatide ($p < 0.0001$ for all comparisons; table 2, figure 3F). In other words, compared to switching to placebo, the odds of maintaining most of the lost bodyweight ($\geq 80\%$) were approximately seven times higher with continued MTD and four times higher with reducing the dose to 5 mg. For the efficacy estimand, 80% or greater of the bodyweight reduction obtained during the weight-loss period was maintained in 80.4% (SE 3.7) of participants treated with tirzepatide MTD, 44.5% (4.5) with 5 mg tirzepatide group, and 11.3% (3.8) with placebo at week 112, with a risk difference relative to placebo of 69.1% (95% CI 58.6 – 79.6) with tirzepatide MTD and 33.2% (21.9 – 44.6) with 5 mg tirzepatide ($p < 0.0001$ for all comparisons; appendix 2 p 12).

For the efficacy estimand, improvements in BMI, waist circumference, glycaemia, blood pressure, and lipid profile were observed with tirzepatide (MTD and 5 mg) compared with placebo (table 2 and appendix 2 pp 13–14, 24–27). At week 112, the proportion of participants with prediabetes at baseline who obtained an HbA1c less than 5.7% was 92.7% with continued tirzepatide MTD and 84.4% with the reduced dose of 5 mg tirzepatide, compared with 51.0% of participants who switched to placebo (appendix 2 p 25). Continuing tirzepatide MTD improved physical function scores by 1.9 points (95% CI 0.5 to 3.4), while reducing to 5 mg improved scores by 1.2 points (-0.2 to 2.6) versus placebo, with greater improvement in the physical component summary observed with tirzepatide MTD (table 2 and appendix 2 pp 13–14). Improvements in role-physical, bodily pain, general health,

vitality, social functioning, and mental health were observed with tirzepatide MTD, while reducing to the 5 mg dose improved vitality and mental health scores compared with switching to placebo (appendix 2 pp 13–14).

Overall, the incidence of adverse events was numerically higher in the tirzepatide groups compared with placebo (table 3). During the weight-loss period, the most frequently reported adverse events with tirzepatide were gastrointestinal disorders, at 291 (66%) of 441 (156 [35%] nausea, 136 [31%] constipation, 106 [24%] diarrhoea, and 73 [17%] vomiting). Most events were transient, generally occurring during dose-escalation, and were typically mild to moderate in severity (appendix 2 p 28). During the weight maintenance period, the most frequently reported adverse events with tirzepatide were also gastrointestinal (vomiting, diarrhoea, upper abdominal pain, and nausea). The incidence of nausea, vomiting, and diarrhoea during the weight maintenance period was 19 (14%) of 139 for tirzepatide MTD (nausea: eight [6%], vomiting: nine [6%], diarrhoea: ten [7%]); ten (7%) of 142 for 5 mg tirzepatide (nausea: six [4%], vomiting: one [1%], diarrhoea: seven [5%]); and three (3%) of 91 for placebo (nausea: two [2%], vomiting: none, diarrhoea: one [1%]). 11 (2%) of 441 participants discontinued study treatment due to gastrointestinal adverse events with tirzepatide MTD during the weight-loss period; overall, 18 (4%) participants discontinued due to any adverse events. Serious adverse events were reported by 20 (5%) participants during the weight-loss period and by three (1%) participants during the weight maintenance period (tirzepatide MTD: none, 5 mg tirzepatide: two [1%], placebo one [1%]; table 3). Adjudication-confirmed major adverse cardiovascular

events was reported in two (<1%) participants during the weight-loss period and one (<1%) participant who switched to placebo during the weight maintenance period (table 3). One death occurred during the weight-loss period due to hypoxic and hypercapnic respiratory failure and was not considered related to study treatment by the investigator (table 3 and appendix 2 p 15). Additional safety measures are detailed in appendix 2 (p 16).

Discussion

As more people living with obesity achieve clinically meaningful bodyweight reductions with effective obesity medications, the question of whether stopping or reducing the dose of obesity medication can maintain the bodyweight reduction has been commonly raised. Furthermore, it remains unknown in obesity management whether the intensity of obesity treatment required to achieve the initial bodyweight reduction versus maintenance of bodyweight reduction should be the same or different given the various hypotheses for (eg, possible decrease in needed medication dose upon substantial bodyweight reduction and altered pharmacokinetics) or against (eg, metabolic adaptation or the chronic progressive disease of obesity) reducing the treatment intensity to maintain bodyweight reduction.^{3,22} To our knowledge, this is the first randomised controlled trial of obesity medication addressing this question. Results demonstrated that most of the participants continuing tirzepatide—either at MTD or reduced to 5 mg—maintained most of the bodyweight reduction initially obtained with tirzepatide MTD, although results varied with the 5 mg dose. Switching to placebo led to a

| Treatment-regimen estimand | 10 mg or 15 mg tirzepatide, MTD (n=138) | Reduce to 5 mg tirzepatide (n=142) | Switch to placebo (n=90) | 10 mg or 15 mg tirzepatide, MTD vs switch to placebo ETD (95% CI); p value | 5 mg tirzepatide vs switch to placebo ETD (95% CI); p value |
|---|---|------------------------------------|--------------------------|--|---|
| Primary endpoint in all participants at week 112* | | | | | |
| Percent change from baseline in bodyweight | -21.9% (-23.5 to -20.3) | -16.6% (-18.0 to -15.1) | -9.9% (-11.1 to -8.8) | -12.0% (-13.8 to -10.1); <0.0001 | -6.6% (-8.3 to -5.0); <0.0001 |
| Key secondary endpoints in all participants at week 112, unless otherwise noted* | | | | | |
| Change from baseline in bodyweight, kg | -24.6 (-26.6 to -22.6) | -18.8 (-20.5 to -17.2) | -11.3 (-12.6 to -10.0) | -13.3 (-15.5 to -11.2); <0.0001 | -7.6 (-9.4 to -5.7); <0.0001 |
| Percent change from random allocation in bodyweight | -0.2% (-1.5 to 1.0) | 7.0% (5.8 to 8.2) | 15.2% (13.6 to 16.8) | -15.4% (-17.5 to -13.4); <0.0001 | -8.2% (-10.1 to -6.2); <0.0001 |
| Change from random allocation in bodyweight, kg | -0.2 (-1.3 to 0.9) | 6.0 (5.0 to 7.0) | 12.8 (11.5 to 14.1) | -13.0 (-14.7 to -11.3); <0.0001 | -6.8 (-8.4 to -5.2); <0.0001 |
| Percent change from baseline in bodyweight at week 84 | -22.4% (-23.8 to -21.1) | -18.7% (-20.1 to -17.4) | -12.3% (-13.7 to -10.9) | -10.1% (-11.9 to -8.4); <0.0001 | -6.4% (-8.2 to -4.7); <0.0001 |
| Percent maintenance of bodyweight reduction obtained during the 60-week weight-loss period in participants who reached a bodyweight plateau† | 96.5% (88.5 to 104.5) | 67.9% (61.9 to 73.9) | 42.8% (36.5 to 49.1) | 53.7% (43.6 to 63.8); <0.0001 | 25.1% (16.7 to 33.6); <0.0001 |
| Percentage of participants maintaining ≥80% of the bodyweight reduction obtained during the 60-week weight-loss period among those who reached a bodyweight plateau, n/N† | 77.5% (3.9) [90/116] | 42.4% (4.4) [50/118] | 10.4% (3.5) [8/76] | 67.1% (56.7 to 77.5); <0.0001 | 32.0% (21.0 to 43.0); <0.0001 |

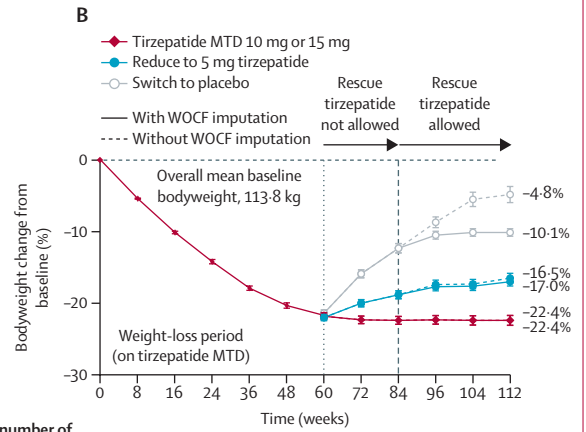
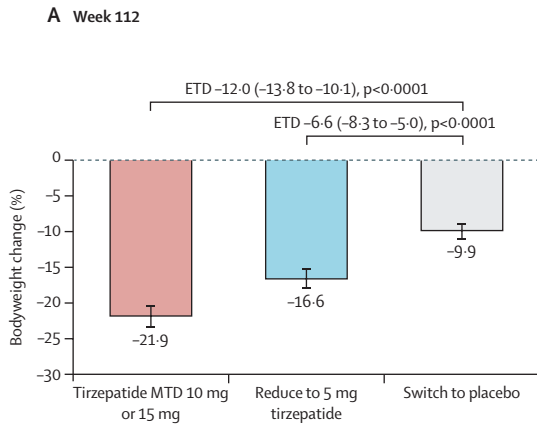
(Table 2 continues on next page)

| | 10 mg or 15 mg tirzepatide, MTD (n=138) | Reduce to 5 mg tirzepatide (n=142) | Switch to placebo (n=90) | 10 mg or 15 mg tirzepatide, MTD vs switch to placebo ETD (95% CI); p value | 5 mg tirzepatide vs switch to placebo ETD (95% CI); p value |
|--|--|---------------------------------------|--------------------------|---|---|
| (Continued from previous page) | | | | | |
| Efficacy estimand | | | | | |
| Additional secondary endpoints in all participants at week 112, unless otherwise noted‡ | | | | | |
| Change from random allocation in waist circumference, cm | -0.6 (-1.6 to 0.4) | 3.8 (2.7 to 4.8) | 9.3 (7.9 to 10.6) | -9.9 (-11.6 to -8.1) | -5.5 (-7.2 to -3.7) |
| Percent maintenance of bodyweight reduction obtained during the 60-week weight-loss period | 102.4% (96.5 to 108.2) | 71.7% (67.4 to 76.1) | 44.6% (39.5 to 49.7) | 57.8% (50.0 to 65.5) | 27.1% (20.4 to 33.8) |
| Percent maintenance of bodyweight reduction obtained during the 60-week weight-loss period at week 84 in participants who reached a bodyweight plateau† | 101.9% (97.4 to 106.5) | 81.7% (76.9 to 86.6) | 52.6% (46.7 to 58.6) | 49.3% (41.8 to 56.8) | 29.1% (21.5 to 36.8) |
| Maintenance of ≥15% bodyweight reduction among those who have already lost ≥15% bodyweight at random allocation† | 94.2% (2.4) [100/106] | 64.9% (4.3) [71/109] | 22.3% (4.8) [16/71] | 71.9% (61.3 to 82.4) | 42.6% (30.1 to 55.0) |
| Exploratory endpoints in all participants at week 112‡ | | | | | |
| Use of rescue tirzepatide for weight regain ≥50% of the bodyweight reduction obtained at random allocation, n/N | 7.9% (2.3) [11/138] | 24.6% (3.5) [35/142] | 67.9% (4.9) [60/90] | -60.0% (-70.6 to -49.4) | -43.3% (-55.0 to -31.6) |
| Change from baseline in BMI, kg/m ² | -9.0 (-9.6 to -8.4) | -6.8 (-7.3 to -6.3) | -4.1 (-4.5 to -3.6) | -4.9 (-5.6 to -4.2) | -2.7 (-3.4 to -2.1) |
| Change from baseline in waist circumference, cm | -20.1 (-21.5 to -18.6) | -16.0 (-17.4 to -14.5) | -8.4 (-10.0 to -6.9) | -11.6 (-13.8 to -9.5) | -7.5 (-9.7 to -5.4) |
| Percent change from baseline in triglycerides, mg/dL | -27.2% (-31.4 to -22.8) | -19.0% (-23.5 to -14.2) | -9.6% (-15.6 to -3.3) | -19.5% (-26.4 to -11.9) | -10.4% (-18.0 to -2.0) |
| Percent change from baseline in HDL cholesterol, mg/dL | 12.6% (9.9 to 15.3) | 13.9% (10.9 to 17.0) | 11.9% (8.6 to 15.3) | 0.6% (-3.1 to 4.5) | 1.8% (-2.2 to 6.0) |
| Percent change from baseline in VLDL cholesterol, mg/dL | -26.7% (-30.9 to -22.2) | -18.8% (-23.4 to -13.9) | -9.2% (-15.2 to -2.7) | -19.3% (-26.3 to -11.6) | -10.6% (-18.3 to -2.2) |
| Percent change from baseline in non-HDL, mg/dL | -11.7% (-15.4 to -7.8) | -7.2% (-10.3 to -4.1) | -1.5% (-5.3 to 2.4) | -10.4% (-15.4 to -5.0) | -5.8% (-10.6 to -0.8) |
| Change from baseline in systolic blood pressure, mm Hg | -8.7 (-10.5 to -6.8) | -4.7 (-6.6 to -2.7) | -0.4 (-2.8 to 2.1) | -8.3 (-11.4 to -5.2) | -4.3 (-7.4 to -1.2) |
| Change from baseline in diastolic blood pressure, mm Hg | -3.8 (-5.2 to -2.4) | -2.7 (-4.0 to -1.3) | -0.1 (-1.6 to 1.5) | -3.7 (-5.8 to -1.7) | -2.6 (-4.6 to -0.6) |
| Change from baseline in HbA1c, % | -0.53% (-0.57 to -0.49) | -0.41% (-0.45 to -0.36) | -0.19% (-0.24 to -0.15) | -0.34% (-0.40 to -0.27) | -0.21% (-0.28 to -0.15) |
| Change from baseline in HbA1c, mmol/mol | -5.8 (-6.3 to -5.3) | -4.4 (-5.0 to -3.9) | -2.1 (-2.6 to -1.6) | -3.7 (-4.4 to -3.0) | -2.3 (-3.1 to -1.6) |
| Change from baseline in fasting serum glucose, mg/dL | -10.6 (-12.1 to -9.1) | -7.4 (-9.3 to -5.5) | -2.6 (-4.5 to -0.8) | -8.0 (-10.4 to -5.6) | -4.8 (-7.4 to -2.2) |
| Percent change from baseline in fasting insulin, pmol/L | -44.9% (-50.6 to -38.5) | -33.0% (-39.7 to -25.7) | -18.4% (-26.0 to -10.0) | -32.5% (-41.7 to -21.8) | -18.0% (-28.9 to -5.3) |
| Change from baseline in physical component summary score | 6.0 (5.0 to 7.0) | 4.6 (3.7 to 5.4) | 3.4 (2.0 to 4.8) | 2.6 (0.9 to 4.3) | 1.2 (-0.4 to 2.8) |
| Change from baseline in mental component summary score | -0.0 (-1.3 to 1.3) | -0.1 (-1.2 to 0.9) | -1.6 (-2.8 to -0.4) | 1.6 (-0.2 to 3.4) | 1.5 (-0.2 to 3.1) |
| Maintenance of ≥20% bodyweight reduction among those who have already lost ≥20% bodyweight at random allocation, n/N† | 84.7% (4.2) [65/77] | 66.5% (5.4) [53/79] | 13.3% (4.8) [7/51] | 71.5% (59.0 to 84.0) | 53.3% (39.2 to 67.4) |
| Data are model-based estimates (95% CI) assessed using analysis of covariance from the modified treatment-regimen estimand for primary and key secondary endpoints and using MMRM for the efficacy estimand for additional secondary and exploratory endpoints. Lipids and fasting insulin are estimate (95% CI) using log transformation. Maintenance of bodyweight reduction endpoints and use of rescue tirzepatide are presented as percentage (SE). CIs were not adjusted for multiplicity and should not be used for hypothesis testing. ETD=estimated treatment difference. HbA1c=glycated haemoglobin. HDL=high-density lipoprotein. MMRM=mixed model for repeated measures. MTD=maximum tolerated dose. VLDL=very low-density lipoprotein. *The primary and key secondary endpoints were tested under type 1 error procedure using an overall two-sided nominal significance level of 0.05. †The denominator includes participants who reached bodyweight plateau at random allocation (week 60). ‡Not controlled for multiplicity. | | | | | |

Table 2: Primary and secondary endpoints by treatment group

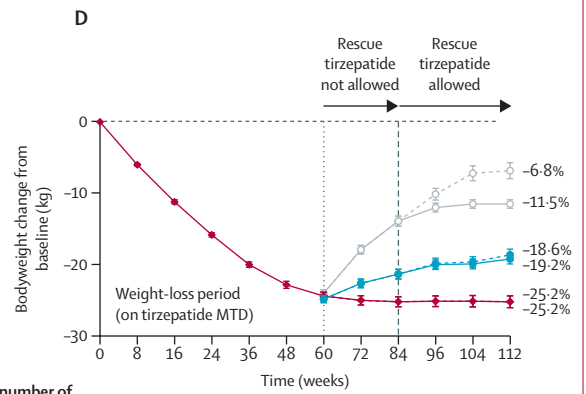
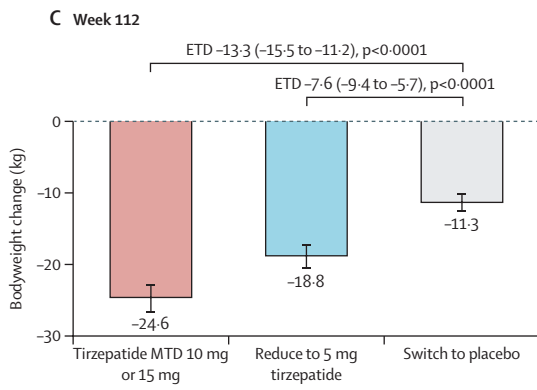
substantial weight regain despite the continued lifestyle intervention, as previously reported in tirzepatide and other obesity medication trials.^{12,23,24} Consistent with other chronic progressive diseases, the current findings show

that discontinuing effective treatment in people living with obesity resulted in reversal of therapeutic benefit and caused significant weight regain, often back towards the pretreatment bodyweight over time.^{23,25,26}



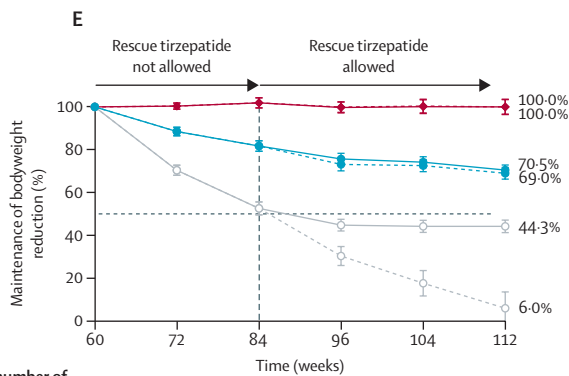
Cumulative number of participants who received rescue tirzepatide

| | | | | | | | | | | | | |
|------------------------|----|----|----|----|----|----|----|----|----|----|----|----|
| Tirzepatide MTD | .. | .. | .. | .. | .. | .. | .. | .. | 2 | 5 | 11 | .. |
| 10 mg or 15 mg group | .. | .. | .. | .. | .. | .. | .. | .. | 19 | 30 | 35 | .. |
| 5 mg tirzepatide group | .. | .. | .. | .. | .. | .. | .. | .. | 41 | 56 | 60 | .. |
| Placebo group | .. | .. | .. | .. | .. | .. | .. | .. | .. | .. | .. | .. |



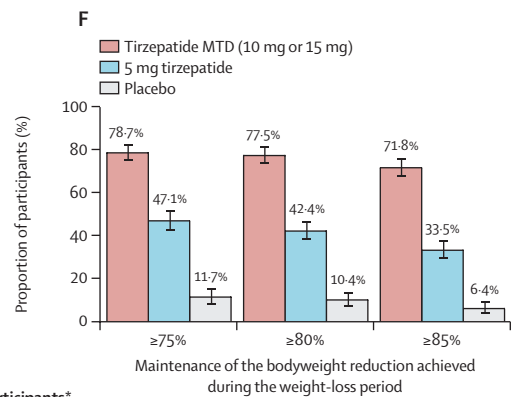
Cumulative number of participants who received rescue tirzepatide

| | | | | | | | | | | | | |
|------------------------|----|----|----|----|----|----|----|----|----|----|----|----|
| Tirzepatide MTD | .. | .. | .. | .. | .. | .. | .. | .. | 2 | 5 | 11 | .. |
| 10 mg or 15 mg group | .. | .. | .. | .. | .. | .. | .. | .. | 19 | 30 | 35 | .. |
| 5 mg tirzepatide group | .. | .. | .. | .. | .. | .. | .. | .. | 41 | 56 | 60 | .. |
| Placebo group | .. | .. | .. | .. | .. | .. | .. | .. | .. | .. | .. | .. |



Cumulative number of participants who received rescue tirzepatide

| | | | | | | |
|------------------------|----|----|----|----|----|----|
| Tirzepatide MTD | .. | .. | 2 | 5 | 11 | .. |
| 10 mg or 15 mg group | .. | .. | 19 | 30 | 35 | .. |
| 5 mg tirzepatide group | .. | .. | 41 | 56 | 60 | .. |
| Placebo group | .. | .. | .. | .. | .. | .. |



Number of participants*

| n | 92 | 56 | 9 | 90 | 50 | 8 | 83 | 40 | 5 |
|---|-----|-----|----|-----|-----|----|-----|-----|----|
| N | 116 | 118 | 76 | 116 | 118 | 76 | 116 | 118 | 76 |

This trial evaluated bodyweight reduction maintenance through various approaches given the absence of a widely accepted definition in the obesity field to date. First, continuing tirzepatide treatment at MTD resulted in clinically meaningful overall bodyweight reduction (21.9%) consistent with previous observations.^{9,12,14} In participants who reduced to 5 mg tirzepatide, their overall bodyweight reduction was 16.6%, which is comparable to the 12.3% bodyweight reduction previously observed in participants who received 5 mg tirzepatide throughout the SURMOUNT-1 3-year study.¹⁴ These findings support the hypothesis that the final maintenance dose, rather than the dosing trajectory, might be an important determinant of efficacy.¹⁴ The possibility of further weight regain over time with the reduced dose of 5 mg tirzepatide should also be considered given the lack of a plateau on the weight change trajectory. In participants who switched to placebo, their overall bodyweight reduction at week 112 was 9.9%. Most (67%) participants treated with placebo received rescue tirzepatide for weight regain. Therefore, percent bodyweight changes after week 84 among participants treated with placebo should be interpreted with this consideration; ongoing weight gain without rescue tirzepatide would be expected, as supported by previous findings¹² and our model simulations.

Weight changes from random allocation were minimal with continuing tirzepatide MTD (−0.2 kg or −0.2%), relatively greater with reducing the dose to 5 mg (6.0 kg or 7.0%), and significantly greater with switching to placebo (12.8 kg or 15.2%). In the recently completed ATTAIN-MAINTAIN trial, tirzepatide MTD followed by a switch to 36 mg daily oral orforglipron or MTD resulted in maintenance of bodyweight reduction, with an average difference of gaining 5 kg, which is similar to reducing to 5 mg tirzepatide reported here.²⁷ Together, these findings support tailoring long-term therapy for individualised obesity care.

Maintenance of bodyweight reduction was high with continued tirzepatide MTD. At week 112, the proportion of initial bodyweight reduction preserved was 96.5% with continued tirzepatide MTD and 67.9% with reducing to 5 mg tirzepatide, compared with 42.8% after switching to placebo. Consistently, the proportion of participants classified as maintainers (ie, those maintaining ≥80% of the bodyweight reduction obtained during the weight-loss period) was significantly greater with continued tirzepatide MTD (90 [77.5%] of 116) and with 5 mg tirzepatide (50 [42.4%] of 118) than with placebo (eight [10.4%] of 76). In other words, compared to switching to placebo, the odds of maintaining ≥80% bodyweight reduction were approximately seven times higher with continued tirzepatide MTD and four times higher with reducing to the 5 mg dose. Similar findings were observed with different thresholds (≥75% or ≥85%) used to define maintenance of most of the lost weight. Together, these findings demonstrate that persistent treatment with tirzepatide MTD resulted in robust maintenance of bodyweight reduction and, to a varying degree, with reduced to 5 mg tirzepatide.

These findings highlight the clinical importance of sustained bodyweight reduction in managing the disease of obesity and maintaining cardiometabolic health. Long-term retention of most intentional bodyweight reduction (≥75%) is associated with ongoing benefits, as shown by studies using various treatment modalities.^{28,29} In this trial, continued tirzepatide MTD led to preserved improvement in waist circumference, blood pressure, and lipids, while those who reduced the dose to 5 mg maintained clinically meaningful benefits to a relatively lesser extent. Conversely, tirzepatide discontinuation led to substantial weight regain and greater reversal of cardiometabolic benefits, consistent with prior studies.^{25,30} The effects of tirzepatide dose adjustment (MTD, 5 mg, or placebo) on body composition—particularly muscle mass and physical function—warrant further study as key considerations in long-term obesity management. Continued tirzepatide at MTD also yielded greater quality-of-life improvements than switching to placebo. Together, these findings support sustained obesity medication for ongoing cardiometabolic and quality-of-life benefits following initial weight loss, although the degree of weight maintenance required to preserve these improvements remains to be defined.

We explored several important components of weight management including a weight-loss period, weight plateau, and a weight maintenance period. The weight-loss period was determined according to tirzepatide's known profile during the trial design but could be tailored in clinical practice based on treatment modality and individual treatment response and goals. In the trial, participants demonstrated varied response in overall bodyweight reduction and maintenance with tirzepatide, consistent with previous studies.^{9,12} These findings

Figure 3: Effects of continued tirzepatide versus switching to placebo on bodyweight reduction and maintenance

Data are MBEs presented with 95% CIs unless otherwise noted. For line plots, data are descriptive mean (SE) in the weight-loss period. Solid lines in the weight maintenance period indicate MBEs with WOCF imputation, whereas dotted lines indicate MBEs without WOCF imputation. Error bars indicate standard error. Bodyweight reduction thresholds of ≥75% and ≥85% were not controlled for multiplicity. (A) Percentage change in bodyweight from baseline at week 112 (modified treatment-regimen estimand). (B) Percentage change in bodyweight from baseline to week 112 (efficacy estimand). (C) Absolute change in bodyweight from baseline to week 112 (modified treatment-regimen estimand). (D) Absolute change in bodyweight from baseline to week 112 (efficacy estimand). (E) Percentage maintenance of the bodyweight obtained during the 60-week weight-loss period among randomly allocated participants who reached a bodyweight plateau (efficacy estimand). (F) For maintenance of bodyweight reduction thresholds, error bars indicate standard error and thresholds of ≥75% and ≥85% were not controlled for multiplicity. ETD=estimated treatment difference. MBEs=model-based estimates. WOCF=worst observation carried forward. *N denotes number of participants with non-missing value at the specified timepoint; n denotes number of participants reaching threshold in observed data.

| | Pre-random allocation | Weight maintenance period | | | Total (n=372) | Risk difference (95% CI) | |
|---|---|---|------------------------------------|--------------------------|---------------|--|---------------------------------------|
| | Weight-loss period with MTD tirzepatide (n=441) | 10 mg or 15 mg tirzepatide, MTD (n=139) | Reduce to 5 mg tirzepatide (n=142) | Switch to placebo (n=91) | | 10 mg or 15 mg tirzepatide, MTD vs switch to placebo | 5 mg tirzepatide vs switch to placebo |
| Any adverse event emerging during treatment | 359 (81%) | 78 (56%) | 71 (50%) | 41 (45%) | 190 (51%) | 11.1 (-2.1 to 24.2) | 4.9 (-8.2 to 18.1) |
| Deaths* | 1 (<1%) | 0 | 0 | 0 | 0 | 0 | 0 |
| Serious adverse events | 20 (5%) | 0 | 2 (1%) | 1 (1%) | 3 (1%) | -1.1 (-3.2 to 1.0) | 0.3 (-2.6 to 3.2) |
| Adverse events or death leading to discontinuation of study treatment | 20 (5%)* | 0 | 1 (1%) | 0 | 1 (<1%) | 0 | 0.7 (-0.7 to 2.1) |
| Gastrointestinal disorders leading to discontinuation of study treatment | 11 (2%) | 0 | 0 | 0 | 0 | 0 | 0 |
| Nausea | 3 (1%) | 0 | 0 | 0 | 0 | 0 | 0 |
| Vomiting | 3 (1%) | 0 | 0 | 0 | 0 | 0 | 0 |
| Constipation | 2 (<1%) | 0 | 0 | 0 | 0 | 0 | 0 |
| Diarrhoea | 1 (<1%) | 0 | 0 | 0 | 0 | 0 | 0 |
| Abdominal pain, upper | 1 (<1%) | 0 | 0 | 0 | 0 | 0 | 0 |
| Obstructive pancreatitis | 1 (<1%) | 0 | 0 | 0 | 0 | 0 | 0 |
| Adverse events that emerged during treatment and occurred in ≥5% of participants in any treatment group | | | | | | | |
| Nausea | 156 (35%) | 8 (6%) | 6 (4%) | 2 (2%) | 16 (4%) | 3.6 (-1.3 to 8.5) | 2.0 (-2.4 to 6.5) |
| Vomiting | 73 (17%) | 9 (6%) | 1 (1%) | 0 | 10 (3%) | 6.5 (2.4 to 10.6) | 0.7 (-0.7 to 2.1) |
| Diarrhoea | 106 (24%) | 10 (7%) | 7 (5%) | 1 (1%) | 18 (5%) | 6.1 (1.3 to 10.9) | 3.8 (-0.3 to 8.0) |
| Constipation | 136 (31%) | 1 (1%) | 5 (4%) | 4 (4%) | 10 (3%) | -3.7 (-8.1 to 0.8) | -0.9 (-6.1 to 4.3) |
| Ercutation | 34 (8%) | 4 (3%) | 1 (1%) | 0 | 5 (1%) | 2.9 (0.1 to 5.7) | 0.7 (-0.7 to 2.1) |
| Dyspepsia | 31 (7%) | 3 (2%) | 1 (1%) | 0 | 4 (1%) | 2.2 (-0.3 to 4.6) | 0.7 (-0.7 to 2.1) |
| Gastro-oesophageal reflux disease | 31 (7%) | 2 (1%) | 1 (1%) | 1 (1%) | 4 (1%) | 0.3 (-2.6 to 3.3) | -0.4 (-2.9 to 2.2) |
| Abdominal pain | 27 (6%) | 2 (1%) | 2 (1%) | 0 | 4 (1%) | 1.4 (-0.5 to 3.4) | 1.4 (-0.5 to 3.3) |
| Abdominal distension | 23 (5%) | 4 (3%) | 2 (1%) | 1 (1%) | 7 (2%) | 1.8 (-1.7 to 5.3) | 0.3 (-2.6 to 3.2) |
| Upper respiratory tract infection | 32 (7%) | 2 (1%) | 5 (4%) | 2 (2%) | 9 (2%) | -0.8 (-4.4 to 2.9) | 1.3 (-3.0 to 5.6) |
| COVID-19 | 30 (7%) | 2 (1%) | 4 (3%) | 0 | 6 (2%) | 1.4 (-0.5 to 3.4) | 2.8 (0.1 to 5.5) |
| Influenza | 23 (5%) | 6 (4%) | 2 (1%) | 4 (4%) | 12 (3%) | -0.1 (-5.5 to 5.3) | -3.0 (-7.6 to 1.7) |
| Sinusitis | 12 (3%) | 7 (5%) | 7 (5%) | 0 | 14 (4%) | 5.0 (1.4 to 8.7) | 4.9 (1.4 to 8.5) |
| Urinary tract infection | 12 (3%) | 7 (5%) | 2 (1%) | 0 | 9 (2%) | 5.0 (1.4 to 8.7) | 1.4 (-0.5 to 3.3) |
| Injection site reaction | 40 (9%) | 8 (6%) | 3 (2%) | 0 | 11 (3%) | 5.8 (1.9 to 9.6) | 2.1 (-0.3 to 4.5) |
| Fatigue | 45 (10%) | 2 (1%) | 0 | 0 | 2 (1%) | 1.4 (-0.5 to 3.4) | 0 |
| Headache | 41 (9%) | 3 (2%) | 5 (4%) | 3 (3%) | 11 (3%) | -1.1 (-5.5 to 3.3) | 0.2 (-4.5 to 5.0) |
| Dizziness | 32 (7%) | 2 (1%) | 1 (1%) | 0 | 3 (1%) | 1.4 (-0.5 to 3.4) | 0.7 (-0.7 to 2.1) |
| Decreased appetite | 24 (5%) | 0 | 0 | 0 | 0 | 0 | 0 |
| Alopecia | 41 (9%) | 1 (1%) | 0 | 0 | 1 (<1%) | 0.7 (-0.7 to 2.1) | 0 |
| Adverse events of special interest occurring in one or more participants | | | | | | | |
| Severe or serious gastrointestinal events | 8 (2%) | 1 (1%) | 2 (1%) | 0 | 3 (1%) | NA | NA |
| Malignancies | 4 (1%) | 0 | 1 (1%) | 0 | 1 (<1%) | NA | NA |
| Adjudication-confirmed MACE | 2 (<1%) | 0 | 0 | 1 (1%) | 1 (<1%) | NA | NA |
| Adjudication-confirmed pancreatic events | 0 | 0 | 0 | 0 | 0 | NA | NA |

Data are number of participants (%). Data obtained during the weight maintenance period after rescue were excluded. The total N for the open-label weight-loss period includes anyone who got treatment, whereas the total N for the double-blind weight maintenance period includes anyone who received treatment during the double-blind period only. Additional information is provided in appendix 2 (p 15). MACE=major adverse cardiovascular event. NA=not available. *Deaths were also counted as serious adverse events.

Table 3: Adverse events

highlight the heterogeneity of obesity phenotypes and treatment response and underscore the importance of tailoring obesity treatment to meet individual needs given the chronic, progressive, and complex nature of obesity.

In our study, 67% of patients treated with placebo, 25% of patients who had their dose lowered to 5 mg

tirzepatide, and 8% of patients treated with tirzepatide MTD received rescue tirzepatide. This novel and patient-centred trial ensured the magnitude of weight regain experienced by participants was no more than 50% given the potential harms associated with weight cycling or repeated bodyweight reductions and regains and likely

contributed to the relatively high rate of study completion in the placebo group in the context of a concurrent rise in the options and availability of obesity medications in the USA.³¹ Combined, these results underscore the importance of long-term continuous treatment to prevent disease recurrence and progression.

Continued tirzepatide treatment (MTD or 5 mg) was generally well-tolerated with a safety profile consistent with previous studies of tirzepatide.^{9–14} Although no direct comparisons were made between the tirzepatide groups, the 5 mg group appeared to have relatively fewer gastrointestinal events, suggesting better tolerability with the lower dose. In a clinical setting, providers might consider reducing the obesity medication dose to improve tolerability, albeit with a slightly lower maintenance of bodyweight reduction. In turn, the safety results further facilitate guiding individualised, patient-centred treatment decisions based on efficacy and tolerability. Furthermore, these observations are consistent with previous findings that bodyweight reduction obtained with tirzepatide appears to be largely independent of the presence or absence of gastrointestinal symptoms.³²

This study has several strengths, including the randomised controlled design and the duration of the open-label weight-loss period that allowed most participants to reach a bodyweight plateau. Furthermore, all participants received ongoing healthy lifestyle counselling and rescue tirzepatide in case of significant ($\geq 50\%$) weight regain was provided to limit the potential harm of weight cycling. To our knowledge, this is one of the first trials in weight management providing rescue obesity medication in response to a prespecified weight regain threshold. Limitations include the requirement of tolerating at least the 10 mg dose of tirzepatide and achieving at least 5% bodyweight reduction during the weight-loss period for random allocation, the exclusion of those with diabetes at baseline, a weight maintenance period limited to 52 weeks, a potential performance bias in participants who had weight regain after random allocation, and restrictions on initiating intensive behavioural therapy during the weight maintenance period.

Long-term therapy is important for maintaining bodyweight reductions and cardiometabolic benefits in adults with obesity.³ Continued tirzepatide at the MTD resulted in sustained maintenance of bodyweight reduction and related health benefits, while reducing the dose to 5 mg provided superior bodyweight reduction and related health benefits compared to discontinuation, although the degree of preserving clinically meaningful benefits varied. Combined, these findings underscore the importance of continued therapy for long-term obesity management and provide evidence for what to expect when reducing the intensity of obesity treatment such as dose lowering is warranted or desired. In turn, these data add to the evidence needed to inform individualised obesity care focused on sustained bodyweight reduction and improved cardiometabolic outcomes.

Contributors

CJL and EG-V contributed to the study design. CJL provided medical oversight during the trial. EGV and SD were responsible for the statistical analyses. CJL is the guarantor of this work and, as such, takes responsibility for the integrity of the data and the accuracy of the data analysis. DBH, EG-V, ADA, SD, JPD, AR, LCG, and CJL had full access to and verified the data. All authors participated in interpretation of the data and critical review of the manuscript, had full access to all the data in the study, and approved this manuscript to be submitted for publication.

Declaration of interests

DBH has acted as a consultant and speaker for Eli Lilly and Company and Novo Nordisk; has served as a consultant for Amgen, AstraZeneca, Boehringer Ingelheim, Kailera, Roche, and Zealand; and has received institutional research funding from Eli Lilly and Company, KVK Tech, Novo Nordisk, and Weight Watchers. LJA reports receiving consulting fees from Amgen, Atria, Boehringer Ingelheim, CinFina Pharma, Coteria, Currax Pharma, Eli Lilly and Company, Enterin, Helicore Biopharma, Jamieson Wellness, Juvena Therapeutics, Kallyope, MBX Bioscience, Novartis, Novo Nordisk, Penguin Bio, Pfizer, Prosciento, Senda Biosciences, Skye Bio, Summit Clinical, Syntis Bio, Verdiva, Veru Pharmaceuticals, and Zealand Pharmaceuticals; receiving lecture fees from Boehringer Ingelheim, Jamieson Wellness, Pfizer, Skye Bioscience, and Zealand Pharmaceuticals; receiving institutional research funding from Eli Lilly and Company, Novo Nordisk, Skye Bioscience, and Viking Therapeutics; having equity interests in Clic Bio, ERX Pharmaceuticals, Flyte Health, Jamieson Wellness, Juvena Therapeutics, Kallyope, MBX Bioscience, Mediflix, Metsera, Penguin Bio, Skye Bio, Syntis Bio, Verdiva, and Veru Pharmaceuticals; serving on a board of directors for ERX Pharmaceuticals, Flyte Health and Jamieson Wellness; receiving travel support from Eli Lilly, Jamieson Wellness, Novo Nordisk, Pfizer, and Zealand Pharma; and reports patents pending with Flyte Health. SW reports receiving non-financial support from Eli Lilly during the conduct of the study and personal fees from AbbVie, Amgen, AstraZeneca, Bausch Health Canada, Boehringer Ingelheim, Eli Lilly, i2o Therapeutics, Merck, Metsera, NGX, Novo Nordisk, and Regeneron outside the submitted work; has served on an advisory board for Boehringer Ingelheim; holds a leadership role for Obesity Canada and Obesity Society; and has received medical writing support from Boehringer Ingelheim, Eli Lilly, and Novo Nordisk. HEB's research site institution has received research grants from 89Bio, AbbVie, Allergan, Alon Medtech/Epitomee, Aligos, Altimune, Amgen, Anji Pharma, AstraZeneca, Bioage, Biohaven, Bionime, Boehringer Ingelheim, Carmot, Chorus/Bioage, Eli Lilly, Esperion, Evidera, Fractyl, Genentec, GlaxoSmithKline, Graviton, HighTide, Home Access, Horizon, Ionis, Kailera, Kallyope, LG-Chem, Marea, Madrigal, Marea, Merck, Metsera, Mineralys, New Amsterdam, Novartis, Novo Nordisk, Pfizer, Regeneron, Satsuma, Selecta, Shionogi, Skye/Birdrock, Tern, TIMI, Veru, Viking, Vivus, and Zomagen. HEB has served as an advisor (eg, executive or national committee member or protocol or drug development advisor) for 89Bio, Altimune, Amgen, Boehringer Ingelheim, Eli Lilly, Eva Pharma, Kiniksa, HighTide, Nestle, Novo Nordisk, Regeneron, Rivus, Veru, Zomagen, and ZyVersa; reports receiving honoraria fees from the American Society for Preventive Cardiology, National Lipid Association, and Obesity Medicine Association; and holds a leadership role as President and Chief Science Officer of the Obesity Medicine Association and as Editor-in-Chief of Obesity Pillars. CWIR reports receiving payments to their institution from Anabio, the Health Research Board, the Irish Research Council, and the Science Foundation Ireland; reports receiving consulting fees from AbbVie, Altimune, Amgen, Arrowhead, AstraZeneca, Boehringer Ingelheim, Eli Lilly, GI Dynamics, Gila Pharmaceuticals, Herbalife, Irish life Health, Johnson & Johnson, Keyron, Metsera, Novo Nordisk, Nymble, Olympus, and Roche; reports receiving payments for presentations from Boehringer Ingelheim, Currax Pharmaceuticals, Eli Lilly, and Rhythm Pharmaceuticals; reports travel support from Boehringer Ingelheim, Eli Lilly and Company, Herbalife, Johnson & Johnson, and Novo Nordisk; holds a leadership position at the Irish Society for Nutrition and Metabolism; is a shareholder of Metsera and Nymble; and is co-owner of Beyond BMI and My Best Weight. RS declares no competing interests. EGV, ADA, SD, JPD, AR, LCG, and CJL are employees and shareholders of Eli Lilly.

Data sharing

Lilly provides access to all individual participant data collected during the trial, after anonymisation, with the exception of pharmacokinetic or genetic data. Data are available to request 6 months after the indication studied has been approved in the USA and EU and after primary publication acceptance, whichever is later. No expiration date of data requests is currently set once data are made available. Access is provided after a proposal has been approved by an independent review committee identified for this purpose and after receipt of a signed data sharing agreement. Data and documents, including the study protocol, statistical analysis plan, clinical study report, and blank or annotated case report forms, will be provided in a secure data sharing environment. For details on submitting a request, see the instructions provided at www.vivli.org.

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References

- Hall KD, Kahan S. Maintenance of lost weight and long-term management of obesity. *Med Clin North Am* 2018; **102**: 183–97.
- Elmaleh-Sachs A, Schwartz JL, Bramante CT, Nicklas JM, Gudzone KA, Jay M. Obesity management in adults: a review. *JAMA* 2023; **330**: 2000–15.
- Alexander L, Purnell JQ, BurrIDGE K, et al. Joint TOS/OMA/OAC expert guidance statement on the pharmacological management of United States adults with overweight or obesity using the GRADE approach. *Obes Pillars* 2026; **18**: 100254.
- Purnell JQ, Le Roux CW. Metabolic and appetitive regulation of adipocyte mass during treatment of obesity. *J Intern Med* 2026; **299**: 66–78.
- van Baak MA, Mariman ECM. Obesity-induced and weight-loss-induced physiological factors affecting weight regain. *Nat Rev Endocrinol* 2023; **19**: 655–70.
- Busetto L, Bettini S, Makaronidis J, Roberts CA, Halford JCG, Batterham RL. Mechanisms of weight regain. *Eur J Intern Med* 2021; **93**: 3–7.
- Kim TN. Barriers to obesity management: patient and physician factors. *J Obes Metab Syndr* 2020; **29**: 244–47.
- Rubino F, Cummings DE, Eckel RH, et al. Definition and diagnostic criteria of clinical obesity. *Lancet Diabetes Endocrinol* 2025; **13**: 221–62.
- Jastreboff AM, Aronne LJ, Ahmad NN, et al, and the SURMOUNT-1 Investigators. Tirzepatide once weekly for the treatment of obesity. *N Engl J Med* 2022; **387**: 205–16.
- Garvey WT, Frias JP, Jastreboff AM, et al. Tirzepatide once weekly for the treatment of obesity in people with type 2 diabetes (SURMOUNT-2): a double-blind, randomised, multicentre, placebo-controlled, phase 3 trial. *Lancet* 2023; **402**: 613–26.
- Wadden TA, Chao AM, Machineni S, et al. Tirzepatide after intensive lifestyle intervention in adults with overweight or obesity: the SURMOUNT-3 phase 3 trial. *Nat Med* 2023; **29**: 2909–18.
- Aronne LJ, Sattar N, Horn DB, et al. Continued treatment with tirzepatide for maintenance of weight reduction in adults with obesity: the SURMOUNT-4 randomized clinical trial. *JAMA* 2024; **331**: 38–48.
- Aronne LJ, Horn DB, le Roux CW, et al. Tirzepatide as compared with semaglutide for the treatment of obesity. *N Engl J Med* 2025; **393**: 26–36.
- Jastreboff AM, le Roux CW, Stefanski A, et al. Tirzepatide for obesity treatment and diabetes prevention. *N Engl J Med* 2025; **392**: 958–71.
- Horn DB, Aronne LJ, Wharton S, et al. Tirzepatide for the maintenance of body weight reduction: rationale, design, and baseline characteristics of SURMOUNT-MAINTAIN. *Obesity (Silver Spring)* 2025; **33**: 1873–85.
- American College of Cardiology/American Heart Association Task Force on Practice Guidelines, Obesity Expert Panel, 2013. Executive summary: guidelines (2013) for the management of overweight and obesity in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Obesity Society published by the Obesity Society and American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Obesity (Silver Spring)* 2014; **22** (suppl 2): S5–39.
- Garvey WT, Mechanick JL, Brett EM, et al. American Association of Clinical Endocrinologists and American College of Endocrinology comprehensive clinical practice guidelines for medical care of patients with obesity. *Endocr Pract* 2016; **22** (suppl 3): 1–203.
- Cappelleri JC, Bushmakin AG, Gerber RA, et al. Evaluating the Power of Food Scale in obese subjects and a general sample of individuals: development and measurement properties. *Int J Obes (Lond)* 2009; **33**: 913–22.
- Lowe MR, Butryn ML, Didie ER, et al. The Power of Food Scale. A new measure of the psychological influence of the food environment. *Appetite* 2009; **53**: 114–18.
- Meule A, Hermann T, Kübler A. A short version of the Food Cravings Questionnaire-Trait: the FCQ-T-reduced. *Front Psychol* 2014; **5**: 190.
- Maruish ME, ed. User's manual for the SF-36v2 health survey, 3rd edn. Lincoln, RI: Quality Metric Incorporated, 2011.
- Hanley MJ, Abernethy DR, Greenblatt DJ. Effect of obesity on the pharmacokinetics of drugs in humans. *Clin Pharmacokinet* 2010; **49**: 71–87.
- Wilding JPH, Batterham RL, Davies M, et al. Weight regain and cardiometabolic effects after withdrawal of semaglutide: the STEP 1 trial extension. *Diabetes Obes Metab* 2022; **24**: 1553–64.
- Rubino D, Abrahamsson N, Davies M, et al. Effect of continued weekly subcutaneous semaglutide vs placebo on weight loss maintenance in adults with overweight or obesity: the STEP 4 randomized clinical trial. *JAMA* 2021; **325**: 1414–25.
- West S, Scragg J, Aveyard P, et al. Weight regain after cessation of medication for weight management: systematic review and meta-analysis. *BMJ* 2026; **392**: e085304.
- Budini B, Luo S, Tam M, et al. Trajectory of weight regain after cessation of GLP-1 receptor agonists: a systematic review and nonlinear meta-regression. *eClinicalMedicine* 2026; **93**: 103796.
- Aronne LJ, Horn DB, le Roux CW, et al. Orforglipron for maintenance of body weight reduction: the double-blind, randomized phase 3b ATTAIN-MAINTAIN trial. *Nat Med* (in press).
- Berger SE, Huggins GS, McCaffery JM, Jacques PF, Lichtenstein AH. Change in cardiometabolic risk factors associated with magnitude of weight regain 3 years after a 1-year intensive lifestyle intervention in type 2 diabetes mellitus: the Look AHEAD trial. *J Am Heart Assoc* 2019; **8**: e010951.
- King WC, Hinerman AS, Belle SH, Wahed AS, Courcoulas AP. Comparison of the performance of common measures of weight regain after bariatric surgery for association with clinical outcomes. *JAMA* 2018; **320**: 1560–69.
- Horn DB, Linetzky B, Davies MJ, et al. Cardiometabolic parameter change by weight regain on tirzepatide withdrawal in adults with obesity: a post hoc analysis of the SURMOUNT-4 trial. *JAMA Intern Med* 2026; **186**: 157–67.
- Berning P, Adhikari R, Schroer AE, et al. Longitudinal analysis of obesity drug use and public awareness. *JAMA Netw Open* 2025; **8**: e2457232.
- Rubino DM, Pedersen SD, Connery L, et al. Gastrointestinal tolerability and weight reduction associated with tirzepatide in adults with obesity or overweight with and without type 2 diabetes in the SURMOUNT-1 to -4 trials. *Diabetes Obes Metab* 2025; **27**: 1826–35.