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

Tirzepatide once weekly for the treatment of obesity in people with type 2 diabetes (SURMOUNT-2): a double-blind, randomised, multicentre, phase 3 trial

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Abstract

Background

Weight reduction is essential for improving health outcomes in people with obesity and type 2 diabetes (T2D). We assessed the efficacy and safety of tirzepatide, a glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1 receptor agonist, versus placebo for weight management in people with obesity and T2D.

Methods

This phase 3, double-blind, randomised, placebo-controlled trial, was conducted across seven countries. Adults with a body mass index (BMI) ≥27 kg/m^2 and glycated haemoglobin (HbA_{1c}) 7-10% (53-86 mmol/mol) were randomly assigned 1:1:1 to receive once-weekly, subcutaneous tirzepatide (10mg or 15mg) or placebo for 72 weeks. Co-primary endpoints were the percent change in body weight from baseline and body weight reduction ≥5%. The treatment-regimen estimand assessed effects regardless of treatment discontinuation or initiation of antihyperglycaemic rescue therapy. This trial is registered with ClinicalTrials.gov, NCT04657003.

Findings

The trial was conducted between March 29, 2021, and April 10, 2023. Of 1514 adults assessed for eligibility, 938 were randomly assigned and received at least one dose of tirzepatide 10mg (n=312), tirzepatide 15mg (n=311), or placebo (n=315). Baseline mean body weight was 100·7 kg, BMI 36·1 kg/m^2, and HbA_{1c} 8·0% (64·1 mmol/mol). Mean change in body weight at week 72 with tirzepatide 10mg and 15mg was -12·8% and -14.7%, respectively, and -3·2% with placebo, resulting in estimated treatment differences versus placebo of -9·6% (95% CI [-11·1, -8·1]) with tirzepatide 10mg and -11·6% (95% CI [-13·0, -10·1]) with tirzepatide 15mg (all

p<0·0001). More participants treated with tirzepatide versus placebo met body weight reduction thresholds of ≥5% (79–83% vs 32%), ≥10% (61–65% vs 10%), ≥15% (40–48% vs 3%), and ≥20% (22–31% vs 1%). Additionally, 46–49% of participants treated with tirzepatide achieved HbA_{1c} <5·7% versus 3% with placebo. Treatment with tirzepatide resulted in improvements in all prespecified cardiometabolic measures. The most frequent adverse events with tirzepatide included nausea, diarrhoea, and vomiting, and were mostly mild to moderate in severity.

Interpretation

In this 72-week trial in adults with obesity and T2D, once weekly tirzepatide 10mg and 15mg provided substantial and clinically meaningful reduction in body weight, with a safety profile comparable to other injectable incretin-based therapies for weight management.

Funding Eli Lilly and Company

Research in context

Evidence before this study

For people living with obesity and T2D, weight reduction is now recommended as a key element of diabetes treatment. Moderate body weight reduction can improve glycaemic control and cardiometabolic risk factors, while greater body weight reduction (≥10%) can lead to remission of diabetes. However, anti-obesity medications are generally less efficacious in people with T2D, resulting in less body weight reduction compared to people without diabetes.

We searched PubMed on January 16, 2023, using the terms "glucose-dependent insulinotropic polypeptide receptor agonist", "glucagon-like peptide-1 receptor agonist", "obesity", "overweight", and "type 2 diabetes" with no date restrictions. GLP-1 receptor agonists, liraglutide 3·0 mg (SCALE Diabetes and SCALE insulin trials) and semaglutide 2·4 mg (STEP 2 trial), resulted in placebo-adjusted body weight reductions from baseline of 4.0%, 4.3%, and 6.2%, respectively, in people with overweight or obesity and T2D. Tirzepatide, a novel, once-weekly, GIP and GLP-1 receptor agonist approved by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for treating adults with T2D, demonstrated significant dose-dependent weight reduction in people with T2D in the SURPASS trials. The SURPASS trials included a treatment period of 40–52 weeks and were primarily designed to evaluate tirzepatide treatment for glycaemic control. Tirzepatide is under investigation for chronic weight management in the phase 3 SURMOUNT trials, which are of longer duration and designed to evaluate weight reduction and maintenance.

Added value of this study

In adults with a BMI ≥27 kg/m^2 and T2D, 72 weeks of treatment with tirzepatide 10 mg and 15 mg once weekly, resulted in clinically meaningful reductions in body weight of 12·8% and 14·7%, respectively, versus 3·2% with placebo. Most participants (79-83%) treated with tirzepatide achieved the benchmark for clinically meaningful effect (≥5% weight reduction), with up to nearly half achieving ≥15% and up to almost one-third achieving ≥20% weight reduction. In addition, nearly half (46–49%) of the participants treated with tirzepatide reached normoglycaemia (HbA_{1c} <5·7%) versus 3% with placebo. Notably, HbA_{1c} targets were reached with tirzepatide without any reported cases of severe hypoglycaemia. Both doses of tirzepatide also resulted in significant improvements in other cardiometabolic risk factors, including systolic blood pressure and fasting triglycerides, HDL cholesterol, and non-HDL cholesterol, compared with placebo. The most frequent adverse events with tirzepatide were mild to moderate gastrointestinal events, similar to other incretin-based therapies, namely nausea, diarrhoea, and vomiting.

Implications of all the available evidence

SURMOUNT-2 is the first randomised trial of tirzepatide in adults with obesity and T2D, specifically designed to assess weight reduction as the primary outcome rather than HbA_{1c} reduction. Both doses of tirzepatide provided substantial, and clinically meaningful body weight reductions with simultaneous significant improvement in HbA_{1c} and other cardiometabolic risk factors. The magnitude of weight reduction achieved with tirzepatide in SURMOUNT-2 exceeded that seen with other approved anti-obesity medications in people with T2D. Tirzepatide presents a promising treatment option for people living with obesity and T2D.

Introduction

The prevalence of obesity is anticipated to rise to 24% globally by 2035, impacting the lives of nearly 2 billion people.[1] Obesity is a chronic disease that is associated with an increased risk of over 200 weight-related complications that impair health and reduce survival, including several cardiovascular diseases (CVD), type 2 diabetes mellitus (T2D), non-alcoholic steatohepatitis (NASH), and chronic kidney disease (CKD).[2-4]

The most recent consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD), emphasizes the importance of weight management as a key component of T2D treatment, with the understanding that a weight reduction of 5 to ≥15% translates to health benefits that go beyond glycaemic control.[5] Tirzepatide is a once-weekly injectable, subcutaneous glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) receptor agonist.[6] It is currently approved by the US Food and Drug Administration (FDA) and European Medicines Agency (EMA) for treatment of T2D in adults and is in development for chronic weight management.[6] Nutrient-stimulated hormones such as GIP and GLP-1 are known to have potent effects on both glucose and lipid homeostasis, and synergistic effects on appetite and food intake.[7,8] In the SURMOUNT-1 study in people with obesity without T2D, tirzepatide reduced body weight by up to 20·9% after 72 weeks of treatment, with associated improvements in cardiometabolic risk factors and patient reported outcomes.[9] However, people with obesity and T2D often have less weight reduction in response to treatment with AOMs,[10,11] compared to those without diabetes. Therefore, a dedicated study specifically designed to investigate the efficacy and safety of tirzepatide as a treatment for overweight and obesity in people with T2D is warranted.[12,13]

Here we present the results of the SURMOUNT-2 study investigating the efficacy and safety of tirzepatide once weekly for chronic weight management in participants with a BMI $\geq$27 kg/m^2 who have T2D.

Methods

Trial design and participants

This 72-week, multicentre, randomised, double-blind, parallel group trial, was conducted in 77 sites across Argentina, Brazil, India, Japan, Russia, Taiwan, and the United States. As required by regulatory authorities for the development of medications for weight management, this trial was placebo-controlled.[12] Eligible participants were ≥18 years of age and had a BMI ≥27 kg/m^2. In addition, participants were diagnosed with T2D, and had HbA_{1c} ≥7% and ≤10% on stable therapy, either diet and exercise alone or oral antihyperglycaemic medication (AHM), for at least 3 months prior to screening. The maximum HbA_{1c} at entry (10%) was selected in accordance with regulatory guidance for ethical considerations since the trial was placebo-controlled with about one third of participants expected to receive placebo.[12] Key exclusion criteria included a change in body weight >5 kg within 3 months prior to screening, prior or planned surgical treatment for obesity, and treatment with AOMs, dipeptidyl peptidase-4 (DPP-4) inhibitors, oral GLP-1 receptor agonist, or any injectable therapy for T2D within 3 months prior to screening. Full eligibility criteria are provided in the Supplementary Appendix.

The protocol was approved by local institutional review boards and the trial complied with the International Conference on Harmonization Good Clinical Practice guidelines and the Declaration of Helsinki. All participants provided written informed consent. The clinical trial design is described in greater detail in a previous publication.[14]

Randomisation and masking

Participants were randomly assigned in a 1:1:1 ratio to receive either tirzepatide 10 mg or 15 mg, or matching placebo, administered subcutaneously using a single-dose pen. Assignment to treatment group was determined by a computer-generated random sequence using a validated interactive web-response system. All participants, investigators, and the sponsor were masked to treatment assignment.

Randomisation was stratified according to country, sex (female, male), and type of AHM used at randomisation (classified according to its potential effect on body weight as promoting weight gain, weight reduction, or weight neutral). Female enrollment was limited to 70% to ensure adequate representation of the male population. In addition, an upper limit of 30% enrollment of participants treated with sulfonylurea was used to allow sufficient enrollment of participants treated with other AHMs.

Procedures

After a 3-week screening period, participants received subcutaneous injections of tirzepatide or matching placebo once a week plus a lifestyle intervention for 72 weeks, followed by a 4-week safety follow-up period without treatment (Figure S1 in Supplementary Appendix). Tirzepatide (or matching placebo) was initiated at 2·5 mg once weekly and increased by 2·5 mg every 4 weeks until the target dose was reached i.e., 10 mg or 15 mg at 12 or 20 weeks, respectively. The lifestyle intervention included regular lifestyle counseling sessions delivered by a dietitian or qualified health care professional. The counselling sessions were focused on healthy, balanced meals with a recommended caloric deficit of 500-calories/day relative to the estimated total daily

energy expenditure and at least 150 minutes per week of physical activity. To increase adherence, participants were encouraged to complete a 3-day diet and exercise log as a self-monitoring tool, and this was reviewed during each counselling session; the diet and exercise log was used because self-monitoring has been shown to have a positive effect on weight loss.[15]

To minimize the risk of hypoglycaemia, participants taking sulfonylureas at randomisation had their dose halved (or stopped if already on the lowest dose). AHM treatment was to be kept stable unless participants reached rescue criteria for persistent hyperglycaemia or developed recurrent hypoglycaemia. Antihyperglycaemic rescue therapy included either a dose increase of existing AHM or addition of new AHM (with the exception of GLP-1R agonists, DPP-4 inhibitors, or amylin analogues/agonists). Metformin was recommended as a first-line rescue therapy for participants who were not on any AHMs at baseline; basal insulin was permitted for participants already receiving combination therapy at the investigator's discretion. Blood glucose meters were provided to measure self-monitored blood glucose (SMBG) values and participants were encouraged to record SMBG values in their study diary. Rescue therapy for obesity treatment was not permitted.

In the event of intolerable gastrointestinal symptoms, mitigation strategies were implemented as described in the protocol and in a previous publication.[14] If these strategies failed, participants were to be discontinued from the study drug; those that discontinued study drug were encouraged to stay in the study, and continue with lifestyle counseling, study visits, and study assessments.

Weight, waist circumference, vital sign measurements, and laboratory measurements were assessed as defined in the protocol (Supplementary Appendix).

Outcomes

To account for baseline body weight, the primary endpoint was the percent change in body weight from baseline to week 72. A weight reduction from baseline of at least 5% at week 72 was included as a co-primary endpoint. Key secondary endpoints controlled for type 1 error rate included body weight reductions of at least 10%, 15%, and 20% at week 72; the change from baseline in HbA_{1c} at week 72; HbA_{1c} <7%, ≤6·5%, and <5·7% at week 72; and the change from baseline in fasting glucose, waist circumference, systolic blood pressure, and fasting lipid levels (triglycerides, high density lipoprotein [HDL] cholesterol, and non-HDL cholesterol) at week 72. Additional secondary objectives included the change in fasting insulin and change in the Short Form-36 Version 2 Health Survey acute form (SF-36v2) physical functioning score, and the Impact of Weight on Quality of Life-Lite-Clinical Trials Version (IWQOL-Lite-CT) physical function composite score. Body weight reduction of at least 25% from baseline at week 72 was a prespecified exploratory endpoint.

Safety endpoints included treatment-emergent adverse events, serious adverse events, and level 2 hypoglycaemia (blood glucose less than 54 mg/dL [<3.0 mmol/L]), or severe hypoglycaemia (level 3 hypoglycaemia). Deaths, major adverse cardiovascular events, and pancreatitis were adjudicated by an independent external adjudication committee.

Statistical analysis

A sample size of 900 participants provided power of greater than 90% to demonstrate the superiority of tirzepatide 10 mg and 15 mg to placebo, for the co-primary endpoints, each at a two-sided significance level of 0·025. The sample-size calculation assumed at least an 11% difference in the mean percent weight reduction from baseline at 72 weeks for each tirzepatide dose (10 mg and 15 mg) as compared with placebo and a common standard deviation of 10%. Based on published data from a trial conducted in a similar population,[16] a dropout rate of 25% was assumed.

Efficacy and safety endpoints were analysed with data from all randomly assigned participants (intention-to-treat population). All randomised participants took at least one dose of study treatment. Safety analyses included all data from the start of treatment to the end of safety follow-up. Two estimands, the "treatment regimen" and the "efficacy" estimands, were used to assess treatment efficacy from different perspectives and accounted for intercurrent events differently. These are explained in greater detail in the Supplementary Appendix.

The treatment regimen estimand represents the average treatment effect of tirzepatide relative to placebo at 72 weeks, for all participants who had undergone randomisation, regardless of adherence to treatment or use of rescue therapy for hyperglycaemia. This estimand is required by the FDA for regulatory approval of tirzepatide for chronic weight management. Continuous endpoints were analysed using an analysis of covariance model (ANCOVA), which is the FDA preferred analysis model. Categorical endpoints were analysed by logistic regression. Both

models included randomised treatment and stratification factors (country, sex, type of AHM used at randomisation) as fixed effects, and baseline measure as a covariate.

The efficacy estimand represents the average treatment effect of tirzepatide relative to placebo at 72 weeks, for all participants who had undergone randomisation had they remained on their randomised treatment for the entire planned 72week treatment duration (applies to all endpoints) and without using rescue medication for hyperglycaemia (applies to glycaemic endpoints only). Continuous endpoints were analysed using a mixed model for repeated measures (MMRM) and categorical endpoints were analysed by logistic regression. MMRM analysis included randomised treatment, visit, treatment-by-visit interaction, and stratification factors as fixed effects, and baseline measure as a covariate. The logistic regression model included randomised treatment, and stratification factors as fixed effects, and baseline measure as a covariate.

All reported results are for the treatment-regimen estimand unless otherwise stated. The type 1 error rate was controlled at a level of 0·05 within each estimand for evaluation of primary and key secondary objectives via a graphical testing approach.

The graphical testing scheme started with testing the superiority of co-primary endpoints for each tirzepatide dose (10 mg and 15 mg) as compared with placebo, each at a significance level of 0.025, followed by testing the superiority of key secondary endpoints related to ≥10% (and ≥15%) weight reduction, waist circumference, and glycemic control outcomes (HbA_{1c} and FSG) in a prespecified hierarchical order for each tirzepatide dose versus placebo. The remaining key secondary endpoints were tested in a dynamic nature with prespecified distribution of different

alpha levels amongst them. Figure S2 in the Supplementary Appendix provides details of the graphical testing approach.

Additional details on estimands, handling of missing values, and statistical analysis methods are provided in the supplementary appendix. Statistical analyses were performed using SAS version 9·4. This study is registered with ClinicalTrials.gov, NCT04657003.

Role of the funding source

The funder designed the study, oversaw its conduct, and collected, and analysed the data. This article was drafted by the authors, with medical writing and editorial support paid for by the funder.

Results

Participants

The study was conducted between March 29, 2021, and April 10, 2023. Of 1514 participants assessed for eligibility, 938 participants were enrolled, randomly assigned, and received at least one dose of tirzepatide 10 mg (N=312), tirzepatide 15 mg (N=311), or placebo (N=315; Figure 1). As expected in pharmacologic weight management trials, there was a higher attrition rate in the placebo group.[17] Overall, 92% [859] of participants completed the study (95% [296], 91% [282], and 89% [281] with tirzepatide 10 mg, tirzepatide 15 mg, and placebo, respectively) and 87% [819] completed the study treatment (91% [283], 86% [268], and 85% [268] with tirzepatide 10 mg, tirzepatide 15 mg, and placebo, respectively; Figure 1). Treatment discontinuations due to adverse events were 4% (12), 7% (23), and 4% (12) with tirzepatide 10 mg, tirzepatide 15 mg, and placebo, respectively (Figure 1).

Baseline demographics and clinical characteristics were well-balanced across groups (Table 1). The mean age of participants was 54·2 years and 50·7% were female. The overall mean baseline body weight was 100·7 kg, BMI 36·1 kg/m^2, and HbA_{1c} 8·0% [64·1 mmol/mol]. Duration of obesity and diabetes was 17·7 and 8·5 years, respectively. Overall, 26·7% of participants were treated with sulfonylureas (Table 1).

Change in body weight

Figure 2A and B show the mean percent body weight reduction during the study. For the treatment-regimen estimand, the mean change in weight at week 72 was -12·8% (SE 0·6) or -12·9 kg (-28·4 lb.) with tirzepatide 10 mg, -14·7% (SE 0·5) or -14·8 kg (-32·6 lb.) with

tirzepatide 15 mg, and -3·2% (SE 0·5) or -3·2 kg (-7·0 lb.) with placebo. Both tirzepatide doses were superior to placebo, with estimated treatment differences relative to placebo of -9·6 percentage points (95% CI -11·1 to -8·1, p<0·0001) for the 10 mg dose and -11·6 percentage points (95% CI -13·0 to -10·1, p<0·0001) for the 15 mg dose (Table 2).

The change in body weight for the efficacy estimand was -13·4% (SE 0·5) or -13·5 kg (-29·8 lb.) with tirzepatide 10 mg, -15·7% (SE 0·5) or -15·6 kg (-34·4 lb.) with tirzepatide 15 mg, and -3·3% (SE 0·5) or -3·2 kg (-7·0 lb.) with placebo. Estimated treatment differences were -10·1 percentage points (95% CI -11·5 to -8·8, p<0·0001) for tirzepatide 10 mg versus placebo, and -12·4 percentage points (95% CI -13·7 to -11·0, p<0·0001) for tirzepatide 15 mg versus placebo.

For the treatment-regimen estimand, 79% (247) and 83% (257) of participants in the 10 mg, and 15 mg tirzepatide groups, respectively, had a body weight reduction of 5% or more at 72 weeks, as compared with 32% (102) of participants in the placebo group (p<0·0001 for all comparisons with placebo). For the efficacy estimand, the respective percentages were 82% (252), 86% (267), and 31% (95). For both estimands, more participants in the tirzepatide groups had reductions in body weight of ≥10%, ≥15%, ≥20%, and ≥25% from baseline than participants in the placebo group (p<0·0001) (Figure 2C, D and Table 2).

Glycaemic control

From a baseline HbA_{1c} of 8·0%, HbA_{1c} improved by -2·1% (SE 0·06) with tirzepatide 10 mg, -2·1% (SE 0·07) with tirzepatide 15 mg, and -0·5% (SE 0·07) with placebo (p<0·0001 for all comparisons versus placebo; Table 2). At week 72, mean HbA_{1c} was 6·0%, 5·9%, and 7·5%,

with tirzepatide 10 mg, 15 mg, and placebo, respectively (Figure 3A). The proportion of participants in each group achieving HbA_{1c} levels of <7·0%, ≤6·5%, or <5·7% at week 72 was significantly higher in tirzepatide 10 and 15 mg groups compared with placebo (84% [262] and 87% [271] vs 36% [114], 80% [249]and 79% [247] vs 20% [63], and 46% [144] and 49% [151] vs 4% [12], respectively; Figure 3B). Improvement in fasting serum glucose, fasting insulin, and seven-point SMBG profiles were also greater among participants treated with tirzepatide compared with placebo (Table 2, Figure 3C, and Supplementary Figure S5).

Additionally, a post-hoc analysis showed that at week 72, the proportion of participants taking ≤1 AHM increased from 62% (193) and 62% (193) to 67% (208) and 69% (213) with tirzepatide 10 mg and 15 mg, respectively, and decreased with placebo from 58% (182) to 47% (149). Inversely, the proportion of participants treated with 2 or more AHMs decreased from 38% (119) and 38% (118) to 33% (104) and 32% (98) with tirzepatide 10 mg and 15 mg, respectively, and increased with placebo from 42% (133) to 53% (166; Figure S6).

Cardiometabolic risk factors and health-related quality of life

Decrease in waist circumference was significantly greater with tirzepatide 10 mg and tirzepatide 15 mg, compared with placebo (Table 2; Figure 3D). In addition, improvements with pooled tirzepatide treatment (10 mg and 15 mg) were significantly greater versus placebo in systolic blood pressure (-6·3 mmHg vs. -1·2 mmHg; p<0.0001), diastolic blood pressure (-2·5 mmHg vs. -0·3 mmHg; p<0.0001), and fasting triglycerides (-27·2% vs. -3·3%; p<0.0001), HDL-cholesterol (9·0% vs. 0·2%; p<0.0001), and non-HDL-cholesterol (-5·9% vs. 3·7%; Figures 3E and 3F; p<0.0001). Results were consistent for the efficacy estimand, showing greater

improvements with tirzepatide treatment compared with placebo for all key secondary endpoints (Table S2 and Figure S7 in Supplementary Appendix).

Participants' physical function improved more with tirzepatide than with placebo (Table S2). For the efficacy estimand, the mean change in physical functioning domain scores for the SF36v2 at week 72 was 3·4 (SE 0·4) with tirzepatide 10 mg (p=0·0013 vs placebo), 3·8 (SE 0·4) with tirzepatide 15 mg (p<0·0001 vs placebo), and 1·6 (SE 0·4) with placebo. For the IWQOL-Lite-CT, the change in the physical function composite score was 14·3 (SE 1·0), 15·2 (SE 1·0), and 7·4 (SE 1·0) with tirzepatide 10 mg, tirzepatide 15 mg, and placebo, respectively (p<0·0001 for all comparisons to placebo). In addition, for the prespecified exploratory endpoint of a change in the psychosocial composite score on the IWQOL-Lite-CT, the mean change at week 72 was 12·5 (SE 0·7; p=0.0001 vs. placebo), 14·2 (SE 0·7; p<0.0001 vs. placebo), and 8·4 (SE 0·7) with tirzepatide 10 mg, tirzepatide 15 mg, and placebo, respectively.

Additional efficacy data for the efficacy estimand are presented in Table S2.

Safety

There was no significant difference between groups in the incidence of adverse events; adverse events were reported by 77·6% (242), 71·4% (222), and 75·9% (239) of participants treated with tirzepatide 10 mg, tirzepatide 15 mg, and placebo, respectively (Table 3). The most frequently reported adverse events with tirzepatide were gastrointestinal disorders (diarrhea, nausea, and vomiting). Most of these events occurred during dose escalation, were mild to moderate in severity, and decreased over time (Supplementary Appendix Figure S8). Serious adverse events

were reported by 7·2% (68) of participants overall, with no significant differences in reporting across groups (Table 3). Two deaths (one due to smoke inhalation and the other cardio-respiratory arrest) were reported during the study, both in the tirzepatide 10 mg group (Table S4). Both of these events were not considered to be related to the study treatment by the investigator.

There were three reported cases of adjudication-confirmed pancreatitis, two (0·6%) in the tirzepatide 15 mg group and one (0·3%) in the placebo group (Table 3). No cases of medullary thyroid or pancreatic cancer were reported. The reported incidence of cholelithiasis and acute cholecystitis were similar among the tirzepatide and placebo groups. There were no cases of severe hypoglycemia. Level 2 hypoglycemia (blood glucose <54 mg/dL or <3·0 mmol/L) was reported by 11 (3·5%) participants treated with tirzepatide 10 mg, 15 (4·8%) with tirzepatide 15 mg, and 4 (1·3%) with placebo. The aggregated rate was 0·04, 0·06, and 0·09 events/patient/year with tirzepatide 10 mg, tirzepatide 15 mg, and placebo, respectively. Overall, six (1.9%), thirteen (4.2%), and four (1.3%) participants had symptoms associated with level 2 hypoglycemia in the tirzepatide 10 mg, tirzepatide 15 mg, and placebo groups, respectively. More participants (9·0-11·5%) treated with sulfonylureas at baseline reported level 2 hypoglycaemia with tirzepatide treatment than those who were not taking sulfonylureas (1·7–2·6%). There were no severe or serious injection site or hypersensitivity reactions. Additional safety variables are described in Table 3 and Supplementary Appendix Table S5.

Discussion

In SURMOUNT-2, adults with BMI ≥27 kg/m^2 and T2D treated with tirzepatide for 72 weeks had a mean body weight reduction of up to 14·7%, with 79–83% achieving weight reduction of 5% or more. On tirzepatide 15 mg, up to 65%, 48%, and 31% of participants achieved body weight reductions ≥10%, ≥15%, and ≥20%, respectively, at week 72. Participants' BMI declined by ~5 kg/m^2 with tirzepatide treatment, representing a downward shift, on average, in one BMI category. In addition, HbA1c levels were markedly reduced by the end of study accompanied by low rates of hypoglycemia and no severe hypoglycemia.

While weight reduction of at least 5% is a recommended component of T2D management,[5] a greater magnitude of weight reduction has been shown to confer additional clinical benefit that extends beyond glycaemic control, improves cardiometabolic risk factors, enhances quality of life, and can lead to diabetes remission.[2,5,11] The Look AHEAD study demonstrated that there were progressive improvements in HbA_{1c}, fasting glucose, blood pressure, triglycerides, and HDL-cholesterol as weight reduction increased above 5% to 15% or more.[18,19] Hence, most guidelines recommend weight reductions of >5% to >15% for people living with T2D and excess weight.[2,5] In SURMOUNT-2, tirzepatide treatment produced a degree of weight loss in the clear majority of participants that may provide a broad range of therapeutic benefits in patients with obesity and T2D.[2]

It is clear that substantial weight reduction is more challenging to achieve in people with obesity and T2D compared to those without T2D.[10,11] This has been demonstrated in studies involving lifestyle interventions and multiple anti-obesity medications.[16,20-25] The magnitude of weight

reduction achieved with tirzepatide 10 mg and 15 mg in SURMOUNT-1 in participants with obesity without T2D was greater than that achieved in the present trial: 19·5% and 20·9% versus 12·8% and 14·7%, respectively. While the differential effectiveness of weight loss interventions in people with obesity with and without T2D is consistently observed, it is noteworthy that treatment with tirzepatide in SURMOUNT-2 resulted in a magnitude of average weight reduction that has previously only been observed in people without T2D on the most effective of medications. In fact, it has been proposed that agents that produce mean weight reduction of about 15% in people with obesity represent a newer generation of AOMs because this degree of weight loss is sufficient to treat or prevent a wide array of obesity-related complications.[26] In contrast, older generation medications had been found to result in <10% weight loss in clinical trials, and even more recently approved GLP-1RAs have achieved less than 10% average weight reduction in clinical trials involving participants with both obesity andT2D.[22] Based on the SURMOUNT-2 results, tirzepatide produces a degree of weight loss that qualifies as a newer generation of obesity medication in people with T2D, sufficient to both improve glycaemia and multiple other obesity complications that beset these patients.[2,22]

HbA_{1c} was reduced by about 2% with tirzepatide treatment resulting in an average HbA_{1c} of ~5·9% at the end of treatment, with nearly half of the participants reaching the normoglycaemic range of HbA_{1c} <5·7%. These sustained effects on glycaemic control are in keeping with findings from the SURPASS trials in which tirzepatide demonstrated similar robust and sustained reductions in HbA_{1c}.[27] Despite these substantial reductions in HbA_{1c}, the incidence of hypoglycaemia was low. There were no reported cases of severe hypoglycaemia, and the incidence of level 2 hypoglycaemia was reported by <5% of participants in each treatment group.

In addition to improved glycaemic control, weight reduction with tirzepatide in SURMOUNT-2 was accompanied by significantly greater improvements in health-related quality of life such as physical function, and cardiometabolic risk factors including waist circumference, systolic and diastolic blood pressure, as well as fasting triglycerides, HDL-cholesterol, and non-HDL cholesterol. These improvements in cardiometabolic risk factors, coupled with the magnitude of weight reduction, have the potential to translate into reduced risk of CVD, CKD, and nonalcoholic fatty liver disease, among other outcomes. Multiple cardiovascular outcome trials (CVOTs) in people with T2D have shown that GLP-1 receptor agonists can reduce risk of major adverse cardiovascular events (MACE).[28] Metabolic surgery, which affords greater weight reduction than lifestyle-based or pharmacologic therapies, has also been associated with a lower risk of incident MACE, major adverse liver outcomes, and obesity-associated cancers.[29-31] Since nearly 1 in 6 participants in SURMOUNT-2 achieved $\geq$25% weight reduction, a surgical-equivalent response, it is intriguing to consider whether tirzepatide will also be associated with the aforementioned clinical benefits in people with T2D and/or obesity. While a meta-analysis of the SURPASS clinical trials in participants with T2D showed that tirzepatide did not increase the risk of MACE compared to the control arms,[32] the ongoing SURPASS-CVOT (NCT04255433) trial comparing tirzepatide and dulaglutide on MACE in people with T2D and the SURMOUNT-MMO (NCT05556512) trial investigating the effect of tirzepatide on the reduction of morbidity and mortality in people with obesity, will directly investigate the potential for these clinical benefits of tirzepatide.

The magnitude of weight reduction in the current trial was greater than that observed in the SURPASS trials in people with T2D. It is possible that differences in study design between the SURPASS and SURMOUNT trials may contribute to these findings. The SURPASS trials were specifically designed to assess the effect of tirzepatide on glycaemic control for the treatment of T2D, and as such, included participants with BMI<27 kg/m^2, had less prescriptive lifestyle interventions, and were generally shorter (40 to 52 weeks) in duration which may not have allowed for capturing the full effect on body weight. In addition, the degree of overall and categorical weight loss with tirzepatide in SURMOUNT-2 was greater than that reported for GLP-1 receptor agonists approved for patients with obesity and T2D. While the period of active treatment was longer in the current trial (72 weeks) compared with semaglutide 2.4 mg in STEP 2 (68 weeks) and liraglutide 3.0 mg in SCALE Diabetes (56 weeks), these differences are due to variations in the duration of the dose escalation phase (20 weeks for tirzepatide 15 mg, 16 weeks for semaglutide 2.4 mg, and 4 weeks for liraglutide 3 mg). Once the full therapeutic dose of the medication was reached, the maintenance period at full dose was 52 weeks in all three studies. Additionally, findings from the 104-week STEP 5 study evaluating semaglutide 2.4 mg showed there was no incremental body weight reduction after 68 weeks of treatment.[33] Thus, differences in efficacy cannot be ascribed to differences in the duration of treatment.

The mechanisms responsible for the enhanced effectiveness of tirzepatide in people with obesity and T2D require greater elucidation. Given that tirzepatide is both a GIP and GLP-1 receptor agonist, it is possible that the greater efficacy observed reflects an additive benefit of targeting multiple endogenous nutrient-stimulated hormone pathways. Both GLP-1 and GIP may have anorexigenic effects mediated via receptor activation on non-overlapping neuronal populations in

the central nervous system thus reducing food intake and increasing satiety, while also providing glycaemic benefit by regulating postprandial insulin secretion via effects on the beta cell.[7,8,34] Slowed gastric emptying may be a potential contributor to the observed reduction in food intake, as suggested by the observed response to GLP-1 receptor agonists in the 'hungry gut' obesity phenotype.[35] However, it is unlikely to be a major driver of weight reduction with tirzepatide since the effect of tirzepatide on body weight reduction continues well after the drug's effect on gastric emptying has waned.[36] Even so, slower gastric emptying during a meal has been associated with a quicker time to satiety and could contribute to reduced caloric intake and weight loss.[37] It is noteworthy, however, that previous analyses of the SURPASS trials showed no association between gastrointestinal adverse events (which may be related to slowed gastric emptying), and weight reduction,[38] and this is consistent with findings with other incretin-based therapies.[39]

The safety profile of tirzepatide was consistent with previous findings in the SURMOUNT-1 trial in people with obesity and in the SURPASS clinical trials in people with T2D.[9,27] As characteristically observed with other incretin-based therapies, the most frequently reported adverse events were gastrointestinal in nature. Most events were mild-to-moderate, occurring primarily during the dose-escalation period, with only a few (<5%) leading to treatment discontinuation. No cases of medullary thyroid or pancreatic cancer were reported. No clinically relevant differences in gallbladder-related events and pancreatitis were observed with tirzepatide treatment.[21,22] As mentioned, despite sizeable reduction in HbA_{1c}, the rates of hypoglycaemia were quite low, and were largely observed in participants also treated with sulfonylureas, an indication that this risk can be mitigated by dose reduction of sulfonylureas.

Strengths of this trial include the global nature and large sample size making results relatively generalizable. The HbA_{1c} entry criteria (≥7% and ≤10%) was expected to be representative of the majority of people with diabetes who would otherwise require intensification of glucose-lowering medication. In addition, participants were stratified by the weight-effect of concomitant AHMs, making it possible to reduce the potential confounding effect of these concomitant medications. SURMOUNT-2 was conducted during the COVID-19 pandemic posing potential challenges for trial participants. Despite these challenges, there was a high study (~92%) and study treatment completion rate (~87%).

Potential limitations are that the efficacy of tirzepatide 5 mg, an approved dose for treating T2D which safely produced significant weight reduction in previous studies in participants with and without T2D,[9,27] was not evaluated in this trial. Over a third of screened individuals were not enrolled into the study, most (56%) having failed to meet a diabetes-related entry criteria as shown in the disposition figure (Figure 1). Gastrointestinal adverse events were self-reported in this trial, and although this approach has been standard practice in most clinical trials, it could contribute to reporting bias. In addition, a nocebo effect related to participant expectations of adverse gastrointestinal effects cannot be ruled out.[40] People treated with insulin were excluded from participation in this study. While this may pose a limitation here, there is current evidence of the efficacy and safety of tirzepatide in patients with T2D on insulin in the SURPASS clinical development trials.[27] Finally, while the primary treatment period in this study was of longer duration in participants with obesity and diabetes (72 weeks) compared with participants in the SURPASS studies with T2D (40-52 weeks), it would be of interest to study even longer term

effects of tirzepatide treatment and what occurs following cessation of treatment. These queries may be addressed in the ongoing two-year additional follow-up period in the SURMOUNT-1 trial, and in the SURMOUNT-4 randomized withdrawal trial, respectively, in people with obesity.[14]

In conclusion, in adults with a BMI > 27kg/m^2 and T2D, tirzepatide once weekly demonstrated substantial, clinically meaningful body weight reductions of up to 15%, with weight reductions ≥20% achieved by up to nearly one-third of tirzepatide-treated participants. Additionally, tirzepatide improved cardiometabolic risk factors and glycaemic control, with almost half of tirzepatide-treated participants reaching HbA_{1c} <5·7%.

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Author contributions

XMZ, NNA, MCB, and SZ contributed to the study design. WTG, JPF, and DA conducted the trial and collected the data. HM and SZ were responsible for the statistical analyses. SZ, HM, NNA, MCB, IB, and XMZ are the guarantors of this work and, as such, take responsibility for the integrity of the data and the accuracy of the data analysis. All authors participated in data interpretation, manuscript writing (assisted by a medical writer paid for by the funder), and critical review of the manuscript, had full access to all the data in the study, and approved of this manuscript to be submitted for publication.

Declaration of interests

WTG has served as a consultant on advisory boards for Boehringer Ingelheim, Eli Lilly, Novo Nordisk, Pfizer, Fractyl Health, Alnylam Pharmaceuticals, Inogen, and Merck, and as a site principal investigator for multi-centered clinical trials sponsored by his university and funded by Novo Nordisk, Eli Lilly, Epitomee, Neurovalens, and Pfizer. JPF reports grants from Eli Lilly and Company, AbbVie, Akcea, Allergan, AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, Cirius, CymaBay, Enanta, Genentech, Intercept, Janssen, Johnson and Johnson, Lexicon, Ligand, Madrigal, Merck, Mylan, NGM Biopharmaceuticals, Novartis, Novo Nordisk, Pfizer,

Sanofi, and Theracos; has served on advisory boards and received consulting fees from Boehringer Ingelheim, Gilead, Johnson and Johnson, Eli Lilly and Company, Merck, Novo Nordisk, and Sanofi; and served on a speaker bureau for Merck and Sanofi. AMJ reports grants/contracts (through her institution) from Novo Nordisk, Eli Lilly and Company, Rhythm Pharmaceutical and NIH/NIDDK; consults for Amgen and Scholar Rock; has received honoraria/travel support from Eli Lilly and Company, Novo Nordisk, and WeightWatchers, and stock options from Intellihealth; she serves on advisory boards for AstraZeneca, Boehringer Ingelheim, Biohaven, Eli Lilly and Company, Intellihealth, Novo Nordisk, Rhythm Pharmaceuticals, Structure Therapeutics, Terns Pharmaceutics, and WeightWatchers. CWLR reports grants from the Irish Research Council, Science Foundation Ireland, Anabio, and the Health Research Board. He serves on advisory boards and speakers' panels of Novo Nordisk, Herbalife, GI Dynamics, Eli Lilly, Johnson & Johnson, Glia, Irish Life Health, and Boehringer Ingelheim; is a member of the Irish Society for Nutrition and Metabolism outside the area of work commented on here; was the chief medical officer and director of the Medical Device Division of Keyron in 2021 (both unremunerated positions); is a previous investor in Keyron; was gifted stock holdings and divested all stock holdings in Keyron in September 2021; he continues to provide scientific advice to Keyron for no remuneration; he provides obesity clinical care in the Beyond BMI clinic and is a shareholder. NS has received grant and personal fees from AstraZeneca, Boehringer Ingelheim, and Novartis; grant from Roche Diagnostics; and personal fees from Abbott Laboratories, Afimmune, Amgen, Eli Lilly, Hanmi Pharmaceuticals, Janssen, Merck Sharp & Dohme, Novartis, Novo Nordisk, Pfizer, and Sanofi outside the submitted work. SZ, HM, NNA, MCB, IB, and XMZ are employees and shareholders of Eli Lilly and Company.

Data sharing

Lilly provides access to all individual participant data collected during the trial, after anonymization, with the exception of pharmacokinetic or genetic data. Data are available to request 6 months after the indication studied has been approved in the US 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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Table 1. Baseline demographic and clinical characteristics

	Tirzepatide 10 mg N=312	Tirzepatide 15 mg N=311	Placebo N=315	Total N=938
Age, years	54·3 ± 10·7	53·6±10·6	54·7 ± 10·5	54·2 ± 10·6
Age <65 years, n (%)	258 (82·7)	257 (82·6)	258 (81·9)	773 (82·4)
Age ≥65 years, n (%)	54 (17·3)	54 (17·4)	57 (18·1)	165 (17·6)
Female, n (%)*	158 (50·6)	159 (51·1)	159 (50·5)	476 (50·7)
Race, n (%)				
Asian	44 (14·1)	42 (13·5)	39 (12·4)	125 (13·3)
Black or African American	33 (10·6)	22 (7·1)	22 (7·0)	77 (8·2)
Native Hawaiian or other Pacific Islander	1 (0·3)	1 (0·3)	1 (0·3)	3 (0·3)
White	228 (73·1)	234 (75·2)	248 (78·7)	710 (75·7)
Multiple	6 (1·9)	12 (3·9)	5 (1·6)	23 (2·5)
Hispanic or Latino, n (%)	184 (59·0)	189 (60·8)	188 (59·7)	561 (59·8)
Duration of obesity, years	17·6 ± 12·0	17·5 ± 11·0	18·1 ± 11·7	17·7 ± 11·5
Body weight, kg	100·9 ± 20·9	99·6 ± 20·1	101·7 ± 22·3	100·7 ± 21·1
BMI, kg/m^2	36·0 ± 6·4	35·7 ± 6·1	36·6 ± 7·3	36·1 ± 6·6
BMI category, n (%)				
<30	60 (19·2)	51 (16·4)	52 (16·5)	163 (17·4)
≥30 to <35	92 (29·5)	114 (36·7)	105 (33·3)	311 (33·2)
≥35 to <40	94 (30·1)	85 (27·3)	71 (22·5)	250 (26·7)
≥40	66 (21·2)	61 (19·6)	87 (27·6)	214 (22·8)
Waist circumference, cm	114·2 ± 14·1	114·6 ± 13·1	116·0 ± 15·7	114·9 ± 14·4

	Tirzepatide 10 mg N=312	Tirzepatide 15 mg N=311	Placebo N=315	Total N=938
Blood pressure, mmHg				
Systolic	130·6 ± 12·2	130·0 ± 12·3	131·0 ± 11·9	130·5 ± 12·1
Diastolic	80·2 ± 8·1	79·7 ± 8·7	79·4 ± 8·4	79·8 ± 8·4
Pulse, bpm	75·9 ± 10·4	75·6 ± 9·4	74·8 ± 9·9	75·4 ± 9·9
Cholesterol, mmol/L				
Total	4·6 ± 1·1	4·5 ± 1·1	4·6 ± 1·1	4·6 ± 1·1
HDL	1·2 ± 0·3	1·1 ± 0·3	1·1 ± 0·3	1·2 ± 0·3
Non-HDL	3·5 ± 1·1	3·3 ± 1·1	3·5 ± 1·0	3·4 ± 1·1
LDL	2·5 ± 0·9	2·4 ± 0·9	2·6 ± 0·9	2·5 ± 0·9
VLDL	0·9 ± 0·4	0·9 ± 0·4	0·9 ± 0·4	0·9 ± 0·4
Triglycerides, mmol/L	2·1 ± 1·6	2·0 ± 1·4	2·1 ± 1·3	2·1 ± 1·4
Free fatty acids, mmol/L	0·60 ± 0·23	0·58 ± 0·22	0·63 ± 0·24	0·60 ± 0·23
Estimated GFR, mL/min/1·73 m^2 †	95·9 ± 17·8	96·2 ± 17·5	93·5 ± 19·1	95·2 ± 18·2
Duration of diabetes, years	8·8 ± 6·9	8·0 ± 6·4	8·8 ± 6·2	8·5 ± 6·5
HbA_{1c}, %	8·00 ± 0·84	8·07 ± 0·99	7·98 ± 0·84	8·02 ± 0·89
HbA_{1c}, mmol/mol	64·0 ± 9·1	64·7 ± 10·8	63·7 ± 9·2	64·1 ± 9·7
Fasting glucose, mg/dL	158·3 ± 44·0	161·2 ± 49·3	158·5 ± 46·5	159·3 ± 46·6
Fasting glucose, mmol/L	8·8 ± 2·4	9·0 ± 2·7	8·8 ± 2·6	8·8 ± 2·6
Fasting insulin geometric mean (CV), pmol/L	84·0 (75·7)	83·6 (68·7)	86·1 (80·7)	84·6 (75·0)
Antihyperglycaemic drug class, n (%)				
Biguanides	282 (90·4)	276 (88·7)	274 (87·0)	832 (88·7)
Sulfonylureas	78 (25·0)	78 (25·1)	94 (29·8)	250 (26·7)

	Tirzepatide 10 mg N=312	Tirzepatide 15 mg N=311	Placebo N=315	Total N=938
SGLT2 inhibitors	63 (20·2)	62 (19·9)	66 (21·0)	191 (20·4)
Thiazolidinediones	11 (3·5)	11 (3·5)	11 (3·5)	33 (3·5)
α-Glucosidase inhibitors	2 (0·6)	2 (0·6)	4 (1·3)	8 (0·9)
Other‡	0	1 (0·3)	1 (0·3)	2 (0·2)
Number of oral antihyperglycaemic drugs				
0	16 (5·1)	23 (7·4)	24 (7·6)	63 (6·7)
1	177 (56·7)	170 (54·7)	158 (50·2)	505 (53·8)
2	99 (31·7)	95 (30·5)	108 (34·3)	302 (32·2)
≥3	20 (6·4)	23 (7·4)	25 (7·9)	68 (7·2)
Weight-related complications, n (%)§				
Hypertension	201 (64·4)	202 (65·0)	217 (68·9)	620 (66·1)
Dyslipidemia	181 (58·0)	182 (58·5)	210 (66·7)	573 (61·1)
ASCVD	24 (7·7)	29 (9·3)	44 (14·0)	97 (10·3)
Obstructive sleep apnea	23 (7·4)	26 (8·4)	29 (9·2)	78 (8·3)
Osteoarthritis	41 (13·1)	44 (14·1)	58 (18·4)	143 (15·2)
Anxiety/Depression	43 (13·8)	34 (10·9)	34 (10·8)	111 (11·8)
NAFLD	49 (15·7)	59 (19·0)	54 (17·1)	162 (17·3)
Asthma or COPD	21 (6·7)	27 (8·7)	30 (9·5)	78 (8·3)
Polycystic ovary syndrome¶	3 (1·9)	1 (0·6)	2 (1·3)	6 (1·3)
Gout	18 (5·8)	17 (5·5)	19 (6·0)	54 (5·8)
Number of weight-related complications, n (%)‖				
1	47 (15·1)	41 (13·2)	31 (9·8)	119 (12·7)

	Tirzepatide 10 mg N=312	Tirzepatide 15 mg N=311	Placebo N=315	Total N=938
2	80 (25·6)	80 (25·7)	77 (24·4)	237 (25·3)
3	85 (27·2)	95 (30·5)	88 (27·9)	268 (28·6)
4	61 (19·6)	51 (16·4)	65 (20·6)	177 (18·9)
≥5	39 (12·5)	44 (14·1)	54 (17·1)	137 (14·6)

Data are mean ± standard deviation or n (%) and include all randomised participants unless otherwise stated. ASCVD=atherosclerotic cardiovascular disease. BMI=body mass index. COPD=chronic obstructive pulmonary disease. CV=coefficient of variation percentage. GFR=glomerular filtration rate. HbA_{1c}=glycated haemoglobin. HDL=high-density lipoprotein. LDL=low-density lipoprotein. NAFLD=non-alcoholic fatty liver disease. SGLT2=sodium-glucose cotransporter-2. VLDL=very low-density lipoprotein.
*Sex was self-reported.
†Estimated GFR was calculated with use of the serum creatinine–based Chronic Kidney Disease Epidemiology Collaboration equation.
‡The category "Other" includes insulin human (one inadvertently enrolled participant), and repaglinide.
§Baseline medical conditions were assessed through a review of the participant's medical history.
¶Percentage is based on total number of female participants in the respective treatment group.
‖Type 2 diabetes was included as a weight-related complication.

Table 2. Primary and Secondary Endpoints by Treatment Group for the Treatment-Regimen Estimand

	Tirzepatide 10 mg (N=312)	**Tirzepatide 15 mg (N=311)**	**Placebo (N=315)**	**Treatment comparison (95% CI)*; p-value**	
		LSM (SE)		**Tirzepatide 10 mg vs placebo**	**Tirzepatide 15 mg vs placebo**
Co-primary endpoints (at week 72)†					
Percent change in weight, %	-12·8 (0·6)	-14·7 (0·5)	-3·2 (0·5)	ETD -9·6 (-11·1, -8·1), p<0·0001	ETD -11·6 (-13·0, -10·1); p<0·0001
Participants with weight reduction ≥5%, n [%]	247 [79·2 ± 2·4]	257 [82·8% ±2·4]	102 [32·5 ±2·9]	OR 8·3 (5·6, 12·3); p<0·0001	OR 10·5 (6·8, 16·1); p<0·0001
Key secondary endpoints (at week 72)†					
Participants with weight reduction ≥10%, n [%]	189 [60·5 ± 2·9]	202 [64·8 ±2·9]	30 [9·5 ± 1·8]	OR 16·1 (9·9, 26·1); p<0·0001	OR 19·4 (11·9, 31·7); p<0·0001
Participants with weight reduction ≥15%, n [%]	124 [39·7 ± 2·9]	149 [48·0 ± 2·9]	8 [2·7 ± 0·9]	OR 25·2 (12·2, 52·1); p<0·0001	OR 36·1 (17·5, 74·5); p<0·0001
Participants with weight reduction	67 [21·5 ± 2·4]	96 [30·8 ± 2·7]	3 [1·0 ± 0·6]	OR 25·6 (8·7,	OR 42·2 (14·4,

	Tirzepatide 10 mg (N=312)	Tirzepatide 15 mg (N=311)	Placebo (N=315)	Treatment comparison (95% CI)*; p-value	
		LSM (SE)		**Tirzepatide 10 mg vs placebo**	**Tirzepatide 15 mg vs placebo**
≥20%, n [%]				75·4); p<0·0001	123·5); p<0·0001
Change in waist circumference, cm	-10·8 (0·6)	-13·1 (0·5)	-3·3 (0·5)	ETD -7·4 (-9·0, -5·9); p<0·0001	ETD -9·8 (-11·2, -8·3); p<0·0001
Change in HbA_{1c}, %	-2·07 (0·06)	-2·08 (0·07)	-0·51 (0·07)	ETD -1·55 (-1·74, -1·37); p<0·0001	ETD -1·57 (-1·76, -1·37); p<0·0001
Change in HbA_{1c}, mmol/mol	-22·6 (0·7)	-22·7 (0·7)	-5·6 (0·8)	ETD -17·0 (-19·0, -14·9); p<0·0001	ETD -17·1 (-19·3, -15·0); p<0·0001
Participants with HbA_{1c} <7%, %	271 [86·9 ± 2·0]	262 [84·2 ± 2·5]	114 [36·2 ± 3·1]	OR 12·6 (7·9, 20·1); p<0·0001	OR 10·7 (6·5, 17·4); p<0·0001
Participants with HbA_{1c} ≤6.5%, %	249 [79·7 ± 2·4]	247 [79·4 ± 2·6]	63 [20·0 ± 2·6]	OR 17·8 (11·1, 28·6); p<0·0001	OR 18·5 (11·2, 30·7); p<0·0001
Participants with HbA_{1c} <5.7%, %	144 [46·0 ± 2·9]	151 [48·6 ± 3·0]	12 [3·9 ± 1·4]	OR 23·3 (10·9,	OR 26·6 (12·3,

	Tirzepatide 10 mg (N=312)	Tirzepatide 15 mg (N=311)	Placebo (N=315)	Treatment comparison (95% CI)*; p-value	
		LSM (SE)		**Tirzepatide 10 mg vs placebo**	**Tirzepatide 15 mg vs placebo**
				50·0); p<0·0001	57·3); p<0·0001
Change in fasting glucose, mg/dL	-48·9 (2·1)	-48·9 (2·3)	-11·0 (2·3)	ETD -37·9 (-44·1, -31·8); p<0·0001	ETD -37·9 (-44·4, -31·4); p<0·0001
Change in fasting glucose, mmol/L	-2·7 (0·1)	-2·7 (0·1)	-0·6 (0·1)	ETD -2·1 (-2·5, -1·8); p<0·0001	ETD -2·1 (-2·5, -1·7); p<0·0001
Additional secondary endpoints (at week 72)					
Percent change in fasting insulin, %	-29·1 (2·5)	-37·8 (2·3)	-16·0 (3·8)	ETD -15·6 (-24·4, -5·7); p=0·0027	ETD -25·9 (-33·8, -17·0); p<0·0001
Participants with weight reduction ≥25%, n [%]‡	28 [9.0 ± 1.7]	48 [15.5 ± 2.1]	1 [0.3 ± 0.3]	OR 21.0 (4.2. 104.5); p=0.0002	OR 39.1 (8.0, 190.6); p<0.0001
Change in:					

	Tirzepatide 10 mg (N=312)	Tirzepatide 15 mg (N=311)	Placebo (N=315)	Treatment comparison (95% CI)*; p-value	
		LSM (SE)		**Tirzepatide 10 mg vs placebo**	**Tirzepatide 15 mg vs placebo**
BMI, kg/m^2	-4·7 (0·2)	-5·4 (0·2)	-1·2 (0·2)	ETD -3·5 (-4·1, -3·0); p<0·0001	ETD -4·2 (-4·7, -3·7); p<0·0001
Body weight, kg	-12·9 (0·6)	-14·8 (0·5)	-3·2 (0·5)	ETD -9·7 (-11·2, -8·2); p<0·0001	ETD -11·6 (-13·1, -10·2); p<0·0001

Data from all participants in the full analysis set are included in the treatment comparisons. All changes are from baseline to week 72. * For some binary outcomes, the 95% confidence interval was large due to the limited number of participants in the placebo group achieving the respective targets. †The primary and key secondary endpoints were tested under a type 1 error–control procedure. ‡This was a pre-specified exploratory endpoint. BMI=body mass index. CI=confidence interval. ETD=estimated treatment difference. HbA_{1c}=glycated haemoglobin. OR=odds ratio.

Table 3. Adverse events

	Tirzepatide 10 mg N=312	Tirzepatide 15 mg N=311	Placebo N=315
Participants with ≥1 treatment-emergent adverse event	242 (77·6)	222 (71·4)	239 (75·9)
Serious adverse events*	18 (5·8)	27 (8·7)	23 (7·3)
Deaths[*]	2 (0·6)	0	0
Adverse events leading to discontinuation of study drug[†]	12 (3·8)	23 (7·4)	12 (3·8)
Diarrhea	0	5 (1·6)	0
Nausea	1 (0·3)	4 (1·3)	0
Vomiting	2 (0·6)	0	0
Elevated blood calcitonin	2 (0·6)	0	0
Elevated pancreatic enzymes	2 (0·6)	0	0
Treatment-emergent adverse events occurring in ≥5% of participants in any treatment group (preferred term)			

	Tirzepatide 10 mg N=312	Tirzepatide 15 mg N=311	Placebo N=315
Diarrhea	62 (19·9)	67 (21·5)	28 (8·9)
Nausea	63 (20·2)	68 (21·9)	20 (6·3)
COVID-19	53 (17·0)	33 (10·6)	53 (16·8)
Vomiting	34 (10·9)	41 (13·2)	10 (3·2)
Decreased appetite	30 (9·6)	31 (10·0)	7 (2·2)
Constipation	25 (8·0)	28 (9·0)	13 (4·1)
Dyspepsia	23 (7·4)	22 (7·1)	10 (3·2)
Hyperglycemia	6 (1·9)	4 (1·3)	45 (14·3)
Upper respiratory tract infection	10 (3·2)	12 (3·9)	21 (6·7)
Abdominal pain	12 (3·8)	23 (7·4)	7 (2·2)
Headache	16 (5·1)	15 (4·8)	9 (2·9)
Nasopharyngitis	9 (2·9)	10 (3·2)	17 (5·4)
Eructation	19 (6·1)	13 (4·2)	2 (0·6)

	Tirzepatide 10 mg N=312	Tirzepatide 15 mg N=311	Placebo N=315
Dizziness	17 (5·4)	8 (2·6)	5 (1·6)
Adverse events of special interest			
Diabetic retinopathy complications‡	1 (0·3)	0	1 (0·3)
Hepatic events‡	2 (0·6)	0	0
Malignancies	1 (0·3)	3 (0·1)	7 (2·2)
Pancreatitis (adjudication-confirmed)	0	2 (0·6)	1 (0·3)
MACE (adjudication-confirmed)	4 (1·3)	3 (1·0)	4 (1·3)
Cardiac disorders§	4 (1·3)	1 (0·3)	1 (0·3)
Gastrointestinal Events‡	5 (1·6)	10 (3·2)	4 (1·3)
Gallbladder disease‡	2 (0·6)	4 (1·3)	3 (1·0)
Renal events‡	3 (1·0)	0	1 (0·3)
Dehydration‡	1 (0·3)	1 (0·3)	0
MDD/suicidal ideation‡	0	0	1 (0·3)

	Tirzepatide 10 mg N=312	Tirzepatide 15 mg N=311	Placebo N=315
Other treatment-emergent adverse events of interest			
Cholelithiasis	2 (0·6)	6 (1·9)	4 (1·3)
Acute cholecystitis	1 (0·3)	3 (1·0)	2 (0·6)
Cholecystectomy	1 (0·3)	0	0

Data are n (%). MACE=major adverse cardiovascular events. MDD=major depressive disorder.
* Deaths were also included as serious adverse events; All deaths were adjudicated by an external committee of physicians as to whether the death was a cardiovascular-related death or not.
†Adverse events are listed according to Medical Dictionary for Regulatory Activities, version 24·1, preferred terms; only preferred terms with n≥2 in at least one arm are presented.
‡ Events were classified as severe or serious adverse events.
§ Events were classified as severe or serious arrhythmias and cardiac conduction disorders.

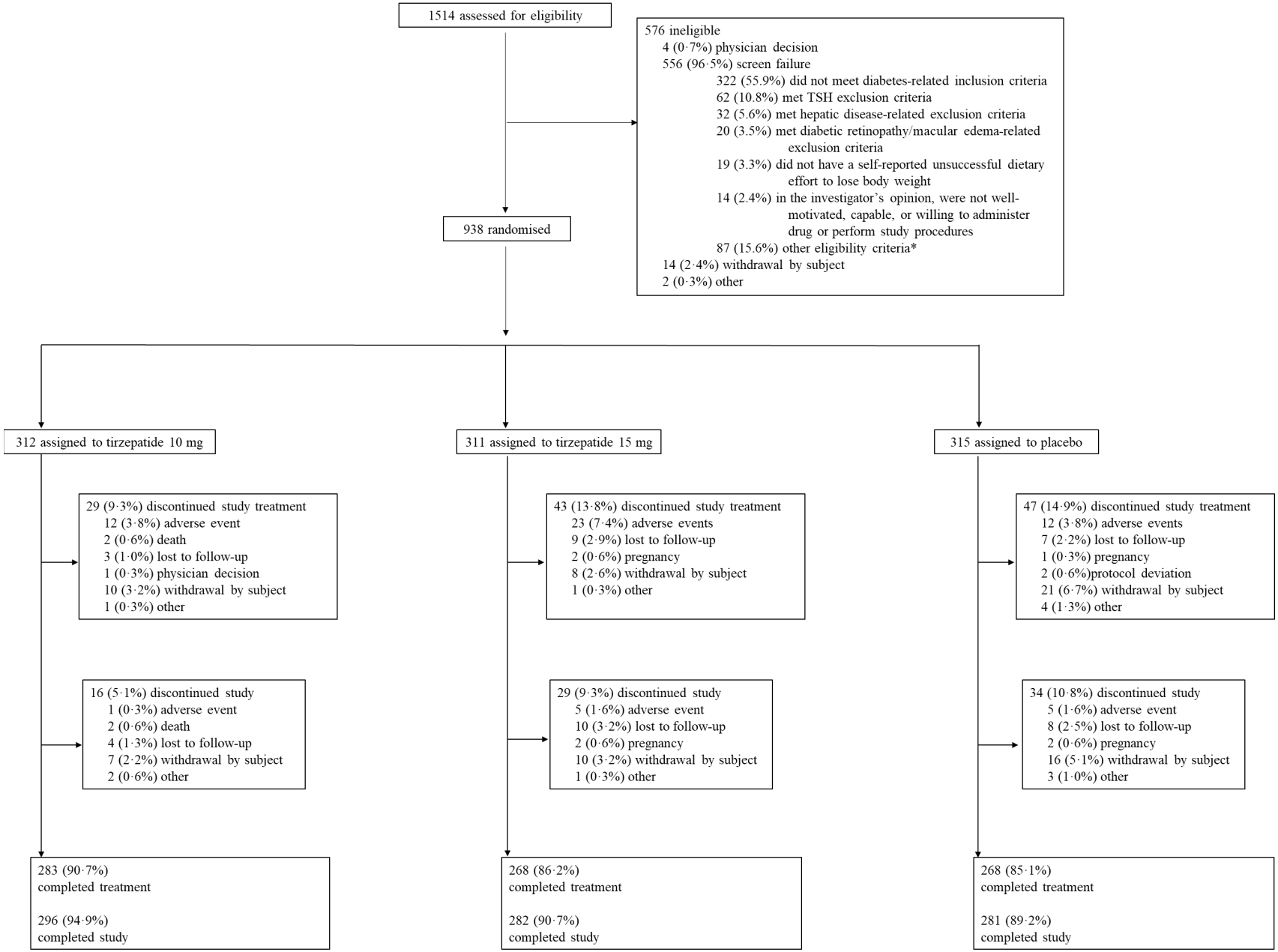
1514 assessed for eligibility
576 ineligible
4 (0·7%) physician decision
556 (96·5%) screen failure
322 (55.9%) did not meet diabetes-related inclusion criteria
62 (10.8%) met TSH exclusion criteria
32 (5.6%) met hepatic disease-related exclusion criteria
20 (3.5%) met diabetic retinopathy/macular edema-related exclusion criteria
19 (3.3%) did not have a self-reported unsuccessful dietary effort to lose body weight
14 (2.4%) in the investigator's opinion, were not well-motivated, capable, or willing to administer drug or perform study procedures
87 (15.6%) other eligibility criteria*
14 (2·4%) withdrawal by subject
2 (0·3%) other
938 randomised
312 assigned to tirzepatide 10 mg
311 assigned to tirzepatide 15 mg
315 assigned to placebo
29 (9·3%) discontinued study treatment
12 (3·8%) adverse event
2 (0·6%) death
3 (1·0%) lost to follow-up
1 (0·3%) physician decision
10 (3·2%) withdrawal by subject
1 (0·3%) other
43 (13·8%) discontinued study treatment
23 (7·4%) adverse events
9 (2·9%) lost to follow-up
2 (0·6%) pregnancy
8 (2·6%) withdrawal by subject
1 (0·3%) other
47 (14·9%) discontinued study treatment
12 (3·8%) adverse events
7 (2·2%) lost to follow-up
1 (0·3%) pregnancy
2 (0·6%)protocol deviation
21 (6·7%) withdrawal by subject
4 (1·3%) other
16 (5·1%) discontinued study
1 (0·3%) adverse event
2 (0·6%) death
4 (1·3%) lost to follow-up
7 (2·2%) withdrawal by subject
2 (0·6%) other
29 (9·3%) discontinued study
5 (1·6%) adverse event
10 (3·2%) lost to follow-up
2 (0·6%) pregnancy
10 (3·2%) withdrawal by subject
1 (0·3%) other
34 (10·8%) discontinued study
5 (1·6%) adverse event
8 (2·5%) lost to follow-up
2 (0·6%) pregnancy
16 (5·1%) withdrawal by subject
3 (1·0%) other
283 (90·7%)
completed treatment
296 (94·9%)
completed study
268 (86·2%)
completed treatment
282 (90·7%)
completed study
268 (85·1%)
completed treatment
281 (89·2%)
completed study

Figure 1. Trial profile. ***** Other represents all eligibility criteria screen failures individually occurring in less than 2% of screened individuals. TSH=thyroid-stimulating hormone.

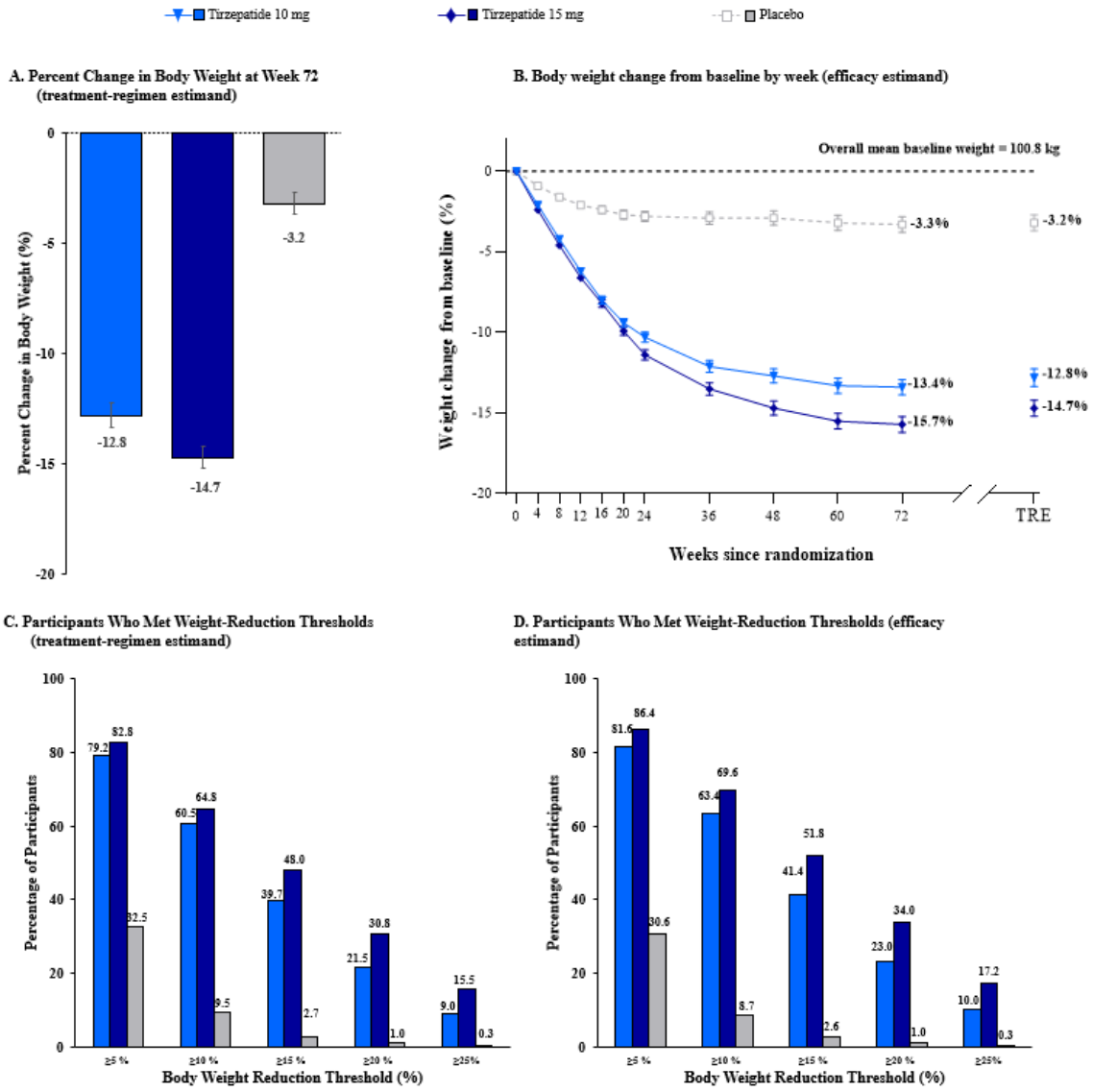

Figure 2. Effect of once weekly tirzepatide, as compared with placebo, on body weight. Least-squares means are presented, unless otherwise noted. Error bars indicate the standard error. Panel A shows the percent change in body weight from baseline to week 72 derived from an analysis of covariance model for the treatment-regimen estimand. Panel B shows the percent change in body weight over time from baseline to 72 weeks, derived from a mixed-model for repeated-measures (MMRM) analysis for the efficacy estimand; week 72 estimates for the treatment-regimen estimand (TRE) are also shown. Panels C and D show the percentages of participants who had body weight reductions of at least 5%, 10%, 15%, 20% and 25% from baseline to week 72. For Panel C, the percentage of participants reaching weight reduction thresholds was calculated using logistic regression with missing value imputed by hybrid imputation and use of Rubin's rule to combine estimation from individually imputed datasets. For Panel D, the percentage of participants reaching weight reduction thresholds was obtained by logistic regression with missing value at Week 72 imputed from MMRM analysis.

Figure 2.pdf

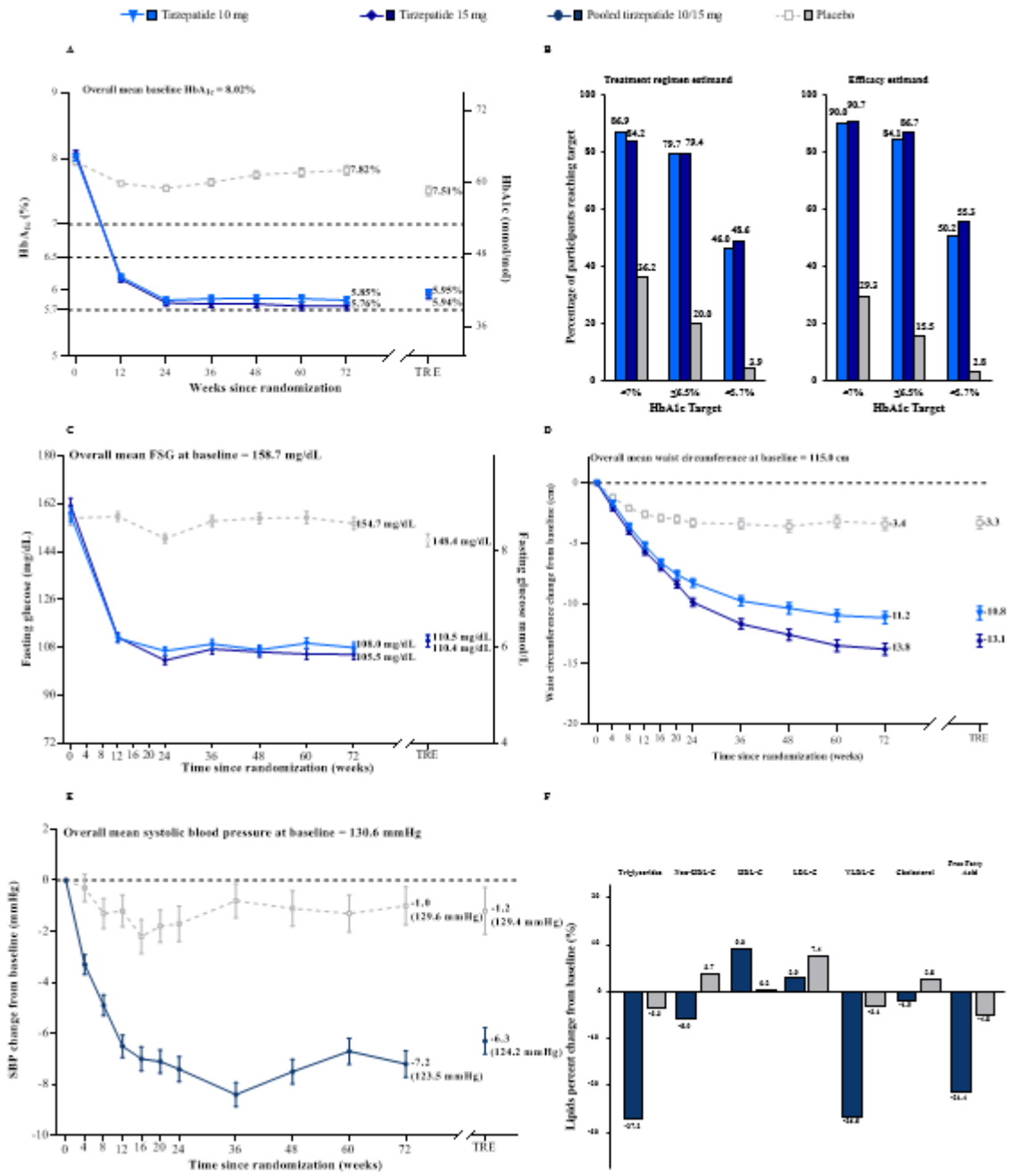

Figure 3. Proportion of participants reaching HbA1c targets, waist circumference, FSG, SBP, and lipid levels. Data are LSM (SE) unless otherwise stated. (A) HbA1c values over time from MMRM analysis for the efficacy estimand and week 72 estimates from ANCOVA for the TRE. (B) Proportion of participants reaching HbA1c targets (<7.0%, ≤6·5%, and <5.7%) from logistic regression analysis for the TRE (left) and the efficacy estimand (right). (C) FSG values over time from MMRM analysis for the efficacy estimand and week 72 estimates from ANCOVA for the TRE. (D) Change in waist circumference over time from MMRM analysis for the efficacy estimand and week 72 estimates from ANCOVA for the TRE. (E) Change in SBP over time for pooled tirzepatide doses and placebo from MMRM analysis for the efficacy estimand and week 72 estimates from ANCOVA for the TRE; numbers in parentheses are actual mean values at week 72; by-dose analysis for tirzepatide versus placebo is available in supplementary appendix Figure S7. (F) Percent change from baseline fasting lipid levels for pooled tirzepatide doses and placebo from ANCOVA for the TRE; data are estimated means; results for the efficacy estimand and the

tirzepatide by-dose analysis are available in supplementary appendix Table S2. CI = confidence interval. ANCOVA=analysis of covariance. FSG=fasting serum glucose. HbA1c=glycated haemoglobin. FSG=fasting serum glucose. LSM=least squares mean. MMRM=mixed model repeated measures. SBP = systolic blood pressure. TRE=treatment-regimen estimand.

Figure 3.pdf

Supplementary Appendix

INCLUSION AND EXCLUSION CRITERIA

Inclusion criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Type of Participant and Disease Characteristics

- Have a BMI ≥27 kg/m^2
- Have a diagnosis of T2DM according to the World Health Organization (WHO) classification or other locally applicable standards (see Section 10.10), with HbA_{1c} ≥7% (≥53 mmol/mol) to ≤10% (86 mmol/mol) at screening, on stable therapy for the last 3 months prior to screening. Type 2 diabetes mellitus may be treated with diet/exercise alone or any **oral** glycemic-lowering agent (as per local labeling) EXCEPT dipeptidyl peptidase 4 (DPP-4) inhibitors or GLP-1R agonists
- Have a history of at least 1 self-reported unsuccessful dietary effort to lose body weight
- In the investigator's opinion, are well-motivated, capable, and willing to:
    - perform finger stick BG monitoring, including weekly fasting glucose measurements and scheduled BG profiles with up to 7 measurements in 1 day
    - learn how to self-inject study drug, as required for this protocol (visually impaired persons who are not able to perform the injections must have the assistance of a sighted individual trained to inject the study drug; persons with physical limitations who are not able to perform the injections must have the assistance of an individual trained to inject the study drug)
    - inject study drug (or receive an injection from a trained individual if visually impaired or with physical limitations)
    - follow study procedures for the duration of the study, including, but not limited to follow lifestyle advice (for example, dietary restrictions and exercise plan), maintain a study diary, and complete required questionnaires

Participant Characteristics

- Are at least 18 years of age and age of majority per local laws and regulations
    - Male participants with partners of childbearing potential should be willing to use reliable contraceptive methods throughout the study and for 5 half-lives of study drug plus 90 days, corresponding to 4 months after the last injection
    - Female participants not of childbearing potential may participate and include those who are:
        - infertile due to surgical sterilization (hysterectomy, bilateral oophorectomy, or tubal ligation), congenital anomaly such as Mullerian agenesis; or
        - postmenopausal – defined as either:
            - A woman at least 40 years of age with an intact uterus, not on hormone therapy, who has cessation of menses for at least 1 year

without an alternative medical cause, AND a follicle-stimulating hormone (FSH) ≥ 40 mIU/mL; women in this category must test negative in pregnancy test prior to study entry

Or

- A woman 55 or older not on hormone therapy, who has had at least 12 months of spontaneous amenorrhea

Or

- A woman at least 55 years of age with a diagnosis of menopause prior to starting hormone replacement therapy (HRT)

- Female participants of childbearing potential (not surgically sterilized and between menarche and 1-year postmenopausal) must:
  - test negative for pregnancy at Visit 1 based on a serum pregnancy test,
  - if sexually active, agree to use 2 forms of effective contraception, where at least 1 form is highly effective for the duration of the trial plus 30 days, corresponding to 2 months after the last injection, and
  - not be breastfeeding

Note: Contraceptive use by men or women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

Informed Consent

- Capable of giving signed informed consent as described in Appendix 1 which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.

Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions

Diabetes-related

- Have type 1 diabetes mellitus (T1DM), history of ketosis or hyperosmolar state/coma, or any other types of diabetes except T2DM
- Have had 1 or more episode of severe hypoglycemia and/or 1 or more episode of hypoglycemia unawareness within the 6 months prior to Visit 1
- Have at least 2 confirmed fasting SMBG values >270 mg/dL (15.0 mmol/L) (on 2 nonconsecutive days) prior to Visit 3
- Have history of:
  - proliferative diabetic retinopathy OR
  - diabetic macular edema OR
  - non-proliferative diabetic retinopathy that requires acute treatment.

  Note: A dilated fundoscopic examination performed by an ophthalmologist or optometrist between Visit 2 and Visit 3 is required to confirm eligibility.
- Current or prior treatment (within 3 months prior to Visit 1) with DPP-4 inhibitors, oral GLP-1R agonist, or **any** injectable therapy for T2DM

Obesity-related

- Have a self-reported change in body weight >5 kg within 3 months prior to screening
- Have a prior or planned surgical treatment for obesity (excluding liposuction or abdominoplasty if performed >1 year prior to screening)
- Have or plan to have endoscopic and/or device-based therapy for obesity or have had device removal within the last 6 months prior to screening
    - mucosal ablation
    - gastric artery embolization
    - intragastric balloon
    - duodenal-jejunal endoluminal liner

Other medical

- Have renal impairment measured as estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2, calculated by Chronic Kidney Disease-Epidemiology as determined by central laboratory during screening
  Note*:* For participants on metformin therapy, their renal function must be greater than the country-specific threshold criteria for discontinuing metformin therapy per local label.
- Have a known clinically significant gastric emptying abnormality (for example, severe gastroparesis or gastric outlet obstruction) or chronically take drugs that directly affect GI motility
- Have a history of chronic or acute pancreatitis
- Have a thyroid-stimulating hormone (TSH) outside of 0.4 to 6.0 mIU/L at the screening visit
  Note*:* Participants receiving treatment for hypothyroidism may be included, provided their thyroid hormone replacement dose has been stable for at least 3 months and their TSH at screening falls within the range indicated above.
  Note: Participants with a history of subclinical hypothyroidism but a TSH at screening within the range indicated above, may be included if, in the investigator's opinion, the participant is unlikely to require initiation of thyroid hormone replacement during the course of the study.
- Have obesity induced by other endocrinologic disorders (for example Cushing syndrome) or diagnosed monogenetic or syndromic forms of obesity (for example, Melanocortin 4 Receptor deficiency or Prader Willi Syndrome)
- Have a history of significant active or unstable Major Depressive Disorder (MDD) or other severe psychiatric disorder (for example, schizophrenia, bipolar disorder, or other serious mood or anxiety disorder) within the last 2 years
  Note: Participants with MDD or generalized anxiety disorder whose disease state is considered stable for the past 2 years and expected to remain stable throughout the course of the study, in the opinion of the investigator, may be considered for inclusion if they are not on excluded medications.
- Have any lifetime history of a suicide attempt
- Have a PHQ-9 score of 15 or more on or before Visit 3
- On the C-SSRS at Visits 1, 2, or 3, prior to randomization:

- a "yes" answer to Question 4 (Active Suicidal Ideation with Some Intent to Act, Without Specific Plan) on the "Suicidal Ideation" portion of the C-SSRS
  or
- a "yes" answer to Question 5 (Active Suicidal Ideation with Specific Plan and Intent) on the "Suicidal Ideation" portion of the C-SSRS
  or
- a "yes" answer to any of the suicide-related behaviors (actual attempt, interrupted attempt, aborted attempt, preparatory act or behavior) on the "Suicidal Behavior" portion of the C-SSRS
  and
- the ideation or behavior occurred within the past month

- Have uncontrolled hypertension (systolic blood pressure [SBP] ≥160 mmHg and/or diastolic blood pressure ≥ 100 mmHg)
- Have any of the following cardiovascular conditions within 3 months prior to randomization: acute myocardial infarction, cerebrovascular accident (stroke), unstable angina, or hospitalization due to congestive heart failure (CHF)
- Have NYHA Functional Classification class IV CHF
- Have acute or chronic hepatitis, signs and symptoms of any liver disease other than nonalcoholic fatty liver disease (NAFLD), or any of the following, as determined by the central laboratory during screening:
  - alanine aminotransferase (ALT) level >3.0X the upper limit of normal (ULN) for the reference range,
  - alkaline phosphatase (ALP) level >1.5X the ULN for the reference range, or
  - total bilirubin level (TBL) >1.2X the ULN for the reference range (except for cases of known Gilbert's Syndrome)

  Note: Participants with NAFLD are eligible to participate in this trial if their ALT level is ≤3.0X the ULN for the reference range.
- Have a serum calcitonin level (at Visit 1) of:
  - ≥20 ng/L, if eGFR ≥60 mL/min/1.73 m^2
  - ≥35 ng/L, if eGFR <60 mL/min/1.73 m^2
- Have a family or personal history of medullary thyroid carcinoma (MTC) or multiple endocrine neoplasia (MEN) syndrome type 2
- Have a history of an active or untreated malignancy or are in remission from a clinically significant malignancy (other than basal or squamous cell skin cancer, in situ carcinomas of the cervix, or in situ prostate cancer) for less than 5 years
- Have any other condition not listed in this section (for example, hypersensitivity or intolerance) that is a contraindication to GLP-1R agonists
- Have a history of any other condition (such as known drug or alcohol abuse, diagnosed eating disorder, or other psychiatric disorder) that, in the opinion of the investigator, may preclude the participant from following and completing the protocol
- Have history of use of marijuana or tetrahydrocannabinol (THC)-containing products within 3 months of enrollment or unwillingness to abstain from marijuana or THC-containing products use during the trial.
  Note: If a participant has used cannabidiol oil during the past 3 months but agrees to refrain from use for the duration of the study, the participant can be enrolled.

- Have had a transplanted organ (corneal transplants [keratoplasty] allowed) or awaiting an organ transplant
- Have any hematological condition that may interfere with HbA_{1c} measurement (for example, hemolytic anemias, sickle cell disease)

Prior/Concomitant Therapy

- Are receiving or have received within 3 months prior to screening chronic (>2 weeks or >14 days) systemic glucocorticoid therapy (excluding topical, intraocular, intranasal, intraarticular, or inhaled preparations) or have evidence of a significant, active autoimmune abnormality (for example, lupus or rheumatoid arthritis) that has required (within the last 3 months) or is likely to require, in the opinion of the investigator, concurrent treatment with systemic glucocorticoids (excluding topical, intraocular, intranasal, intraarticular, or inhaled preparations) during the course of the study
- Have a current or history of (within 3 months prior to randomization) treatment with medications that may cause significant weight gain, including but not limited to: tricyclic antidepressants, atypical antipsychotics, and mood stabilizers
  Examples:
  - Imipramine
  - Amitriptyline
  - Mirtazapine
  - Paroxetine
  - Phenelzine
  - Chlorpromazine
  - Thioridazine
  - Clozapine
  - Olanzapine
  - valproic acid (and its derivatives), or
  - lithium

  Note: Selective serotonin reuptake inhibitors (SSRIs) other than paroxetine are permitted. Antihyperglycemic medications (for example, sulfonylureas, thiazolidinediones) for the management of T2DM are permitted.
- Have taken within 3 months prior to randomization, medications (prescribed or over-the-counter) or alternative remedies that promote weight loss
  Examples include, but are not limited to:
  - Saxenda (liraglutide 3.0 mg)
  - Xenical®/Alli® (orlistat)
  - Meridia® (sibutramine)
  - Acutrim® (phenylpropanolamine)
  - Sanorex® (mazindol)
  - Apidex® (phentermine)
  - BELVIQ® (lorcaserin)
  - Bontril® (phendimetrazine)
  - Qsymia™ (phentermine/topiramate combination)
  - Contrave® (naltrexone/bupropion)

Note: Antihyperglycemic medications for the management of T2DM (for example, sodium-glucose cotransporter [SGLT]-2 inhibitors) are permitted.

- Have started implantable or injectable contraceptives (such as Depo Provera®) within 18 months prior to screening

Prior/Concurrent Clinical Study Experience

- Are currently enrolled in any other clinical study involving an investigational product (IP) or any other type of medical research judged not to be scientifically or medically compatible with this study
- Within the last 30 days, have participated in a clinical study and received treatment, whether active or placebo. If the study involved an IP, 5 half-lives or 30 days, whichever is longer, should have passed
- Have previously completed or withdrawn from this study or any other study investigating tirzepatide after receiving at least 1 dose of IP

Other Exclusions

- Are investigator site personnel directly affiliated with this study and/or their immediate family. Immediate family is defined as a spouse, parent, child, or sibling, whether biological or legally adopted
- Are Lilly employees

STATISTICAL ANALYSIS METHODS

In this study, two estimands were prespecified in the protocol and both intended to estimate the treatment effect for all randomized participants. Both estimands are based on the newly released ICH E9 (R1) for estimands and sensitivity analyses.

Treatment-regimen estimand

This estimand represents the average treatment effect of tirzepatide relative to placebo at 72 weeks, as an adjunct to a reduced-calorie diet and increased physical activity, for the randomized participants irrespective of the adherence to treatment or initiation of rescue antihyperglycaemic medication (AHM). This estimand uses a treatment policy strategy to handle intercurrent events [ICH E9(R1)] and is intended to give an estimation of the population-level treatment effect comparing tirzepatide and placebo including the effect of diet and exercise for all randomized participants regardless of premature study drug discontinuation or initiation of rescue antihyperglycaemic therapy. For the estimation for this estimand, the intercurrent events (ICEs) and the resulting missing values were handled by a hybrid approach of using retrieved dropouts imputation from the same treatment group or using all non-missing data assuming missing at random. Thus, this estimand is also referred to as “hybrid” estimand in the study protocol.

For analyses related to the treatment-regimen estimand, analysis of covariance (ANCOVA) was used for continuous outcomes (e.g., percent weight change) at Week 72 and logistic regression was used for binary outcomes (e.g., achieving 5% weight reduction target) at 72 weeks. Both models included treatment group, country/pooled country, sex, and type of AHM used at randomization as fixed effects and baseline measure as a covariate. The analyses were conducted with hybrid imputation of missing body weight at 72 weeks and statistical inference over hybrid imputation of missing data guided by Rubin (1987). Specifically, for missing data solely due to COVID-19, the missing data were considered as missing at random and imputed using all available non-missing data of the primary outcome measurement from the same treatment arm; for missing data due to other intercurrent events, missing data were imputed based on retrieved dropouts in the same treatment arm, defined as observed primary outcome measurements, from participants in the same treatment group, who had their efficacy assessed after early discontinuation of the study drug or initiation of rescue AHM.

Efficacy estimand

This estimand represents the average treatment effect of tirzepatide relative to placebo at 72 weeks, as an adjunct to a reduced-calorie diet and increased physical activity, in the randomized participants had they remained on their randomized treatment for the entire planned 72 weeks treatment duration. This estimand uses a hypothetical strategy to handle intercurrent events [ICH E9(R1)] and is intended to provide an estimation of the achievable study treatment effect when participants take the treatment as planned. The resulting missing values (unobserved, discarded after treatment discontinuation (all endpoints) or initiation of rescue medication for

hyperglycaemia (glycemic endpoints only)) were implicitly handled by using a mixed model for repeated measures (MMRM) under the assumption of missing at random.

For MMRM the independent variables of analysis model include treatment group, visit, treatment-by-visit interaction, stratification factors (country/pooled country, sex, and type of AHM used at randomization) as fixed effects, and baseline measure as a covariate.

A logistic regression model with terms of treatment group, country/pooled country, sex, and type of AHM used at randomization as fixed effects, and baseline measure as a covariate, were conducted for binary outcomes. Missing values were imputed by the predicted value from MMRM model aforementioned, then the continuous measurements were dichotomized to binary outcomes.

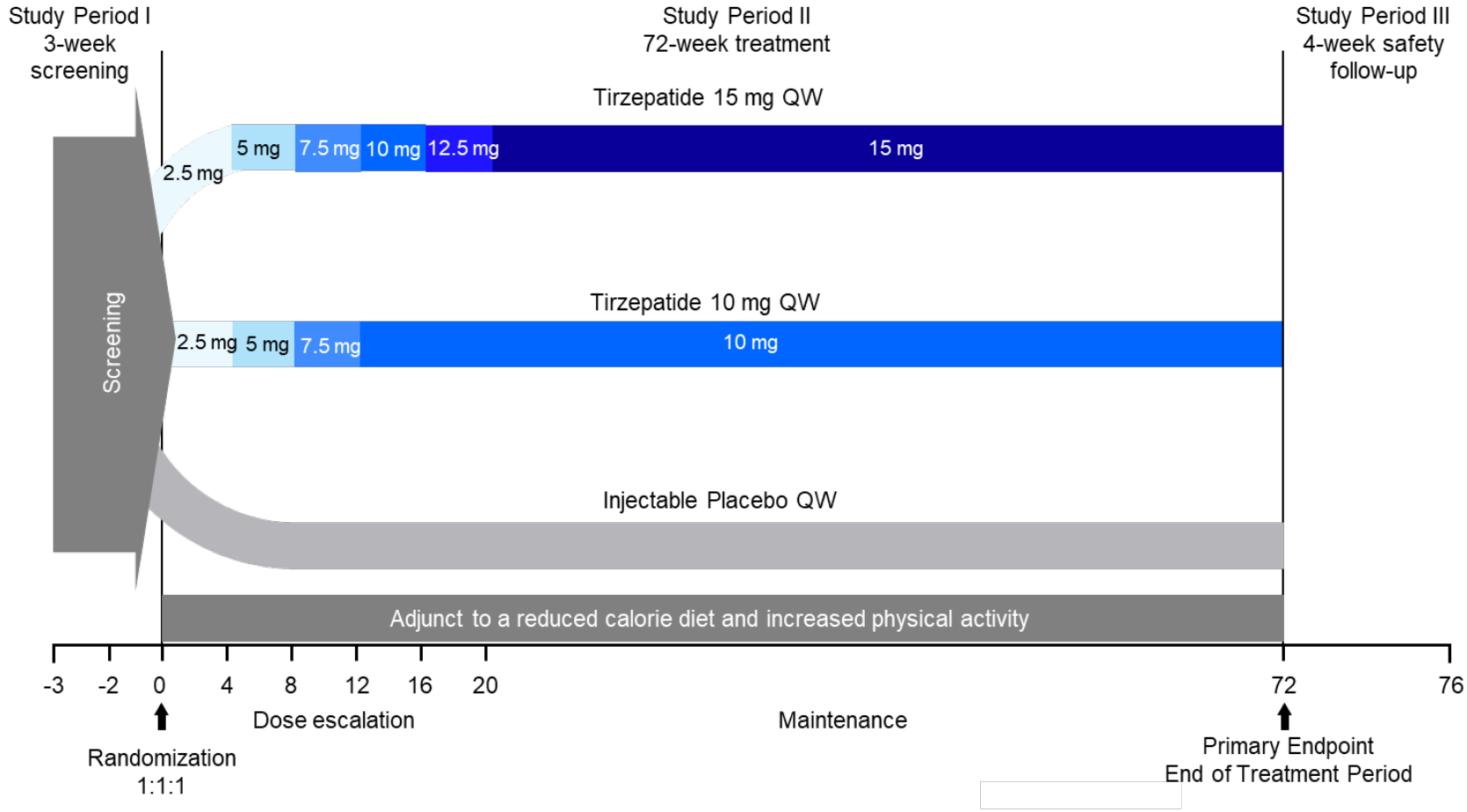

Figure S1 SURMOUNT-2 study design. This is a phase 3, multicentre, randomised, placebo-controlled, double-blind, 72-week clinical trial investigating the safety and efficacy of tirzepatide 10 mg and 15 mg administered once weekly (QW) subcutaneously compared with placebo on weight management, as an adjunct to a reduced-calorie diet and increased physical activity, in participants with T2D who have a BMI ≥27 kg/m^2.

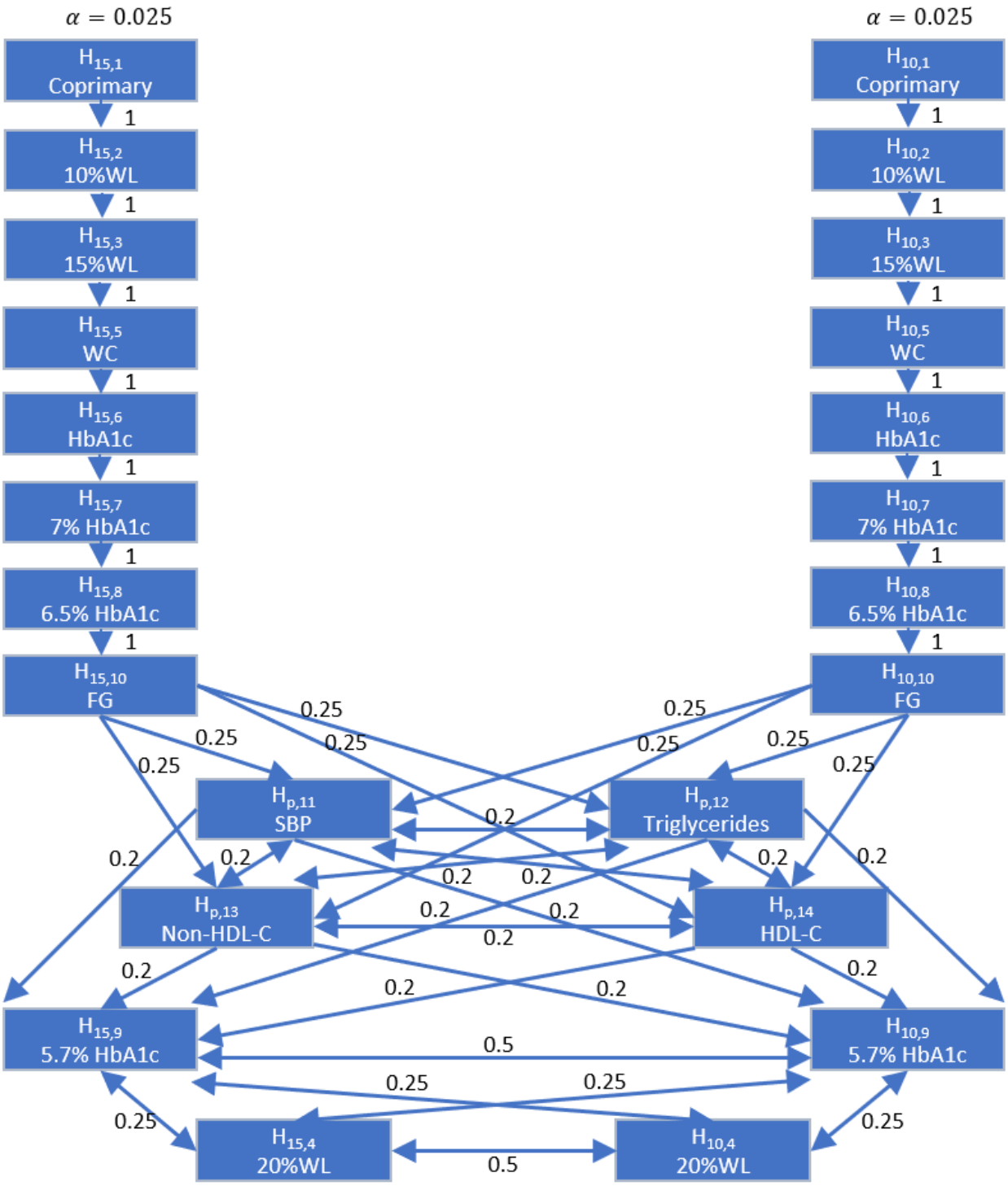

Figure S2. Type 1 error control strategy for primary and key secondary efficacy endpoints.

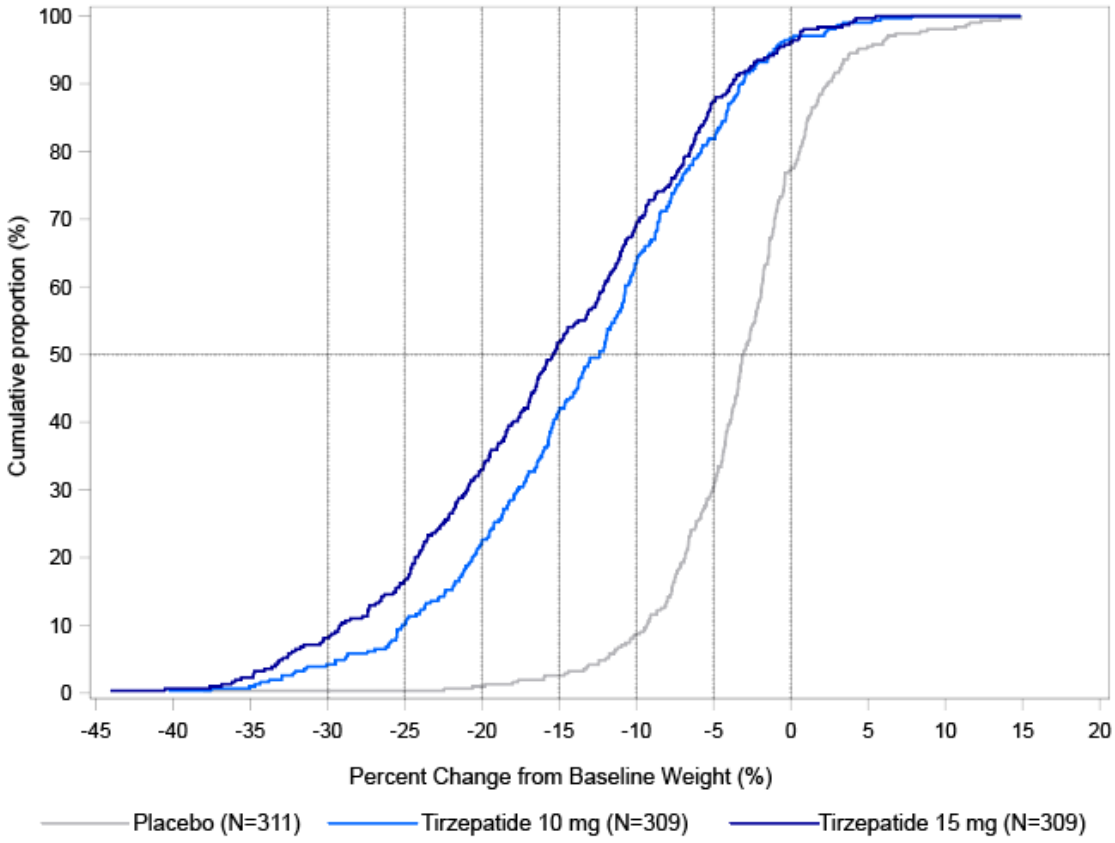

Figure S3. Cumulative distribution plot of percentage change from baseline in body weight for participants in the efficacy analysis set (including data obtained during treatment period from the intention-to-treat population, excluding data after discontinuation of study drug). Only participants with non-missing baseline values and at least one non-missing post-baseline value of the response variable are included in the plot. Missing data was imputed from a mixed-model for repeated measures for post-baseline measures. Reference values for percent changes (-30%, -25%, -20%, - 15%, -10%, -5%, 0%) are marked with gray, solid lines on the x-axis; 50th percentile is marked with a gray, solid line on the y-axis.

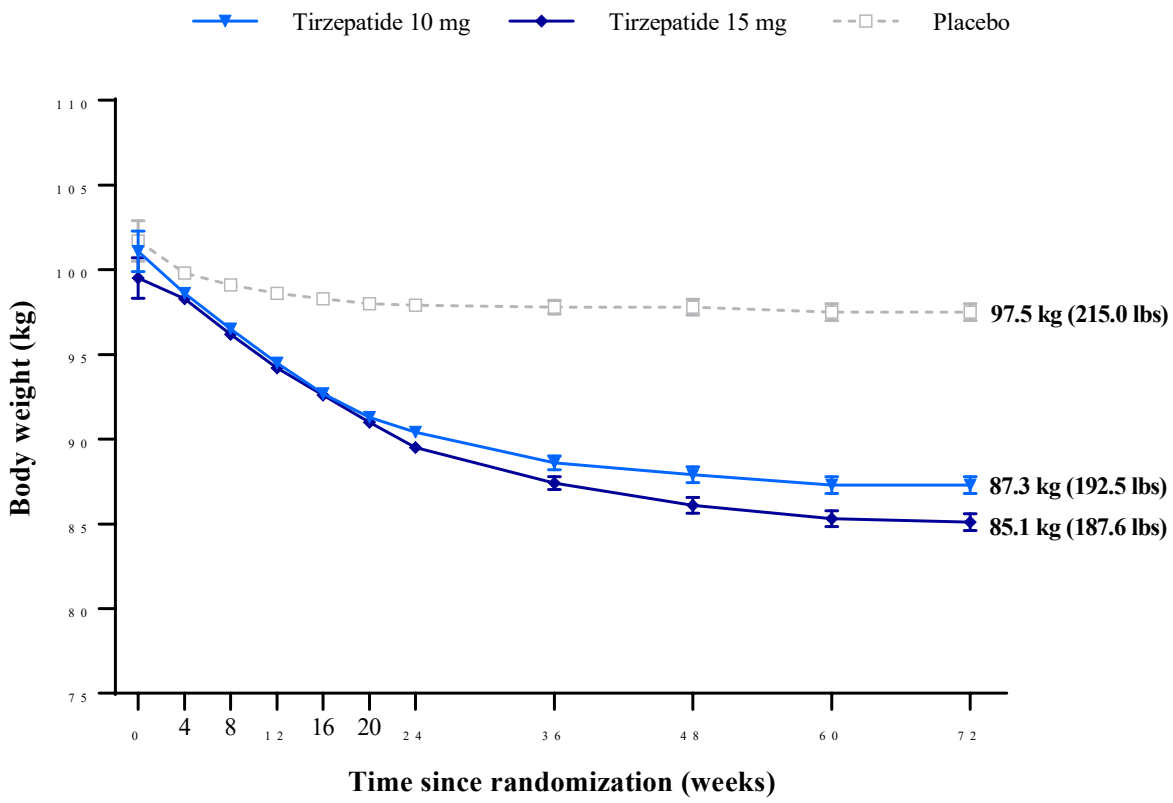

Figure S4. Mean body weight (kg) over time from baseline to 72 weeks derived from a mixed-model for repeated measures (MMRM) analysis for the efficacy estimand. Only participants with non-missing baseline value and at least one non-missing post-baseline value of the response variable were included in analysis. Error bars indicate standard error.

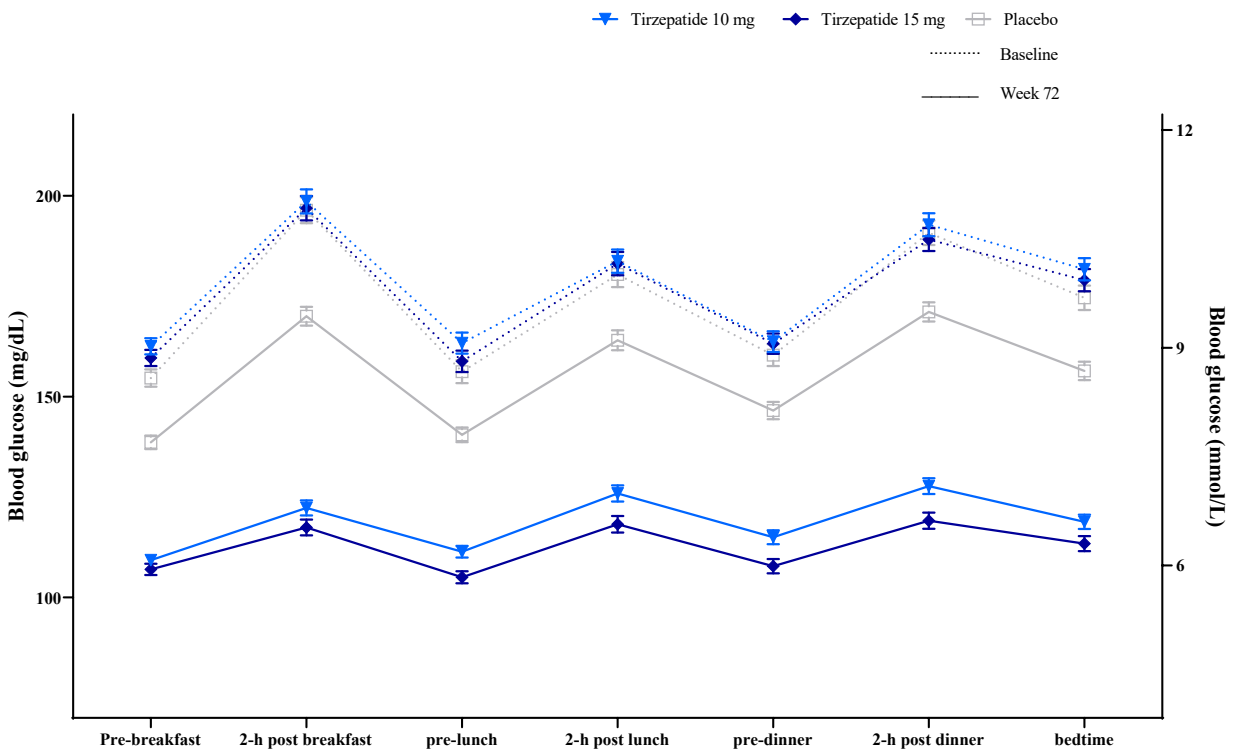

Figure S5. Seven-point SMBG at baseline and at week 72 derived from a mixed-model for repeated measures (MMRM) analysis for the efficacy estimand. Only participants with non-missing baseline value and at least one non-missing post-baseline value of the response variable were included in analysis. Error bars indicate standard error.

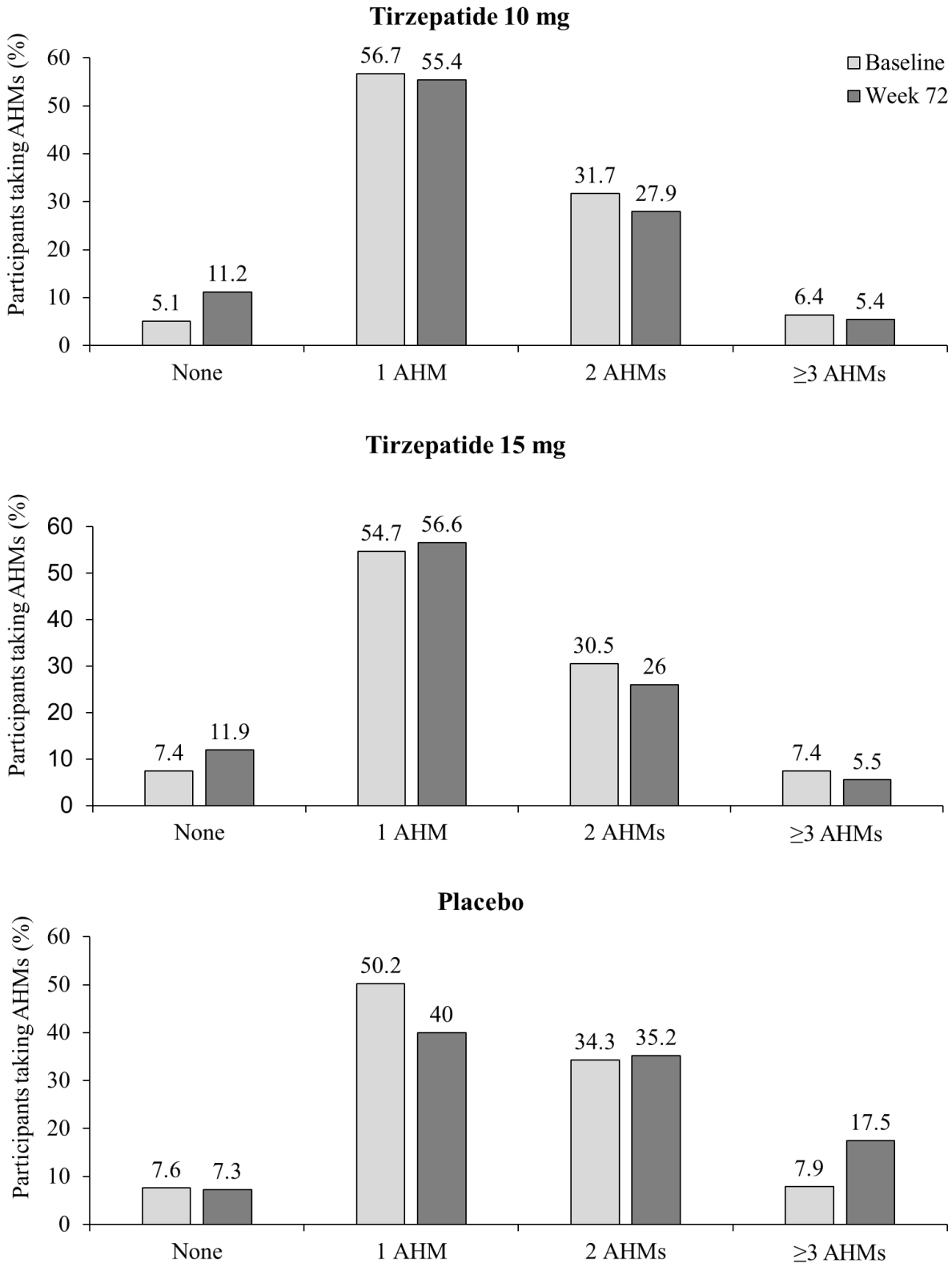

Figure S6. Antihyperglycaemic use at baseline and week 72. AHM = antihyperglycaemic medication.

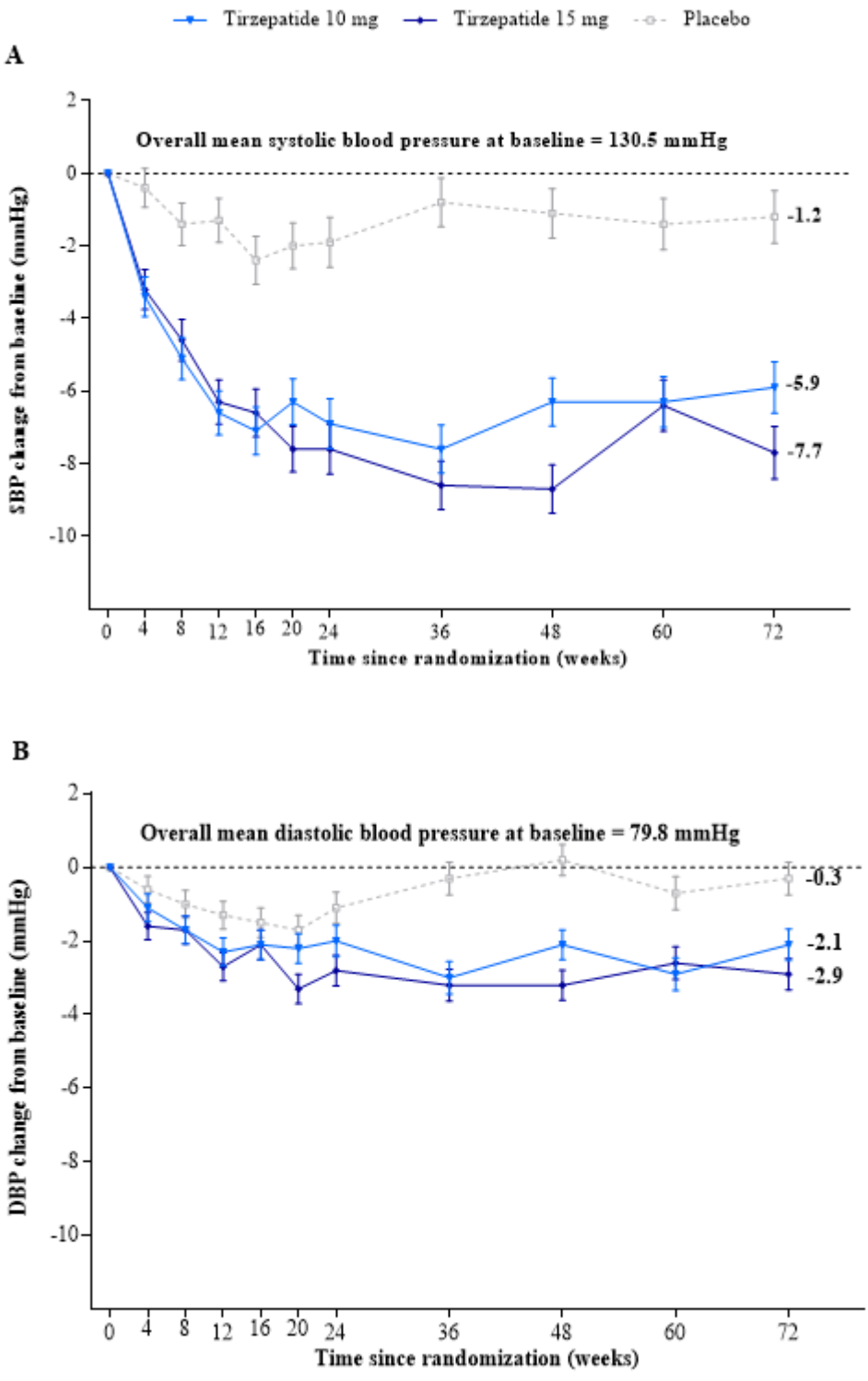

Figure S7. Mean change from baseline over time in systolic blood pressure (A), and diastolic blood pressure (B) from randomization to 72 weeks derived from a mixed-model for repeated-measures (MMRM) including all observed values during the treatment period. Only participants with non-missing baseline value and at least one non-missing post-baseline value of the response variable were included in analysis. Error bars indicate standard error.

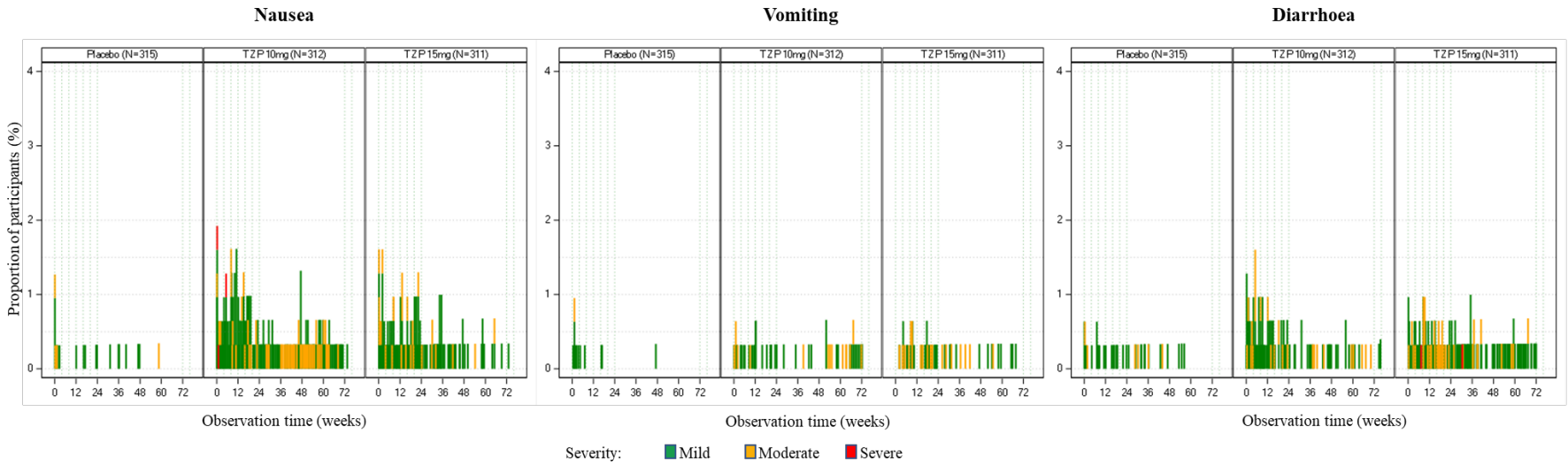

Figure S8. Incidence of nausea, vomiting, and diarrhea over time. The percentage of participants receiving tirzepatide or placebo who reported nausea (Panel A), vomiting (Panel B), or diarrhea (Panel C) are presented. TZP, tirzepatide. Percentages are based on number of participants at risk at specific observation time. Events were classed as mild (shown in green), moderate (shown in orange), or severe (shown in red).

Table S1 Additional baseline characteristics

	Tirzepatide 10 mg N=312	**Tirzepatide 15 mg N=311**	**Placebo N=315**	**Total N=938**
Pre-existing gastrointestinal disorders, n (%)	81 (26)	91 (29)	84 (27)	256 (27)
Country, n (%)				
Argentina	115 (36.9)	115 (37.0)	116 (36.8)	346 (36.9)
Brazil	29 (9.3)	30 (9.6)	30 (9.5)	89 (9.5)
India	8 (2.6)	9 (2.9)	9 (2.9)	26 (2.8)
Japan	24 (7.7)	22 (7.1)	21 (6.7)	67 (7.1)
Russian federation	13 (4.2)	13 (4.2)	17 (5.4)	43 (4.6)
Taiwan	9 (2.9)	8 (2.6)	8 (2.5)	25 (2.7)
United States	114 (36.5)	114 (36.7)	114 (36.2)	342 (36.5)

Table S2 Additional efficacy findings for the efficacy estimand

	Tirzepatide 10 mg	**Tirzepatide 15 mg**	**Placebo**	**Treatment comparison versus placebo (95% CI)**	
	N=312	**N=311**	**N=315**		
		LSM (SE)		**Tirzepatide 10 mg vs placebo**	**Tirzepatide 15 g vs placebo**
Key secondary endpoints (at week 72)					
Change in					
Waist circumference, cm	-11.2 (0.5)	-13.8 (0.5)	-3.4 (0.5)	ETD -7.8(-9.2, -6.4); p<0.0001	-10.4 (-11.8, -8.9); p<0.0001
HbA_{1C}, %	-2.14 (0.06)	-2.22 (0.06)	-0.16 (0.07)	-1.97 (-2.15, -1.80); p<0.0001	-2.06 (-2.24, -1.88); p<0.0001
HbA_{1c}, mmol/mol	-23.4 (0.7)	-24.3 (0.7)	-1.8 (0.7)	ETD -21.6 (-23.5, -19.6); p<0.0001	-22.5 (-24.4, -20.6); p<0.0001
Fasting glucose, mg/dL	-49.2 (1.9)	-51.7 (2.0)	-2.4 (2.3)	-46.8 (-52.7, -40.9); p<0.0001	-49.3 (-55.2, -43.3); p<0.0001
Fasting glucose, mmol/L	-2.7 (0.1)	-2.9 (0.1)	-0.1 (0.1)	-2.6 (-2.9, -2.3); p<0.0001	-2.7 (-3.1, -2.4); p<0.0001
Participants with HbA_{1C} <7%, n [%]	271 [90.0]	272 [90.7]	85 [29.3]	OR 28.0 (17.2, 45.6); p<0.0001	OR 34.2 (20.3, 57.7); p<0.0001

	Tirzepatide 10 mg N=312	Tirzepatide 15 mg N=311	Placebo N=315	Treatment comparison versus placebo (95% CI)	
		LSM (SE)		**Tirzepatide 10 mg vs placebo**	**Tirzepatide 15 g vs placebo**
Participants with HbA_{1C} ≤6.5%, n [%]	253 [84.1]	260 [86.7]	45 [15.5]	42.1 (25.6, 69.3); p<0.0001	58.7 (34.3, 100.4); p<0.0001
Participants with HbA_{1C} <5.7%, n [%]	151 [50.2]	166 [55.3]	8 [2.8]	42.6 (20.5, 88.5); p<0.0001	54.3 (26.0, 113.4); p<0.0001
Additional secondary endpoints (at week 72)					
Change in:					
Body weight, kg	-13.5 (0.5)	-15.6 (0.5)	-3.2 (0.5)	-10.3 (-11.7, -8.8); p<0.0001	-12.4 (-13.8, -11.0); p<0.0001
BMI, kg/m^2	-4.9 (0.2)	-5.7 (0.2)	-1.2 (0.2)	-3.7 (-4.2, -3.2); p<0.0001	-4.5 (-5.0, -4.0); p<0.0001
Percent change in fasting:					
Insulin	-29.6 (2.3)	-40.3 (2.0)	-14.5 (3.4)	-17.6 (-25.5, -8.9); p=0.0002	-30.2 (-37.0, -22.7); p<0.0001
Triglycerides	-26.8 (1.8)	-30.6 (1.7)	-5.8 (2.3)	-22.2 (-27.3, -16.8); p<0.0001	-26.3 (-31.1, -21.0); p<0.0001

	Tirzepatide 10 mg N=312	Tirzepatide 15 mg N=311	Placebo N=315	Treatment comparison versus placebo (95% CI)	
		LSM (SE)		**Tirzepatide 10 mg vs placebo**	**Tirzepatide 15 g vs placebo**
Non-HDL cholesterol	-6.6 (1.4)	-6.7 (1.4)	2.3 (1.6)	-8.7 (-12.5, -4.8); p<0.0001	-8.8 (-12.6, -4.8); p<0.0001
HDL cholesterol	6.9 (1.1)	9.6 (1.1)	1.1 (1.0)	5.7 (2.7, 8.7); p=0.0001	8.4 (5.3, 11.6); p<0.0001
Additional secondary endpoints (at week 72)					
Change in SF-36v2 Physical Function score	3.4 (0.4)	3.8 (0.4)	1.6 (0.4)	1.8 (0.7, 2.9); p=0.0013	2.3 (1.1, 3.4); p<0.0001
Change in IWQOL-Lite-CT Physical Function score	14.3 (1.0)	15.2 (1.0)	7.4 (1.0)	6.9 (4.1, 9.7); p<0.0001	7.8 (5.0, 10.7); p<0.0001
Percent change in fasting:					
Total cholesterol	-3.0 (1.1)	-2.2 (1.1)	2.1 (1.1)	-5.0 (-7.8, -2.0); p=0.0010	-4.2 (-7.1, -1.2); p=0.0065
LDL cholesterol	2.3 (1.8)	3.2 (1.8)	6.3 (1.9)	-3.7 (-8.3, 1.0); p=0.12	-3.0 (-7.6, 1.9); p=0.23
VLDL cholesterol	-26.3 (1.7)	-29.5 (1.6)	-6.0 (2.2)	-21.6 (-26.4, -16.5); p<0.0001	-25.0 (-29.7, -20.1); p<0.0001
Free fatty acids	-22.9 (2.1)	-24.3 (2.1)	0.0 (2.8)	-22.9 (-28.7, -16.7); p<0.0001	-24.3 (-30.1, -18.2); p<0.0001

Data are from the efficacy analysis set. All changes are from baseline to week 72. BMI=body mass index. ETD=estimated treatment difference. HbA_{1c}=glycated haemoglobin. HDL=high-density lipoprotein. IWQOL-Lite-CT=Impact of Weight on Quality of Life-Lite-Clinical Trials Version. LDL=low-density lipoprotein. OR=odds ratio. SF-36v2=Short Form-36 version 2 Health Survey acute form. VLDL=very low-density lipoprotein.

Table S3. COVID-19-Related Adverse Events

	Tirzepatide 10 mg (N=312)	Tirzepatide 15 mg (N=311)	Placebo (N=315)	Total (N=938)
Deaths related to COVID-19	0	0	0	0
Serious adverse events related to COVID-19	1 (0.3)	1 (0.3)	2 (0.6)	4 (0.4)
TEAEs related to COVID-19	56 (17.9)	38 (12.2)	63 (20.0)	157 (16.7)

Data are number of participants (%). COVID-19, coronavirus disease 2019; TEAE, treatment-emergent adverse events.

Table S4. Reported Deaths During the Study

Patient (age, sex)	Treatment Group	Description	Days from Randomization	Days since Last Dose of Study Drug	Cause of Death as Reported by the Adjudication Committee
male	Tirzepatide 10 mg	Respiratory fume inhalation disorder	158	24	Non-cardiovascular
male	Tirzepatide 10 mg	Cardio-respiratory arrest	85	≤28*	Undetermined

*The last recorded dose was 28 days before the date of death. Information on further dosing was not available. However, it is possible that additional doses were taken after the last recorded dose.

Table S5. Additional Safety Measures

	Normal range	Tirzepatide 10 mg	Tirzepatide 15 mg	Placebo
Pulse, bpm	60-100			
Baseline		75.9 ± 0.6	75.6 ± 0.6	74.8 ± 0.6
Week 72		76.1 ± 0.5	76.4 ± 0.5	75.0 ± 0.5
Change at week 72		0.6 ± 0.5	1.0 ± 0.5 (p=0.027)	-0.5 ± 0.5
Pancreatic-amylase, U/L	3 – 46			
Baseline		23.9 ± 46.90	23.5 ± 44.69	24.7 ± 49.20
Week 72		32.2 ± 52.28	31.4 ± 50.94	25.1 ± 57.22
% change at week 72		33.2 ± 3.04***	31.6 ± 3.05***	2.6 ± 2.40
Lipase, U/L	0 – 100			
Baseline		35.3 ± 49.18	35.1 ± 50.23	37.0 ± 52.47
Week 72		47.5 ± 64.63	46.1 ± 60.12	38.7 ± 61.45
% change at week 72		32.7 ± 3.82***	29.3 ± 3.78***	5.6 ± 3.12
Aspartate aminotransferase, U/L	8 – 40			
Baseline		21.9 ± 0.5	20.7 ± 0.5	21.8 ± 0.5
Week 72		17.7 ± 0.3	18.1 ± 0.3	19.8 ± 0.4
% change at week 72		-17.6 ± 1.5	-16.0 ± 1.6	-8.3 ± 1.7
Alanine aminotransferase, U/L	Female: 4 – 43; Male: 5 – 48			
Baseline		26.7 ± 0.8	25.3 ± 0.8	26.4 ± 0.8
Week 72		17.3 ± 0.4	18.2 ± 0.5	22.8 ± 0.6
% change at week 72		-33.9 ± 1.7	-30.6 ± 1.8	-13.1 ± 2.3
Calcitonin, ng/L	Female: < 5.0 ng/L (<1.46 pmol/L); Male: < 8.4 ng/L (<2.46 pmol/L)			
Baseline		1.60 ± 98.77	1.62 ± 97.43	1.66 ± 93.44
Week 72		1.93 ± 115.77	1.88 ± 114.57	1.67 ± 101.32
% change at week 72		20.5 ± 3.35***	15.8 ± 3.26 (p=0.0004)	0.4 ± 2.84
Urine Albumin-to-Creatinine Ratio, mg/g	0 – 30			
Baseline		17.4 ± 1.5	17.3 ± 1.5	16.4 ± 1.4
Week 72		9.4 ± 0.5	9.7 ± 0.5	14.3 ± 0.8
% change at week 72		-45.3 ± 2.9***	-43.4 ± 3.1***	-16.3 ± 4.5

Data presented are model based estimate ± standard error. Note: except for pulse, all other measures were analyzed with log-transformation. ***p<0.0001 treatment comparison to placebo.