Efficacy and safety of once-weekly tirzepatide in Japanese patients with obesity disease (SURMOUNT-J): a multicentre, randomised, double-blind, placebo-controlled phase 3 trial

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Summary

Background Data on tirzepatide in Asian patients with obesity are limited. This study aimed to gain a better understanding of tirzepatide for treatment of Japanese patients with obesity disease (BMI ≥25 kg/m² with excessive fat accumulation) as defined by the Japanese Society for the Study of Obesity.

Methods This was a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial of the efficacy and safety of tirzepatide as an adjunct to lifestyle modifications. Japanese adults with obesity disease (BMI ≥27 kg/m² accompanied by ≥2 obesity-related health disorders or ≥35 kg/m² accompanied by ≥1 obesity-related health disorders), excluding diabetes, were assigned 1:1:1 via computer-generated random sequence to receive once weekly subcutaneous tirzepatide (10 mg or 15 mg) or placebo. Coprimary endpoints were the mean percent change in bodyweight and the proportion of participants achieving at least 5% bodyweight reduction at week 72, using the efficacy estimand. Efficacy and safety were assessed in the modified intention-to-treat (mITT) population. This study is registered with ClinicalTrials.gov, NCT04844918.

Findings Between May 10, 2021, and June 24, 2023, 413 participants were screened, and 267 were randomly assigned. Due to exclusion of one study site, the mITT population was 225 participants (133 [59%] men and 92 [41%] women, mean age 50·8 [SD 10·7] years), with 73 in the tirzepatide 10 mg group, 77 in the tirzepatide 15 mg group, and 75 in the placebo group, of whom 192 (85%) completed both study and treatment. Estimated treatment differences relative to placebo in change in bodyweight at week 72 were −16·1% (95% CI −18·7 to −13·5; p<0·0001) and −21·1% (95% CI −23·6 to −18·5; p<0·0001) following tirzepatide 10 mg and 15 mg, respectively. At week 72, a higher proportion of participants achieved at least 5% bodyweight reduction with tirzepatide 10 mg (67 [94%] of 71) and 15 mg (73 [96%] of 76) compared with placebo (15 [20%] of 75; both p<0·0001). Cardiometabolic and body composition indices were also improved with tirzepatide. Participants treated with tirzepatide experienced treatment-emergent adverse events more frequently (10 mg: n=61 [84%]; 15 mg: n=66 [86%]) than those who received placebo (52 [69%]), most commonly gastrointestinal symptoms. Study discontinuations due to adverse events were infrequent (placebo: n=3 [4%]; tirzepatide 10 mg: n=1 [1%]; tirzepatide 15 mg: n=0).

Interpretation In Japanese adults with obesity disease, tirzepatide provided clinically a meaningful reduction in bodyweight compared with placebo over 72 weeks, with a safety profile consistent with that observed in global populations.

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For the Japanese translation of the abstract see Online for appendix 1

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Introduction

Obesity is a chronic metabolic disease associated with increased risk of comorbidities such as type 2 diabetes, cardiovascular disease, metabolic dysfunction-associated steatotic liver disease (MASLD), and several types of cancer.[1,2] The prevalence of obesity is increasing globally, including in Japan.[1] In 2019, 33·0% of men and 22·3% of women were estimated to have obesity based on Japanese Society for the Study of Obesity (JASSO) criteria, which define obesity disease in Japanese individuals as excessive fat accumulation with a BMI of 25 kg/m² or greater.[3] This classification differs from that for individuals of European descent, which uses the higher threshold of BMI (≥30 kg/m²).[4] The Japanese definition of obesity disease is based on the higher prevalence of obesity-related health disorders, such as hypertension, dyslipidaemia, and glucose intolerance, at or above BMI of 25 kg/m² in Japanese patients.[4]

As higher rates of cardiometabolic abnormalities are associated with higher levels of visceral adiposity in Japanese patients,[5,6] it is notable that Japanese and other east Asian populations have a higher percentage of body fat, particularly visceral adipose tissue and hepatic fat, at any given BMI compared with non-Asian populations.[4,5,7] As such, JASSO defines obesity disease as BMI of 25 kg/m² or greater accompanied by obesity-related

Research in context

Evidence before this study

We searched PubMed on May 31, 2024, using the terms "glucose-dependent insulinotropic polypeptide receptor agonist," "glucagon-like peptide-1 receptor agonist," "obesity," "overweight," and "Japanese" with no date or language restrictions. Prior clinical studies examined semaglutide, a selective glucagon-like peptide-1 (GLP-1) receptor agonist, in east Asian populations with overweight or obesity with and without type 2 diabetes. The first of these trials was STEP 6, which reported bodyweight reductions of up to −13·2% in Japanese and Korean participants at week 68 following treatment with semaglutide 2·4 mg compared with placebo. STEP 7 subsequently reported weight reduction up to −12·1% at week 44 with semaglutide 2·4 mg compared with placebo in a predominantly east Asian population. Tirzepatide is a glucose-dependent insulinotropic polypeptide and GLP-1 receptor agonist. In Japan, tirzepatide is approved for the treatment of type 2 diabetes and is under review for chronic weight management. In participants of the global SURMOUNT clinical development programme, tirzepatide has shown clinically meaningful improvements in bodyweight over 72 weeks as monotherapy compared with placebo in participants with obesity or overweight plus at least one weight-related complication (SURMOUNT-1) and in participants with overweight or obesity plus type 2 diabetes (SURMOUNT-2). Tirzepatide has also shown efficacy for weight reduction in participants with overweight or obesity following a 12-week intensive lifestyle management programme (SURMOUNT-3) and for weight reduction management following a 36-week lead-in period of tirzepatide treatment (SURMOUNT-4). In a recently published study of Chinese adults with obesity or overweight plus at least one obesity-related complication, tirzepatide 10 mg and 15 mg resulted in bodyweight reductions of −14·4% and −19·9%, respectively, at week 52 (SURMOUNT-CN). In previous SURMOUNT trials, tirzepatide had a safety profile similar to that of selective GLP1 receptor agonists.

Added value of this study

Japanese patients were under-represented in the global SURMOUNT phase 3 trials examining tirzepatide for chronic weight management. This study assessed the efficacy and safety of tirzepatide 10 mg and 15 mg versus placebo in Japanese participants with obesity disease and without diabetes, who met the Japanese Society for the Study of Obesity (JASSO) criteria for pharmacological treatment (ie, BMI ≥27 kg/m^2 accompanied by ≥2 obesity-related health disorders or ≥35 kg/m^2 accompanied by ≥1 obesity-related health disorders).

This study shows that tirzepatide 10 mg and 15 mg, combined with lifestyle modifications, achieved superior and clinically meaningful bodyweight reduction compared with placebo in Japanese participants with obesity disease. Mean percent change from baseline to week 72 in bodyweight was −17·8% and −22·7% in the tirzepatide 10 mg and 15 mg groups compared with −1·7% in the placebo group. Concurrent with bodyweight reduction, clinically meaningful improvements were observed with tirzepatide compared with placebo at week 72 in multiple glycaemic and cardiometabolic indices and in several body-mass-related parameters, including mean reductions in visceral fat, subcutaneous fat, and hepatic fat fraction. Additionally, tirzepatide 10 mg and 15 mg improved obesity-related health disorders in 70% or more of Japanese participants at week 72, as indicated by achievement of normoglycaemia, triglycerides less than 150 mg/dL (or reduced by 30% from baseline), and hepatic fat fraction less than 5% (or reduced by 30% from baseline) in subpopulations of participants with impaired glucose tolerance, hyperlipidaemia, and metabolic dysfunction-associated steatotic liver disease, respectively, at baseline. Treatment-emergent adverse events occurred at a higher frequency in the tirzepatide groups compared with placebo and were most commonly gastrointestinal symptoms, generally consistent with the safety profiles of other incretin-based therapies.

Greater weight reduction was observed with tirzepatide in the current study compared with that achieved in east Asian populations treated with the selective GLP-1 receptor agonist semaglutide 2·4 mg in STEP 6 and STEP 7. However, comparisons between these studies should be done with caution as the study designs differed in several aspects—eg, treatment duration and inclusion of participants with type 2 diabetes. A direct comparison of tirzepatide and semaglutide in participants with obesity or overweight is ongoing (NCT05822830).

Implications of all the available evidence

Obesity is associated with many comorbidities, and its prevalence is increasing in Japan and other Asian countries. This is the first trial to show clinically meaningful bodyweight reductions and improvements in body composition with tirzepatide in Japanese participants with obesity disease. These findings are of therapeutic relevance as the levels of bodyweight reduction observed with tirzepatide exceed the current recommendations for bodyweight reduction for Japanese patients with obesity disease (≥3%) and high-degree obesity disease (5% to 10%). Furthermore, tirzepatide reduced the prevalence of obesity-related health disorders in over two-thirds of participants. Collectively, the results indicate that tirzepatide 10 mg and 15 mg are potential new treatment options for Japanese patients with obesity disease.

health disorders or by visceral adipose tissue accumulation of 100 cm² or greater and high-degree obesity disease as BMI of 35 kg/m² or greater accompanied by obesity-related health disorders or by visceral adipose tissue accumulation of 100 cm² or greater, in recognition of the need for more extensive medical treatment for these conditions.[4]

Japanese guidelines recommend dietary, exercise, and behavioural therapies for the initial treatment of obesity disease, including a recommended bodyweight reduction of at least 3% for obesity disease and 5% to 10% for high-degree obesity disease.[4] However, lifestyle interventions alone are insufficient to meet these goals for many patients. Tirzepatide is a glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1 (GLP-1) receptor agonist approved for the treatment of type 2 diabetes and under development for obesity disease in Japan. The global SURMOUNT phase 3 clinical trial programme is examining the efficacy and safety of tirzepatide as an adjunct to diet and exercise in participants with obesity and overweight. In SURMOUNT-1–4, tirzepatide showed superiority over placebo in reducing bodyweight in participants with obesity or overweight with and without type 2 diabetes.[8–11] However, Asian participants comprised a minority of the study populations in SURMOUNT-1–4 (0·7–13·3%).[8–11] A recent study on tirzepatide for chronic weight management in Chinese adults with obesity or overweight, using criteria specific for Chinese populations, reported mean bodyweight reductions of –14·4% and –19·9% at 52 weeks with tirzepatide 10 mg and 15 mg, respectively.[12]

To gain a better understanding of tirzepatide for chronic weight management in a Japanese population, the primary objective of the current study was to assess the efficacy of tirzepatide versus placebo over 72 weeks in Japanese participants with obesity disease.

Methods

Study design and participants

SURMOUNT-J was a randomised, double-blind, placebo-controlled, parallel-group phase 3 trial of the efficacy and safety of once weekly tirzepatide 10 mg and 15 mg compared with placebo when used in conjunction with a reduced-calorie diet and increased physical activity in participants with obesity disease. The study design included a 4-week screening period followed by a 72-week treatment period and a 4-week safety follow-up period (appendix 2 p 14).

The study was conducted at 18 medical research centres in Japan. Due to a regulatory noncompliance issue at one study site, the Pharmaceuticals and Medical Devices Agency, the Japanese regulatory body, mandated that patients from this site be excluded from the analyses to ensure data reliability.

Eligible participants were aged 20 years or older with a BMI of 27 kg/m² or greater and less than 35 kg/m² and at least two obesity-related health disorders or with a BMI of 35 kg/m² or greater and at least one obesity-related health disorder at screening. Obesity-related health disorders included impaired glucose tolerance, hyperlipidaemia, or MASLD. Impaired glucose tolerance was defined as having an oral glucose tolerance test (OGTT) 0-h glucose of at least 110 mg/dL or 2-h glucose of at least 140 mg/dL, or both, inclusive of borderline type impaired fasting serum glucose as defined by Japanese clinical practice guidelines for diabetes.[13] Hyperlipidaemia was defined as fasting triglycerides of 150 mg/dL or greater. MASLD was defined as having a hepatic fat fraction of 5% or greater as measured by MRI-proton density fat fraction (MRI-PDFF).

Key exclusion criteria included all diabetes, as defined by Japanese clinical practice guidelines;[13] treatment with dipeptidyl peptidase-4 (DPP-4) inhibitors, oral GLP-1 receptor agonists, or any injectable type 2 diabetes therapy within 3 months before screening; and liver disease other than MASLD. Full eligibility criteria are listed in the protocol (appendix 2 pp 87–93).

The protocol (appendix 2 pp 35–183) was approved by ethical review boards at each study site. The study was conducted in accordance with consensus ethical principles derived from international guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical guidelines, Good Clinical Practice guidelines, and applicable local laws and regulations. Written informed consent was obtained from all participants or their legally authorised representatives prior to enrolment. This trial is registered with ClinicalTrials.gov, NCT04844918.

Randomisation and masking

Participants were randomly assigned 1:1:1 to receive tirzepatide (10 mg or 15 mg) or placebo vehicle (disodium hydrogen phosphate heptahydrate and sodium chloride in water, adjusted to pH 7·0), administered subcutaneously via a single-use pen. Randomisation was stratified by baseline impaired glucose tolerance (yes or no), baseline hyperlipidaemia (yes or no), baseline MASLD (yes or no), and sex (female or male). Treatment assignment was determined by a computer-generated random sequence using a central interactive web response system. Investigators, site staff, participants, and sponsor were blinded to treatment assignments.

Procedures

See Online for appendix 2

The starting dose of tirzepatide was 2·5 mg once weekly, which was escalated by 2·5 mg every 4 weeks until the final assigned dose was reached. Participants also received lifestyle intervention through counselling sessions to establish diet and exercise goals (ie, a healthy calorie-reduced diet and ≥150 minutes per week of physical activity, based on JASSO guidelines).[14] Other medications for weight management were not permitted. Concomitant medications taken for obesity-related

health disorders were permitted if on a stable dose for 3 months or longer before study entry. Participants who developed type 2 diabetes during the study were allowed to initiate medication for glucose control, except for DPP-4 inhibitors or GLP-1 receptor agonists (appendix 2 pp 98–99).

Hepatic fat fraction was measured by MRI-PDFF. Visceral adipose tissue and subcutaneous adipose tissue were measured by single-slice imaging at the umbilicus level in a supine position using CT or MRI-PDFF. Clinical and laboratory assessments, physical examinations, and vital sign measurements were conducted according to the protocol schedule (appendix 2 pp 53–74). Laboratory assessments and image analyses were performed centrally.

Outcomes

The coprimary endpoints were the mean percent change in bodyweight and the proportion of participants achieving at least 5% bodyweight reduction at week 72. Secondary efficacy endpoints included the proportion of participants at week 72 who showed improvement in impaired glucose tolerance, hyperlipidaemia, and MASLD at week 72 for those who had the specified obesity-related health disorders at baseline and the proportion of participants who showed a reduction in the number of obesity-related health disorders from baseline to week 72, resulting in a categorical shift from (1) two or more to none or one obesity-related health disorders for those with baseline BMI of 27 kg/m² or greater and less than 35 kg/m² and (2) one or more to no obesity-related health disorders for those with baseline BMI of 35 kg/m² or greater. Improvement was defined as the return to normal ranges for the relevant parameters: OGTT 0-h glucose of less than 110 mg/dL and 2-h glucose of less than 140 mg/dL for participants with baseline impaired glucose tolerance, triglycerides of less than 150 mg/dL or reduced by 30% from baseline for participants with baseline hyperlipidaemia, and hepatic fat fraction of less than 5% or reduced by 30% from baseline for participants with baseline MASLD. Additional secondary endpoints included the proportion of participants achieving at least 7%, at least 10%, at least 15%, and at least 20% bodyweight reduction and visceral adipose tissue of less than 100 cm² (for those with >100 cm² at baseline) and mean change from baseline to week 72 in bodyweight, BMI, waist circumference, visceral adipose tissue, subcutaneous adipose tissue, visceral adipose tissue to subcutaneous adipose tissue ratio, systolic and diastolic blood pressure, and uric acid concentrations.

For participants with baseline impaired glucose tolerance, secondary endpoints included mean change from baseline in fasting serum glucose, OGTT 2-h glucose, HbA_{1c} (%), fasting insulin, C-peptide, and updated homeostasis model assessment (HOMA2) parameters. For participants with baseline hyperlipidaemia, secondary endpoints included mean change from baseline in fasting lipids. For participants with baseline MASLD, secondary endpoints included mean percent change from baseline in hepatic fat fraction and liver enzymes, including aspartate aminotransferase (AST), alanine aminotransferase (ALT), and AST to ALT ratio.

Patient-reported outcomes were assessed at week 72 using questionnaires translated into Japanese and linguistically validated, including mean change from baseline in the 36-item Short Form Health Survey version 2 acute form (SF-36v2) physical functioning domain score and the Impact of Weight on Quality of Life-Lite Clinical Trials Version (IWQOL-lite-CT) physical function score.

Prespecified exploratory outcomes included change from baseline to week 72 in estimated glomerular filtration rate calculated using the Japanese Society of Nephrology formula ($194 \times \text{creatinine}^{-1.094} \times \text{age}^{-0.287}$ [if female, $\times 0.739$]),[15] percent change from baseline in the urinary albumin to creatinine ratio, and time to type 2 diabetes onset during treatment.

Safety was assessed as incidence of treatment-emergent adverse events, serious adverse events, adverse events of special interest, and discontinuations due to adverse events. Fatal and nonfatal major adverse cardiovascular events and suspected cases of pancreatitis were adjudicated by an independent clinical endpoint committee blinded to study treatment.

Statistical analysis

Approximately 348 participants were planned to be screened to achieve 261 participants randomly assigned 1:1:1 to study intervention. The chosen sample size and randomisation ratio provided >90% power to establish superiority of each tirzepatide dose to placebo for the coprimary endpoints, assuming evaluation of superiority of tirzepatide 10 mg and 15 mg to placebo would be conducted in parallel, with a two-sided significance level of 0·025 for each tirzepatide dose. The sample size calculation assumed: (1) a difference of at least 11% mean bodyweight reduction from baseline at week 72 for each tirzepatide dose compared with placebo and a common SD of 10%; (2) 25% of placebo-treated participants and 90% of tirzepatide-treated participants would achieve the goal of at least 5% bodyweight reduction at week 72; and (3) a dropout rate of 25% (based on published literature)[16] for an expected 195 participants completing the study and treatment. Additionally, the study planned to enrich for participants who had obesity-related health disorders, such that more than 60% of the study population would have impaired glucose tolerance and more than 40% would have MASLD.

Efficacy and safety were assessed using the modified intention-to-treat (mITT) population, which comprised all randomly assigned participants who received at least

one dose of study drug. Data were analysed as randomised. The primary efficacy analysis was guided by the efficacy estimand, defined as the average tirzepatide treatment effect relative to placebo at week 72 when used in conjunction with lifestyle modifications for all participants who remained on their randomised treatment for the 72-week treatment period. For these analyses, the efficacy analysis set was used, which included data obtained during the treatment period, excluding data after discontinuation of study drug. Supplementary efficacy analyses were conducted using the treatment regimen estimand (appendix 2 pp 23–25).

For the primary analysis, a mixed model for repeated measures (MMRM) was used to analyse bodyweight percentage change over time, with treatment group, visit, treatment-by-visit interaction, and stratification factors as fixed effects and baseline bodyweight as a covariate. For the proportion of participants achieving at least 5% bodyweight reduction from randomisation over time, a logistic regression model was used. The logistic regression model included treatment group stratification factors as fixed effects and baseline bodyweight as a covariate. Missing bodyweight measurements at week 72 were imputed using predicted values from MMRM, and the continuous measurements were dichotomised by the status of achieving at least 5% bodyweight reduction (yes or no). Type-1 error rate was controlled at the two-sided significance level of 0·05 because the coprimary endpoints for each tirzepatide dose versus placebo were tested in parallel, each at a two-sided significance level of 0·025. Since the coprimary endpoints were to be achieved simultaneously, no multiplicity adjustment was planned for these two tests.

For other categorical outcomes, improvement of individual and composite obesity-related health disorders, logistic regression analysis was used. For improvement of hyperlipidaemia and other categorical efficacy endpoints, longitudinal logistic regression was used. Other continuous efficacy endpoints were analysed using an MMRM. Both logistic regression models and MMRM included stratification factors as terms. Tests of treatment effects were conducted at a two-sided α level of 0·05, and CIs were calculated at 95% (two-sided). Statistical models, including the handling of missing data, are described in more detail in appendix 2 (pp 23–25).

Safety assessments were conducted on the safety analysis set, which included all data obtained during treatment and follow-up periods from the mITT population regardless of adherence to study drug. Safety data are descriptively summarised by treatment, including the number and percentage of participants experiencing treatment-emergent adverse events, serious adverse events, adverse event of special interests, and discontinuations due to adverse events. A post-hoc analysis was conducted of hypoglycaemia events of blood glucose of less than 54 mg/dL by OGTT visit.

Sensitivity analyses included assessing the effect of the COVID-19 pandemic on data integrity and participant safety; and the exclusion of one study site on efficacy and safety outcomes, using data from all 18 study sites.

Statistical analyses were conducted using SAS (version 9.4) or R (version 4.2.2).[17]

Role of the funding source

The study sponsor took part in the study design; data collection, data analysis, data interpretation, and writing of the report; and decision to publish.

Results

The trial was conducted from May 10, 2021, to June 24, 2023. In total, 413 participants were screened, of whom 267 were randomly assigned to treatment and received at least one dose of study drug (figure 1). This Article presents data excluding 65 screened and

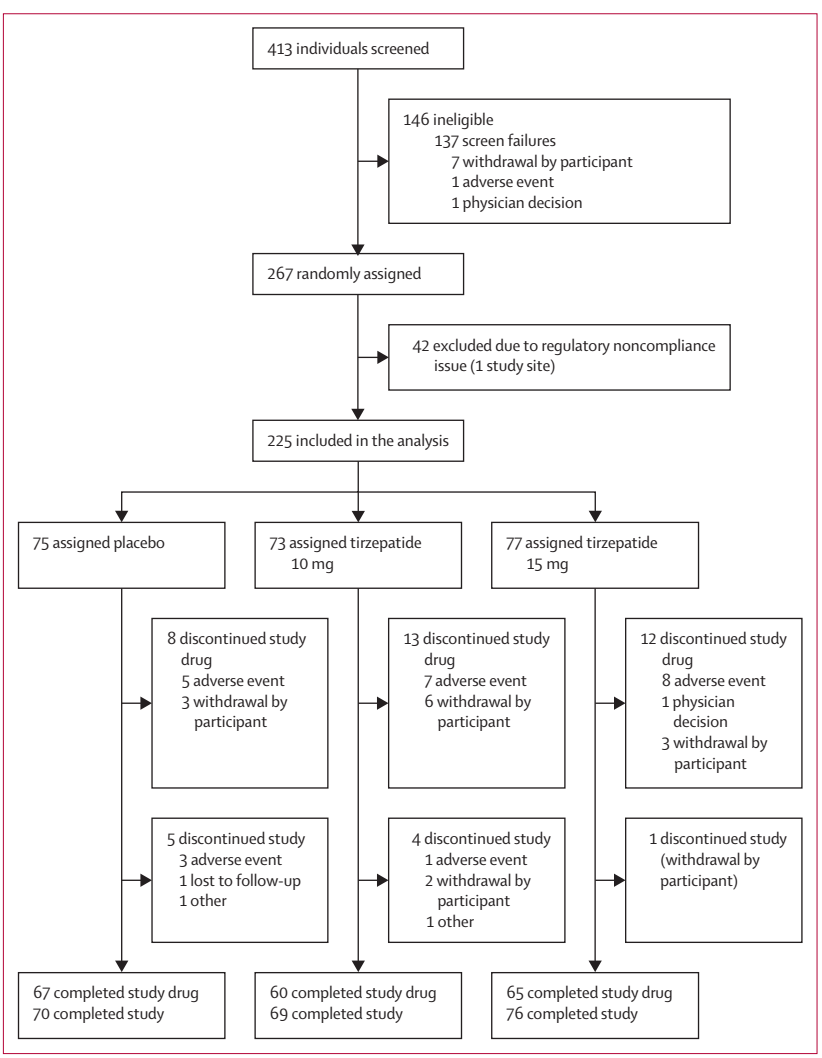

Figure 1: **Trial profile**
Flow diagram of SURMOUNT-J participants included in the main analyses (one study site excluded due to regulatory noncompliance issues).

42 randomly assigned participants due to the exclusion of one study site resulting in 225 randomly assigned participants included in this analysis. Of 225 participants, 192 (85%) completed both study and treatment whereas 215 (96%) completed the study regardless of whether they completed treatment (figure 1).

	Placebo (n=75)	Tirzepatide 10 mg (n=73)	Tirzepatide 15 mg (n=77)	Total (n=225)
Age, years	52·3 (10·9)	49·0 (10·9)	51·1 (10·3)	50·8 (10·7)
Men	45 (60%)	43 (59%)	45 (58%)	133 (59%)
Women	30 (40%)	30 (41%)	32 (42%)	92 (41%)
Japanese	75 (100%)	73 (100%)	77 (100%)	225 (100%)
Weight, kg	92·0 (15·3)	92·4 (15·0)	91·7 (14·8)	92·0 (14·9)
BMI, kg/m²	33·7 (4·9)	33·2 (4·1)	33·6 (4·3)	33·5 (4·4)
BMI <35 kg/m²	49 (65%)	49 (67%)	50 (65%)	148 (66%)
BMI ≥35 kg/m²	26 (35%)	24 (33%)	27 (35%)	77 (34%)
Waist circumference, cm	108·7 (10·9)	107·7 (9·8)	107·6 (10·4)	108·0 (10·4)
Systolic blood pressure (sitting), mmHg	125·0 (13·0)	125·4 (12·9)	125·7 (12·0)	125·4 (12·6)
Diastolic blood pressure (sitting), mmHg	80·0 (9·7)	79·6 (9·2)	79·9 (8·4)	79·8 (9·0)
Pulse rate, bpm	73·0 (10·2)	75·1 (12·1)	71·1 (9·3)	73·0 (10·7)
HbA_{1c}, %	5·67 (0·32)	5·65 (0·33)	5·66 (0·36)	5·66 (0·33)
HbA_{1c}, mmol/mol	38·4 (3·5)	38·3 (3·6)	38·4 (3·9)	38·4 (3·7)
Fasting serum glucose, mg/dL	97·1 (9·8)	96·1 (9·4)	97·3 (10·8)	96·9 (10·0)
Triglycerides, mg/dL	183·9 (95·0)	182·0 (83·9)	191·7 (91·8)	186·0 (90·1)
eGFR, mL/min per 1·73 m²	70·6 (13·1)	74·7 (13·5)	72·6 (12·9)	72·6 (13·2)
Uric acid, mg/dL	6·4 (1·4)	6·4 (1·3)	6·5 (1·3)	6·4 (1·3)
Hepatic fat fraction, %	14·9 (6·6; n=73)	18·4 (9·0; n=71)	17·4 (9·0; n=76)	16·9 (8·4; n=220)
Number of predefined baseline obesity-related health disorders*				
1	8 (11%)	10 (14%)	8 (10%)	26 (12%)
2	44 (59%)	43 (59%)	48 (62%)	135 (60%)
3	23 (31%)	20 (27%)	21 (27%)	64 (28%)
Impaired glucose tolerance subpopulation*	51 (68%)	45 (62%)	48 (62%)	144 (64%)
Hyperlipidaemia subpopulation*	41 (55%)	40 (55%)	44 (57%)	125 (56%)
MASLD subpopulation*	73 (97%)	71 (97%)	75 (97%)	219 (97%)
Other baseline obesity-related health disorders				
Hypertension	41 (55%)	39 (53%)	40 (52%)	120 (53%)
Hyperuricaemia and gout	30 (40%)	25 (34%)	25 (32%)	80 (36%)
Dyslipidaemia	66 (88%)	63 (86%)	72 (94%)	201 (89%)
Dysmenorrhoea and infertility	1 (1%)	4 (5%)	0	5 (2%)
Obstructive sleep apnoea	9 (12%)	4 (5%)	7 (9%)	20 (9%)
Osteoarthritis and motor dysfunction	7 (9%)	3 (4%)	8 (10%)	18 (8%)
Renal disease	5 (7%)	4 (5%)	0	9 (4%)
Cardiovascular disease; myocardial infarction and angina	2 (3%)	1 (1%)	2 (3%)	5 (2%)
Cerebral infarction	0	0	0	0

Data are mean (SD) or n (%). eGFR=estimated glomerular filtration rate. MASLD=metabolic dysfunction-associated steatotic liver disease. *Predefined baseline obesity-related health disorders included impaired glucose tolerance (oral glucose tolerance test 0-h glucose of ≥110 mg/dL or 2-h glucose of ≥140 mg/dL, or both); hyperlipidaemia (fasting triglycerides ≥150 mg/dL); and MASLD (hepatic fat fraction ≥5% as measured by magnetic resonance imaging-proton density fat fraction).

Table 1: **Demographic and baseline clinical characteristics of randomised participants (17 study sites)**

Discontinuations from study treatment occurred at a higher frequency with tirzepatide 10 mg (13 [18%]) and 15 mg (12 [16%]) compared with placebo (eight [11%]; figure 1). Adverse events were the most common reason for discontinuation from the study drug across all groups (tirzepatide 10 mg: n=7 [10%]; tirzepatide 15 mg: n=8 [10%]; placebo n=5 [7%]) and for discontinuation from the study for the placebo group (three [4%]). Withdrawal by participant was the most common reason for study discontinuation for the tirzepatide 10-mg (two [3%]) and 15-mg (one [1%]) groups.

Clinical characteristics were well balanced at baseline across the treatment groups (table 1). The study population included more men (133 [59%]) than women (92 [41%]) and had a mean age of 50·8 (SD 10·7) years. At baseline, the overall mean bodyweight was 92·0 (SD 14·9) kg and the overall mean BMI was 33·5 (SD 4·4) kg/m². Most participants had two (135 [60%]) or three (64 [28%]) obesity-related health disorders at baseline, with 144 (64%), 125 (56%), and 219 (97%) participants meeting the criteria for impaired glucose tolerance, hyperlipidaemia, and MASLD, respectively. Concomitant medications for obesity-related health disorders are summarised in appendix 2 (p 2).

At week 72, the least-squares mean percent change from baseline in bodyweight was –17·8%, –22·7%, and –1·7% in the tirzepatide 10-mg, tirzepatide 15-mg, and placebo groups, respectively, with estimated treatment differences (ETDs) relative to placebo of –16·1% (95% CI –18·7 to –13·5; p<0·0001) and –21·1% (95% CI –23·6 to –18·5; p<0·0001) in the 10-mg and 15-mg groups, respectively (table 2). At week 72, the percentage of participants achieving bodyweight reductions of at least 5% was 94% (67 of 71) with tirzepatide 10 mg and 96% (73 of 76) with tirzepatide 15 mg compared with 20% (15 of 75) with placebo (both p<0·0001; table 2). Results for the coprimary endpoints using the treatment regimen estimand were consistent with those obtained using the efficacy estimand (table 2).

Significant weight reduction was observed with tirzepatide at week 4 and throughout the treatment period (figure 2A). The level of weight reduction was similar between tirzepatide 10 mg and 15 mg during the 20-week escalation period, after which tirzepatide 15 mg showed numerically greater mean reductions in bodyweight to week 72 (figure 2A). The proportion of participants who achieved additional bodyweight reduction targets at week 72 (≥7%, ≥10%, ≥15%, and ≥20%) was higher in both tirzepatide groups compared with placebo (figure 2B; table 2; all p<0·0001, except tirzepatide 10 mg versus placebo ≥20%, for which p<0·0011).

The proportion of participants who achieved improvement in obesity-related health disorders at week 72 with tirzepatide 10 mg and 15 mg (42 [70%] of 60 and 51 [80%] of 64, respectively) was significantly higher than with placebo (seven [11%] of 63; both p<0·0001;

	Placebo (n=75)	Tirzepatide 10 mg (n=73)	Tirzepatide 15 mg (n=77)	Tirzepatide 10 mg *vs* placebo (95% CI; p value)	Tirzepatide 15 mg *vs* placebo (95% CI; p value)
Coprimary endpoints—efficacy estimand					
Percent change in bodyweight, %*	−1·7 (0·9)	−17·8 (0·9)	−22·7 (0·9)	ETD −16·1 (−18·7 to −13·5); p<0·0001	ETD −21·1 (−23·6 to −18·5); p<0·0001
Participants with ≥5% bodyweight reduction†	15/75 (20%)	67/71 (94%)	73/76 (96%)	OR 119·7 (29·1 to 492·7); p<0·0001	OR 153·6 (36·0 to 654·5); p<0·0001
Participants with ≥5% bodyweight reduction (complete case)	14/66 (21%)	56/59 (95%)	63/65 (97%)	..	..
Treatment regimen estimand					
Percent change in bodyweight, %‡	−1·8 (1·0)	−15·8 (1·0)	−20·8 (0·9)	ETD −14·0 (−16·6 to −11·3); p<0·0001	ETD −19·0 (−21·6 to −16·4); p<0·0001
Participants with ≥5% bodyweight reduction§	16/75 (22%)	63/73 (86%)	71/77 (92%)	OR 27·4 (9·8 to 76·3); p<0·0001	OR 51·3 (16·3 to 161·2); p<0·0001
Secondary endpoints—efficacy estimand					
Participants with improvement in obesity-related health disorders¶‖**	7/63 (11%)	42/60 (70%)	51/64 (80%)	OR 24·3 (8·6 to 68·3); p<0·0001	OR 38·3 (13·2 to 110·9); p<0·0001
Participants achieving improvements in obesity-related health disorder who had obesity-related health disorder at baseline**					
Impaired glucose tolerance‖	14/50 (28%)	37/40 (93%)	45/46 (98%)	OR 25·4 (7·3 to 89·1); p<0·0001	OR 70·7 (12·7 to 392·2); p<0·0001
Hyperlipidaemia††	9/36 (25%)	21/29 (72%)	30/37 (81%)	OR 9·3 (2·9 to 30·2); p=0·0003	OR 15·7 (4·8 to 51·4) p<0·0001
MASLD‖	6/61 (10%)	41/59 (69%)	48/62 (77%)	OR 27·5 (9·4 to 80·9); p<0·0001	OR 40·0 (13·3 to 120·6) p<0·0001
Body mass-related parameters					
Participants with ≥7% bodyweight reduction†	8/75 (11%)	65/71 (92%)	72/76 (95%)	OR 116·8 (33·6 to 405·7); p<0·0001	OR 170·8 (46·1 to 632·0); p<0·0001
Participants with ≥10% bodyweight reduction†	3/75 (4%)	61/71 (86%)	70/76 (92%)	OR 185·9 (46·4 to 745·2); p<0·0001	OR 318·0 (74·5 to 1357·8); p<0·0001
Participants with ≥15% bodyweight reduction†	1/75 (1%)	45/71 (63%)	63/76 (83%)	OR 100·2 (18·6 to 538·7); p<0·0001	OR 286·7 (50·7 to 1622·1); p<0·0001
Participants with ≥20% bodyweight reduction†	0/75 (0%)	28/71 (39%)	49/76 (64%)	OR 98·0 (6·2 to 1547·8); p=0·0011	OR 265·2 (16·8 to 4189·1); p<0·0001
Change in bodyweight, kg*	−1·5 (0·8)	−16·0 (0·9)	−20·8 (0·8)	ETD −14·5 (−16·8 to −12·2); p<0·0001	ETD −19·3 (−21·6 to −17·0); p<0·0001
Change in BMI, kg/m²*	−0·6 (0·3)	−5·8 (0·3)	−7·7 (0·3)	ETD −5·2 (−6·1 to −4·4); p<0·0001	ETD −7·1 (−8·0 to −6·3); p<0·0001
Change in waist circumference, cm*	−1·3 (0·8)	−12·7 (0·9)	−16·6 (0·8)	ETD −11·4 (−13·8 to −9·0); p<0·0001	ETD −15·3 (−17·7 to −13·0); p<0·0001
Percent change in visceral adipose tissue, %‡‡	−3·4 (2·4)	−39·4 (2·4)	−44·5 (2·4)	ETD −36·1 (−42·9 to −29·3); p<0·0001	ETD −41·1 (−47·8 to −34·4); p<0·0001
Percent change in subcutaneous adipose tissue, %‡‡	−5·0 (1·9)	−32·2 (1·9)	−36·5 (1·9)	ETD −27·2 (−32·6 to −21·9); p<0·0001	ETD −31·5 (−36·7 to −26·2); p<0·0001
Change in the ratio of visceral adipose tissue to subcutaneous adipose tissue‡‡	0·01 (0·02)	−0·09 (0·02)	−0·08 (0·02)	ETD −0·10 (−0·16 to −0·03); p=0·0040	ETD −0·09 (−0·15 to −0·03); p=0·0063
Participants achieving <100 cm² visceral adipose tissue‖	1/61 (2%)	15/57 (26%)	23/62 (37%)	OR 28·5 (4·3 to 188·5); p=0·0005	OR 57·7 (8·7 to 383·9); p<0·0001
Change in systolic blood pressure, mmHg*	1·9 (1·4)	−11·2 (1·4)	−12·0 (1·4)	ETD −13·2 (−17·0 to −9·3); p<0·0001	ETD −13·9 (−17·7 to −10·1); p<0·0001
Change in diastolic blood pressure, mmHg*	0·5 (1·0)	−5·9 (1·1)	−6·3 (1·0)	ETD −6·3 (−9·3 to −3·4); p<0·0001	ETD −6·8 (−9·7 to −3·9); p<0·0001
Change in uric acid, mg/dL*	−0·1 (0·1)	−1·2 (0·1)	−1·3 (0·1)	ETD −1·1 (−1·4 to −0·8); p<0·0001	ETD −1·2 (−1·5 to −1·0); p<0·0001

(Table 2 continues on next page)

figure 2C, table 2). The proportion of participants achieving improvement on obesity-related health disorders at week 72 in each obesity-related health disorder subpopulation was also significantly higher with tirzepatide compared with placebo (table 2).

In the mITT population, change from baseline in body-mass parameters, including BMI, waist circumference, visceral adipose tissue, and subcutaneous adipose tissue, were statistically significantly greater at week 72 in the tirzepatide groups compared with placebo (p<0·0001

	Placebo (n=75)	Tirzepatide 10 mg (n=73)	Tirzepatide 15 mg (n=77)	Tirzepatide 10 mg *vs* placebo (95% CI; p value)	Tirzepatide 15 mg *vs* placebo (95% CI; p value)
(Continued from previous page)					
Patient-reported outcomes					
Change in SF-36v2 physical functioning score‡‡	−0·1 (0·4)	1·1 (0·4)	2·0 (0·4)	ETD 1·3 (0·2 to 2·3); p=0·022	ETD 2·1 (1·1 to 3·2); p<0·0001
Change in IWQoL-Lite-CT physical function composite score‡‡	2·2 (2·0)	15·2 (2·1)	13·0 (2·0)	ETD 13·0 (7·4 to 18·7); p<0·0001	ETD 10·8 (5·4 to 16·3); p=0·0001
Impaired glucose tolerance subpopulation					
Change in HbA_{1c}, %*	−0·02 (0·04)	−0·67 (0·05)	−0·68 (0·04)	ETD −0·65 (−0·77 to −0·53); p<0·0001	ETD −0·66 (−0·77 to −0·55); p<0·0001
Change in fasting serum glucose, mg/dL*	2·2 (1·3)	−12·8 (1·5)	−10·6 (1·4)	ETD −15·0 (−18·9 to −11·1); p<0·0001	ETD −12·8 (−16·6 to −9·1); p<0·0001
Percent change in fasting insulin, %*§§	−18·7 (6·8)	−53·0 (4·5)	−58·6 (3·8)	ETD −42·2 (−55·1 to −25·5); p<0·0001	ETD −49·1 (−60·2 to −34·9); p<0·0001
Change in 2-h glucose during oral glucose tolerance test, mg/dL	−5·7 (4·6)	−61·5 (5·3)	−70·6 (5·0)	ETD −55·8 (−69·7 to −41·8); p<0·0001	ETD −64·8 (−78·2 to −51·4); p<0·0001
Hyperlipidaemia subpopulation (fasting state)					
Percent change in triglycerides, %*§§	−11·0 (5·1)	−47·3 (3·3)	−50·6 (2·8)	ETD −40·7 (−50·0 to −29·7); p<0·0001	ETD −44·5 (−52·7 to −34·9); p<0·0001
MASLD subpopulation					
Percent change in hepatic fat fraction, %‡‡	−19·6 (3·1)	−63·9 (3·1)	−69·9 (3·0)	ETD −44·4 (−53·0 to −35·7); p<0·0001	ETD −50·4 (−58·8 to −41·9); p<0·0001
Liver biomarkers*§§					
Percent change in ALT, %	−24·5 (3·9)	−54·3 (2·5)	−56·9 (2·2)	ETD −39·6 (−47·9 to −29·8); p<0·0001	ETD −42·9 (−50·6 to −33·9); p<0·0001
Percent change in AST, %	−14·8 (3·0)	−36·7 (2·3)	−35·5 (2·2)	ETD −25·6 (−32·7 to −17·9); p<0·0001	ETD −24·3 (−31·3 to −16·6); p<0·0001
Percent change in AST to ALT ratio, %	13·6 (3·3)	37·9 (4·1)	49·6 (4·3)	ETD 21·4 (11·8 to 31·7); p<0·0001	ETD 31·7 (21·5 to 42·6); p<0·0001

Data are least-squares mean (SE) or n/N (%), unless otherwise specified. All changes are from baseline to week 72. Analyses included all data obtained during treatment of the mITT population (efficacy analysis set, unless otherwise specified). For the efficacy estimand, only participants with a non-missing baseline value and at least one non-missing post-baseline value were included in the analysis. For the treatment regimen estimand, only participants with a non-missing baseline value were included in the analysis. ALT=alanine aminotransferase. ANCOVA=analysis of covariance. AST=aspartate aminotransferase. ETD=estimated treatment difference. IWQoL-Lite-CT=Impact of Weight on Quality of Life-Lite Clinical Trials Version. mITT=modified intention-to-treat. MMRM=mixed model for repeated measures. MASLD=metabolic dysfunction-associated steatotic liver disease. OR=odds ratio. SF-36v2=36-item Short Form Health Survey version 2 acute form. *Data are from an MMRM analysis. †Data were assessed using logistic regression with missing values imputed by MMRM at week 72. ‡Data were assessed by an ANCOVA model with placebo imputation by treatment for missing data at 72 weeks (full analysis set). §Data were assessed by logistic regression with placebo imputation analysis (full analysis set). ¶Data represent the proportion of participants who showed a reduction in the number of obesity-related health disorders from baseline to week 72, resulting in a categorical shift from (1) ≥2 to 0 or 1 obesity-related health disorders for those with baseline BMI ≥27 kg/m² to <35 kg/m² and (2) ≥1 to 0 obesity-related health disorders for those with baseline BMI ≥35 kg/m². ||Data were assessed using logistic regression with missing values imputed by last observation carried forward at week 72. **Predefined baseline obesity-related health disorders, including impaired glucose tolerance (oral glucose tolerance test 0-h glucose of ≥110 mg/dL or 2-h glucose of ≥140 mg/dL, or both); hyperlipidaemia (fasting triglycerides ≥150 mg/dL); and MASLD (hepatic fat fraction ≥5% as measured by magnetic resonance imaging-proton density fat fraction). ††Data were assessed using longitudinal logistic regression from baseline to week 72. ‡‡Postbaseline data were from an ANCOVA model with missing values imputed by last observation carried forward at week 72. Baseline data were assessed using an analysis of variance model. §§Data were log-transformed.

Table 2: **Summary of efficacy endpoints and patient-reported outcomes at week 72 (mITT population from 17 study sites)**

for all comparisons; table 2, appendix 2 pp 3–4, 15–16). Significant treatment differences compared with placebo in BMI and waist circumference were observed as early as week 4 (appendix 2 p 16). In addition, statistically significantly greater reductions in mean systolic and diastolic blood pressure and uric acid concentrations were observed in the tirzepatide groups compared with placebo (p<0·0001 for all comparisons; table 2, appendix 2 pp 3–4).

In the impaired glucose tolerance subpopulation, glycaemic parameters improved across the tirzepatide treatment period (table 2, appendix 2 pp 5–8, 17). The mean change from baseline in HbA_{1c} at week 72 was greater with tirzepatide 10 mg and 15 mg (–0·67% [SE 0·05] and –0·68% [0·04], respectively, compared with placebo (–0·02% [0·04]; both p<0·0001). Both tirzepatide 10-mg and 15-mg groups also showed significant mean reductions at week 72 in fasting serum glucose (–12·8 [SE 1·5] mg/dL and –10·6 [1·4] mg/dL, respectively, *vs* 2·2 [1·3] mg/dL for placebo; both p<0·0001). Tirzepatide was associated with significant improvement from baseline to 72 weeks in insulin sensitivity (HOMA2-%S) and insulin and C-peptide concentrations under fasting conditions and in glucose, insulin, and C-peptide concentrations at 0-h and 2-h during the OGTT (appendix 2 pp 5–8).

Within the hyperlipidaemia subpopulation, significant improvements were observed with tirzepatide 10 mg and 15 mg compared with placebo in triglycerides (–47·3% and –50·6%, respectively, *vs* –11·0%; table 2) and across the lipid profile (appendix 2 pp 5–8, 18–19). In the MASLD subpopulation, the tirzepatide 10-mg and 15-mg groups showed significantly greater reductions in mean hepatic fat fraction (–63·9% [SE 3·1] and –69·9% [3·0], respectively) compared with the placebo group (–19·6% [3·1]; both p<0·0001; table 2), as well as improvements in liver enzyme levels (appendix 2 pp 5–8, 20).

Patient-reported physical function was higher at week 72 in the tirzepatide groups compared with placebo (table 2). The mean change from baseline in the SF-36v2 physical functioning domain score was 1·1 (SE 0·4) and 2·0 (0·4) with tirzepatide 10 mg and 15 mg, respectively, compared with –0·1 (0·4) with placebo (p=0·022 and p<0·0001, respectively). The mean change in the IWQOL-Lite-CT physical function composite score was 15·2 (2·1) and 13·0 (2·0) with tirzepatide 10 mg and 15 mg, respectively, and 2·2 (2·0) with placebo (p<0·0001 and p=0·0004, respectively).

For the exploratory endpoints (appendix 2 pp 3–4), the mean change from baseline to week 72 in estimated glomerular filtration rate was numerically higher with tirzepatide 15 mg compared with placebo (ETD 2·7 [–0·1 to 5·5]; p=0·056). The urinary albumin to creatinine ratio was significantly reduced from baseline to 72 weeks with tirzepatide 15 mg and increased with placebo (ETD –26·1 [–42·9 to –4·3]; p=0·022; appendix 2 pp 3–4). In participants with baseline impaired glucose tolerance, onset of type 2 diabetes was observed in the placebo group (three of 51 participants) but was not observed in a pooled tirzepatide population (none of 93 participants; log-rank test p=0·018).

A greater proportion of participants in the tirzepatide 10-mg and 15-mg groups experienced treatment-emergent adverse events (61 [84%] and 66 [86%], respectively) compared with the placebo group (52 [69%]; table 3). With tirzepatide, the most common treatment-emergent adverse events were gastrointestinal symptoms, including constipation, nausea, diarrhoea, and vomiting (table 3). The most common non-gastrointestinal events were COVID-19 and pyrexia, which were reported at similar rates across treatment groups (table 3).

Seven (10%) participants in the tirzepatide 10-mg group and eight (10%) participants in the 15-mg group discontinued from the study drug due to a treatment-emergent adverse event compared with five (7%) participants in the placebo group. The treatment-emergent adverse event most frequently leading to discontinuation of study drug in the tirzepatide groups was nausea (appendix 2 p 9). Three participants (4%) in the placebo group and one participant (1%) in the tirzepatide 10-mg group permanently discontinued from the study due to a treatment-emergent adverse event (table 3).

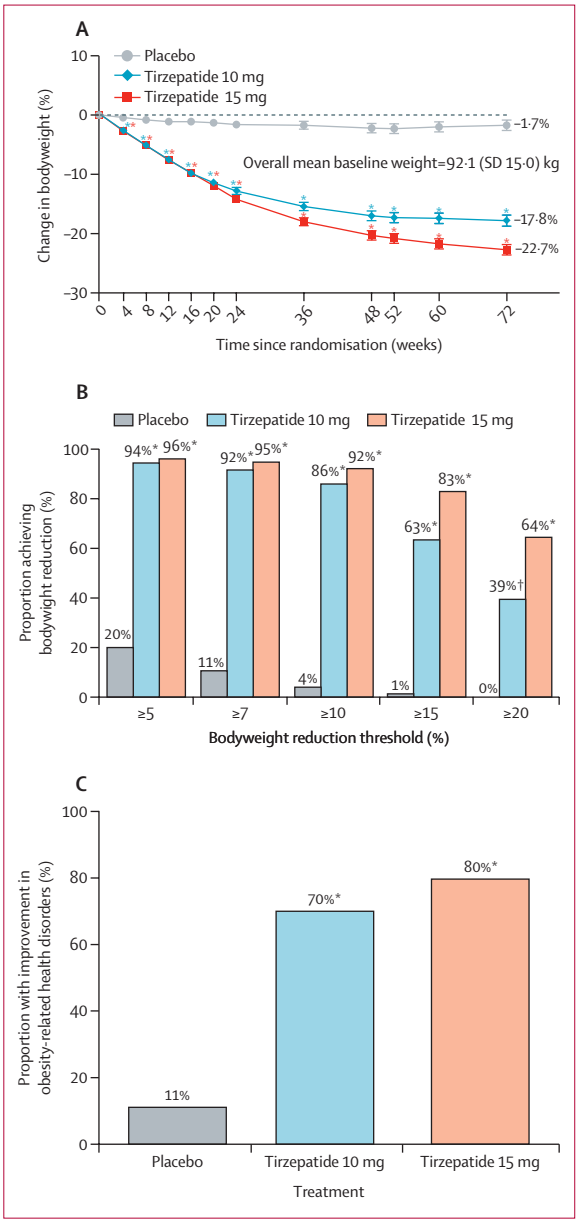

Figure 2: **Effect of tirzepatide on bodyweight and obesity-related health disorders**

(A) Mean percent change in bodyweight over 72 weeks. (B) Proportion of participants who achieved bodyweight reduction targets at week 72. (C) Proportion of participants with improvements in obesity-related health disorders at week 72, with responders defined as participants with obesity disease (BMI ≥27 kg/m² accompanied by ≥2 obesity-related health disorders or ≥35 kg/m² accompanied by ≥1 obesity-related health disorders). Data are from the modified intention-to-treat population (efficacy analysis set) and are presented as least-squares means (SE). Post-baseline data in (A) are from MMRM analyses. Results in (B) are from logistic regression with missing values imputed by MMRM. Data in (C) are from logistic regression analysis with missing values imputed by last observation carried forward. For each parameter, only participants with a non-missing baseline value and at least one non-missing postbaseline value were included in the analysis. MMRM=mixed model for repeated measures. *p<0·0001 versus placebo. †p<0·0011.

	Placebo (n=75)	Tirzepatide 10 mg (n=73)	Tirzepatide 15 mg (n=77)
Participants with ≥1 treatment-emergent adverse event*	52 (69%)	61 (84%)	66 (86%)
Mild	44 (59%)	48 (66%)	56 (73%)
Moderate	6 (8%)	9 (12%)	7 (9%)
Severe	2 (3%)	4 (5%)	3 (4%)
Serious adverse events	5 (7%)	8 (11%)	5 (6%)
Deaths	0	0	0
Discontinuation from study due to adverse event	3 (4%)	1 (1%)	0
Discontinuation from study treatment due to adverse event	5 (7%)	7 (10%)	8 (10%)
Treatment-emergent adverse event related to study treatment	8 (11%)	41 (56%)	49 (64%)
Treatment-emergent adverse events with ≥5% frequency in total (preferred term)†			
COVID-19	13 (17%)	16 (22%)	15 (19%)
Constipation	5 (7%)	12 (16%)	21 (27%)
Pyrexia	11 (15%)	10 (14%)	11 (14%)
Nausea	3 (4%)	10 (14%)	18 (23%)
Diarrhoea	3 (4%)	9 (12%)	7 (9%)
Vomiting	3 (4%)	5 (7%)	9 (12%)
Decreased appetite	1 (1%)	9 (12%)	6 (8%)
Nasopharyngitis	8 (11%)	7 (10%)	1 (1%)
Back pain	4 (5%)	4 (5%)	3 (4%)
Abdominal discomfort	0	5 (7%)	4 (5%)
Headache	5 (7%)	2 (3%)	2 (3%)
Immunisation reaction	4 (5%)	1 (1%)	4 (5%)
Injection site reaction	0	4 (5%)	4 (5%)
Arthralgia	1 (1%)	1 (1%)	4 (5%)
Other treatment-emergent adverse events of interest			
Injection site reactions (high-level term)	0	6 (8%)	7 (9%)
Adjudicated major adverse cardiovascular event	1 (1%)	2 (3%)	0
Acute myocardial infarction‡	1 (1%)	0	0
Catheterisation cardiac‡	1 (1%)	0	0
Brain stem infarction	0	1 (1%)	0
Cerebral infarction	0	1 (1%)	0
Acute gallbladder disease	0	0	1 (1%)
Cholelithiasis	0	0	1 (1%)
Adjudicated pancreatitis	0	0	0
Pancreatic cancer	0	0	0
C-cell hyperplasia and thyroid malignancies	0	0	0
Major depressive disorder or suicidal ideation events	0	0	0
Hypoglycaemia			
Blood glucose <54 mg/dL	1 (1%)	4 (5%)	7 (9%)
Blood glucose <70 mg/dL	2 (3%)	22 (30%)	37 (48%)
Severe	0	0	0

Data are shown for all parameters in the modified intention-to-treat population (safety analysis set). Participants can be counted in more than one category. *The severity of treatment-emergent adverse events was assessed by investigators based on the categories of mild (event is usually transient, requires minimal treatment, and generally does not interfere with the usual activities of daily living), moderate (event interferes with the usual activities of daily living, causing discomfort but poses no substantial or permanent risk of harm, and is usually alleviated with additional specific therapeutic interventions), and severe (event interrupts the usual activities of daily living, substantially affects clinical status, or might require intensive therapeutic intervention). †Adverse events were coded using the Medical Dictionary for Regulatory Activities (version 26.0). ‡Occurred in the same participant.

Table 3: **Safety overview**

A greater proportion of participants in the tirzepatide 10-mg group experienced serious adverse events (eight [11%]) compared with the placebo (five [7%]) and tirzepatide 15-mg (five [6%]) groups (table 3). All serious adverse events occurred at low frequency (one each [1–3%], appendix 2 p 10). Other treatment-emergent adverse events of interest are summarized in table 3, and protocol-specified adverse event of special interests are detailed in appendix 2 (pp 11–12). An adjudication-confirmed major adverse cardiovascular events of myocardial infarction was reported for one participant (1%) in the placebo group. Two (3%) adjudication-confirmed major adverse cardiovascular events (cerebral infarction and brain stem infarction) were reported for two participants in the tirzepatide 10-mg group. No adjudication-confirmed deaths, events of pancreatitis, pancreatic cancer, or major depression or suicide ideation were reported.

The proportion of participants experiencing clinically significant hypoglycaemia (blood glucose <54 mg/dL) was higher with tirzepatide 10 mg and 15 mg (four [5%] and seven [9%], respectively) compared with placebo (one [1%]; table 3). All events of blood glucose of less than 54 mg/dL occurred during an OGTT (appendix 2 p 13). No events of severe hypoglycaemia were reported.

Vital signs are summarised in appendix 2 (p 21). From baseline to week 72, statistically significant increases in pulse rate were observed in the tirzepatide 10-mg and 15-mg groups (week 72 mean change 2·7 beats per minute and 4·3 beats per minute, respectively), which declined below baseline at safety follow-up. Reductions in blood pressure were observed from baseline to week 72 and sustained at safety follow-up.

The proportion of participants who decreased their antihypertensive drug treatment in the tirzepatide 10-mg (seven [10%]) and 15-mg (five [6%]) groups was higher than that in the placebo group (one [1%]). Similar proportions of participants (two [3%]) in each treatment group increased their antihypertensive drug treatment during the study.

The impact of the COVID-19 pandemic on safety and efficacy outcomes was deemed minimal (appendix 2 p 22). Similar efficacy and safety findings were obtained when including data from all 18 study sites (appendix 2 pp 26–33).

Discussion

In SURMOUNT-J, tirzepatide, as an adjunct to lifestyle modifications, achieved superior and clinically meaningful bodyweight reduction compared with placebo in Japanese participants without diabetes with obesity disease. The coprimary objectives were met with both doses of tirzepatide. Greater bodyweight reduction was observed with tirzepatide compared with placebo as early as week 4, increasing in magnitude throughout treatment and reaching up to –22·7% at week 72. Additionally, over 94% of participants in the tirzepatide groups achieved at least 5% bodyweight reduction at 72 weeks, with over half achieving at least 20% bodyweight reduction. These findings are of clinical relevance as these levels meet and exceed the current therapeutic

thresholds for bodyweight reduction for obesity disease (≥3%) and high-degree obesity disease (5–10%).[7] Concurrent with bodyweight reduction, significant improvements were observed in both tirzepatide groups compared with placebo for body-mass, glycaemic, cardiometabolic, hepatic, and renal indices, as well as for patient-reported outcomes.

The level of bodyweight reduction in SURMOUNT-J was similar to that observed for tirzepatide 10 mg and 15 mg in a global population with obesity or overweight without diabetes (up to –22·5% at week 72 in the efficacy estimand)[10] and slightly greater than that observed in Chinese participants with obesity or overweight without diabetes (up to –19·9% at week 52 in the efficacy estimand).[12] In Zhao and colleagues study,[12] weight reduction appeared to reach maximum levels by week 44 with tirzepatide 15 mg, unlike in the current study, which showed continued reductions to week 72. The reason for this difference is not currently clear, although the SURMOUNT-CN study enrolled a younger population (mean age 36·1[12] *vs* 50·8 years) and a lower proportion of males (51%[12] *vs* 59%) with slightly lower mean BMI (32·3[12] *vs* 33·5 kg/m²) and waist circumference (104·8[12] *vs* 108·0 cm) than the SURMOUNT-J study.

In SURMOUNT-J, tirzepatide improved obesity-related health disorders at week 72 in 70% or more of participants. The improvements observed in insulin sensitivity and other glycaemic parameters in Japanese participants with obesity plus impaired glucose tolerance, assessed while on study treatment, are consistent with those observed with tirzepatide in study populations with type 2 diabetes.[18–22] Additionally, the improvements observed in blood pressure in the mITT population and in the lipid profile in the hyperlipidaemia subpopulation are consistent with the previous report that tirzepatide improves several cardiometabolic parameters in patients with type 2 diabetes.[23] Improvements in glycaemic and cardiometabolic parameters in SURMOUNT-J could be linked with the observed improvements in body composition, as excess visceral fat accumulation has been associated with insulin resistance, a greater burden of cardiovascular risk factors, and higher mortality in Japanese populations.[5,6,24] In this regard, it is notable that more than 97% of participants in SURMOUNT-J had MASLD by MRI-PDFF measurement at baseline, which is a much higher baseline prevalence than reported in other SURMOUNT studies.[8,9,11,12] MASLD is strongly associated with obesity,[2] and interventions that reduce bodyweight, including lifestyle modifications and therapeutic agents, result in 25–35% reductions in hepatic fat fraction and improvement in liver biomarkers.[2,25–27] In comparison, in the current study, tirzepatide as an adjunct to lifestyle modifications reduced hepatic fat fraction by up to 69·9% at week 72 compared with 19·6% with lifestyle modifications alone in the placebo group. This finding could be of particular clinical relevance in Japanese patients with obesity disease, as it has been previously reported that Japanese men have a substantially higher liver fat content compared with non-Hispanic White men, at the same BMI.[7]

Overall, the safety results of SURMOUNT-J are consistent with those of GLP-1 receptor agonists[16,28,29] as well as the known safety profile of tirzepatide in other study populations who have obesity or overweight.[8–12] The most commonly reported treatment-emergent adverse events within tirzepatide groups were gastrointestinal-related symptoms, which generally did not result in discontinuation from the study or study drug. No new safety signals were identified in participants treated with tirzepatide with regards to the safety topics of interest. Level 1 and 2 events of hypoglycaemia were more frequent than in other SURMOUNT trials[8–12] or in the STEP 6 trial,[28] occurring during the OGTT. Hypoglycaemic events during OGTTs have similarly been reported in the SCALE trial[30] and following Roux-Y gastric bypass surgery.[31] The higher number of hypoglycaemic events in SURMOUNT-J might be due to more OGTT visits or the greater degree of weight reduction in this trial. Greater weight reduction has previously been shown to parallel improvement in HOMA2 indices, as well as improvements in multiple biomarkers of β-cell function and insulin sensitivity in tirzepatide-treated patients with type 2 diabetes.[20]

A strength of the current study was its investigation of multiple body-mass parameters in conjunction with glycaemic, cardiometabolic, and hepatic assessments, which provides an overall picture of the effect of tirzepatide on obesity disease in Japanese participants. The inclusion of visceral adipose tissue and hepatic fat fraction is particularly informative, given the noted higher visceral and liver adiposity of east Asian populations and the associated higher risk for cardiometabolic diseases.[4,5,7] However, this study had limitations. Notably, lean body mass, which is of clinical interest given the potential risk for sarcopenia with bodyweight loss, was not assessed. Previous results from SURMOUNT-1 found that 72 weeks of tirzepatide treatment were associated with a mean percentage fat mass reduction of –33·9% and lean body-mass reduction of –10·9%, with a similar ratio of fat mass to lean body mass reduction observed in the placebo group (–8·2% to –2·6%, respectively).[10] An additional limitation in SURMOUNT-J is that only Japanese participants with obesity disease were enrolled, with a focus on participants with hyperlipidaemia, MASLD, or impaired glucose tolerance. Therefore, the current findings might not be generalisable to patients with more mild obesity or other types of obesity-related health disorders. This study also excluded patients with obesity plus type 2 diabetes. As such, further study is required to determine the efficacy and safety of tirzepatide in Japanese patients with obesity and type 2 diabetes, as it is recognised that weight reduction in this population of patients is particularly

challenging.[28] Tirzepatide has previously shown efficacy and safety in Japanese patients with type 2 diabetes in the SURPASS clinical trial programme[21,22] and in a global study population with both obesity and type 2 diabetes in SURMOUNT-2.[9] It should also be noted that tirzepatide-mediated bodyweight reduction did not plateau at 72 weeks, indicating that longer-term studies are needed to fully assess tirzepatide in Japanese people with obesity disease, including studies focusing on cardiovascular events. Longer-term studies are also warranted given the chronic nature of obesity disease and the resulting need for long-term clinical management. Finally, this study did not include an active comparator, and a better understanding of the relative efficacy and safety of tirzepatide and selective GLP-1 receptor agonists in chronic weight management awaits the outcome of SURMOUNT-5, an ongoing head-to-head trial of tirzepatide and semaglutide in participants with obesity or overweight (NCT05822830).

Tirzepatide 10 mg and 15 mg were generally well tolerated and led to substantial weight reduction concurrent with improvement in body composition and several metabolic and glycaemic parameters over 72 weeks of treatment in Japanese adults with obesity disease. Tirzepatide also resulted in improvements in obesity-related health disorders, cardiometabolic risk factors, hepatic factors, and patient-reported outcomes, indicating that tirzepatide is a potential new treatment for Japanese patients with obesity disease.

Contributors

TS and TO were involved in the tirzepatide development programme, contributed to the concept and design of the study, and drafted the Article. TS and TO are the guarantors of this work and, as such, take responsibility for the integrity of the data and the accuracy of the data analysis. TO was responsible for the statistical analyses. All authors participated in data collection and interpretation and in the writing 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

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Data sharing

Eli Lilly and Company 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 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 will be 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 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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