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

W Timothy Garvey, Juan P Frias, Ania M Jastreboff, Carel W le Roux, Naveed Sattar, Diego Aizenberg, Huzhang Mao, Shuyu Zhang, Nadia N Ahmad, Mathijs C Bunck, Imane Benabbad, Xiaotian M Zhang, for the SURMOUNT-2 investigators

Summary

Background Weight reduction is essential for improving health outcomes in people with obesity and type 2 diabetes. 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 living with obesity and type 2 diabetes.

Methods This phase 3, double-blind, randomised, placebo-controlled trial was conducted in seven countries. Adults (aged ≥18 years) with a body-mass index (BMI) of 27 kg/m² or higher and glycated haemoglobin (HbA_{1c}) of 7–10% (53–86 mmol/mol) were randomly assigned (1:1:1), using a computer-generated random sequence via a validated interactive web-response system, to receive either once-weekly, subcutaneous tirzepatide (10 mg or 15 mg) or placebo for 72 weeks. All participants, investigators, and the sponsor were masked to treatment assignment. Coprimary endpoints were the percent change in bodyweight from baseline and bodyweight reduction of 5% or higher. The treatment-regimen estimand assessed effects regardless of treatment discontinuation or initiation of antihyperglycaemic rescue therapy. Efficacy and safety endpoints were analysed with data from all randomly assigned participants (intention-to-treat population). This trial is registered with ClinicalTrials.gov, NCT04657003.

Findings Between March 29, 2021, and April 10, 2023, of 1514 adults assessed for eligibility, 938 (mean age 54·2 years [SD 10·6], 476 [51%] were female, 710 [76%] were White, and 561 [60%] were Hispanic or Latino) were randomly assigned and received at least one dose of tirzepatide 10 mg (n=312), tirzepatide 15 mg (n=311), or placebo (n=315). Baseline mean bodyweight was 100·7 kg (SD 21·1), BMI 36·1 kg/m² (SD 6·6), and HbA_{1c} 8·02% (SD 0·89; 64·1 mmol/mol [SD 9·7]). Least-squares mean change in bodyweight at week 72 with tirzepatide 10 mg and 15 mg was –12·8% (SE 0·6) and –14·7% (0·5), respectively, and –3·2% (0·5) with placebo, resulting in estimated treatment differences versus placebo of –9·6% percentage points (95% CI –11·1 to –8·1) with tirzepatide 10 mg and –11·6% percentage points (–13·0 to –10·1) with tirzepatide 15 mg (all p<0·0001). More participants treated with tirzepatide versus placebo met bodyweight reduction thresholds of 5% or higher (79–83% *vs* 32%). The most frequent adverse events with tirzepatide were gastrointestinal-related, including nausea, diarrhoea, and vomiting and were mostly mild to moderate in severity, with few events leading to treatment discontinuation (<5%). Serious adverse events were reported by 68 (7%) participants overall and two deaths occurred in the tirzepatide 10 mg group, but deaths were not considered to be related to the study treatment by the investigator.

Interpretation In this 72-week trial in adults living with obesity and type 2 diabetes, once-weekly tirzepatide 10 mg and 15 mg provided substantial and clinically meaningful reduction in bodyweight, with a safety profile that was similar to other incretin-based therapies for weight management.

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UAB Diabetes Research Center, University of Alabama at Birmingham, Birmingham, AL, USA (Prof W T Garvey MD); **Velocity Clinical Research, Los Angeles, CA, USA** (J P Frias MD); **Department of Medicine (Endocrinology and Metabolism) and Pediatrics (Pediatric Endocrinology), Yale University School of Medicine, New Haven, CT, USA** (A M Jastreboff MD); **Diabetes Complications Research Centre, University College Dublin, Dublin, Ireland** (Prof C W le Roux MD); **Diabetes Research Centre, Ulster University, Coleraine, UK** (Prof C W le Roux); **School of Cardiovascular and Metabolic Health, University of Glasgow, Glasgow, UK** (Prof N Sattar MD); **Centro Médico Viamonte, Buenos Aires, Argentina** (D Aizenberg MD); **Eli Lilly and Company, Indianapolis, IN, USA** (H Mao PhD, S Zhang MS, N N Ahmad MD, M C Bunck MD, I Benabbad MD, X M Zhang MD)

Correspondence to: Prof Timothy Garvey, UAB Diabetes Research Center, University of Alabama at Birmingham, Birmingham, AL 35294-3360, USA **garveyt@uab.edu**

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, type 2 diabetes, non-alcoholic steatohepatitis, and chronic kidney disease.[2–4]

The most recent consensus report by the American Diabetes Association and the European Association for the Study of Diabetes emphasises the importance of weight management as a key component of type 2 diabetes treatment, with the understanding that reaching weight reduction thresholds of more than 5% to more than 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

Research in context

Evidence before this study

For people living with obesity and type 2 diabetes, weight reduction is now recommended as a key element of diabetes treatment. Moderate bodyweight reduction can improve glycaemic control and cardiometabolic risk factors, whereas greater bodyweight reduction (≥10%) can lead to remission of diabetes. However, anti-obesity medications are generally less efficacious in people with type 2 diabetes, resulting in less bodyweight reduction compared with people without diabetes. We searched PubMed on Jan 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 or language restrictions. Glucagon-like peptide-1 (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 bodyweight reductions from baseline of 4·0%, 4·3%, and 6·2%, respectively, in people with overweight or obesity and type 2 diabetes. Tirzepatide—a novel, once weekly glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 receptor agonist approved by the US Food and Drug Administration and the European Medicines Agency for treating adults with type 2 diabetes—demonstrated significant dose-dependent weight reduction in people with type 2 diabetes 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 of 27 kg/m^2 or higher and type 2 diabetes, 72 weeks of treatment with tirzepatide 10 mg and tirzepatide 15 mg once weekly resulted in clinically meaningful reductions in bodyweight of 12·8% (SE 0·6) and 14·7% (0·5), respectively, versus 3·2% (0·5) with placebo. Most participants (79–83%) treated with tirzepatide reached the benchmark for clinically meaningful effect (≥5% weight reduction), with up to nearly half reaching 15% or higher and up to almost one-third reaching 20% or higher weight reduction. Nearly half (46–49%) of the participants treated with tirzepatide reached normoglycaemia (glycated haemoglobin [HbA_{1c}] <5·7%) versus 3% treated 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 type 2 diabetes specifically designed to assess weight reduction as the primary outcome rather than HbA_{1c} reduction. Both doses of tirzepatide provided substantial and clinically meaningful bodyweight reductions with simultaneous significant improvement in HbA_{1c} and other cardiometabolic risk factors. The magnitude of weight reduction reached with tirzepatide in SURMOUNT-2 exceeded that shown with other approved anti-obesity medications in people with type 2 diabetes. Tirzepatide presents a promising treatment option for people living with obesity and type 2 diabetes.

for treatment of type 2 diabetes 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 homoeostasis, and synergistic effects on appetite and food intake.[7,8] In the SURMOUNT-1 study[9] in people with obesity without type 2 diabetes, tirzepatide reduced bodyweight by up to 20·9% after 72 weeks of treatment, with associated improvements in cardiometabolic risk factors and patient-reported outcomes. However, people with obesity and type 2 diabetes often have less weight reduction in response to treatment with anti-obesity medications, compared with those without diabetes.[10,11] Therefore, a dedicated study specifically designed to investigate the efficacy and safety of tirzepatide as a treatment for overweight and obesity in people with type 2 diabetes is warranted.[12,13]

In this Article, 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 body-mass index (BMI) of 27 kg/m² or higher who have type 2 diabetes.

Methods

Study 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 USA. As required by regulatory authorities for the development of medications for weight management, this trial was placebo-controlled.[12] Eligible participants were adults (aged 18 years or older) and had a BMI of 27 kg/m² or higher. Additionally, participants were diagnosed with type 2 diabetes, and had an HbA_{1c} of 7–10% (53–86 mmol/mol) on stable therapy, either diet and exercise alone or oral antihyperglycaemic medication, for at least 3 months before 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 bodyweight of more than 5 kg within 3 months before screening, previous or planned surgical treatment for obesity, and treatment with anti-obesity medications, dipeptidyl peptidase-4 (DPP-4) inhibitors, oral glucagon-like peptide-1 (GLP-1) receptor agonist, or any injectable therapy for type 2 diabetes within 3 months before screening. Full eligibility criteria are shown in the appendix (p 2).

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 (1:1:1) to receive either tirzepatide 10 mg, tirzepatide 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 or male), and type of antihyperglycaemic medication used at randomisation (classified according to its potential effect on bodyweight as promoting weight gain, weight reduction, or weight neutrality). Female enrolment was limited to 70% to ensure adequate representation of males. Additionally, an upper limit of 30% enrolment of participants treated with sulfonylurea was used to allow sufficient enrolment of participants treated with other antihyperglycaemic medications.

Procedures

After a 3-week screening period, participants received subcutaneous injections of tirzepatide (Eli Lilly and Company, Indianapolis, IN, USA) or matching placebo once a week, plus a lifestyle intervention, for 72 weeks, followed by a 4-week safety follow-up period without treatment (appendix p 8). 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 (ie, 10 mg or 15 mg at 12 weeks or 20 weeks, respectively). The lifestyle intervention included regular lifestyle counselling 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 per day relative to the estimated total daily energy expenditure and at least 150 min 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 minimise the risk of hypoglycaemia, participants taking sulfonylureas at randomisation had their dose halved (or stopped if already on the lowest dose). Antihyperglycaemic medication 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 anti-hyperglycaemic medication or addition of new anti-hyperglycaemic medication (with the exception of GLP-1 receptor agonists, DPP-4 inhibitors, or amylin analogues or agonists). Metformin was recommended as a first-line rescue therapy for participants who were not on any antihyperglycaemic medications 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.

See Online for appendix

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 were unsuccessful, 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 counselling, study visits, and study assessments.

Weight, waist circumference, vital sign measurements, and laboratory measurements were assessed as defined in the protocol (appendix p 24).

Outcomes

To account for baseline bodyweight, one of the coprimary endpoints was the percent change in bodyweight from baseline to week 72. A weight reduction from baseline of at least 5% at week 72 was included as the other coprimary endpoint. Prespecified key secondary endpoints controlled for type 1 error rate included bodyweight reductions of at least 10%, 15%, and 20% at week 72 (endpoints were prespecified in the statistical analysis plan); the change from baseline in HbA_{1c} at week 72; HbA_{1c} <7%, ≤6·5%, and <5·7% at week 72 (endpoints were prespecified in the statistical analysis plan); and the change from baseline in fasting glucose, waist circumference, systolic blood pressure, and fasting lipid levels (triglycerides, HDL-cholesterol, and non-HDL cholesterol; endpoints were prespecified in the statistical analysis plan) at week 72. Additional prespecified secondary endpoints included the change from baseline in bodyweight, BMI, diastolic blood pressure, seven-point SMBG profile, fasting insulin, fasting lipids (total cholesterol, LDL cholesterol, VLDL

cholesterol, and free fatty acids), 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. Bodyweight reduction of at least 25% from baseline at week 72 and the change in the psychosocial composite score on the IWQOL-Lite-CT were prespecified exploratory endpoints.

In addition to the prespecified endpoints, a post-hoc analysis was performed to evaluate the change in the number of antihyperglycaemic medications taken by participants from baseline to the end of the 72-week treatment period.

Safety endpoints included treatment-emergent adverse events, serious adverse events, and level 2 hypoglycaemia (blood glucose <54 mg/dL [<3·0 mmol/L]), or level 3 (severe) hypoglycaemia (an episode with severe cognitive impairment requiring the assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions). Deaths, major adverse cardiovascular events (eg, myocardial infarction, hospitalisation due to unstable angina or heart failure, coronary revascularisation, and cerebrovascular events), and pancreatitis were adjudicated by an independent external adjudication committee.

Statistical analysis

A sample size of 900 participants provided a power of greater than 90% to demonstrate the superiority of tirzepatide 10 mg and 15 mg to placebo, for the coprimary endpoints, each at a two-sided significance level of 0·025. The sample-size calculation assumed at least an

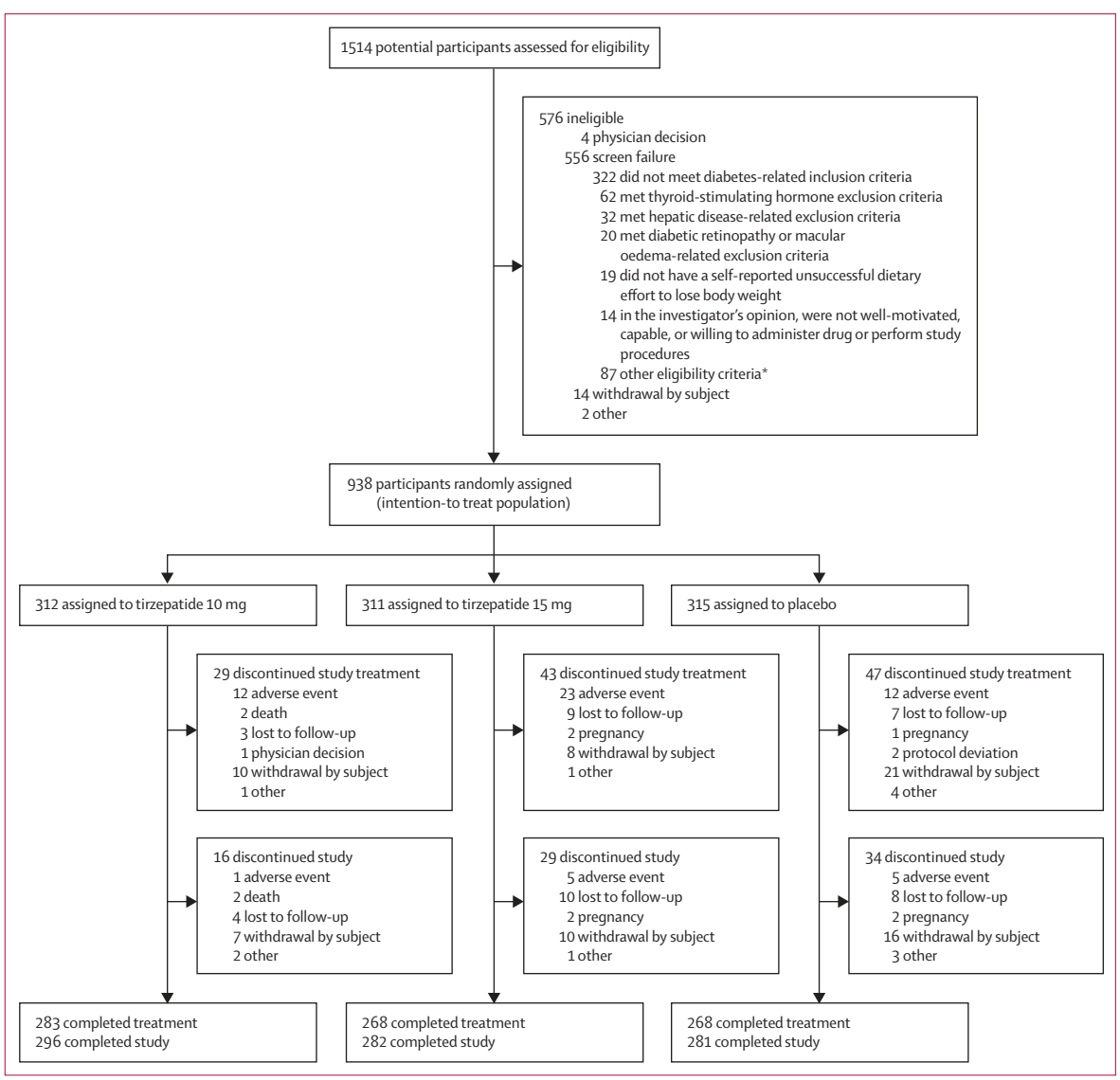

Figure 1: **Trial profile**

*Other represents all eligibility criteria screen failures individually occurring in less than 2% of screened individuals.

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 [ITT] population). All randomly assigned participants had at least one dose of study treatment. Two estimands, the treatment regimen and the efficacy estimands, were used to assess treatment efficacy from different perspectives and accounted for intercurrent events differently.

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 (ANCOVA) model, which is the FDA-preferred analysis model. Categorical endpoints were analysed by logistic regression and treatment difference was assessed by odds ratio (OR). Both models included randomised treatment and stratification factors (country, sex, and type of antihyperglycaemic medication 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 72-week 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 (MMRMs) and categorical endpoints were analysed by logistic regression (treatment difference was assessed by OR). MMRM analysis included randomised treatment, visit, treatment-by-visit interaction, and stratification factors as fixed effects, and the baseline measure as a covariate. The logistic regression model included randomised treatment and stratification factors as fixed effects, and baseline measure as a covariate.

For analysis using the treatment regimen estimand, the full analysis set (defined as data obtained during the treatment period from the ITT population, regardless of adherence to study drug or initiation of rescue antihyperglycaemic medication) was used. For analysis using the efficacy estimand, the efficacy analysis set (defined as data obtained during the treatment period from the ITT population, excluding data after initiation of rescue antihyperglycaemic medication or premature discontinuation of study drug) was used. For safety analysis, the safety analysis set (defined as data obtained during the treatment period plus safety follow-up period from the ITT population, regardless of adherence to

	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	258 (83%)	257 (83%)	258 (82%)	773 (82%)
Age ≥65 years	54 (17%)	54 (17%)	57 (18%)	165 (18%)
Sex*				
Female	158 (51%)	159 (51%)	159 (50%)	476 (51%)
Male	154 (49%)	152 (49%)	156 (50%)	462 (49%)
Race*				
Asian	44 (14%)	42 (14%)	39 (12%)	125 (13%)
Black or African American	33 (11%)	22 (7%)	22 (7%)	77 (8%)
Native Hawaiian or other Pacific Islander	1 (<1%)	1 (<1%)	1 (<1%)	3 (<1%)
White	228 (73%)	234 (75%)	248 (79%)	710 (76%)
Multiple	6 (2%)	12 (4%)	5 (2%)	23 (2%)
Ethnicity*				
Hispanic or Latino	184 (59%)	189 (61%)	188 (60%)	561 (60%
Not Hispanic or Latino	124 (40%)	112 (36%)	122 (39%)	358 (38%)
Not reported	4 (1%)	10 (3%)	5 (2%)	19 (2%)
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/m²	36·0 (6·4)	35·7 (6·1)	36·6 (7·3)	36·1 (6·6)
BMI category, kg/m²				
<30	60 (19%)	51 (16%)	52 (17%)	163 (17%)
≥30 to <35	92 (29%)	114 (37%)	105 (33%)	311 (33%)
≥35 to <40	94 (30%)	85 (27%)	71 (23%)	250 (27%)
≥40	66 (21%)	61 (20%)	87 (28%)	214 (23%)
Waist circumference, cm	114·2 (14·1)	114·6 (13·1)	116·0 (15·7)	114·9 (14·4)
Blood pressure, mm Hg				
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 glomerular filtration rate, mL/min per 1·73 m²†	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)	7·89 (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 (coefficient of variation percentage), pmol/L	84·0 (75·7)	83·6 (68·7)	86·1 (80·7)	84·6 (75·0)

(Table 1 continues on next page)

	Tirzepatide 10 mg (n=312)	Tirzepatide 15 mg (n=311)	Placebo (n=315)	Total (n=938)
(Continued from previous page)				
Antihyperglycaemic drug class				
Biguanides	282 (90%)	276 (89%)	274 (87%)	832 (89%)
Sulfonylureas	78 (25%)	78 (25%)	94 (30%)	250 (27%)
Sodium–glucose cotransporter 2 inhibitors	63 (20%)	62 (20%)	66 (21%)	191 (20%)
Thiazolidinediones	11 (4%)	11 (4%)	11 (3%)	33 (4%)
α-Glucosidase inhibitors	2 (1%)	2 (1%)	4 (1%)	8 (1%)
Other‡	0	1 (<1%)	1 (<1%)	2 (<1%)
Number of oral antihyperglycaemic drugs				
0	16 (5%)	23 (7%)	24 (8%)	63 (7%)
1	177 (57%)	170 (55%)	158 (50%)	505 (54%)
2	99 (32%)	95 (31%)	108 (34%)	302 (32%)
≥3	20 (6%)	23 (7%)	25 (8%)	68 (7%)
Weight-related complications§				
Hypertension	201 (64%)	202 (65%)	217 (69%)	620 (66%)
Dyslipidaemia	181 (58%)	182 (59%)	210 (67%)	573 (61%)
Atherosclerotic cardiovascular disease	24 (8%)	29 (9%)	44 (14%)	97 (10%)
Obstructive sleep apnoea	23 (7%)	26 (8%)	29 (9%)	78 (8%)
Osteoarthritis	41 (13%)	44 (14%)	58 (18%)	143 (15%)
Anxiety or depression	43 (14%)	34 (11%)	34 (11%)	111 (12%)
Non-alcoholic fatty liver disease	49 (16%)	59 (19%)	54 (17%)	162 (17%)
Asthma or chronic obstructive pulmonary disease	21 (7%)	27 (9%)	30 (10%)	78 (8%)
Polycystic ovary syndrome¶	3 (2%)	1 (1%)	2 (1%)	6 (1%)
Gout	18 (6%)	17 (5%)	19 (6%)	54 (6%)
Number of weight-related complications‖				
1	47 (15%)	41 (13%)	31 (10%)	119 (13%)
2	80 (26%)	80 (26%)	77 (24%)	237 (25%)
3	85 (27%)	95 (31%)	88 (28%)	268 (29%)
4	61 (20%)	51 (16%)	65 (21%)	177 (19%)
≥5	39 (13%)	44 (14%)	54 (17%)	137 (15%)

Data are mean (SD) or n (%) and include all randomised participants unless otherwise stated. BMI=body mass index. HbA_{1c}=glycated haemoglobin. *Sex, ethnicity, and race were self-reported. †Estimated glomerular filtration rate was calculated with use of the serum creatinine-based Chronic Kidney Disease Epidemiology Collaboration equation. ‡Other includes insulin human (one inadvertently enrolled participant) and repaglinide. §Baseline medical conditions were assessed through a review of the participants' 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 1: **Baseline demographic and clinical characteristics**

study drug or initiation of rescue antihyperglycaemic medication) was used.

All reported efficacy 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 coprimary 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% or higher (and 15% or higher) weight reduction, waist circumference, and glycaemic control outcomes (HbA_{1c} and fasting serum glucose) 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 among them. Details of the graphical testing approach are provided in the appendix (p 9).

Additional details on estimands, handling of missing values, and statistical analysis methods are provided in the appendix (p 7). Statistical analyses were performed using SAS version 9.4. This study is registered with ClinicalTrials.gov, NCT04657003.

Role of the funding source

The funder had a role in study design, data collection, data analysis, and data interpretation. This Article was drafted by the authors, with medical writing and editorial support paid for by the funder.

Results

Between March 29, 2021, and April 10, 2023, of 1514 participants assessed for eligibility, 938 participants were enrolled and randomly assigned to tirzepatide 10 mg (n=312), tirzepatide 15 mg (n=311), or placebo (n=315; intent-to-treat population; figure 1). As expected in pharmacological weight management trials, there was a higher attrition rate in the placebo group.[17] 859 (92%) participants completed the study (296 [95%], 282 [91%], and 281 [89%] with tirzepatide 10 mg, tirzepatide 15 mg, and placebo, respectively) and 819 [87%] completed the study treatment (283 [91%], 268 [86%], and 268 [85%] with tirzepatide 10 mg, tirzepatide 15 mg, and placebo, respectively; figure 1). 12 (4%), 23 (7%), and 12 (4%) participants with tirzepatide 10 mg, tirzepatide 15 mg, and placebo, respectively, discontinued treatment due to adverse events (figure 1).

Baseline demographics and clinical characteristics were well balanced across groups (table 1). The mean age of participants was 54·2 years (SD 10·6), 476 (51%) were female, 710 (76%) were White, and 561 (60%) were Hispanic or Latino. The overall mean baseline bodyweight was 100·7 kg (SD 21·1), BMI 36·1 kg/m² (SD 6·6), and HbA_{1c} 8·02% (SD 0·89; 64·1 mmol/mol [SD 9·7]). Duration of obesity and diabetes was 17·7 years (SD 11·5) and 8·5 years (SD 6·5), respectively. 250 (27%) participants were treated with sulfonylureas (table 1).

For the treatment-regimen estimand, the least-squares mean percent change from baseline (week 0) in bodyweight at week 72 was –12·8% (SE 0·6) or –12·9 kg (–28·4 lbs) with tirzepatide 10 mg, –14·7% (SE 0·5) or –14·8 kg (–32·6 lbs) with tirzepatide 15 mg, and –3·2% (SE 0·5) or –3·2 kg (–7·0 lbs) with placebo (figure 2A,B). 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

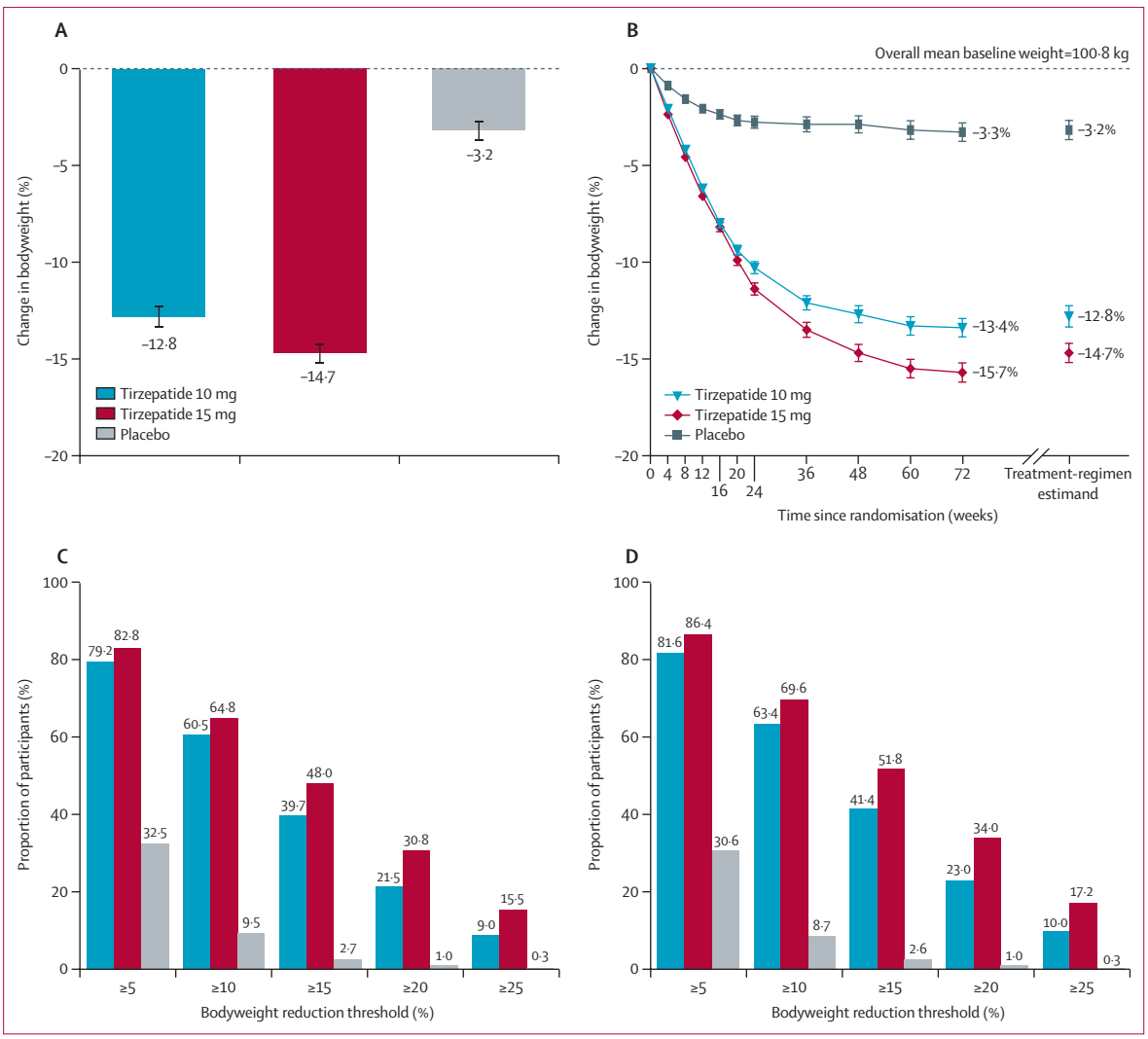

***Figure 2*: Effect of once weekly tirzepatide, compared with placebo, on bodyweight**

Least-squares means are presented, unless otherwise noted. Error bars indicate the standard error. (A) Percent change in bodyweight from baseline to week 72 derived from an analysis of covariance model for the treatment-regimen estimand. (B) Percent change in bodyweight over time from baseline to 72 weeks, derived from a mixed-model for repeated-measures analysis for the efficacy estimand; week 72 estimates for the treatment-regimen estimand are also shown. (C) Percentage of participants reaching weight reduction thresholds (treatment-regimen estimand); 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. (D) Percentage of participants reaching weight reduction thresholds (efficacy estimand); percentage of participants reaching weight reduction thresholds was obtained by logistic regression with missing value at week 72 imputed from mixed-model for repeated-measures analysis.

points (95% CI –13·0 to –10·1; p<0·0001) for the 15 mg dose (table 2).

The change in bodyweight for the efficacy estimand was –13·4% (SE 0·5) or –13·5 kg (–29·8 lbs) with tirzepatide 10 mg, –15·7% (SE 0·5) or –15·6 kg (–34·4 lbs) with tirzepatide 15 mg, and –3·3% (SE 0·5) or –3·2 kg (–7·0 lbs) 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% (n=247) and 83% (n=257) of participants in the tirzepatide 10 mg, and tirzepatide 15 mg groups, respectively, had a bodyweight reduction of 5% or more at 72 weeks, as compared with 32% (n=102) of participants in the placebo group (p<0·0001 for all comparisons with placebo). For the efficacy estimand, the respective percentages were 82% (n=252), 86% (n=267), and 31% (n=95). For both estimands, more participants in the tirzepatide groups had reductions in bodyweight of 10% or higher, 15% or higher, 20% or higher, and 25% or higher from baseline than did participants in the placebo group (figure 2C, D; table 2).

From a baseline HbA_{1c} of 8·02% (64·1 mmol/mol), HbA_{1c} improved by –2·1% (SE 0·06) with tirzepatide

	Tirzepatide 10 mg (n=312)	Tirzepatide 15 mg (n=311)	Placebo (n=315)	Tirzepatide 10 mg *vs* placebo (95% CI);* p value	Tirzepatide 15 mg *vs* placebo (95% CI);* p value
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 to −8·1), p<0·0001	ETD −11·6 (−13·0 to −10·1); p<0·0001
Participants with weight reduction ≥5%	247 (79%)	257 (83%)	102 (32%)	OR 8·3 (5·6 to 12·3); p<0·0001	OR 10·5 (6·8 to 16·1); p<0·0001
Key secondary endpoints (at week 72)†					
Participants with weight reduction ≥10%	189 (61%)	202 (65%)	30 (9%)	OR 16·1 (9·9 to 26·1); p<0·0001	OR 19·4 (11·9 to 31·7); p<0·0001
Participants with weight reduction ≥15%	124 (40%)	149 (48%)	8 (3%)	OR 25·2 (12·2 to 52·1); p<0·0001	OR 36·1 (17·5 to 74·5); p<0·0001
Participants with weight reduction ≥20%	67 (22%)	96 (31%)	3 (1%)	OR 25·6 (8·7 to 75·4); p<0·0001	OR 42·2 (14·4 to 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 to−5·9); p<0·0001	ETD −9·8 (−11·2 to−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 to −1·37); p<0·0001	ETD −1·57 (−1·76 to −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 to −14·9); p<0·0001	ETD −17·1 (−19·3 to −15·0); p<0·0001
Participants with HbA_{1c} <7%	271 (87%)	262 (84%)	114 (36%)	OR 12·6 (7·9 to 20·1); p<0·0001	OR 10·7 (6·5 to 17·4); p<0·0001
Participants with HbA_{1c} ≤6·5%	249 (80%)	247 (79%)	63 (20%)	OR 17·8 (11·1 to 28·6); p<0·0001	OR 18·5 (11·2 to 30·7); p<0·0001
Participants with HbA_{1c} <5·7%	144 (46%)	151 (49%)	12 (4%)	OR 23·3 (10·9 to 50·0); p<0·0001	OR 26·6 (12·3 to 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 to −31·8); p<0·0001	ETD −37·9 (−44·4 to −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 to −1·8); p<0·0001	ETD −2·1 (−2·5 to −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 to −5·7); p=0·0027	ETD −25·9 (−33·8 to −17·0); p<0·0001
Participants with weight reduction ≥25%‡	28 (9%)	48 (15%)	1 (<1%)	OR 21·0 (4·2 to 104·5); p=0·0002	OR 39·1 (8·0 to 190·6); p<0·0001
Mean change in BMI, kg/m^2	−4·7 (0·2)	−5·4 (0·2)	−1·2 (0·2)	ETD −3·5 (−4·1 to −3·0); p<0·0001	ETD −4·2 (−4·7 to −3·7); p<0·0001
Change in bodyweight, kg	−12·9 (0·6)	−14·8 (0·5)	−3·2 (0·5)	ETD −9·7 (−11·2 to −8·2); p<0·0001	ETD −11·6 (−13·1 to −10·2); p<0·0001

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

Table 2: **Primary and secondary endpoints by treatment group for the treatment-regimen estimand**

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, tirzepatide 15 mg, and placebo, respectively (figure 3A). The proportion of participants in each group reaching HbA_{1c} levels of less than 7·0%, 6·5% or less, or less than 5·7% at week 72 was significantly higher in tirzepatide 10 mg and tirzepatide 15 mg groups compared with placebo (87% [n=271] and 84% [n=262] *vs* 36% [n=114], 80% [n=249] and 79% [n=247] *vs* 20% [n=63], and 46% [n=144] and 49% [n=151] *vs* 4% [n=12], respectively; figure 3B). Improvements 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; appendix p 12).

Additionally, a post-hoc analysis showed that, at week 72, the proportion of participants taking one or no antihyperglycaemic medication increased from 62% (n=193) and 62% (n=193) to 67% (n=208) and 68% (n=213) with tirzepatide 10 mg and tirzepatide 15 mg, respectively, and decreased with placebo from 58% (n=182) to 47% (n=149). Inversely, the proportion of participants treated with two or more antihyperglycaemic medications decreased from 38% (n=119) and 38% (n=118) to 33% (n=104) and 32% (n=98) with tirzepatide 10 mg and tirzepatide 15 mg, respectively, and increased with placebo from 42% (n=133) to 53% (n=166; appendix p 13).

Reduction in waist circumference was significantly greater with tirzepatide 10 mg and tirzepatide 15 mg, compared with placebo (table 2; figure 3D). Improvements with pooled tirzepatide treatment (10 mg and 15 mg) were significantly greater versus placebo in terms of systolic blood pressure (−6·3 mm Hg *vs* −1·2 mm Hg; p<0·0001), diastolic blood pressure (−2·5 mm Hg *vs* −0·3 mm Hg; p=0·0012), 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%; p<0·0001; figure 3E, F). Results were consistent for the efficacy estimand, showing greater improvements with tirzepatide treatment compared with placebo for all key secondary endpoints (appendix pp 14, 17–19).

Participants' physical function improved more with tirzepatide than with placebo (appendix pp 17–19). For the efficacy estimand, the mean change in physical functioning domain scores for the SF-36v2 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). 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 the appendix (pp 17–19).

There was no significant difference between groups in the overall incidence of adverse events; treatment-

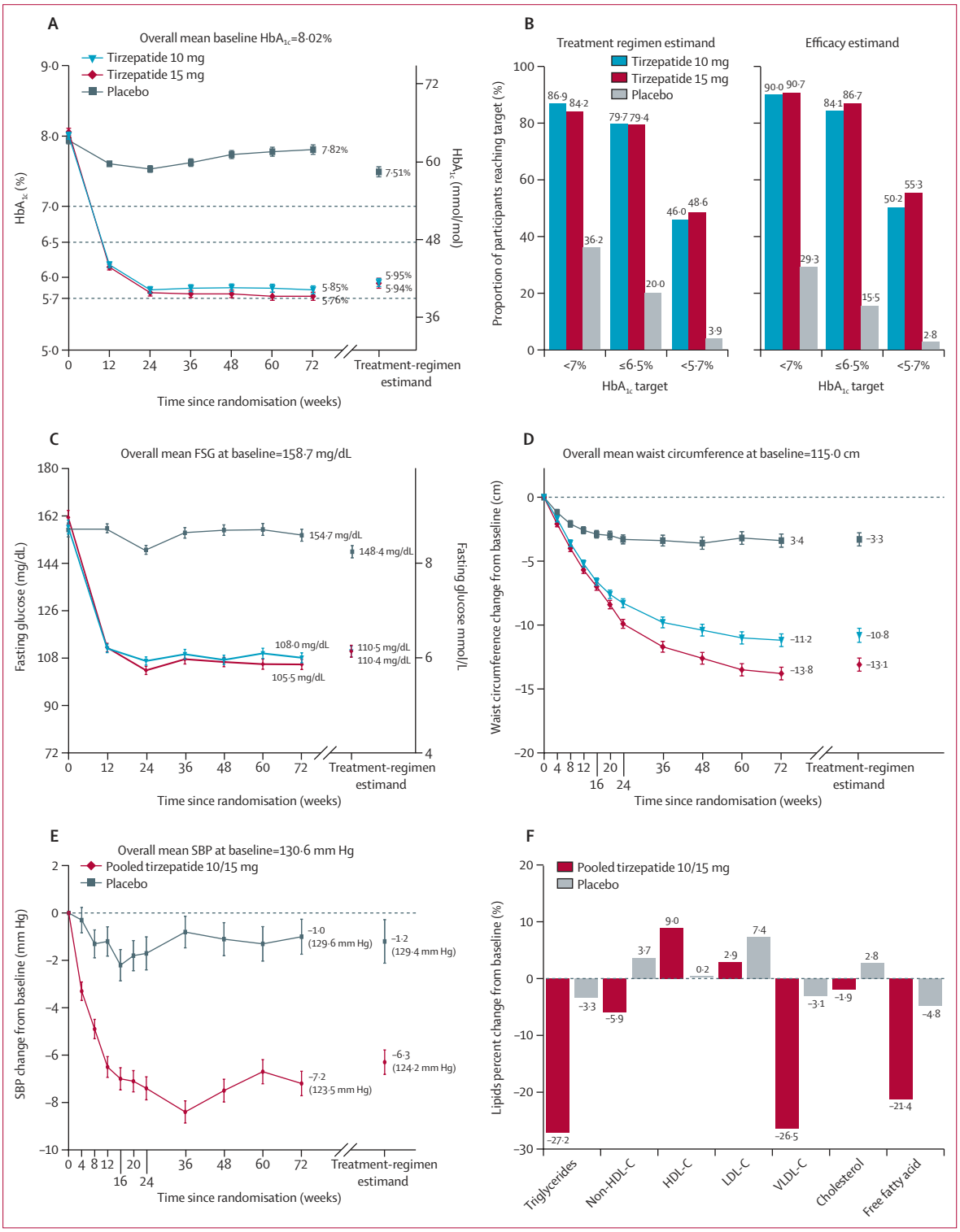

***Figure 3*: HbA$_{1c}$ over time and proportion of participants reaching HbA$_{1c}$ targets, FSG, waist circumference, SBP,and lipid levels**

Data are least-squares mean (SE) unless otherwise stated. (A) HbA$_{1c}$ values over time from MMRM analysis for the efficacy estimand and week 72 estimates from ANCOVA for the treatment-regimen estimand. (B) Proportion of participants reaching HbA$_{1c}$ targets (<7·0%, ≤6·5%, and <5·7%) from logistic regression analysis for the treatment-regimen estimand (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 treatment-regimen estimand. (D) Change in waist circumference over time from MMRM analysis for the efficacy estimand and week 72 estimates from ANCOVA for the treatment-regimen estimand. (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 treatment-regimen estimand; numbers in parentheses are actual mean values at week 72; by-dose analysis for tirzepatide versus placebo is available in the appendix (p 14). (F) Percent change from baseline fasting lipid levels for pooled tirzepatide doses and placebo from ANCOVA for the treatment-regimen estimand; data are estimated means; results for the efficacy estimand and the tirzepatide by-dose analysis are available in the appendix (p 17). ANCOVA=analysis of covariance. FSG=fasting serum glucose. HbA$_{1c}$=glycated haemoglobin. MMRM=mixed model for repeated measures. SBP=systolic blood pressure.

	Tirzepatide 10 mg (n=312)	Tirzepatide 15 mg (n=311)	Placebo (n=315)
Participants with ≥1 treatment-emergent adverse event	242 (78%)	222 (71%)	239 (76%)
Serious adverse events*	18 (6%)	27 (9%)	23 (7%)
Deaths*	2 (1%)	0	0
Adverse events leading to discontinuation of study drug†	12 (4%)	23 (7%)	12 (4%)
Diarrhoea	0	5 (2%)	0
Nausea	1 (<1%)	4 (1%)	0
Vomiting	2 (1%)	0	0
Elevated blood calcitonin	2 (1%)	0	0
Elevated pancreatic enzymes	2 (1%)	0	0
Treatment-emergent adverse events occurring in ≥5% of participants in any treatment group (preferred term)			
Diarrhoea	62 (20%)	67 (22%)	28 (9%)
Nausea	63 (20%)	68 (22%)	20 (6%)
COVID–19	53 (17%)	33 (11%)	53 (17%)
Vomiting	34 (11%)	41 (13%)	10 (3%)
Decreased appetite	30 (10%)	31 (10%)	7 (2%)
Constipation	25 (8%)	28 (9%)	13 (4%)
Dyspepsia	23 (7%)	22 (7%)	10 (3%)
Hyperglycaemia	6 (2%)	4 (1%)	45 (14%)
Upper respiratory tract infection	10 (3%)	12 (4%)	21 (7%)
Abdominal pain	12 (4%)	23 (7%)	7 (2%)
Headache	16 (5%)	15 (5%)	9 (3%)
Nasopharyngitis	9 (3%)	10 (3%)	17 (5%)
Eructation	19 (6%)	13 (4%)	2 (1%)
Dizziness	17 (5%)	8 (3%)	5 (2%)
Adverse events of special interest			
Diabetic retinopathy complications‡	1 (<1%)	0	1 (<1%)
Hepatic events‡	2 (1%)	0	0
Malignancies	1 (<1%)	3 (1%)	7 (2%)
Pancreatitis (adjudication-confirmed)	0	2 (1%)	1 (<1%)
MACE (adjudication-confirmed)	4 (1%)	3 (1%)	4 (1%)
Cardiac disorders§	4 (1%)	1 (<1%)	1 (<1%)
Gastrointestinal events‡	5 (2%)	10 (3%)	4 (1%)
Gallbladder disease‡	2 (1%)	4 (1%)	3 (1%)
Renal events‡	3 (1%)	0	1 (<1%)
Dehydration‡	1 (<1%)	1 (<1%)	0
Major depressive disorder or suicidal ideation‡	0	0	1 (<1%)
Other treatment-emergent adverse events of interest			
Cholelithiasis	2 (1%)	6 (2%)	4 (1%)
Acute cholecystitis	1 (<1%)	3 (1%)	2 (1%)
Cholecystectomy	1 (<1%)	0	0

Data are n (%). MACE=major adverse cardiovascular event. *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 the Medical Dictionary for Regulatory Activities, version 24.1, preferred terms; only preferred terms with n≥2 in at least one group are presented. ‡Events were classified as severe or serious adverse events. §Events were classified as severe or serious arrhythmias and cardiac conduction disorders.

Table 3: **Adverse events (intention-to-treat population)**

emergent adverse events were reported by 242 (78%), 222 (71%), and 239 (76%) 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 (diarrhoea, nausea, and vomiting). Most of these events occurred during dose escalation, were mild to moderate in severity, and decreased over time (appendix p 15). Serious adverse events were reported by 68 (7%) 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 (appendix p 21). 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 (1%) in the tirzepatide 15 mg group and one (<1%) in the placebo group (table 3). No cases of medullary thyroid or pancreatic cancer were reported. The reported incidence of cholelithiasis and acute cholecystitis was similar among the tirzepatide and placebo groups. There were no cases of severe hypoglycaemia. Level 2 hypoglycaemia (blood glucose <54 mg/dL or <3·0 mmol/L) was reported by 11 (4%) participants treated with tirzepatide 10 mg, 15 (5%) with tirzepatide 15 mg, and four (1%) with placebo. The aggregated rate was 0·04, 0·06, and 0·09 events per patient per year with tirzepatide 10 mg, tirzepatide 15 mg, and placebo, respectively. Six (2%), 13 (4%), and four (1%) participants had symptoms associated with level 2 hypoglycaemia in the tirzepatide 10 mg, tirzepatide 15 mg, and placebo groups, respectively. More participants (9–12%) treated with sulfonylureas at baseline reported level 2 hypoglycaemia with tirzepatide treatment than those who were not taking sulfonylureas (2–3%). There were no severe or serious injection site or hypersensitivity reactions. Additional safety variables are described in table 3 and the appendix (p 22).

Discussion

In SURMOUNT-2, adults with a BMI 27 kg/m² or higher and type 2 diabetes treated with tirzepatide for 72 weeks had a mean bodyweight reduction of up to 14·7%, with 79–83% reaching a weight reduction of 5% or more. On tirzepatide 15 mg, up to 65%, 48%, and 31% of participants had bodyweight reductions of 10% or higher, 15% or higher, and 20% or higher, respectively, at week 72. Participants' BMI declined by around 5 kg/m² with tirzepatide treatment, representing a downward shift, on average, in one BMI category. In addition, HbA_{1c} levels were markedly reduced by the end of study and accompanied by low rates of hypoglycaemia and no instances of severe hypoglycaemia.

Although weight reduction of at least 5% is a recommended component of type 2 diabetes 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 (≥5% to ≥15%).[18,19] Hence, most guidelines recommend weight reductions of 5% or more to 15% or more for people living with type 2 diabetes and excess weight.[2,5] In SURMOUNT-2, tirzepatide treatment produced a degree of weight loss in the majority of participants and might provide a broad range of therapeutic benefits in patients with obesity and type 2 diabetes.[2]

Substantial weight reduction is more challenging in people with obesity and type 2 diabetes compared with those without type 2 diabetes.[10,11] This finding has been demonstrated in studies involving lifestyle interventions and multiple anti-obesity medications.[16,20–25] The magnitude of weight reduction reached with tirzepatide 10 mg and tirzepatide 15 mg in SURMOUNT-1 in participants with obesity without type 2 diabetes was greater than that reached in the present trial: 19·5% and 20·9% versus 12·8% and 14·7%, respectively. Although the differential effectiveness of weight loss interventions in people with obesity with and without type 2 diabetes is consistently observed, treatment with tirzepatide in SURMOUNT-2 resulted in a magnitude of mean weight reduction that has previously only been observed in people without type 2 diabetes 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 anti-obesity medications because this degree of weight loss is sufficient to treat or prevent a wider array of obesity-related complications.[26] In a clinical trial involving participants with both obesity and type 2 diabetes,[22] the more recently approved GLP-1 receptor agonist, semaglutide, achieved just higher than 10% mean weight reduction (10·6% based on the trial product estimand [on treatment]). Based on the SURMOUNT-2 results, tirzepatide produces a degree of weight loss (15·7% based on the efficacy estimand [on treatment]) allowing for greater improvements in glycaemia and potentially multiple other obesity-related complications that beset these patients.[2,22,26]

HbA_{1c} was reduced by about 2% with tirzepatide treatment, resulting in an average HbA_{1c} of approximately 5·9% at the end of treatment, with nearly half of the participants reaching the normoglycaemic range of HbA_{1c} less than 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% or less 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, and 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 over time to reduced cardiovascular disease, chronic kidney disease, and non-alcoholic fatty liver disease, among other outcomes. Multiple cardiovascular outcome trials in people with type 2 diabetes have shown that GLP-1 receptor agonists can reduce risk of major adverse cardiovascular events.[28] Metabolic surgery, which affords greater weight reduction than lifestyle-based or pharmacologic therapies, has also been associated with a lower risk of incident major adverse cardiovascular events, major adverse liver outcomes, and obesity-associated cancers.[29–31] Since nearly one in six participants treated with tirzepatide 15 mg in SURMOUNT-2 reached a weight reduction of 25% or greater—within the range of weight loss achieved by bariatric surgery procedures—it is intriguing to consider whether tirzepatide will also be associated with the aforementioned clinical benefits in people with type 2 diabetes or obesity, or both. Although a meta-analysis of the SURPASS clinical trials in participants with type 2 diabetes showed that tirzepatide did not increase the risk of major adverse cardiovascular events compared with the control groups,[32] the ongoing SURPASS-CVOT (NCT04255433) trial comparing tirzepatide and dulaglutide on major adverse cardiovascular events in people with type 2 diabetes and the SURMOUNT-MMO (NCT05556512) trial investigating the effect of tirzepatide on the reduction of morbidity and mortality in people with obesity without type 2 diabetes, 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 type 2 diabetes. 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 type 2 diabetes, and as such, included participants with a BMI less than 27 kg/m², had less prescriptive lifestyle interventions, and were generally shorter (40–52 weeks) in duration, which might not have allowed for capturing the full effect of tirzepatide on bodyweight. Additionally, 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 type 2 diabetes. Although the period of active treatment was longer in the current trial (72 weeks) compared with semaglutide 2·4 mg in STEP 2[22] (68 weeks) and liraglutide 3·0 mg in SCALE Diabetes[16] (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 bodyweight 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 type 2 diabetes 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 might 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 β-cell.[7,8,34] Slowed gastric emptying might be a potential contributor to the observed reduction in food intake and has been associated with a quicker time to satiety.[35,36] However, it is unlikely to be a major driver of weight reduction with tirzepatide since the effect of tirzepatide on bodyweight reduction continues well after the drug's effect on gastric emptying has waned.[37] Furthermore, previous analyses of the SURPASS trials showed no association between weight reduction and gastrointestinal adverse events (which might be related to slowed gastric emptying),[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 type 2 diabetes.[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 generalisable. The HbA_{1c} entry criteria (≥7% and ≤10%) were expected to be representative of the majority of people with diabetes who would otherwise require intensification of glucose-lowering medication. Additionally, participants were stratified by the weight-effect of concomitant antihyperglycaemic medications, 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 type 2 diabetes that safely produced significant weight reduction in previous studies in participants with and without type 2 diabetes,[9,27] was not evaluated in this trial. Over a third of screened individuals were not enrolled into the study; most (56%) did not meet diabetes-related entry criteria. 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. 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. Although this exclusion could pose a limitation in our study, there is current evidence of the efficacy and safety of tirzepatide in patients with type 2 diabetes 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 type 2 diabetes (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 might be addressed in the ongoing 2-year additional follow-up period in the SURMOUNT-1 trial, and in the SURMOUNT-4 randomised withdrawal trial, respectively, in people with obesity.[14]

In conclusion, in adults with a BMI of 27 kg/m² or higher and type 2 diabetes, once-weekly treatment with tirzepatide demonstrated substantial, clinically meaningful bodyweight reductions of up to 15%, with weight reductions of 20% or higher reached 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 an HbA_{1c} less than 5·7%.

Contributors

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 and Company, Novo Nordisk, Pfizer, Fractyl Health, Alnylam Pharmaceuticals, Inogen, and Merck, and as a site principal investigator for multicentred clinical trials sponsored by his university

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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 USA and the 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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