Efficacy and safety of a novel dual GIP and GLP-1 receptor agonist tirzepatide in patients with type 2 diabetes (SURPASS-1): a double-blind, randomised, phase 3 trial

Julio Rosenstock, Carol Wysham, Juan P Frías, Shizuka Kaneko, Clare J Lee, Laura Fernández Landó, Huzhang Mao, Xuewei Cui, Chrisanthi A Karanikas, Vivian T Thieu

Summary

Background Despite advancements in care, many people with type 2 diabetes do not meet treatment goals; thus, development of new therapies is needed. We aimed to assess efficacy, safety, and tolerability of novel dual glucose-dependent insulinotropic polypeptide and GLP-1 receptor agonist tirzepatide monotherapy versus placebo in people with type 2 diabetes inadequately controlled by diet and exercise alone.

Methods We did a 40-week, double-blind, randomised, placebo-controlled, phase 3 trial (SURPASS-1), at 52 medical research centres and hospitals in India, Japan, Mexico, and the USA. Adult participants (≥18 years) were included if they had type 2 diabetes inadequately controlled by diet and exercise alone and if they were naive to injectable diabetes therapy. Participants were randomly assigned (1:1:1:1) via computer-generated random sequence to once a week tirzepatide (5, 10, or 15 mg), or placebo. All participants, investigators, and the sponsor were masked to treatment assignment. The primary endpoint was the mean change in glycated haemoglobin (HbA_{1c}) from baseline at 40 weeks. This study is registered with ClinicalTrials.gov, NCT03954834.

Findings From June 3, 2019, to Oct 28, 2020, of 705 individuals assessed for eligibility, 478 (mean baseline HbA_{1c} 7·9% [63 mmol/mol], age 54·1 years [SD 11·9], 231 [48%] women, diabetes duration 4·7 years, and body-mass index 31·9 kg/m²) were randomly assigned to tirzepatide 5 mg (n=121 [25%]), tirzepatide 10 mg (n=121 [25%]), tirzepatide 15 mg (n=121 [25%]), or placebo (n=115 [24%]). 66 (14%) participants discontinued the study drug and 50 (10%) discontinued the study prematurely. At 40 weeks, all tirzepatide doses were superior to placebo for changes from baseline in HbA_{1c}, fasting serum glucose, bodyweight, and HbA_{1c} targets of less than 7·0% (<53 mmol/mol) and less than 5·7% (<39 mmol/mol). Mean HbA_{1c} decreased from baseline by 1·87% (20 mmol/mol) with tirzepatide 5 mg, 1·89% (21 mmol/mol) with tirzepatide 10 mg, and 2·07% (23 mmol/mol) with tirzepatide 15 mg versus +0·04% with placebo (+0·4 mmol/mol), resulting in estimated treatment differences versus placebo of –1·91% (–21 mmol/mol) with tirzepatide 5 mg, –1·93% (–21 mmol/mol) with tirzepatide 10 mg, and –2·11% (–23 mmol/mol) with tirzepatide 15 mg (all p<0·0001). More participants on tirzepatide than on placebo met HbA_{1c} targets of less than 7·0% (<53 mmol/mol; 87–92% *vs* 20%) and 6·5% or less (≤48 mmol/mol; 81–86% *vs* 10%) and 31–52% of patients on tirzepatide versus 1% on placebo reached an HbA_{1c} of less than 5·7% (<39 mmol/mol). Tirzepatide induced a dose-dependent bodyweight loss ranging from 7·0 to 9·5 kg. The most frequent adverse events with tirzepatide were mild to moderate and transient gastrointestinal events, including nausea (12–18% *vs* 6%), diarrhoea (12–14% *vs* 8%), and vomiting (2–6% *vs* 2%). No clinically significant (<54 mg/dL [<3 mmol/L]) or severe hypoglycaemia were reported with tirzepatide. One death occurred in the placebo group.

Interpretation Tirzepatide showed robust improvements in glycaemic control and bodyweight, without increased risk of hypoglycaemia. The safety profile was consistent with GLP-1 receptor agonists, indicating a potential monotherapy use of tirzepatide for type 2 diabetes treatment.

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Dallas Diabetes Research Center at Medical City, Dallas, TX, USA (J Rosenstock MD); **MultiCare Rockwood Clinic, Spokane, WA, USA** (C Wysham MD); **National Research Institute, Los Angeles, CA, USA** (J P Frías MD); **Takatsuki Red Cross Hospital, Osaka, Japan** (S Kaneko MD); **Eli Lilly and Company, Indianapolis, IN, USA** (C J Lee MD, L Fernández Landó MD, H Mao PhD, X Cui PhD, C A Karanikas MS, V T Thieu PhD)

Correspondence to: Dr Julio Rosenstock, Dallas Diabetes Research Center at Medical City, Dallas, TX 75230, USA **juliorosenstock@dallasdiabetes.com**

Introduction

GLP-1 receptor agonists deliver substantial improvements in glucose control, and some, especially once a week GLP-1 receptor agonists dulaglutide and semaglutide, can induce clinically significant but variable weight loss.[1,2] Similar to GLP-1, glucose-dependent insulinotropic polypeptide (GIP) also enhances meal-stimulated insulin secretion in a glucose-dependent manner. It is the dominant incretin hormone in healthy individuals, contributing the majority of the incretin effect,[3] but the insulin response after GIP secretion in type 2 diabetes is diminished.[4] GIP differs from GLP-1 in its role of stimulating glucagon secretion during hypoglycaemia and exerting a direct effect on lipid homoeostasis.[2,5,6] GIP might also promote weight loss by signalling satiety through its receptors present in

Research in context

Evidence before this study

We searched PubMed on Sept 10, 2020, using the terms "tirzepatide", "liraglutide", "exenatide", "lixisenatide", "dulaglutide", "albiglutide", "semaglutide", "glucose-dependent insulinotropic polypeptide", "glucagon-like peptide 1 receptor agonist", and "type 2 diabetes" with no date or study duration restrictions. Non-English references were excluded.
We designed this study based on the evidence obtained from the clinical development of tirzepatide, including in-vitro and preclinical studies, phase 1 single-dose and multi-dose pharmacokinetic and pharmacodynamic studies, a phase 2 efficacy and safety trial, and a phase 2 dose-escalation trial. Although there are several long-acting GLP-1 receptor agonists approved for the treatment of type 2 diabetes, tirzepatide is a novel once a week dual GIP and GLP-1 receptor agonist that integrates the actions of both incretins into a single molecule, representing a promising medication for type 2 diabetes treatment.

Added value of this study

Findings from this study showed that 40 weeks of tirzepatide treatment resulted in robust and clinically significant reductions in glycated haemoglobin (HbA_{1c}) at all doses compared with placebo. Furthermore, all three doses of tirzepatide led to significantly greater improvements in fasting serum glucose as early as 4 weeks and postprandial self-monitored blood glucose profiles as early as 12 weeks. Most patients given tirzepatide reached HbA_{1c} targets, with 87–92% reaching an HbA_{1c} concentration of less than 7·0% and 81–86% reaching 6·5% or less, and 31–52% reaching normoglycaemia (HbA_{1c} <5·7%), compared with participants given placebo in whom 20% reached less than 7·0%, 10% reached 6·5% or less, and 1% reached normoglycaemia. Notably, HbA_{1c} targets were reached with tirzepatide without severe or clinically significant cases of hypoglycaemia. Significant bodyweight loss of –7·0 kg to –9·5 kg was observed with tirzepatide treatment (*vs* –0·7 kg with placebo), with 67–78%, 31–47%, and 13–27% of participants given tirzepatide compared with 14%, 1%, and 0% of participants given placebo reaching bodyweight reductions of 5% or greater, 10% or greater, and 15% or greater, respectively. The effect of tirzepatide on bodyweight loss was dose-dependent and progressive, and did not plateau at the end of the 40-week treatment period, similar to the safety and tolerability profile of selective GLP-1 receptor agonists. The most frequent adverse events with tirzepatide versus placebo were mild to moderate gastrointestinal events, including nausea (12–18% *vs* 6%), diarrhoea (12–14% *vs* 8%), and vomiting (2–6% *vs* 2%), which decreased over time.

Implications of all the available evidence

To our knowledge, SURPASS-1 is the first randomised controlled trial of tirzepatide, a once a week dual GIP and GLP-1 receptor agonist, which showed potent glucose-lowering effects towards near-normal ranges with robust weight loss of a magnitude not previously reported in people with type 2 diabetes and without increased risk of severe or clinically significant hypoglycaemia (<54 mg/dL). The advantageous therapeutic effects for glycaemic control and bodyweight reduction will be further assessed in the SURPASS clinical trial programme when compared with the selective GLP-1 receptor agonist semaglutide in people with type 2 diabetes.

the hypothalamus, as shown in preclinical animal models.[7,8]

Notably, in preclinical studies, the combined effect of GIP and GLP-1 has shown robust weight loss effects independent of insulin sensitivity and lipid metabolism.[9] In diet-induced obese mice, combined GIP and GLP-1 agonism showed greater anorectic action compared with semaglutide by enhancing satiety and satiation, reducing preference for high-fat diets, and lowering sweet taste preference.[8] In addition, combined agonism of GIP and GLP-1 receptors has shown greater improvements in glycaemia and bodyweight than selective GLP-1 receptor agonists in clinical studies, and thus it serves as the rationale for targeting both incretin hormones to treat type 2 diabetes.[10]

Tirzepatide is a novel once a week dual GIP and GLP-1 receptor agonist. It is a 39-amino acid synthetic peptide with agonist activity at both GIP and GLP-1 receptors.[11] Its structure is based on the GIP sequence and includes a C20 fatty di-acid moiety, helping with half-life extension (half-life of around 5 days) allowing once a week subcutaneous administration.[11] In a 26-week phase 2B study in type 2 diabetes, tirzepatide significantly reduced glycated haemoglobin (HbA_{1c}) and bodyweight compared with placebo and the selective GLP-1 receptor agonist dulaglutide 1·5 mg, with or without metformin.[10] More gastrointestinal events and decreased appetite of mild to moderate severity were reported with tirzepatide than with placebo.[10] More patients reported gastrointestinal events and decreased appetite with tirzepatide 15 mg than with dulaglutide 1·5 mg.[10] To further improve gastrointestinal tolerability, we adopted an optimised dose-escalation scheme in the phase 3 SURPASS clinical programme, with a lower starting dose of tirzepatide and slower monthly dose escalation.[12]

In this trial, we aimed to assess the glycaemic efficacy and safety of three doses of once a week tirzepatide (5, 10, and 15 mg) as monotherapy versus placebo in people with type 2 diabetes.

Methods

Study design and participants

This 40-week, multicentre, randomised, double-blind, placebo-controlled, parallel group trial (SURPASS-1) was

done in 52 medical research centres and hospitals in India, Japan, Mexico, and the USA. Key inclusion criteria included adult participants (≥18 years) with type 2 diabetes inadequately controlled with diet and exercise alone and who were naive to injectable diabetes therapy. Eligible participants had an HbA_{1c} of 7·0% or more (≥53 mmol/mol) to 9·5% or less (≤80 mmol/mol) at screening, body-mass index (BMI) of 23 kg/m² or greater, and with stable weight (no change outside of 5%) during the previous 3 months with agreement to not initiate a diet or exercise programme during the study with the intent of reducing bodyweight other than the lifestyle and dietary measures for diabetes treatment. Additionally, per the protocol, sites needed to educate participants on diabetes management including management of hypoglycaemia, hyperglycaemia, and general counselling on diet and exercise. Key exclusion criteria included type 1 diabetes, history of pancreatitis, history of proliferative diabetic retinopathy, diabetic maculopathy, or non-proliferative diabetic retinopathy that requires acute treatment, estimated glomerular filtration rate of less than 30 mL/min per 1·73 m², and use of any oral antihyperglycaemia medication for 3 months before screening. A full list of eligibility criteria is provided in the appendix (pp 1–3).

The protocol was approved by local institutional review boards and the trial was done in accordance with the Declaration of Helsinki guidelines on good clinical practice. All participants provided written informed consent.

Randomisation and masking

Participants were randomly assigned (1:1:1:1) to receive once a week tirzepatide (5, 10, or 15 mg) or volume-matched placebo in a single dose pen. All pens were similar in appearance. Assignment to treatment group was determined by a computer-generated random sequence using the Eli Lilly and Company interactive web-response system. This system is externally validated and compliant with the Code of Federal Regulations 21 part 11.

Participants were stratified at randomisation based on country, baseline HbA_{1c} (≤8·5% [≤69 mmol/mol] or >8·5% [>69 mmol/mol]) and previous use of any oral antihyperglycaemia medication (yes or no). All participants, investigators, and the sponsor were masked to treatment assignment. The randomisation data was only assessed by a very limited group of personnel (interactive web-response system support team, Data Movement Group associates, demand forecasters and clinical supply coordinators, and unmasked analysts for expedite pharmacokinetic and pharmacodynamic analysis).

Procedures

After a 3-week screening or lead-in period, participants received subcutaneous injections of tirzepatide or matched placebo once a week for 40 weeks, followed by a 4-week safety follow-up period (appendix p 16).

Participants given tirzepatide followed a slow dose escalation regimen fixed at 2·5 mg-dose increments of tirzepatide every 4 weeks until the maintenance dose was reached. The maintenance doses of 5, 10, and 15 mg were achieved at 4, 12, and 20 weeks in respective tirzepatide groups. Vital sign measurements were assessed at the fasting state, except for visit one, and taken before obtaining an electrocardiogram tracing and before collection of blood samples for laboratory testing, at visits when required. The participant sat quietly for 5 min before blood pressure and heart rate measurements were taken. For each parameter, each measure was assessed twice using the same arm and the recordings were taken at least 1 min apart. Blood pressure was taken with an automated blood pressure machine. Initiation of new antihyperglycaemic medications was allowed according to specific rescue criteria: (1) for protocol-defined persistent hyperglycaemia; (2) in those participants who require permanent discontinuation of study drug, but remain in the study; or (3) during the safety follow-up period, if the participants needed additional glycaemic control. Additional details on the initiation of new antihyperglycaemic medications are described in the appendix (pp 3–4).

See Online for appendix

Outcomes

The primary endpoint was mean change from baseline in HbA_{1c} at 40 weeks. Key secondary endpoints, included in the type 1 error control at 40 weeks (appendix pp 6, 17), were mean change from baseline in fasting serum glucose, the proportion of participants with HbA_{1c} target values of less than 7·0% (<53 mmol/mol) and less than 5·7% (<39 mmol/mol), and mean change from baseline in bodyweight. Other efficacy endpoints were the proportion of participants with an HbA_{1c} target of 6·5% or less (≤48 mmol/mol), proportions reaching 5% or greater, 10% or greater, and 15% or greater weight loss, and mean change from baseline in daily mean seven-point self-monitored blood glucose (SMBG) profiles at 40 weeks.

Safety endpoints were treatment-emergent adverse events; study drug discontinuation due to adverse events; adjudicated pancreatic adverse events (appendix p 4); serum calcitonin, allergic and hypersensitivity reactions, and treatment-emergent antidrug antibodies for tirzepatide; mean changes from baseline in pulse rate, systolic, and diastolic blood pressure; hypoglycaemia events of blood glucose less than 70 mg/dL (<4 mmol/L) and clinically significant concentrations less than 54 mg/dL (<3 mmol/L); and severe hypoglycaemia.

Statistical analysis

The sample size calculation assumed at least –0·65% difference of mean change from baseline in HbA_{1c} between tirzepatide groups and placebo, a common SD of 1·1% up to 25%, and 35% dropout rate in respective tirzepatide and placebo groups. It was estimated that 472 participants

provided at least 90% power to establish superiority for a tirzepatide dose compared with placebo at a two-sided significance level of 0·0167. Detailed type 1 error control strategy is shown in the appendix (pp 6, 17).

Efficacy analyses were done in the modified intention-to-treat population, comprised of all randomly assigned participants who were exposed to at least one dose of study drug. Participants who discontinued study drug due to inadvertent enrolment were excluded from efficacy analysis. Analyses of efficacy measures to align with the efficacy estimand, representing on-treatment efficacy without the influence of rescue therapy, was done using the efficacy analysis set. In addition, primary and key secondary objectives were assessed to align with the treatment-regimen estimand, representing efficacy regardless of premature study drug discontinuation and use of rescue medication, using the full analysis set data and with missing endpoint values imputed by multiple imputation based on the placebo group. 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 (appendix pp 6, 17). The graphical testing scheme started with testing the superiority of mean change from baseline to 40 weeks in HbA_{1c} for the tirzepatide 15 mg group versus placebo at a significance level of 0·0167, followed by testing superiority of key secondary endpoints for the tirzepatide 15 mg group versus placebo in the order of mean change from baseline to 40 weeks in bodyweight, proportion of participants with HbA_{1c} target values of less than 7·0% (53 mmol/mol) at 40 weeks, mean change from baseline to 40 weeks in fasting serum glucose, and proportion of patients with HbA_{1c} target values of less than 5·7% (39 mmol/mol) at 40 weeks. This procedure was repeated to test superiority of primary and key secondary endpoints for the tirzepatide 10 mg group versus placebo comparison and tirzepatide 5 mg group versus placebo comparison. Safety analyses were done on the modified intention-to-treat population with all data from start of treatment to end of safety follow-up.

Statistical analyses were done using SAS version 9.4, unless otherwise specified. Additional statistical analyses methods are provided in the appendix (pp 4–6). This study is registered with ClinicalTrials.gov, NCT03954834.

Role of the funding source

The funder of the study had a role in study design, data collection, data analysis, data interpretation, and writing of the report.

Results

Between June 3, 2019, and Oct 28, 2020, 705 participants were assessed for eligibility; 478 participants (mean baseline HbA_{1c} 7·94% [63 mmol/mol], age 54·1 years [SD 11·9], 231 [48%] women, diabetes duration 4·7 years, and BMI 31·9 kg/m²) were randomly assigned and received at least one dose of tirzepatide 5 mg (n=121 [25%]), tirzepatide 10 mg (n=121 [25%]), tirzepatide 15 mg (n=121 [25%]), or placebo (n=115 [24%]; figure 1). 66 (14%) participants discontinued the study drug and 50 (10%) discontinued the study prematurely. Time to study drug discontinuation and time to study discontinuation are shown in Kaplan-Meier plots in the appendix (p 18). Reasons for premature study drug

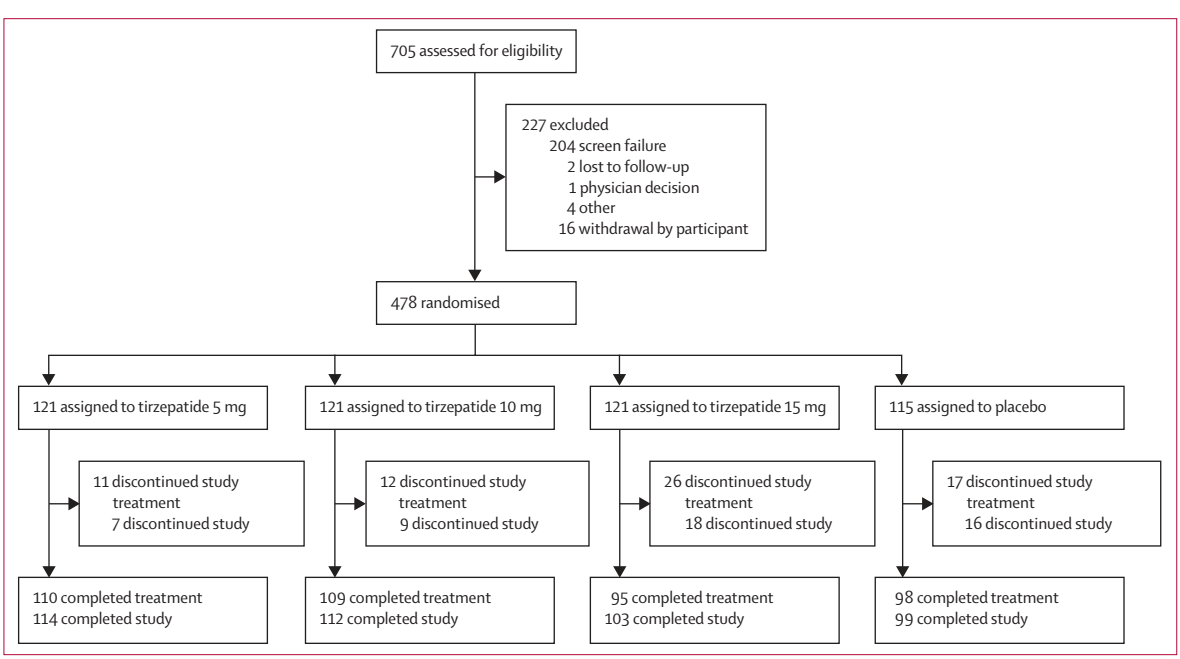

Figure 1: **Trial profile**
Reasons for study discontinuation up until safety follow-up were death, loss to follow-up, withdrawal by participant, or other.

	Tirzepatide 5 mg (n=121)	Tirzepatide 10 mg (n=121)	Tirzepatide 15 mg (n=121)	Placebo (n=115)	Total (n=478)
Age, years	54·1 (11·9)	55·8 (10·4)	52·9 (12·3)	53·6 (12·8)	54·1 (11·9)
Sex					
Women	65 (54%)	49 (40%)	58 (48%)	59 (51%)	231 (48%)
Men	56 (46%)	72 (60%)	63 (52%)	56 (49%)	247 (52%)
Race					
American Indian or Alaska Native	31 (26%)	31 (26%)	30 (25%)	26 (23%)	118 (25%)
Asian	45 (37%)	43 (36%)	42 (35%)	38 (33%)	168 (35%)
Black or African American	7 (6%)	4 (3%)	6 (5%)	5 (4%)	22 (5%)
White	38 (31%)	43 (36%)	43 (36%)	46 (40%)	170 (36%)
Ethnicity					
Hispanic or Latino	50 (41%)	54 (45%)	55 (45%)	48 (42%)	207 (43%)
Not Hispanic or Latino	48 (40%)	49 (40%)	42 (35%)	45 (39%)	184 (38%)
Not reported	23 (19%)	18 (15%)	24 (20%)	22 (19%)	87 (18%)
Country					
India	18 (15%)	20 (17%)	18 (15%)	17 (15%)	73 (15%)
Japan	23 (19%)	22 (18%)	23 (19%)	21 (18%)	89 (19%)
Mexico	42 (35%)	40 (33%)	42 (35%)	40 (35%)	164 (34%)
USA	38 (31%)	39 (32%)	38 (31%)	37 (32%)	152 (32%)
HbA_{1c} concentration					
In percentage	7·97 (0·84)	7·90 (0·78)	7·85 (1·02)	8·05 (0·80)	7·94 (0·87)
In mmol/mol	63·59 (9·19)	62·86 (8·50)	62·27 (11·11)	64·52 (8·75)	63·29 (9·46)
≤8·5%	95 (79%)	98 (81%)	98 (81%)	87 (76%)	378 (79%)
>8·5%	26 (21%)	23 (19%)	23 (19%)	28 (24%)	100 (21%)
Fasting serum glucose concentration					
In mg/dL	153·7 (37·3)	152·6 (41·7)	153·3 (40·4)	154·8 (40·3)	153·6 (39·8)
In mmol/L	8·5 (2·1)	8·5 (2·3)	8·5 (2·2)	8·6 (2·2)	8·5 (2·2)
Body-mass index, kg/m²	32·2 (7·0)	32·2 (7·6)	31·5 (5·5)	31·7 (6·1)	31·9 (6·6)
Weight, kg	87·0 (21·2)	86·2 (19·5)	85·4 (18·5)	84·8 (20·0)	85·9 (19·8)
eGFR, CKD-EPI calculation, mL/min per 1·73 m²	94·7 (20·6)	92·1 (18·2)	96·2 (19·7)	93·4 (20·2)	94·1 (19·7)
Diabetes duration, years	4·6 (5·1)	4·9 (5·6)	4·8 (5·0)	4·5 (5·9)	4·7 (5·4)
Previous oral antihyperglycaemic medication use	55 (45%)	53 (44%)	56 (46%)	55 (48%)	219 (46%)
Systolic blood pressure, mm Hg	128·2 (15·7)	127·8 (12·6)	126·8 (13·8)	127·8 (14·1)	127·6 (14·1)
Diastolic blood pressure, mm Hg	79·9 (9·0)	78·7 (8·2)	79·2 (8·8)	79·7 (9·3)	79·4 (8·8)
Pulse rate, beats per min	72·7 (9·3)	73·0 (9·8)	74·3 (8·3)	74·9 (10·0)	73·7 (9·4)

Data are mean (SD) or n (%). Data are for the all-randomised population. n=all randomly assigned participants who took at least one dose of study drug (modified intention-to-treat population). CKD-EPI=chronic kidney disease-epidemiology. eGFR=estimated glomerular filtration rate. HbA_{1c}=glycated haemoglobin.

Table 1: **Baseline characteristics**

discontinuation were adverse event, death, did not meet randomisation criteria, loss to follow-up, physician decision, protocol deviation, withdrawal by participant, or other. A greater number of study drug discontinuations were observed with tirzepatide 15 mg, and most discontinuations in the tirzepatide 15 mg group were for reasons other than adverse events. Three participants (tirzepatide 15 mg [n=1], placebo [n=2]) discontinued study drug due to inadvertent enrolment for violation of exclusion criteria related to gastric abnormalities or retinopathy. All other participants who were inadvertently enrolled continued in the study on study drug.

Demographics and clinical characteristics were similar between groups (table 1). The overall mean duration of diabetes was 4·7 years with a mean HbA_{1c} of 7·94% (63 mmol/mol) and BMI of 31·9 kg/m². 54% of participants had no previous use of oral antihyperglycaemia medication, which was similarly distributed across groups.

Data presented are based on the efficacy analysis set. At 40 weeks, HbA_{1c} significantly decreased from baseline by a least squares mean (LSM) of –1·87% (SE 0·09; –20 [1 mmol/mol]) with tirzepatide 5 mg, –1·89% (0·10; –21 [1 mmol/mol]) with tirzepatide 10 mg, and –2·07% (0·10; –23 [1 mmol/mol]) with tirzepatide 15 mg,

versus +0·04% (SE 0·11; +0·4 [1 mmol/mol]) with placebo (figure 2A, B, table 2). Estimated mean treatment differences versus placebo were –1·91% (95% CI –2·18 to –1·63; –21 mmol/mol [–24 to –18]) with tirzepatide 5 mg, –1·93% (–2·21 to –1·65; –21 mmol/mol [–24 to –18]) with tirzepatide 10 mg, and –2·11% (–2·39 to –1·83; –23 mmol/mol [–26 to –20]) with tirzepatide 15 mg (all p<0·0001). Significant decreases in HbA_{1c} with tirzepatide versus placebo were evident by the first assessment at week 4 (figure 2A). Mean HbA_{1c} concentrations reached near-normal values of 6·08% (43 mmol/mol) with tirzepatide 5 mg, 6·06% (43 mmol/mol) with tirzepatide 10 mg, and 5·88% (41 mmol/mol) with tirzepatide 15 mg at week 40 (figure 2A). At 40 weeks, previous use of oral antihyperglycaemic medication did not affect HbA_{1c} change from baseline with tirzepatide (treatment by oral antihyperglycaemic medication status interaction p=0·33; appendix p 20).

A significantly higher proportion of participants given tirzepatide reached HbA_{1c} target concentrations of less than 7·0% (<53 mmol/mol), 6·5% or less (≤48 mmol/mol), and less than 5·7% (<39 mmol/mol) at 40 weeks versus placebo (p<0·0001, all tirzepatide groups; figure 2F). An HbA_{1c} concentration of less than 7·0% (<53 mmol/mol) was reached in 87–92% of participants with tirzepatide versus 19% with placebo, an HbA_{1c} concentration of 6·5% or less (≤48 mmol/mol) was reached in 81–86% of participants with tirzepatide versus 10% with placebo, and an HbA_{1c} concentration of less than 5·7% (<39 mmol/mol) was reached in 31–50% of participants with tirzepatide versus 1% with placebo.

At 40 weeks, fasting serum glucose significantly decreased from baseline by an LSM of –43·6 mg/dL (SE 3·4; –2 [0·2 mmol/L]) with tirzepatide 5 mg, –45·9 mg/dL (3·5; –3 [0·2 mmol/L]) with tirzepatide 10 mg, and –49·3 mg/dL (3·6; –3 [0·2 mmol/L]) with tirzepatide 15 mg, versus +12·9 mg/dL (4·0; +1 [0·2 mmol/L]) with placebo (figure 2D, E, table 2). Estimated mean treatment differences versus placebo were –56·5 mg/dL (95% CI –66·8 to –46·1; –3 mmol/L [–4 to –3]) with tirzepatide 5 mg, –58·8 mg/dL (–69·2 to –48·4; –3 mmol/L [–4 to –3]) with tirzepatide 10 mg, and –62·1 mg/dL (–72·7 to –51·5; –3 mmol/L [–4 to –3]) with tirzepatide 15 mg (all p<0·0001). The seven-point SMBG profiles showed significant lowering of the mean daily, pre-meal, and 2-h post-meal glucose values with tirzepatide versus placebo at 12 weeks and 40 weeks (p<0·0001, all tirzepatide groups at both timepoints; figure 2F, appendix p 21). Decreases in mean 2-h post-meal glucose values ranged from –61 to –65 mg/dL (–3 to –4 mmol/L) with tirzepatide versus –11 (–1 mmol/L) with placebo. Mean post-meal glucose values in participants given tirzepatide were less than 140 mg/dL (<8 mmol/L) based on SMBG profiles (figure 2F).

At 40 weeks, bodyweight significantly decreased from baseline by an LSM of –7·0 kg (SE 0·52) with tirzepatide 5 mg, –7·8 kg (0·53) with tirzepatide 10 mg, and –9·5 kg (0·54) with tirzepatide 15 mg, versus –0·7 kg (0·57) with placebo (figure 3A, C, table 2). Estimated mean treatment differences versus placebo were –6·3 kg (95% CI –7·8 to –4·7) with tirzepatide 5 mg, –7·1 (–8·6 to –5·5) with tirzepatide 10 mg, and –8·8 kg (–10·3 to –7·2) with tirzepatide 15 mg (all p<0·0001). The reduction in weight was observed by week 4 and did not plateau by week 40 (figure 3A, C). The effect of tirzepatide on bodyweight was progressive and dose dependent. A greater proportion of participants had bodyweight reductions of 5% or greater (67–78%), 10% or greater (31–47%), and 15% or greater (13–27%) with tirzepatide versus 14%, 1%, and 0% with placebo (p≤0·011, all tirzepatide groups; figure 3D, table 2). Similarly, mean BMI and waist circumference reduced significantly from baseline with tirzepatide versus placebo (p<0·0001 all tirzepatide groups; appendix p 22).

At 40 weeks, total cholesterol, triglycerides, and serum VLDL cholesterol decreased from baseline and HDL cholesterol increased from baseline with all tirzepatide doses versus placebo (figure 3E, appendix pp 7–8). LDL cholesterol decreased with tirzepatide 15 mg versus placebo. Homoeostatic model assessment of insulin resistance decreased with all tirzepatide doses versus placebo (appendix p 9). No significant differences were seen in study drug discontinuation due to adverse events across treatment groups (table 3). The proportion of participants reporting any adverse events and the number of reported serious adverse events were similar between groups (table 3). Study drug discontinuations due to gastrointestinal adverse events were 2–7% with tirzepatide versus 1% with placebo.

The most frequent adverse events with tirzepatide were gastrointestinal. Nausea was reported in 14 (12%) participants who received tirzepatide 5 mg, 16 (13%) who received tirzepatide 10 mg, and 22 (18%) who received tirzepatide 15 mg, versus seven (6%) participants who received placebo (table 3). Diarrhoea was reported in 14 (12%) participants in each group who received tirzepatide 5 mg and 15 mg, and in 17 (14%) participants who received tirzepatide 10 mg, versus nine (8%) participants who received placebo. Vomiting was reported in four (3%) participants who received tirzepatide 5 mg, three (2%) who received tirzepatide 10 mg, and seven (6%) who received tirzepatide 15 mg, versus two (2%) participants who received placebo. Most reports of nausea, vomiting, and diarrhoea were mild to moderate in severity and decreased over time in all groups (appendix pp 10–12, 23–24).

One death occurred in a participant randomly assigned to placebo due to myocardial infarction confirmed by adjudication (table 2).

Clinically significant (<54 mg/dL [<3 mmol/L]) or severe hypoglycaemia was not reported in patients given tirzepatide (table 3). Hypoglycaemia (<70 mg/dL [<4 mmol/L]) was reported in seven (6%) participants

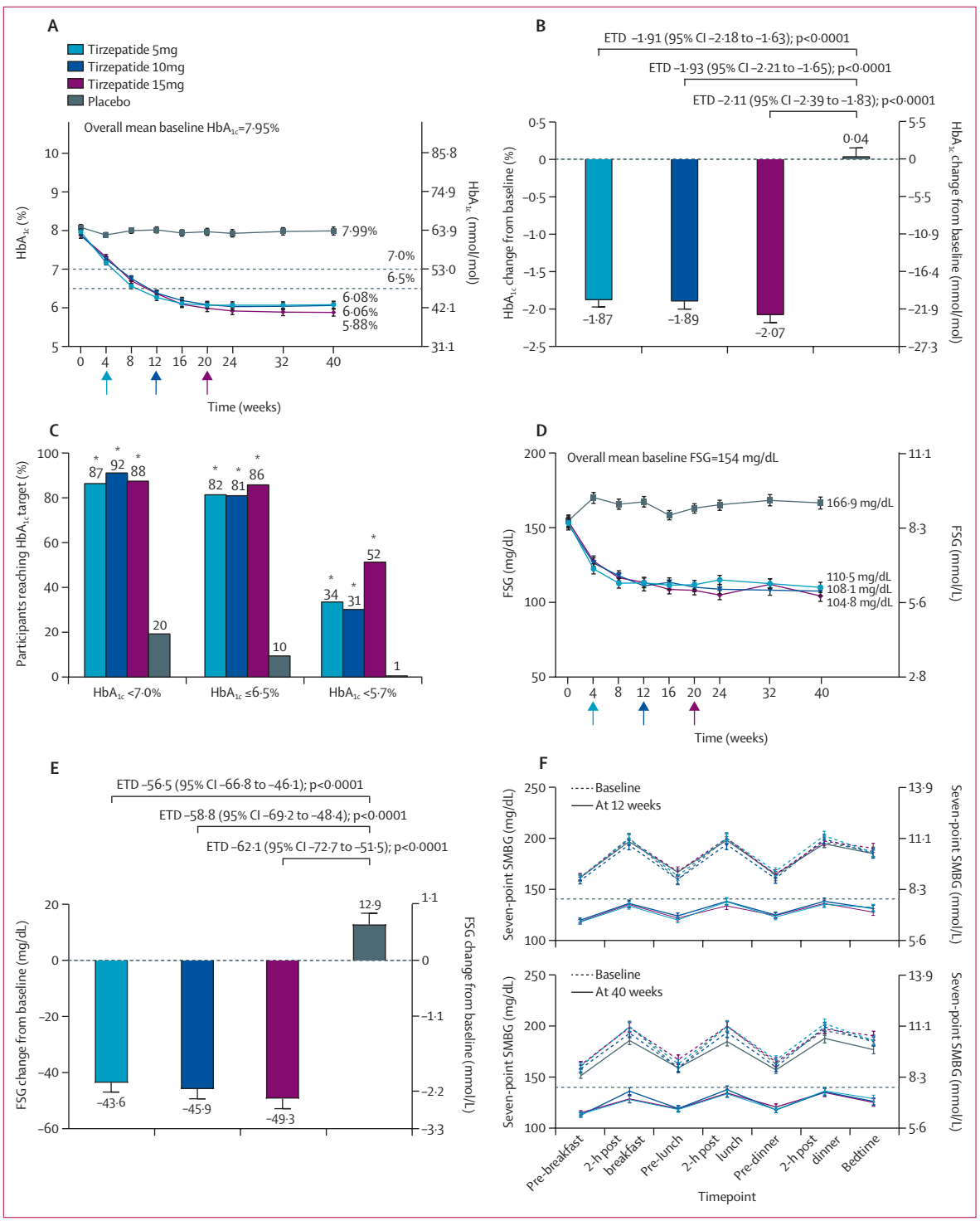

Figure 2: **Proportion of participants reaching HbA_{1c} targets, FSG, and seven-point SMBG profiles**
Data are LSM (SE), unless otherwise noted. Estimated treatment differences are LSM (95% CI) at 40 weeks, modified intention-to-treat population (efficacy analysis set). Arrows indicate when the maintenance dose of tirzepatide 5, 10, and 15 mg was reached. (A) HbA_{1c} values over time from MMRM analysis. (B) Change from baseline in HbA_{1c} at 40 weeks from MMRM analysis. (C) Proportion of participants reaching HbA_{1c} targets (<7·0%, ≤6·5%, and <5·7%) from logistic regression analysis. (D) FSG values over time from MMRM analysis. (E) Change from baseline in FSG at 40 weeks from MMRM analysis. (F) Seven-point SMBG profiles at baseline, 12 weeks, and 40 weeks. Dotted lines represent baseline values. ANOVA analysis (baseline) and MMRM analysis (12 weeks and 40 weeks). Data are estimates. ETD=estimated treatment difference. FSG=fasting serum glucose. HbA_{1c}=glycated haemoglobin. LSM=least squares mean. MMRM=mixed model repeated measures. SMBG=self-monitored blood glucose. *p<0·0001 versus placebo at 40 weeks.

	Tirzepatide 5 mg (n=121)		Tirzepatide 10 mg (n=121)		Tirzepatide 15 mg (n=120)		Placebo (n=113)	
	Mean*	p value	Mean*	p value	Mean*	p value	Mean*	p value
HbA_{1c}, %								
Baseline	7·97 (0·08)	..	7·88 (0·08)	..	7·88 (0·08)	..	8·08 (0·08)	..
Change from baseline	−1·87 (0·09)	<0·0001	−1·89 (0·10)	<0·0001	−2·07 (0·10)	<0·0001	0·04 (0·11)	0·72
Versus placebo	−1·91 (−2·18 to −1·63)	<0·0001	−1·93 (−2·21 to −1·65)	<0·0001	−2·11 (−2·39 to −1·83)	<0·0001	..	..
HbA_{1c}, mmol/mol								
Baseline	63·60 (0·86)	..	62·60 (0·87)	..	62·60 (0·88)	..	64·80 (0·89)	..
Change from baseline	−20·40 (1·03)	<0·0001	−20·70 (1·05)	<0·0001	−22·70 (1·07)	<0·0001	0·40 (1·15)	0·72
Versus placebo	−20·80 (−23·90 to −17·80)	<0·0001	−21·10 (−24·10 to −18·00)	<0·0001	−23·10 (−26·20 to −20·00)	<0·0001	..	..
Weight, kg								
Baseline	87·0 (1·8)	..	85·7 (1·8)	..	85·9 (1·8)	..	84·4 (1·9)	..
Change from baseline	−7·0 (0·5)	<0·0001	−7·8 (0·5)	<0·0001	−9·5 (0·5)	<0·0001	−0·7 (0·6)	0·22
Versus placebo	−6·3 (−7·8 to −4·7)	<0·0001	−7·1 (−8·6 to −5·5)	<0·0001	−8·8 (−10·3 to −7·2)	<0·0001	..	..
Participants reaching HbA_{1c} <7·0%†	105 (87%)	..	108 (92%)	..	102 (88%)	..	22 (19%)	..
Versus placebo	49·0 (21·1 to 113·7)	<0·0001	80·4 (31·8 to 203·2)	<0·0001	52·9 (22·3 to 125·7)	<0·0001	..	..
Fasting serum glucose, mg/dL								
Baseline	153·7 (3·7)	..	152·6 (3·7)	..	154·6 (3·7)	..	155·2 (3·8)	..
Change from baseline	−43·6 (3·4)	<0·0001	−45·9 (3·5)	<0·0001	−49·3 (3·6)	<0·0001	12·9 (4·0)	0·0014
Versus placebo	−56·5 (−66·8 to −46·1)	<0·0001	−58·8 (−69·2 to −48·4)	<0·0001	−62·1 (−72·7 to −51·5)	<0·0001	..	..
Fasting serum glucose, mmol/L								
Baseline	8·5 (0·2)	..	8·5 (0·2)	..	8·6 (0·2)	..	8·6 (0·2)	..
Change from baseline	−2·4 (0·2)	<0·0001	−2·6 (0·2)	<0·0001	−2·7 (0·2)	<0·0001	0·7 (0·2)	0·0014
Versus placebo	−3·1 (−3·7 to −2·6)	<0·0001	−3·3 (−3·8 to −2·7)	<0·0001	−3·4 (−4·0 to −2·9)	<0·0001	..	..
Participants with HbA_{1c} <5·7%†	41 (34%)	..	36 (31%)	..	60 (52%)	..	1 (1%)	..
Versus placebo	40·3 (7·7 to 209·7)	<0·0001	34·1 (6·5 to 178·2)	<0·0001	85·1 (16·4 to 443·1)	<0·0001	..	..
Participants with HbA_{1c} ≤6·5%†	99 (82%)	..	96 (81%)	..	100 (86%)	..	11 (10%)	..
Versus placebo	74·8 (30·6 to 183·0)	<0·0001	69·1 (28·5 to 167·6)	<0·0001	105·8 (41·3 to 271·4)	<0·0001	..	..
Participants with ≥5% weight loss†	81 (67%)	..	92 (78%)	..	89 (77%)	..	16 (14%)	..
Versus placebo	12·4 (6·4 to 23·9)	<0·0001	21·1 (10·6 to 42·2)	<0·0001	20·1 (10·1 to 40·0)	<0·0001	..	..
Participants with ≥10% weight loss†	37 (31%)	..	47 (40%)	..	55 (47%)	..	1 (1%)	..
Versus placebo	34·9 (6·8 to 180·5)	<0·0001	50·6 (9·8 to 260·4)	<0·0001	71·5 (13·9 to 368·4)	<0·0001	..	..
Participants with ≥15% weight loss†	16 (13%)	..	20 (17%)	..	31 (27%)	..	0	..
Versus placebo	35·6 (2·2 to 565·3)	0·011	46·5 (3·0 to 733·2)	0·0063	83·6 (5·4 to >999·0)	0·0016	..	..

MMRM (mean) or logistic regression (odds ratio) analysis with missing value imputed by MMRM using the efficacy analysis set at 40 weeks, mITT population (efficacy analysis set). HbA_{1c}=glycated haemoglobin. LSM=least squares mean. n=mITT population on treatment without rescue therapy and excluding patients who discontinued study drug due to inadvertent enrolment (efficacy analysis set). mITT=modified intention-to-treat. MMRM=mixed model repeated measures. *Baseline and change from baseline at 40 weeks data are LSM (SE) and treatment differences are LSM (95% CI), except for HbA_{1c} targets and weight loss of 5% or more, 10% or more, or 15% or more versus placebo, which are n (%) or odds ratio (95% CI). †Proportion of people reaching HbA_{1c} or weight loss goal were obtained by dividing the number reaching respective goals at endpoint by the number with baseline value and at least one non-missing post-baseline value in mITT efficacy analysis set (121, 118, 116, 112 patients were the denominator for tirzepatide 5, 10, and 15 mg, and placebo, respectively). No participants had weight loss of 15% or more with placebo; therefore, 95% CI was not calculated.

Table 2: **Efficacy measures at 40 weeks**

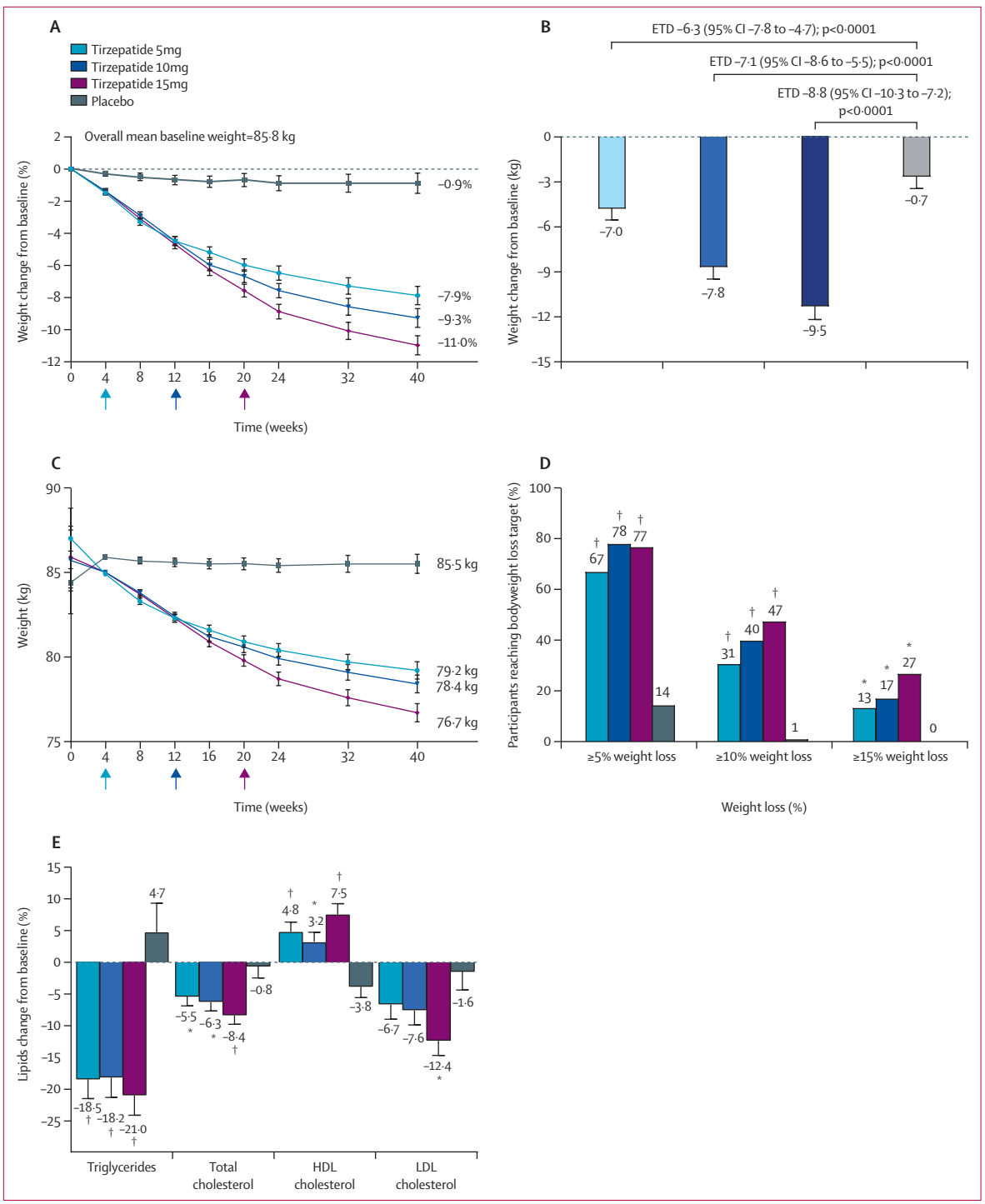

***Figure 3*: Bodyweight and proportion of participants reaching weight loss aims and lipid profile**

Data are LSM (SE), unless otherwise noted. Estimated treatment differences are LSM (95% CI) at 40 weeks, modified intention-to-treat population (efficacy analysis set). Arrows indicate when the maintenance dose of tirzepatide 5, 10, and 15 mg was reached. (A) Percentage change from baseline in bodyweight over time from MMRM analysis. (B) Change from baseline in bodyweight at 40 weeks from MMRM analysis. (C) Bodyweight values over time from MMRM analysis. (D) Proportion of participants reaching weight loss aims (≤5%, ≤10%, and ≤15%) was obtained by dividing the number of patients reaching respective goals at week 40 by the number of patients with baseline value and at least one non-missing post-baseline value. Missing value at week 40 was predicted from MMRM analysis. Data are estimates. (E) Percentage change from baseline in lipids at 40 weeks. Data are estimated percentage means (SE) using log transformation. ETD=estimated treatment difference. MMRM=mixed model repeated measures. *p<0·05 versus placebo at 40 weeks. †p<0·0001 versus placebo at 40 weeks.

	Tirzepatide 5 mg (n=121)	Tirzepatide 10 mg (n=121)	Tirzepatide 15 mg (n=121)	Placebo (n=115)	Total (n=478)
Participants with ≥1 treatment-emergent adverse event	83 (69%)	81 (67%)	77 (64%)	76 (66%)	317 (66%)
Serious adverse events	5 (4%)	2 (2%)	1 (1%)	3 (3%)	11 (2%)
Deaths*	0	0	0	1 (1%)	1 (<1%)
Adverse event leading to study drug discontinuation	4 (3%)	6 (5%)	8 (7%)	3 (3%)	21 (4%)
Gastrointestinal disorder (system order class)	3 (2%)	6 (5%)	8 (7%)	1 (1%)	18 (4%)
Gastrointestinal disorder (preferred term)	1 (1%)	2 (2%)	2 (2%)	0	5 (1%)
Diarrhoea	0	2 (2%)	2 (2%)	0	4 (1%)
Nausea	0	2 (2%)	1 (1%)	1 (1%)	4 (1%)
Abdominal discomfort	0	0	2 (2%)	0	2 (<1%)
Dyspepsia	1 (1%)	0	1 (1%)	0	2 (<1%)
Colitis ischaemic	1 (1%)	0	0	0	1 (<1%)
Treatment-emergent adverse events occurring in ≥5% of participants in any treatment group (preferred term)					
Nausea	14 (12%; 31)	16 (13%; 82)	22 (18%; 50)	7 (6%; 8)	59 (12%; 171)
Diarrhoea	14 (12%; 21)	17 (14%; 19)	14 (12%; 20)	9 (8%; 15)	54 (11%; 75)
Hyperglycaemia	4 (3%)	5 (4%)	3 (2%)	31 (27%)	43 (9%)
Nasopharyngitis	7 (6%)	8 (7%)	8 (7%)	10 (9%)	33 (7%)
Dyspepsia	11 (9%)	8 (7%)	7 (6%)	4 (3%)	30 (6%)
Decreased appetite	5 (4%)	8 (7%)	10 (8%)	1 (1%)	24 (5%)
Headache	5 (4%)	4 (3%)	5 (4%)	9 (8%)	23 (5%)
Constipation	7 (6%)	6 (5%)	8 (7%)	1 (1%)	22 (5%)
Vomiting	4 (3%; 6)	3 (2%; 3)	7 (6%; 9)	2 (2%; 3)	16 (3%; 21)
Influenza	7 (6%)	3 (2%)	0	2 (2%)	12 (3%)
Gastritis	6 (5%)	0	3 (2%)	0	9 (2%)
All gastrointestinal adverse events	46 (38%)	50 (41%)	50 (41%)	22 (19%)	168 (35%)
Other adverse events					
Hypoglycaemia (blood glucose <70 mg/dL)	7 (6%; 16)	8 (7%; 19)	8 (7%; 19)	1 (1%; 6)	24 (5%; 60)
Hypoglycaemia (blood glucose <54 mg/dL)	0	0	0	1 (1%; 3)	1 (<1%; 3)
Severe hypoglycaemia	0	0	0	0	0
Injection site reactions	4 (3%; 6)	4 (3%; 31)	3 (2%; 15)	0	11 (2%; 52)
Adjudicated pancreatitis†	0	0	0	0	0
Pancreatic cancer†	1 (1%)	0	0	0	1 (<1%)
Cholelithiasis†	1 (1%)	0	0	0	1 (<1%)
Hypersensitivity‡	3 (2%; 3)	2 (2%; 2)	1 (1%; 1)	1 (1%; 1)	7 (1%; 7)

Data are n (%), or n (%; number of episodes). Patients could be counted in more than one category. Number of episodes were reported if available. n=all randomly assigned participants who took at least one dose of study drug (modified intention-to-treat population). *Deaths are also included as serious adverse events and discontinuations due to adverse events. †Medical Dictionary for Regulatory Activities preferred term. ‡Includes immediate (≤24 h after study drug administration) and non-immediate (>24 h after study drug administration) hypersensitivity events. One immediate event was reported in the tirzepatide 15 mg group.

Table 3: **Adverse events**

who received tirzepatide 5 mg and eight (7%) participants in each group who received tirzepatide 10 mg and 15 mg, versus one (1%) with placebo. Rescue therapy for persistent hyperglycaemia was required for two (2%) participants who received tirzepatide 5 mg, four (3%) who received tirzepatide 10 mg, and two (2%) who received tirzepatide 10 mg and 15 mg, versus 29 (25%) with placebo. Metformin was the most common anti-hyperglycaemic medication used as rescue therapy for persistent hyperglycaemia during the study.

No adjudicated-confirmed cases of pancreatitis were seen. At 40 weeks, increases from baseline in lipase and pancreatic amylase concentrations were significant with tirzepatide versus placebo, while remaining within the normal range ($p \leq 0 \cdot 0019$, all tirzepatide groups; appendix p 13). One case of pancreatic cancer was diagnosed during evaluation of haematuria in the tirzepatide 5 mg group during the safety follow-up period and one case of cholelithiasis was reported in the same individual. No clinically relevant changes in mean calcitonin concentrations were observed. No cases of medullary thyroid cancer or treatment-emergent diabetic retinopathy were reported.

At 40 weeks, increases in mean pulse rate of 1–2 beats per min were observed with tirzepatide (appendix pp 13, 25). At 40 weeks, decreases in mean systolic blood pressure ranged from –4·7 to –5·2 mm Hg with tirzepatide versus with –2·0 mm Hg placebo, and differed

significantly with tirzepatide 10 mg (appendix pp 13, 25). Decreases in diastolic blood pressure did not differ from placebo. Decreases in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) concentrations differed significantly with tirzepatide, except with tirzepatide 10 mg for AST, compared with placebo (appendix p 13).

Injection site reactions occurred in 11 (2–3%) participants with tirzepatide versus no reports with placebo (table 3). Hypersensitivity reactions occurred in 1–2% of participants given tirzepatide and 1% with placebo; no systemic hypersensitivity events were reported. No hypersensitivity cases and injection site reactions were severe or serious and none of the cases led to discontinuation of study drug. Overall, there was no evidence of a diminished effect of tirzepatide in tirzepatide pharmacokinetics or HbA_{1c}. None of the participants who showed treatment-emergent antidrug antibody-positivity had severe or serious hypersensitivity or injection site reactions (data not shown).

Overall, results from the treatment-regimen estimand for HbA_{1c}, fasting serum glucose, bodyweight, and proportion of participants reaching HbA_{1c} targets and weight loss aims were similar to those reported from the efficacy estimand (appendix pp 14–15).

Discussion

SURPASS-1 showed significant improvement in glycaemic control and robust bodyweight reductions with all three tirzepatide doses compared with placebo in people with type 2 diabetes treated with diet and exercise alone. Importantly, 87–92% of participants given tirzepatide reached the American Diabetes Association (ADA)-recommended HbA_{1c} target of less than 7·0% (<53 mmol/mol). Furthermore, 31–52% of participants reached normoglycaemia (HbA_{1c} <5·7% [<39 mmol/mol]) without an increased risk of clinically significant (<54 mg/dL [<3 mmol/L]) or severe hypoglycaemia. This result was further supported by the significant improvements in fasting serum glucose and SMBG profiles towards the normal range, which were observed as early as 12 weeks after study initiation and were maintained at 40 weeks. The marked improvement in postprandial hyperglycaemia observed in SMBG data are probably achieved by the role of tirzepatide in glucose-dependent insulin secretion and are likely to be unrelated to slowed gastric emptying given the persistence of improved postprandial hyperglycaemia at 40 weeks, well after the transient effect of tirzepatide in delaying gastric emptying has waned.[13,14]

In addition to robust glycaemic effects, significant, dose-dependent weight reductions were observed at 40 weeks, with 13–27% of the participants given tirzepatide having a 15% or greater weight loss versus none with placebo. Importantly, 67–78% of participants given tirzepatide reached the ADA-recommend weight loss of 5% or greater in individuals with type 2 diabetes and obesity,[1,2] versus 14% of participants in the placebo group, probably due to the placebo effect. Weight loss occurred irrespective of participants reporting gastrointestinal adverse events and did not plateau over time.

In this study, HbA_{1c} reduction plateaued at around 20 weeks, whereas weight reductions were progressive during the trial, suggesting that HbA_{1c} improved via both weight-dependent and weight-independent mechanisms. A mechanism of action study is ongoing, which will help to further elucidate the relationship between HbA_{1c} and bodyweight reduction (NCT03951753).

Similarly, GLP-1 receptor agonist monotherapy trials evaluating dulaglutide injection (0·75 mg and 1·5 mg once a week), semaglutide injection (0·5 mg and 1·0 mg once a week), and oral semaglutide (7 mg and 14 mg once a day) also showed small differences in HbA_{1c} reduction with the higher doses of each drug (an increase of around 0·1–0·2%).[15–17] Compared with other incretin-based monotherapy trials, our results showed a higher proportion of participants reaching HbA_{1c} targets of less than 7·0%[1] or 6·5% or less[18,19] with tirzepatide treatment. The proportion of participants with HbA_{1c} concentrations of less than 7·0% was 87–92% for tirzepatide (5, 10, and 15 mg), 63% for exenatide once a week (2·0 mg),[20] 61–63% for dulaglutide (0·75 mg and 1·5 mg),[15] and 72–74% for semaglutide once a week (0·5 mg and 1·0 mg).[16]

Near-normalisation or complete normalisation of glucose concentrations (HbA_{1c} <5·7%) without increasing hypoglycaemic risk is expected to further reduce the risk of complications. An analysis of UK Prospective Diabetes Study data reported a continuous association of microvascular and macrovascular diabetes complications with the lowest risk being in those with HbA_{1c} values in the normal range (<6·0%).[21] Newer, glucose-dependent, glucose-lowering agents (such as tirzepatide) that safely lower HbA_{1c} without increasing the risk of hypoglycaemia could help to reduce long-term microvascular and macrovascular complications. The ongoing trial SURPASS-CVOT (NCT04255433) of tirzepatide versus dulaglutide 1·5 mg will help to shed light on the potential clinical relevance of reaching and maintaining near-normoglycaemia in type 2 diabetes management and the effect of tirzepatide on cardiovascular outcomes.

In SURPASS-1, tirzepatide treatment resulted in robust HbA_{1c} reductions in a population with early type 2 diabetes and 54% of participants were naive to any diabetes treatment, thus the legacy effect of tirzepatide remains to be investigated. Furthermore, we observed favourable changes in fasting lipids, insulin sensitivity, and systolic blood pressure with tirzepatide. The cardiovascular effects of GIP receptor agonism are under debate and are being assessed.[9]

Robust HbA_{1c} reductions with tirzepatide 5 mg observed in this study are likely to be related to the relatively early course of type 2 diabetes in the participants studied and the greater preservation of pancreatic β cell function expected in this population. All three tirzepatide doses

leading to near-normoglycaemia (mean HbA_{1c} of 5·9–6·1%) at 40 weeks and presumably reaching a floor effect (ie, reaching HbA_{1c} values within the normal range) with no room for further reductions might explain the absence of apparent dose-response on HbA_{1c} reductions. Similarly, a less pronounced dose-response has also been observed in GLP-1 receptor agonist monotherapy trials with lesser glucose-lowering effects.[15–17,20]

The safety profile in the SURPASS-1 trial was similar to that of selective GLP-1 receptor agonists with gastrointestinal side-effects as the most frequently reported adverse events. The optimised slow dose escalation scheme used in the phase 3 programme resulted in an improved tolerability profile compared with the phase 2 studies.[10,12] Overall, gastrointestinal adverse events were reported more frequently in the tirzepatide groups than for placebo. Increases in pulse rate reported in this study were consistent with previous data for GLP-1 receptor agonists.[15,16,20,22] Reductions in ALT and AST were also observed with tirzepatide, supporting the potential role of tirzepatide in fatty liver disease.[23] No clinically relevant changes in mean calcitonin concentrations were observed and no cases of medullary thyroid cancer were reported. Of note, there were no signals of hyperplasia or neoplasia in the thyroid of rats or monkeys administered tirzepatide for up to 6 months in duration or in a 6-month carcinogenicity study in rasH2 mice (unpublished). A 2-year carcinogenicity study in rats is ongoing.

For **details** see https://vivli.org/

One limitation of the SURPASS-1 trial was the relatively short duration of 40 weeks. A longer study duration could provide further insights on the full weight loss effects of tirzepatide. Additionally, gastrointestinal adverse events were self-reported. Study strengths include the randomised, placebo-controlled design with use of a placebo single dose pen that was similar in appearance to the tirzepatide single dose pen.

In conclusion, tirzepatide once a week, a novel dual GIP and GLP-1 receptor agonist, at doses of 5, 10, and 15 mg as monotherapy for type 2 diabetes, showed robust reductions compared with placebo in glycaemic control with 31–52% of participants reaching normoglycaemia (HbA_{1c} <5·7% [<39 mmol/mol]), and meaningful reductions in bodyweight, without increased risk of clinically significant (<54 mg/dL [<3 mmol/L]) or severe hypoglycaemia, and a safety profile consistent with GLP-1 receptor agonists, indicating a potential use of tirzepatide as an option for type 2 diabetes treatment.

Contributors

VTT, LFL, and XC contributed to the study design. JR, VTT, LFL, and CJL conducted and provided medical oversight during the trial. XC and HM were responsible for the statistical analyses. CJL, LFL, HM, XC, CAK, and VTT 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 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.

Declarations of interest

CJL, LFL, HM, XC, CAK, and VTT are employees and shareholders of Eli Lilly and Company. JR serves on scientific advisory boards and received honoraria or consulting fees from Applied Therapeutics, Eli Lilly and Company, Sanofi, Novo Nordisk, Hanmi, Oramed, Boehringer Ingelheim, and Intarcia; and also received grants and research support from Applied Therapeutics, Merck, Pfizer, Sanofi, Novo Nordisk, Eli Lilly and Company, GlaxoSmithKline, Genentech, Hanmi, Oramed, Janssen, Lexicon, Boehringer Ingelheim, and Intarcia. CW has received consulting and advisory board fees from AstraZeneca, Janssen, and Sanofi; research support from AstraZeneca and Novo Nordisk; and speaker fees from AstraZeneca, Boehringer Ingelheim, Eli Lilly and Company, Janssen, Novo Nordisk, and Sanofi. JPF declares grants from Eli Lilly and Company, AbbVie, Akcea, Allergan, AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, Cirius, CymaBay, Enanta, Genentech, Intercept, Janssen, Johnson and Johnson, Lexicon, Ligand, Madrigal, Merck, Mylan, NGM Biopharmaceuticals, Novartis, Novo Nordisk, Pfizer, Sanofi, and Theracos; has served on advisory boards and received consulting fees from Boehringer Ingelheim, Gilead, Johnson and Johnson, Eli Lilly and Company, Merck, Novo Nordisk, and Sanofi; and served on a speaker bureau for Merck and Sanofi. SK received research support from Novo Nordisk, Poxel SA, and Eli Lilly Japan; received honoraria for lectures from Sumitomo Dainippon Pharma, Novo Nordisk, Eli Lilly Japan, AstraZeneca, Boehringer Ingelheim, and Mitsubishi Tanabe Pharma; and received consulting and advisory board fees from Novo Nordisk.

Data sharing

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

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