Efficacy and safety of tirzepatide monotherapy compared with dulaglutide in Japanese patients with type 2 diabetes (SURPASS J-mono): a double-blind, multicentre, randomised, phase 3 trial

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Summary

Background As the disease progresses, many patients with type 2 diabetes have difficulty in reaching treatment goals. We aimed to assess the efficacy and safety of tirzepatide, a novel GIP and GLP-1 receptor agonist, compared with dulaglutide in Japanese patients with type 2 diabetes.

Methods This multicentre, randomised, double-blind, parallel, active-controlled, phase 3 trial was conducted in 46 medical research centres and hospitals in Japan. Adults aged 20 years or older with type 2 diabetes who had discontinued oral antihyperglycaemic monotherapy or were treatment-naïve were included. Participants were randomly assigned (1:1:1:1) to receive tirzepatide (5, 10, or 15 mg) or dulaglutide (0·75 mg) once per week using a computer-generated random sequence with an Interactive Web Response System. Participants were stratified based on baseline HbA_{1c} (≤8·5% or >8·5%), baseline BMI (<25 or ≥25 kg/m²), and washout of antidiabetic medication. Participants, investigators, and the sponsor were masked to treatment assignment. The starting dose of tirzepatide was 2·5 mg once per week for 4 weeks, which was then increased to 5 mg in the tirzepatide 5 mg treatment group. For the tirzepatide 10 and 15 mg treatment groups, increases by 2·5 mg occurred once every 4 weeks until the assigned dose was reached. The primary endpoint was mean change in HbA_{1c} from baseline at week 52 measured in the modified intention-to-treat population. This trial is registered with ClinicalTrials.gov, NCT03861052.

Findings Between May 7, 2019, and March 31, 2021, 821 participants were assessed for study eligibility and 636 were randomly assigned to receive at least one dose of tirzepatide 5 mg (n=159), 10 mg (n=158), or 15 mg (n=160), or dulaglutide 0·75 mg (n=159). 615 (97%) participants completed the study and 21 (3%) discontinued. Participants had a mean age of 56·6 years (SD 10·3) and were mostly male (481 [76%]). At week 52, HbA_{1c} decreased from baseline by a least squares mean of –2·4 (SE 0·1) for tirzepatide 5 mg, –2·6 (0·1) for tirzepatide 10 mg, –2·8 (0·1) for tirzepatide 15 mg, and –1·3 (0·1) for dulaglutide. Estimated mean treatment differences versus dulaglutide were –1·1 (95% CI –1·3 to –0·9) for tirzepatide 5 mg, –1·3 (–1·5 to –1·1) for tirzepatide 10 mg, and –1·5 (–1·71 to –1·4) for tirzepatide 15 mg (all p<0·0001). Tirzepatide was associated with dose-dependent reductions in bodyweight with a least square mean difference of –5·8 kg (SE 0·4; –7·8% reduction) for 5 mg, –8·5 kg (0·4; –11·0% reduction) for 10 mg, and –10·7 kg (0·4; –13·9% reduction) for 15 mg of tirzepatide compared with –0·5 kg (0·4; –0·7% reduction) for dulaglutide. The most common treatment-emergent adverse events were nausea (19 [12%] participants in the 5 mg group *vs* 31 [20%] in the 10 mg group *vs* 32 [20%] in the 15 mg group all receiving tirzepatide *vs* 12 (8%) in the group receiving dulaglutide), constipation (24 [15%] *vs* 28 [18%] *vs* 22 [14%] *vs* 17 [11%]), and nasopharyngitis (29 [18%] *vs* 25 [16%] *vs* 22 [14%] *vs* 26 [16%]). The most frequent adverse events were gastrointestinal (23 [4%] of 636).

Interpretation Tirzepatide was superior compared with dulaglutide for glycaemic control and reduction in bodyweight. The safety profile of tirzepatide was consistent with that of GLP-1 receptor agonists, indicating a potential therapeutic use in Japanese patients with type 2 diabetes.

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Introduction

The incretin hormones, GIP and GLP-1, are secreted from the intestine after ingestion of glucose and other nutrients and directly stimulate insulin secretion from the pancreas.[1,2] GLP-1 has well established effects on insulin stimulation in hyperglycaemia, suppression of glucagon hypersecretion, and deceleration of gastric emptying which reduces post-meal glycaemic excursions.[3] Similar to GLP-1, GIP enhances glucose-dependent insulin secretion[1,2] and might improve insulin sensitivity in people with obesity.[4]

Oral glucose elicits a greater insulin secretory response than intravenous glucose administration despite a similar increase in plasma glucose concentration.[5] This response

Research in context

Evidence before this study

We searched PubMed for articles published from database inception to Sept 27, 2021, using the terms "tirzepatide", "liraglutide", "exenatide", "lixisenatide", "dulaglutide", "albiglutide", "semaglutide", "glucose-dependent insulinotropic polypeptide", "glucagon-like peptide 1 receptor agonist", "type 2 diabetes mellitus", and "Japan", with no language restrictions. The study design was based on evidence from clinical development of tirzepatide, including in vitro and preclinical studies, phase 1 single and multiple dose-escalation pharmacokinetic and pharmacodynamic studies, a phase 1 multiple ascending dose in Japanese participants, a phase 2 efficacy and safety trial, and a phase 2 dose-escalation trial. Several long-acting GLP-1 receptor agonists are approved for the treatment of type 2 diabetes. Tirzepatide is a novel GIP and GLP-1 receptor agonist, administered once per week, with potential therapeutic benefits for the treatment of patients with type 2 diabetes. It has shown clinically meaningful improvements in HbA_{1c} and bodyweight in phase 3 trials, with a similar safety profile to that of a GLP-1 receptor agonist.

Added value of this study

To our knowledge, this is the first study examining the efficacy and safety of tirzepatide compared with dulaglutide in a trial recruiting Japanese patients with type 2 diabetes, a population characterised as leaner than those in other high-income countries, such as the USA. Findings from this study showed that treatment with 5, 10, or 15 mg of tirzepatide for 52 weeks resulted in statistically greater reductions in HbA_{1c} and bodyweight than with 0·75 mg of dulaglutide, which is currently the only marketed dose of dulaglutide in Japan. Most participants receiving tirzepatide reached HbA_{1c} targets of less than 7·0% (range 94–99% *vs* 67% of participants receiving dulaglutide 0·75 mg), 6·5% or less (92–97% *vs* 40%), and less than 5·7% (51–79% *vs* 3%). Importantly, HbA_{1c} targets were reached without an increased risk of clinically significant hypoglycaemia. Tirzepatide was associated with dose-dependent reductions in bodyweight ranging from −5·8 kg to −10·7 kg, compared with −0·5 kg for dulaglutide. Most adverse events were mild or moderate, and the most common was nasopharyngitis (range 14–18% *vs* 16% for dulaglutide), nausea (12–20% *vs* 8%), and constipation (14–18% *vs* 11%).

Implications of all the available evidence

The SURPASS J-mono trial showed that tirzepatide significantly improves glycaemic control and reduces bodyweight compared with dulaglutide in Japanese patients with type 2 diabetes who had discontinued oral antihyperglycemic monotherapy or were treatment-naïve. There was no increased risk of clinically significant or severe hypoglycaemia. The safety profile of tirzepatide was consistent with a GLP-1 receptor agonist, indicating a potential therapeutic use of tirzepatide in this population.

is known as the incretin effect. In healthy individuals with normal glucose tolerance, GIP plays an important role in the incretin effect, generating a more substantial impact on insulin secretion compared with GLP-1.[6] Although secretion of incretin hormones is maintained in patients with type 2 diabetes, the incretin effect is diminished or absent.[6,7]

Dulaglutide, a once per week selective GLP-1 receptor agonist, was approved for the treatment of type 2 diabetes in Japan in 2015. In a phase 3 clinical trial[8] in Japan, dulaglutide 0·75 mg reduced HbA_{1c} by 1·39% (from 8·15% at baseline to 6·74% at week 52) after 52 weeks and was well tolerated with an acceptable safety profile. Dulaglutide has since become the most prescribed GLP-1 receptor agonist in Japanese clinical practice.[9]

Multifunctional peptides with GIP and GLP-1 activity have been suggested as novel therapeutic agents for glycaemic and weight control. Tirzepatide is a GIP and GLP-1 receptor agonist, combining the effects of both incretins into a single molecule. This 39 amino acid synthetic peptide is engineered from the GIP sequence and includes a C20 fatty diacid moiety, which assists with half-life extension (half-life of approximately 5 days), thus allowing subcutaneous administration once per week.[10] Global SURPASS clinical trials[11–15] have collectively shown that administration of tirzepatide (5, 10, and 15 mg) once per week results in clinically meaningful reductions in HbA_{1c} and bodyweight in a non-Asian population.

Here, we aimed to assess the efficacy and safety of tirzepatide compared with dulaglutide in Japanese patients with type 2 diabetes who discontinued oral antihyperglycemic monotherapy or were treatment-naïve.

Methods

Study design and participants

This multicentre, randomised, double-blind, parallel, active-controlled, phase 3 trial was conducted in 46 medical research centres and hospitals in Japan. Participants were adults aged 20 years or older diagnosed with type 2 diabetes on the basis of WHO classification at least 8 weeks before the screening visit, antihyperglycaemic medication-naïve (only controlled diabetes with diet and exercise; HbA_{1c} ≥7·0% and ≤10·0% at screening) or receiving antihyperglycaemic monotherapy (except for thiazolidinedione; HbA_{1c} 6·5–9·0% at visit 1 and 7·0–10·0% at visit 2) and willing to discontinue the medication with an 8-week washout period before visit 2, stable weight (change not higher than 5%) for 3 months before visit 1, BMI of 23 kg/m^2 or higher at visit 1, and agreed not to initiate an intensive diet or exercise

programme (or both) during the study. Key exclusion criteria included type 1 diabetes, history of any use of an injectable therapy for type 2 diabetes, chronic or acute pancreatitis, proliferative diabetic retinopathy, diabetic maculopathy, non-proliferative diabetic retinopathy requiring acute treatment, acute or chronic hepatitis, and an estimated glomerular filtration rate of less than 30 mL/min per 1·73 m². A full list of eligibility criteria is shown in the appendix 2 (pp 2–3).

All participants provided written informed consent. This trial was conducted in accordance with the Declaration of Helsinki and International Ethical Guidelines by the Council for International Organizations of Medical Sciences. The protocol and its amendments (appendix 3 p 78) was approved by local institutional review boards (appendix 2 pp 31–35).

Randomisation and masking

Participants were randomly assigned (1:1:1:1) by the investigator to receive tirzepatide (5, 10, or 15 mg) or dulaglutide (0·75 mg) using a computer-generated random sequence with an Interactive Web Response System (appendix 2 p 4). Participants were stratified based on baseline HbA_{1c} (≤8·5% or >8·5%), baseline BMI (<25 or ≥25 kg/m²), and washout of antidiabetic medication (yes or no). Participants, investigators, and the sponsor were masked to treatment assignment. The randomisation data was only accessed by a small number of personnel.

Procedures

Following a 4-week (for antihyperglycaemic medication-naïve participants) or 10-week (for those with at least 8-week antihyperglycaemic medication washout) lead-in period, subcutaneous injections of tirzepatide or dulaglutide were given once per week for 52 weeks, followed by a 4-week safety follow-up period (appendix 2 p 26). The starting dose of tirzepatide was 2·5 mg once per week for 4 weeks in all tirzepatide groups. This dose was increased to 5 mg once per week for the duration of the study in the tirzepatide 5 mg treatment group. For the tirzepatide 10 and 15 mg treatment groups, increases by 2·5 mg once every 4 weeks occurred until the assigned dose was reached and maintained for the duration of the trial. Dulaglutide was administered at 0·75 mg once per week. All study drugs were administered using unified single-use pens with identical injection volumes (0·5 mL). Participants were advised to administer the injections on the same day and at the same time each week. Participants were permitted to use required concomitant medications during the study except for those that could interfere with the study treatments, such as antihyperglycaemic medications, weight loss medications, and chronic systemic glucocorticoid therapies. Clinical assessments and laboratory tests were performed at each study visit as outlined in the protocol (appendix 3 pp 14–16).

Outcomes

The primary endpoint was mean change in HbA_{1c} from baseline at week 52 measured in the modified intention-to-treat population. Secondary efficacy endpoints were measured in the modified intention-to-treat population and included mean change in HbA_{1c}, fasting serum glucose (FSG), seven-point self-monitored blood glucose profiles, bodyweight, fasting insulin, fasting C-peptide, triglycerides, total cholesterol, very low-density lipoprotein cholesterol, and low-density lipoprotein cholesterol, updated Homeostasis Model Assessment (HOMA2), the proportion of participants reaching HbA_{1c} targets (<7·0%, ≤6·5%, and <5·7%), and the proportion of participants with weight loss (≥5%, ≥10%, and ≥15%). Safety endpoints were the incidence of patient-reported treatment-emergent adverse events, discontinuation of the study drug due to adverse events, adjudicated deaths and non-fatal major cardiovascular events, adjudicated pancreatic adverse events, incidence of injection site reactions, change in systolic or diastolic blood pressure and heart rate from baseline, and occurrence of hypoglycaemic episodes. The diagnosis of acute pancreatitis required two of the following three features: abdominal pain, characteristic of acute pancreatitis; serum amylase (total or pancreatic, or both) or lipase (or both) at least three times higher than the upper limit of normal; and characteristic findings of acute pancreatitis on CT or MRI. Blood sampling for laboratory tests and measurements for vital sign assessments were taken in the fasted state.

See Online for appendix 2

See Online for appendix 3

Statistical analysis

The sample size calculation assumed that up to 15% of participants will initiate rescue medication or discontinue treatment; at least 0·5% (tirzepatide 15 mg), 0·5% (tirzepatide 10 mg), and 0·4% (tirzepatide 5 mg) will have a superior mean reduction in HbA_{1c} (ie, a clinically meaningful difference) at week 52 compared with dulaglutide 0·75 mg; and participants will have a common SD of 1·0%. We estimated that 636 participants in total with 159 participants randomly assigned to each group provided at least 90% power to establish superiority of tirzepatide at 10 mg and 15 mg over dulaglutide 0·75 mg at a two-sided significance level of 0·025, followed by superiority of tirzepatide 5 mg over dulaglutide 0·75 mg only when superiority of tirzepatide at 10 mg or 15 mg was declared.

Efficacy and safety were assessed using the modified intention-to-treat population (defined as all randomly assigned participants who received at least one dose of the study drug). Two estimands were used to assess treatment efficacy from different perspectives. The efficacy estimand represents efficacy among all randomly assigned patients who continued to receive tirzepatide or dulaglutide without rescue medication (efficacy analysis set) and was used for the primary efficacy assessment. The treatment regimen estimand represents efficacy irrespective of study

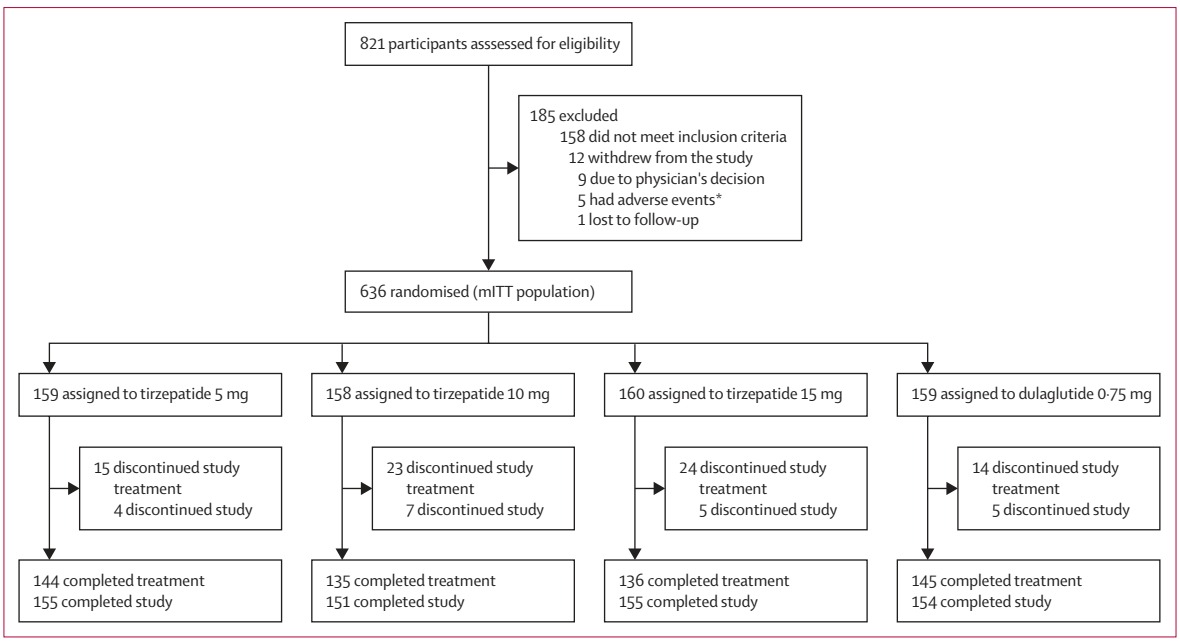

Figure 1: **Trial profile**
Primary efficacy analyses were based on the mITT population (defined as all randomly assigned patients who received at least one dose of the study drug). Reasons for study treatment discontinuation before the primary endpoint visit were adverse events (n=53), loss to follow-up (n=1), withdrawal (n=12), physician's decision (n=5), protocol deviation (n=4), or other (n=1; relocation to a new city; appendix 2 p 6). mITT=modified intention-to-treat. *Occurred before randomisation (unrelated to study drug; n=1 of each: positive for influenza A virus, fracture of lower epiphysis of femur, hyperglycaemia, cerebral infarction, and suspected acute pancreatitis).

drug discontinuation and use of rescue medication (appendix 2 p 7). All the reported results are for the efficacy estimand. Database, data handling procedures, and additional statistical analyses methods are described in the appendix 2 (pp 4–5).

Type 1 error rate was controlled at a level of 0·05 within each estimand for evaluation of change from baseline in HbA_{1c} and bodyweight via a graphical testing approach (appendix 2 pp 5, 29). All tests of treatment effect were conducted at a two-sided α level of 0·05, with 95% CIs. Summary statistics for continuous measures included sample size, mean (SD), median (IQR). The analysis model for comparisons between treatment groups relative to continuous measurements was the mixed model repeated measures. A restricted maximum likelihood repeated measures approach was used in combination with Kenward-Roger approximation to analyse change from baseline in HbA_{1c}. For binary efficacy measurements, the logistic regression was used with missing values imputed from mixed model repeated measures and then dichotomised. Missing data were implicitly handled or imputed from the mixed model repeated measures under the assumption of missing at random. An unstructured covariance structure was used to model within-patient errors (appendix 2 p 5). The safety analysis was conducted on the safety analysis set using a modified intention-to-treat population with all data from the start of treatment to the end of safety follow-up, regardless of adherence to the study drug or initiation of rescue therapy. Statistical analysis was done using SAS (version 9.4). This trial is registered with ClinicalTrials.gov, NCT03861052.

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 May 7, 2019, and March 31, 2021, 821 participants were assessed for study eligibility and 636 were randomly assigned to receive at least one dose of tirzepatide 5 mg (n=159), tirzepatide 10 mg (n=158), tirzepatide 15 mg (n=160), or dulaglutide 0·75 mg (n=159; figure 1). 615 (97%) participants completed the study and 21 (3%) discontinued before the primary endpoint visit due to withdrawal from the study, an adverse event, loss to follow up, or physician decision. 62 (13%) participants in the tirzepatide groups and 14 (9%) in the dulaglutide group discontinued the study drug (appendix 2 p 6). Withdrawal of the study drug due to adverse events, primarily gastrointestinal-related, was higher in the tirzepatide 10 mg (16 [10%] of 158) and 15 mg (16 [10%] of 160) groups than the tirzepatide 5 mg (12 [8%] of 159) and dulaglutide (nine [6%] of 159) groups. Discontinuation of the study drug for non-adverse event reasons included loss to follow-up, withdrawal, physician's decision, protocol deviation, or other.

	Tirzepatide 5 mg (n=159)	Tirzepatide 10 mg (n=158)	Tirzepatide 15 mg (n=160)	Dulaglutide 0·75 mg (n=159)	Total (n=636)
Age, years	56·8 (10·1)	56·2 (10·3)	56·0 (10·7)	57·5 (10·2)	56·6 (10·3)
Sex					
Male	113 (71%)	119 (75%)	132 (83%)	117 (74%)	481 (76%)
Female	46 (29%)	39 (25%)	28 (18%)	42 (26%)	155 (24%)
Japanese	159 (100%)	158 (100%)	160 (100%)	159 (100%)	636 (100%)
Bodyweight, kg	78·5 (16·3)	78·9 (13·7)	78·9 (14·3)	76·5 (13·2)	78·2 (14·5)
BMI, kg/m²	28·6 (5·4)	28·0 (4·1)	28·1 (4·4)	27·8 (3·7)	28·1 (4·4)
Duration of type 2 diabetes, years	4·5 (2·1–7·5)	5·1 (2·2–8·4)	5·1 (2·2–8·4)	5·0 (1·9–8·4)	4·8 (2·1–8·3)
Fasting serum glucose concentration					
mg/dL	159 (142–185)	159 (138–183)	162 (141–194)	159 (139–180)	160 (140–187)
mmol/L	8·8 (7·9–10·3)	8·8 (7·7–10·2)	9·0 (7·8–10·8)	8·8 (7·7–10·0)	8·9 (7·8–10·4)
HbA_{1c} concentration					
%	8·2 (0·9)	8·2 (0·9)	8·2 (0·9)	8·2 (0·9)	8·2 (0·9)
mmol/mol	65·9 (9·7)	66·0 (9·4)	66·1 (9·7)	65·6 (9·4)	65·9 (9·5)
≤8·5%	108 (68%)	106 (67%)	109 (68%)	110 (69%)	433 (68%)
>8·5%	51 (32%)	52 (33%)	51 (32%)	49 (31%)	203 (32%)
eGFR, mL/min per 1·73 m²	78 (68–86)	80 (72–86)	80 (71–86)	79 (71–86)	79 (71–86)
Systolic blood pressure, mm Hg	130·2 (12·7)	130·0 (15·6)	132·2 (13·8)	130·6 (15·4)	130·8 (14·4)
Diastolic blood pressure, mm Hg	82·4 (9·7)	82·6 (10·0)	83·9 (10·0)	82·1 (10·2)	82·8 (9·9)
Pulse rate, beats per min	72·8 (10·8)	72·9 (10·2)	72·8 (9·7)	73·0 (10·8)	72·9 (10·3)
Washout of antidiabetic medication					
Yes	63 (40%)	64 (41%)	64 (40%)	61 (38%)	252 (40%)
No	96 (60%)	94 (60%)	96 (60%)	98 (62%)	384 (60%)

Data are mean (SD), median (IQR), or n (%). Percentages might not equal to 100% as a result of rounding. Ethnicity data were not collected. eGFR=estimated glomerular filtration rate.

Table 1: **Baseline characteristics**

Baseline demographic and clinical or disease-related characteristics were similar across treatment groups (table 1). Participants had a mean age of 56·6 years (SD 10·3) and were mostly male (481 [76%]). The median duration of diabetes was 4·8 years (IQR 2·1–8·3), mean BMI of 28·1 kg/m² (SD 4·4), and mean HbA_{1c} at baseline of 8·2% (0·9; table 1).

At week 52, HbA_{1c} decreased from baseline by a least squares mean of –2·4 (SE 0·1) for tirzepatide 5 mg, –2·6 (0·1) for tirzepatide 10 mg, –2·8 (0·1) for tirzepatide 15 mg, and –1·3 (0·1) for dulaglutide (table 2). Estimated mean treatment differences versus dulaglutide were –1·1 (95% CI –1·3 to –0·9) for tirzepatide 5 mg, –1·3 (–1·5 to –1·1) for tirzepatide 10 mg, and –1·5 (–1·7 to –1·4) for tirzepatide 15 mg (all p<0·0001; figure 2B; table 2; appendix 2 pp 8–9). Participants in tirzepatide groups had statistically significant mean reductions in HbA_{1c} from baseline compared with those in the dulaglutide group, which began at week 4, were near the maximum around week 24, and were maintained until week 52. At week 52, mean HbA_{1c} was 5·8% (40 mmol/mol) for 5 mg, 5·6% (38 mmol/mol) for 10 mg, and 5·4% (35 mmol/mol) for 15 mg of tirzepatide compared with 6·9% (52 mmol/mol) for dulaglutide (figure 2A).

A significantly higher proportion of participants receiving tirzepatide at any dose reached HbA_{1c} targets compared with those receiving dulaglutide (457 [97%] of 473 in tirzepatide groups *vs* 107 [67%] of 159 in the dulaglutide group reached HbA_{1c} <7·0%; 450 [95%] *vs* 64 [40%] reached HbA_{1c} ≤6·5%; and 297 [63%] *vs* four [3%] reached HbA_{1c} <5·7%; figure 2C; appendix 2 p 10).

At baseline, mean FSG values were similar across treatment groups. At week 52, mean FSG was 109·2 mg/dL (SE 1·7) for 5 mg, 102·5 mg/dL (1·8) for 10 mg, and 99·5 mg/dL (1·8) for 15 mg of tirzepatide, and 135·2 mg/dL (1·7) for dulaglutide (figure 2D). At week 52, FSG had a statistically significant decrease from baseline in all treatment groups; least squares mean of –57·9 mg/dL (SE 1·7) for 5 mg, –64·6 mg/dL (1·8) for 10 mg, and –67·6 mg/dL (1·8) for 15 mg of tirzepatide, and –31·9 mg/dL (1·7) for dulaglutide (table 2; appendix 2 pp 10–11). Compared with dulaglutide, estimated mean treatment differences were –25·9 mg/dL (95% CI –30·7 to –21·1) for 5 mg, –32·7 mg/dL (–37·5 to –27·8) for 10 mg, and –35·7 mg/dL (–40·6 to –30·9) for 15 mg of tirzepatide (all p<0·0001; table 2; appendix 2 p 11). Mean change from baseline in FSG, and estimated treatment differences in FSG are shown in the appendix 2 (pp 10–11, 27).

Seven-point self-monitored blood glucose showed lower glucose values at all timepoints than at baseline for all treatment groups. At week 52, treatment with all

	Tirzepatide 5 mg (n=159)		Tirzepatide 10 mg (n=158)		Tirzepatide 15 mg (n=160)		Dulaglutide 0·75 mg (n=159)	
	Mean	p value	Mean	p value	Mean	p value	Mean	p value
HbA_{1c}, %								
Baseline	8·2 (0·1)	..	8·2 (0·1)	..	8·2 (0·1)	..	8·2 (0·1)	..
Change from baseline	−2·4 (0·1)	..	−2·6 (0·1)	..	−2·8 (0·1)	..	−1·3 (0·1)	..
Versus dulaglutide	−1·1 (−1·3 to −0·9)	<0·0001	−1·3 (−1·5 to −1·1)	<0·0001	−1·5 (−1·7 to −1·4)	<0·0001	..	..
Participants with HbA_{1c} <7·0%	148/158 (94%)	..	151/156 (97%)	..	158/159 (99%)	..	107/159 (67%)	..
Participants with HbA_{1c} ≤6·5%	146/158 (92%)	..	150/156 (96%)	..	154/159 (97%)	..	64/159 (40%)	..
Participants with HbA_{1c} <5·7%	81/158 (51%)	..	91/156 (58%)	..	125/159 (79%)	..	4/159 (3%)	..
HbA_{1c}, mmol/mol								
Baseline	65·8 (0·8)	..	66·1 (0·8)	..	66·1 (0·8)	..	65·6 (0·8)	..
Change from baseline	−26·0 (0·7)	..	−27·9 (0·7)	..	−30·8 (0·7)	..	−14·1 (0·1)	..
Versus dulaglutide	−11·9 (−13·9 to −9·9)	<0·0001	−13·8 (−15·8 to −11·8)	<0·0001	−16·7 (−18·7 to −14·7)	<0·0001	..	..
Fasting serum glucose, mg/dL								
Baseline	166·6 (3·1)	..	165·6 (3·1)	..	173·0 (3·1)	..	163·3 (3·1)	..
Change from baseline	−57·9 (1·7)	..	−64·4 (1·8)	..	−67·6 (1·8)	..	−31·9 (1·7)	..
Versus dulaglutide	−25·9 (−30·7 to −21·1)	<0·0001	−32·7 (−37·5 to −27·8)	<0·0001	−35·7 (−40·6 to −30·9)	<0·0001	..	..
Fasting serum glucose, mmol/L								
Baseline	9·3 (0·2)	..	9·2 (0·2)	..	9·6 (0·2)	..	9·1 (0·2)	..
Change from baseline	−3·2 (0·1)	..	−3·6 (0·1)	..	−3·8 (0·1)	..	−1·8 (0·1)	..
Versus dulaglutide	−1·4 (−1·7 to −1·2)	<0·0001	−1·8 (−2·1 to −1·5)	<0·0001	−2·0 (−2·3 to −1·7)	<0·0001	..	..
Bodyweight, kg								
Baseline	78·6 (1·2)	..	79·1 (1·2)	..	78·9 (1·2)	..	76·5 (1·2)	..
Change from baseline	−5·8 (0·4)	..	−8·5 (0·4)	..	−10·7 (0·4)	..	−0·5 (0·4)	..
Versus dulaglutide	−5·2 (−6·4 to −4·1)	<0·0001	−7·9 (−9·1 to −6·8)	<0·0001	−10·1 (−11·3 to −9·0)	<0·0001	..	..
Participants with ≥5% weight loss	96/158 (61%)	..	128/156 (82%)	..	142/159 (89%)	..	17/159 (11%)	..
Participants with ≥10% weight loss	54/158 (34%)	..	78/156 (50%)	..	106/159 (67%)	..	5/159 (3%)	..
Participants with ≥15% weight loss	26/158 (16%)	..	40/156 (26%)	..	71/159 (45%)	..	1/159 (<1%)	..

Data are least squares mean (SE or 95% CIs), or n/N (%). Denominators are the numbers of participants with baseline and postbaseline values available at the specified timepoint.

Table 2: **Efficacy measures at 52 weeks in the modified intention-to-treat population**

three doses of tirzepatide enabled participants to maintain significantly lower blood glucose concentrations throughout the day than those seen with dulaglutide (figure 2E; appendix 2 pp 12–13). Additionally, postprandial mean self-monitored blood glucose values across all three tirzepatide doses were less than 140 mg/dL, considered within the normal range.

At baseline, mean bodyweight was similar across all groups. At week 52, bodyweight had a statistically significant decrease from baseline in each tirzepatide group, with a least square mean difference of −5·8 kg (SE 0·4; −7·8% reduction) for 5 mg, −8·5 kg (0·4; −11·0% reduction) for 10 mg, and −10·7 kg (0·4; −13·9% reduction) for 15 mg of tirzepatide (figure 3A; table 2; appendix 2 pp 14–15). A non-significant least square mean change of −0·5 kg (−0·7% [0·4]) was observed from baseline for the dulaglutide group. Estimated mean treatment differences in bodyweight were −5·2 kg (95% CI −6·4 to −4·1) for 5 mg, −7·9 kg (−9·1 to −6·8) for 10 mg, and −10·1 kg (−11·3 to −9·0) for 15 mg of tirzepatide versus dulaglutide (all p<0·0001; figure 3B). The reduction in bodyweight was evident at week 4, and the effect of tirzepatide on bodyweight was dose-dependent and maintained until week 52. A significantly greater proportion of participants receiving tirzepatide reached weight loss targets of 5% or higher (61–89% *vs* 11% receiving dulaglutide), 10% or higher (34–67% *vs* 3%), and 15% or higher (17–45% *vs* 1%; figure 3C; appendix 2 pp 15–16). At week 52, mean waist circumference was also reduced with tirzepatide versus dulaglutide (appendix 2 pp 17–18, 28). Findings using the treatment-regimen estimand for HbA_{1c} and bodyweight were similar to those from the efficacy estimand (appendix 2 p 7).

All three doses of tirzepatide significantly reduced triglycerides, total cholesterol, VLDL cholesterol, and LDL cholesterol, and significantly increased HDL cholesterol at week 52 compared with dulaglutide (figure 3D; appendix 2 pp 19–20). At week 52, fasting insulin and C-peptide also showed a statistically significant reduction with all doses of tirzepatide versus dulaglutide. Whereas, HOMA2 insulin sensitivity and β cell function significantly increased with all tirzepatide doses (appendix 2 pp 20–21). The rate of study drug discontinuation due to an adverse event was low (53 [8%] of 636) and similar across all treatment groups (table 3).

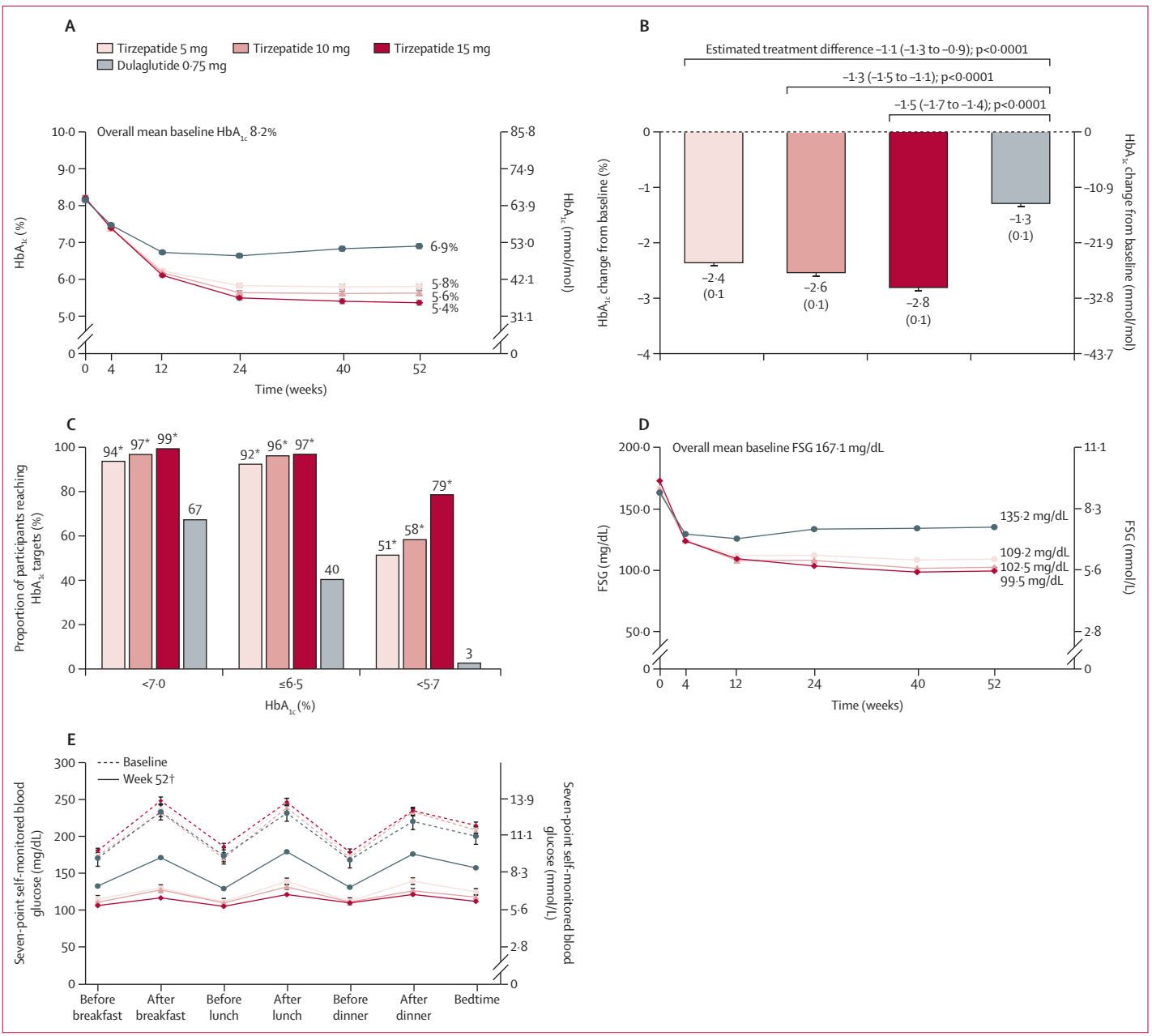

Figure 2: **Participants reaching HbA_{1c} targets, FSG, and seven-point self-monitored blood glucose profiles**

Data are least squares mean (SE), unless stated otherwise. Estimated treatment differences are measured in the modified intention-to-treat population (efficacy analysis set). (A) HbA_{1c} values over time. (B) Change from baseline in HbA_{1c} at 52 weeks. (C) Proportion of participants reaching HbA_{1c} targets (<7·0%, ≤6·5%, and <5·7%) from logistic regression at week 52. (D) FSG values over time. (E) Seven-point self-monitored blood glucose profiles. Bars indicate SE. FSG=fasting serum glucose. *p value of p<0·001 (*vs* dulaglutide 0·75 mg). †At 52 weeks, all tirzepatide treatment groups were significantly lower than the dulaglutide group for each timepoint (p<0·0001 *vs* dulaglutide 0·75 mg).

The proportion of participants reporting treatment-emergent adverse events in the tirzepatide groups (131 [82%] in the 5 mg group, 121 [77%] in the 10 mg group, and 134 [84%] in the 15 mg group) was similar to the dulaglutide group (123 [77%]; table 3). The most frequent adverse events were gastrointestinal (23 [4%] of 636; severity grading shown in the appendix 2 p 22). Of the treatment-emergent adverse events reported by ≥5% of participants in any treatment group, the most common were nausea (19 [12%] participants in the 5 mg group *vs* 31 [20%] in the 10 mg group *vs* 32 [20%] in the 15 mg group all receiving tirzepatide *vs* 12 (8%) in the group receiving dulaglutide), constipation (24 [15%] *vs* 28 [18%] *vs* 22 [14%] *vs* 17 [11%]), and nasopharyngitis (29 [18%] *vs* 25 [16%] *vs* 22 [14%] *vs* 26 [16%]). There were six cases of serious

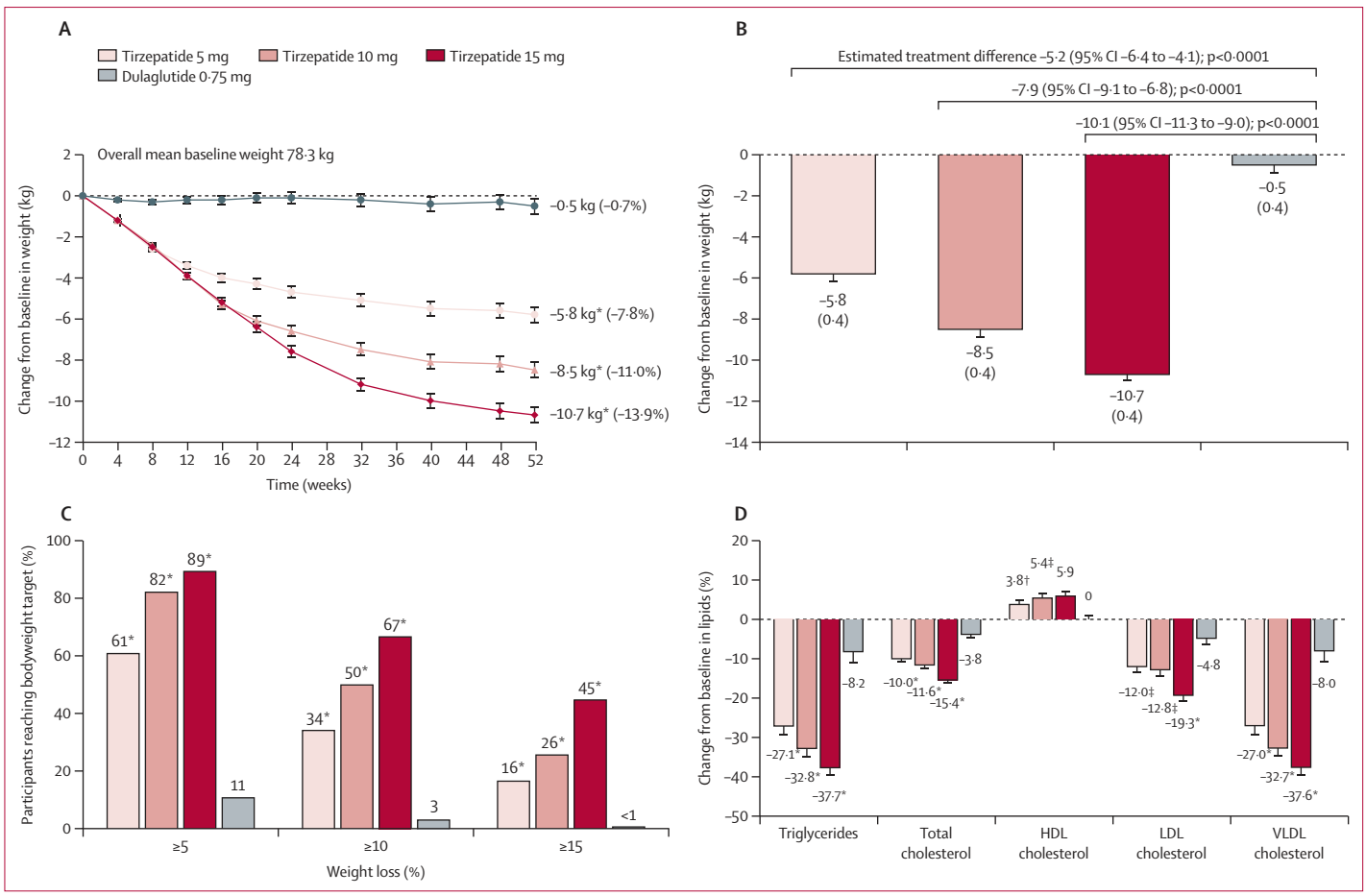

Figure 3: **Effect of tirzepatide on bodyweight, weight loss targets, and lipid profile**
Data are least squares mean (SE), unless stated otherwise. Percentage change from baseline in bodyweight over time (A) and at 52 weeks (B). (C) Proportion of participants reaching bodyweight targets (≥5%, ≥10%, and ≥15%) at week 52. (D) Percentage change in lipids at week 52 from baseline. *p value of p<0·001 (*vs* dulaglutide 0·75 mg). †p value of p<0·05. ‡p value of p<0·01.

gastrointestinal events (one patient with inguinal hernia and one with a rectal polyp in the tirzepatide 5 mg group, one with gastric ulcer in the tirzepatide 10 mg group, one with gastric ulcer haemorrhage and one with a colorectal polyp in the tirzepatide 15 mg group, and one with duodenal ulcer in the dulaglutide group). Most treatment-emergent adverse events were mild or moderate in intensity across all treatment groups. One case of treatment-emergent severe nausea occurred in the 10 mg treatment group, which resulted in withdrawal of the study drug. 12 (2%) participants had 16 treatment-emergent adverse events of arrhythmias and cardiac conduction disorders, all cases were mild in severity. 39 (6%) participants reported 51 serious adverse events. The proportion of participants reporting a serious adverse event was higher in the dulaglutide group (14 [9%] of 159) than in the tirzepatide groups (eight [5%] of 159 in the 5 mg group, ten [6%] of 158 in the 10 mg group, and seven [4%] of 160 in the 15 mg group; appendix 2 p 23–24). There were no deaths reported during the study.

Hyperglycaemia of mild and moderate severity was reported by one participant receiving 5 mg and one receiving 15 mg of tirzepatide (table 3). Nine participants in the dulaglutide treatment group reported hyperglycaemia, of which two were of severe intensity. Eleven participants were prescribed rescue therapy for persistent hyperglycaemia, with six receiving metformin. No severe hypoglycaemia events were reported during the study. Two participants receiving tirzepatide 15 mg had two episodes of clinically significant hypoglycaemia with blood glucose lower than 54 mg/dL (<3·0 mmol/L); neither was considered nocturnal and both continued the study treatment.

One participant receiving tirzepatide 15 mg reported an event adjudicated as acute pancreatitis and asymptomatic lipase increase. The event was mild, non-serious, and assessed by the investigator as unrelated to the study drug. Injection site reactions were reported in six (4%) participants in the 5 mg tirzepatide group, 11 (7%) in the 10 mg tirzepatide group, 13 (8%) in the 15 mg tirzepatide group, and 14 (9%) in the dulaglutide group, all mostly

mild in severity. There were no cases of serious or severe immediate hypersensitivity (occurring within 24 h of study drug administration).

Compared with dulaglutide, a dose-dependent increase in pulse rate was observed in all tirzepatide groups from baseline to week 52 (3·3 beats per min [bpm] to 7·5 bpm; appendix 2 p 25). At week 52, mean systolic blood pressure decreased with tirzepatide treatment (–6·5 to –11·0 mm Hg) versus –1·4 mm Hg with dulaglutide; whereas diastolic blood pressure decreased (–3·2 to –5·6 mm Hg) with tirzepatide compared with an increase of 0·1 mm Hg with dulaglutide. Vital signs and additional safety laboratory measures are shown in the appendix 2 (p 25). The COVID-19 pandemic did not affect the efficacy and safety outcomes of this study (appendix 2 p 30).

Discussion

In this SURPASS J-mono trial, tirzepatide was superior at all three doses compared with dulaglutide in terms of reducing HbA_{1c} at 52 weeks in Japanese patients with type 2 diabetes. Overall, a significantly greater proportion of participants reached HbA_{1c} targets with tirzepatide than with dulaglutide, and the highest proportion was seen in the 15 mg tirzepatide group. Around 98% of participants receiving tirzepatide reached HbA_{1c} targets of less than 7·0% or 6·5% or less, and 79% reached HbA_{1c} of less than 5·7%.

The observed reductions in HbA_{1c} are numerically greater than those observed in the global SURPASS 1–5 studies.[11–15] For example, mean HbA_{1c} decreased with tirzepatide by 1·9% for 5 mg, 1·9% for 10 mg, and 2·1% for 15 mg in SURPASS-1 and by 2·1% for 5 mg, 2·4% for 10 mg, and 2·5% for 15 mg in SURPASS-2.[11,12] In SURPASS J-mono, mean HbA_{1c} decreased from baseline by 2·4% for 5 mg, 2·6% for 10 mg, and 2·8% for 15 mg of tirzepatide. These findings support the observation that the HbA_{1c} lowering efficacy of GLP-1 receptor agonist and DPP-4 inhibitors is greater in Asian compared with White populations.[16,17] Asian patients with type 2 diabetes have less severe obesity and are physiologically characterised by lower β-cell function and a lesser degree of insulin resistance than White populations,[18] which might result in different treatment responses. Incretin-related drugs, such as GLP-1 receptor agonist and DPP-4 inhibitors, enhance the incretin effect and mainly decrease postprandial glucose.

Superiority was also achieved with all three doses of tirzepatide versus dulaglutide in terms of reduction in bodyweight, which was dose-dependent with tirzepatide. Similarly, a significantly greater proportion of participants in all three tirzepatide dose groups reached mean bodyweight reductions (≥5%, ≥10%, or ≥15%) than those in the dulaglutide group, and weight loss targets were greater with the highest dose of tirzepatide. Japanese treatment guidelines recommend 3% weight reduction in people with obesity (BMI >25 kg/m²).[19] A higher proportion of participants receiving tirzepatide reached 5% or greater weight reduction than participants receiving dulaglutide.

	Tirzepatide 5 mg (n=159)	Tirzepatide 10 mg (n=158)	Tirzepatide 15 mg (n=160)	Dulaglutide 0·75 mg (n=159)	Total (n=636)
Summary of adverse events					
Participants with ≥1 treatment-emergent adverse event	131 (82%)	121 (77%)	134 (84%)	123 (77%)	509 (80%)
Serious adverse events	8 (5%)	10 (6%)	7 (4%)	14 (9%)	39 (6%)
Deaths	0	0	0	0	0
Adverse event leading to study drug discontinuation	12 (8%)	16 (10%)	16 (10%)	9 (6%)	53 (8%)
Gastrointestinal disorders	7 (4%)	4 (3%)	11 (7%)	1 (1%)	23 (4%)
Metabolism and nutrition disorders	2 (1%)	3 (2%)	4 (3%)	0	9 (1%)
Neoplasms benign, malignant, and unspecified	1 (1%)	3 (2%)	0	2 (1%)	6 (1%)
General disorders and administration site conditions	0	2 (1%)	0	1 (1%)	3 (1%)
Nervous system disorders	1 (1%)	1 (1%)	0	1 (1%)	3 (1%)
Skin and subcutaneous tissue disorders	1 (1%)	1 (1%)	0	1 (1%)	3 (1%)
Infections and infestations	0	0	0	2 (1%)	2 (<1%)
Cardiac disorders	0	1 (1%)	0	0	1 (<1%)
Treatment-emergent adverse events occurring in ≥5% of participants in any treatment group (preferred term)					
Nasopharyngitis	29 (18%)	25 (16%)	22 (14%)	26 (16%)	102 (16%)
Nausea	19 (12%)	31 (20%)	32 (20%)	12 (8%)	94 (15%)
Constipation	24 (15%)	28 (18%)	22 (14%)	17 (11%)	91 (14%)
Decreased appetite	22 (14%)	21 (13%)	35 (22%)	7 (4%)	85 (13%)
Diarrhoea	27 (17%)	14 (9%)	18 (11%)	11 (7%)	70 (11%)
Vomiting	13 (8%)	8 (5%)	19 (12%)	2 (1%)	42 (7%)
Abdominal discomfort	10 (6%)	11 (7%)	16 (10%)	4 (3%)	41 (6%)
Lipase increased	12 (8%)	7 (4%)	10 (6%)	5 (3%)	34 (5%)
Back pain	8 (5%)	5 (3%)	9 (6%)	7 (4%)	29 (5%)
Dyspepsia	9 (6%)	8 (5%)	10 (6%)	2 (1%)	29 (5%)
Injection site reaction	2 (1%)	5 (3%)	9 (6%)	12 (8%)	28 (4%)
Gastroenteritis	10 (6%)	2 (1%)	8 (5%)	4 (3%)	24 (4%)
Headache	8 (5%)	8 (5%)	2 (1%)	6 (4%)	24 (4%)
Amylase increased	8 (5%)	3 (2%)	5 (3%)	1 (1%)	17 (3%)
Hyperglycaemia	1 (1%)	0	1 (1%)	9 (6%)	11 (2%)
Adverse events of special interest					
Hypoglycaemia (blood glucose <70 mg/dL)	0	3 (2%)	8 (5%)	1 (1%)	12 (2%)
Hypoglycaemia (blood glucose <54 mg/dL)	0	0	2 (1%)	0	2 (<1%)
Severe hypoglycaemia	0	0	0	0	0
Injection site reaction	6 (4%)	11 (7%)	13 (8%)	14 (9%)	44 (7%)
Adjudicated MACE	1 (1%)	3 (2%)	0	2 (1%)	6 (1%)
Adjudicated pancreatitis	0	0	1 (1%)	0	1 (<1%)
Pancreatic cancer	0	0	0	0	0
Acute gallbladder disease	1 (1%)	1 (1%)	2 (1%)	0	4 (<1%)
Cholelithiasis	1 (1%)	0	2 (1%)	0	3 (<1%)
Cholangitis	0	1 (1%)	0	0	1 (<1%)
Cholangitis acute	0	1 (1%)	0	0	1 (<1%)

Data are n (%). Participants might be counted in more than one category. MACE=major adverse cardiovascular events.

Table 3: **Adverse events in the safety analysis set**

GLP-1 receptor agonist monotherapy trials have been conducted in Japan evaluating dulaglutide (0·75 mg),[8] liraglutide (0·9 mg),[20] semaglutide (0·5 or 1·0 mg),[21] and oral semaglutide (3, 7, or 14 mg).[22] These studies collectively showed decreases in HbA_{1c} by 1·4–2·2% from 8·0–8·9% at 24–52 weeks. In our study, tirzepatide showed a greater decrease in HbA_{1c} from baseline in Japanese patients with type 2 diabetes than seen in previous studies of dulaglutide, semaglutide, and liraglutide. The Japanese Clinical Practice Guidelines[23] specify a HbA_{1c} target of less than 6·0% as the ideal to achieve normal glycaemia without the risk of developing hypoglycaemia. Epidemiological studies have shown that high HbA_{1c} concentrations are associated with increased risk of all-cause mortality and death from cardiovascular disease, coronary heart disease, stroke, and cancer in east Asian populations.[24–26] In the current study, tirzepatide lowered HbA_{1c} without increasing the risk of hypoglycaemia, and therefore, might assist in reducing long-term microvascular and macrovascular complications. Furthermore, favourable changes in fasting lipids, insulin sensitivity, and systolic blood pressure were observed with tirzepatide treatment.

Tirzepatide was well tolerated at all three doses in Japanese patients with type 2 diabetes. The safety profile was consistent with the GLP-1 receptor agonist class and the global SURPASS trials.[11,12] The most frequent adverse events were mild to moderate in severity, gastrointestinal-related, and occurred primarily during the dose-escalation period. The incidence of gastrointestinal-related adverse events was higher with tirzepatide than with dulaglutide. Approximately 10% of participants in the tirzepatide 10 and 15 mg groups discontinued treatment due to adverse events. There were no reported cases of severe hypoglycaemia. Two participants in the tirzepatide 15 mg group had clinically significant hypoglycaemia during the 52 weeks; however, both participants completed study treatment.

A dose-dependent increase in pulse rate was observed for tirzepatide. Increases in pulse rate reported in this study were consistent with previous data for GLP-1 receptor agonist.[27] Increases in pulse rate were also observed in Japanese patients in the SURPASS J-combo study. The clinical relevance of tirzepatide associated increases in pulse rate is not yet known.[28]

A limitation of this trial was that only a few participants aged 75 years or older were included. Participants were mostly younger and with a shorter duration of illness than those generally seen in clinical practice.[29] Older patients with type 2 diabetes tend to develop sarcopenia and frailty as a result of poor energy intake.[30] Additionally, dose reductions were not permitted during the study when patients had gastrointestinal adverse events, which is not the case in clinical practice where the dose can be adjusted according to each patient's condition. Subcutaneous administration of dulaglutide 0·75 mg once per week is currently the only approved dose in Japan. This dose is low compared with most global markets. Hence, there are limitations in forming comparisons between dulaglutide and tirzepatide treatment groups in populations outside of Japan. Study strengths included the randomised, multicentre design, and an active comparator (dulaglutide). Importantly, this is the first confirmatory study of the efficacy and safety of tirzepatide compared with dulaglutide in Japanese patients with type 2 diabetes. Further findings come from a trial[28] assessing the safety and efficacy of tirzepatide administered once per week as add-on treatment to antihyperglycaemic medication, which showed that tirzepatide was well tolerated and resulted in improvements in glycaemic control and bodyweight in Japanese patients with type 2 diabetes, irrespective of the antihyperglycaemic medication class.

In conclusion, we have shown that tirzepatide administered once per week at 5, 10, and 15 mg significantly improves glycaemic control and reduces bodyweight compared with dulaglutide, without an increased risk of clinically significant or severe hypoglycaemia. The safety profile of tirzepatide was consistent with a GLP-1 receptor agonist, indicating a potential therapeutic use in Japanese patients with type 2 diabetes.

Contributors

NI and YS provided medical insights before initiating the trial. MT, TO, and TI contributed to the study design. MT and TI provided medical oversight during the trial. TO was responsible for the statistical analyses. All authors were involved in the data interpretation and critical review of the manuscript. All authors had full access to all the data in the study and accept responsibility to submit for publication. MT and TO have accessed and verified all the data in the study.

Declaration of interests

NI received research grants and had contracts from Terumo, Drawbridge, Asken, Novartis, Novo Nordisk, Astellas Pharma, Tsumura, Kyowa Kirin, Taisho Pharmaceutical Holdings, Ono Pharmaceutical, Eli Lilly Japan, Sanwa Kagaku Kenkyusho, MSD, Kowa, Kissei Pharmaceutical, Sanofi, Daiichi-Sankyo, Japan Tobacco, Sumitomo Pharma, Mitsubishi Tanabe Pharma, Takeda Pharmaceutical, Nippon Boehringer Ingelheim, Teijin Pharma, Pfizer Japan, FUJIFILM Toyama Chemical, Roche Japan, and LifeScan Japan; honoraria from Kowa, MSD, Astellas Pharma, Kissei Pharmaceutical, Sanofi, Novartis, Novo Nordisk, Ono Pharmaceutical, Kyowa Kirin, Sumitomo Pharma, Daiichi-Sankyo, Eli Lilly Japan, Nippon Boehringer Ingelheim, Takeda Pharmaceutical, Mitsubishi Tanabe Pharma, Taisho Pharmaceutical Holdings, Terumo, AstraZeneca, Sanwa Kagaku Kenkyusho, Abbott Japan, Ajinomoto, Teijin Healthcare, Bayer Yakuhin, Arkray, Johnson and Johnson, and Roche Japan; holds patents with UHA Mikakuto, Asken, and Shiratori Pharmaceutical; and was a member of advisory boards for Bayer Yakuhin, Terumo, Mitsubishi Tanabe Pharma, Sanofi, Novartis, Kowa, Abbott Japan, Novo Nordisk, Scohia Pharma, Sumitomo Pharma, Kissei Pharmaceutical, Nippon Boehringer Ingelheim, and Eli Lilly Japan. YS received grants and contracts from Terumo, Nippon Boehringer Ingelheim, Arkray, Taisho Pharmaceutical Holdings, Novo Nordisk, and Ono Pharmaceutical; and honoraria from MSD, Kao Corporation, Taisho Pharmaceutical Holdings, Takeda Pharmaceutical, Nippon Becton Dickinson, Nippon Boehringer Ingelheim, Novo Nordisk, Sumitomo Pharma, and Ono Pharmaceutical. MT, TO, and TI are employees of Eli Lilly Japan and shareholders in Eli Lilly and Company. TI is a senior director and operating officer for Eli Lilly Japan.

Data sharing

Eli Lilly and Company provides access to all individual participant data collected during the trial, after anonymisation, except for pharmacokinetic or genetic data. Data are available at request 6 months after the drug studied has been approved in the USA and EU or after

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primary publication acceptance, whichever occurs later. There is no expiration date for requests once the data are made available. Access will be provided after a proposal has been approved by an independent review committee 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.

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