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Change in pharmacodynamic variables following once-weekly tirzepatide treatment versus dulaglutide in Japanese patients with type 2 diabetes (SURPASS J-mono substudy)

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Abstract

Aim: To evaluate the pharmacodynamic effects of tirzepatide, a novel dual glucagon-like peptide-1 receptor and glucose-dependent insulinotropic polypeptide receptor agonist, compared with dulaglutide in patients with type 2 diabetes.

Materials and Methods: SURPASS J-mono was a 52-week, multicentre, randomized, double-blind, parallel, active-controlled, Phase 3 study, conducted in Japan. This substudy of SURPASS J-mono evaluated postprandial metabolic variables and appetite after a meal tolerance test, and body composition measured by bioelectrical impedance analysis.

Results: Of 636 participants in SURPASS J-mono, 48 were included in this substudy and assigned to tirzepatide 5 mg (n = 9), tirzepatide 10 mg (n = 11), tirzepatide 15 mg (n = 9), or dulaglutide 0.75 mg (n = 19). Participants had a mean (standard deviation) age of 58.6 (7.5) years, duration of diabetes of 6.0 (6.3) years, and body mass index of 27.5 (3.5) kg/m^2. Mean glycated haemoglobin at baseline was 66 mmol/mol (8.22%). Following a standardized meal test, statistically significant differences in change from baseline in area under the concentration versus time curve from time zero to 6 h after dose for glucose, insulin, glucagon, C-peptide and triglycerides were observed in all tirzepatide treatment arms, except triglycerides at 10 mg, compared with dulaglutide at Week 32. For body composition, tirzepatide 10 mg and 15 mg resulted in a significant reduction in body weight, and all doses of tirzepatide resulted in a significant reduction in body fat mass at Week 52.

Conclusions: Compared with dulaglutide, tirzepatide showed greater potential for normalizing metabolic factors after a standardized meal. Tirzepatide reduced body weight and body fat mass.

KEYWORDS
body composition, Japan, pharmacodynamics, tirzepatide, type 2 diabetes

1 | INTRODUCTION

Treatment of type 2 diabetes mellitus (T2D) generally consists of a combination of changes in lifestyle, including diet and exercise, and pharmacological treatments. As T2D progresses, patients become increasingly insulin-deficient and/or insulin-resistant, and eventually require more intensive therapy. The American Diabetes Association recommends a patient-centred and collaborative approach for glycaemic management.[1] Factors such as cardiovascular and renal comorbidities, efficacy, hypoglycaemia risk, impact on weight, cost, risk of side effects, and patient preferences should guide the choice of pharmacological agents.[1]

Data from cardiovascular outcome trials have highlighted that glucagon-like peptide-1 receptor agonists (GLP-1RAs) and sodium-glucose cotransporter-2 (SGLT2) inhibitors confer protection against major cardiovascular disease and all-cause mortality.[2] Since 2017, there has been a steady increase in the use of GLP-1RAs among patients with T2D.[3] In addition to GLP-1RAs, dual and triple agonists for GLP-1, glucose-dependent insulinotropic polypeptide (GIP) and glucagon receptors are under clinical development as potential therapeutic options for T2D.[3]

Tirzepatide is a GIP/GLP-1RA for the treatment of T2D.[4] This 39-amino-acid synthetic peptide has a C20 fatty di-acid moiety, which assists with half-life extension, thus allowing once-weekly subcutaneous administration.[4] In Phase 2 and 3 clinical trials, participants treated with tirzepatide (5, 10 and 15 mg) demonstrated greater reductions in glycated haemoglobin (HbA1c) and body weight compared with those treated with placebo, GLP-1RAs and basal insulin.[5-9]

The SURPASS J-mono trial was a Phase 3 study evaluating the efficacy and safety of tirzepatide monotherapy in Japanese patients with T2D. Findings from the SURPASS J-mono trial demonstrated superiority of tirzepatide compared with dulaglutide in terms of glycaemic control; estimated mean treatment differences were −1.09 (95% confidence interval [CI] −1.27, −0.90) for tirzepatide 5 mg, −1.27 (95% CI −1.45, −1.08) for tirzepatide 10 mg and −1.53 (95% CI −1.71, −1.35) for tirzepatide 15 mg compared with dulaglutide 0.75 mg (all $p < 0.001$).[10] Furthermore, tirzepatide was associated with dose-dependent reductions in body weight ranging from −5.8 to −10.7 kg, compared with −0.5 kg for dulaglutide.[10] In the current study, we evaluated the pharmacodynamic characteristics of tirzepatide in comparison with dulaglutide, including postprandial metabolic characteristics and appetite after a standardized test meal, and body composition measured by bioelectrical impedance analysis, in a subset of participants from the SURPASS J-mono study.

2 | MATERIALS AND METHODS

2.1 | Study design and participants

This was a 52-week, multicentre, randomized, double-blind, parallel, active-controlled, Phase 3 study conducted in Japan (SURPASS J-mono). Participants, investigators and the sponsor were masked to treatment assignment. Of the 636 participants enrolled in the SURPASS J-mono study, 48 participants from three study sites were included in this exploratory substudy (Supplementary Table 1) and were randomized in a 1:1:1:1 ratio to receive tirzepatide (5, 10 or 15 mg) or dulaglutide (0.75 mg). Assignment to treatment arms was determined by a computer-generated random sequence using an interactive web-response system. Participants were stratified based on baseline HbA1c (≤69 mmol/mol [≤8.5%] or >69 mmol/mol [>8.5%]), baseline body mass index (BMI; <25 or ≥ 25 kg/m^2) and washout of antidiabetic medication (yes or no).

Key inclusion criteria included: age ≥20 years; diagnosis of T2D based on World Health Organization classification at least 8 weeks prior to the screening visit; being oral antihyperglycaemic medication (OAM)-naive (diet and exercise only) or taking OAM monotherapy except tirzepatide and willingness to discontinue the medication; HbA1c ≥53 mmol/mol to ≤86 mmol/mol (≥7.0% to ≤10.0%) at both Visit 1 and Visit 2 for patients who were OAM-naïve or ≥48 mmol/mol to ≤75 mmol/mol (≥6.5%–≤9.0%) at Visit 1 and ≥53 mmol/mol to ≤86 mmol/mol (≥7.0%–≤10.0%) at Visit 2 for patients taking OAM monotherapy; stable weight (±5%) for 3 months prior to Visit 1; BMI ≥23 kg/m^2 at Visit 1; and agreement not to initiate an intensive diet and/or exercise programme during the study. Key exclusion criteria included: diagnosis of type 1 diabetes; history of use of any injectable therapy for T2D; chronic or acute pancreatitis; diabetic retinopathy requiring acute treatment; acute or chronic hepatitis; and an estimated glomerular filtration rate <30 mL/min/1.73 m^2.

The study protocol was approved by local institutional review boards. The trial was conducted in accordance with the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines. All participants provided written informed consent. This study is registered with ClinicalTrials.gov (NCT03861052).

2.2 | Procedures and outcomes

Following a 4-week (OAM-naïve) or 10-week (at least 8-week OAM washout) lead-in period, participants received tirzepatide or dulaglutide via subcutaneous injection once weekly for 52 weeks, followed by a 4-week safety follow-up period. The starting dose of tirzepatide was 2.5 mg once weekly for 4 weeks. This was followed by an increase of 2.5 mg every 4 weeks until the required dose was reached. The final dose was then maintained for the duration of the trial. Dulaglutide was administered at 0.75 mg once weekly and maintained for the duration of the trial. The study design is outlined in Supplementary Figure 2. Three out of 46 study sites participated in this substudy.

The meal tolerance test (MTT) was performed at baseline and Week 32 as previously described.[11] A standardized test meal of 494 kcal was used, consisting of pre-packaged meals (303 kcal) and white rice (191 kcal). The percentages of carbohydrate, protein and fat were 58%, 16% and 26%, respectively. Appetite was assessed for up to 6 h following each MTT, with fullness and hunger assessed

using a visual analogue scale.[12] Body composition was measured by bioelectrical impedance analysis using InBody770 (InBody Japan) at Weeks 0, 12, 32 and 52 (Supplementary Table 2).

The objectives of this substudy were to assess the pharmacodynamic effects of tirzepatide at 3 doses (5, 10 and 15 mg) compared with dulaglutide (0.75 mg). Postprandial metabolic characteristics included appetite (fullness and hunger) and area under the concentration versus time curve from time zero to 6 h after dose ($AUC_{[0-6h]}$) for plasma glucagon and serum glucose, insulin, C-peptide and triglycerides. Body composition characteristics included total body water, protein, minerals and body fat mass.

2.3 | Statistical analysis

Pharmacodynamic analyses were conducted using data from all participants who received at least one dose of investigational product and who had evaluable pharmacodynamic effects. The total sample size of 48 (12 per treatment arm) for this substudy provided 79% power to demonstrate a statistically significant difference between the tirzepatide dose levels and dulaglutide 0.75 mg in terms of glucose AUC based on a two-sample *t*-test with a two-sided significance level of 0.05 and assuming two dropouts per arm. Difference between the tirzepatide and dulaglutide treatment arms assumed true difference in glucose $AUC_{(0-6h)}$ was 18.3 mmol*h/L with a common standard deviation (SD) of 13.9 mmol*h/L. This assumption is based on previous findings.[11,13-16] The change in pharmacodynamic variables from baseline to Week 32 was analysed by an analysis of covariance model with treatment, baseline BMI (<25 or ≥25 kg/m^2), washout of OAM (yes or no), and baseline value of the dependent variable as a covariate. For postprandial metabolic characteristics and appetite, the $AUC_{(0-6h)}$ was calculated using the linear trapezoidal method. The least squares (LS) mean, standard error and 95% CIs were used for analyses of change from baseline. Treatment comparisons are displayed showing the treatment difference LS mean and 95% CI of differences along with the *p* values.

For body composition variables, data were collected for total body water, protein, minerals and body fat mass. Baseline and change in body composition variables from baseline were summarized. In this analysis, lean body mass was calculated as the sum of total body water, protein and minerals, and body weight was calculated as the sum of total body water, protein, minerals and body fat mass.

3 | RESULTS

3.1 | Patients

Between May 7, 2019 and March 31, 2021, 95 participants were randomized from three of the 46 sites that participated in the SURPASS J-mono study, to tirzepatide 5 mg (n = 22), tirzepatide 10 mg (n = 21), tirzepatide 15 mg (n = 19) or dulaglutide 0.75 mg (n = 33). Of the 95 participants, 48 participants provided informed consent for this substudy: tirzepatide 5 mg (n = 9), tirzepatide 10 mg (n = 11), tirzepatide 15 mg (n = 9) and dulaglutide 0.75 mg (n = 19) (Supplementary Figure 1). Of the 43 participants who completed study treatment, one participant in the dulaglutide 0.75-mg arm required rescue medication (metformin 500 mg from Day 158). Overall, two participants in the tirzepatide 5-mg treatment arm and one participant in the dulaglutide 0.75-mg treatment arm discontinued study treatment prior to Week 32, and two participants in the tirzepatide 10-mg treatment arm discontinued study treatment after Week 32. Reasons for discontinuation are outlined in Supplementary Table 1.

Baseline demographic and clinical/disease-related characteristics are shown in Table 1. The mean age of participants was 58.6 (SD 7.5) years. Most participants were male (85.4%) with median (Q1, Q3) duration of diabetes of 4.4 (2.3, 8.5) years and BMI of 27.5 (3.5) kg/m^2. There were differences between treatment arms in some baseline patient characteristics. Body weight was lower in the dulaglutide arm (73.2 kg vs. 77.5 kg, 82.7 kg and 84.9 kg for the tirzepatide 5-mg, 10-mg and 15-mg arms). Baseline HbA1c was 65.0 mmol/mol (8.07%) in the dulaglutide arm and 62.0 mmol/mol (7.81%), 70.0 mmol/mol (8.55%) and 70.0 mmol/mol (8.54%) in the tirzepatide 5-mg, 10-mg and 15-mg treatment arms.

3.2 | Standardized meal test

A time course of postprandial metabolic variables from 0 to 360 minutes after a standardized meal test at baseline and Week 32 is shown in Figure 1 and the $AUC_{(0-6h)}$ for postprandial metabolic variables and appetite are summarized in Table 2. Following a standardized meal test, statistically significant reductions from baseline were observed at Week 32 for both glucose and glucagon $AUC_{(0-6h)}$ with all doses of tirzepatide. In addition, statistically significant increases from baseline in insulin and C-peptide $AUC_{(0-6h)}$ were observed for dulaglutide and statistically significant reductions from baseline in triglyceride $AUC_{(0-6h)}$ were observed for tirzepatide 5 mg and 15 mg at Week 32. Compared with dulaglutide, statistically significant reductions in change from baseline in $AUC_{(0-6h)}$ after dose for glucose, insulin, glucagon, C-peptide and triglycerides $AUC_{(0-6h)}$ were observed at Week 32 in participants randomized to tirzepatide, except in the case of triglycerides with tirzepatide 10 mg. There were no significant differences between absolute change and percent change in postprandial metabolic variables. The percent change in postprandial metabolic variables at Week 32 is shown in Supplementary Table 4.

In terms of appetite, a statistically significant increase was observed at Week 32 from baseline in the $AUC_{(0-6h)}$ for fullness with all doses of tirzepatide and dulaglutide. In addition, a statistically significant decrease was observed in the $AUC_{(0-6h)}$ for hunger for the tirzepatide 10-mg and 15-mg treatment arms. However, no statistically significant differences in change from baseline in $AUC_{(0-6h)}$ for either fullness or hunger were observed between tirzepatide treatment arms and dulaglutide.

TABLE 1 Baseline characteristics

	Tirzepatide 5 mg (n = 9)	Tirzepatide 10 mg (n = 11)	Tirzepatide 15 mg (n = 9)	Dulaglutide 0.75 mg (n = 19)	Total (n = 48)
Age, years	59.0 (4.2)	59.5 (9.2)	55.6 (5.1)	59.3 (8.6)	58.6 (7.5)
Male, n (%)	7 (77.8)	10 (90.9)	8 (88.9)	16 (84.2)	41 (85.4)
Weight, kg	77.5 (13.0)	82.7 (17.4)	84.9 (11.0)	73.2 (8.1)	78.4 (12.7)
Body mass index, kg/m^2	27.2 (2.6)	27.6 (4.3)	29.8 (4.3)	26.5 (2.6)	27.5 (3.5)
Duration of T2D, years, median (Q1, Q3)	3.5 (0.9, 7.0)	8.6 (3.3, 13.5)	3.6 (3.0, 4.8)	4.0 (2.7, 9.6)	4.4 (2.3, 8.5)
Fasting serum glucose concentration, mg/dL	157.4 (25.5)	185.6 (29.7)	189.4 (47.6)	171.8 (37.5)	175.6 (36.8)
HbA1c concentration, % (SD), mmol/mol	7.81 (0.87), 62.0	8.55 (0.66), 70.0	8.54 (0.96), 70.0	8.07 (0.82), 65.0	8.22 (0.85), 66.0
eGFR, CKD-EPI calculation, mL/min per 1.73m^2	74.1 (11.0)	71.0 (12.4)	81.0 (11.7)	76.1 (7.4)	75.5 (10.4)
Systolic blood pressure, mm Hg	132.5 (5.0)	122.9 (15.4)	120.4 (12.4)	129.7 (16.7)	126.9 (14.4)
Diastolic blood pressure, mm Hg	82.3 (4.7)	78.2 (9.6)	78.9 (6.3)	80.4 (8.5)	80.0 (7.7)
Pulse rate, beats per minute	73.8 (12.8)	73.6 (7.5)	75.5 (7.0)	77.7 (10.6)	75.6 (9.7)

Note: Data presented as mean (SD) unless otherwise indicated.
Abbreviations: CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; HbA1c, glycated haemoglobin; N, number of participants; SD, standard deviation.

3.3 | Body composition

Change from baseline in body composition variables for each treatment arm is outlined in Figure 2 and Supplementary Figure 3. Tirzepatide at 10 mg and 15 mg resulted in significant reductions in lean body mass and body weight, and all doses of tirzepatide resulted in a significant reduction in body fat mass at Week 52. Compared with dulaglutide, significant reductions in body fat mass and body weight were observed at Week 52 in the tirzepatide 10-mg and 15-mg arms, and significant reductions in lean body mass were observed at Week 52 in the tirzepatide 15-mg arms (Figure 2A and Supplementary Table 2). In terms of percentage of body composition, body fat percentage decreased in all tirzepatide treatment arms at Week 52, while the percentage of body water, protein and minerals increased (Figure 2B and Supplementary Table 2). The observed reductions in lean body mass are mainly attributed to body water reduction. The percent change from baseline in body composition at Week 52 is shown in Supplementary Figure 4. The percent change from baseline was significantly decreased in body fat mass and body weight in all tirzepatide treatment arms, with no decrease observed in the dulaglutide 0.75-mg treatment group.The COVID-19 pandemic did not appear to impact the outcomes of the study.

4 | DISCUSSION

In this substudy of the SURPASS J-mono trial, we observed statistically significant reductions in glucose and glucagon $AUC_{(0-6h)}$ following all doses of tirzepatide. In addition, compared with dulaglutide, significant differences in $AUC_{(0-6h)}$ values after dose for glucose, insulin, C-peptide, glucagon and triglycerides were observed with all doses of tirzepatide, except in the case of triglycerides at the tirzepatide 10-mg dose. Several studies have undertaken MTTs in patients with T2D treated with short- and long-acting GLP-1RAs. These studies have shown that short-acting GLP-1RAs, such as lixisenatide and exenatide, reduced glycaemic excursions, insulin secretion and glucagon levels via delayed gastric emptying.[17-21] Long-acting GLP-1RAs, such as liraglutide and dulaglutide, reduced overall glucose and glucagon levels, and increased postprandial insulin secretion, which peaked at approximately 90 min following the start of a standardized meal.[11,22] Interestingly, the long-acting GLP-1RA semaglutide, unlike dulaglutide and liraglutide, reduced overall glucose levels without increasing insulin, and suppressed glucagon levels in a 24-hour meal test.[23] Similarly, the current study demonstrated that postprandial secretions of insulin and glucagon were suppressed in patients receiving tirzepatide. It is conceivable that postprandial insulin secretion was not considerably enhanced by tirzepatide (and semaglutide) due to body weight reduction and subsequent enhancement of insulin sensitivity. It was also reported that tirzepatide improves insulin sensitivity independent of body weight reduction in diet-induced obese mice, although the exact mechanisms are yet to be fully defined.[24] It is also possible that postprandial insulin secretion was not overly enhanced by tirzepatide due to suppression of postprandial glucagon secretion, which is known to enhance insulin secretion.[25-27] However, it was recently reported that GIP enhances postprandial glucagon secretion, thereby stimulating insulin secretion.[28] Thus, it remains to be determined how tirzepatide suppresses postprandial glucagon secretion.

In terms of triglycerides, postprandial levels were not increased due to the low-fat diet employed in this study. It has been reported

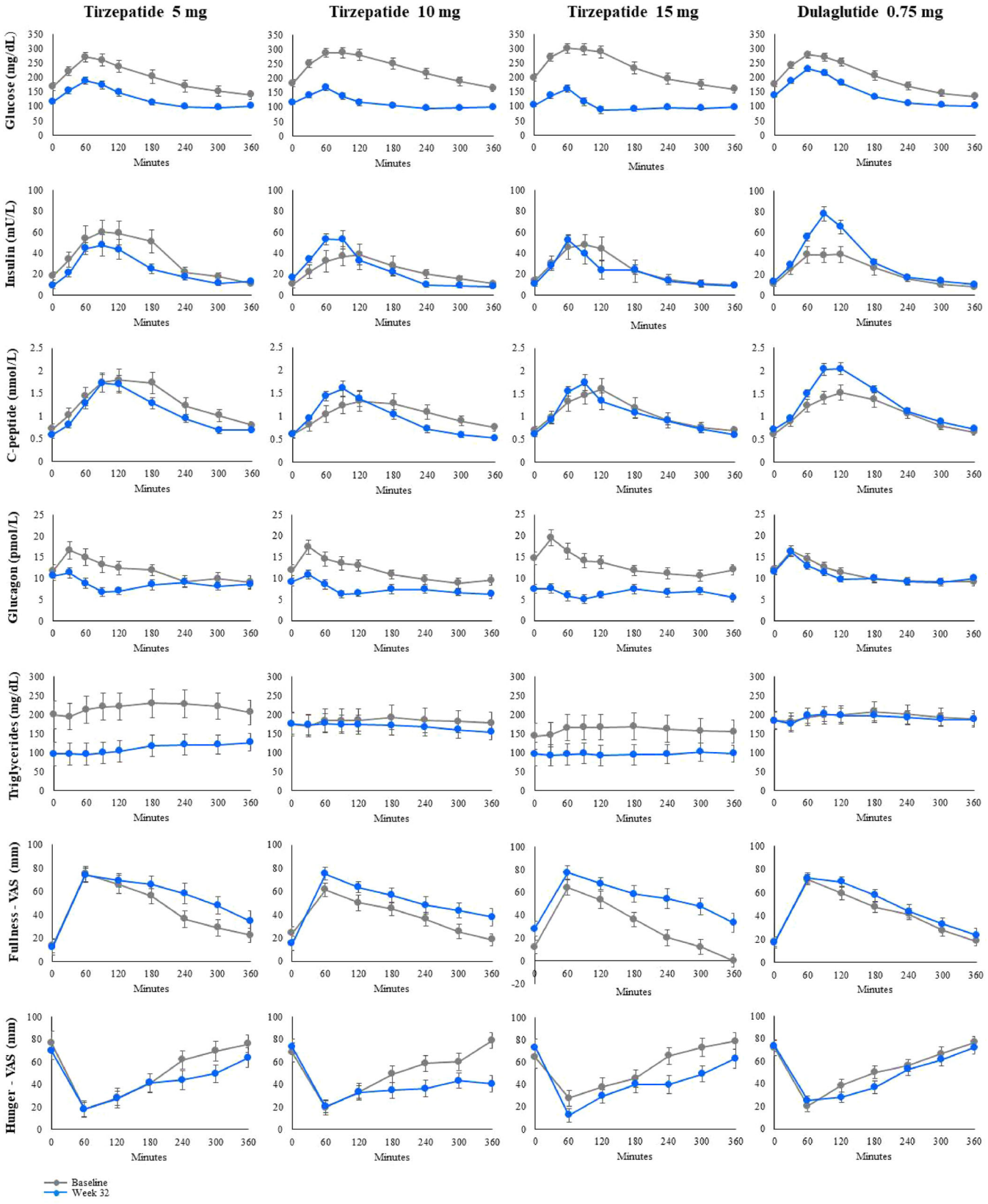

FIGURE 1 Mean postprandial metabolic and appetite variables after a standardized meal. Time course of pharmacodynamic and appetite variables for tirzepatide (5 mg, 10 mg and 15 mg) and dulaglutide 0.75 mg at baseline and at Week 32 following administration of a standardized meal. VAS, visual analogue scale.

TABLE 2 Postprandial metabolic and appetite variables at Week 32

		Tirzepatide 5 mg (n = 8)	Tirzepatide 10 mg (n = 11)	Tirzepatide 15 mg (n = 9)	Dulaglutide 0.75 mg (n = 18)
Glucose, mmol × h/L	Change from baseline	−30.6 (2.0)†††	−34.3 (1.8)†††	−37.2 (2.0)†††	−23.0 (1.4)†††
	Versus dulaglutide 0.75 mg (95% CI)	−7.5** (−12.5, −2.6)	−11.2*** (−16.0, −6.5)	−14.2*** (−19.3, −9.1)	–
Insulin, mU × h/L	Change from baseline	−9.7 (19.8)	−12.7 (16.9)	−21.3 (18.4)	43.9 (13.2)††
	Versus dulaglutide 0.75 mg (95% CI)	−53.6* (−101.8, −5.3)	−56.6* (−100.9, −12.3)	−65.2** (−112.0, −18.4)	–
C−peptide, nmol × h/L	Change from baseline	−0.21 (0.5)	−0.90 (0.5)	−0.40 (0.5)	1.09 (0.4)††
	Versus dulaglutide 0.75 mg (95% CI)	−1.30* (−2.6, −0.03)	−1.99** (−3.2, −0.8)	−1.49* (−2.7, −0.2)	–
Glucagon, pmol × h/L	Change from baseline	−19.3 (5.5)††	−27.7 (5.1)†††	−32.4 (4.9)†††	−5.9 (3.5)
	Versus dulaglutide 0.75 mg (95% CI)	−13.4* (−26.6, −0.2)	−21.8** (−34.8, −8.9)	−26.5*** (−39.2, −13.9)	–
Triglycerides, mg.h/dL	Change from baseline	−485.7 (167.1)††	−113.1 (144.7)	−564.3 (159.0)††	11.7 (112.5)
	Versus dulaglutide 0.75 mg (95% CI)	−497.4* (−903.3, −91.5)	−124.8 (−503.8, 254.2)	−576.0** (−981.4, −170.6)	–
		Tirzepatide 5 mg (n = 9)	**Tirzepatide 10 mg (n = 11)**	**Tirzepatide 15 mg (n = 9)**	**Dulaglutide 0.75 mg (n = 19)**
Appetite: Fullness[a]	Change from baseline	89.4 (33.8)†	63.2 (29.1)†	94.9 (32.8)††	47.1 (22.8)†
	Versus dulaglutide 0.75 mg (95% CI)	42.3 (−39.3, 124.0)	16.1 (−60.5, 92.7)	47.8 (−36.2, 131.9)	–
Appetite: Hunger[a]	Change from baseline	−56.8 (33.2)	−78.5 (28.9)†	−65.2 (31.4)†	−27.3 (22.4)
	Versus dulaglutide 0.75 mg (95% CI)	−29.5 (−110.6, 51.5)	−51.2 (−126.9, 24.4)	−37.9 (−117.9, 42.0)	–

Note: Data presented as least squares mean (standard error).

Abbreviations: CI, confidence interval; n, number of participants.

[a]A score of 0 on the visual analogue scale indicates hunger and 0 indicates fullness, corresponding area under curve scores were 0–600.

$^{\dagger}p < 0.05$, $^{\dagger\dagger}p < 0.01$, $^{\dagger\dagger\dagger}p < 0.001$ vs. baseline; $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$ vs. dulaglutide 0.75mg.

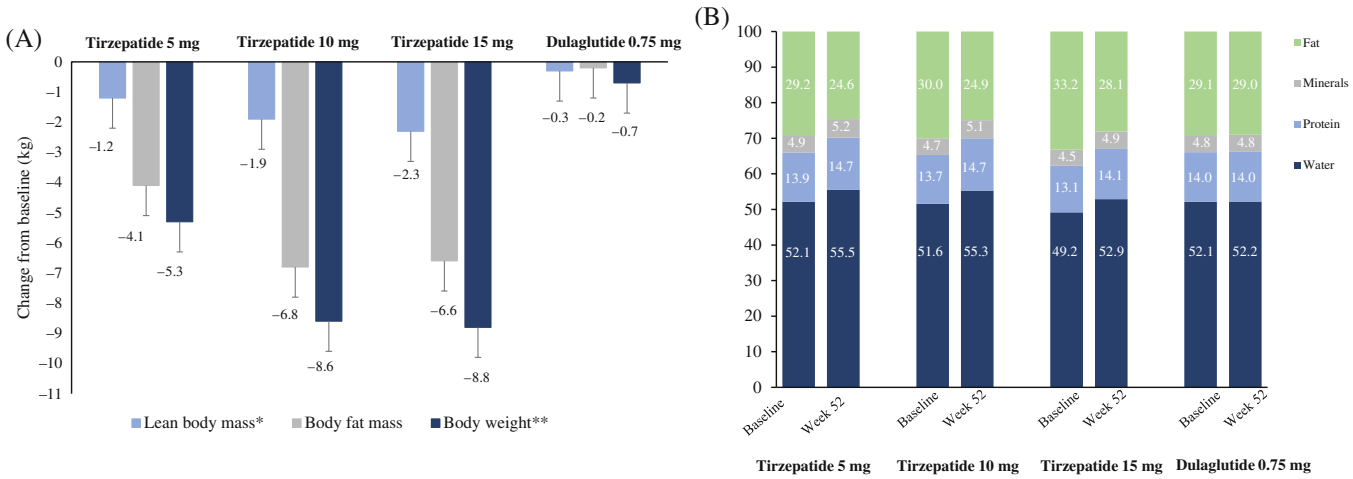

FIGURE 2 Body composition. A, Change from baseline in body composition variables for tirzepatide (5, 10 and 15 mg) and dulaglutide 0.75 mg at 52 weeks. B, Body composition at baseline and Week 52 for tirzepatide (5, 10 and 15 mg) and dulaglutide 0.75 mg. *Lean body mass consists of total body water, protein and minerals. **Body weight consists of lean body mass and body fat mass.

that tirzepatide improves lipoprotein biomarkers such as triglycerides in patients with T2D.[29] It is unclear why no significant change in triglycerides was observed in the tirzepatide 10-mg arm, but a significant reduction of triglycerides in the tirzepatide 5-mg and 15-mg arms is consistent with previous findings.

For appetite, a statistically significant increase in fullness was observed for all doses of tirzepatide and for dulaglutide 0.75 mg, and statistically significant decreases in hunger were observed in the tirzepatide 10-mg and 15-mg treatment arms. In this study, patients were required to consume the entire meal, hence the volume of meal consumption was not assessed, but it was reported that meal consumption decreased in a dose-dependent manner in a Phase 1 study of tirzepatide in Japanese patients with T2D.[13] This appetite change may be a factor in the reduction in body weight with tirzepatide administration.

In terms of body composition, significant reductions in body weight and body fat mass at Week 52 were observed in the tirzepatide 10-mg and 15-mg treatment arms. Body fat reduction for tirzepatide 5–15 mg (−4.1 to −6.8 kg) was greater than that observed for semaglutide and canagliflozin in the SUSTAIN-8 study (−2.6 to −3.4 kg, respectively) despite a lower baseline body weight (78.4 kg) compared with SUSTAIN-8 (88.3 kg).[30] The observed reductions in body fat mass were mainly attributed to the reduction in body weight and the observed reductions in body water were mainly attributed to the reduction in lean body mass.

This is the first clinical study to investigate long-term pharmacodynamic effects and body composition in Japanese patients treated with tirzepatide. This study has some limitations. A notable limitation of this substudy was the relatively small sample size in each treatment arm, which included only a subset of patients from the main study. Due to the limited sample size, differences in some baseline characteristics between treatment arms were observed, however, statistical analyses were based on a model adjusted for baseline variables. In addition, only one endpoint measurement following the MTT at Week 32 was performed. Compared with baseline, blood glucose levels were reduced at study endpoint, making comparisons of postprandial variables difficult between baseline and study endpoint due to less insulin being required to lower glucose levels. Although participants agreed not to initiate an intensive diet and/or exercise programme at any point during the study, dietary and physical activity were not formally assessed.

In conclusion, tirzepatide at 5 mg, 10 mg and 15 mg was capable of normalizing glucose, insulin, C-peptide and glucagon levels after a standardized meal test at Week 32, with statistically significant changes from baseline in comparison with dulaglutide in Japanese patients with T2D from the SURPASS J-mono study. In terms of appetite, all three doses of tirzepatide were effective in increasing fullness, and doses of 10 mg and 15 mg decreased hunger, although no statistical differences between tirzepatide and dulaglutide were observed. Body composition analyses revealed significant body weight reductions with tirzepatide, mainly due to a decrease in body fat mass. The ability of tirzepatide to target both glycaemic factors and weight loss in Japanese patients with T2D is an advantage over standard approaches for T2D that may increase or have little effect on weight.

AUTHOR CONTRIBUTIONS

Masakazu Takeuchi and Tomonori Oura contributed to the study design. Daisuke Yabe provided medical insights before initiating the trial. Masakazu Takeuchi provided medical oversight during the trial. Tomonori Oura was responsible for the statistical analyses. All authors (Daisuke Yabe, Dan Kawamori, Yusuke Seino, Tomonori Oura, Masakazu Takeuchi) were involved in data interpretation and critical review of the manuscript, had full access to the data, and approved this manuscript to be submitted for publication.

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CONFLICT OF INTEREST

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PEER REVIEW

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DATA AVAILABILITY STATEMENT

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

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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