Received: 6 March 2025 | Revised: 1 September 2025 | Accepted: 1 September 2025

DOI: 10.1111/dom.70111

ORIGINAL ARTICLE

WILEY

Efficacy and safety in tirzepatide-treated Korean adults with type 2 diabetes—A post hoc analysis of SURPASS-AP-combo and SURPASS-3

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Funding information
Eli Lilly and Company

Abstract

Aims: This post hoc analysis assessed the efficacy and safety data in tirzepatide-treated Korean patients with type 2 diabetes (T2D).

Materials and Methods: Data specifically from Korean patients treated with tirzepatide 5, 10, or 15 mg in the multicentre, randomised, open-label, parallel-group, phase 3 trials SURPASS-AP-Combo and SURPASS-3 were extracted and analysed. Efficacy (change from baseline in glycated haemoglobin [HbA1c] and body weight, and proportions of participants achieving HbA1c and body weight targets) and safety endpoints were evaluated at week 40 (SURPASS-AP Combo) and week 52 (SURPASS-3).

Results: In the SURPASS-AP-Combo and SURPASS-3, 79 of 687 and 27 of 1079 tirzepatide recipients, respectively, were Korean. In Korean participants in SURPASS-AP-Combo across all tirzepatide doses, least squares mean (LSM) HbA1c was reduced from baseline by 2.75% to 3.25% and HbA1c targets of <7.0% and ≤6.5% were achieved by 84.6% to 100% at week 40; LSM body weight reductions of −6.8% to

Funding: The two studies reported were funded by Eli Lilly and Company. The study sponsor had a role in the study designs, data collection, data analysis, interpretation of data, writing of this report, and in the decision to submit this paper for publication.

−10.9% from baseline were achieved. The composite endpoint of HbA1c ≤6.5% without body weight gain or clinically significant documented symptomatic or severe hypoglycaemia was achieved by 69.2% to 85.2% of tirzepatide recipients. Findings were similar in Korean participants of SURPASS-3. The safety profile of tirzepatide in Korean participants was generally consistent with that in the overall SURPASS-AP-Combo and SURPASS-3 populations.

Conclusions: Consistent with the overall results of the SURPASS-AP-Combo and SURPASS-3 trials, this post hoc subgroup analysis found clinically meaningful reductions in HbA1c and body weight after treatment periods of 40 to 52 weeks in Koreans with T2D treated with tirzepatide.

KEYWORDS

antidiabetic drug, clinical trial, glycaemic control, incretin therapy, randomised trial, type 2 diabetes

Plain Language Summary

What is the context and purpose of this research study?

Tirzepatide is a treatment for type 2 diabetes (T2D) that has been shown to be effective for reducing both blood glucose and body weight. It has recently been approved for treatment of people with T2D in Korea, a country where the management of T2D is not optimal. A contributing factor could be that most research is Western-based and may not apply to Korean patients due to ethnic or cultural differences between Asian and Western populations. Therefore, this post hoc analysis assessed efficacy and safety data specifically in Korean patients with T2D treated with tirzepatide who participated in either of two large tirzepatide studies.

What was done?

We extracted the information obtained from Korean patients treated with tirzepatide 5, 10, or 15 mg once weekly in the SURPASS-AP-Combo and SURPASS-3 studies, including patients' characteristics and the effects of treatment measured at the end of the studies (after 40 or 52 weeks). This information was contrasted with the corresponding information from all patients (including Korean patients) in each trial who received tirzepatide treatment.

What were the main results?

Consistent with the overall results of each of the two trials, this post hoc analysis found clinically meaningful reductions in glucose measures and body weight after treatment periods of 40 or 52 weeks in Koreans with T2D treated with tirzepatide. These beneficial effects were not affected by the baseline body mass index, age, or duration of diabetes of the treated Korean patients. In addition, Korean patients treated with tirzepatide had improved lipid levels and blood pressure. The safety profile of tirzepatide was also generally consistent with that in the overall trials, with the most common side effects being gastrointestinal.

What is the originality and relevance of this study?

It is increasingly being recognised that people may experience the same disease and/or respond to treatment differently, so results for one group of patients cannot necessarily be applied to other groups of patients. We looked at the effects of tirzepatide specifically in Korean patients and found that all tested doses (5, 10 and 15 mg) were associated with improved glucose control and reduction of body weight in Korean patients, with acceptable safety. Our findings were consistent with findings in the overall trials that included patients with a mix of ethnicities.

1 | INTRODUCTION

Type 2 diabetes (T2D) is a chronic metabolic disease characterised by hyperglycaemia; those affected need lifestyle and behavioural therapy, with treatment intensification as the disease progresses to prevent or delay complications and maintain quality of life.[1,2] In Korea, the prevalence of T2D among adults was estimated to be 13.9% in 2020, with more men than women affected (15.8% vs. 12.1%), although this rate increased to 30.1% (29.8% vs. 30.2%) in those aged ≥65 years.[3] Although an increasing number of options are available for the treatment of people with T2D,[1,2] only 61.4% of people with T2D in Korea reported using antihyperglycaemic medications in nationally representative, cross-sectional surveys.[3] Fewer than 1% of people with T2D were receiving glucagon-like peptide-1 (GLP-1) receptor agonists in 2018, although 55.1% had concomitant obesity and 23.1% had overweight.[3]

Tirzepatide is the first single molecule approved for therapy that activates the glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 receptors.[4] Tirzepatide has been approved by regulatory agencies and is indicated as an adjunct to diet and exercise for the treatment of adults with T2D and for chronic weight management in adults with obesity or overweight and at least one weight-related complication[5,6]; it was recently approved in Korea for the treatment of people with T2D.[7] In phase 3 clinical trials, tirzepatide produced reductions in glycated haemoglobin (HbA1c) and body weight, with a safety and tolerability profile comparable to that of the selective GLP-1 receptor agonists, enabling many people with T2D to achieve normalisation of glucose control (HbA1c <5.7%).[8] Two phase 3 SURPASS studies (SURPASS-AP-Combo and SURPASS-3) compared the efficacy and safety of tirzepatide with that of insulin glargine or insulin degludec in patients with T2D inadequately controlled with metformin with or without sulphonylureas or sodium-glucose co-transporter 2 (SGLT2) inhibitors, respectively. These multinational studies showed that tirzepatide (5, 10 and 15 mg) was superior to titrated insulin therapy, with greater reductions in HbA1c and body weight at the end of the treatment period, and a lower risk of hypoglycaemia.[9,10]

The management of T2D in primary care settings in Korea is suboptimal; in one large analysis of 2915 patients with T2D enrolled at 191 clinics across Korea, only 22.5% of patients had HbA1c levels <6.5% and 5.9% had achieved all three metabolic targets (HbA1c, blood pressure and low-density lipoprotein levels)[11] despite these being the recommended goals set by the Korean Diabetes Association guidelines.[12] The lack of published data concerning the use of GLP-1 receptor agonists specifically in Korean patients with T2D may have been a contributing factor to this suboptimal management of T2D, as it is possible that ethnic differences between Asian and Western populations or differences in lifestyle and diet treatment approaches in Asian countries could confound the results of predominantly Western-based research. As both SURPASS-AP-Combo and SURPASS-3 included patients from Korea, this post hoc analysis assessed the efficacy and safety of tirzepatide in Korean patients with T2D who participated in the SURPASS-AP-Combo and SURPASS-3 trials. Findings in Korean patients were contrasted with those for all patients (including Korean patients) from each trial population at the end of the treatment period.

2 | MATERIALS AND METHODS

The current analyses extracted data specifically from Korean patients treated with tirzepatide in the SURPASS-AP-Combo and SURPASS-3 trials.

SURPASS-AP-Combo and SURPASS-3 were multicentre, randomised, open-label, parallel-group, phase 3 trials in which adults with T2D were randomised (1:1:1:1) to receive, by subcutaneous injection, once-weekly tirzepatide 5, 10, or 15 mg, or once-daily basal insulin (Figure S1). SURPASS-AP-Combo was conducted at 66 medical research centres and hospitals in China, South Korea ($n = 13$), Australia, and India, and had a 40-week treatment period. SURPASS-3 was conducted at 122 medical research centres and hospitals in Argentina, Austria, Greece, Hungary, Italy, Poland, Puerto Rico, Romania, South Korea ($n = 10$), Spain, Taiwan, Ukraine, and the USA, and had a 52-week treatment period. Full details of these studies have been published.[9,10]

2.1 | Participants

In summary, eligible participants were aged ≥18 years, had T2D that was inadequately controlled (HbA1c ≥7.5% to ≤11.0% in SURPASS-AP-Combo; 7.0%–10.5% in SURPASS-3) on stable treatment with metformin alone or in combination with a sulphonylurea (SURPASS-AP-Combo) or SGLT2 inhibitor (SURPASS-3), a body mass index (BMI) of ≥23 kg/m^2 (SURPASS-AP-Combo) or ≥25 kg/m^2 (SURPASS-3) and stable body weight during the previous 3 months. Key exclusion criteria included type 1 diabetes, history of pancreatitis, history of proliferative diabetic retinopathy or maculopathy (or non-proliferative diabetic retinopathy requiring acute treatment) or an estimated glomerular filtration rate (eGFR) of ≤45 mL/min/1.73 m^2.

2.2 | Outcomes

The primary efficacy endpoint of each trial was mean change from baseline in HbA1c at week 40 (SURPASS-AP-Combo) or week 52 (SURPASS-3) to determine non-inferiority of tirzepatide 10 mg or 15 mg, or both, versus basal insulin. Key and other secondary outcomes of interest for the current analyses included: (i) the change in HbA1c and (ii) body weight loss from baseline to week 40/52; (iii) the proportions of patients achieving HbA1c <7.0%, ≤6.5% and <5.7% and (iv) attaining body weight loss from baseline of ≥5%, ≥10% and ≥15% at week 40/52; (v) the mean change from baseline in fasting serum glucose (FSG) to week 40/52; and (vi) the mean change from baseline in 7-point self-monitoring of blood glucose (SMBG) profiles. Laboratory endpoints included changes in lipid levels, urine albumin to creatinine ratio [UACR] and eGFR.

Safety endpoints considered in the current analyses included the incidence of treatment-emergent adverse events (TEAEs), serious TEAEs (SAEs) and discontinuation of study treatment due to TEAEs. Adverse events (AEs) of special interest included hypoglycaemia (<54 mg/dL) and gastrointestinal disorders. Further safety endpoints included change from baseline in vital signs (systolic blood pressure [SBP], diastolic blood pressure [DBP] and heart rate [HR]).

2.3 | Statistical analyses

Least squares mean (LSM) change in HbA1c level from baseline to study endpoint was evaluated using mixed model repeat measures (MMRM) with the variables baseline value + country + baseline oral antihyperglycaemic medication use + treatment + time + treatment*time (Type III sum of squares). The LSM change in body weight from baseline to study endpoint was evaluated using MMRM as for HbA1c with inclusion of the variable baseline HbA1c ≤8.5%/>8.5%. The proportions of patients achieving HbA1c targets (<7.0%, ≤6.5%, <5.7%) and body weight loss targets (≥5%, ≥10%, ≥15%) at the study endpoint were calculated descriptively. Missing data were handled by MMRM.

The composite endpoint of percentage of patients meeting combined HbA1c target (≤6.5% or <7.0%) with no body weight gain (<0.1 kg) or clinically significant, documented symptomatic hypoglycaemia (blood glucose <54 mg/dL) or severe hypoglycaemia was also determined via logistic regression, with missing value handled by MMRM, for participants in SURPASS-AP-Combo.

HbA1c and body weight response were analysed according to BMI level (23 to <25, 25 to <30, ≥30 kg/m^2), age (<65, ≥65 years) and duration of T2D (≤5, >5 to ≤10, >10 years) for participants in SURPASS-AP-Combo using MMRM as for the primary efficacy endpoint.

Other continuous variables analysed, including additional glycaemic measures and vital signs, were evaluated using MMRM. All missing data were handled using MMRM.

All analyses were carried out using SAS Version 9.4. Due to the limited sample size of the Korean population and the consequent risk of bias, findings in Korean patients treated with tirzepatide were descriptively contrasted with those from each overall trial population treated with tirzepatide for each dose and were not statistically compared.

3 | RESULTS

In SURPASS-AP-Combo, 1232 participants were screened, of whom 907 were randomised and received at least one dose of study drug (Figure S2a); baseline demographics and clinical characteristics were similar across the tirzepatide and insulin glargine groups.[9] The LSM reduction in HbA1c from baseline to week 40 was 2.24%, 2.44% and 2.49% with tirzepatide 5, 10 and 15 mg, respectively, and 0.95% with insulin glargine. Non-inferiority and superiority were demonstrated for tirzepatide 5, 10 and 15 mg versus insulin glargine.

In SURPASS-3, 1947 participants were screened, of whom 1437 were randomised and received at least one dose of the study drug (Figure S2b); baseline demographics and clinical characteristics were similar across the tirzepatide and insulin degludec groups.[10] Mean baseline HbA1c was decreased after 52 weeks of treatment by 1.93%, 2.20% and 2.37% with tirzepatide 5, 10 and 15 mg, respectively, and by 1.34% with insulin degludec. Non-inferiority and superiority were demonstrated for tirzepatide 10 and 15 mg versus insulin degludec.

In SURPASS-AP-Combo, 79 of 687 tirzepatide recipients were Korean; 26 received tirzepatide 5 mg, 26 received tirzepatide 10 mg, and 27 received tirzepatide 15 mg. In SURPASS-3, 27 of 1079 tirzepatide recipients were Korean; 9 received tirzepatide 5 mg, 10 received tirzepatide 10 mg, and 8 received tirzepatide 15 mg. Characteristics of these patients are summarised in Table 1.

3.1 | Glycaemic and body weight effects of tirzepatide in Korean participants

3.1.1 | SURPASS-AP-Combo

Across all tirzepatide doses, LSM HbA1c steadily decreased from baseline to week 16, followed by smaller declines depending on dose, and then remained stable from about week 24 to week 40 (Figure 1A). LSM HbA1c decreased from baseline by 2.75% to 3.25% at week 40 (Figure 1C), with BMI, age, and duration of diabetes having no significant effect on the change in HbA1c achieved with tirzepatide (Figure S3). HbA1c targets of <7.0% and ≤6.5% were achieved by 84.6% to 100% of each tirzepatide dose group at week 40, while 23.1% to 63.0% achieved HbA1c <5.7% at this time point (Figure 2A).

Body weight also decreased in all tirzepatide dose groups over the treatment period (Figure 3A); by week 40, dose-related body weight loss of 5.5 kg to 8.2 kg was seen across the tirzepatide groups (Figure 3C). These reductions equated to LSM (standard error [SE]) percentage body weight reductions of −6.8 (1.3)%, −8.9 (1.3)% and −10.9 (1.3)% from baseline in Korean patients receiving tirzepatide 5, 10 and 15 mg. BMI, age and duration of diabetes categories had no significant effect on the change in body weight achieved with tirzepatide (Figure S4). Additionally, notable proportions of Korean participants achieved body weight loss targets of ≥5%, ≥10%, ≥15% (Figure 2C).

The percentage of participants achieving the composite endpoints of HbA1c ≤6.5% or <7.0% without body weight gain or clinically significant documented symptomatic or severe hypoglycaemia ranged from 69.2% to 85.2% and 69.2% to 92.6%, respectively, with the largest proportions of participants achieving the composite endpoint in the tirzepatide 15 mg group (Figure 2E). The data presented in Figures 1–3 are also summarised in Table S1.

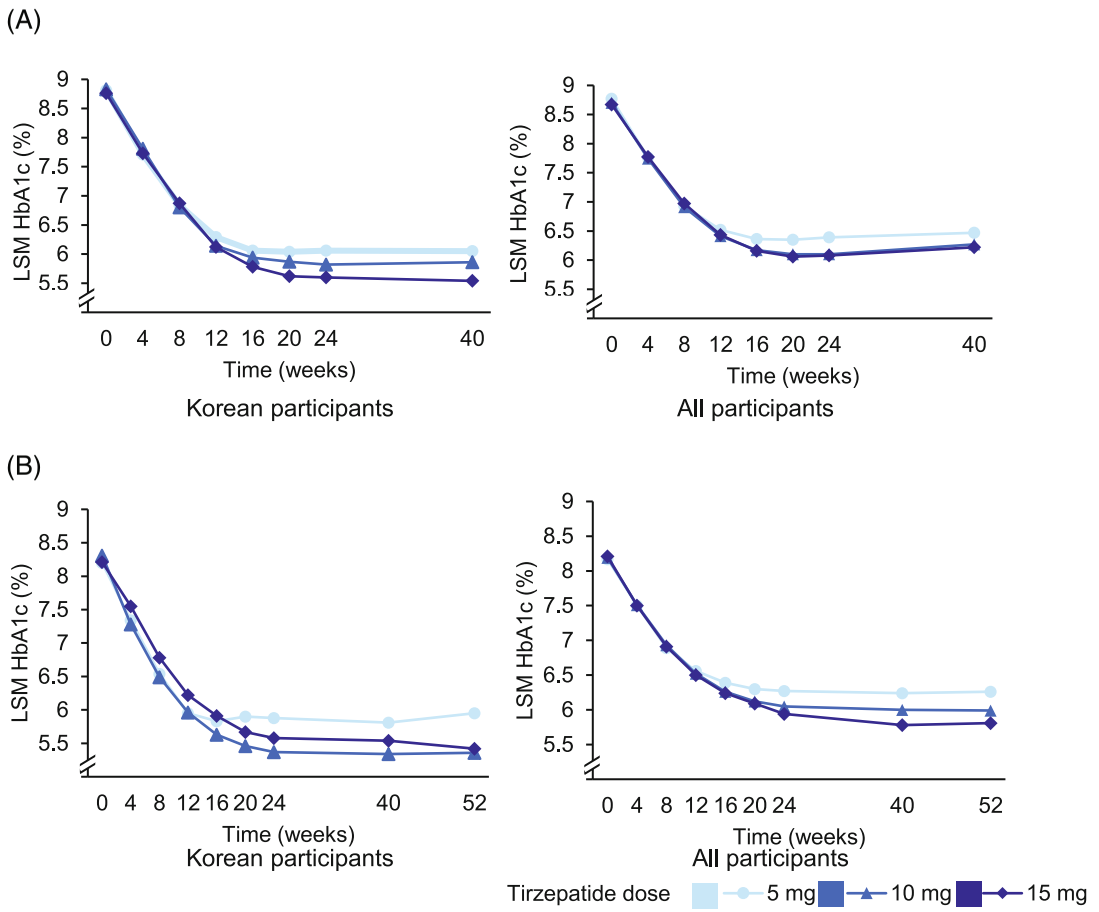
TABLE 1 Baseline demographics and characteristics of Korean participants and all participants in SURPASS-AP-Combo and SURPASS-3.

	SURPASS-AP-Combo						SURPASS-3					
	Korean participants			All participants			Korean participants			All participants		
Tirzepatide dose group	5 mg, ($n = 26$)	10 mg, ($n = 26$)	15 mg, ($n = 27$)	5 mg, ($n = 230$)	10 mg, ($n = 228$)	15 mg, ($n = 229$)	5 mg, ($n = 9$)	10 mg, ($n = 10$)	15 mg, ($n = 8$)	5 mg, ($n = 358$)	10 mg, ($n = 360$)	15 mg, ($n = 359$)
Age, years	53.9 (14.2)	50.8 (12.2)	54.2 (14.1)	53.1 (11.2)	53.5 (11.1)	54.3 (11.6)	53.3 (7.0)	60.5 (12.1)	62.4 (10.5)	57.2 (10.1)	57.4 (9.7)	57.5 (10.2)
Male, *n* (%)	12 (46.2)	13 (50.0)	15 (55.6)	134 (58.3)	126 (55.3)	129 (56.3)	6 (66.7)	7 (70.0)	4 (50.0)	200 (55.9)	195 (54.2)	194 (54.0)
HbA1c, %	8.8 (1.1)	8.8 (1.0)	8.8 (0.9)	8.8 (1.0)	8.7 (1.0)	8.7 (1.0)	8.2 (1.1)	8.2 (0.9)	8.2 (0.7)	8.2 (0.9)	8.2 (0.9)	8.2 (0.9)
HbA1c ≤8.5%, *n* (%)	10 (38.5)	12 (46.2)	11 (40.7)	99 (43.0)	108 (47.4)	113 (49.3)	7 (77.8)	7 (70.0)	7 (87.5)	248 (69.3)	249 (69.2)	252 (70.2)
HbA1c >8.5%, *n* (%)	16 (61.5)	14 (53.8)	16 (59.3)	131 (57.0)	120 (52.6)	116 (50.7)	2 (22.2)	3 (30.0)	1 (12.5)	110 (30.7)	111 (30.8)	107 (29.8)
FSG, mg/dL	180.4 (48.0)	185.3 (47.0)	185.0 (50.9)	180.9 (47.1)	175.8 (40.9)	177.2 (46.8)	158.3 (38.4)	143.2 (26.5)	163.5 (31.1)	171.7 (47.9)	170.4 (47.6)	168.4 (46.0)
Body weight, kg	77.1 (12.1)	80.9 (18.4)	74.8 (14.5)	77.7 (14.2)	76.3 (15.0)	76.1 (13.6)	80.0 (8.6)	76.4 (7.6)	77.2 (15.7)	94.4 (18.9)	93.8 (19.8)	94.9 (21.0)
BMI, kg/m^2	28.2 (2.6)	29.3 (5.1)	27.0 (3.7)	28.1 (3.9)	27.7 (3.8)	27.8 (3.8)	28.7 (3.5)	27.3 (2.8)	29.1 (4.0)	33.6 (5.9)	33.4 (6.2)	33.7 (6.1)
Duration of diabetes, years	12.2 (8.1)	10.3 (8.4)	10.1 (5.4)	7.4 (5.9)	7.9 (5.7)	7.6 (5.6)	7.8 (3.4)	11.4 (4.2)	9.3 (5.0)	8.5 (5.8)	8.4 (6.6)	8.5 (6.5)
DBP, mmHg	78.7 (7.5)	80.4 (8.4)	74.6 (8.4)	83.4 (8.8)	83.0 (9.0)	82.1 (9.6)	77.9 (6.9)	77.2 (9.5)	73.3 (6.2)	78.6 (8.5)	79.2 (8.7)	79.3 (9.2)
SBP, mmHg	131.0 (12.0)	132.5 (13.3)	124.8 (8.2)	129.5 (13.8)	129.2 (14.7)	129.0 (13.0)	127.3 (9.8)	128.7 (12.7)	119.4 (7.2)	130.7 (13.6)	131.1 (13.1)	131.9 (12.9)
Heart rate, beats/min	80.6 (11.5)	78.7 (11.8)	79.5 (9.5)	77.9 (10.5)	77.4 (10.8)	78.0 (9.9)	70.5 (10.3)	80.7 (12.2)	77.9 (13.8)	74.9 (9.9)	75.2 (9.5)	75.7 (9.5)
eGFR, mL/min/1.73 m^2	97.6 (18.0)	104.7 (14.2)	97.7 (18.5)	102.1 (14.6)	102.0 (14.3)	100.5 (16.0)	95.0 (13.1)	89.6 (14.9)	93.4 (12.5)	95.1 (17.2)	93.6 (16.9)	93.1 (17.3)
eGFR <60 mL/min/1.73 m^2, *n* (%)	0	0	1 (3.7)	2 (0.9)	2 (0.9)	4 (1.7)	0	0	0	16 (4.5)	13 (3.6)	12 (3.3)
eGFR ≥60 mL/min/1.73 m^2, *n* (%)	26 (100.0)	26 (100.0)	26 (96.3)	228 (99.1)	226 (99.1)	225 (98.3)	9 (100.0)	10 (100.0)	8 (100.0)	342 (95.5)	347 (96.4)	347 (96.7)
UACR, g/kg	91.4 (172.3)	63.9 (134.6)	49.8 (62.1)	86.7 (205.8)	91.3 (374.5)	69.8 (144.1)	48.3 (78.0)	170.8 (324.3)	35.0 (31.4)	109.9 (554.6)	70.4 (269.4)	51.2 (151.8)
Metformin alone, *n* (%)	3 (11.5)	3 (11.5)	3 (11.1)	121 (52.6)	121 (53.1)	118 (51.5)	4 (44.4)	4 (40.0)	3 (37.5)	246 (68.7)	242 (67.2)	247 (68.8)
Metformin combination[a], *n* (%)	23 (88.5)	23 (88.5)	24 (88.9)	109 (47.4)	107 (46.9)	111 (48.5)	5 (55.6)	6 (60.0)	5 (62.5)	112 (31.3)	118 (32.8)	112 (31.2)

Note: Data presented are mean (standard deviation) unless stated otherwise.

Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; FSG, fasting serum glucose; HbA1c, glycated haemoglobin; SBP, systolic blood pressure; UACR, urine albumin to creatine ratio.

[a]Metformin could be administered in combination with sulphonylureas in SURPASS-AP-Combo and with sodium-glucose co-transporter 2 inhibitors in SURPASS-3.



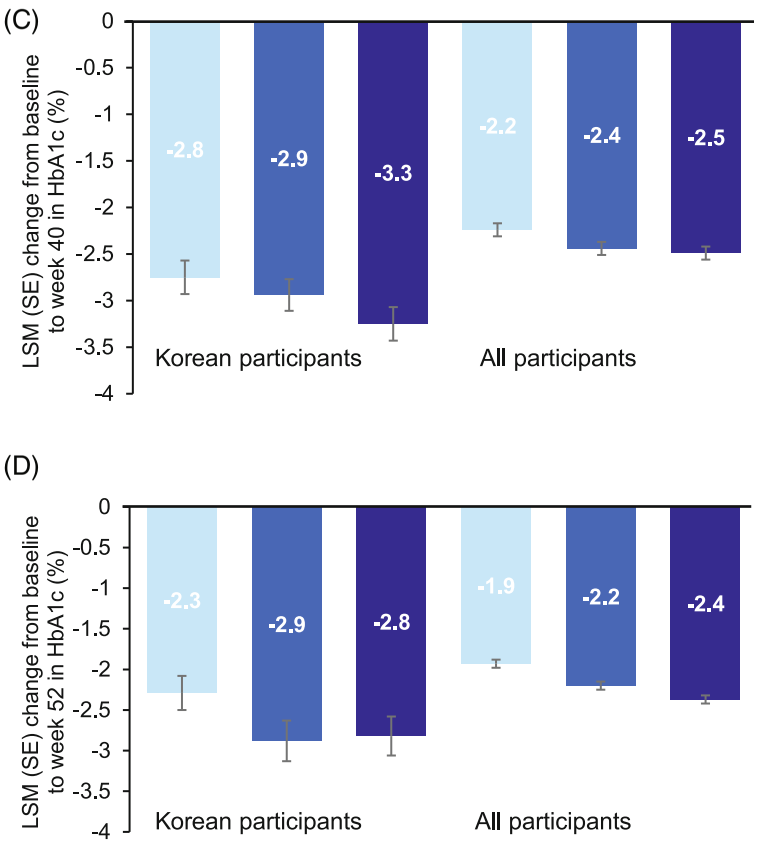


FIGURE 1 Change in HbA1c in Korean participants and all participants: (A) change over time in SURPASS-AP-Combo and (B) SURPASS-3, and change from baseline to (C) week 40 in SURPASS-AP-Combo and (D) week 52 in SURPASS-3. HbA1c, glycated haemoglobin; LSM, least squares mean; SE, standard error.

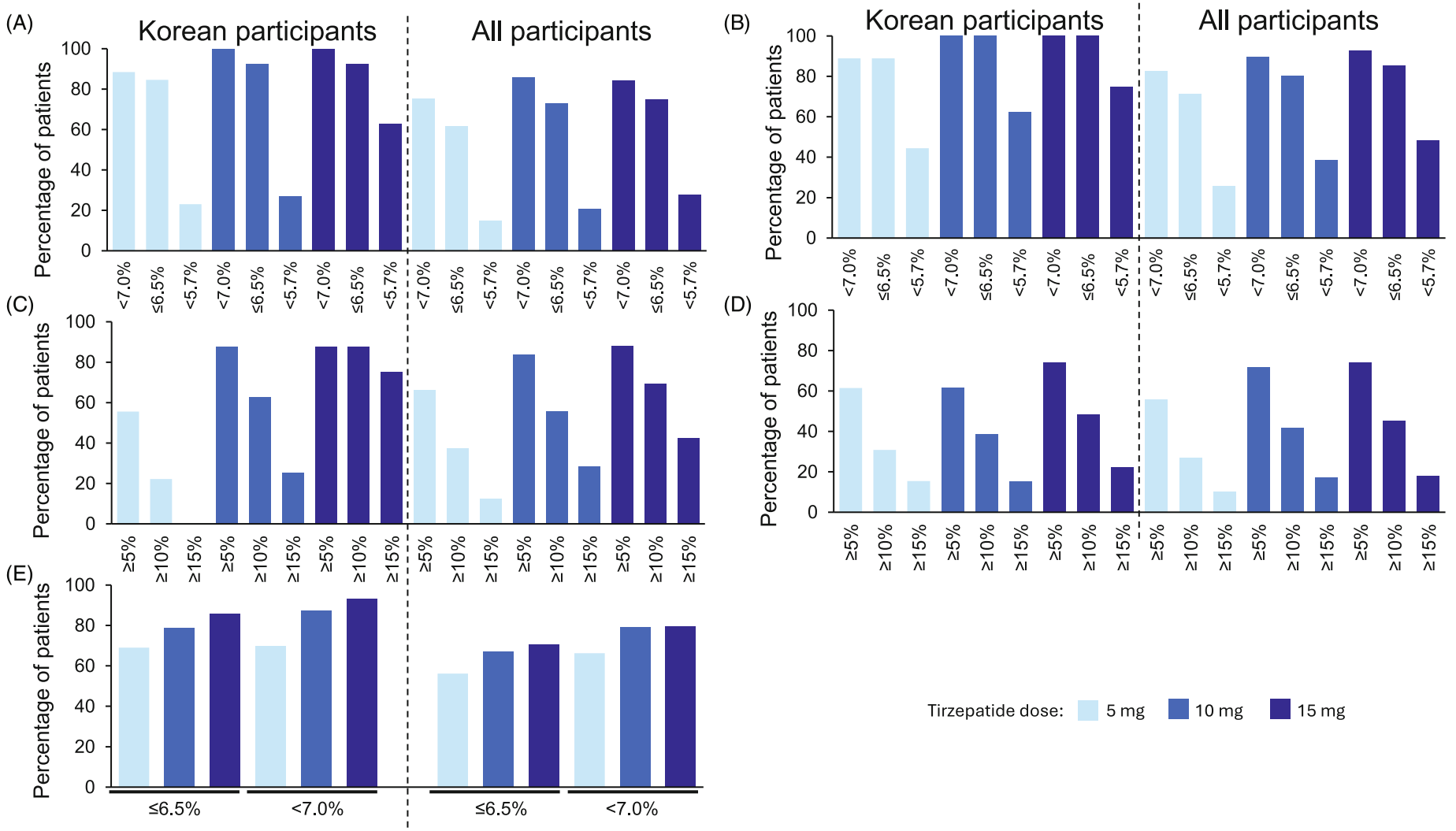


FIGURE 2 Percentage of Korean participants and all participants achieving therapeutic targets: (A) percentage achieving HbA1c targets at week 40 in SURPASS-AP-Combo and (B) at week 52 in SURPASS-3; (C) percentage achieving body weight targets at week 40 in SURPASS-AP-Combo and (D) at week 52 in SURPASS-3; and (E) percentage achieving HbA1c targets with no body weight gain or clinically significant documented symptomatic or severe hypoglycaemia at week 40 in SURPASS-AP-Combo. HbA1c, glycated haemoglobin.

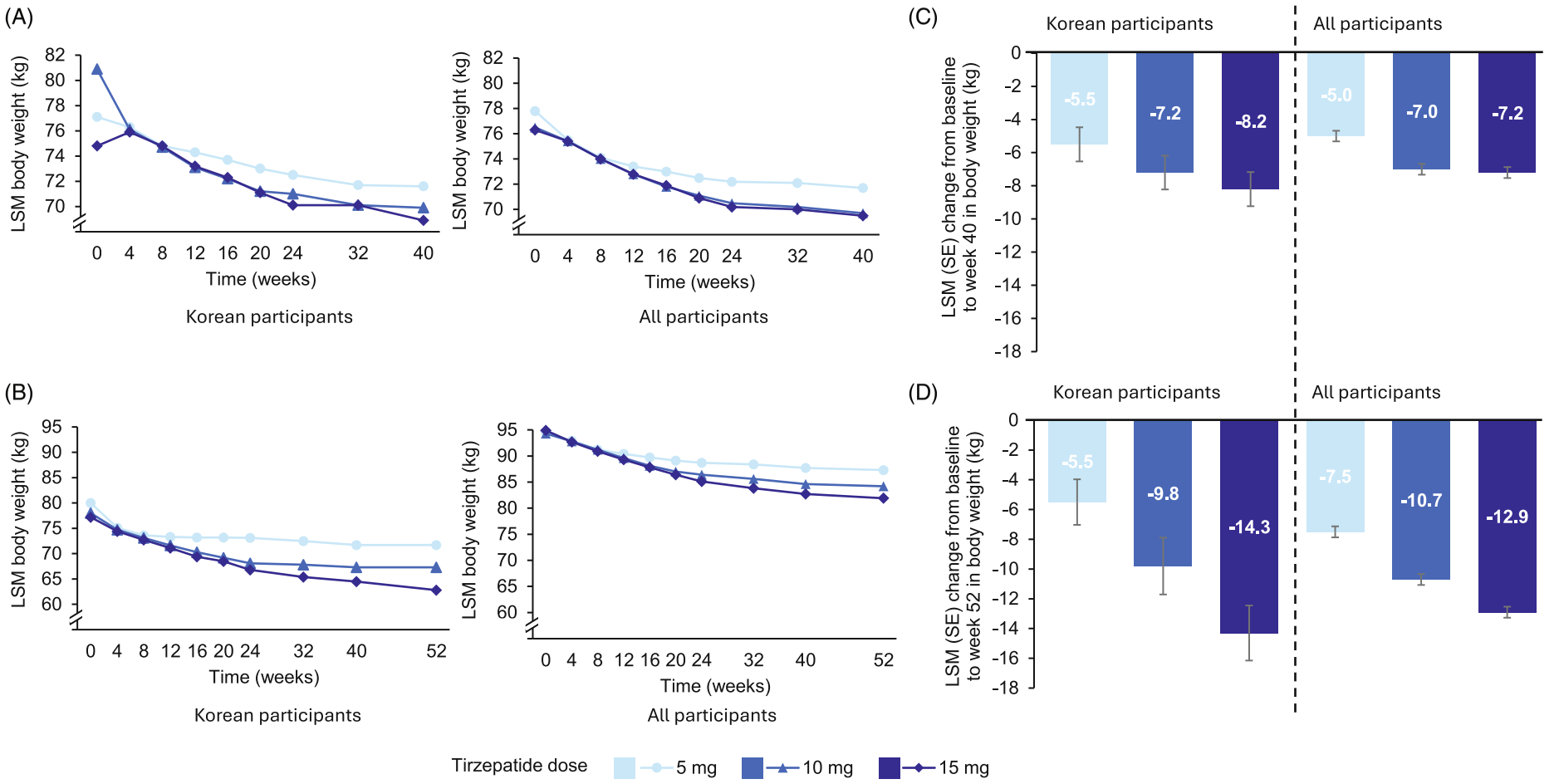


FIGURE 3 Change in body weight in Korean participants and all participants: Change over time in (A) SURPASS-AP-Combo; (B) SURPASS-3, and change from baseline to (C) week 40 in SURPASS-AP-Combo; and (D) week 52 in SURPASS-3. LSM, least squares mean; SE, standard error.

Across all tirzepatide doses, LSM FSG decreased from baseline to week 40 in a dose-related manner (Figure S5a) and SMBG profiles improved in all tirzepatide dose groups from baseline to week 40 (Figure S6).

Glycaemic and body weight outcomes in Korean participants were consistent with those of the overall trial population in SURPASS-AP-Combo (Figures 1–3; Figures S5 and S6).

3.1.2 | SURPASS-3

Across all tirzepatide doses, HbA1c steadily decreased from baseline to about week 24 and then remained stable for the remainder of the treatment period (Figure 1B). HbA1c was decreased from baseline by 2.29% to 2.82% at week 52 (Figure 1D). HbA1c targets of <7.0% and ≤6.5% were achieved by 100% of the tirzepatide 10 mg and 15 mg groups, and 88.9% of the tirzepatide 5 mg group at week 52; HbA1c <5.7% was achieved by 44.4% to 75.0% of tirzepatide recipients across doses at this time point (Figure 2B).

Body weight decreased in all tirzepatide dose groups over the treatment period (Figure 3B); by week 52, dose-related body weight loss of 5.5 kg to 14.3 kg was seen across the tirzepatide groups (Figure 3D). These reductions corresponded with LSM (SE) percentage body weight reductions of −6.8 (2.3)%, −13.0 (2.8)% and −20.1 (2.7)% from baseline in Korean patients receiving tirzepatide 5, 10, and 15 mg. In addition, notable proportions of Korean participants achieved body weight loss targets of ≥5%, ≥10%, and ≥15% with tirzepatide 10 or 15 mg (Figure 2D). The data presented in Figures 1–3 are also summarised in Table S1.

Across all tirzepatide doses, LSM FSG decreased from baseline to week 52 in a dose-related manner (Figure S5b) and SMBG profiles improved in all tirzepatide dose groups from baseline to week 52 (Figure S6).

Glycaemic and body weight outcomes in Korean participants were consistent with those of the overall trial population in SURPASS-3 (Figures 1–3; Figures S5 and S6).

3.2 | Laboratory changes in Korean participants

3.2.1 | SURPASS-AP-Combo

Lipid levels generally improved from baseline in tirzepatide dose groups (Table S2). Although eGFR declined by 2.1 to 3.4 mL/min/1.73 m^2 across all tirzepatide dose groups, improvements were observed in UACR (Table S2).

3.2.2 | SURPASS-3

Lipid levels generally improved from baseline in tirzepatide dose groups (Table S2). Although eGFR declined in the tirzepatide 5 mg and 15 mg dose groups by 3.0 and 7.8 L/min/1.73 m^2, respectively, improvements were observed in UACR in all dose groups (Table S2).

3.3 | Safety and tolerability of tirzepatide in Korean participants

3.3.1 | SURPASS-AP-Combo

TEAEs were reported in 50.0% to 80.8%, and treatment-related TEAEs in 30.8% to 59.3% of Korean participants across the tirzepatide dose groups, with the lowest rates seen in the tirzepatide 5 mg group (Table 2). The most common TEAEs were gastrointestinal disorders, specifically nausea, diarrhoea, and dyspepsia (Table 2). In most instances, nausea, vomiting, and diarrhoea events were mild or moderate in severity. Overall, four Korean participants in the SURPASS-AP-Combo experienced SAEs (acute cholecystitis in one tirzepatide 10 mg recipient and one tirzepatide 15 mg recipient, and colitis and herpes zoster, each in one tirzepatide 5 mg recipient); no deaths were reported. TEAEs infrequently resulted in treatment discontinuation by Korean participants ($n = 2$); events leading to discontinuation were decreased appetite and nausea (each in one tirzepatide 15 mg recipient).

Hypoglycaemia (<54 mg/dL) was reported during the 44-week study period (treatment plus safety follow-up) for 7.7% to 18.5% of each tirzepatide dose group, and the annual event rate was 0.146 with tirzepatide 5 mg, 0.178 with tirzepatide 10 mg, and 0.368 with tirzepatide 15 mg in Korean participants. These rates were slightly higher than those for the overall SURPASS-AP-Combo population (0.066, 0.089 and 0.070 with tirzepatide 5, 10 and 15 mg, respectively).

When vital signs were considered, changes in HR, DBP, or SBP showed no consistent patterns between dose groups or with time in tirzepatide-treated Korean patients over the treatment plus safety follow-up period of SURPASS-AP-Combo, likely due to the limited sample size (Figure S7).

3.3.2 | SURPASS-3

TEAEs were reported in 60.0% to 88.9%, and treatment-related TEAEs in 44.4% to 60.0%, of Korean participants receiving tirzepatide 5, 10, or 15 mg, with no apparent dose relationship observed (Table 2). The most common TEAEs were gastrointestinal disorders, specifically nausea, diarrhoea, vomiting, dyspepsia, and constipation (Table 2). No severe nausea, vomiting, or diarrhoea was reported; all of these events were mild or moderate in severity. No Korean participants in SURPASS-3 experienced an SAE, and no deaths were reported. TEAEs resulted in treatment discontinuation for four Korean participants in SURPASS-3; events leading to discontinuation were decreased appetite (two tirzepatide 10 mg recipients), body weight decreased (one tirzepatide 15 mg recipient) and dyspepsia (one tirzepatide 10 mg recipient).

TABLE 2 Incidence of adverse events during treatment with tirzepatide in Korean participants and all participants in the SURPASS-AP-Combo and SURPASS-3 trials.

	SURPASS-AP-Combo						SURPASS-3					
	Korean participants			All participants			Korean participants			All participants		
Tirzepatide dose group	5 mg, ($n = 26$)	10 mg, ($n = 26$)	15 mg, ($n = 27$)	5 mg, ($n = 230$)	10 mg, ($n = 228$)	15 mg, ($n = 229$)	5 mg, ($n = 9$)	10 mg, ($n = 10$)	15 mg, ($n = 8$)	5 mg, ($n = 358$)	10 mg, ($n = 360$)	15 mg, ($n = 359$)
TEAE	13 (50.0)	21 (80.8)	20 (74.1)	200 (87.0)	216 (94.7)	213 (93.0)	8 (88.9)	6 (60.0)	5 (62.5)	219 (61.2)	248 (68.9)	263 (73.3)
Treatment-related TEAE	8 (30.8)	13 (50.0)	16 (59.3)	171 (74.3)	195 (85.5)	188 (82.1)	4 (44.4)	6 (60.0)	4 (50.0)	118 (33.0)	170 (47.2)	195 (54.3)
Study discontinuation because of TEAE	0	0	0	7 (3.0)	19 (8.3)	19 (8.3)	0	3 (30.0)	1 (12.5)	6 (1.7)	9 (2.5)	4 (1.1)
Treatment discontinuation because of TEAE	0	0	2 (7.4)	10 (4.3)	30 (13.2)	28 (12.2)	0	3 (30.0)	1 (12.5)	25 (7.0)	37 (10.3)	39 (10.9)
SAE	2 (7.7)	1 (3.8)	1 (3.7)	15 (6.5)	14 (6.1)	15 (6.6)	0	0	0	29 (8.1)	20 (5.6)	26 (7.2)
Death	0	0	0	0	0	1 (0.4)	0	0	0	1 (0.3)	2 (0.6)	1 (0.3)
Most common TEAEs[a]												
GI disorders	8 (30.8)	15 (57.7)	16 (59.3)	141 (61.3)	175 (76.8)	177 (77.3)	6 (66.7)	5 (50.0)	3 (37.5)	121 (33.8)	154 (42.8)	173 (48.2)
Nausea	3 (11.5)	11 (42.3)	9 (33.3)	46 (20.0)	75 (32.9)	73 (31.9)	0	3 (30.0)	2 (25.0)	41 (11.5)	81 (22.5)	85 (23.7)
Diarrhoea	3 (11.5)	9 (34.6)	9 (33.3)	77 (33.5)	103 (45.2)	101 (44.1)	2 (22.2)	3 (30.0)	2 (25.0)	55 (15.4)	60 (16.7)	56 (15.6)
Vomiting	0	2 (7.7)	0	21 (9.1)	34 (14.9)	29 (12.7)	0	2 (20.0)	1 (12.5)	21 (5.9)	34 (9.4)	36 (10.0)
Dyspepsia	2 (7.7)	3 (11.5)	2 (7.4)	6 (2.6)	11 (4.8)	12 (5.2)	2 (22.2)	1 (10.0)	0	15 (4.2)	32 (8.9)	18 (5.0)
Constipation	0	1 (3.8)	2 (7.4)	12 (5.2)	17 (7.5)	23 (10.0)	2 (22.2)	0	0	11 (3.1)	13 (3.6)	17 (4.7)
Infections and infestations	1 (3.8)	1 (3.8)	3 (11.1)	43 (18.7)	34 (14.9)	43 (18.8)	3 (33.3)	1 (10.0)	0	67 (18.7)	71 (19.7)	67 (18.7)
Metabolism and nutrition disorders[b]	1 (3.8)	5 (19.2)	3 (11.1)	103 (44.8)	133 (58.3)	127 (55.5)	2 (22.2)	3 (30.0)	1 (12.5)	38 (10.6)	63 (17.5)	60 (16.7)
Investigations[c]	2 (7.7)	2 (7.7)	1 (3.7)	45 (19.6)	55 (24.1)	47 (20.5)	2 (22.2)	0	2 (25.0)	44 (12.3)	40 (11.1)	57 (15.9)
General disorders and administration site conditions	1 (3.8)	4 (15.4)	2 (7.4)	25 (10.9)	46 (20.2)	41 (17.9)	0	1 (10.0)	1 (12.5)	21 (5.9)	34 (9.4)	44 (12.3)
Nervous system disorders	2 (7.7)	4 (15.4)	8 (29.6)	23 (10.0)	26 (11.4)	40 (17.5)	2 (22.2)	0	0	24 (6.7)	36 (10.0)	30 (8.4)
Musculoskeletal and connective tissue disorders	3 (11.5)	4 (15.4)	1 (3.7)	15 (6.5)	22 (9.6)	17 (7.4)	1 (11.1)	1 (10.1)	1 (12.5)	28 (7.8)	25 (6.9)	22 (6.1)

Note: Data shown are the number (%) with at least one adverse event per event type.

Abbreviations: GI, gastrointestinal; SAE, serious TEAE; TEAE, treatment-emergent adverse event.

[a]Events reported by more than 10% of Korean participants (and $n > 2$) in any dose group in either trial.

[b]Decreased appetite in the majority of instances in Korean participants (all in SURPASS-3) and in the majority of instances in the overall trial population.

[c]Lipase increased was the most frequently reported investigation in Korean participants and the overall study population.

Consistent with the overall SURPASS-3 population, for whom hypoglycaemia (<54 mg/dL) was infrequently reported, hypoglycaemia (<54 mg/dL) was not reported during the 56-week study period (treatment plus safety follow-up) in Korean participants.

When vital signs were considered, changes in HR, DBP or SBP showed no consistent patterns between dose groups or with time in tirzepatide-treated Korean patients over the treatment plus safety follow-up period of SURPASS-3, again likely because of the small sample size (Figure S7).

4 | DISCUSSION

Consistent with the overall results of the SURPASS-AP-Combo and SURPASS-3 trials,[9,10] this post hoc subgroup analysis found clinically meaningful reductions in HbA1c and body weight after treatment periods of 40 to 52 weeks in Koreans with T2D treated with tirzepatide. These beneficial associations of tirzepatide with lower HbA1c and body weight were not significantly affected by the baseline BMI, age, or duration of diabetes of the treated Korean patients in SURPASS-AP-Combo. In addition, patterns of TEAEs and SAEs during treatment with tirzepatide in Korean participants were generally consistent with those in the overall SURPASS-AP-Combo and SURPASS-3 populations, with no deaths and few SAEs or hypoglycaemic events reported. The most common TEAEs in Korean participants in both trials were gastrointestinal (nausea, diarrhoea and dyspepsia), and the tolerability and safety profile of tirzepatide appeared to be comparable to that of the overall populations of SURPASS-AP-Combo and SURPASS-3.

The main HbA1c results were supported by reductions in FSG and the near-normalisation of SMBG profiles, which is consistent with a previous study of tirzepatide,[13] as well as changes seen in the overall populations of SURPASS-AP-Combo and SURPASS-3. These findings might be partially explained by the improvements in beta-cell function and insulin sensitivity seen with the dual agonism of GIP and GLP-1 with tirzepatide,[14] potentially allowing for the achievement of normoglycaemia (HbA1c <5.7%) in many patients, particularly those receiving the 15 mg dose, without increasing hypoglycaemia.

Laboratory results also showed numerical improvements in lipid levels in Korean participants in both studies and, although eGFR generally numerically declined with tirzepatide treatment, improvements were observed in UACR. These results are in line with those of a post hoc analysis of the SURPASS-4 study, which showed that participants treated with tirzepatide had a slower rate of eGFR decline than participants treated with insulin glargine and had clinically meaningful reductions (improvements) in UACR by study week 104, suggesting nephroprotective effects for tirzepatide, including in patients with pre-existing kidney disease.[15] Potential nephroprotective effects of tirzepatide have also been suggested given the observed beneficial effects of the drug on glucose levels, body weight, blood pressure, dyslipidaemia, endothelial dysfunction, and inflammation.[16–18] However, further trials are needed, including those examining the effect on kidney protection in patients at high risk of diabetic kidney disease progression. Results of the SURPASS-CVOT will help clarify the effects of tirzepatide on cardiovascular risk.[19]

Analyses such as this one are important. It is increasingly being recognised that people may experience the same disease and/or respond to treatment differently.[20,21] For example, although many of the known genetic loci associated with the development of T2D are common to both European and East Asian populations, a number of novel loci and greater effect sizes have been identified in East Asian populations.[22] It is thought that these differences may result in an altered pathogenesis of T2D in people of East Asian versus European descent. Consequently, it is possible that these genetic factors may cause heterogeneity in drug response. In addition, race and ethnicity can be associated with particular lifestyle and living conditions and behaviours that can have epigenetic or other effects that affect treatment responses.[20,21] It is therefore essential that clinical trials involve a range of people, including those of different race and ethnicity, age and sex, so that all communities can benefit from scientific advances. Accordingly, improving representation of historically underrepresented people has been a priority of organisations such as the United States National Institutes of Health and Food and Drug Administration. However, to date, there have been only modest increases in clinical trial participation by racial and ethnic minority population groups and older populations, and these groups remain underrepresented. This has meant that assessment of treatment efficacy within particular subgroups has been challenging, preventing identification of clinically important differences in treatment efficacy between groups that are underrepresented and those that are overrepresented, due to small sample sizes.[20,21]

In these analyses, the baseline demographics and characteristics of Korean participants in SURPASS-AP-Combo and SURPASS-3 generally appeared similar to those of the total population of each trial, although the proportions of Korean participants receiving metformin in combination with another oral antihyperglycaemic drug were higher than would be expected given the proportions of the overall population of each trial. Korean participants in SURPASS-AP-Combo had a longer duration of diabetes, and those in SURPASS-3 had lower body weight and BMI than the respective overall trial population. This difference in body weight seen in SURPASS-3, but not SURPASS-AP-Combo, likely reflects the overall trial populations—SURPASS-3 included predominantly White participants whereas SURPASS-AP-Combo was predominantly conducted in Asian countries.

The prevalence of overweight and obesity among individuals with T2D in Korea is high, with an estimated prevalence of obesity among female and male adults of 52.5% and 57.0%, respectively (55.1% overall). Class I obesity (BMI 25.0–29.9 kg/m^2) was reported in 41.3% of adults with T2D and overweight (BMI 23.0–24.9 kg/m^2) in 23.1%.[3] Overweight or obesity and T2D are linked; obesity accelerates the progression of T2D and increases the risk of complications, and as such must both be treated in affected individuals.[23] The reductions in body weight of 5.5 kg to 14.3 kg, with up to 100% of patients achieving body weight reductions of ≥5% and ≥10% over 40 or 52 weeks (and up to 75.0% of patients achieving ≥15% reduction over these periods), are therefore notable. In addition, 69.2% to 85.2% of Korean

adults treated with tirzepatide in SURPASS-AP-Combo achieved HbA1c ≤6.5% without body weight gain or clinically significant documented symptomatic or severe hypoglycaemia.

These analyses are limited by the fact that they were post hoc, that the studies included small numbers of Korean patients, and the lack of a comparator group in the current analyses. In addition, dropout percentages for the tirzepatide 10 mg and 15 mg groups among Korean patients were relatively high in SURPASS-3 due to the small sample sizes. Absolute numbers were relatively low (a total of 7 patients) and the reasons for withdrawal were similar to those of discontinuing subjects from the overall study population. Some analyses were performed only using data from participants in SURPASS-AP-Combo because the available number of Korean participants in SURPASS-3 was insufficient. Nevertheless, this is the first analysis to report outcomes for tirzepatide specifically in Korean adults with T2D.

In conclusion, this post hoc analysis found meaningful HbA1c and body weight improvements and acceptable safety in Korean patients receiving all doses of tirzepatide, which is consistent with findings in the overall trial populations.

AUTHOR CONTRIBUTIONS

Byung Wan Lee has made substantial contributions to the conception and design of the work; Soo Lim, Sin Gon Kim, Nan Hee Kim, and Woo Je Lee have made substantial contributions to the acquisition of data; Byung Wan Lee and Li Ying Du have made substantial contributions to the analysis of data; Byung Wan Lee, Chang Beom Lee, Soo Lim, Sin Gon Kim, Nan Hee Kim, Jong Chul Won, Woo Je Lee, Min Ju Kang, Ju Young Yuh, Li Ying Du, Hyojin Lim and Kyu Jeung Ahn have made substantial contributions to the interpretation of data; Byung Wan Lee, Chang Beom Lee, Soo Lim, Sin Gon Kim, Nan Hee Kim, Jong Chul Won, Woo Je Lee, Min Ju Kang, Ju Young Yuh, Li Ying Du, Hyojin Lim and Kyu Jeung Ahn have been involved in drafting the manuscript or revising it critically for important intellectual content; All authors have given final approval of the version to be published; have participated sufficiently in the work to take public responsibility for appropriate portions of the content; and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

ACKNOWLEDGEMENTS

The authors would also like to acknowledge Caroline Spencer and Sheridan Henness (Rx Communications, Mold, UK) for medical writing assistance with the preparation of this manuscript, funded by Eli Lilly and Company.

CONFLICT OF INTEREST STATEMENT

Chang Beom Lee, Soo Lim, Sin Gon Kim, Nan Hee Kim, Woo Je Lee, Kyu Jeung Ahn, Byung Wan Lee, and Jong Chul Won have nothing to disclose. Min Ju Kang, Ju Young Yuh, Li Ying Du, Hyojin Lim are employees of Lilly Korea Limited, the manufacturer of tirzepatide.

PEER REVIEW

The peer review history for this article is available at https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/dom.70111.

DATA AVAILABILITY STATEMENT

Eli Lilly and Company provides access to all individual participant data collected during the trials, after anonymisation, with the exception of pharmacokinetic or genetic data. Data are available to request from 6 months after the indication studied was approved in the USA and EU and after primary publication acceptance, whichever was later. No expiration date for 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 protocols, statistical analysis plans, clinical study reports, 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 https://www.vivli.org.

ETHICS STATEMENT

The studies included in these post-hoc analyses received approval from the Ethics Review Board for each study site, as reported for each primary publication. Korean sites in SURPASS-AP-Combo were Hallym University Kangnam Sacred Heart Hospital, 1 Singil-ro, Yeongdeungpo-gu, Seoul, Seoul-teukbyeolsi, Republic of Korea; Bucheon St. Marys Hospital, 327 Sosa-ro, Bucheon-si, Gyeonggi-do, Republic of Korea; Yonsei University-Wonju Severance Christian Hospital 20 Ilsan-ro, Wonju, Kangwon-do, Republic of Korea; Ulsan University Hospital, 877 Bangeojinsunhwan-doro, Dong-gu, Ulsan, Ulsan-Kwangyŏkshi, Republic of Korea; Keimyung University Dongsan Hospital, 1035, dalgubeol-daero, Dalseo-gu, Daegu, Taegu-Kwangyŏkshi, Republic of Korea; Korea University Anam Hospital, 73 Goryedae-ro, Seongbuk-gu, Seoul, Seoul-teukbyeolsi, Republic of Korea; Kyung Hee University Hospital at Gangdong, 892 Dongnam-ro, Gangdong-gu, Seoul, Seoul-teukbyeolsi, Republic of Korea; Hanyang University Guri Hospital, 153 Gyeongchun-ro, Guri-si, Gyeonggido, Republic of Korea; Korea University Ansan Hospital, 123 Jeokgeum-ro, Danwon-gu, Ansan-si, Gyeonggi-do, Republic of Korea; Severance Hospital, Yonsei University Health System, 50-1 Yonsei-ro, Seodaemun-gu, Seoul, Seoul-teukbyeolsi, Republic of Korea; Asan Medical Center, 2F, Clinical Research Center, 88, Olympic-ro 43-gil, Songpa-gu, Seoul, Seoul-teukbyeolsi, Republic of Korea; Inje University Sanggye Paik Hospital, 1342 Dongil-ro, Nowon-gu, Seoul, Seoul-teukbyeolsi, Republic of Korea; Seoul National University Bundang Hospital, ERB Department, 82 Gumi-ro 173 beon-gil, Bundang-Gu, Seongnam, Gyeonggi-do, Republic of Korea. Korean sites in SURPASS-3 were Korea University Ansan Hospital, Ansan-si, Republic of Korea, 15355; Korea University Anam Hospital, Seoul, Republic of Korea, 02841; Seoul National University Hospital, Seoul, Republic of Korea, 03080; Severance Hospital, Yonsei University Health System, Seoul, Republic of Korea, 03722; Kyunghee University Hospital at Gangdong, Seoul, Republic of Korea, 05278;

Samsung Medical Center, Seoul, Republic of Korea, 06351; Bucheon St. Mary's Hospital, Bucheon, Gyeonggi-do, Republic of Korea, 14 647; Seoul National University Bundang Hospital, Seongnam-si, Gyeonggi-do, Republic of Korea, 13620; Hanyang University Guri Hospital, Guri-si, Gyeonggido, Republic of Korea, 11923; Seoul St. Mary's Hospital, Seoul, Republic of Korea, 06591. The trials were conducted in accordance with the principles of international ethics guidelines, including the Declaration of Helsinki, and applicable laws and regulations. Written informed consent was obtained from each patient before any study procedures.

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SUPPORTING INFORMATION

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

How to cite this article: Lee BW, Lee CB, Lim S, et al. Efficacy and safety in tirzepatide-treated Korean adults with type 2 diabetes—A post hoc analysis of SURPASS-AP-combo and SURPASS-3. *Diabetes Obes Metab*. 2025;1-13. doi:10.1111/dom.70111