

Tirzepatide for the treatment of adults with type 2 diabetes: An endocrine perspective

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Abstract

Tirzepatide is a novel glucose-dependent insulinotropic polypeptide/glucagon-like peptide 1 (GLP-1) receptor agonist approved in the United States as an adjunct to diet and exercise to improve glycaemic control in adults with type 2 diabetes and under investigation for use in chronic weight management, major adverse cardiovascular events and the management of other conditions, including heart failure with preserved ejection fraction and obesity and non-cirrhotic non-alcoholic steatohepatitis. The Phase 3 SURPASS 1-5 clinical trial programme was designed to assess efficacy and safety of once-weekly subcutaneously injected tirzepatide (5, 10 and 15 mg), as monotherapy or combination therapy, across a broad spectrum of people with type 2 diabetes. Use of tirzepatide in clinical studies was associated with marked reductions of glycated haemoglobin (−1.87 to −2.59%, −20 to −28 mmol/mol) and body weight (−6.2 to −12.9 kg), as well as reductions in parameters commonly associated with heightened cardiometabolic risk such as blood pressure, visceral adiposity and circulating triglycerides. In SUPPASS-2, these reductions were greater than with the GLP-1 receptor agonist semaglutide 1 mg. Tirzepatide was well tolerated, with a low risk of hypoglycaemia when used without insulin or insulin secretagogues and showed a generally similar safety profile to the GLP-1 receptor agonist class. Accordingly, evidence from these clinical trials suggests that tirzepatide offers a new opportunity for the effective lowering of glycated haemoglobin and body weight in adults with type 2 diabetes.

1 | INTRODUCTION

Type 2 diabetes is characterized by a multiplicity of pathophysiological components, which includes insulin resistance, defective insulin secretion, adiposity, decreased incretin effect, increased glucagon secretion and dyslipidaemia.^{1–5} Consequently, type 2 diabetes is more than a challenge of hyperglycaemia. For example, a retrospective study of more than one million adults with type 2 diabetes in the

United States [median age of 65 years, diabetes duration of 4 years and glycated haemoglobin (HbA1c 6.8%)] reported that 82% had hypertension, 78% had obesity or overweight, 24% had chronic kidney disease and 22% cardiovascular disease.⁶ Furthermore, a meta-analysis of observational studies from 20 countries reported that the global prevalence of non-alcoholic fatty liver disease among people with type 2 diabetes was 56% and the prevalence of non-alcoholic steatohepatitis was 37%.⁷

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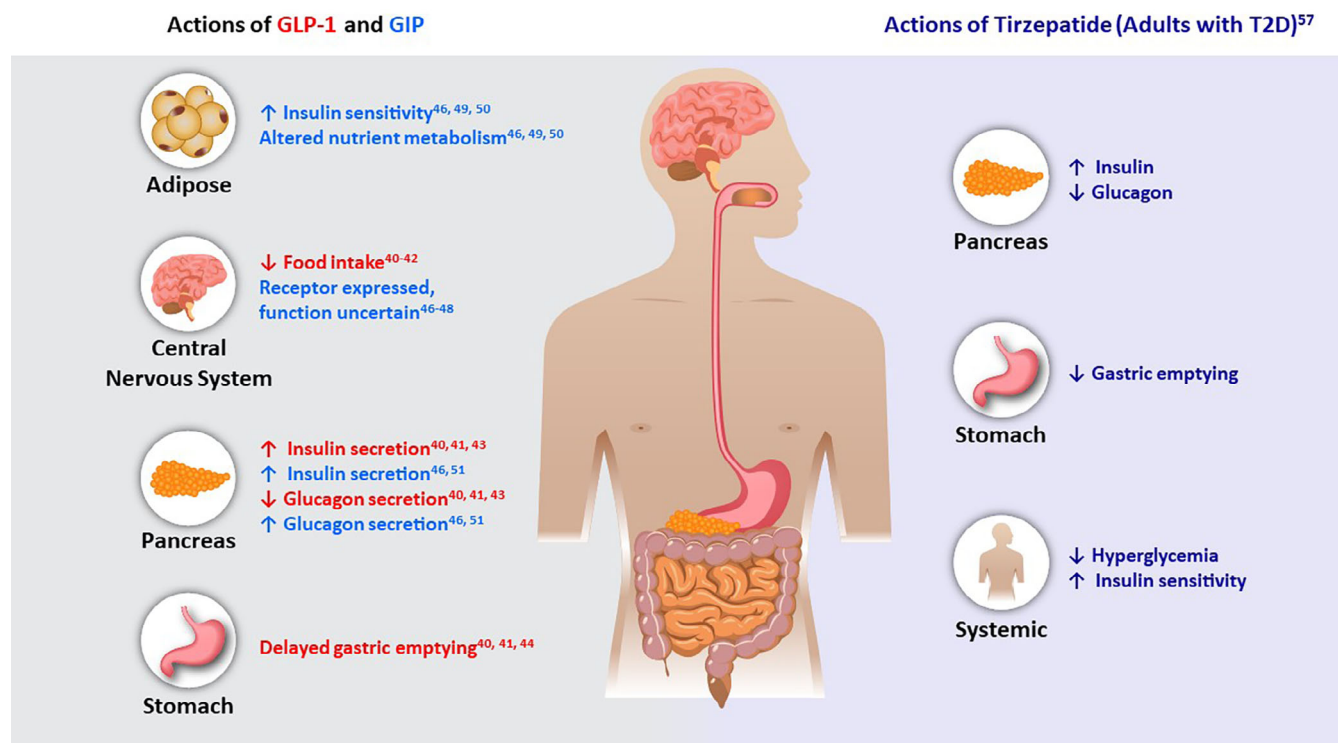


FIGURE 1 Gluco-regulatory actions of GIP and GLP-1 proposed based on preclinical and clinical studies, and actions of tirzepatide in adults with type 2 diabetes. GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide-1; T2D, type 2 diabetes

Obesity is the strongest risk factor for type 2 diabetes,^{8,9} a major contributor to insulin resistance,^{2,10} and is involved in the pathophysiology of hypertension, dyslipidaemia and non-alcoholic fatty liver disease.^{11,12} Given their intertwined pathophysiology, body weight loss can have beneficial effects on glycaemic control, insulin sensitivity and comorbidities.^{10,13} The American Diabetes Association (ADA) recommends weight loss of at least 5% through diet, physical activity and behavioural therapy for most people with type 2 diabetes who have overweight or obesity.¹⁴ Greater weight loss may offer the possibility of reversing the metabolic abnormalities of type 2 diabetes resulting in improvement of glycaemia up to the achievement of diabetes remission.¹⁵⁻¹⁹ The possibility of achieving remission of type 2 diabetes associated with weight loss was reported in several studies evaluating different types of intervention (lifestyle changes, medication, bariatric surgery, or a combination of those), having different designs and conducted in different settings. The exact definitions of remission, based generally on the ability to maintain non-diabetes glycaemia without glucose-lowering treatment, differed between these studies. Nonetheless, the beneficial effects of greater weight loss on glycaemia reinforce the importance of weight management for people with type 2 diabetes.¹⁹ Modest weight loss of at least 5% can improve cardiovascular risk factors such as blood pressure and lipids,^{14,20,21} and weight losses of $\geq 7\%$ may improve non-alcoholic fatty liver disease.^{22,23}

Although several classes of glucose-lowering agents are available as treatments for type 2 diabetes, half to three-quarters of people may not meet individualized glycaemic targets.²⁴⁻²⁸ With lifestyle intervention in the trial setting, as few as two-fifths of participants

achieve modest weight loss of $\geq 5\%$ or $\geq 7\%$ in the first year.²⁹⁻³¹ There is currently a need for more effective therapies to enable people to achieve glycaemic control, address the metabolic disorders associated with type 2 diabetes, and meet more ambitious weight loss targets, as part of individualized treatment plans.

Two gut-derived incretin hormones, glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide 1 (GLP-1) are secreted in response to nutrients, mediate the incretin effect and facilitate glycaemic control (Figure 1).³² This effect is diminished in people with type 2 diabetes but can be partially restored with glucose-lowering interventions.³³⁻³⁷ GLP-1 receptor agonists can improve glycaemic control and reduce body weight in people with type 2 diabetes through enhancement of glucose-stimulated insulin secretion, reduced food intake, inhibition of glucagon secretion in hyperglycaemic or euglycaemic states, and delayed gastric emptying.^{33,38-44} GIP also enhances glucose-stimulated insulin secretion in people without type 2 diabetes whereas this effect is diminished in people with type 2 diabetes, but unlike GLP-1, it stimulates glucagon secretion in hypoglycaemic states.⁴⁵⁻⁵¹ In normal physiology, these two incretin hormones exert relatively short-lived effects at their respective receptors because of their rapid degradation by the dipeptidyl peptidase-4 enzyme and a resulting half-life of minutes.⁵² Tirzepatide is a single modified peptide with GIP and GLP-1 receptor agonism approved for treatment of people with type 2 diabetes in the United States and under investigation for its effects on chronic weight management, heart failure with preserved ejection fraction and obesity, major adverse cardiovascular events (MACE) and non-cirrhotic non-alcoholic steatohepatitis (NASH).

1.1 | Tirzepatide molecule overview

Tirzepatide is a single modified GIP/GLP-1 receptor agonist engineered from the GIP sequence to also have GLP-1 activity. Tirzepatide was designed to achieve GIP receptor affinity comparable with that of native GIP and to bind the GLP-1 receptor with approximately 5-fold weaker affinity than native GLP-1 (Panel).⁵³ The molecule is a 39 amino acid linear peptide that includes a C20 fatty diacid moiety and has a half-life of approximately 5 days to enable once-weekly subcutaneous injection.⁵⁴ In preclinical models, tirzepatide engages the GLP-1 receptor as a biased agonist signalling towards the generation of cyclic adenosine monophosphate (cAMP) with reduced recruitment of β -arrestin potentially leading to diminished GLP-1 receptor internalization.⁵³ These experiments suggest this mechanism may enable sustained signalling of tirzepatide at the GLP-1 receptor potentially contributing to a greater insulinotropic effect at pancreatic beta cells.⁵³ However, the clinical implications of biased agonism remain unclear.

Clinical studies showed that the effects of tirzepatide on glycaemic control are underpinned by concurrent improvements in β -cell function, insulin sensitivity and α -cell function.⁵⁵⁻⁵⁷ Tirzepatide (15 mg) significantly improved first phase, second phase, and total insulin secretion and insulin sensitivity.⁵⁷ In meal tolerance testing, tirzepatide also reduced fasting and meal-stimulated glucagon secretion.⁵⁷ Evidence from studies in mice suggest that the improvements in insulin resistance with tirzepatide are both weight dependent and independent.⁵⁸ Initial studies in humans indicate that weight loss may only partly account for improvement in insulin sensitivity and that tirzepatide may provide greater improvement in insulin sensitivity than a selective GLP-1 receptor agonist per unit weight loss, with this effect being most evident in those with greater weight loss.^{55,59}

Additional results from mechanism of action studies indicate that tirzepatide reduced energy intake and may reduce appetite, as assessed via a visual analogue scale.^{60,61} However, these reductions did not differ from the GLP-1 receptor agonist semaglutide.⁶¹

PANEL. PRECLINICAL CHARACTERIZATION, PHARMACOKINETICS AND PHARMACODYNAMICS OF TIRZEPATIDE

Tirzepatide binds with high affinity to human GLP-1 and GIP receptors expressed on transfected HEK293 cells.⁵⁴

Binding affinity [K_i \pm SEM (nM)]

- GIP receptors: 0.135 \pm 0.020
- GLP-1 receptors: 4.23 \pm 0.23

Tirzepatide potently stimulates cAMP accumulation by human GLP-1 and GIP receptors expressed on transfected HEK293 cells.⁵⁴

Intracellular cAMP accumulation [EC_{50} \pm SEM (nM)]

- GIP receptors: 0.0224 \pm 0.0053
- GLP-1 receptors: 0.934 \pm 0.068

Tirzepatide stimulated cAMP accumulation in differentiated human adipocytes that express GIP receptors but not GLP-1 receptors. The effect was comparable with that of GIP alone.⁵⁴

Pharmacokinetics below are average values from healthy single ascending dose cohorts administered 0.25-8.0 mg doses subcutaneously. Pharmacokinetics in healthy participants are comparable with those with type 2 diabetes⁵⁴

- Geometric mean maximum observed drug concentration (C_{max}) for 5.0 mg: 397 ng/ml
 - Intersubject variability for C_{max} \leq 30% across doses
- $t_{1/2}$: \sim 5 days
- CL/F: 0.056 L/h
- V_z /F: 9.5 L

Pharmacokinetics appear dose proportional, C_{max} reached within 24-48 h post-dose.

Average accumulation following four weekly doses: 1.58.

Tirzepatide delays gastric emptying; e greatest after 1 dose and undergoes tachyphylaxis with repeated once-weekly dosing.⁶⁴

Intrinsic factors

- no clinically meaningful effect of renal or hepatic impairment^{62,63};
- dose adjustment may not be required in patients with renal impairment;
- dose adjustment may not be required in patients with hepatic impairment.

Binding affinity and cAMP potency data are mean \pm SEM, C_{max} , CL/F and V_z /F are geometric mean (% CV). Where, CL/F, apparent total body clearance of drug following subcutaneous administration; $T_{1/2}$, half-life associated with the terminal rate constant in non-compartmental analysis; V_z /F, apparent volume of distribution of drug during terminal phase following subcutaneous administration.

1.2 | Dosing and administration

The preclinical characterization, clinical pharmacokinetics and pharmacodynamics of tirzepatide are presented in the Panel. Tirzepatide pharmacokinetics were similar in participants with renal impairment (lowest estimated glomerular filtration rate category: end stage renal disease (ESRD)) or hepatic [up to severe (class C) on Child-Pugh score] impairment compared with healthy subjects, indicating that dose adjustment may not be required for these groups.^{62,63} Tirzepatide also delays gastric emptying with this effect diminishing over time.⁶⁴ An approximate 20% reduction in the overall exposure of oral contraceptives was observed following the administration of a single 5 mg dose of tirzepatide.⁶⁵ These results were observed in a study conducted at a point where the effect on gastric emptying was maximal, namely following a single 5 mg dose.⁶⁵ This study reflects the effect of a single 5 mg dose of tirzepatide on oral contraceptive absorption and does

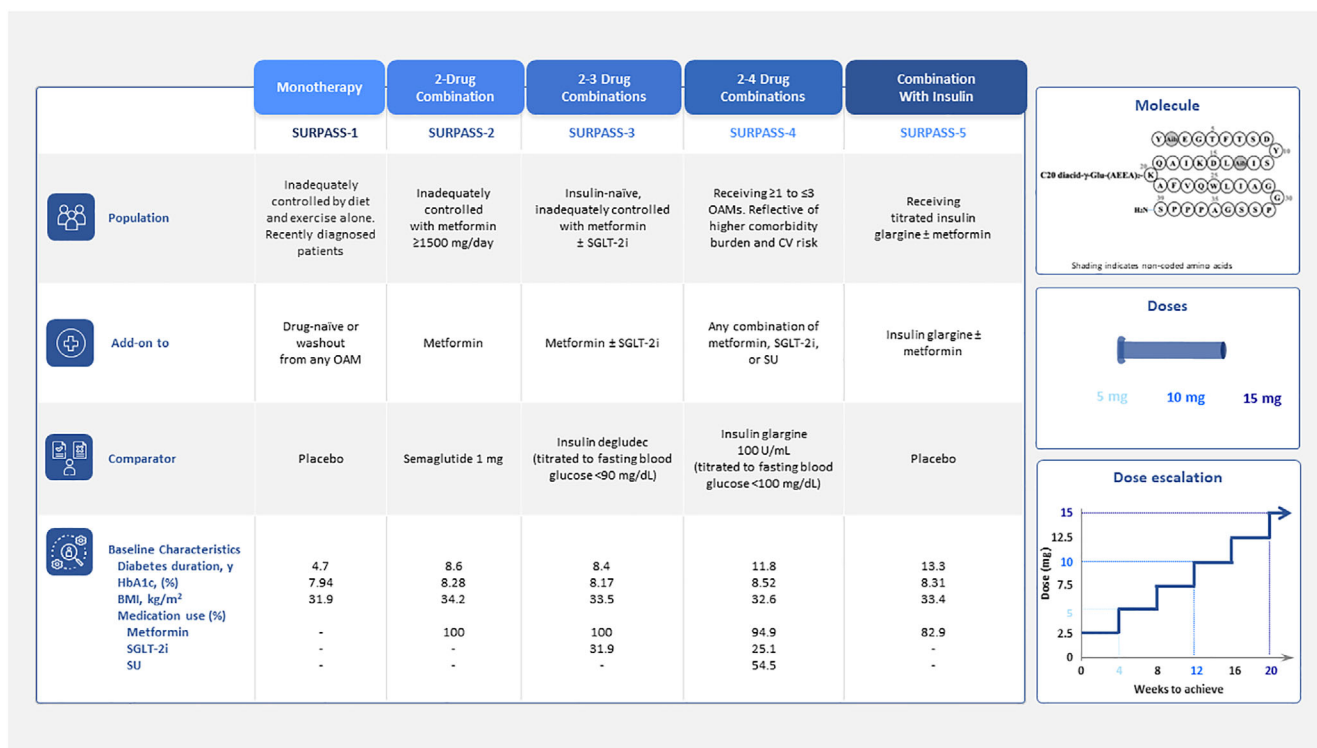


FIGURE 2 Overview of the Phase 3 SURPASS 1-5 clinical programme^{56,73-76} presenting population, baseline therapeutics, comparators and key baseline demographics for SURPASS 1-5 reflecting the progression of disease; molecule structure (tirzepatide is a 39 amino acid synthetic peptide, GIP/GLP-1 receptor agonist conjugated to a C20 fatty diacid moiety); and dose escalation scheme (doses initiated at 2.5 mg once weekly and increased by 2.5 mg every 4 weeks until assigned dose was reached and maintained for duration of trial). BMI, body mass index; CV, cardiovascular; GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide-1; HbA1c, glycosylated haemoglobin A1c; OAM, oral antihyperglycaemic medication; SGLT-2i, sodium-glucose cotransporter-2 inhibitor; SU, sulphonylurea

not take into account tachyphylaxis observed with repeated dosing.⁶⁵ A gastric emptying delay is also observed in patients taking other GLP-1 receptor agonists and the effect diminishes over time.⁶⁶⁻⁷² The dosing recommendation for tirzepatide is to initiate treatment at 2.5 mg and escalate in 2.5 mg doses at 4-week intervals.⁶⁵

In the Phase 3 studies, as in the approved prescribing information, the tirzepatide initiating dose was 2.5 mg once weekly and tirzepatide was increased by 2.5 mg every 4 weeks. In the Phase 3 studies, this was done until the target dose (5, 10 or 15 mg) was reached (Figure 2). The prescribing information indicates that the 2.5 mg dose is for treatment initiation and is not intended for glycaemic control.⁶⁵ This gradual dose escalation scheme was informed by earlier studies that indicated a low starting dose with small dose increments improved tolerability and was associated with a more favourable side-effect profile.^{77,78}

1.3 | Design of the SURPASS 1-5 clinical programme

The Phase 3 SURPASS 1-5 clinical trial programme was designed to capture a spectrum of patient populations reflective of the disease

continuum and differing treatment options seen within clinical practice for type 2 diabetes.^{56,73-76}

Figure 2 provides an overview of the SURPASS 1-5 studies. In addition to HbA1c measurement, SURPASS-3 included a continuous glucose monitoring substudy to evaluate 24-hour glucose profiles, as well as a magnetic resonance imaging (MRI) substudy to examine the effect of treatment on liver fat content and other measures, such as visceral fat.^{79,80} The criteria for increased cardiovascular risk in SURPASS-4 were known coronary, peripheral arterial or cerebrovascular disease, or aged ≥ 50 years with either history of chronic kidney disease and an estimated glomerular filtration rate of < 60 ml/min per 1.73 m² or history of congestive heart failure (New York Heart Association Class II or III).⁷⁵

As different populations were recruited to reflect the type 2 diabetes disease continuum, baseline characteristics (such as diabetes duration and mean HbA1c) varied across the studies (Figure 2).

Data presented here are from the efficacy estimand of each study, which represents on-treatment efficacy without the influence of rescue therapy. Results from the efficacy estimand are generally aligned with those from the treatment-regimen estimand, which represents efficacy irrespective of adherence to study drug or initiation of rescue therapy.^{56,73-76}

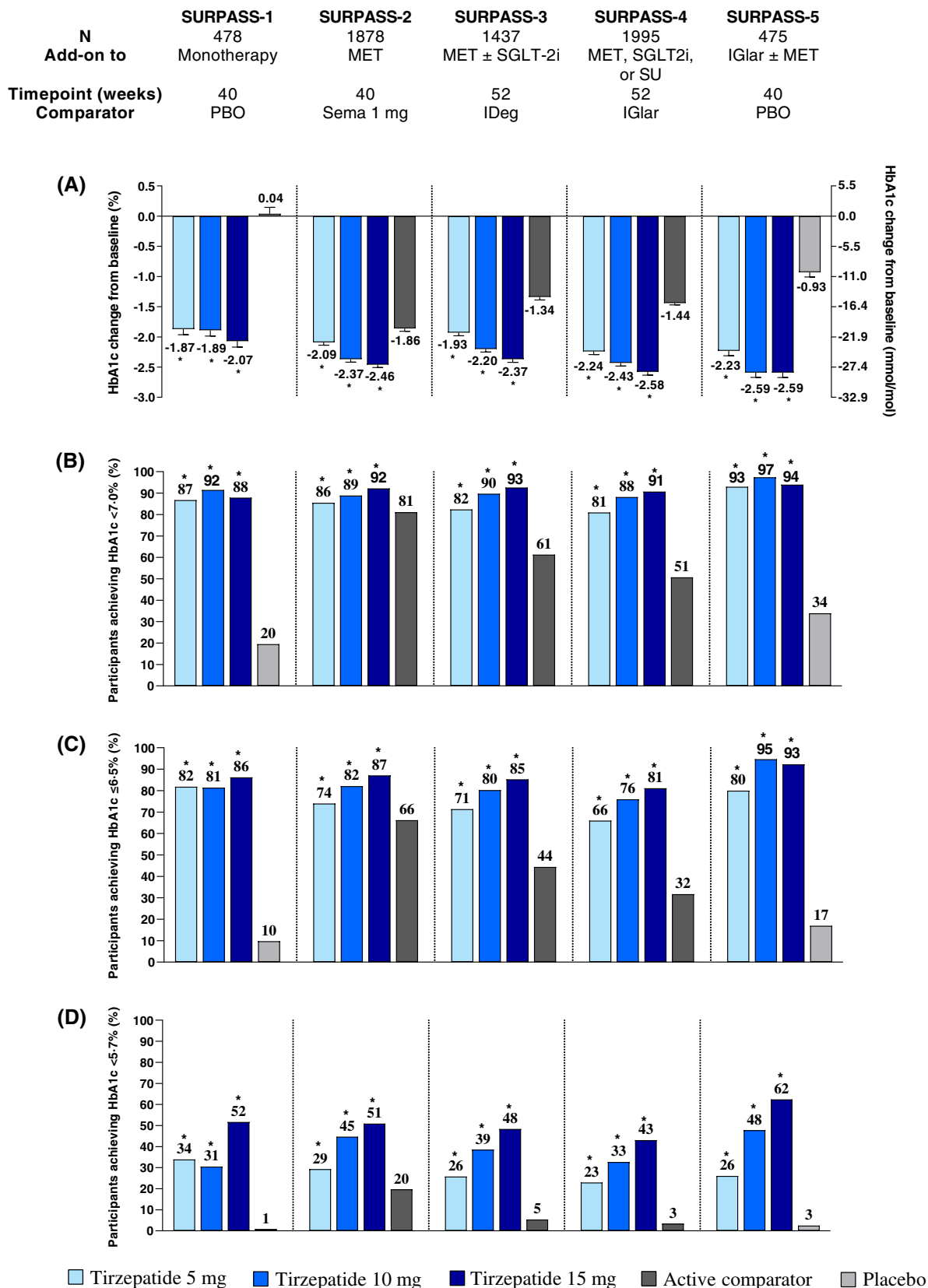


FIGURE 3 Glycaemic efficacy of tirzepatide in SURPASS 1-5.^{56,75-78,87} Data are estimated mean (SE) or percentage and from the modified intention-to-treat population (efficacy analysis set) of each study. (A) HbA1c change from baseline to the primary study endpoint; proportion of participants achieving HbA1c targets (B) <7.0%, (C) ≤6.5% and (D) <5.7%. **p* < .05 versus placebo or active comparator. HbA1c, glycosylated haemoglobin A1c; IDeg, insulin degludec; IGlar, insulin glargine 100 U/ml; MET, metformin; N, number of patients who were randomly assigned and received at least one dose of study drug; PBO, placebo; Sema, semaglutide; SGLT-2i, sodium-glucose cotransporter-2 inhibitor; SU, sulphonylurea

1.3.1 | Study durations

Study durations of 40 weeks (SURPASS-1, -2 and -5) and 52 weeks (SURPASS-3) allowed for the gradual dose escalation scheme of up to 20 weeks to reach the 15 mg dose and a maintenance period to assess therapeutic efficacy of the 15 mg dose for periods up to 32 weeks. In SURPASS-4, the primary endpoint was at 52 weeks with treatment continued to a maximum of 104 weeks for some participants.

1.3.2 | Study comparators

Comparators included placebo (SURPASS-1 and -5), the GLP-1 receptor agonist semaglutide 1 mg, which was the highest available dose at trial initiation (SURPASS-2), and titrated basal insulins, insulin degludec 100 U/ml (SURPASS-3) and insulin glargine 100 U/ml (SURPASS-4).

1.3.3 | Insulin use in SURPASS-3, -4 and -5

In SURPASS-3 and -4, the basal insulin comparators were titrated using well-established treat-to-target algorithms to reach a prespecified fasting blood glucose value.^{74,75} The HbA1c change from baseline results in the insulin arms using this treat-to-target algorithm were comparable with those disclosed in Phase 3 trials.⁸¹⁻⁸³ The mean daily use at Week 52 was 48.8 U for insulin degludec and 43.5 U for insulin glargine 100 U/ml. In SURPASS-5, background daily insulin glargine 100 U/ml (mean baseline: 0.4 U/kg/day) could be adjusted to maintain a target fasting blood glucose using self-monitored blood glucose of <100 mg/dl. Whereas participants taking insulin glargine alone had an increase of 25.1 U (75%) from baseline at Week 40, participants taking tirzepatide required significantly less insulin [4.4 to -3.8 U (13% to -11%)].⁷⁶ Of note, participants could lower insulin use but, per protocol, could not discontinue insulin therapy.

2 | EFFICACY

2.1 | Glycaemic efficacy

The primary endpoint for all five studies was change from baseline in HbA1c at either 40 or 52 weeks, with a baseline HbA1c of 7.94% to 8.52% (63-70 mmol/mol).^{56,73-76} In all five studies, tirzepatide was associated with mean reductions from baseline in HbA1c ranging from -1.87% to -2.59% (-20 to -28 mmol/mol) (Figure 3A). These reductions were dose dependent and significantly greater with tirzepatide 5, 10 and 15 mg than placebo (0.04%, SURPASS-1), semaglutide 1 mg (-1.86%, SURPASS-2), insulin degludec (-1.34%, SURPASS-3), insulin glargine 100 U/ml (-1.44%, SURPASS-4) and placebo with background insulin (-0.93%, SURPASS-5). Data from SURPASS-4 indicate that HbA1c reductions were maintained at 78 and 104 weeks, although participant numbers were smaller at the

latter time point, providing evidence for sustained glycaemic control with tirzepatide treatment beyond 1 year.⁷⁵ Across the five studies, the magnitude of HbA1c reductions achieved were greatest in SURPASS-4 and -5, probably reflecting higher baseline HbA1c in these studies. In SURPASS-1, the less pronounced dose-response could reflect the relatively early course of type 2 diabetes and potentially more β -cell function in this population, as all three tirzepatide doses led to near-normoglycaemia at 40 weeks and presumably reaching a floor effect (mean HbA1c of 5.9%-6.1%; 41-43 mmol/mol).

Corresponding with the marked HbA1c reductions from baseline, substantial proportions of tirzepatide-treated participants in each study achieved an HbA1c of <7.0% (53 mmol/mol) and \leq 6.5% (48 mmol/mol), corresponding to treatment guideline recommendations for most people by the ADA and European Association for the Study of Diabetes (EASD).^{84,85} Across the five trials, 81%-97% of participants receiving tirzepatide achieved HbA1c <7% (53 mmol/mol) and 66%-95% HbA1c \leq 6.5% (48 mmol/mol) (Figure 3B,C).^{56,73-76} For all doses and both treatment goals, these results were significantly greater compared with either placebo, semaglutide 1 mg, insulin degludec, insulin glargine 100 U/ml, or placebo with background insulin. More participants who received tirzepatide also achieved HbA1c <5.7% (39 mmol/mol) compared with all comparators (Figure 3D).^{56,73-76}

In SURPASS-2, a composite endpoint assessing the proportion of participants who achieved HbA1c \leq 6.5% (48 mmol/mol) without clinically significant (<54 mg/dl) or severe hypoglycaemia and with \geq 10% weight loss was met by 32%-60% of participants who received tirzepatide compared with 22% who received semaglutide 1 mg.⁵⁶

Fasting serum glucose (FSG) was significantly reduced by all tirzepatide doses in SURPASS-1, -2 and -5 at either 40 or 52 weeks compared with placebo, semaglutide 1 mg and placebo with background insulin, respectively.^{56,73,76} FSG levels at endpoint did not differ from insulin degludec in the 10- and 15-mg groups in SURPASS-3 and in SURPASS-4 did not differ from insulin glargine 100 U/ml in the 5- and 10-mg groups but were significantly lower in the 15-mg group (Figure S1). In SURPASS-3 and -4, significant reductions in FSG compared with baseline were apparent as early as 2 weeks (the earliest measurement) after treatment initiation when all participants received 2.5 mg.^{74,75} Across the two studies and three dose groups, the magnitude of this change at 2 weeks was -30.3 to -34.0 mg/dl (-18% to -20%). In a small Phase 1 study, 24 h following treatment with a 2.5 mg initiating dose of tirzepatide, there was a non-statistically significant (vs. placebo) decrease from baseline of -19 mg/dl in FSG. However, on Day 8 (pre-dose) a statistically significant (vs. placebo) reduction of -39 mg/dl occurred, indicating early glucose-lowering potential following tirzepatide initiation.⁸⁶

Overall daily mean, premeal daily mean and 2-h postmeal daily mean measured during 7-point self-monitored blood glucose profiles indicate that tirzepatide enabled participants to maintain a significantly lower blood glucose level throughout the day in all five studies at 40 or 52 weeks.^{56,73-76}

In addition to the significant reductions in HbA1c and FSG, tirzepatide treatment significantly increased (to 73%) the proportion of a

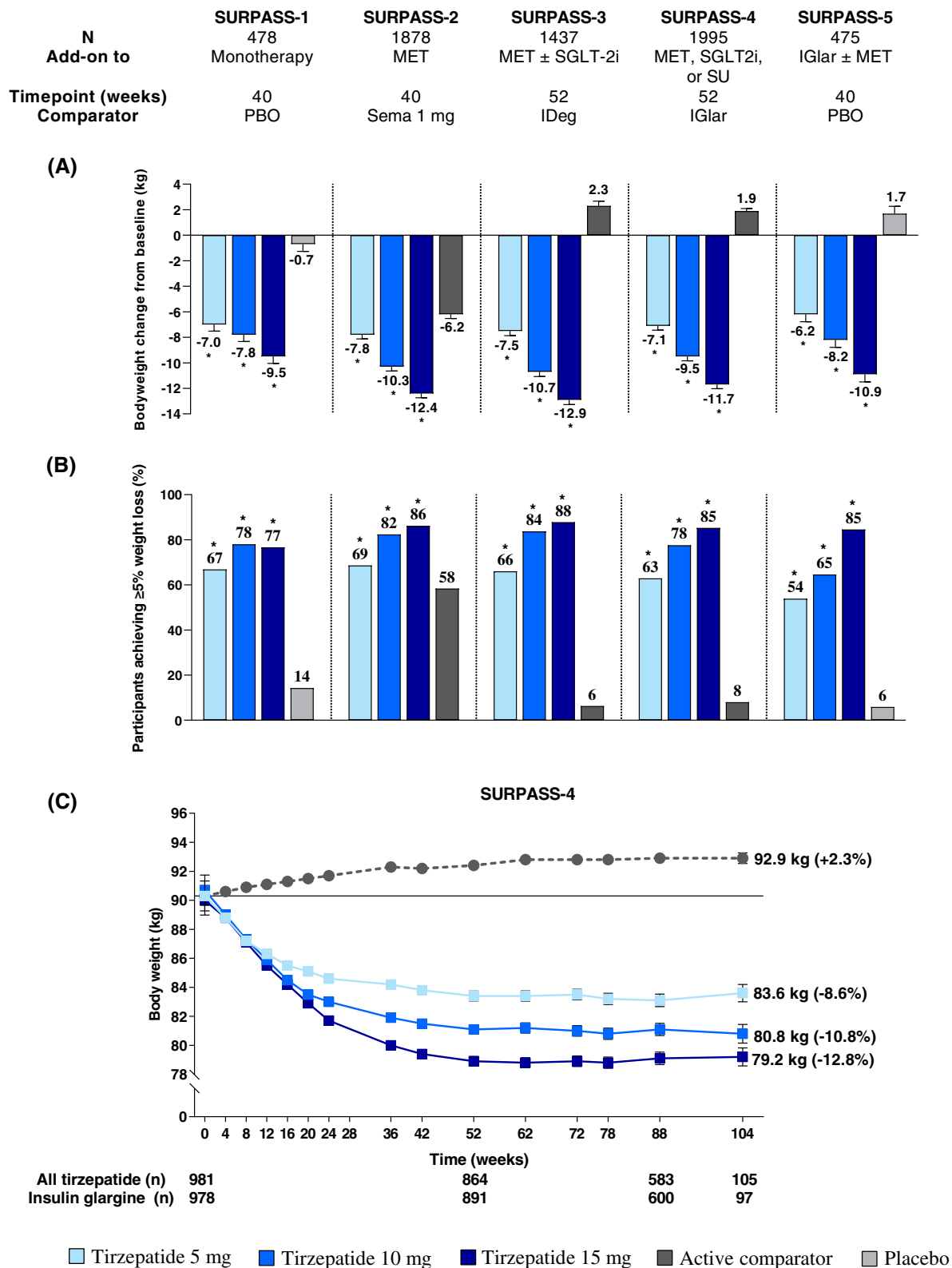


FIGURE 4 Body weight loss with tirzepatide in SURPASS 1-5.^{56,73-76,87} Data are estimated mean (SE) or percentage and from the modified intention-to-treat population (efficacy analysis set) of each study. (A) Body weight change from baseline to the primary study endpoint; (B) proportion of participants achieving ≥5% weight loss at the primary study endpoint; (C) body weight change from baseline over time in SURPASS-4. Solid line indicates baseline values. **p* < .05 versus placebo or active comparator. IDeg, insulin degludec; IGlar, insulin glargine 100 U/ml; MET, metformin; N, number of patients who were randomly assigned and received at least one dose of study drug; PBO, placebo; Sema, semaglutide; SGLT-2i, sodium-glucose cotransporter-2 inhibitor; SU, sulphonylurea

24-h period spent within a tight target glucose range (71–140 mg/dl, 3.9–7.8 mmol/L) compared with insulin degludec treatment (48%) at 52 weeks.⁷⁹ This time spent in tight target glucose range was also accompanied with a smaller within-day glucose coefficient of variation (CV %) and significant reduction in CV% compared with insulin degludec, indicating low glycaemic variability with tirzepatide.

2.2 | Weight loss

Across the five SURPASS studies and the spectrum of people with type 2 diabetes represented in them, the mean baseline body weight ranged from 86 to 95 kg.^{56,73–76} Tirzepatide showed clinically meaningful reductions in body weight and a significantly higher proportion of participants achieving 5%, 10% and 15% body weight loss targets versus placebo and active comparators.^{56,73–76}

The average weight loss ranged from 6.2 to 12.9 kg across the three dose groups for all five studies. Weight loss followed an approximately dose proportional pattern where tirzepatide 5 mg was associated with 6.2 to 7.8 kg loss, 10 mg with 7.8 to 10.7 kg loss and for 15 mg 9.5 to 12.9 kg loss (Figure 4A).^{56,73–76} All tirzepatide doses significantly reduced body weight compared with semaglutide 1 mg, and weight loss with tirzepatide 15 mg (–12.4 kg) was double that with semaglutide 1 mg (–6.2 kg).⁵⁶ Body weight reductions were also evident when tirzepatide was combined with therapies associated with weight gain, such as insulin or sulphonylureas.^{39,75,76,85}

Up to 88% of participants who were assigned tirzepatide 15 mg reached at least 5% weight loss from baseline at Week 52, where the average starting weight was 94.3 kg and 32% were being treated with metformin plus an sodium-glucose cotransporter-2 (SGLT2) inhibitor (range 77%–88% for SURPASS 1–5) (Figure 4B).^{56,73–76} Among participants who received tirzepatide 15 mg, at least 10% weight loss was achieved by up to 69% (range 47%–69%), and at least 15% weight loss was achieved by up to 43% (range 27%–43%) (Figure S2A,B).^{56,73–76} The proportion of participants assigned to tirzepatide who reached these weight loss targets was consistently higher compared with semaglutide 1 mg (Figures 4B and S2A,B).^{56,87} In tirzepatide-treated participants who used background insulin, 7% to 85% reached the weight loss targets of at least 5%, 10% or 15% (Figures 4B and S2A,B).⁷⁶

Weight reduction with tirzepatide began during the dose-escalation phase as early as 4 weeks after treatment initiation and continued without appearing to plateau by the primary study endpoints at 40 or 52 weeks.^{56,73–76} In SURPASS-4, with a variable treatment period up to 104 weeks, weight loss reached a plateau at about 1 year and was sustained for up to 18 months to 2 years (Figure 4C).⁷⁵

2.3 | Cardiometabolic measures

The substantial reductions in body weight achieved with tirzepatide were accompanied by significant reductions in waist circumference compared with placebo or active comparator in each study.^{56,73–76} For

example, in SURPASS-2 waist circumference decreased by 6.9 to 9.9 cm with tirzepatide and 5.6 cm with semaglutide 1 mg at Week 40 from a mean baseline waist circumference of 109.3 cm.⁵⁶ Similarly in SURPASS-4, a reduction in waist circumference was observed to 52 weeks in the tirzepatide arms and this was sustained through to 104 weeks, although participant numbers gradually decreased beyond 52 weeks.⁷⁵

Regarding lipid profile changes, at 40 weeks in SURPASS-2, triglyceride levels were lower in those who received tirzepatide (–19.0% to –24.8%) than semaglutide 1 mg (–11.5%) and high-density lipoprotein cholesterol levels were higher (6.8%–7.9% vs. 4.4%).⁵⁶ Changes in low-density lipoprotein cholesterol (–5.2% to –7.7% vs. –6.4%) and total cholesterol (–5.5% to –6.3% vs. –4.8%) levels were similar between tirzepatide and semaglutide 1 mg. In the high cardiovascular risk population of SURPASS-4, all tirzepatide arms reduced triglycerides (–16.3% to –22.5% vs. –6.4%), low-density lipoprotein cholesterol (–6.8% to –8.3% vs. 1.4%) and total cholesterol (–5.1% to –5.6% vs. 0%) and increased high-density lipoprotein cholesterol (6.7%–10.8% vs. 2.9%) compared with baseline and insulin glargine 100 U/ml.⁷⁵ These improvements occurred on top of background lipid-lowering therapy use, which 82% used at baseline with little change throughout the study.⁷⁵

Normal liver fat content is generally considered to be <5%, although this varies depending on the measurement method used.⁸⁸ A ≥30% relative reduction in liver fat assessed by MRI-proton density fat fraction (PDFF) has been associated with improvement in NASH.⁸⁹ In a meta-analysis, people with a ≥30% relative decline in MRI-PDFF were more likely to have a histological response (51% vs. 14%, $p < .001$) and NASH resolution (41% vs. 7%; $p < .001$) than those with a smaller decline.⁹⁰ In people with type 2 diabetes, elevated liver fat content and increased visceral fat have been associated with an increased risk of cardiometabolic complications.^{91,92} In the MRI substudy of SURPASS-3, tirzepatide reduced liver fat content (measured by MRI-PDFF) to a significantly greater extent than insulin degludec (–8.09% vs. –3.38%) at Week 52.⁸⁰ More tirzepatide-treated participants achieved a liver fat content of ≤10% (60%–78% vs. 35%) and a relative decrease in liver fat content from baseline of ≥30% (67%–81% vs. 32%). In addition, up to 48% of participants who received tirzepatide reached a liver fat content <6%. Tirzepatide was also associated with clinically meaningful reductions in abdominal visceral adipose tissue (–1.10 to –1.65 L) and abdominal subcutaneous adipose tissue (–1.40 to –2.25 L) volumes, both of which increased in the insulin degludec arm (0.38 and 0.63 L, respectively).

3 | SAFETY

3.1 | Overview and adverse events

The safety profile of tirzepatide was generally similar to that of the GLP-1 receptor agonist class and tirzepatide-related safety findings were consistent across SURPASS 1–5.^{56,73–76} Tirzepatide was generally well tolerated. However, discontinuation because of adverse events varied between tirzepatide and comparators in some studies

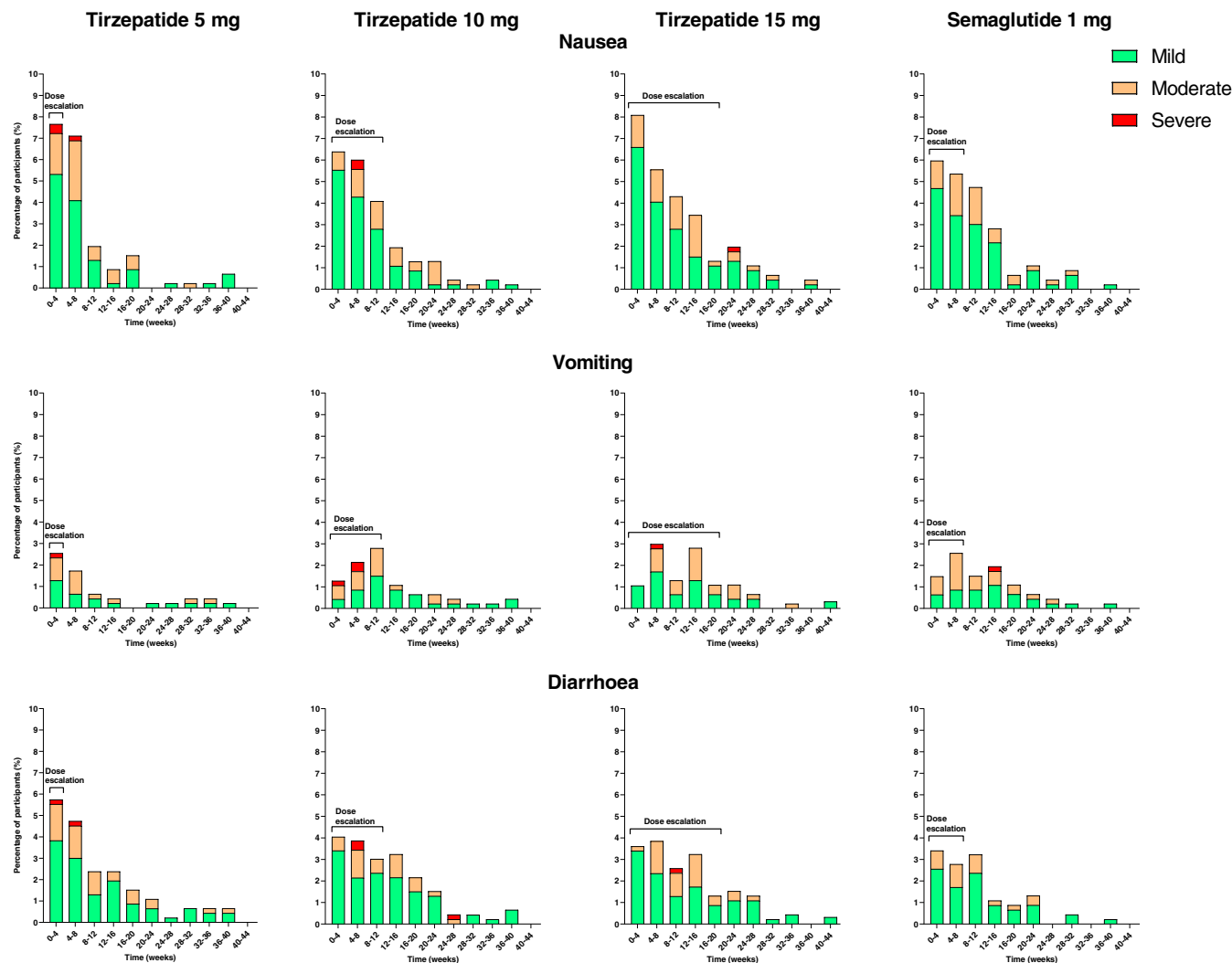


FIGURE 5 Incidence of nausea, vomiting and diarrhoea in SURPASS-2.⁵⁶ Data are percentage of participants who reported a new event relative to participants at risk during a time interval (incidence) and from the modified intention-to-treat population (safety analysis set). Dose escalation indicates the time period before reaching the maintenance dose of tirzepatide 5 mg (4 weeks), 10 mg (12 weeks), and 15 mg (20 weeks) and semaglutide 1 mg (8 weeks)

(Table S1).^{56,73-76} Overall, 3% to 11% of participants who received tirzepatide reported treatment discontinuation because of adverse events, in comparison with placebo (3%), semaglutide 1 mg (4%), basal insulins (1%-5%) and placebo with background insulin (3%). Considering SURPASS-2 specifically, adverse events were the most common reason for treatment discontinuation with tirzepatide and semaglutide. This was more common with tirzepatide 10 [40 participants (9%)] and 15 mg [40 participants (9%)] than with tirzepatide 5 mg [28 participants (6%)] and semaglutide 1 mg [19 participants (4%)].⁵⁶ The proportion of participants experiencing ≥ 1 treatment-emergent adverse event (TEAE) was similar between tirzepatide and comparator in each study (Table S1), and similar TEAEs emerged as common across the studies (Table S2).^{56,73-76}

Generally, the proportions of participants who reported serious adverse events (SAEs) were similarly distributed between tirzepatide and comparator treatment arms (Table S1), and the range of SAEs

reported is consistent with that reported for semaglutide 1 mg in the SUSTAIN programme.⁹³⁻⁹⁷ A higher number of SAEs was reported in tirzepatide-treated participants than those who received semaglutide 1 mg in SURPASS-2. The most frequent SAE reported was COVID-19-related pneumonia in both the tirzepatide (0.4%) and semaglutide 1 mg (0.9%) groups.⁵⁶ Overall, 79 deaths occurred in the SURPASS 1-5 studies, 41 (1%) in the tirzepatide arms and 38 (2%) in the comparator arms (Table S1). In SURPASS-2, there were five deaths related to COVID-19, with the death of a sixth being adjudicated as from cardiovascular causes but with suspected COVID-19.⁵⁶ These occurred in five (0.4%) participants who received tirzepatide and one who received semaglutide (0.2%). In the high-risk population of SURPASS-4, six (0.6%) COVID-19-related deaths were reported in the tirzepatide arms and eight (0.8%) in the insulin glargine 100 U/ml arm.⁷⁵ There was one COVID-19-related death in a tirzepatide-treated participant in

SURPASS-3 (<0.1%) and none in SURPASS-1 or -5.^{73,74,76} No deaths were considered related to study medications.

3.2 | Gastrointestinal adverse events

As expected from the GLP-1 receptor agonist class, gastrointestinal adverse events (including nausea, vomiting and diarrhoea) occurred; their incidence was similar to those in the semaglutide 1-mg group of the SUSTAIN programme.⁹³⁻⁹⁷ In SURPASS-2, with direct comparison with semaglutide 1 mg, gastrointestinal adverse events (40%-46% vs. 41%), nausea (17%-22% vs. 18%), vomiting (6%-10% vs. 8%) and diarrhoea (13%-16% vs. 12%) were reported for participants on tirzepatide and semaglutide 1 mg.⁵⁶ As shown in time-course plots (Figure 5), most events were mild or moderate in severity and occurred more frequently in the dose-escalation phase in all groups. In SURPASS-4 (a population with a relatively long duration of diabetes, high background medication use, high number of comorbidities and the longest follow-up period) nausea was reported in 12%-23% on tirzepatide and 2% on insulin glargine 100 U/ml; vomiting in 5%-9% and 2%; and diarrhoea in 13%-22% and 4%, respectively.⁷⁵ Gastrointestinal side effects were also reported more frequently than insulin glargine 100 U/ml with GLP-1 receptor agonists.^{94,98,99} Consistent with the low rate of study treatment discontinuation, $\leq 3\%$ of participants who received at least one dose of tirzepatide discontinued treatment because of either nausea, vomiting or diarrhoea (Table S1).^{56,73-76}

3.3 | Hypoglycaemia

Despite the magnitude of the observed effect of tirzepatide on glycaemia, the incidence of hypoglycaemia, defined as clinically significant [blood glucose <54 mg/dl (<3 mmol/L)] or severe, was low across the SURPASS studies.^{56,73-76} The incidence of hypoglycaemia was lower for insulin-naïve participants assigned to tirzepatide (1%-2%) compared with insulin degludec (7%) and for tirzepatide (6%-9%) compared with insulin glargine 100 U/ml (19%).^{74,75} In the high cardiovascular risk population of SURPASS-4, 145 hypoglycaemic episodes occurred in the tirzepatide arms and 492 in the insulin glargine 100 U/ml arm.⁷⁵ The incidence appeared to be dependent on concomitant medication use; hypoglycaemia occurred in 10%-14% of tirzepatide-treated participants using a sulphonylurea at baseline and 1%-3% of those who did not use a sulphonylurea. In SURPASS-5 (in which participants used background insulin) tirzepatide did not increase hypoglycaemia compared with placebo (14%-19% vs. 13%, respectively).⁷⁶ These results suggest that the risk of hypoglycaemia attributable to tirzepatide is low when not combined with an insulin secretagogue or insulin.

3.4 | Blood pressure and cardiovascular outcomes

A cardiovascular meta-analysis, including people across the diabetes clinical spectrum, indicated that tirzepatide did not increase the risk of

major cardiovascular events versus control (placebo or active comparator).¹⁰⁰ Overall, 142 people had at least one MACE-4 (cardiovascular death, myocardial infarction, stroke and hospitalization because of unstable angina) event, and the hazard ratio for tirzepatide versus pooled control was 0.80 (95% CI: 0.57-1.11). Per regulatory guidance, an upper bound of the 95% CI <1.8 for MACE-4 indicates that a drug is not associated with an unacceptably high risk for cardiovascular events versus comparators.¹⁰¹⁻¹⁰⁴ There was also no increased risk in the secondary composite outcome MACE-3 (cardiovascular death, myocardial infarction and stroke). The ongoing SURPASS-CVOT, which is anticipated to be completed in 2024, will evaluate the cardiovascular efficacy of tirzepatide compared with dulaglutide 1.5 mg (NCT04255433); as such there is no cardiovascular indication reflected on the prescribing information for tirzepatide.

Across the SURPASS studies, tirzepatide generally decreased blood pressure over time with no return to baseline by the primary endpoint.^{56,73-76} Taking SURPASS-2 as an example, from a mean baseline systolic blood pressure of 130.6 mmHg and diastolic blood pressure of 79.2 mmHg, mean systolic and diastolic blood pressure decreased with tirzepatide (up to -6.5 and -2.9 mmHg, respectively), compared with decreases of -3.6 and -1.0 mmHg, respectively, with semaglutide 1 mg at 40 weeks.⁵⁶ In SURPASS-4, mean systolic and diastolic blood pressures decreased with tirzepatide (up to -4.8 and -1.0 mmHg, respectively) and increased with insulin glargine 100 U/ml (1.3 and 0.7 mmHg, respectively) at 52 weeks.⁷⁵ A similar trend was observed over the remainder of the study. As expected from the GLP-1 class, transient increases in pulse rate were seen in the SURPASS studies, with the magnitude of increase being similar to that observed with GLP-1 receptor agonists in the literature and semaglutide 1 mg in SURPASS-2.^{56,73-76,105-107} Although the mechanistic pathway is not fully known, GLP-1 receptor agonists have shown neutral or protective cardiovascular effects in cardiovascular outcomes trials.¹⁰⁸

3.5 | Adverse events of special interest

The occurrence of adverse events of special interest are presented in Table S3.^{56,73-76} Family or personal history of medullary thyroid carcinoma was an exclusion criterion of SURPASS 1-5. No cases of medullary thyroid carcinoma were reported during any of the trials.^{56,73-76} The prescribing information for tirzepatide includes a warning for the risk of thyroid C-cell tumours. Hypersensitivity and injection site reactions were infrequent with tirzepatide treatment.^{56,73-76} Few cases of adjudicated pancreatitis and cholelithiasis were reported.^{56,73-76} Participants with a history of proliferative diabetic retinopathy, diabetic maculopathy, or non-proliferative diabetic retinopathy requiring acute treatment were excluded from the Phase 3 studies. Few TEAEs of diabetic retinopathy were reported.^{56,73-76}

In SURPASS-2 reductions in estimated glomerular filtration rate, urine albumin/creatinine ratio, alanine transaminase and aspartate aminotransferase at 40 weeks were comparable for tirzepatide and semaglutide 1 mg.⁵⁶ Although antidrug antibodies have been detected in 51.1% among antidrug antibody-evaluable participants treated with

tirzepatide across the Phase 3 studies there was no discernible impact on efficacy, safety, or pharmacokinetics. Antidrug antibodies have also been reported to varying extents with GLP-1 receptor agonists, again with little apparent clinical relevance.^{109,110}

4 | DISCUSSION

When considering treatment options for type 2 diabetes, in addition to glycaemic effects, factors such as comorbidities, hypoglycaemia risk, effects on body weight, side effects and patient preferences, including frequency of administration, should be considered.^{39,85,111} In addition to improving glycaemia, the take away from the SURPASS 1-5 studies showed efficacy of tirzepatide to reduce visceral adiposity, blood pressure, triglycerides, waist circumference, body weight and liver fat content. These improvements were apparent across the diabetes continuum when used as monotherapy in people newly diagnosed with type 2 diabetes and as combination therapy with metformin, SGLT2 inhibitors and/or sulphonylureas or insulin. The head-to-head SURPASS-2, -3 and -4 trials showed that tirzepatide achieved greater glucose lowering and weight lowering than semaglutide 1 mg, titrated insulin glargine 100 U/ml and titrated insulin degludec.

The vast majority of participants treated with tirzepatide achieved HbA1c targets of <7.0% and ≤6.5% (53 and 48 mmol/mol) recommended by ADA/EASD and AACE/ACE for most people with type 2 diabetes.^{84,85,111} A higher proportion of participants who received tirzepatide also reached an HbA1c <5.7% (39 mmol/mol; reflecting near-normoglycaemia) than with comparators, including semaglutide 1 mg.^{56,73-76} This may offer further benefit in reducing the risk of micro- and macrovascular complications, provided it can be achieved without significant hypoglycaemia.^{84,112} The risk of hypoglycaemia with tirzepatide treatment remained low when not combined with an insulin secretagogue or insulin.

Treatment options for people with type 2 diabetes that provide clinically meaningful weight loss have been limited to selective GLP-1 receptor agonists in high doses and to a lesser extent SGLT2 inhibitors.^{39,113} Consistent with the current awareness that weight management is an important factor in overall diabetes care,^{14,19,39} tirzepatide provided clinically meaningful weight reductions, even when used in conjunction with therapies associated with weight gain. These reductions were of a greater magnitude than with semaglutide 1 mg in SURPASS-2. Ameliorative effects of 15% weight loss on type 2 diabetes progression to date have been shown with non-pharmacotherapy means, but to date pharmacotherapies have not been able to achieve this.¹⁹ However, the weight loss results in people with type 2 diabetes treated with tirzepatide suggest that the more ambitious targets of 10% or 15% weight loss may be feasible for some people taking tirzepatide, thus potentially conferring additional glycaemic benefit. Data from SURMOUNT-1 also indicate the potential of tirzepatide as a therapeutic for people living with obesity without type 2 diabetes. After 72 weeks of tirzepatide treatment (up to 15 mg), mean body

weight changes were up to -23.6 kg (-23%), and up to 96%, 90% and 78% achieved ≥5%, ≥10% and ≥15% body weight loss, respectively.¹¹⁴

As semaglutide 2 mg has only been recently approved (2022) for use in Europe and the United States, the SURPASS Phase 3 clinical trial programme was limited to those doses available at the time (1.0 mg) and did not include the semaglutide 2 mg dose. However, an adjusted indirect treatment comparison using data from SURPASS-2 and SUSTAIN FORTE, leveraged the semaglutide 1 mg comparator to assess the treatment effect of semaglutide 2 mg and tirzepatide 5, 10 and 15 mg on an aggregate data population.¹¹⁵ In this adjusted indirect treatment comparison, tirzepatide 10 and 15 mg significantly reduced HbA1c and body weight versus semaglutide 2 mg whereas there were no differences between tirzepatide 5 mg and semaglutide 2 mg. The magnitude of these differences were also clinically meaningful, with an estimated treatment difference for HbA1c reduction of 0.4% and body weight reduction of 3-5 kg for tirzepatide 10 and 15 mg compared with semaglutide 2 mg.

Use of a GLP-1 receptor agonist is recommended by ADA/EASD in people with type 2 diabetes and established atherosclerotic cardiovascular disease and should be considered for those at high risk of cardiovascular disease to reduce MACE risk.¹¹⁶ The ongoing SURPASS-CVOT (NCT04255433) will provide definitive evidence on the impact of tirzepatide on cardiovascular risk relative to the GLP-1 receptor agonist dulaglutide, which is also indicated for the reduction in cardiovascular risk for people with established cardiovascular disease or multiple risk factors. Cardiovascular outcome trials for some GLP-1 receptor agonists, including semaglutide 1 mg, focused on populations with established cardiovascular disease.¹¹⁷⁻¹¹⁹ In contrast, most participants in the REWIND cardiovascular outcome trial for dulaglutide 1.5 mg, which showed reduced cardiovascular outcomes with a similar effect size to other GLP-1 receptor agonist trials, had cardiovascular risk factors without established cardiovascular disease.^{120,121} This indicates that dulaglutide may be a robust comparator for tirzepatide in the SURPASS-CVOT. Currently available data from SURPASS indicate beneficial effects on blood pressure and lipids. Data from the cardiovascular meta-analysis, including the high cardiovascular risk population in SURPASS-4, suggest no increased cardiovascular risk with tirzepatide.¹⁰⁰

SURPASS 1-5 did not include all population groups. For example, women who were pregnant or breastfeeding were excluded from the studies. Although there was no upper age limit across SURPASS 1-5 and the age profile varied across the studies, reflecting the different inclusion and exclusion criteria, few participants were ≥85 years of age. While SURPASS 1-5 excluded people <18 years of age, study NCT05260021 will evaluate tirzepatide in paediatric and adolescent participants.

5 | CONCLUSION

In the Phase 3 SURPASS-1-5 studies, which included >6000 people with type 2 diabetes, tirzepatide was associated with

clinically meaningful reductions in both HbA1c and body weight when used across the diabetes treatment continuum, from monotherapy to combination with basal insulin. These data were generally representative of a broad spectrum of people with type 2 diabetes in terms of disease duration, comorbidities and complications, similar to clinical practice. In each study, the magnitude of glucose-lowering efficacy and weight loss with tirzepatide was greater than with comparators, which included semaglutide 1 mg and titrated basal insulin glargine 100 U/ml and insulin degludec. Tirzepatide was well tolerated, and its safety profile appears generally similar to the GLP-1 receptor agonist class. These findings suggest that tirzepatide may be a useful therapy for many people with type 2 diabetes as part of individualized patient-centred care.

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CONFLICT OF INTEREST

CDB reports consulting fees from Eli Lilly and Company, Novo Nordisk, AstraZeneca, Boehringer-Ingelheim and Abbott Diagnostics; and payment/honoraria from Eli Lilly and Company and Novo Nordisk. CB reports consulting fees from Abbott, BI, Eli Lilly and Company, and Merck; and payment/honoraria from BI, Intas, Merck and Novo. CW reports research funding from Eli Lilly and Company, Abbott, Corcept, Regeneron, Mylan and Novo Nordisk; participation on a Data Safety Monitoring Board for the NIH Artificial Pancreas Project; and is president of the Endocrine Society. AH, SEA and JP are employees and shareholders of Eli Lilly and Company.

DATA AVAILABILITY STATEMENT

Lilly 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 US and EU and after primary publication acceptance, whichever is later. No expiration date of data requests is currently set once data are made available. Access is provided after a proposal has been approved by an independent review committee identified for this purpose and after receipt of a signed data sharing agreement. Data and documents, including the study protocol, statistical analysis plan, clinical study report, 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>.

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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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