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REVIEW

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Tirzepatide for overweight and obesity management

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ABSTRACT

Introduction: Tirzepatide is a once-weekly dual agonist, acting on glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) receptors. It is approved at the same doses (5, 10 and 15 mg) for both type 2 diabetes (T2D) and chronic weight management.

Areas Covered: Following a search in PubMed, clinicaltrials.gov, conference abstracts and Lilly website, we review herein the global phase 3 SURMOUNT program on tirzepatide's safety and efficacy for chronic weight management. Additionally, we discuss findings from the regional SURMOUNT-CN and SURMOUNT-J trials (in East-Asian populations) and the phase 2 SYNERGY-NASH, phase 3 SURMOUNT-OSA and SUMMIT studies on tirzepatide's impact on obesity-related complications. We also explore the clinical implications of SURMOUNT program results, considerations for tirzepatide prescribing for overweight/obesity, ongoing research and evidence gaps.

Expert Opinion: Tirzepatide marks a new era in overweight/obesity treatment, enabling many to achieve ≥ 20% weight loss. It is well-tolerated with a safety profile similar to GLP-1 receptor agonists. Tirzepatide also results in clinically important improvements in multiple obesity-related complications including sleep apnea, metabolic-dysfunction associated steatohepatitis, heart failure with preserved ejection fraction and diabetes prevention. Ongoing trials will provide further data on tirzepatide's long-term safety, efficacy (including cardiovascular outcomes) and potential cost-effectiveness for managing overweight/obesity and/or T2D.

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1. Introduction

Obesity is a chronic, progressive and relapsing disease process characterized by excess adiposity that impairs health, currently affecting about 650 million people worldwide [1]. Obesity increases also the risk for multiple metabolic complications such as type 2 diabetes (T2D), hypertension, dyslipidaemia, cardiovascular disease (CVD), chronic kidney disease (CKD), metabolic dysfunction-associated steatotic liver disease (MASLD) and certain types of cancer as well as for mechanical complications such as obstructive sleep apnea (OSA) and osteoarthritis [2].

Weight loss (WL) of ≥ 10% and even ≥ 15% results in multiple health benefits and may induce remission of some obesity-related complications [3,4]. Lifestyle interventions are the cornerstone of obesity management [5]. However, even with the most intensive lifestyle interventions, the mean WL typically does not exceed 10% and long-term weight maintenance remains challenging due to physiological compensatory mechanisms (such as increased appetite and reduced energy expenditure) that promote weight regain [6–8]. Bariatric surgery can result in 25–30% mean WL and long-term weight maintenance, but is not scalable at population level – additionally some people may not be fit enough for bariatric surgery, while others may be hesitant due to the perceived risk of postoperative complications [9].

In recent years, glucagon-like peptide-1 (GLP-1) receptor agonists (RAs) have changed the landscape in obesity and T2D management, not only due to their glucose-lowering and WL efficacy, but also their cardio-renal benefits [10–12]. Semaglutide 2.4 mg once weekly is the latest GLP-1 RA approved for obesity management and can result in 15–17% mean WL in people without diabetes and ≈ 10% WL in people with T2D after 68 weeks of treatment [10,13,14]. The difference in WL observed between people with and without T2D when using GLP-1 RAs is not fully understood, but it highlights the heterogeneity in WL with GLP-1 RAs. Moreover, GLP-1 RAs use may also be limited by dose-dependent gastrointestinal side effects [15]. As a result, a considerable proportion of people will not meet the individualized metabolic and WL targets with use of the currently available GLP-1 RAs [16].

Looking for the next step in obesity pharmacotherapies, combinations of GLP-1 with other entero-pancreatic hormones with diverse metabolic actions are under development, with the aim to enhance and/or complement the GLP-1 RA actions [17]. Tirzepatide, a dual GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) RA, is the first combination of entero-pancreatic hormones approved for T2D management

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Article highlights

- Tirzepatide is the first licensed dual agonist [acting on both glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) receptors] for type 2 diabetes (T2D) management and chronic weight management.
- The SURMOUNT program (phase 3 clinical trials) assessed the safety and efficacy of tirzepatide for chronic weight management. In SURMOUNT-1, tirzepatide (5, 10, and 15 mg) led to 16–22.5% mean weight loss (WL) in people with overweight/obesity (without T2D) which was sustained over a period of 3 years. In SURMOUNT-3 and SURMOUNT-4, the maximum tolerated dose of tirzepatide resulted in 26–26.6% mean WL vs. 3.8–9.5% with placebo. In SURMOUNT-2, tirzepatide (10 and 15 mg) achieved up to 15.7% mean WL in people with overweight/obesity and T2D vs. 3.3% with placebo.
- Across the SURMOUNT trials, tirzepatide improved also blood pressure, lipid profile, glycemia, waist circumference and self-reported physical function. Moreover, in a subgroup analysis of SURMOUNT-1, body composition was also improved with tirzepatide compared to placebo.
- The safety profile of tirzepatide was similar to GLP-1 receptor agonists and overall, it was well-tolerated. Mild to moderate gastrointestinal symptoms were the most commonly reported adverse events.
- Tirzepatide significantly reduced the apnea-hypopnea index by 50.7–58.7% in people with obesity and moderate to severe obstructive sleep apnea (SURMOUNT-OSA). The SYNERGY-NASH phase 2 trial showed that in people with MASH and moderate to severe liver fibrosis, tirzepatide resolved MASH without worsening fibrosis in 44–62% and improved liver fibrosis without worsening MASH in 51–55% of participants. The SUMMIT phase 3 trial found also that in people with heart failure with preserved ejection fraction and obesity, tirzepatide reduced heart failure outcomes by 38% and improved symptoms and physical limitations. The SURMOUNT-1 three-year data demonstrates 93% risk reduction in T2D progression with tirzepatide in those with prediabetes.
- Tirzepatide marks a new era in obesity management, where a large proportion of people with obesity can achieve WL ≥ 20% and improve multiple obesity-related complications with pharmacotherapy. Further data on long-term safety and efficacy (including cardiovascular, morbidity and mortality outcomes) as well as the potential cost-effectiveness for people with overweight/obesity and/or T2D is awaited from large clinical trials (SURPASS-CVOT and SURMOUNT-MMO).

and more recently for chronic weight management in people with overweight/obesity [18].

In this review, we will discuss the potential mechanisms of action of tirzepatide and the data from clinical trials evaluating tirzepatide as treatment for overweight/obesity (SURMOUNT phase 3 program) as well as for obesity-related complications. We will also explore the clinical implications of the SURMOUNT program, considerations in prescribing tirzepatide for overweight/obesity management and future directions, including evidence gaps and ongoing research with tirzepatide.

2. Combining GLP-1 and GIP receptor agonists

GLP-1 and GIP are gut hormones secreted from the gastrointestinal tract within minutes of food ingestion [19]. GLP-1 is predominantly released from the L-cells of the ileum and colon [19]. It slows the gastric emptying, promotes satiety and reduces food intake, whilst it also stimulates insulin secretion in response to glucose levels and reduces glucagon secretion (Figure 1) [20].

GIP is secreted from the K-cells in duodenum and jejunum [19]. It promotes insulin secretion and stimulates glucagon in people without diabetes, though GIP's insulinotropic action diminishes in people with T2D, possibly due to downregulation and/or desensitization of GIP receptors [18,21,22]. GIP also enhances energy storage and insulin sensitivity in adipose tissue, whilst it reduces nausea and animal studies suggest that it may also reduce appetite (Figure 1) [19,23,24].

Animal studies have shown that co-administration of GLP-1 and GIP RAs can reduce food intake and body weight to a greater extent than either agent alone, indicating an additive effect [18,25,26]. Further preclinical studies showed that a combined preparation of acylated GLP-1 and GIP RAs had superior glucose-lowering efficacy compared to GLP-1 or GIP RAs given individually [18,27]. These preclinical findings increased the interest in developing unimolecular agonists of GLP-1 and GIP receptors, such as tirzepatide. Interestingly, pharmacological inhibition of the GIP receptor has also demonstrated effectiveness in preventing weight gain in animal models with obesity [28]. Additionally, the combination of GIP receptor antagonism and GLP-1 receptor activation has shown a synergistic effect in reducing body weight in animal models with obesity [28]. Based on these findings, maridebart cafraglutide, a monoclonal antibody that antagonizes the GIP receptor and is conjugated to two modified GLP-1 peptides, which activate the GLP-1 receptor, is also in early-phase clinical trials as obesity treatment [17,29,30].

3. Tirzepatide

3.1. Tirzepatide molecule and mechanism of action

Tirzepatide is a once weekly unimolecular dual GLP-1 and GIP receptor agonist which consists of 39-amino acids, modified to include a C20 fatty acid diacid moiety that prolongs its half-life [31]. Tirzepatide achieves GIP receptor affinity comparable to native GIP while binds to the GLP-1 receptor with approximately 5-fold weaker affinity than native GLP-1 [32]. At the GLP-1 receptor, tirzepatide shows bias in favor of cyclic adenosine monophosphate generation over b-arrestin recruitment [33]. This mechanism may enable sustained signaling of tirzepatide at the GLP-1 receptor and may contribute to a greater overall efficacy [33]. In summary, tirzepatide appears to be an imbalanced (toward GIP receptor) and biased (at the GLP-1 receptor) dual GIP and GLP-1 agonist [33].

Experimental studies in mice have shown that chronic treatment with tirzepatide (10 nmol/kg) lead to a dose-dependent decrease in body weight which was greater than with semaglutide (30 nmol/kg) [32]. This WL was primarily driven by loss in fat mass due to reduction of food intake and a small increase in energy expenditure.

Clinical studies demonstrate that tirzepatide reduces food intake and appetite by increasing satiety and decreasing hunger. For instance, in a study in people with T2D, tirzepatide 15 mg reduced food intake by ≈ 310 kcal more than placebo in an ad-libitum lunch [34]. Further mechanistic studies in people with obesity without diabetes confirmed that tirzepatide markedly reduces food intake versus placebo and it also increased fat oxidation, but without an effect on metabolic adaptation [35].

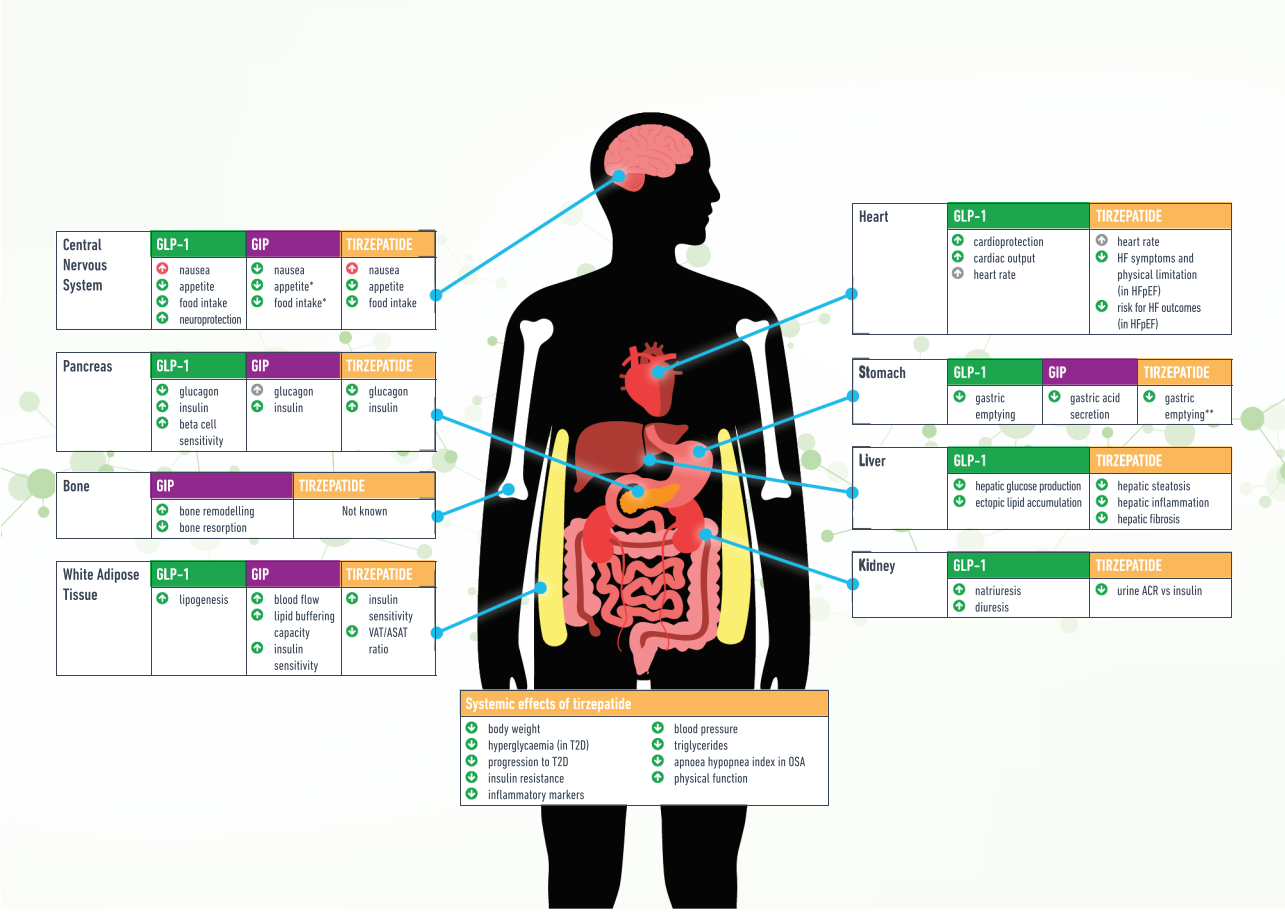


Figure 1. Main actions of glucagon-like peptide-1 (GLP-1), glucose-dependent insulinotropic polypeptide (GIP) and tirzepatide.

GLP-1 and GIP actions refer mainly to actions of physiological levels of these hormones. Tirzepatide actions are based on data from clinical trials.

GLP-1: Glucagon-like peptide-1; GIP: Glucose-dependent insulinotropic polypeptide; HF: Heart failure; HFpEF: Heart failure with preserved ejection fraction; ACR: Albumin creatinine ratio; VAT: Visceral adipose tissue; ASAT: Abdominal subcutaneous adipose tissue; T2D: Type 2 diabetes; OSA: Obstructive sleep apnea. *data from preclinical studies,**transient effect.

Tirzepatide improves glycemic control by lowering fasting and postprandial glucose levels in people with T2D through several mechanisms, including improved beta-cell function and insulin sensitivity, reduced glucagon levels and delayed gastric emptying (although this delay diminishes over time) [36,37].

The exact role of GIP receptor activation by tirzepatide in WL and glycemic improvement remains unclear. Several hypotheses have been proposed, including both GIP receptor activation and functional GIP receptor antagonism (through chronic GIP receptor activation) as potential mechanisms to tirzepatide's efficacy [38,39]. Recent experimental studies have also shown that tirzepatide improves the adipocyte nutrient metabolism in both fasting and postprandial state through long-acting GIP receptor agonism [40].

3.2. Tirzepatide in clinical trials for people with T2D

The efficacy and safety of tirzepatide in people with T2D (from monotherapy to insulin add-on) was assessed extensively in the SURPASS phase 3 program [18]. Over treatment periods up to 104 weeks, once weekly tirzepatide (5, 10 or 15 mg) achieved HbA1c reductions of 1.9–2.6% across the T2D spectrum [18,41]. Additionally, there was a marked reduction in body weight, particularly with the higher doses, with tirzepatide 15 mg leading to 11.7–12.9 kg WL at 52 weeks in SURPASS-3, −4 and −6 and between 9.5 and 12.4 kg at 40 weeks in SURPASS-1, −2 and −5 [18,42]. Improvements in multiple other cardiometabolic risk factors were also observed [18].

In three clinical trials in people with T2D, tirzepatide was directly compared with other commonly used GLP-1 RAs, such as semaglutide 1 mg or dulaglutide 1.5 mg [43–45]. Tirzepatide at doses 5, 10 and 15 mg demonstrated greater HbA1c and weight reduction compared to these GLP-1 RAs. The marked WL efficacy of tirzepatide in the SURPASS program justified the development of the SURMOUNT program, which assessed tirzepatide's efficacy and safety for chronic weight management in people with overweight/obesity [46]. The SURMOUNT phase 3 trials are discussed below.

3.3. SURMOUNT trials on overweight/obesity management

3.3.1. SURMOUNT-1,-2,-3 and –4 trials design (key global studies)

Table 1 provides the main aspects of the design, inclusion criteria, participant demographics and baseline characteristics

Table 1. Summary of baseline characteristics and trial design for key global SURMOUNT trials for overweight/obesity management.

	SURMOUNT-1 [47] *Weight management*	SURMOUNT-2 [48] *Weight management in type 2 diabetes*	SURMOUNT-3 [49] *Weight management after intensive lifestyle intervention*	SURMOUNT-4 [50] *Weight maintenance, medication withdrawal study*
Number of participants	2539	938	579	670
Population	Adults with BMI ≥30 kg/m^2, or BMI ≥27 kg/m^2 with ≥ 1 comorbidity, and without diabetes	Adults with BMI ≥27 kg/m^2 and type 2 diabetes (HbA1c 7–10%)	Adults with BMI ≥30 kg/m^2, or BMI ≥27 kg/m^2 with ≥ 1 comorbidity, and without diabetes, who achieved ≥ 5% WL after 12-week intensive lifestyle intervention	Adults with BMI ≥30 kg/m^2, or BMI ≥27 kg/m^2 with ≥ 1 comorbidity, and without diabetes
Treatment arms and randomization ratios	Tirzepatide 5 mg Tirzepatide 10 mg Tirzepatide 15 mg Placebo 1:1:1:1	Tirzepatide 10 mg Tirzepatide 15 mg Placebo 1:1:1	Tirzepatide MTD Placebo 1:1	Tirzepatide MTD Placebo 1:1
Time of randomization	Week 0	Week 0	Week 12	Week 36
Duration of study	72 weeks	72 weeks	84 weeks (12 weeks lead in +72 weeks post randomization)	88 weeks (36 weeks lead in +52 weeks post randomization)
Primary endpoints	(1) % Change in body weight (2) ≥5% WL	(1) % Change in body weight (2) ≥5% WL	(1) % Change in body weight from randomization (week 12 to 84) (2) ≥5% WL from randomization (week 12 to 84)	(1) % Change in body weight from randomization (week 36 to 88)
Intervention during the lead-in period	NA	NA	***Intensive lifestyle intervention for 12 weeks aiming to achieve ≥ 5% WL:*** Reduced calorie diet (women: 1200 kcal/day, men: 1500 kcal/day) which may include 2 meal replacements per day for 12 weeks and increased physical activity (at least 150 min/week)	**Tirzepatide MTD** (starting dose 2.5 mg once weekly and gradually increased by 2.5 mg every 4 weeks until a MTD of 10 or 15 mg was achieved) Additionally, reduced calorie diet (500 kcal/day deficit) and increased physical activity (at least 150 min/week)
Lifestyle intervention post-randomisation	Reduced calorie diet (500 kcal/day deficit) and increased physical activity (at least 150 min/week)	Reduced calorie diet (500 kcal/day deficit) and increased physical activity (at least 150 min/week)	Reduced calorie diet (500 kcal/day deficit) and increased physical activity (at least 150 min/week)	Reduced calorie diet (500 kcal/day deficit) and increased physical activity (at least 150 min/week)
Sex, female, n (%)	1714 (67.5)	476 (51)	364 (62.9)	473 (70.6)
Age, years	44.9 (12.5)	54.2 (10.6)	45.6 (12.2)	48 (12)
White, n (%)	1792 (70.6)	710 (76)	498 (86)	537 (80.1)
Body weight, kg	104.8 (22.1)	100.7 (21.1)	109.5 (23)	107.3 (22.3)
BMI, kg/m^2	38 (6.8)	36.1 (6.6)	38.6 (6.7)	38.4 (6.6)
Waist circumference, cm	114.1 (15.2)	114.9 (14.4)	116.1 (15.4)	115.2 (14.5)
HbA1c, %	5.6 (0.4)	8.0 (0.9)	5.5 (0.4)	5.5 (0.4)
SBP, mmHg	123.3 (12.7)	130.5 (12.1)	126 (13)	126 (13)
DBP, mmHg	79.5 (8.2)	79.8 (8.4)	81.5 (8.5)	81 (8)

(*Continued*)

Table 1. (Continued).

	SURMOUNT-1 [47] *Weight management*	SURMOUNT-2 [48] *Weight management in type 2 diabetes*	SURMOUNT-3 [49] *Weight management after intensive lifestyle intervention*	SURMOUNT-4 [50] *Weight maintenance, medication withdrawal study*
Total cholesterol, mg/dl	187.9 (20.3)	177.9 (42.5)*	193.8 (38)	192.3 (39.6)
HDL cholesterol, mg/dl	47.3 (26.3)	46.4 (11.6)*	50.1 (13.9)	51.5 (13.1)
Non-HDL cholesterol, mg/dl	138 (26.6)	131.5 (42.5)*	143.7 (36.7)	140.8 (37.5)
LDL cholesterol, mg/dl	109.5 (30.2)	96.7 (34.8)*	115.9 (31.5)	113.8 (32.9)
Triglycerides, mg/dl	128.4 (50)	186 (123.9)*	139.7 (94.7)	136.2 (80.9)
Number of weight-related complications, n (%)				
0	944 (37.2)	0	196 (33.9)	205 (30.6)
1–2	1153 (45.4)	356 (38)	285 (49.2)	307 (45.8)
3–4	379 (14.9)	445 (48)	86 (14.8)	128 (18.3)
≥5	63 (2.5)	137 (15)	12 (2.1)	30 (4.5)

*Calculated from mmol/L to mg/dl. All results are presented as mean (standard deviation) unless stated otherwise. BMI, Body Mass Index; WL: Weight Loss; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MTD: Maximum tolerated dose (tirzepatide 10 or 15 mg once weekly); NA, Not available.

of the key global SURMOUNT trials for obesity management (SURMOUNT-1, −2, −3 and −4). SURMOUNT-1 and −2 used fixed tirzepatide doses, when in SURMOUNT-3 and −4 tirzepatide was used at clinically relevant maximum tolerated dose (MTD, 10 or 15 mg) [46].

In SURMOUNT-1, 2539 participants were randomized to receive tirzepatide 5, 10 or 15 mg or matching placebo for 72 weeks, alongside a moderate intensity lifestyle intervention (500 kcal/day deficit diet plus 150 min/week physical activity). Participants with prediabetes at baseline ($n = 1032$) were followed for 176 weeks to provide sufficient follow-up time to detect potential differences in T2D progression and assess long-term weight changes and safety with tirzepatide [47].

In SURMOUNT-2, 938 adults with T2D and BMI ≥27 kg/m^2 were enrolled and randomized to tirzepatide 10 mg, 15 mg or placebo for 72 weeks [48]. Participants on insulin, GLP-1 RAs or dipeptidyl peptidase 4 inhibitors were excluded. A similar to SURMOUNT-1 lifestyle intervention was provided.

SURMOUNT-3 was an 84-week trial evaluating the safety and efficacy of tirzepatide MTD (10 or 15 mg) for weight management in people with overweight/obesity that achieved ≥ 5% WL after a 12-week intensive lifestyle program [49]. The study enrolled 806 adults during the 12 week lead-in phase, which included face-to-face lifestyle counseling sessions (including behavior modification strategies), reduced calorie diet with up to two meal replacements/day (1,200 kcal/day in women and 1,500 kcal/day in men) and advice for 150 min/week moderate-intensity physical activity. Only those achieved ≥ 5% WL at the end of the 12-week lead-in period ($n = 579$) were randomized to tirzepatide MTD or placebo for a further 72 weeks.

SURMOUNT-4 was a 88-week withdrawal trial, designed to assess the safety and efficacy of tirzepatide MTD (10 or 15 mg) compared to placebo for maintaining weight reduction after an initial 36-week open-label tirzepatide run-in period [50]. After the 36-week run-in period, 670 participants were randomized to either continue with tirzepatide MTD or switch to placebo. Throughout the trial, participants received lifestyle counseling sessions encouraging healthy, balanced diet and physical activity.

Similar dose escalation schemes were employed in all the SURMOUNT trials. The starting dose was 2.5 mg once weekly and escalated gradually by 2.5 mg every 4 weeks up to the assigned dose [46].

Additional studies assessing the safety and efficacy of tirzepatide for chronic weight management in different ethnicities (SURMOUNT-CN, SURMOUNT-J) and for specific obesity-related complications (SURMOUNT-OSA, SUMMIT and SYNERGY-NASH) are discussed at sections 3.3.8 and 4.

3.3.2. Baseline characteristics in global SURMOUNT trials

In the SURMOUNT-1,-3 and −4 studies, participants' baseline characteristics and demographics were broadly similar (Table 1); 63–70% were female, mean BMI 38–38.6 kg/m^2, mean age 45–48 years old and 31–37% without any obesity-related complication. In SURMOUNT-2 study, all participants

had T2D (mean HbA1c 8%, mean T2D duration 8.5 years) and they were older (mean age 54.2 years), with lower baseline BMI (36.1 kg/m^2) and more obesity-related complications compared to SURMOUNT-1,-3 and −4, while only 51% of participants were female [46].

3.3.3. Weight change in global SURMOUNT trials

In SURMOUNT-1 trial, mean WL was −16% with tirzepatide 5 mg, −21.4% with 10 mg and −22.5% with 15 mg compared to −2.4% WL with placebo at 72 weeks (Table 2, Figure 2(a)) [47]. The proportion of participants achieving ≥ 5% WL at the 72 weeks was 89–96% with tirzepatide compared to 29% with placebo. Notably, with tirzepatide 15 mg, 90% achieved ≥ 10% WL, 78% ≥15% WL and 63% achieved ≥ 20% WL compared to only 13.5%, 6% and 1.3% with placebo, respectively (Table 2, Figure 2(b)).

A recent publication of the 176-week SURMOUNT-1 trial findings in adults with prediabetes at baseline, demonstrated sustained WL with tirzepatide. Weight reductions were 15.4%, 19.9%, and 22.9% for tirzepatide 5, 10, and 15 mg, respectively, compared to 2.1% with placebo [51]. Moreover, at 176 weeks, 71–89% of tirzepatide users achieved ≥ 10% WL versus 15% with placebo, 47–79% achieved ≥ 15% WL versus 8% with placebo, and 28–63% achieved ≥ 20% WL versus 4% with placebo [51].

People with overweight/obesity and T2D often lose less weight compared to those without T2D. In the SURMOUNT-2 trial, which lasted 72 weeks, tirzepatide 10 and 15 mg were evaluated in people with overweight/obesity and T2D. Mean WL was −13.4% with tirzepatide 10 mg and −15.7% with 15 mg compared to −3.3% with placebo. Furthermore, 81.6% of those on tirzepatide 10 mg and 86.4% on 15 mg achieved ≥ 5% WL compared to 30.6% with placebo [48]. Key secondary end-points showed weight reductions of ≥ 10% in 63–70% of participants receiving tirzepatide versus 8.7% with placebo; ≥15% in 41–52% versus 2.6% with placebo; and ≥ 20% in 23–34% versus 1% with placebo [48].

In SURMOUNT-3, participants achieving ≥ 5% WL during the lead-in period with an intensive lifestyle program were randomized to tirzepatide MTD or placebo for further 72 weeks. The mean WL during the initial 12-week run-in period was −6.9% for the people randomized. The mean %WL from the beginning of the lead-in period to the end of the study (0–84 weeks) was −26.6% with tirzepatide MTD versus −3.8% with placebo (Table 2, Figure 2(a)) [49].

From randomization to week 72 (12–84 weeks), tirzepatide MTD led to a further 21.1% WL compared to + 3.3% weight gain with placebo. A total of 94.4% of participants on tirzepatide MTD achieved ≥ 5% WL from randomization (12–84 weeks) compared to 10.7% with placebo. Additionally, 88%, 73.9% and 54.9% of participants on tirzepatide MTD achieved ≥ 10%, ≥15% and ≥ 20% WL from randomization (12–84 weeks) versus 4.8%, 2.1% and 1% with placebo (Table 2, Figure 2(b)) [49].

The SURMOUNT-4 trial assessed the effect of continuing vs discontinuing once weekly tirzepatide MTD on weight maintenance after an initial open label 36-week tirzepatide run-in period. The mean %WL from the lead-in period to the end of

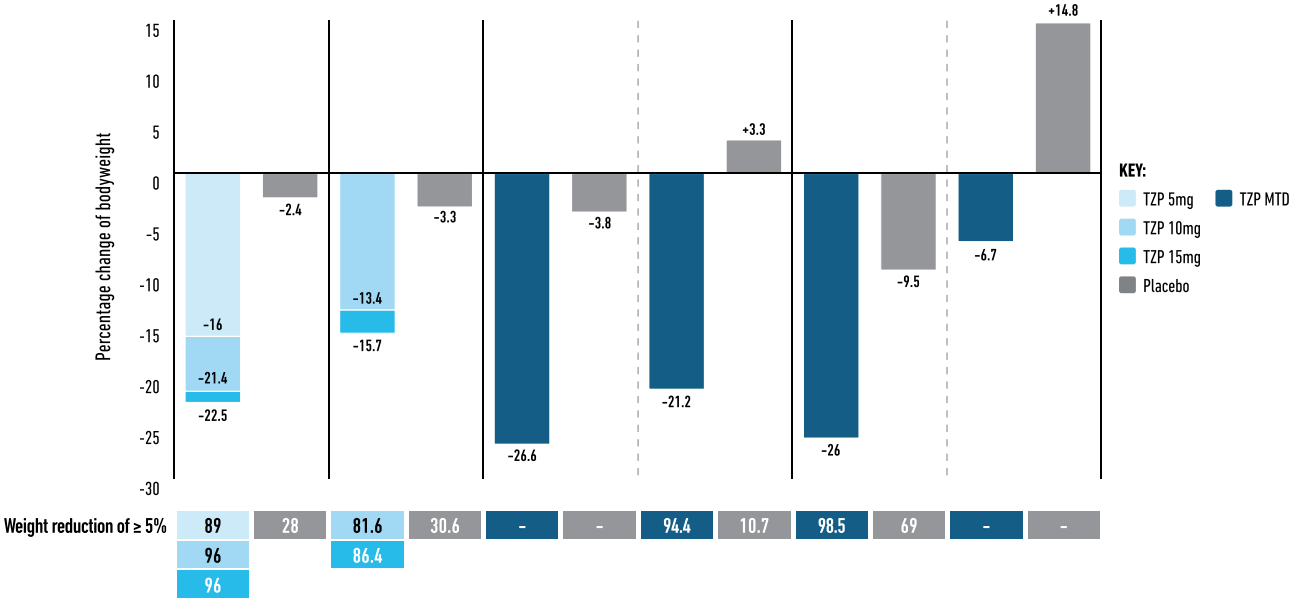
Table 2. Efficacy data for key global SURMOUNT studies for overweight/obesity management.

OUTCOMES	SURMOUNT-1 [47] *Weight management*				SURMOUNT-2 [48] *Weight management in type 2 diabetes*			SURMOUNT-3 [49] *Weight maintenance after intensive lifestyle intervention*				SURMOUNT-4 [50] *Weight maintenance, medication withdrawal study*			
	0 to 72 weeks				0 to 72 weeks			0 to 84 weeks		12 to 84 weeks		0 to 88 weeks		36 to 88 weeks	
Intervention	5 mg TZP	10 mg TZP	15 mg TZP	Placebo	10 mg TZP	15 mg TZP	Placebo	MTD TZP	Placebo	MTD TZP	Placebo	MTD TZP	Placebo	MTD TZP	Placebo
% Change in body weight	−16	−21.4	−22.5	−2.4	−13.4	−15.7	−3.3	−26.6	−3.8	−21.2	+3.3	−26	−9.5	−6.7	+14.8
Treatment difference vs placebo	−13.5	−18.9	−20.1		−10.1	−12.4		−22.8		−24.5		−16.5		−21.4	
% Participants with weight reduction of:															
≥5%	89	96	96	28	81.6	86.4	30.6		–	94.4	10.7	98.5	69	–	–
≥10%	73.4	85.9	90.1	13.5	63.4	69.6	8.7	–	–	88	4.8	94	44.4	–	–
≥15%	50.2	73.6	78.2	6	41.4	51.8	2.6	–	–	73.9	2.1	87.1	24	–	–
≥20%	31.6	55.5	62.9	1.3	23	34	1	–	–	54.9	1	72.6	11.6	–	–
≥25%	16.5	35	39.7	0.3	10	17.2	0.3	–	–	36.3	0.3	56.5	4	–	–
Change in:															
BMI, kg/m^2	–	–	–	–	−4.9	−5.7	−1.2	−10.4	−1.4	−7.7	+1.2	−10	−3.6	−2.1	+4.3
Bodyweight, kg	–	–	–	–	−13.5	−15.6	−3.2	−29.2	−4.1	–	–	−27.6	−10	−5.7	+11.9
Waist circumference, cm	−14.6	−19.4	−19.9	−3.4	−11.2	−13.8	−3.4	−23.4	−5.6	−16.8	+1.1	−22.8	−9.1	−4.6	+8.3
Systolic blood pressure, mmHg	−7	−8.2	−7.6	−1.2	−5.9	−7.7	−1.2	−10.5	−0.9	−5.1	+4.1	−9.3	−2.4	+2.1	+8.4
Diastolic blood pressure, mmHg	−5.2	−5.5	−4.6	−1	−2.1	−2.9	−0.3	−6.2	−0.8	−3.2	+2.3	−5.5	−1.7	−0.4	+3.2
HbA1c, %	−0.4	−0.49	−0.51	−0.07	−2.14	−2.22	−0.16	−0.6	−0.1	−0.5	0	−0.57	−0.22	−0.05	+0.25
Fasting glucose, mg/dl	−7.7	−9.7	−10.6	0.9	−49.2	−51.7	−2.4	–	–	–	–	–	–	−0.9	+7.7
Total cholesterol, mg/dl	−4.9	−5.6	−7.4	−1.1	−3	−2.2	+2.1	−6.3	−0.3	−3	+5.2	−5	+2.2	+2.3	+8.3
HDL cholesterol, mg/dl	+7	+8.6	+8.2	+0.2	+6.9	+9.6	+1.1	+13.1	+1.4	+15.4	+3.6	+12.3	+9.4	+18.3	+14.6
Non-HDL cholesterol, mg/dl	−9.5	−11	−13.4	−1.8	−6.6	−6.7	2.3	−13.1	−0.9	−9.8	+5.6	−11.5	−0.8	−4	+5.5
LDL cholesterol. mg/dl	−5.3	−6.6	−8.6	−0.9	2.3	3.2	6.3	−7.4	+1.3	−6.1	+6.1	−5.2	+2.6	−3.4	+3.4
Triglycerides, mg/dl	−24.3	−27	−31.4	−6.3	−26.8	−30.6	−5.8	−33.2	−8.8	−25.8	+3	−33.3	−15.3	−8.2	+15.6
SF-36v2 physical function score[a]	+3.9	+3.9	+4.2	+1.9	+3.4	+3.8	+1.6	+6.1	+2.5	+3.3	−0.6	+6.4	+3.7	+0.8	−1.8
IWQOL-Lite-CT – change in physical function[b]	–	–	–	–	+14.3	+15.2	+7.4	+27.8	+14.5	+13.9	+1.1	+26	+16.7	+4.3	−5.1

Efficacy estimand outcome data reported. TZP: Tirzepatide, BMI, Body Mass Index; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; SF-36 V2, Short Form-36 v.2 health survey acute form; IWQOL-Lite-CT, Impact of Weight on Quality of Life-Lite-Clinical Trials Version. [a] SF-36v2 measures health-related quality of life and general health status An increase in score represents an improvement in health status. [b] IWQOL-Lite-CT measures weight-specific, health-related quality of life. Higher scores reflect better levels of functioning.

a

	SURMOUNT-1	SURMOUNT-2	SURMOUNT-3		SURMOUNT-4	
Participants randomised	n=2539	n=938	n=579		n=670	
Trial details	Adults with overweight or obesity without T2D	Adults with overweight or obesity and T2D	Adults with overweight or obesity without T2D who achieved ≥5% WL during the 12 week lead-in period with intensive lifestyle		Adults with overweight or obesity without T2D who reached maximum tolerated TZP dose during the 36-week lead-in period	
Treatment Duration	0-72 weeks	0-72 weeks	0-84 weeks	12-84 weeks (from randomisation)	0-88 weeks	36-88 weeks (from randomisation)
Baseline BW	104.8 kg	100.7 kg	109.5 kg	102.5 kg	107.3 kg	84.6 kg – 85.8 kg



b

	SURMOUNT-1	SURMOUNT-2	SURMOUNT-3	SURMOUNT-4
Participants randomised	n=2539	n=938	n=579	n=670
Trial details	Adults with overweight or obesity without T2D	Adults with overweight or obesity and T2D	Adults with overweight or obesity without T2D who achieved ≥5% WL during the 12 week lead-in period with intensive lifestyle	Adults with overweight or obesity without T2D who reached maximum tolerated TZP dose during the 36-week lead-in period
Treatment Duration	0-72 weeks	0-72 weeks	12-84 weeks	0-88 weeks
Baseline BW	104.8 kg	100.7 kg	102.5 kg	107.3 kg

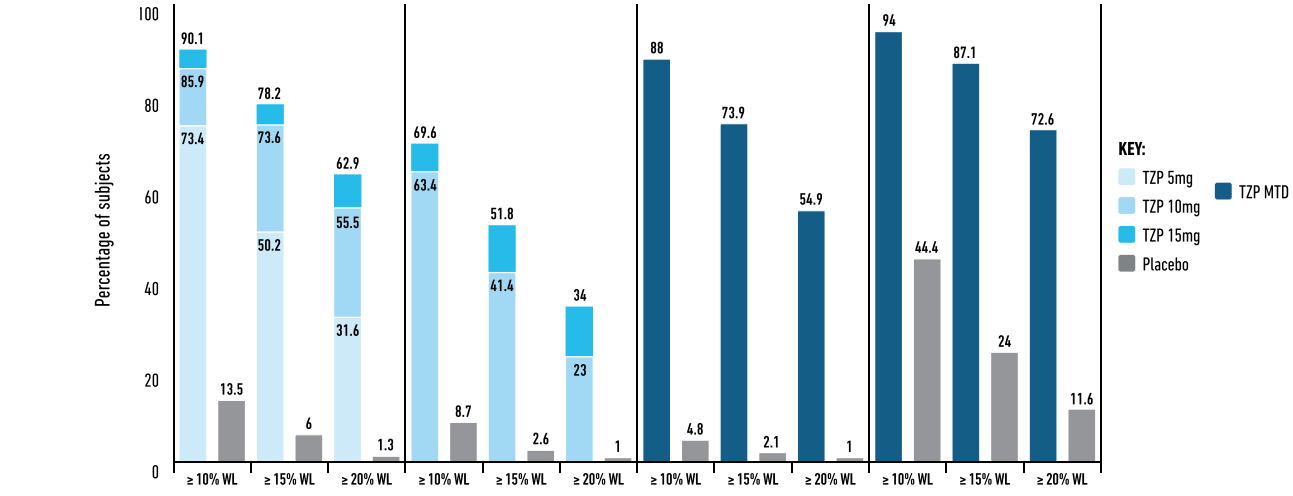


Figure 2. (a) Change in bodyweight and proportion of people achieving ≥ 5% weight loss with different doses of tirzepatide vs placebo in global SURMOUNT studies for overweight/obesity management. (b) Proportion of people achieving ≥ 10%, ≥15% and ≥ 20% weight loss with different doses of tirzepatide compared to placebo in global SURMOUNT studies for overweight/obesity management.

T2D: Type 2 diabetes, TZP: Tirzepatide, MTD: Maximum tolerated dose (tirzepatide 10 or 15 mg), BW: Body weight, WL: Weight loss.

the trial (0–88 weeks) was −26% with tirzepatide MTD versus −9.5% with placebo [50]. Furthermore, 98.5% of participants on tirzepatide MTD achieved ≥ 5% WL from lead-in to 88 weeks versus 69% of participants on placebo. More people on tirzepatide MTD achieved ≥ 10%, ≥15% and ≥ 20% WL from lead-in period to 88 weeks compared to placebo (94%, 87.1% and 72.6% respectively with tirzepatide MTD compared to 44.4%, 24% and 11.6% with placebo).

The mean body weight change from randomization (36–88 weeks) was −6.7% with tirzepatide MTD versus + 14.8% with placebo [50].

3.3.4. Changes in body composition and waist circumference from global SURMOUNT trials

In SURMOUNT-1 trial, body composition changes were assessed by dual-energy x-ray absorptiometry (DEXA) at baseline and 72 weeks in a subgroup of 160 participants [47]. Tirzepatide resulted in 33.9% reduction in mean total body fat mass compared to 8.2% reduction with placebo, but also in a greater reduction in total lean mass (10.9% vs 2.6%). However, the ratio of total fat mass to total lean mass decreased more with tirzepatide (from 0.93 at baseline to 0.70 at week 72) than with placebo (from 0.95 to 0.88) [47,52].

Clinically important reductions in waist circumference were also observed with tirzepatide across SURMOUNT studies (Table 2). For example, in SURMOUNT-1, waist circumference decreased by 14.6–19.9 cm with the different tirzepatide doses compared to 3.4 cm reduction with placebo [47].

3.3.5. Other cardiometabolic benefits in global SURMOUNT trials

There were improvements in multiple other cardiovascular risk factors in SURMOUNT trials, including glycemic parameters, blood pressure and lipid levels.

3.3.5.1. Changes in glycaemia. In the SURMOUNT-1 trial, participants did not have T2D, but 40.6% had prediabetes at baseline. After 72 weeks, 95% of those with prediabetes treated with tirzepatide converted to normoglycaemia, compared to 62% in the placebo group [47]. At 176 weeks, 13.3% of people with prediabetes and overweight/obesity in the placebo group had progressed to T2D compared to only 1.3% of those in tirzepatide groups (pooled doses) – a 93% risk reduction in T2D progression with tirzepatide [51]. Additionally, 91.5% of tirzepatide-treated participants reverted to normoglycaemia, compared to 59% in the placebo group [51].

SURMOUNT-2 recruited people with overweight/obesity and T2D on oral glucose-lowering treatments. HbA1c levels improved by 2.1–2.2% with tirzepatide (10 and 15 mg), with 84–87% of participants achieving HbA1c ≤ 6.5% compared to only 16% with placebo [48].

The effect of tirzepatide on glycemia in people with T2D has also been extensively assessed at the SURPASS program as described above. Overall, tirzepatide showed superior efficacy than placebo and other commonly used glucose-lowering medications such as semaglutide 1 mg, insulin degludec, insulin glargine and insulin lispro, even at the lowest dose of tirzepatide 5 mg [18,42].

3.3.5.2. Changes in blood pressure, lipids and 10-year cardiovascular risk score. In SURMOUNT trials, systolic blood pressure (BP) decreased by 5.9–10.5 mmHg with tirzepatide compared to a reduction of 0.9–2.4 mmHg with placebo (Table 2). Diastolic BP also improved, showing decreases of 2.1–6.2 mmHg with tirzepatide versus 0.3–1.7 mmHg in the placebo groups (Table 2).

In a subset of 600 participants from SURMOUNT-1 study, 24-hour ambulatory BP was measured at baseline and at week 36 (mean baseline systolic BP was 124.6 mmHg and diastolic BP was 72.1 mmHg) [53]. At 36 weeks, the change from baseline in the placebo-adjusted systolic BP was −7.4 mmHg for 5 mg tirzepatide, −10.6 mmHg for 10 mg, and −8.0 mmHg for 15 mg. Diastolic BP decreased from baseline versus placebo with tirzepatide 5 mg (−2.0 mmHg) and 10 mg (−2.9 mmHg), but not with 15 mg (−0.5 mmHg). Additionally, heart rate increased with tirzepatide by 2.1–5.4 bpm more than with placebo [53].

Tirzepatide also improved the lipid profile, particularly triglycerides across the SURMOUNT program (Table 2). A post-hoc analysis of SURMOUNT-1 assessed the change in the 10-year predicted risk of atherosclerotic cardiovascular disease (ASCVD) with tirzepatide vs placebo in people without ASCVD history [54]. While the median ASCVD risk score at baseline was low (1.5–1.6%), the relative change in ASCVD risk from baseline to week 72 was greater for tirzepatide (−16.4% to −23.5%) than placebo (+12.7%) [54].

3.3.6. Self-reported physical function and other quality of life parameters in global SURMOUNT trials

There was an overall improvement in self-reported physical function outcomes with tirzepatide compared to placebo in the SURMOUNT program (Table 2). Physical function was evaluated using (i) the physical domain score from the short form-36 version 2 health survey acute form (SF-36v2) which assesses health-related quality of life (QoL) and general health status and (ii) the physical function composite score from the impact of weight on QoL-Lite- Clinical Trials version (IWQOL-Lite-CT) which measures weight-specific, health-related QoL (Table 2).

Regarding mental health outcomes, an exploratory analysis from the SURMOUNT-3 study examined changes in the SF-36v2 Mental Component Summary (MCS) and its domain scores as well as the IWQoL-Lite-CT Psychosocial composite score from randomization to week 72 [55]. While the improvement in SF-36v2 MCS score was comparable between tirzepatide MTD and placebo, tirzepatide MTD significantly improved the SF36v2 vitality, social functioning, role-emotional and mental health domain scores [55]. Tirzepatide MTD improved also the IWQoL-Lite-CT Psychosocial composite score compared to placebo in SURMOUNT-3.

In SURMOUNT-4 study, improvements in role-physical, role-emotional and mental health domain from the SF-36v2 score were also observed with tirzepatide MTD compared to placebo (0 to 88 weeks) [50].

3.3.7. Safety data from global SURMOUNT trials

Similar to GLP-1 RAs, the most common adverse events (AEs) reported with tirzepatide were gastrointestinal, including

nausea, diarrhea, vomiting, constipation and abdominal pain across SURMOUNT-1 (72 weeks), −2, −3 and −4 (Table 3). These AEs were generally mild to moderate in severity and tirzepatide was mostly well tolerated. Serious AE (SAEs) occurred in 5–9% of participants on tirzepatide compared to 3–7% with placebo. Additionally, AEs leading to treatment discontinuation at SURMOUNT trials affected 4–10.5% of participants on tirzepatide versus 2.1–4% on placebo.

Across the SURMOUNT-1 (72 weeks), −2 and −3 trials, there were 6 cases of adjudication-confirmed pancreatitis in tirzepatide groups (0.21%, 6/2806 participants) compared to 3 cases in placebo groups (0.24%, 3/1250 participants), with no cases of pancreatitis reported in SURMOUNT-4. The incidence of severe or serious gallbladder disease across the SURMOUNT program ranged from 0.7–1.7% in tirzepatide arms, compared to 0–1% in placebo arms. The reported malignancies were comparable between tirzepatide and placebo arms across the SURMOUNT trials (0.5–1.7% in tirzepatide arms and 1–2% in placebo arms) – there were no cases of medullary thyroid or pancreatic cancer.

The recently published 176-week data from the SURMOUNT-1 program ($n = 1,032$ participants with prediabetes) revealed that serious adverse events (SAEs) occurred in 12.6–14.5% of participants receiving tirzepatide, compared to 11.9% in the placebo group [51]. Adverse events (AEs) leading to medication discontinuation were reported in 7.3–12.3% of tirzepatide users versus 5.9% for placebo [51]. Additionally, pancreatitis was observed in three participants in the tirzepatide group (3/762, 0.4%) and one in the placebo group (1/270, 0.4%). Severe or serious gallbladder disease occurred in 22 participants receiving tirzepatide (22/764, 2.9%) compared to two cases in the placebo group (2/270, 0.7%) [51]. Importantly, no new safety signals were identified in the 176-week data from the SURMOUNT-1 program.

In SURMOUNT-2, which recruited people with T2D on oral glucose-lowering agents, no cases of severe hypoglycemia were reported. However, blood glucose levels <3.0 mmol/mol occurred in 4–5% of those on tirzepatide, compared to 1% on placebo – these episodes were more common in people taking sulphonylureas. Overall, tirzepatide does not increase hypoglycemia risk unless combined with insulin or sulphonylureas [18].

3.3.8. Tirzepatide as obesity treatment in other ethnicities

The SURMOUNT-CN study assessed the efficacy and safety of tirzepatide (10 mg and 15 mg) compared to placebo in a Chinese population without T2D living with overweight/obesity (BMI ≥28 kg/m^2 or BMI ≥24 kg/m^2 and at least one obesity-related complication) [56]. Overall, 210 participants were randomized: 70 to tirzepatide 10 mg, 71 to 15 mg and 69 to placebo. Mean weight at baseline was 91.8 kg, mean BMI 32.3 kg/m^2, mean age 36 years and 49% of participants were female. At 52 weeks, the mean WL was −14.4% with tirzepatide 10 mg and −19.9% with 15 mg versus −2.4% with placebo. The proportion of participants achieving ≥ 15% WL with tirzepatide 10 mg and 15 mg was 49–72% compared to 3% with placebo [56]. SAEs occurred in 4.3–11.3% of participants on tirzepatide compared to 8.7% on placebo. The most common AEs with tirzepatide were diarrhea, nausea

Table 3. Adverse events in key global SURMOUNT studies for overweight/obesity management.

	SURMOUNT-1 [47] *Weight management*				SURMOUNT-2 [48] *Weight management in type 2 diabetes*			SURMOUNT-3 [49] *Weight maintenance after intensive lifestyle intervention*		SURMOUNT-4 [50] *Weight maintenance, medication withdrawal study*			
Intervention	5 mg TZP ($n = 630$)	10 mg TZP ($n = 636$)	15 mg TZP ($n = 630$)	Placebo ($n = 643$)	10 mg TZP ($n = 312$)	15 mg TZP ($n = 311$)	Placebo ($n = 315$)	MTD TZP ($n = 287$) 12 to 84 weeks	Placebo ($n = 292$) 12 to 84 weeks	MTD TZP (run-in) ($n = 783$) 0 to 36 weeks	MTD TZP (post-randomization) ($n = 335$) 36 to 88 weeks		Placebo ($n = 335$) 36 to 88 weeks
Participants with ≥ 1 AE	510 (81)	520 (81.8)	497 (78.9)	463 (78.9)	242 (78)	222 (71)	239 (76)	250 (87.1)	224 (76.7)	634 (81)	202 (60.3)		187 (55.8)
Serious AE	40 (6.3)	44 (6.9)	32 (5.1)	44 (6.8)	18 (6)	27 (9)	23 (7)	17 (5.9)	14 (4.8)	16 (2)	10 (3)		10 (3)
AE leading to discontinuation	27 (4.3)	45 (7.1)	39 (6.2)	17 (2.6)	12 (4)	23 (7)	12 (4)	30 (10.5)	6 (2.1)	55 (7)	6 (1.8)		3 (0.9)
Deaths[a]	4 (0.6)	2 (0.3)	1 (0.2)	4 (0.6)	2 (1)	0	0	1 (0.3)	1 (0.3)	1 (0.1)	1 (0.3)		1 (0.3)
Selected GI AEs reported in ≥ 5% of participants in tirzepatide treatment groups:													
Nausea	155 (24.6)	212 (33.3)	195 (31)	61 (9.5)	63 (20)	68 (22)	20 (6)	114 (39.7)	41 (14)	278 (35.5)	27 (8.1)		9 (2.7)
Diarrhoea	118 (18.7)	135 (21.2)	145 (23)	47 (7.3)	62 (20)	67 (22)	28 (9)	89 (31)	27 (9.2)	165 (21.1)	27 (8.1)		9 (2.7)
Abdominal pain	31 (4.9)	34 (5.3)	31 (4.9)	21 (3.3)	12 (4)	23 (7)	7 (2)	30 (10.5)	7 (2.4)	48 (6.1)	–		–
Vomiting	52 (8.3)	68 (10.7)	77 (12.2)	11 (1.7)	34 (11)	41 (13)	10 (3)	52 (18.1)	4 (1.4)	128 (16.3)	19 (5.7)		4 (1.2)
Constipation	106 (16.8)	109 (17.1)	74 (11.7)	37 (5.8)	25 (8)	28 (9)	13 (4)	66 (23)	20 (6.8)	162 (20.7)	–		–
Selected AE of special interest:													
Pancreatitis	1 (0.2)	1 (0.2)	1 (0.2)	1 (0.2)	0	2 (1)	1 (<1)	1 (0.3)	1 (0.3)	0	0		0
Severe or serious gallbladder disease	5 (0.8)	11 (1.7)	6 (1)	5 (0.8)	2 (1)	4 (1)	3 (1)	2 (0.7)	0	7 (0.9)	0		3 (0.9)
Malignant neoplasms	9 (1.4)	3 (0.5)	5 (0.8)	7 (1.1)	1 (<1)	3 (1)	7 (2)	5 (1.7)	3 (1)	2 (0.3)	3 (0.9)		3 (0.9)

Results reported in Number (percent). TZP: Tirzepatide, MTD: Maximum tolerated dose (tirzepatide 10 or 15 mg once weekly), AE: Adverse events. [a]Deaths were also included as serious adverse events and discontinuation due to adverse events.

and vomiting and the proportion of participants discontinuing the treatment due to AEs was < 5%.

The SURMOUNT-J also evaluated the safety and efficacy of tirzepatide in a Japanese population without T2D living with overweight/obesity (BMI ≥35 kg/m^2 and at least one obesity-related complication or BMI ≥27 kg/m^2 and at least two obesity-related complications, including impaired glucose tolerance, hyperlipidemia and MASLD) [57]. The study [results available at clinicaltrials.gov (NCT04844918)] included 225 participants at the final analysis; 73 on tirzepatide 10 mg, 77 on 15 mg and 75 on placebo. At baseline, the mean age was 50.8 years and 40.8% were female. After 72 weeks, the mean WL was −17.8% with tirzepatide 10 mg, −22.7% with 15 mg and −1.7% with placebo. From those on tirzepatide, 63.4–82.9% achieved ≥ 15% WL compared to 1.3% with placebo. SAEs occurred in 6.5–11% of those on tirzepatide compared to 6.7% on placebo, while constipation and nausea were the most common AEs [57].

4. Impact of tirzepatide on other obesity-related complications

4.1. MASLD/Metabolic-dysfunction associated steatohepatitis

MASLD is the most common cause of chronic liver disease globally, affecting up to 75% of those living with obesity. Metabolic-dysfunction associated steatohepatitis (MASH) is the progressive form of MASLD, associated with higher risk of progression to liver fibrosis and liver-related morbidity and mortality as well as increased risk of CVD.

In a sub-study of SURPASS-3, tirzepatide was compared to insulin degludec in reducing liver fat content (LFC) for people with T2D at risk for MASLD. After 52 weeks, tirzepatide reduced LFC by 30–47% compared to baseline, while insulin degludec reduced it by 11% [58]. Moreover, 67–81% of those on tirzepatide reached at least 30% relative reduction in LFC, a degree of response associated with improvements in liver histology.

The phase 2 SYNERGY-NASH trial assessed the safety and efficacy of tirzepatide in 190 adults with biopsy proven MASH and moderate or severe fibrosis (58% with T2D) [59]. Tirzepatide treatment for 52 weeks was more effective than placebo in achieving MASH resolution without worsening fibrosis on liver histology (44–62% of participants with tirzepatide vs 10% with placebo) which was the primary outcome [59]. Moreover, improvement of ≥ 1 stage in fibrosis without worsening in MASH was observed in more participants at the tirzepatide group (51–55%) than placebo (30%) [59]. The body weight reduction after 52 weeks with tirzepatide 5, 10 or 15 mg in SYNERGY-NASH trial was between 10.7% and 15.6% versus 0.8% WL with placebo.

4.2. Obstructive sleep apnoea (OSA)

Obesity is a major risk factor for OSA and 60–70% of individuals with OSA are living with overweight/obesity. The apnea-hypopnea index (AHI) measures the number of times a person's breathing shows a restricted or complete block of airflow per hour, evaluating OSA severity and treatment effectiveness. Moderate to severe OSA (AHI >15/hour) is associated with multiple cardiometabolic complications, such as hypertension, cardiovascular disease, heart failure (HF), atrial fibrillation and T2D [60]. Although positive airway pressure (PAP) therapy is considered the gold standard treatment for moderate to severe OSA, adherence is often suboptimal. Optimal treatment of OSA and the associated complications involves, beyond PAP therapy, effective WL strategies for obesity/overweight which can reduce OSA severity, improve blood oxygen saturation parameters and QoL [61–63]. However, OSA is also an independent risk factor for early onset sarcopenia and sarcopenic obesity and loss of lean body mass may worsen the condition [64].

The SURMOUNT-OSA phase 3 trials assessed the impact of tirzepatide MTD (10 or 15 mg) vs placebo on OSA parameters and were conducted on two study groups with obesity (without T2D) and moderate to severe OSA. SURMOUNT-OSA study 1 included people not on PAP therapy, while SURMOUNT-OSA study 2 was conducted in people using PAP therapy [60].

After 52 weeks of treatment, the WL observed with tirzepatide MTD across these two studies was ≈ 18–20%. In study 1, tirzepatide MTD reduced the AHI by 27.4 events/hour (baseline AHI was 51.5 events/hour) compared to 4.8 events/hour reduction with placebo. In study 2, 52 weeks of tirzepatide MTD reduced AHI by 30.4 events/hour while placebo reduced it by 6 events/hour (baseline AHI was also 51.5 events/hour) [65]. Overall, tirzepatide MTD led to 50.7–58.7% reduction in AHI from baseline in these two trials and it also improved sleep-related patient reported outcomes compared to placebo [65].

4.3. Heart failure with preserved ejection fraction

Heart failure with preserved ejection fraction (HFpEF) accounts for over half of all HF cases in the United States and is increasingly common among people with overweight/obesity [66]. Excess adiposity is believed to contribute both to the development and progression of HFpEF, which is characterized by a high burden of symptoms and physical limitations affecting daily life.

The SUMMIT study (NCT04847557) was a global, randomized, double-blind, placebo-controlled trial evaluating tirzepatide's safety and efficacy in adults with HFpEF and obesity (with or without T2D). The study enrolled 731 participants (48.2% with T2D), aged ≥40 years with chronic heart failure (New York Heart Association class II – IV), a left ventricular ejection fraction of ≥ 50%, and a BMI of ≥30 kg/m^2. Participants were randomized to receive either tirzepatide MTD ($n = 364$), or placebo ($n = 367$) [67]. The two primary endpoints were: 1) a composite measure of HF outcomes (adjudicated cardiovascular death, or exacerbated symptoms of HF resulting in hospitalization, intravenous therapy in an urgent care setting or oral diuretic intensification) (median follow-up of 104 weeks) and 2) change in HF symptoms and physical limitations assessed by the Kansas City Cardiomyopathy Questionnaire (KCCQ) Clinical Summary Score (CSS) from baseline to week 52.

In the tirzepatide group, 36 participants (9.9%) experienced either adjudicated cardiovascular death or a worsening heart failure (HF) event, compared to 56 participants (15.3%) in the placebo group, representing a 38% reduction in HF outcomes with tirzepatide (95% CI: 0.41–0.95, $p = 0.03$) [67]. This reduction was primarily driven by a decrease in worsening HF events, which occurred in 29 participants (8.0%) in the tirzepatide group versus 52 participants (14.2%) in the placebo group. Adjudicated cardiovascular deaths were reported in 8 participants (2.2%) receiving tirzepatide compared to 5 participants (1.4%) in the placebo group [67].

At 52 weeks, tirzepatide demonstrated also significant improvements in HF symptoms and physical limitations, as measured by the KCCQ-CSS. Scores improved by 19.5 points with tirzepatide compared to 12.7 points with placebo ($p < 0.001$) [67]. Tirzepatide also led to substantial WL, with patients achieving an average reduction of 15.7% compared to 2.2% with placebo (efficacy-estimand) [67]. Furthermore, tirzepatide met all key secondary endpoints, including enhanced exercise capacity at 52 weeks, as patients treated with tirzepatide walked approximately 18 meters farther in six minutes compared to those receiving placebo [67].

5. Key ongoing studies with tirzepatide (with focus on SURMOUNT program)

Currently there is an extensive global program assessing the safety and efficacy of tirzepatide as treatment for overweight/obesity in different populations as well as in comparison with other obesity pharmacotherapies (Figure 3). The SURMOUNT-5 study (NCT05822830) will compare the efficacy and safety of tirzepatide vs semaglutide 2.4 mg once weekly for people with obesity (without T2D) in a head-to-head comparison of the two most effective currently approved obesity pharmacotherapies. Moreover, the SURMOUNT-MAINTAIN trial (NCT06047548) will compare the efficacy of tirzepatide MTD vs tirzepatide 5 mg vs placebo for long-term weight maintenance after WL achieved during a 60-week open label period with tirzepatide MTD. The SURMOUNT-Adolescents (NCT06075667) and the SURMOUNT-Adolescents-2 (NCT06439277) are phase 3 global studies which will assess the safety and efficacy of tirzepatide in people 12–17 years old with obesity.

Aside from the efficacy of tirzepatide on WL, studies are also investigating its effect in obesity-related complications. The phase 2 TREASURE-CKD study (NCT05536804) will assess tirzepatide's potential mechanisms of action in people with CKD (with or without T2D). The STOP Knee – OA phase 4 study (NCT06191848) will explore the impact of tirzepatide (vs placebo) in people with obesity and moderate to severe knee osteoarthritis who are awaiting knee replacement (primary outcome is the percentage of people undergoing knee replacement at the target joint after 72 weeks of treatment).

The SURMOUNT-MMO (NCT05556512) aims to recruit > 15000 people with obesity (without diabetes) and high cardiovascular risk. The study will investigate the effect of tirzepatide vs placebo on the reduction of morbidity and mortality (the primary outcome is a composite of all-cause mortality, nonfatal myocardial infarction, nonfatal stroke, coronary

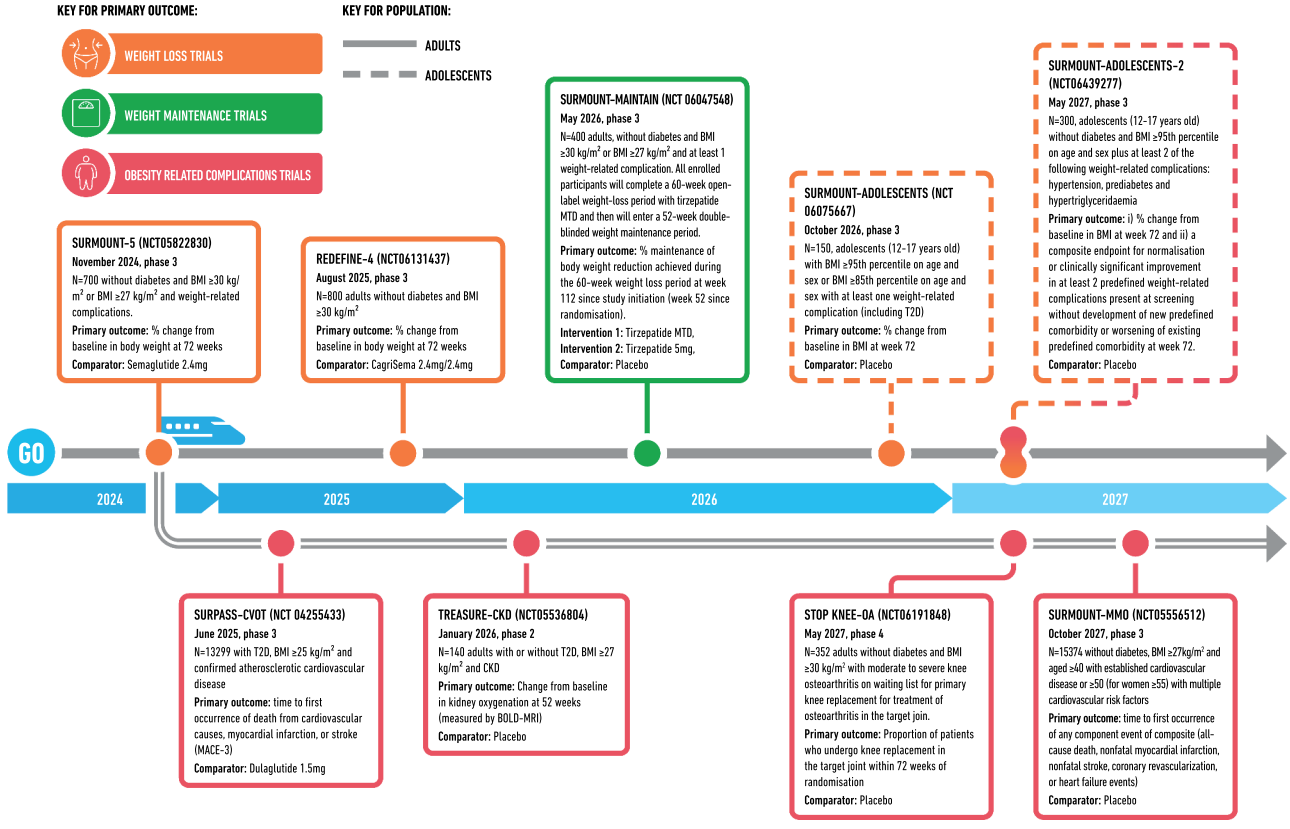


Figure 3. Key ongoing studies with tirzepatide for people with obesity and obesity-related complications.

BMI: Body Mass Index. T2D: Type 2 diabetes, CKD: Chronic Kidney Disease, MTD: Maximum tolerated dose, MACE: Major Adverse Cardiovascular Event.

revascularization, or HF events) – expected completion date is October 2027. Moreover, the SURPASS-CVOT trial (NCT04255433) will assess the non-inferiority of tirzepatide against dulaglutide 1.5 mg on cardiovascular safety in people with T2D and established cardiovascular disease (expected completion date June 2025) [68].

The SURMOUNT-MMO and SURPASS CVOT trials will also provide long-term safety and efficacy data for tirzepatide, helping to understand better its long-term risks and benefits. As new obesity pharmacotherapies like tirzepatide approach the efficacy of bariatric surgery regarding WL, we need to evaluate whether long-term complications of bariatric surgery such as increased fracture risk and nutrient deficiencies will also arise with pharmacotherapy [69]. Findings from these two large trials as well as real-world studies will provide further information on the potential cost-effectiveness of tirzepatide [69].

6. Conclusion

Tirzepatide is the first GLP-1/GIP co-agonist approved for management of overweight/obesity and T2D and marks a new era in obesity pharmacotherapy where combination of gut hormones can result in mean WL ≥ 20% and weight maintenance alongside marked improvements in multiple cardiometabolic risk factors, physical function and obesity-related complications. Tirzepatide has similar safety profile to GLP-1 RAs and overall was well-tolerated. Additional research assessing long-term safety and efficacy of tirzepatide in people living with obesity and/or T2D (including cardiovascular, morbidity and mortality outcomes) which will also provide further information on its cost-effectiveness are awaited over the next years to help us understand better its position in the treatment algorithms for these populations.

7. Expert opinion

7.1. Clinical implications of the SURMOUNT program

While modest WL (5–10%) is clinically meaningful for people with overweight and obesity, greater and sustained WL (≥10% and ideally ≥ 15% WL) may be required to achieve improvements or remission of certain obesity-related complications such as T2D, HFpEF, MASH, OSA and knee osteoarthritis, as well as to improve QoL and reduce the risk for cardiovascular events [3,70,71]. Until recently, the approved pharmacotherapies for chronic weight management (phentermine/topiramate, bupropion/naltrexone, liraglutide 3 mg, orlistat) typically led to 5–10% mean WL [69].

In 2021, semaglutide 2.4 mg, a once weekly GLP-1 RA, became the first approved obesity pharmacotherapy leading to ≈ 15–17% WL (in people without T2D) with a favorable safety profile while improving also multiple obesity-related complications [13,14]. In those with obesity and HFpEF (with or without T2D) semaglutide 2.4 mg improved the symptoms, physical limitations and exercise function compared to placebo, while in people with obesity and knee osteoarthritis improved the WOMAC pain score, a widely used tool to assess pain, stiffness and function in people with osteoarthritis [72,73]. Moreover, the SELECT trial, showed that semaglutide 2.4 mg reduces the major adverse cardiovascular events by 20% compared to placebo in people with obesity (without diabetes) and established CVD, while also providing kidney benefits [12,74]. Additionally, for people with T2D and CKD, semaglutide 1 mg weekly reduced major kidney disease events by 24% versus placebo [75].

The potential of tirzepatide in achieving greater WL than semaglutide 1 mg (dose approved for T2D management) was demonstrated in SURPASS-2 study. After 40 weeks, all tirzepatide doses (5, 10 and 15 mg) were superior to semaglutide 1 mg both for WL and glycemia, with 36% of participants on tirzepatide 15 mg achieving ≥ 15% WL compared to 8% with semaglutide 1 mg [45].

In the SURMOUNT-1 study, 72 weeks of tirzepatide 10 or 15 mg in people with overweight/obesity (without diabetes) resulted in 35–39.7% of them achieving ≥ 25% WL. These outcomes closely approach those observed with sleeve gastrectomy (≈25% mean WL at one year), the most commonly performed bariatric surgery worldwide [9]. Using data from the SURMOUNT-1 and STEP-1 studies, a matching-adjusted indirect treatment comparison demonstrated that tirzepatide 10 and 15 mg resulted in greater WL than semaglutide 2.4 mg in people without diabetes [76]. Moreover, the 176-week SURMOUNT-1 results in people with prediabetes confirm that WL with tirzepatide is sustained over time and that tirzepatide decreases significantly the risk of progression to T2D in this population compared to placebo [77].

Similar to other chronic diseases such as hypertension, obesity requires long term treatment, as discontinuing effective medications lead to weight regain in most patients [29,78]. This is reflected in SURMOUNT-4, where those who switched from tirzepatide MTD to placebo experienced marked weight gain over 52 weeks (+14.8%), even though lifestyle intervention continued.

As observed in previous studies with GLP-1 RAs, participants with overweight/obesity and T2D in the SURMOUNT-2 trial experienced less WL compared to those in the SURMOUNT-1 trial (without diabetes), despite the similarity in study designs and interventions [47,48]. Although differences in baseline characteristics between SURMOUNT-1 and SURMOUNT-2 were suggested as potential explanation for this finding, a recent propensity score-matched analysis found that the WL disparity persisted, indicating additional contributing factors [79].

The SURMOUNT-3 demonstrated that tirzepatide MTD can significantly enhance the WL achieved through intensive lifestyle interventions. Participants who achieved ≥ 5% WL during a 12-week intensive lifestyle program and then used tirzepatide MTD for 72 weeks achieved ≈ 26% mean WL, which is very similar to the WL achieved with tirzepatide MTD in SURMOUNT-4 study, where tirzepatide MTD was combined with a moderate-intensity lifestyle intervention for 88 weeks. These findings may suggest that the added benefits of intensive lifestyle interventions on WL may be limited when used alongside highly effective obesity pharmacotherapies like tirzepatide.

The SURMOUNT-CN and SURMOUNT-J studies confirmed also tirzepatide's efficacy and safety as treatment for overweight/obesity in Chinese and Japanese populations respectively.

Tirzepatide's safety profile in the global SURMOUNT studies for overweight/obesity management was similar to the GLP-1 RAs and aligns with findings from the SURPASS program [18]. However, large amounts of WL may also lead to substantial lean body mass loss, which may impair physical function and strength, potentially leading to deterioration in quality of life and overall health [80]. In the SURMOUNT-1 trial, tirzepatide use led to a 10.9% reduction in total lean mass, but the total fat mass decreased more substantially (−33.9%), and the self-reported physical function improved in the tirzepatide group compared to placebo across the SURMOUNT program (Table 2), consistent with findings from other GLP-1 RA trials [81,82]. Future research will need to directly and objectively assess the effect of tirzepatide on physical function and strength in different populations. Additionally, in SURMOUNT-3 and SURMOUNT-4, tirzepatide improved multiple domains of mental health and weight-related psychosocial function [55].

Despite marked improvements in multiple cardiometabolic risk factors with tirzepatide in the SURMOUNT program, robust cardiovascular outcome data are lacking and long-term safety and efficacy data on glycemic control and weight maintenance are limited for people with obesity and/or T2D. A meta-analysis of seven clinical trials in people with T2D provided some initial cardiovascular safety data on tirzepatide, but with a median follow-up of just over a year [83]. Currently, the longest follow-up periods in published tirzepatide trials are 104 weeks for T2D (SURPASS-4) and 176 weeks for obesity (SURMOUNT-1 for people with prediabetes) [51,84]. However, large ongoing clinical trials like SURPASS-CVOT and SURMOUNT-MMO are expected to deliver definitive evidence on cardiovascular safety, morbidity, and mortality outcomes, along with more comprehensive long-term safety and efficacy data for individuals with T2D and/or obesity.

Looking at the impact of tirzepatide on obesity-related complications, in the SURMOUNT-OSA studies, 52 weeks of tirzepatide MTD resulted in clinically meaningful improvements in moderate to severe OSA with 42.2–50.2% of those on tirzepatide for 52 weeks reaching OSA severity levels where PAP therapy may not be recommended anymore [65]. In people with MASH and moderate or severe fibrosis, tirzepatide is the first approved obesity pharmacotherapy with evidence from phase 2 trials that not only reduces liver inflammation, but it also improves liver fibrosis [59]. Additionally, in people with obesity and HFpEF, tirzepatide not only improved HF symptoms and physical limitations, but it also reduced the relative risk of HF outcomes, including a 56% reduction in worsening HF events leading to hospitalization (3.3% of participants in tirzepatide group vs 7.1% in placebo group) [67].

Currently, there is lack of evidence on tirzepatide's safety and efficacy in some obesity-related complications that semaglutide has already shown benefit (e.g. CKD and osteoarthritis). However, ongoing clinical trials will evaluate tirzepatide's impact on these conditions (see section 5), expanding our understanding of the full potential of this molecule.

Overall, tirzepatide stands out as the most effective approved pharmacotherapy for obesity, achieving WL at higher doses that approach the efficacy of sleeve gastrectomy, while it also improves multiple obesity-related complications including OSA, HFpEF, MASH as well as prevention and management of T2D. Tirzepatide's potent glucose-lowering actions make it an excellent treatment choice for individuals with obesity and T2D (without established cardiovascular or kidney disease) and the updated international guidelines for management of hyperglycemia in T2D have endorsed tirzepatide as a highly effective treatment for achieving both glycemic control and WL [85]. Additionally, it offers another treatment option for individuals with obesity (with or without diabetes) who have not achieved their individualized WL targets to improve health and QoL through lifestyle changes or other interventions for WL. Tirzepatide provides also a potentially effective treatment for some people with severe and complex obesity that either are not suitable for bariatric surgery or prefer non-surgical treatment options.

However, further research is needed to confirm its long-term safety, efficacy (including cardiovascular outcome data) and cost-effectiveness, along with efforts to address challenges regarding equal and long-term access to treatment as well as medication affordability. Until robust cardiovascular outcome data are available for tirzepatide, GLP-1 RAs with proven cardiovascular benefits, such as semaglutide 2.4 mg, should be prioritized for people with obesity and established cardiovascular disease.

7.2. Clinical considerations

Tirzepatide has now been approved in multiple countries (including Europe, U.S.A. and the UK) for chronic weight and T2D management alongside diet and increased physical activity. However, some key clinical considerations should be taken into account when prescribing tirzepatide (Figure 4).

Limited data is available on strategies for management of gastrointestinal AEs with GLP-1 RA based therapies (including tirzepatide) from clinical trials [70]. Patients should be counseled about potential gastrointestinal AEs which are usually transient and mild to moderate in severity [70,86]. In SURMOUNT-3 and −4 trials, that aimed to use tirzepatide MTD, gastrointestinal AEs were managed initially with dietary modifications, over the counter medications for symptom control and if symptoms did not improve, a medication dose was omitted. In those with intolerable gastrointestinal AEs despite the previous steps, de-escalation and re-escalation of dose was trialed [46]. If these measures were not effective, down-titration to a lower dose was used [46]. The multiple approved tirzepatide doses for weight management allow a flexible and individualized dosing scheme, as even tirzepatide 5 mg results in ≈ 15% WL, with only 4% of participants discontinuing this dose due to AEs. However, for those needing to reach the maximum tirzepatide dose (15 mg), the six-step titration process and the 5-month titration period may pose challenges in real-world settings, increasing the risk for therapeutic inertia during dose escalation.

Patients initiated on tirzepatide should be informed about the symptoms and the possibility of acute gallbladder-related events. Although substantial WL is associated with gallbladder-related AE, mechanisms beyond WL related to GLP-1 activity may also be involved [87].

Therapeutic Indications	• Weight management as an adjunct to a reduced-calorie diet and increased physical activity in adults with a BMI of ≥ 30 kg/m^2 or ≥ 27 kg/m^2 with at least one weight-related comorbid condition. • Treatment of adults with insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise.
Administration	• Tirzepatide should be injected subcutaneously once weekly in the abdomen, thigh, or upper arm and injection sites should be rotated • The dose can be administered at any time of day.
Dose Escalation Schedule	• Starting dose is 2.5 mg once weekly. Increase to 5 mg once weekly after 4 weeks. • If needed, increase in 2.5 mg increments after a minimum of 4 weeks on the current dose. The maximum dose is 15 mg once weekly. • Recommended maintenance doses: 5, 10, and 15 mg.
Missed Doses	• Missed dose should be administered within 4 days; if more than 4 days have passed, skip and administer the next dose on the regularly scheduled day.
Changing the Dosing Schedule	• The weekly administration day can be changed if at least 3 days have passed between two doses.
Contraindications	• Personal or family history of medullary thyroid carcinoma (MTC) or Multiple Endocrine Neoplasia syndrome type 2 (MEN-2). • Known serious hypersensitivity to tirzepatide or any excipients in Mounjaro.
Concomitant Medication Use	• Monitor patients on medications with a narrow therapeutic index (e.g., warfarin), especially at initiation of tirzepatide and following dose increase. • Advise patients on oral hormonal contraceptives to switch to non-oral methods or add a barrier method for 4 weeks after initiation and each dose escalation of tirzepatide.
Common Adverse Effects (≥ 5%)	• Nausea, diarrhea, decreased appetite, vomiting, constipation, dyspepsia, and abdominal pain.
Precautions and Warnings	• Not studied in people with a history of pancreatitis, severe gastrointestinal disease, or in people with non-proliferative diabetic retinopathy requiring acute therapy, proliferative diabetic retinopathy, diabetic macular oedema. • Consider reducing the dose of insulin secretagogue or insulin to reduce the risk of hypoglycemia.
Special Populations	• No dose adjustment needed for renal or hepatic impairment or based on age, gender, race, ethnicity, or body weight. • Discontinue at least 4 weeks prior to pregnancy. • Safety and effectiveness not established in pediatric populations.

Figure 4. Important clinical considerations for using once-weekly subcutaneous tirzepatide.
BMI: Body Mass Index.

As tirzepatide delays the gastric emptying, it may also impact the absorption of concomitantly administered medications. Patients on oral medications dependent on threshold concentrations for efficacy and those with narrow therapeutic index (e.g. warfarin) will need closer monitoring, especially during tirzepatide escalation period. Women on oral contraceptives should be advised to switch to a non-oral contraceptive method, or add a barrier method of contraception for 4 weeks after initiation and for 4 weeks after each dose escalation [88,89].

Women planning to become pregnant should discontinue the medication four weeks in advance. Tirzepatide is not licensed in pediatric populations or in pregnancy [88].

Based on pharmacokinetics studies no dose adjustment for tirzepatide is recommended in people with renal or hepatic impairment. However, there is limited data with tirzepatide in people with severe renal and hepatic impairment from the currently completed SURPASS and SURMOUNT studies [88,89].

In people with a history of pancreatitis, tirzepatide should be used with caution, as this population was excluded from the SURMOUNT and SURPASS programs.

Tirzepatide's efficacy for weight management was not impacted by age, gender, race, ethnicity, region, baseline BMI, or presence or absence of prediabetes. As mentioned previously, there are concerns that marked WL induced by GLP-1-based obesity pharmacotherapies may induce

sarcopenia and physical frailty due to significant amount of lean muscle mass loss. Although the currently available data do not support these concerns, lean muscle mass preservation may be of particular importance for people at higher risk of sarcopenia (such as elderly, frail population or people with CKD) [52,88]. Sarcopenia is closely linked to obesity and its complications, and is also common in various diseases, though its prevalence differs between different studies based on diagnostic criteria used [90]. Adequate nutrition and protein intake as well as support for resistance exercise during the rapid WL phase, along with slower dose titration in high risk for sarcopenia populations may preserve lean muscle mass and optimize physical function [91].

7.3. Additional clinical considerations for people with T2D

Using tirzepatide together with insulin secretagogues (e.g. sulphonylureas) or insulin may increase the risk of hypoglycemia, including severe hypoglycemia. In the SUPRASS program, basal insulin doses were reduced by 20–30% at tirzepatide initiation, while in SURMOUNT-2 sulphonylurea dose was halved or if already at the lower dose stopped [18,47,84].

People with non-proliferative diabetic retinopathy requiring acute therapy, proliferative diabetic retinopathy and macular edema were excluded from the SURPASS or SURMOUNT-2 studies. Rapid improvements in glucose control can temporarily worsen diabetic retinopathy, so caution is needed when starting tirzepatide in these populations, especially in those with uncontrolled glycemia [91]. Slower medication titration, retinal screening before treatment initiation and close monitoring by ophthalmology team may be required in these cases [91].

7.4. Future directions on research with tirzepatide

While multiple ongoing studies will provide long-term safety and efficacy data for tirzepatide, several areas warrant further investigation (Figure 5).

People with obesity and type 1 diabetes (T1D) were excluded from the SURMOUNT program due to safety concerns. Limited data from small observational/retrospective studies highlight the need for clinical trials on tirzepatide's safety and efficacy in this population [92]. Given the rising prevalence of obesity in people with T1D (28% in a recent US survey) and the potential benefits of WL in this population, such clinical trials are urgently needed (NCT06180616) [93].

Another area that requires further investigation is the use of tirzepatide in combination with bariatric surgery. As obesity is a complex, progressive and relapsing disease process, even people who have undergone bariatric surgery may experience inadequate WL or weight regain and recurrence of obesity-related complications [29,91]. Clinical trials with GLP-1 RAs suggest that these treatments may remain effective in improving glycemic control and WL in people after bariatric surgery [94,95].

Emerging evidence suggests that GLP-1 RAs have also neuroprotective effects. Early-phase clinical trials indicate less progression of motor disability with GLP-1 RAs in Parkinson's disease, and further studies show reduced incidence of cognitive impairment and dementia in people with T2D [96–98].

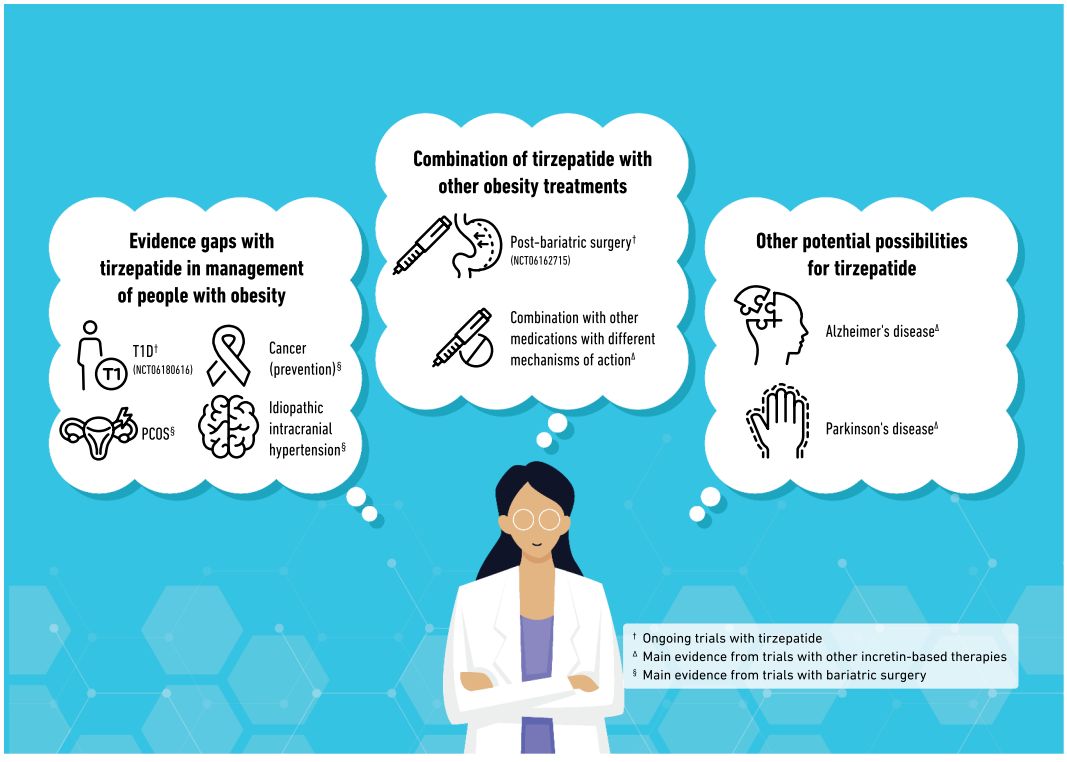


Figure 5. Potential future directions on research with tirzepatide.

T1D: Type 1 diabetes, PCOS: Polycystic ovary syndrome.

Currently, there are two ongoing phase 3 clinical trials (NCT04777396 and NCT04777409) assessing oral semaglutide's impact on early Alzheimer's disease [99]. As tirzepatide demonstrates also neuroprotective effects in experimental studies, further research is needed to understand its potential in preventing or treating Parkinson's disease and cognitive impairment [100].

Additionally, marked WL and maintenance through bariatric surgery reduces the risk for some cancers, especially in women [101]. Retrospective cohort studies indicate that GLP-1 RAs use instead of insulin is also associated with significant reduction in 10 out of 13 obesity-related cancers in people with T2D [102]. Considering that tirzepatide approaches bariatric surgery's efficacy in WL and there is evidence from experimental studies that it may mitigate the pro-cancer effects of obesity, further research on tirzepatide's potential for cancer prevention (primary and secondary) in people with obesity is warranted [103]. Preliminary evidence from a 'hypothesis-generating' meta-analysis of clinical trials in people with T2D (with short follow-up and relatively small number of participants) suggests that tirzepatide may not affect the risk for cancer, however, large and long-term studies are required to assess its effect on cancer risk [104]. Marked WL in people with severe obesity through bariatric surgery can induce spontaneous ovulation in women with polycystic ovary syndrome, as well as aid in treating idiopathic intracranial hypertension [105,106]. Exploring tirzepatide's efficacy in addressing these obesity-related complications may also be valuable.

Finally, while tirzepatide is the first approved combination of entero-pancreatic hormones for T2D and chronic weight management, several new obesity pharmacotherapies combining GLP-1 with other entero-pancreatic hormones with diverse actions are currently in phase 3 trials (e.g. cagrisema, retatrutide, mazdutide, survodutide) [17]. Some of these treatments may offer similar or even superior WL efficacy than tirzepatide, further bridging the gap between pharmacotherapy and bariatric surgery. Additionally, pharmacotherapies targeting different mechanisms of action to entero-pancreatic hormones, such as bimagrumab (a human monoclonal antibody that stimulates skeletal muscle growth), are also in early phase clinical trials for obesity management and may improve the body composition during WL [17]. Combinations of treatments for obesity with different mechanisms of action (e.g. tirzepatide with bimagrumab) may further optimize WL and improve the overall health outcomes.

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