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Tirzepatide for the treatment of obesity: Rationale and design of the SURMOUNT clinical development program

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Abstract

Objective: Obesity is a growing global concern compounded by limited availability of effective treatment options. The SURMOUNT development program aims to evaluate the efficacy and safety of tirzepatide as an adjunct to lifestyle intervention compared with placebo on chronic weight management in adults with BMI ≥ 27 kg/m^2 with or without type 2 diabetes.

Methods: The SURMOUNT program includes four global phase 3 trials NCT04184622 (SURMOUNT-1), NCT04657003 (SURMOUNT-2), NCT04657016 (SURMOUNT-3), and NCT04660643 (SURMOUNT-4). Participants are randomized to once-weekly subcutaneous tirzepatide versus placebo in a double-blind manner. The primary end point in all trials is the percentage change in body weight from randomization to end of treatment. Results for the primary end point for SURMOUNT-1 were published recently and results for the other trials are expected in 2023.

Results: Across trials, participants have a mean age of 44.9 to 54.2 years, are mostly female (50.7% to 69.7%), and have a mean BMI of 36.1 to 38.9.

Conclusions: The extensive assessment of once-weekly tirzepatide in the global SURMOUNT program will detail the clinical effects of this first-in-class glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1 receptor agonist in chronic weight management.

INTRODUCTION

Obesity is a chronic, progressive disease affecting more than 13% of the adult population worldwide [1]. Not only does it affect health-related quality of life, but obesity is also a major contributor to morbidity and mortality by increasing the risk of type 2 diabetes (T2D), cardiovascular disease (CVD), nonalcoholic steatohepatitis, renal disease, osteoarthritis, obstructive sleep apnea, malignancies, and premature death [2, 3].

Foundational to weight management in obesity is lifestyle-based therapy that combines personalized reduced-calorie diet, physical activity, and behavioral counseling [4, 5]. This type of intervention typically leads to relatively moderate weight reduction (5% to 10%), which may provide some clinical benefit, but greater weight reduction yields more clinically meaningful benefits [4, 6–9]. Although most people with obesity attempt lifestyle interventions, only approximately 20% to 40% achieve durable (i.e., >1 year), clinically meaningful weight reduction (≥5%) [10–13], and, for those who do, the degree of weight reduction does not conclusively show long-term benefit on survival [14, 15].

Metabolic surgery is currently the most effective therapy for chronic weight management (CWM), providing long-term benefits on

survival, cardiovascular outcomes, and other complications [16–19]. Although it is generally indicated for people with class 2 obesity (BMI ≥35 kg/m^2) with ≥1 obesity-related complication or class 3 obesity (BMI ≥ 40 kg/m^2), less than 2% of people with class 2 or class 3 obesity undergo metabolic surgery [20, 21]. With the limited efficacy and durability of lifestyle-based monotherapy, and limited scalability of surgical treatments, there is an urgent need for pharmacological treatment options that yield safe, substantial, and sustained weight reduction.

Pharmacotherapy as an adjunct to lifestyle intervention is recommended by current treatment guidelines in people with BMI ≥ 30 or BMI ≥ 27 with at least one obesity-related complication [3, 22]. Historically, though, most approved antiobesity medications (AOMs) have been shown to provide modest placebo-subtracted weight reduction of 3% to 9%, with some drugs being significantly limited by their propensity for side effects [23, 24]. However, the most recently approved glucagon-like peptide-1 (GLP-1) receptor agonist, semaglutide 2.4 mg, exhibits greater efficacy compared with existing AOMs [25, 26].

Tirzepatide is a 39-amino acid synthetic peptide with agonist activity at the glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 receptors. Preclinical data demonstrated that tirzepatide had equal affinity for GIP receptors compared with native GIP while it bound GLP-1 receptors with approximately fivefold weaker affinity than native GLP-1 [27]. As a GIP and GLP-1 receptor agonist, tirzepatide could result in weight reduction beyond that achieved with selective GLP-1 receptor agonists by affecting tissues not targeted by these mono-agonist agents and integrating the activation signals of both GIP and GLP-1 receptor pathways in the brain [27,28]. In two clinical trials comparing tirzepatide with semaglutide 1 mg and dulaglutide 1.5 mg in people with T2D, tirzepatide 5 to 15 mg doses were associated with dose-dependent weight reduction, significantly greater than the weight reduction observed with the selective GLP-1 receptor agonists [29, 30]. Tirzepatide was recently approved by the Food and Drug Administration (FDA) as an adjunct to diet and exercise to improve glycemic control in adults with T2D.

The SURMOUNT clinical development program is evaluating tirzepatide administered subcutaneously once weekly for CWM in people with obesity. The purpose of the program is to demonstrate the safety, tolerability, and efficacy of tirzepatide and to support regulatory approval of tirzepatide for CWM. Overall, the program seeks to determine whether tirzepatide results in clinically meaningful weight reduction for people with obesity and improves obesity-related cardiometabolic risk factors and physical function. It further aims to determine the degree to which treatment with tirzepatide adds to the weight reduction achieved through intensive lifestyle therapy and maintains weight reduction over time. This article presents the trial designs, objectives, end points, and baseline characteristics of the global SURMOUNT clinical development program.

Study Importance

What is already known?

- Current guidelines for the treatment of obesity recommend combining antiobesity medications with lifestyle intervention; therapies that provide substantial and sustained weight reduction are expected to provide more clinically meaningful benefits for people with obesity.
- The selective glucagon-like peptide-1 (GLP-1) receptor agonist semaglutide has shown greater efficacy than older antiobesity medications and was recently approved for chronic weight management in adults with obesity.
- Tirzepatide, a novel glucose-dependent insulinotropic polypeptide and GLP-1 receptor agonist, showed greater weight reduction than selective GLP-1 receptor agonists in type 2 diabetes studies.

What does this study add?

- The SURMOUNT clinical development program is designed to demonstrate whether tirzepatide administered subcutaneously once weekly is effective in patients with or without diabetes as an adjunct to lifestyle intervention for chronic weight management.
- In the SURMOUNT-1 trial, once-weekly tirzepatide provided substantial, clinically meaningful, and sustained reductions in body weight in participants without diabetes.

How might these results change the direction of research or the focus of clinical practice?

- The SURMOUNT trials will provide data on the efficacy and safety of tirzepatide for chronic weight management; initial data for tirzepatide support greater efficacy for clinically meaningful weight reduction beyond that achieved with agents currently approved for obesity.

METHODS

The SURMOUNT program includes the following trials:

- Fixed-dose efficacy and safety studies, SURMOUNT-1 and -2.
- Clinically relevant maximum tolerated dose studies, SURMOUNT-3 and -4.

The SURMOUNT clinical trials are phase 3, multicenter, randomized, placebo-controlled, double-blind studies assessing the safety and efficacy of tirzepatide administered subcutaneously once weekly compared with placebo, when used in conjunction with a reduced-calorie diet and increased physical activity for weight management, in participants with BMI ≥30 kg/m or BMI ≥27 kg/m^2 with ≥1 obesity-related complication (Tables 1 and 2). Assignment to treatment groups is determined by a computer-generated, random sequence using an interactive web response system.

TABLE 1 Trial designs, objectives, and end points

	SURMOUNT-1, NCT04184622	SURMOUNT-2, NCT04657003	SURMOUNT-3, NCT04657016	SURMOUNT-4, NCT04660643
Participants enrolled, *N*	2539[a]	938[a]	806	783
Trial design: randomized, double-blind, placebo-controlled	X	X	X	X
Treatment arms, randomization	TZP 5, 10, and 15 mg and PBO, 1:1:1:1	TZP 10 and 15 mg and PBO, 1:1:1	MTD (TZP 10 or 15 mg) and PBO, 1:1	MTD (TZP 10 or 15 mg) and PBO, 1:1
Randomization stratification	Country, sex, and prediabetes status	Country, sex, and weight effect of AHM used at randomization	Country, sex, and % WL at end of lead-in (<10% or ≥10%)	Country, sex, TZP MTD dose at 36 weeks (10 mg or 15 mg), and % WL at end of lead-in (<10% or ≥10%)
Treatment duration	72 weeks to primary end point; 176 weeks to final end point if diagnosed with prediabetes at baseline	72 weeks	72 weeks	88 weeks total: 36-week open-label lead-in on TZP then 52-week double-blind treatment period
Safety follow-up period	4 weeks for participants with normoglycemia at randomization and those with prediabetes who discontinue during the first 72 weeks; 17 weeks for participants with prediabetes at randomization	4 weeks	4 weeks	4 weeks
Trial objectives	To demonstrate that TZP is superior to PBO on WL and compare safety in participants without T2D but who have obesity or overweight	To demonstrate that TZP is superior to PBO on WL and compare safety in participants with T2D who have obesity or overweight	To evaluate WL with TZP compared with placebo in participants without T2D but who have obesity or overweight and who responded to an intensive lifestyle modification program	To evaluate maintained effect of TZP compared with PBO on WL after 36-week open-label TZP lead-in in participants without T2D but who have obesity or overweight
Primary end point				
Percentage change in body weight	X	X	X	X
Percentage of participants achieving ≥5% WL	X	X	X	NA[b]
Key secondary end point				
Weight loss at 1 year				
Change in body weight	X	X	NA[c]	X
Percentage of participants with ≥10% WL	X	X	X	X[d]
Percentage of participants with ≥15% WL	X	X	X	X[d]
Percentage of participants with ≥20% WL	X	X	X	X[d]
Change in waist circumference	X	X	X	X
Weight loss at 3 years[e]				
Percentage change in body weight from	X	NA	NA	NA

(Continues)

TABLE 1 (Continued)

	SURMOUNT-1, NCT04184622	SURMOUNT-2, NCT04657003	SURMOUNT-3, NCT04657016	SURMOUNT-4, NCT04660643
randomization to 176 weeks[d]				
Weight maintenance				
Percentage of participants maintaining ≥80% of body weight lost during lead-in	NA	NA	X	X
Time after randomization (in weeks) to regain of >95% weight lost during lead-in	NA	NA	NA	X
Cardiometabolic				
Change in triglycerides, non-HDL cholesterol, and HDL cholesterol	X	X	NA	NA
Change in systolic blood pressure	X	X	NA[c]	NA[c]
Physical function				
Change in SF-36v2 acute form physical functioning domain score	X	NA[c]	NA[c]	NA[c]
Glycemia-related				
Change in fasting glucose	NA[c]	X	NA[c]	NA[c]
Change in HbA1c	NA[c]	X	NA[c]	NA[c]
Percentage of participants with HbA1c < 7%	NA	X	NA	NA
Change in fasting insulin	X	NA[c]	NA[c]	NA[c]
Time to onset of T2D at the end of 176 weeks or 193 weeks[e]	X	NA	NA	NA

Note: Primary and secondary end points are from randomization to week 72 (SURMOUNT-1, -2, and -3) or week 88 (SURMOUNT-4), unless otherwise stated.

Abbreviations: HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; MTD, maximum tolerated dose; PBO, placebo; SF-36v2, the short form (36) health survey version; T2D, type 2 diabetes mellitus; TZP, tirzepatide; WL; weight loss.

[a]Number of participants enrolled is the same as the number randomized.

[b]Percentage of participants who achieve ≥5% body weight loss from Week 0 to the end of the double-blind treatment period (week 88) is included as a key secondary end point.

[c]Included as an additional secondary end point.

[d]Percentage of participants who achieve ≥10%, ≥15%, and ≥20% body weight loss from week 0 to week 88.

[e]Assessed in participants with prediabetes at randomization.

Participants are adults ≥18 years of age with a history of ≥1 self-reported unsuccessful dietary effort to lose weight, excluding those with type 1 diabetes and adults with a self-reported change in body weight >5 kg within 90 days before screening. Further trial-specific eligibility criteria are shown in Table 2. To ensure a sufficient population of males, female enrollment is capped at 70% in each trial. All trials are being conducted in accordance with good clinical practice guidelines and the principles of the Declaration of Helsinki. Independent Ethics Committee or Institutional Review Board approval was received for each of the participating sites. All participants provided written informed consent prior to trial participation.

Participants are receiving lifestyle intervention throughout the studies. This includes regular lifestyle counseling sessions delivered by a dietitian or qualified health care professional, focused on healthy, balanced meals with a 500-kcal/d deficit, and at least 150 min/wk of physical activity in accordance with guidelines [5]. Participants have the option to use food and exercise logs and a Fitbit activity tracker to facilitate self-monitoring and behavioral change.

Tirzepatide doses of 5, 10, and 15 mg once weekly are being evaluated in the SURMOUNT program. These doses and associated dose-escalation schemes were selected based on assessment of safety,

TABLE 2 Key eligibility criteria for SURMOUNT trials

Eligibility Criteria	SURMOUNT-1	SURMOUNT-2	SURMOUNT-3	SURMOUNT-4
Key inclusion criteria				
Adult male or female aged ≥ 18 years[a]	X	X[b]	X	X
BMI ≥ 27 with T2D according to WHO classification	NA	X	NA	NA
BMI ≥ 30 or ≥27 with ≥1 previously diagnosed comorbidity: hypertension, dyslipidemia, obstructive sleep apnea, CVD	X	NA	X	X
History of ≥1 self-reported unsuccessful dietary effort to lose weight	X	X	X	X
HbA1c ≥ 7% to ≤10%	NA	X	NA	NA
On stable diabetes therapy ≥3 months prior to screening	NA	X	NA	NA
Key exclusion criteria				
Diabetes-related				
History of T1D	X	X	X	X
History of T2D	X	NA	X	X
Obesity-related				
Change in body weight >5 kg within 3 months prior to screening	X	X	X	X
Obesity induced by other endocrinologic disorders or monogenetic or syndromic forms of obesity	X	X	X	X
Medical				
Renal impairment, eGFR < 30 mL/min/1.73 m^2	X	X	X	X
History of pancreatitis	X	X	X	X
Uncontrolled thyroid disease: thyroid-stimulating hormone outside of 0.4 to 6.0 mIU/L at screening	X	X	X	X
Uncontrolled hypertension (SBP ≥ 160 mm Hg and/or DBP ≥ 100 mm Hg)	X	X	X	X
Acute MI, cerebrovascular accident (stroke), unstable angina, or hospitalization due to CHF within 3 months prior to randomization	X	X	X	X
NYHA Functional Classification IV CHF	X	X	X	X
Calcitonin level ≥20 ng/L at screening, if eGFR ≥ 60 mL/min/1.73 m^2, or ≥35 ng/L, if eGFR < 60 mL/min/1.73 m^2	X	X	X	X
Acute or chronic hepatitis or other liver disease (excluding NAFLD)	X	X	X	X
ALT level > 3 times the ULN for the reference range or ALP level > 1.5 times the ULN or TBL > 1.2 times the ULN (except for Gilbert syndrome)	X	X	X	X
History of or in remission from malignancy (other than basal- or squamous-cell skin cancer, *in situ* carcinomas of the cervix, or *in situ* prostate cancer) for <5 years	X	X	X	X
Family or personal history of MTC or MEN syndrome type 2	X	X	X	X
Psychiatric				
History of significant active or unstable MDD or other severe psychiatric disorder within the last 2 years	X	X	X	X
Any lifetime history of a suicide attempt	X	X	X	X
Concomitant therapy (current or within 3 months prior to screening)				
DPP-4 inhibitors, oral GLP-1R agonist, or any injectable therapy for T2D	NA	X	NA	NA

(Continues)

TABLE 2 (Continued)

Eligibility Criteria	SURMOUNT-1	SURMOUNT-2	SURMOUNT-3	SURMOUNT-4
Metformin or any other glucose-lowering medication (whether prescribed for PCOS or diabetes prevention)	X	NA	X	X
Systemic glucocorticoid therapy	X	X	X	X
Medications that may cause weight gain such as tricyclic antidepressants, atypical antipsychotics, and mood stabilizers	X	X	X	X
Medication or alternative therapies that promote weight loss	X	X	X	X

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; CHF, congestive heart failure; CVD, cardiovascular disease; DBP, diastolic blood pressure; DPP-4, dipeptidyl peptidase-4; eGFR, estimated glomerular filtration rate; GLP-1R, glucagon-like peptide-1 receptor; HbA1c, glycated hemoglobin; MDD, major depressive disorder; MEN, multiple endocrine neoplasia; MI, myocardial infarction; MTC, medullary thyroid carcinoma; NAFLD, nonalcoholic fatty liver disease; NYHA, New York Heart Association; PCOS, polycystic ovary syndrome; SBP, systolic blood pressure; T1D, type 1 diabetes mellitus; T2D, type 2 diabetes mellitus; TBL, total bilirubin; ULN, upper limit of normal; WHO, World Health Organization.

[a]Male participants with partners of childbearing potential should be willing to use reliable contraceptive methods throughout the study and for five half-lives of study drug plus 90 days; female participants of childbearing potential require negative screening for pregnancy before randomization, and contraception counseling is provided to avoid pregnancy during the trial and soon after the trial is completed; female participants of childbearing potential and who are sexually active must agree to use two forms of effective contraception, of which at least one form is highly effective for the duration of the trial plus 30 days, corresponding to 2 months after the last injection.

[b]Participants are at least 18 years of age and age of majority per local laws and regulations.

efficacy, and gastrointestinal tolerability data, followed by exposure-response modeling of data in participants in phase 1 and phase 2 studies [27, 29, 31]. In the phase 1 study, doses from 0.25 mg escalated up to 15 mg once weekly were evaluated for safety and tolerability [27]. Results from the study supported further development of tirzepatide in the phase 2 studies. In participants with T2D, once-weekly tirzepatide 5 to 15 mg demonstrated significantly greater reduction in glycated hemoglobin (HbA1c) and weight compared with dulaglutide 1.5 mg [29]. The phase 2b dose titration study further demonstrated that gastrointestinal tolerability of tirzepatide was improved with a low starting dose and smaller dose increments [31]. As such, a 20-week dose-escalation period was included in the phase 3 SURPASS clinical trials that investigated the efficacy and safety of tirzepatide for the treatment of T2D. The same dose-escalation scheme is included in all the SURMOUNT trials, with a starting dose of 2.5 mg once weekly (or matching placebo), increased by 2.5 mg (or matching placebo) every 4 weeks up to 20 weeks as the assigned dose requires. During the double-blind treatment phase, if study drug is interrupted for three or more consecutive weekly doses for any reason, participants restart escalation from 5 mg up to the assigned dose (SURMOUNT-1 and -2) or maximum tolerated dose (SURMOUNT-3 and -4).

Discontinuation of study drug is decided by the participant or the investigator. Clinical considerations for discontinuation of study drug include initiation of open-label GLP-1 receptor agonist or dipeptidyl peptidase-4 inhibitor, significantly elevated calcitonin levels, diagnosis of pancreatitis, or pregnancy. Participants who stop study drug permanently during the double-blind treatment period are encouraged to continue to attend all scheduled study visits to collect all planned efficacy and safety measurements, unless pregnant. A participant is considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and cannot be contacted by the study site.

In each trial, the effects of drug cessation will be assessed in a safety follow-up period following completion of the treatment phase or study drug discontinuation (Table 1).

Fixed-dose efficacy and safety studies

Study design

The primary study period of SURMOUNT-1 (NCT04184622) was completed and included 2539 adults without diabetes. Participants were randomized in a 1:1:1:1 ratio to tirzepatide (5, 10, or 15 mg) or placebo to study the effects of tirzepatide on CWM (Figure 1, Table 1). Randomization was stratified by country, sex, and glycemic status (normoglycemia vs. prediabetes) as defined by the 2019 American Diabetes Association Standards of Medical Care in Diabetes [32]. All randomized participants were planned to undergo a 72-week treatment period (primary study period) that included a dose-escalation period of up to 20 weeks and allowed for 52 weeks of follow-up on the highest dose (15 mg). A subset of participants ($n = 255$) underwent further assessment to evaluate effects of tirzepatide on body composition. Heart rate and blood pressure were assessed in more detail in an additional subset of participants owing to potential effects of GLP-1 receptor agonists on hemodynamics.

Participants with prediabetes at randomization will be studied for a total of 176 weeks of treatment to provide sufficient follow-up time to detect potential differences in progression to T2D. In addition, the extended treatment phase will allow investigators to evaluate tirzepatide's effects on long-term body weight changes.

Evidence suggests that, compared with people without diabetes, people with T2D and obesity often respond less robustly to weight management treatments and therefore warrant dedicated clinical trials

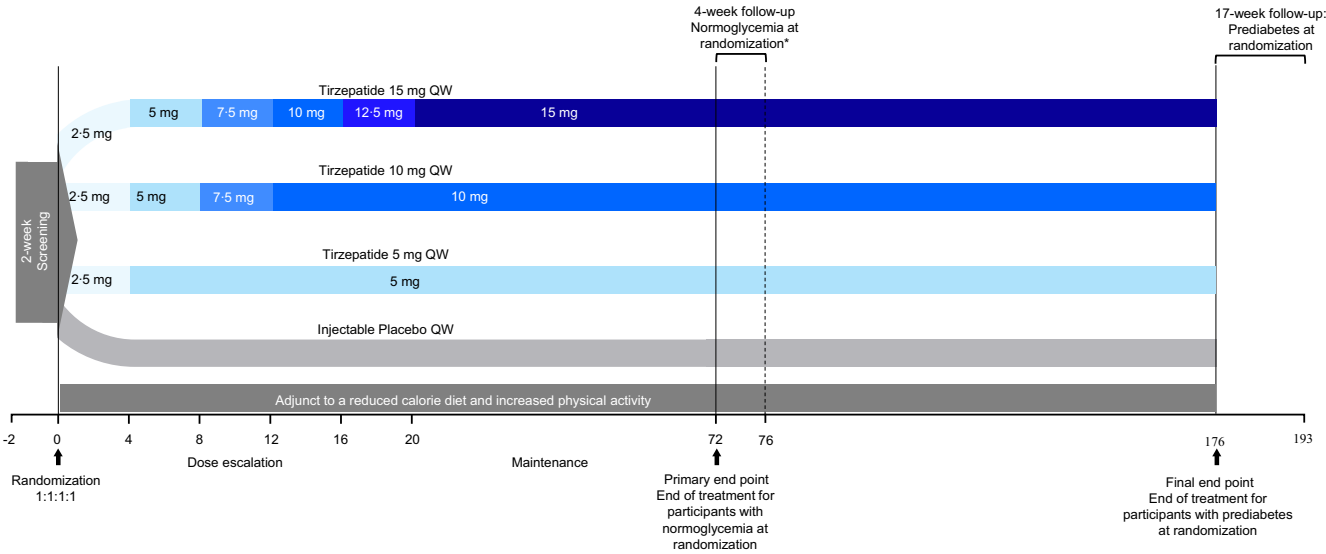

FIGURE 1 SURMOUNT-1 study design. This is a phase 3, multicenter, randomized, placebo-controlled, double-blind clinical trial investigating the safety and efficacy of 5, 10, and 15 mg tirzepatide administered QW subcutaneously compared with placebo for weight management as an adjunct to a reduced-calorie diet and increased physical activity in participants with BMI ≥ 30 or ≥27 with obesity-related complications (excluding type 2 diabetes).*Participants who had prediabetes at randomization but discontinued the study during the 72-week treatment period were included in the 4-week safety follow-up. QW, once weekly

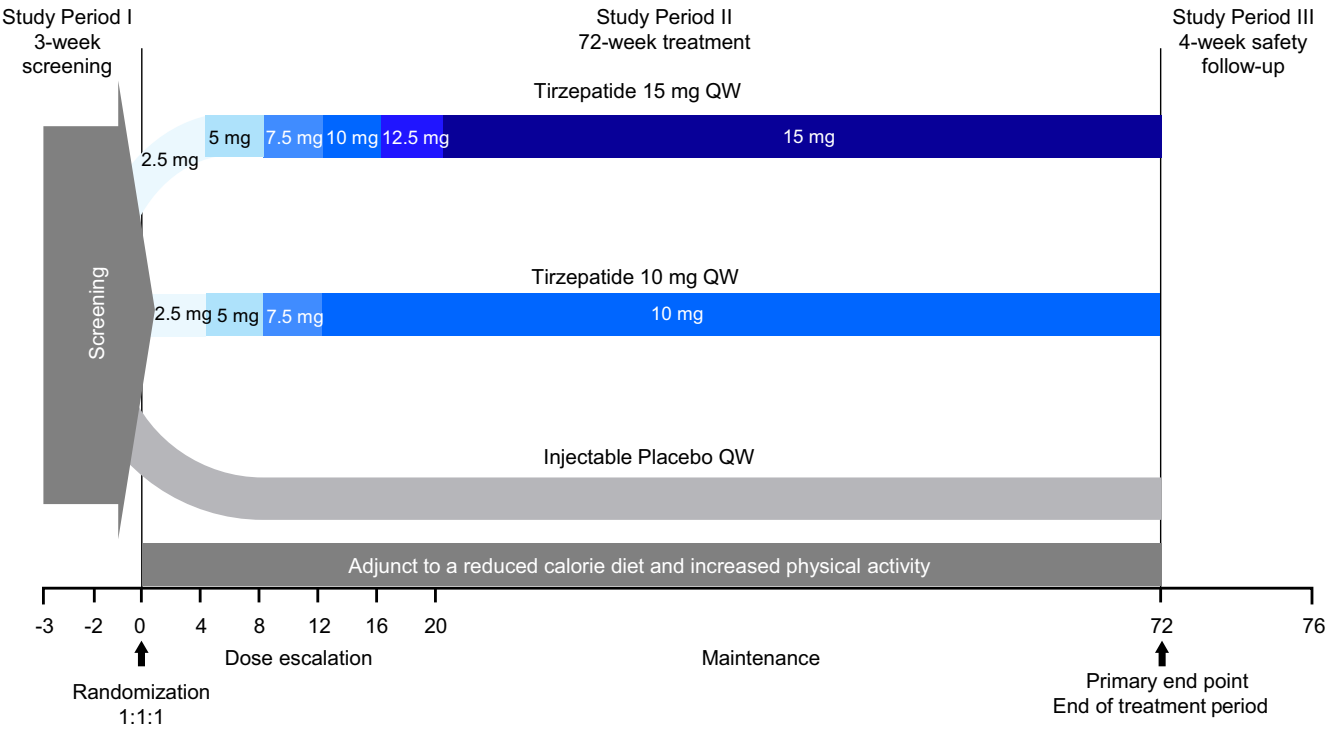

FIGURE 2 SURMOUNT-2 study design. This is a phase 3, multicenter, randomized, placebo-controlled, double-blind, 72-week clinical trial investigating the safety and efficacy of tirzepatide 10 and 15 mg administered QW subcutaneously compared with placebo on weight management, as an adjunct to a reduced-calorie diet and increased physical activity, in participants with type 2 diabetes and BMI ≥ 27. QW, once weekly

[33]. As such, SURMOUNT-2 (NCT04657003) includes 938 adults with T2D, BMI ≥ 27, and HbA1c 7% to 10% and on stable treatment ≥3 months prior to screening (excluding dipeptidyl peptidase-4 inhibitors, oral GLP-1 receptor agonist, or any injectable therapy for T2D). Participants are randomized to 72 weeks of treatment in a 1:1:1 ratio to tirzepatide (10 or 15 mg) or placebo to assess the effects of tirzepatide on CWM in the T2D population (Figure 2, Table 1). Randomization is stratified by country, sex, and potential weight effect of concomitant antihyperglycemic medications (AHMs; categorized as promoting weight gain, weight reduction, or weight neutral). An upper

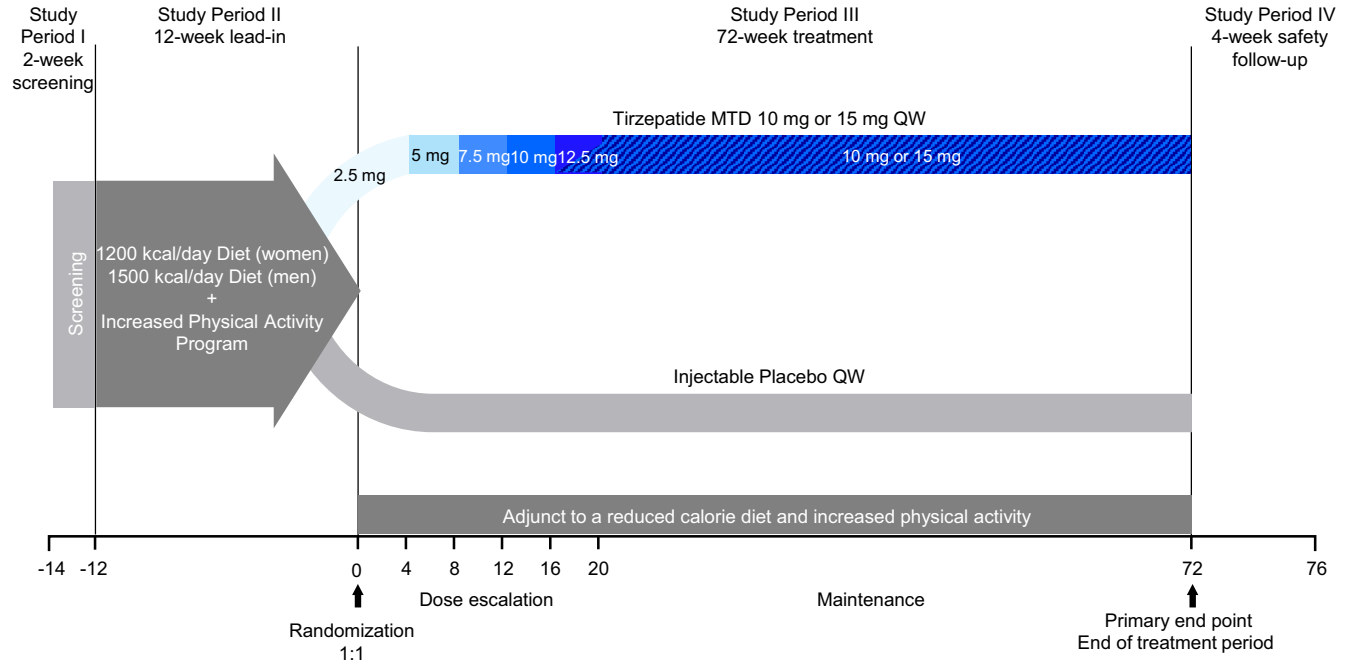

FIGURE 3 SURMOUNT-3 study design. This is a phase 3, multicenter, randomized, placebo-controlled, double-blind, 84-week clinical trial investigating the safety and efficacy of the MTD of tirzepatide (10 or 15 mg), administered subcutaneously QW, compared with placebo, on body weight management in participants who have BMI ≥ 30 or ≥27 with obesity-related complications (excluding type 2 diabetes) and achieve ≥5.0% weight reduction after a 12-week lead-in period on an intensive lifestyle modification program. MTD, maximum tolerated dose; QW, once weekly

limit of 30% enrollment of participants treated with sulfonylureas is used to allow a sufficient number of participants treated with other AHMs. To minimize the risk of hypoglycemia, participants taking sulfonylureas at randomization will have their dose halved (or stopped if already on the lowest dose). Rescue therapy for the management of severe, persistent hyperglycemia may be introduced during the study.

Dose modification

Limited study drug dose modification is permitted during the treatment period specifically for management of intolerable gastrointestinal symptoms. Participants experiencing intolerable gastrointestinal symptoms are offered the following mitigations in a stepwise fashion: dietary counseling, symptomatic treatment (e.g., antidiarrheal, antiemetic) per investigator's discretion, temporary drug interruption for one dose followed by reinitiation, or, if these measures do not resolve symptoms, a de-escalation of blinded study drug to the next-lowest maintenance dose. If all these measures fail, the participant is discontinued from study drug.

If BMI ≤ 22 is reached any time during the study, the recommended energy intake is recalculated with no caloric deficit for the remainder of the trial. If BMI reaches ≤ 18.5 during any treatment period, study drug is discontinued.

In SURMOUNT-1, during the additional 2-year treatment period, if weight reduction continues despite these measures, drug dose reduction may be considered if the dose was not already reduced in the 72-week primary treatment phase because of gastrointestinal adverse events.

Outcome measures

Table 1 describes the primary and key secondary end points. The co-primary end points for SURMOUNT-1 and SURMOUNT-2 are mean percentage change in body weight and the percentage of study participants achieving ≥5% body weight reduction from randomization to 72 weeks.

Key secondary end points include the proportion of participants achieving a body weight reduction ≥10%, ≥15%, or ≥20%, mean change in weight, waist circumference, selected lipid parameters, and systolic blood pressure from randomization to 72 weeks, and, for SURMOUNT-1, the time to onset of T2D from randomization to 176 weeks.

Maximum tolerated dose studies

Study design

SURMOUNT-3 (NCT04657016) includes 806 enrolled adults without diabetes undergoing a 12-week lead-in period on an intensive lifestyle modification program. The program includes recommendations for 150 min/wk of physical activity and dietary intervention with partial

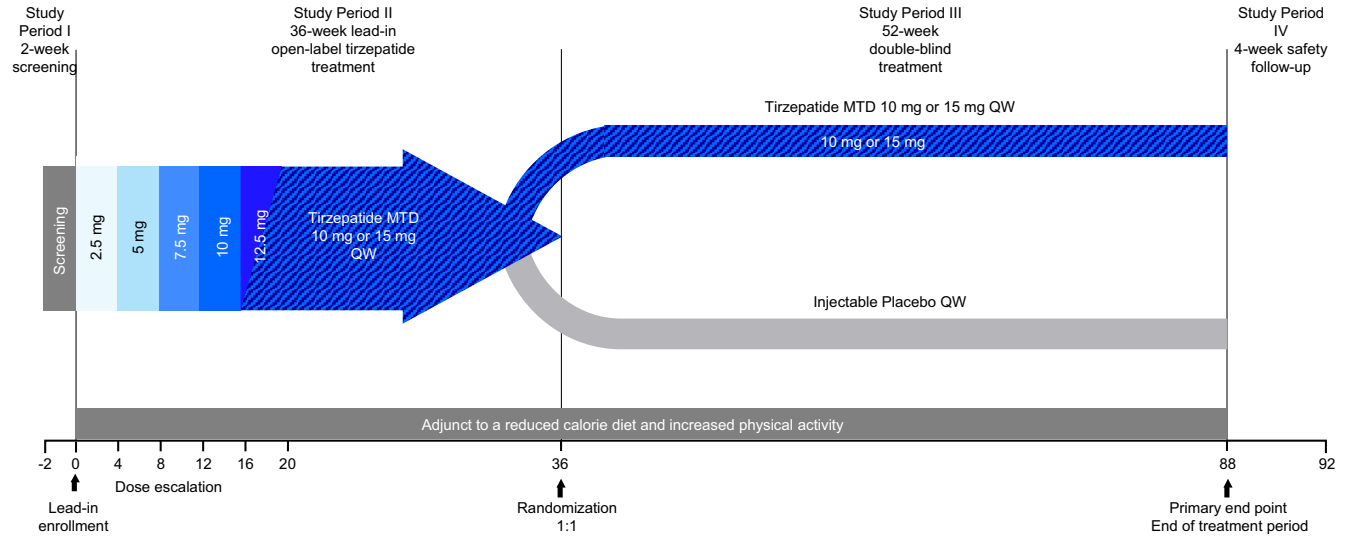

FIGURE 4 SURMOUNT-4 study design. This is a phase 3, multicenter, randomized, placebo-controlled, double-blind, 88-week clinical trial investigating the safety and efficacy of the MTD of tirzepatide (10 or 15 mg), administered subcutaneously QW, compared with placebo, on the maintenance of weight reduction after an initial 36-week open-label tirzepatide lead-in treatment period in participants with BMI ≥ 30 or ≥27 with obesity-related complications (excluding type 2 diabetes). MTD, maximum tolerated dose; QW, once weekly

meal replacements (≤2 meal replacements/d) to achieve a daily caloric goal of 1200 kcal for women and 1500 kcal for men. In addition, behavioral counseling with a registered dietitian or equivalent practitioner is provided. Individuals achieving ≥5% weight reduction after completing the entire 12-week lead-in (~600 participants) are randomized to 72 weeks of treatment in a 1:1 ratio to the maximum tolerated dose of tirzepatide (10 mg or 15 mg) or placebo (Figure 3, Table 1) to assess the degree to which tirzepatide adds to or maintains the weight reduction achieved with intensive lifestyle intervention. Randomization is stratified by country, sex, and weight reduction response to intensive lifestyle modification during lead-in (<10% or ≥10% weight reduction).

SURMOUNT-4 (NCT04660643) includes 783 enrolled adults without diabetes undergoing a 36-week, open-label, lead-in period on tirzepatide to achieve a maximum tolerated dose of 10 or 15 mg. Those completing lead-in (~600 participants) are randomized in a 1:1 ratio to either continue tirzepatide at the maximum tolerated dose or switch to placebo for an additional 52 weeks to assess maintenance of weight reduction (Figure 4, Table 1). Randomization is stratified by country, sex, maximum tolerated dose achieved at the end of lead-in (10 or 15 mg), and weight reduction response to open-label tirzepatide at the end of lead-in (<10% or ≥10% weight reduction).

Dose modification

Dose de-escalation and subsequent re-escalation is allowed during the first 24 weeks after randomization in SURMOUNT-3 and during the 36-week open-label period in SURMOUNT-4 in order to allow participants greater opportunity to achieve the maximum tolerated dose. The de-escalation and subsequent re-escalation are allowed only for the management of intolerable gastrointestinal symptoms when other mitigations such as dietary counseling, symptomatic treatment, or temporary drug interruption for one dose have failed. If intolerable gastrointestinal symptoms persist with the 15 mg dose (or the 12.5 mg step-through dose) despite de-escalation and re-escalation, 10 mg is chosen as the maximum tolerated dose. In SURMOUNT-3, if 10 mg is not tolerated despite de-escalation and re-escalation, then study drug is discontinued through the interactive web response system while maintaining blinding. In SURMOUNT-4, if 10 mg is not tolerated the participant is discontinued from the study in the open-label period. Dose modification beyond 24 weeks in SURMOUNT-3 or after randomization in SURMOUNT-4 is not permitted.

As with the fixed-dose studies, if BMI ≤ 22 is reached during these trials, the recommended energy intake is recalculated with no caloric deficit for the remainder of the trial. If BMI reaches ≤18.5, study drug is discontinued.

Outcome measures

The primary end point in SURMOUNT-3 and SURMOUNT-4 is the mean percentage change in body weight from randomization to end of treatment. The percentage of study participants achieving ≥5% or ≥10% body weight reduction from randomization to end of treatment are either co-primary or key secondary end points. In addition, SURMOUNT-3 and SURMOUNT-4 evaluate weight maintenance as the percentage of study participants who maintain ≥80% of the body

weight lost during the 12-week intensive lifestyle lead-in period (SURMOUNT-3) or the 36-week open-label tirzepatide period (SURMOUNT-4). The 80% cutoff is based on prior studies that demonstrated that a regain of ~20% of lost weight results in clinically meaningful worsening of cardiometabolic risk factors [34, 35]. SURMOUNT-4 further evaluates time to near-complete weight regain, defined as the time to regain >95% of the weight lost during the lead-in period (Table 1).

Assessments

Efficacy assessments of all randomized participants are collected throughout the SURMOUNT trials as specified in the protocols and they include fasting body weight, BMI, waist circumference, glucose metabolism (fasting insulin, HbA1c, and fasting glucose), blood pressure, and fasting lipids. A central laboratory is used for all laboratory assessments. In SURMOUNT-1, in addition to other glucose metabolism assessments, glycemic status is assessed in all participants with 2-hour oral glucose tolerance tests (comprising 75 g of glucose) before randomization and throughout the trial. Additionally, in SURMOUNT-1, body composition is assessed by dual-energy x-ray absorptiometry in the dual-energy x-ray absorptiometry substudy, while an ambulatory blood pressure monitoring device is used for detailed analysis of blood pressure and heart rate in the ambulatory blood pressure monitoring substudy.

Patient-reported outcome assessments are carried out throughout the duration of the SURMOUNT trials and include the following self-administered questionnaires: Short Form 36 version 2, acute, 1-week recall version [36], Impact of Weight on Quality of Life-Lite Clinical Trials Version [37], EQ-5D-5L [38], and the Patient Global Impression of Status for Physical Activity.

Safety assessments are carried out throughout the SURMOUNT trials as specified in the protocols and they include physical examinations, pulse, electrocardiograms (ECG), and laboratory assessments (including hepatic, renal, pancreatic, calcitonin, hematology, and immunogenicity assessments). In addition, participants are monitored for depression and suicidal ideation and behavior risk through mental health questionnaires (Patient Health Questionnaire-9, Columbia-Suicide Severity Rating Scale, and Columbia-Suicide Severity Rating Scale Self-Harm Form). Adverse event and concomitant medication information is collected throughout the trial periods, including the safety follow-up.

Statistical analysis

Sample sizes in each SURMOUNT trial were selected to provide >90% power to establish superiority of tirzepatide over placebo for the primary efficacy end points (and co-primary end points in SURMOUNT-1, -2, and -3), with assumptions of a dropout rate of 25%, common SD of 10% (8% for SURMOUNT-4), and that the evaluation of superiority of tirzepatide to placebo will be conducted at a two-sided significance level of 0.025 for SURMOUNT-1 and SURMOUNT-2 and 0.05 for SURMOUNT-3 and SURMOUNT-4.

Efficacy end points will be analyzed using data obtained during the treatment period from all randomized participants exposed to at least one treatment dose (modified intention-to-treat [mITT] population). Safety end points will be analyzed using data obtained during the treatment and safety follow-up periods from the mITT population.

In general, efficacy analysis is guided by the "efficacy" estimand, which represents "on-treatment" efficacy of tirzepatide relative to placebo. This analysis will be conducted using data obtained during the treatment period from the mITT population and it excludes data after discontinuation of study drug. A mixed model for repeated measures will be used to analyze percentage change in body weight over time for all trials and logistic regression analysis for percentage of participants achieving ≥5% body weight reduction.

A further analysis will assess the primary and key secondary end points guided by the "treatment-regimen" estimand. This estimand represents the average treatment effect of tirzepatide relative to placebo regardless of premature study drug discontinuation. As such, the analysis will be conducted using data from the mITT population during treatment period, regardless of adherence to study drug. An ANCOVA model will be used to analyze percentage change in body weight in all trials and logistic regression analysis for the percentage of participants achieving ≥5% body weight reduction. For analysis guided by the treatment-regimen estimand, if a missing body weight value is solely due to COVID-19, the missing data will be imputed assuming missing at random; for missing due to other reasons, the missing data will be imputed by multiple imputation based on retrieved dropouts in the same treatment arm (defined as the observed primary outcome measurements from participants in the same treatment group who had their efficacy assessed after early discontinuation of study drug).

Mixed model for repeated measures models will include terms of treatment, visit, treatment-by-visit interaction, stratification factors, and baseline measurement as a covariate. Logistic regression and ANCOVA models will include terms of treatment, stratification factors, and baseline measurement as a covariate. Fisher's exact test will be used to examine the treatment difference for categorical measures if there is no need to adjust for covariates.

RESULTS

The 72-week primary study period of the SURMOUNT-1 trial was completed and results are published elsewhere [39]. The other SURMOUNT trials are ongoing and expected to read out by mid-2023. A total of 5066 participants were enrolled across the four trials. Table 3 presents the baseline demographic and clinical characteristics of participants in each trial. Across the SURMOUNT trials, mean age was 44.9 to 54.2 years with BMI of 36.1 to 38.9. Most participants were female (50.7%-69.7%) and White (70.6%-82.6%). In SURMOUNT-1, 40.6% of participants had prediabetes at baseline. Mean triglycerides

TABLE 3 Key baseline demographics and clinical characteristics of enrolled participants

	SURMOUNT-1, *N* = 2539	SURMOUNT-2, *N* = 938	SURMOUNT-3, *N* = 806	SURMOUNT-4, *N* = 783
Age (y)	44.9 ± 12.5	54.2 ± 10.6	44.9 ± 12.5	47.6 ± 12.9
Age < 65 y, *n* (%)	2387 (94.0)	773 (82.4)	763 (94.7)	701 (89.5)
Age ≥ 65 y, *n* (%)	152 (6.0)	165 (17.6)	43 (5.3)	82 (10.5)
Female, *n* (%)	1714 (67.5)	476 (50.7)	534 (66.3)	546 (69.7)
Race, *n* (%)				
White	1792 (70.6)	710 (75.7)	666 (82.6)	628 (80.2)
Asian	276 (10.9)	125 (13.3)	6 (0.7)	57 (7.3)
Black or African American	201 (7.9)	77 (8.2)	109 (13.5)	88 (11.2)
Hispanic or Latino, *n* (%)	1214 (47.8)	561 (59.8)	426 (52.9)	343 (43.8)
Body weight (kg)	104.8 ± 22.1	100.7 ± 21.1	109.7 ± 24.2	107.0 ± 22.5
BMI (kg/m^2)	38.0 ± 6.8	36.1 ± 6.6	38.9 ± 7.1	38.3 ± 6.6
BMI category, *n* (%)				
<30	140 (5.5)	162 (17.3)	27 (3.3)	23 (2.9)
≥30 to <35	876 (34.5)	312 (33.3)	248 (30.8)	254 (32.4)
≥35 to <40	720 (28.4)	250 (26.7)	231 (28.7)	250 (31.9)
≥40	803 (31.6)	214 (22.8)	300 (37.2)	256 (32.7)
Waist circumference (cm)	114.1 ± 15.2	115.0 ± 14.4	116.2 ± 16.2	115.1 ± 14.6
Blood pressure (mmHg)				
Systolic	123.3 ± 12.7	130.5 ± 12.1	125.6 ± 13.3	126.1 ± 13.0
Diastolic	79.5 ± 8.2	79.8 ± 8.4	81.3 ± 8.8	80.9 ± 8.3
Cholesterol (mg/dL)				
Total	191.7 ± 38.8	176.8 ± 42.0	194.6 ± 37.4	191.9 ± 39.2
HDL	48.9 ± 13.0	44.3 ± 11.5	50.3 ± 13.9	51.1 ± 13.1
LDL	114.2 ± 32.7	96.5 ± 34.7	116.8 ± 31.1	113.8 ± 32.9
VLDL	63.9 ± 29.6	77.7 ± 33.6	60.8 ± 28.4	60.4 ± 27.9
Triglycerides (mg/dL)	145.7 ± 105.1	184.4 ± 127.9	138.2 ± 87.9	135.7 ± 78.6
Free fatty acids (mEq/L)	0.51 ± 0.21	0.60 ± 0.23	0.55 ± 0.22	0.53 ± 0.22
HbA1c (%)	5.6 ± 0.4	8.0 ± 0.9	5.5 ± 0.4	5.5 ± 0.4
Overall eGFR (mL/min/1.73 m^2)	98.1 ± 18.0	95.2 ± 18.2	100.1 ± 16.8	97.6 ± 17.5
Duration of diabetes (y)	N/A	8.5 ± 6.5	N/A	N/A
Comorbidities,[a] *n* (%)				
Hypertension	819 (32.3)	616 (65.7)	259 (32.1)	274 (35.0)
Dyslipidemia	757 (29.8)	570 (60.8)	186 (23.1)	250 (31.9)
ASCVD	78 (3.1)	96 (10.2)	24 (3.0)	38 (4.9)
Polycystic ovary syndrome[b]	39 (2.3)	6 (1.3)	20 (3.7)	12 (2.2)
Obstructive sleep apnea	197 (7.8)	76 (8.1)	50 (6.2)	55 (7.0)
Osteoarthritis	326 (12.8)	141 (15.0)	88 (10.9)	106 (13.5)
Anxiety/depression	422 (16.6)	109 (11.6)	172 (21.3)	176 (22.5)
NAFLD	180 (7.1)	159 (17.0)	32 (4.0)	37 (4.7)
Asthma or COPD	267 (10.5)	76 (8.1)	75 (9.3)	79 (10.1)
Gout	136 (5.4)	54 (5.8)	14 (1.7)	32 (4.1)
Number of obesity-related complications, *n* (%)				
None	944 (37.2)	0	298 (37.0)	260 (33.2)
1-2	1153 (45.4)	358 (38.2)	394 (48.9)	369 (47.1)

(Continues)

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TABLE 3 (Continued)

	SURMOUNT-1, *N* = 2539	SURMOUNT-2, *N* = 938	SURMOUNT-3, *N* = 806	SURMOUNT-4, *N* = 783
3-4	379 (14.9)	448 (47.8)	102 (12.7)	134 (17.1)
≥5	63 (2.5)	132 (14.1)	12 (1.5)	20 (2.6)

Note: Data are mean ± SD unless otherwise stated.

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NAFLD, nonalcoholic fatty liver disease; VLDL, very low-density lipoprotein.

[a]Comorbidities were assessed through a review of medical history.

[b]Percentage is based on total number of female participants in the respective trial.

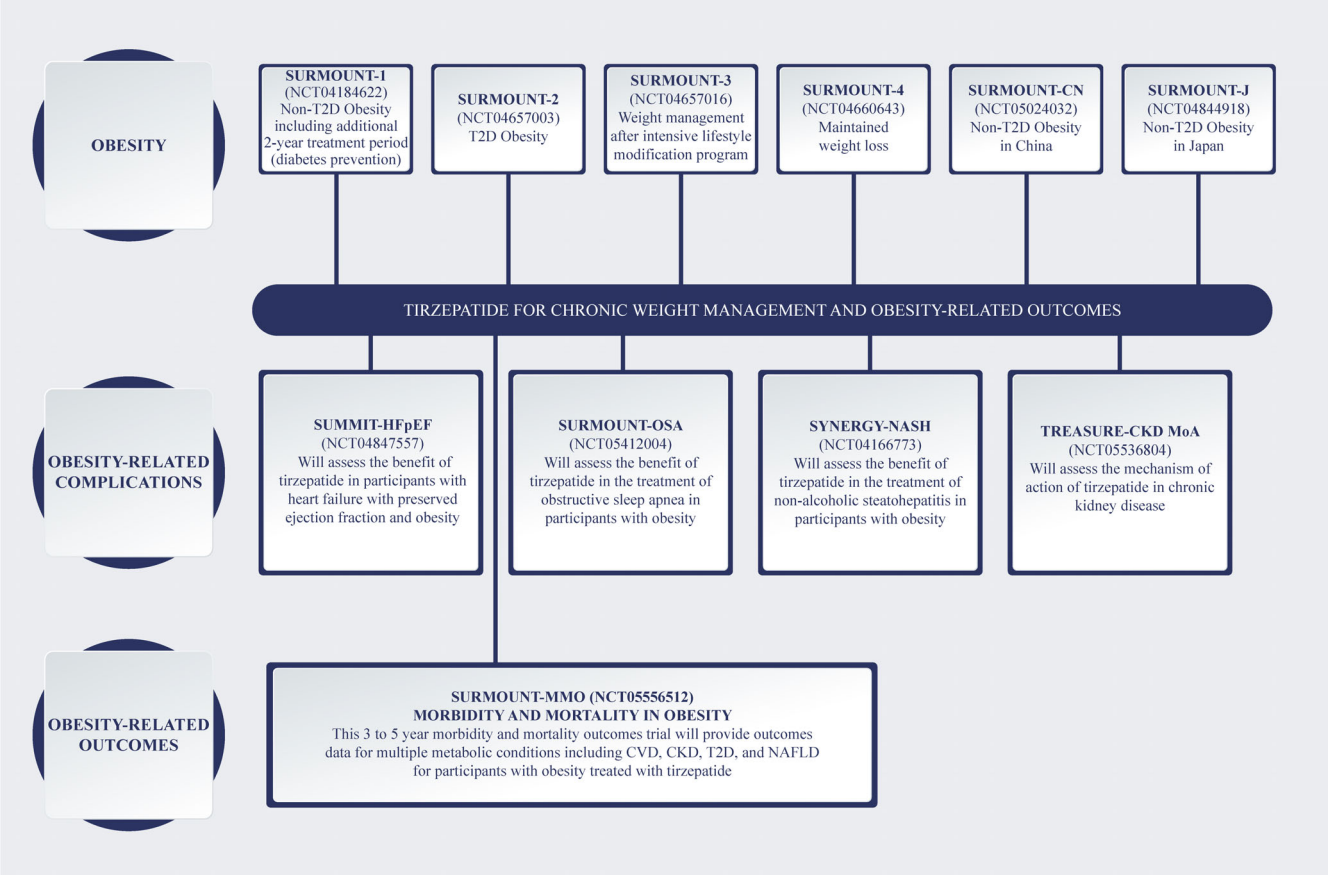

FIGURE 5 Schematic presentation of trials in the global obesity program. CKD, chronic kidney disease; CVD, cardiovascular disease; NAFLD, nonalcoholic fatty liver disease; T2D, type 2 diabetes

and HbA1c were higher in SURMOUNT-2, whereas other lipid levels, waist circumference, and blood pressure were generally similar across trials.

DISCUSSION

There remains an unmet need in the pharmacological treatment of obesity for drugs that are safe, efficacious, and well-tolerated. The SURMOUNT program aims to evaluate the efficacy of the novel, GIP/GLP-1 receptor agonist tirzepatide, administered subcutaneously once weekly, on CWM in people with obesity.

Across the SURMOUNT trials, the relatively high percentage of Hispanic or Latino participants is expected given the participation of Central and South American countries in the trials. Overall, the proportion of men (30%-49%) is high compared with other CWM trials [40, 41], likely owing to capping female enrollment in the SURMOUNT trials at 70%. Baseline mean BMI and waist circumference were comparable to those

observed in the STEP trials for semaglutide 2.4 mg and satiety and clinical adiposity-liraglutide evidence trial for liraglutide 3.0 mg [40, 41].

Achieving and sustaining clinically meaningful weight reduction remains a key goal in obesity treatment. Several trials have demonstrated the promising effects of tirzepatide on weight management in people with T2D [29, 30, 42–45]. Efficacy of tirzepatide for CWM in people with T2D is further being evaluated in the SURMOUNT-2 trial. Of note, in this trial, randomization to treatment is stratified by the potential weight effects of background T2D therapy. AHMs are known to have varying effects on weight, which has not always been considered in CWM studies. It will be important to determine if concomitant administration of AHMs has an impact on outcomes in people with T2D.

Long-term maintenance of lost weight is the desired goal of weight management, but it is often prevented by a myriad of factors [11]. Recent guidelines recommend the addition of AOMs in those responding to lifestyle intervention who require additional weight reduction or are unable to maintain the weight reduction. The SURMOUNT-3 trial investigates whether treatment with tirzepatide promotes maintenance and/or augments weight reduction after initial success with lifestyle intervention. Notably, in prior studies investigating AOM efficacy after lead-in with intensive lifestyle modification, lead-in duration was variable, with weight reduction fixed at 5% and participants randomized to treatment soon after attaining 5% weight reduction. In contrast, SURMOUNT-3 has a fixed duration lead-in of 12 weeks, allowing participants to complete the intensive lifestyle modification program and potentially lose beyond 5% body weight. As a result, a fuller effect of the lifestyle intervention is captured, against which the benefit of AOMs can be more accurately assessed. Similarly, in SURMOUNT-4, a long 36-week lead-in period on tirzepatide treatment affords participants the potential to achieve substantial weight reduction prior to randomized tirzepatide withdrawal. The benefit of continued tirzepatide treatment versus discontinuation is then more accurately assessed. By design, results from the primary end point in SURMOUNT-4, that is the percentage change in body weight from randomization to end of treatment, will not reflect the full weight reduction potential expected to be observed in the other trials.

Obesity is a complex, progressive disease impacting morbidity and mortality. For people living with obesity, reducing the risk of complications such as CVD, T2D, renal disease, obstructive sleep apnea, and malignancies is a necessity. It is posited that tirzepatide, through both direct and indirect actions, will meaningfully impact obesity-related complications. Cardiometabolic risk factors for obesity-related complications such as systolic blood pressure and lipid levels are being monitored in SURMOUNT-1 and -2. Furthermore, in the SURMOUNT-1 trial, participants with prediabetes at randomization continue for an additional 2 years after the 72-week primary end point to assess the effects of tirzepatide on preventing progression to T2D. Several studies are underway that evaluate the impact of tirzepatide on other obesity-related complications and these are briefly described in Figure 5.

CONCLUSION

Given the rising prevalence of obesity and the limited options of safe, effective therapies, it is more important now than ever to find efficacious treatments that provide substantial and sustained results for people with obesity. The extensive assessment of once-weekly subcutaneous administration of tirzepatide in the SURMOUNT program will provide relevant evidence into its safety and efficacy in weight reduction and maintenance in adults with obesity. We anticipate that the results of the SURMOUNT program will demonstrate that tirzepatide represents a novel and effective pharmacological intervention with positive outcomes for adults with obesity.

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CONFLICT OF INTEREST

Carel W. le Roux serves on advisory boards of Novo Nordisk A/S, Herbalife, GI Dynamics, Eli Lilly and Company, Johnson & Johnson, Glia, and Boehringer Ingelheim. Carel W. le Roux was gifted stock holdings in September 2021 and divested all stock holdings in Keyron in September 2021. He continues to provide scientific advice to Keyron for no remuneration. Louis J. Aronne reports receiving grants from Allurion, Altimmune, Aspire Bariatrics, AstraZeneca, Eisai, Eli Lilly and Company, Gelesis, Janssen Pharmaceuticals, and Novo Nordisk A/S, consulting fees from Altimmune, Eisai, Eli Lilly and Company, Gelesis, Jamieson Wellness, Janssen Pharmaceuticals, Novo Nordisk A/S, Pfizer, Optum, and Senda Biosciences, speaker fees honoraria from Cardiometabolic Health Congress, Harvard Obesity CME Course, and Obesity Medicine Association, a patent with Intellihealth, participating on scientific advisory boards for Altimmune, Eisai, Eli Lilly and Company, ERX Pharmaceuticals, Gelesis, Jamieson Wellness, Janssen Pharmaceuticals, Jazz Pharmaceuticals, Novo Nordisk A/S, Pfizer, Optum, and Senda Biosciences, serves as the chair emeritus on the American Board of Obesity Medicine, and on the board of directors for ERX Pharmacueticals, Intellihealth, Jamieson Wellness, and MYOS Corp, and is a shareholder of Allurion, ERX Pharmaceuticals, Gelesis, Intellihealth, Jamieson Wellness and MYOS Corp. Sriram Machineni receives research funding from Eli Lilly and Company, Novo Nordisk, Rhythm Pharmaceuticals, and Boeringher Ingelheim and serves as a aconsultant for Novo Nordisk and Rhythm Pharmaceuticals and on the Scientific Advisory Board for Eli Lilly and Company. Shuyu Zhang, Julia Dunn, Farai B. Chigutsa, Nadia N. Ahmad, and Mathijs C. Bunck are employees and shareholders of Eli Lilly and Company. Robert F. Kushner reports receiving advisory board fees from Novo Nordisk A/S and WW International, Inc. Ariana M. Chao reports grant support from Eli Lilly and Company and WW International, Inc. No other potential conflicts of interest were reported.

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 United States and European Union and after primary publication acceptance, whichever is later. No expiration date of data requests is currently set once data are

made available. Access is provided after a proposal has been approved by an independent review committee identified for this purpose and after receipt of a signed data sharing agreement. Data and documents, including the study protocol, statistical analysis plan, clinical study report, and blank or annotated case report forms, will be provided in a secure data sharing environment. For details on submitting a request, see the instructions provided at www.vivli.org.

CLINICAL TRIAL REGISTRATION

ClinicalTrials.gov identifiers NCT04184622 (SURMOUNT-1), NCT04657003 (SURMOUNT-2), NCT04657016 (SURMOUNT-3), and NCT04660643 (SURMOUNT-4).

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