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Product Monograph

once weekly yurpeak® (tirzepatide) injection **is a GIP/GLP-1 RA**

Clinical Trials for Weight Management

SURMOUNT-1, SURMOUNT-2, SURMOUNT-3, SURMOUNT-4, SURMOUNT-5

GIP=glucose-dependent insulinotropic polypeptide;
GLP-1=glucagon-like peptide-1; RA=receptor agonist.

WEIGHT MANAGEMENT

THERAPEUTIC INDICATION[1]:

Weight management

Yurpeak® is indicated as an adjunct to a reduced-calorie diet and increased physical activity for weight management, including weight loss and weight maintenance, in adults with an initial Body Mass Index (BMI) of

- ≥ 30 kg/m² (obesity) or
- ≥ 27 kg/m² to < 30 kg/m² (overweight) in the presence of at least one weight-related comorbid condition

(e.g., hypertension, dyslipidaemia, obstructive sleep apnoea, cardiovascular disease, prediabetes, or type 2 diabetes mellitus).

Type 2 diabetes mellitus

Yurpeak® is indicated for the treatment of adults with insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise

- as monotherapy when metformin is considered inappropriate due to intolerance or contraindications
- in addition to other medicinal products for the treatment of diabetes.

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OVERVIEW

Yurpeak® (tirzepatide) clinical trial programme

Yurpeak® is a long-acting GIP and GLP-1 receptor agonist. Both receptors are present on the pancreatic alpha and beta endocrine cells, heart, vasculature, immune cells (leukocytes), gut, and kidney. GIP receptors are also present on adipocytes. In addition, both GIP and GLP-1 receptors are expressed in the areas of the brain important for appetite regulation.[1]

Yurpeak® is highly selective to human GIP and GLP-1 receptors. Yurpeak® has high affinity to both the GIP and GLP-1 receptors. The activity of Yurpeak® on the GIP receptor is similar to native GIP hormone. The activity of Yurpeak® on the GLP-1 receptor is lower compared with native GLP-1 hormone.[1]

Yurpeak® has been evaluated for weight management in the SURMOUNT phase 3 clinical trial programme,[1,2] including a head-to-head trial vs semaglutide (SURMOUNT-5).[3] The SURMOUNT clinical trial programme is designed to assess whether Yurpeak®:

- Results in clinically meaningful weight reduction for people with obesity and overweight[2]
- Improves obesity-related cardiometabolic risk factors and physical function[2]
- Adds to the weight reduction achieved through intensive lifestyle therapy[2]
- Supports weight reduction over time, ie, supports maintenance of body weight reduction[1]

The SURMOUNT-1 to SURMOUNT-4 trials were randomized studies that assessed the efficacy and safety of Yurpeak® in combination with lifestyle interventions compared to placebo[1,2], whereas the SURMOUNT-5 trial evaluated Yurpeak® against Semaglutide.[3]

SURMOUNT Clinical Trial Programme

Overview of Phase 3 Trials[a]				
Trial	Objective	Participant population[*,b]	Treatment period	Completion date
SURMOUNT-1[1,4,8]	Assess efficacy and safety of Yurpeak® (tirzepatide) vs placebo	Adult PwO[c]	72 weeks	April 2022
SURMOUNT-2[1,5]	Assess efficacy and safety of Yurpeak® vs placebo	Adult PwO with T2D[c]	72 weeks	April 2023
SURMOUNT-3[6]	Assess efficacy and safety of Yurpeak® vs placebo after an intensive lifestyle programme	Adult PwO[c]	72 weeks	May 2023
SURMOUNT-4[7]	Assess efficacy and safety of Yurpeak® vs placebo for the maintenance of weight loss	Adult PwO[c]	88 weeks	May 2023
Overview of Phase 3 Trials				
SURMOUNT-5[3]	Assess efficacy and safety of Yurpeak® vs semaglutide in adults with obesity	Adult PwO[c]	72 weeks	November 2024

PwO - People with Obesity

Trials cannot be compared due to differences in study design, population, and key inclusion/exclusion criteria.

*Participants in all trials had obesity or overweight[b]

BMI= body mass index; PwO= Patients with Obesity; T2D= Type 2 Diabetes; QW= once weekly

[a]All SURMOUNT trials are multicentre, randomised, and QW administered. With the exception of SURMOUNT-5, which is a head-to-head open-label trial, the SURMOUNT trials are double-blind and placebo-controlled.[1,4]

[b]All participants were adults 18 years or older with obesity (BMI ≥30), or overweight (BMI ≥27) with 1 or more weight-related complications.[1,3,4]

[c]These studies included participants who reported ≥1 unsuccessful dietary effort to lose weight.[3,4]

Efficacy Overview

Efficacy Results for Completed Phase 3 Trials[a]					
Trial	Variable study arms	Participants (n)	Change in body weight (%,efficacy estimand)		Participants having reduction of ≥5% body weight (%, efficacy estimand)
			72 Week	88 Week	
SURMOUNT-1[1,4,8]	Yurpeak® (tirzepatide) 5 mg	630	-16.0[a]	-	89.4[b]
	Yurpeak® 10 mg	636	-21.4[a]	-	96.2[b]
	Yurpeak® 15 mg	630	-22.5[a]	-	96.3[b]
	Placebo	643	-2.4	-	27.9
SURMOUNT-2[1,5]	Yurpeak® 10 mg	312	-13.4[a]	-	81.6[b]
	Yurpeak® 15 mg	311	-15.7[b]	-	86.4[b]
	Placebo	315	-3.3	-	30.6
SURMOUNT-3[6]	Yurpeak® MTD*	287	-21.1	-	94.4
	Placebo	292	3.3	-	10.7
SURMOUNT-4[7]	Yurpeak® MTD*	335	-	-26.0	98.5
	Placebo	335	-	-9.5	69
Efficacy Results for Completed Phase 3b Trial					
SURMOUNT-5[3]	Yurpeak® MTD*	374	-21.6	-	86.7[$]
	Semaglutide MTD#	376	-15.4	-	67.3[$]

Trials cannot be compared due to differences in study design, population, and key inclusion/exclusion criteria.

*MTD= maximum tolerated dose for Yurpeak® - 10 mg or 15 mg.
#MTD= maximum tolerated dose for Semaglutide - 1.7 mg or 2.4 mg
[a]p<0.001 vs baseline.[1]
[b]p<0.001 vs placebo, adjusted for multiplicity.[1]
[$] ≥10% weight loss

SURMOUNT-1:

Yurpeak® (tirzepatide) vs placebo in participants with obesity or overweight without T2D

Summary

SURMOUNT-1 was a multicentre, randomised, double-blind 72-week study that assessed the efficacy and safety of Yurpeak® among participants without type 2 diabetes (T2D).
In SURMOUNT-1, Yurpeak® plus lifestyle intervention* demonstrated significant weight reductions that were greater across higher doses at week 72 compared with placebo plus lifestyle intervention. The efficacy results align with the efficacy estimand. At week 72, participants taking Yurpeak® saw an overall mean percentage change in body weight from baseline of -16.0% with the 5 mg dose, -21.4% with the 10 mg dose, -22.5% with the 15 mg dose, and -2.4% with placebo. Additionally, 89.4%, 96.2%, and 96.3% of participants given the Yurpeak® 5 mg, 10 mg, or 15 mg doses, respectively, had weight reductions of ≥5% from baseline at week 72. In the placebo group, 27.9% of participants had ≥5% weight reduction from baseline at week 72. Compared with those on placebo, participants taking Yurpeak® saw improvements in obesity-related cardiometabolic risk factors such as blood pressure and lipid levels.[1,4,8] The most common adverse events (AEs) were gastrointestinal and mild to moderate in severity. These occurred most often during dose escalation and decreased over time.[1,4,8]

* All participants consulted with a dietitian or another qualified expert to receive lifestyle interventions and counselling at weeks 0, 4, 8, and 12 during the period of dose escalation. At the third visit, participants received diet counselling consisting of advice on healthy food choices and adhering to a hypocaloric diet. Participants came back to this same provider for continued counselling at week 24 and then again every 12 weeks through 72 weeks. Participants were also advised at the third visit to have at least 150 minutes of physical activity each week[3].

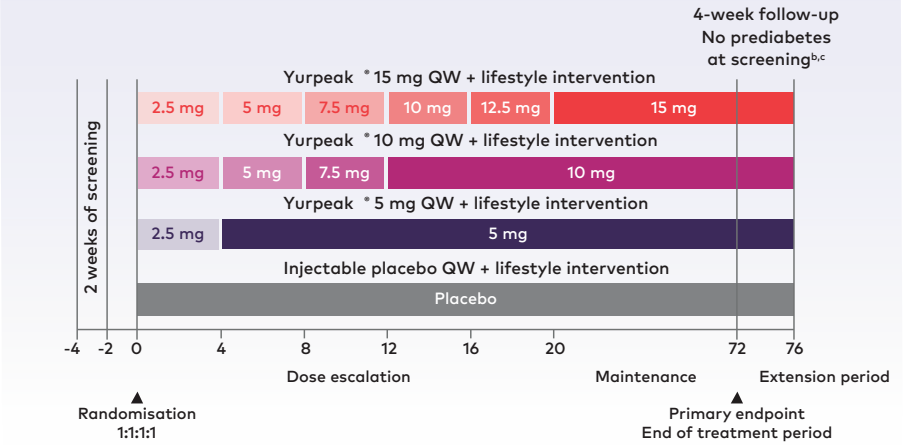
SURMOUNT-1 study

SURMOUNT-1 aimed to compare the Efficacy and safety of Yurpeak® (5 mg, 10 mg, and 15 mg) as an add-on treatment to lifestyle intervention for participants with obesity or overweight vs placebo with lifestyle intervention. The study lasted 72 weeks and concluded in April 2022.[1,4,8] Key inclusion criteria were a body mass index (BMI) ≥30 kg/m^2 or a BMI ≥27 kg/m^2 with 1 or more weight-related complications and having 1 or more unsuccessful dietary attempts to lose weight.[1,4,8] The study excluded participants with T2D.[1,4,8]

Study Design

This was a phase 3 trial with 2539 participants. Participants were randomised in a 1:1:1:1 ratio to receive Yurpeak® (tirzepatide) 5 mg, 10 mg, or 15 mg with lifestyle intervention or placebo with lifestyle intervention for 72 weeks.[1,4,8] This included a dose-escalation period of up to 20 weeks. Participants started at a dose of Yurpeak® 2.5 mg, and Yurpeak® doses increased every 4 weeks for participants to reach a maintenance dose of up to 15 mg once weekly. The 2 coprimary endpoints were a reduction in weight of ≥5% from baseline at week 72 and percentage change in body weight from baseline at week 72. The secondary endpoints included weight reduction of ≥10%, ≥15%, or ≥20% at week 72; change from baseline weight at week 20; and change from baseline in waist circumference, systolic blood pressure, diastolic blood pressure, fasting insulin and lipid levels, and SF-36v2® Physical Functioning score at week 72.[1,4,8]

SURMOUNT-1 Study Design[a,1,4,8]



All participants received lifestyle intervention, which included counselling to help them adhere to a healthful, balanced diet (with a deficit of 500 calories per day) and at least 150 minutes of physical activity per week.[1,4,8]

Coprimary endpoints[1,4,8]

Percentage change in body weight from baseline to week 72

Weight reduction of ≥5% at week 72

Key inclusion criteria[1,4,8]

- ≥18 years
- BMI ≥30, or BMI ≥27 and at least 1 weight-related complication (hypertension dyslipidemia, obstructive sleep apnea, or cardiovascular disease)
- One or more unsuccessful dietary efforts to lose weight

QW= once weekly; SF-36v2=36-Item Short Form Health Survey, version 2, acute form. SF-36v2 is a registered trademark of QualityMetric.

[a]Key exclusion criteria included diabetes, change in body weight of >5 kg within 90 days before screening, previous or planned surgical treatment for obesity, and treatment with a medication that promotes weight loss within 90 days before screening.[4]

[b]Participants who had prediabetes at randomisation but discontinued the study during the 72-week treatment period were included in the 4-week safety follow-up.[4]

[c]Extension period for those with prediabetes at randomisation was 2 years.[4]

Participant demographics

Participants enrolled in SURMOUNT-1 had obesity or overweight and were unable to achieve weight loss through lifestyle intervention alone. People with T2D were not included in the study. The overall average duration of obesity was 14.4 years.[1,4,8] The mean baseline weight across all study groups was 104.8 kg, and the mean baseline BMI across all groups was 38.0 kg/m^2.[1,4,8] Additionally, 40.6% of participants had prediabetes at baseline,[1,4,8] and nearly two-thirds had 1 or more weight-related complications. The mean age of participants across all groups was 44.9 years.[1,4,8]

Baseline Characteristics[1,4,8]

	Yurpeak® (tirzepatide)			Placebo	Total
Characteristics[a]	**5 mg (n=630)**	**10 mg (n=636)**	**15 mg (n=630)**	**(n=643)**	**(N=2539)**
Age	45.6±12.7	44.7±12.4	44.9±12.3	44.4±12.5	44.9±12.5
Female sex, n (%)	426 (67.6)	427 (67.1)	425 (67.5)	436 (67.8)	1714 (67.5)
Duration of obesity, years	14.0±10.81	14.7±11.05	14.8±10.75	14.0±10.71	14.4±10.83
Body weight, kg	102.9±20.71	105.8±23.32	105.6±22.92	104.8±21.37	104.8±22.12
Mean body mass index	37.4±6.63	38.2±7.01	38.1±6.69	38.2±6.89	38.0±6.81
Waist circumference, cm	113.2±14.25	114.8±15.80	114.4±15.59	114.0±14.92	114.1±15.16
Prediabetes, n (%)	247 (39.2)	262 (41.2)	253 (40.2)	270 (42.0)	1032 (40.6)
SF-36v2 Physical Functioning score	49.6±8.3	49.6±7.5	49.6±7.8	49.7±7.7	49.6±7.8
Race or ethnic group, n (%)[b]					
American Indian or Alaska Native	56 (8.9)	58 (9.1)	59 (9.4)	58 (9.0)	231 (9.1)
Asian	68 (10.8)	71 (11.2)	66 (10.5)	71 (11.0)	276 (10.9)
Black or African American	48 (7.6)	47 (7.4)	51 (8.1)	55 (8.6)	201 (7.9)
Hispanic or Latino	308 (48.9)	297 (46.7)	299 (47.5)	310 (48.2)	1214 (47.8)
Native Hawaiian or other	2 (0.3)	2 (0.3)	3 (0.5)	2 (0.3)	9 (0.4)
White	447 (71.0)	452 (71.1)	443 (70.3)	450 (70.0)	1792 (70.6)
Multiple	9 (1.4)	6 (0.9)	8 (1.3)	7 (1.1)	30 (1.2)
Body mass index category, n (%)					
<30	38 (6.0)	38 (6.0)	40 (6.3)	24 (3.7)	140 (5.5)
≥30-<35	241 (38.3)	209 (32.9)	199 (31.6)	227 (35.3)	876 (34.5)
≥35-<40	174 (27.6)	187 (29.4)	179 (28.4)	180 (28.0)	720 (28.4)
≥40	177 (28.1)	202 (31.8)	212 (33.7)	212 (33.0)	803 (31.6)
Blood pressure, mm Hg					
Systolic	123.6±12.45	123.8±12.77	123.0±12.94	122.9±12.77	123.3±12.73
Diastolic	79.3±8.14	79.9±8.32	79.3±8.23	79.6±7.95	79.5±8.16
Lipid levels, geometric mean, mg/dL (%)					
Total cholesterol	187.1 (21.1)	190.7 (19.9)	187.4 (19.9)	186.4 (20.3)	187.9 (20.3)
HDL cholesterol	47.6 (26.6)	47.5 (26.1)	47.5 (25.5)	46.5 (26.9)	47.3 (26.3)
LDL cholesterol	108.7 (30.2)	111.5 (30.3)	109.5 (30.0)	108.4 (30.5)	109.5 (30.2)
Triglycerides	128.9 (51.7)	126.5 (51.5)	127.9 (47.5)	130.5 (49.2)	128.4 (50.0)

HDL= high-density lipoprotein; LDL=low-density lipoprotein.
[a]Plus–minus values are mean ± standard deviation.[4]
[b]Race or ethnic group was reported by the participants.[4]

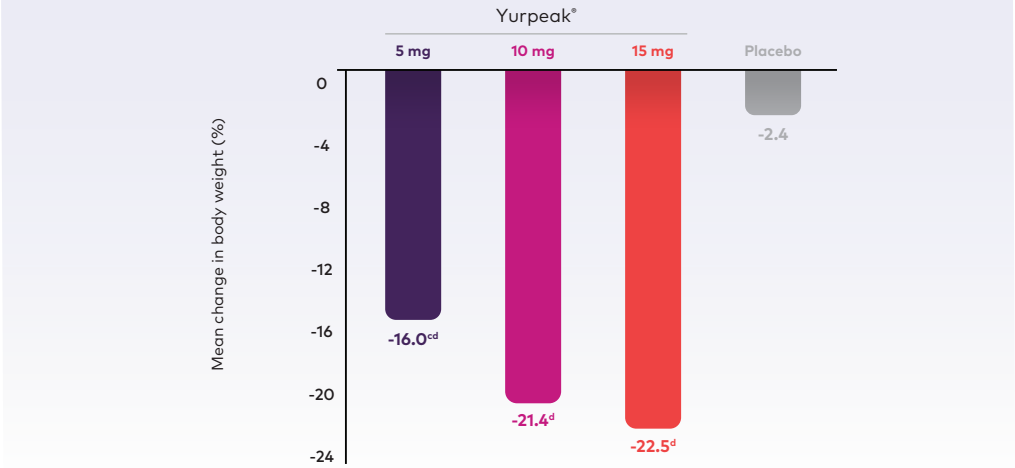
Efficacy

The results shown below align with the Efficacy estimand, representing the average treatment effect of Yurpeak® (tirzepatide) relative to placebo for all participants who had undergone randomisation, if the treatment was administered as intended.[1,4,8]

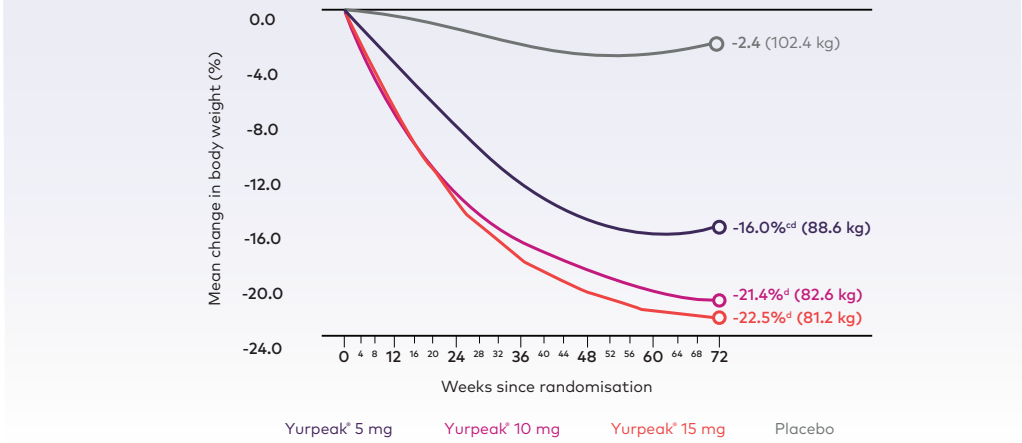
Primary outcome measures

In SURMOUNT-1, participants taking the Yurpeak® 5 mg, 10 mg, and 15 mg doses saw means of 16.0%, 21.4%, and 22.5% in body weight reduction, respectively. Participants in the placebo group saw a mean of 2.4% weight reduction.[1,4,8] EASO considers a reduction target of ≥5% to be clinically meaningful and recommends weight loss goals of 5% to 15% over 6 months and a cumulative weight reduction of ≥20% for participants with BMI ≥35 kg/m^2.[1,4,8]

Coprimary Endpoint:
Change in Body Weight From Baseline at Week 72[a,b,1,4,8]



Percentage Change in Body Weight From Baseline Over Time
(Mean Body Weight at Week 72)[a,b,1,4,8]



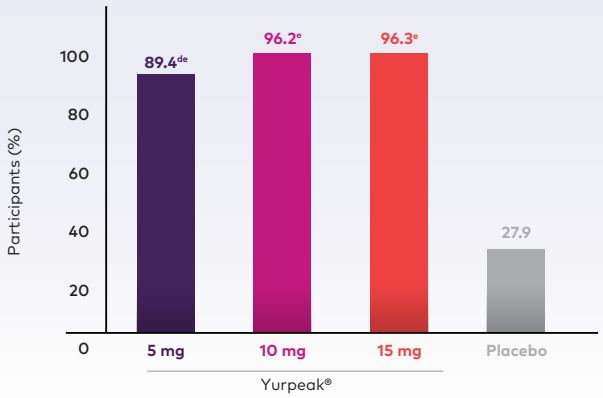
EASO= European Association for the Study of Obesity; MMRM=mixed model for repeated measures.
[a]Data derived from an MMRM analysis for the efficacy estimand.[4]
[b]Baseline weight: 102.9±20.71 kg for Yurpeak ® 5 mg, 105.8±23.32 kg for Yurpeak ® 10 mg, 105.6±22.92 kg for Yurpeak ® 15 mg, and 104.8±21.37 kg for placebo.[4]
[c]The change in body weight in the Yurpeak® 5 mg group was not a coprimary endpoint and was analysed as a key secondary endpoint. [4]
[d]p<0.001 vs baseline.[1]

Primary outcome measures[1,4,8]

In the Yurpeak® (tirzepatide) treatment group, 89.4%, 96.2%, and 96.3% of participants given Yurpeak® 5 mg, 10 mg, or 15 mg doses, respectively, saw body weight reduction of ≥5% at 72 weeks. In the placebo group, 27.9% of participants saw a reduction of ≥5%.

In SURMOUNT-1, more participants taking Yurpeak® 10 mg and 15 mg met the coprimary endpoint of ≥5% weight loss vs participants taking placebo.

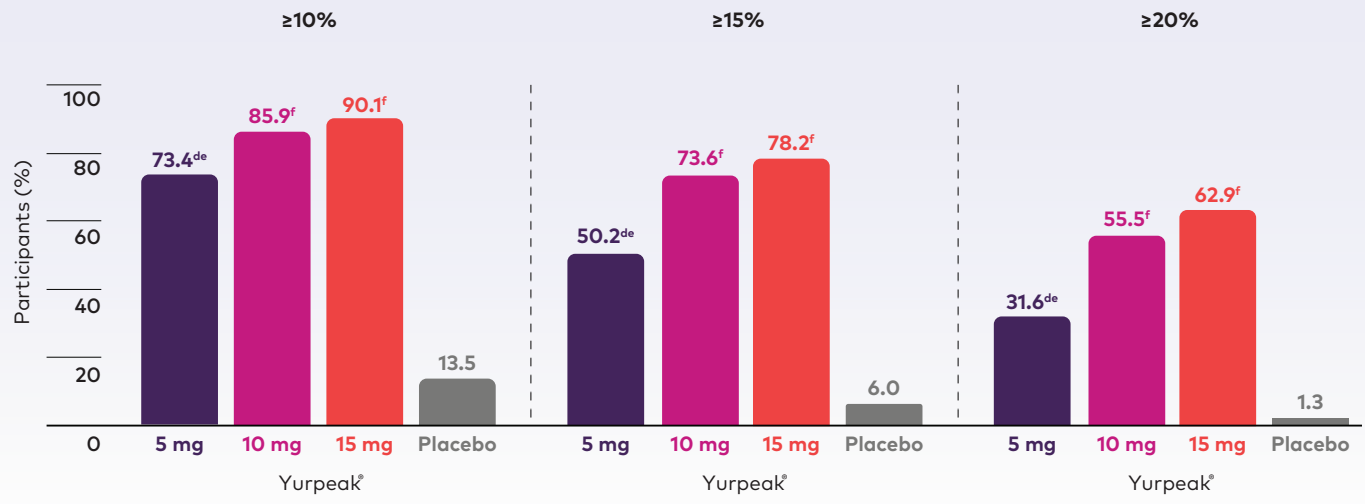
Coprimary Endpoint:
≥5% Weight Reduction From Baseline at Week 72 [a-c,1,4,8]



Secondary endpoints: ≥10%, ≥15%, and ≥20% weight loss[1,4,8]

At week 72, a significantly greater proportion of participants on Yurpeak® treatment than on placebo achieved body weight reductions of ≥10%, ≥15%, and ≥20% from baseline.[1,4,8] In addition, at week 72, 16.5% of participants taking Yurpeak® 5 mg, 35% taking 10 mg, and 39.7% taking 15 mg met the exploratory endpoint of ≥25% weight loss, but only 0.3% of participants taking placebo met it.[1,4,8]

Secondary Endpoint:
Participants Who Met Weight-Reduction Targets From Baseline at Week 72 [a,b,1,4,8]



[a]Data derived from an MMRM analysis for the efficacy estimand.[4]
[b]Baseline weight: 102.9±20.71 kg for Yurpeak ® 5 mg, 105.8±23.32 kg for Yurpeak ® 10 mg, 105.6±22.92 kg for Yurpeak ® 15 mg, and 104.8±21.37 kg for placebo.[4]
[c]The percentage of participants who met weight-reduction targets was obtained by dividing the number of participants reaching respective goals at week 72 by the number of participants with a baseline value and at least 1 non-missing postbaseline value. Missing values at week 72 were imputed from MMRM analysis.[4]
[d]The change in body weight in the Yurpeak ® 5 mg group was not a coprimary endpoint and was analysed as a key secondary endpoint.[4]
[e]p<0.001 vs placebo, adjusted for multiplicity.[1]
[f]p<0.001 vs placebo, not adjusted for multiplicity.[1]

Select additional secondary endpoints

Physical Functioning score[1,4,8]

Patients with obesity or overweight without diabetes who received Yurpeak® (tirzepatide) showed small improvements in health-related quality of life, including physical functioning. The improvements were greater in the tirzepatide-treated patients than in those who received placebo. Health-related quality of life was assessed using the generic questionnaire SF-36v2.

Cardiometabolic parameters[1,4,8]

In SURMOUNT-1, of Yurpeak® 15 mg led to a significant improvement compared to placebo in systolic blood pressure (-7.6 mm Hg vs -1.2 mm Hg), triglycerides (-31.4 mg/dl vs -6.3 mg/dl), non-HDL cholesterol (-13.4 vs -1.8mg/dl), HDLcholesterol (8.2 vs 0.2 mg/dl), and fasting insulin (-49.6 mIU/L vs -9.7 mIU/L).

Change From Baseline in Cardiometabolic Parameters for Yurpeak® Groups vs Placebo at Week 72[a,1,4,8]

	Yurpeak®			Placebo
Secondary endpoint	**5 mg[b]**	**10 mg[b]**	**15 mg[b]**	
Change in:				
Systolic blood pressure (mm Hg)[c]	-7.0	-8.2	-7.6	-1.2
Diastolic blood pressure (mm Hg)[c,d]	-5.2	-5.5	-4.6	-1.0
HbA1c (%)[d,e]	-0.40	-0.49	-0.51	-0.07[b]
Percent change in[f,g]:				
Triglycerides (mg/dL)	-24.3	-27.0	-31.4	-6.3[b]
HDL cholesterol (mg/dL)	7.0	8.6	8.2	0.2
LDL cholesterol (mg/dL)[d]	-5.3	-6.6	-8.6	-0.9
Total cholesterol (mg/dL)[d]	-4.9	-5.6	-7.4	-1.1

Waist circumference

Waist circumference is associated with cardiovascular risk and should be considered in conjunction with BMI to assess obesity-related health risks.[1,4,8] In SURMOUNT-1, the mean decrease in waist circumference from baseline to week 72 was 14.6 cm* for participants in the Yurpeak® 5 mg group, 19.4 cm* for those in the Yurpeak® 10 mg group, 19.9 cm* for participants in the Yurpeak® 15 mg group, and 3.4 cm* for participants taking placebo.[1,4,8]

The mean waist circumference across all groups at baseline was 114.1 cm. Improvements in waist circumference were seen by week 4 and continued through the remainder of the study.[1,4,8]

*p<0.001 vs baseline.[1]
[a]Data represent efficacy estimand. Data are least-squares means.[4]
[b]p<0.001 vs baseline.[1]
[c]Systolic blood pressure and diastolic blood pressure results were based on safety analysis at week 72.[4]
[d]Additional secondary endpoint.[4,8]
[e]Baseline HbA1c level for total patient population: 5.6±0.38.[4]
[f]Lipid parameters and fasting insulin were analysed using log-transformation. Data presented are a model-based estimate.[4]
[g]The estimated treatment differences from placebo in the percentage changes in levels are expressed as percentage points.[8]

SAFETY AND TOLERABILITY

In SURMOUNT-1, the most common AEs with Yurpeak® (tirzepatide) were gastrointestinal (nausea, diarrhoea, constipation), were mostly mild to moderate in severity, and occurred primarily during the dose escalation period. Serious AEs were reported in 5.1% to 6.9% of participants across all Yurpeak® doses and in 6.8% of participants taking placebo. Across doses, 78.9% to 81.8% of participants who were treated with Yurpeak® and 72.0% of participants in the placebo group reported at least 1 AE during the treatment period.[1,4,8]

AEs leading to discontinuation were nausea, diarrhoea, abdominal pain, and vomiting. In addition, 4.3% of participants taking Yurpeak® 5 mg, 7.1% of those taking Yurpeak® 10 mg, 6.2% of those taking Yurpeak® 15 mg, and 2.6% of those taking placebo had AEs that led to discontinuation of treatment or placebo. All-cause discontinuation rates were 14.3% in the 5 mg Yurpeak® group, 16.4% in the 10 mg group, 15.1% in the 15 mg group, and 26.4% in the placebo group.[1,4,8]

Adverse Events[1,4,8]

	Yurpeak®			Placebo
	5 mg (n=630) n (%)	**10 mg** (n=636) n (%)	**15 mg** (n=630) n (%)	(n=643) n (%)
Participants with ≥1 AE during treatment period	510 (81.0)	520 (81.8)	497 (78.9)	463 (72.0)
Serious AEs	40 (6.3)	44 (6.9)	32 (5.1)	44 (6.8)
Death[a]	4 (0.6)	2 (0.3)	1 (0.2)	4 (0.6)
Adverse events occurring in ≥5% of participants in any treatment group[b]				
Nausea	155 (24.6)	212 (33.3)	195 (31.0)	61 (9.5)
Diarrhoea	118 (18.7)	135 (21.2)	145 (23.0)	47 (7.3)
COVID-19	94 (14.9)	98 (15.4)	82 (13.0)	90 (14.0)
Constipation	106 (16.8)	109 (17.1)	74 (11.7)	37 (5.8)
Dyspepsia	56 (8.9)	62 (9.7)	71 (11.3)	27 (4.2)
Vomiting	52 (8.3)	68 (10.7)	77 (12.2)	11 (1.7)
Decreased appetite	59 (9.4)	73 (11.5)	54 (8.6)	21 (3.3)
Headache	41 (6.5)	43 (6.8)	41 (6.5)	42 (6.5)
Abdominal pain	31 (4.9)	34 (5.3)	31 (4.9)	21 (3.3)
Alopecia	32 (5.1)	31 (4.9)	36 (5.7)	6 (0.9)
Dizziness	26 (4.1)	35 (5.5)	26 (4.1)	15 (2.3)
Eructation	24 (3.8)	33 (5.2)	35 (5.6)	4 (0.6)
Injection-site reaction[c]	18 (2.9)	36 (5.7)	29 (4.6)	2 (0.3)

[a]All deaths were adjudicated by an external committee of physicians, who determined whether the death was cardiovascular related.[4]
[b]Adverse events are listed according to Medical Dictionary for Regulatory Activities, version 24.1, preferred terms.[4]
[c]None of the events were reported as severe or serious.[4]

SURMOUNT-2:

Yurpeak® (tirzepatide) vs placebo in participants with obesity or overweight and T2D

Summary

SURMOUNT-2 was a multicentre, randomised, double-blind 72-week study that assessed the efficacy and safety of Yurpeak® among participants with type 2 diabetes (T2D) who had obesity or overweight. The study involved 938 participants. In this study, Yurpeak® plus lifestyle intervention* demonstrated weight reductions that were greater across higher doses at week 72 compared with placebo plus lifestyle intervention. At week 72, participants taking Yurpeak® saw an overall mean change in body weight from baseline of -13.4% with the 10 mg dose, -15.7% with the 15 mg dose, and -3.3% with placebo. Additionally, 82% and 86% of participants given the Yurpeak® 10 mg and 15 mg doses, respectively, had weight reductions of ≥5% from baseline at week 72. In the placebo group, 31% of participants had ≥5% weight reduction from baseline at week 72. Compared to those taking placebo, participants taking Yurpeak® saw improvements in cardiometabolic parameters such as blood pressure and lipid levels. The most common adverse events (AEs) were gastrointestinal (GI) and mild to moderate in severity. These occurred most often during dose escalation and decreased over time.[1,5]

BMI=body mass index.
* All participants consulted with a dietitian or another qualified expert to receive lifestyle interventions and counselling at weeks 0, 4, 8, and 12 during the period of dose escalation. At the beginning of the study period, participants received diet counselling consisting of advice on healthy food choices and adhering to a hypocaloric diet. Participants came back to this same provider for continued counselling at week 24 and then again every 12 weeks through 72 weeks. Participants were also advised at the beginning of the study period and all subsequent visits to engage in at least 150 minutes of physical activity each week.[5]

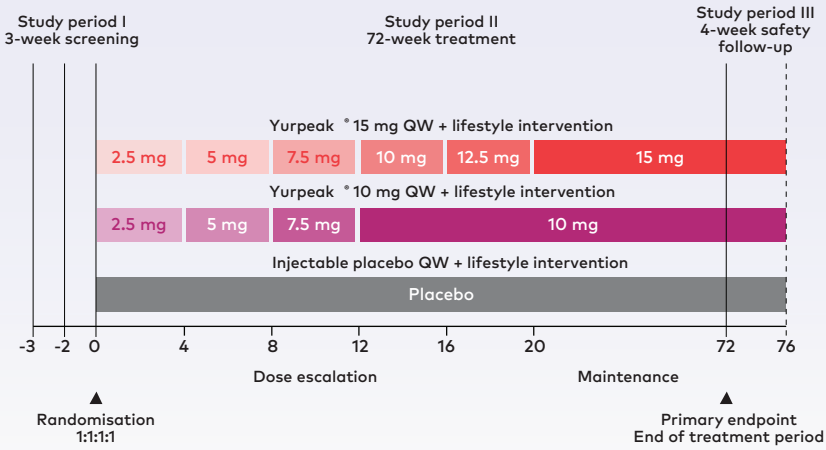
SURMOUNT-2 study[1,5]

SURMOUNT-2 was designed to compare the Efficacy and safety of Yurpeak® (10 mg and 15 mg) as an add-on treatment to lifestyle intervention for adults aged ≥18 years with T2D and obesity or overweight vs placebo with lifestyle intervention. The study lasted 72 weeks and concluded in April 2023. Key inclusion criteria were a diagnosis of T2D, BMI ≥27 kg/m^2, and an HbA1c of 7% to 10% on stable therapy, either diet and exercise alone or oral antihyperglycaemic medication.

Study Design

SURMOUNT-2 was a phase 3 trial with 938 participants. Participants were randomised in a 1:1:1 ratio to receive Yurpeak® (tirzepatide) 10 mg or 15 mg with lifestyle intervention or placebo with lifestyle intervention for 72 weeks. This included a dose escalation period of up to 20 weeks. Participants started at Yurpeak® 2.5 mg, and Yurpeak® doses increased every 4 weeks for participants to reach a maintenance dose of 10 mg or 15 mg once weekly.
The 2 coprimary endpoints were a reduction in weight of ≥5% from baseline at week 72 and percentage change in body weight from baseline at week 72.

SURMOUNT-2 Study Design[a,b,1,5]



All participants received lifestyle intervention, which included counselling to help them adhere to a healthful, balanced diet (with a deficit of 500 calories per day) and at least 150 minutes of physical activity per week.[5]

The secondary endpoints included body weight reductions of ≥10%, ≥15%, and ≥20% at week 72; change from baseline in HbA1c at week 72; HbA1c <7%, ≤6.5%, and <5.7% at week 72; and change from baseline in fasting glucose, waist circumference, systolic blood pressure, and fasting lipid levels (triglycerides, HDL cholesterol, and non-HDL cholesterol) at week 72.[1,5]

Coprimary endpoints[1,5]

Percentage change in body weight from baseline to week 72

Weight reduction of ≥5% at week 72

Key inclusion criteria[1,5]

≥18 years

BMI ≥27 kg/m^2

T2D with HbA1c 7% to 10% (on stable therapy for ≥3 months before screening)

HDL= high-density lipoprotein; QW= once weekly
[a]Key exclusion criteria included a change in body weight of >5 kg within 3 months before screening, previous or planned surgical treatment for obesity, and treatment with a medication that promotes weight loss within 90 days before screening.[5]
[b]Efficacy and safety endpoints were analysed with data from all randomly assigned participants (intention-to-treat [ITT] population).[5]

Participant demographics

Participants enrolled in SURMOUNT-2 had T2D and obesity or overweight and were unable to achieve weight loss through lifestyle intervention alone. The average duration of obesity and diabetes was 17.7 years and 8.5 years, respectively. The mean baseline weight across all study groups was 100.7 kg and the mean baseline BMI across all groups was 36.1 kg/m^2. The mean age of participants across all groups was 54.2 years.[1,5]

Baseline Characteristics[1,5]

	Yurpeak® (tirzepatide)		Placebo	Total
Characteristics	10 mg (n=312)	15 mg (n=311)	(n=315)	(N=938)
Age, years	54.3 (10.7)	53.6 (10.6)	54.7 (10.5)	54.2 (10.6)
Age <65 years	258 (83)	257 (83)	258 (82)	773 (82)
Age ≥65 years	54 (17)	54 (17)	57 (18)	165 (18)
Sex[a]				
Female	158 (51)	159 (51)	159 (50)	476 (51)
Male	154 (49)	152 (49)	156 (50)	462 (49)
Duration of obesity, years	17.6 (12.0)	17.5 (11.0)	18.1 (11.7)	17.7 (11.5)
Body weight, kg	100.9 (20.9)	99.6 (20.1)	101.7 (22.3)	100.7 (21.1)
Body mass index, kg/m^2	36.0 (6.4)	35.7 (6.1)	36.6 (7.3)	36.1 (6.6)
Waist circumference, cm	114.2 (14.1)	114.6 (13.1)	116.0 (15.7)	114.9 (14.4)
Race, n (%)[a]				
Asian	44 (14)	42 (14)	39 (12)	125 (13)
Black or African American	33 (11)	22 (7)	22 (7)	77 (8)
Native Hawaiian or other Pacific Islander	1 (<1)	1 (<1)	1 (<1)	1 (<1)
White	228 (73)	234 (75)	248 (79)	710 (76)
Multiple	6 (2)	12 (4)	5 (2)	23 (2)
Body mass index category				
<30	60 (19)	51 (16)	52 (17)	163 (17)
≥30-<35	92 (29)	114 (37)	105 (33)	311 (33)
≥35-<40	94 (30)	85 (27)	71 (23)	250 (27)
≥40	66 (21)	61 (20)	87 (28)	214 (23)
Blood pressure, mm Hg				
Systolic	130.6 (12.2)	130.0 (12.3)	131.0 (11.9)	130.5 (12.1)
Diastolic	80.2 (8.1)	79.7 (8.7)	79.4 (8.4)	79.8 (8.4)
Lipid levels, mmol/L				
Total cholesterol	4.6 (1.1)	4.5 (1.1)	4.6 (1.1)	4.6 (1.1)
HDL cholesterol	1.2 (0.3)	1.1 (0.3)	1.1 (0.3)	1.2 (0.3)
LDL cholesterol	2.5 (0.9)	2.4 (0.9)	2.6 (0.9)	2.5 (0.9)
Triglycerides	2.1 (1.6)	2.0 (1.4)	2.1 (1.3)	2.1 (1.4)
Duration of diabetes, years	8.8 (6.9)	8.0 (6.4)	8.8 (6.2)	8.5 (6.5)
HbA1c, %	8.00 (0.84)	8.07 (0.99)	7.89 (0.84)	8.02 (0.89)
HbA1c, mmol/mol	64.0 (9.1)	64.7 (10.8)	63.7 (9.2)	64.1 (9.7)
Fasting glucose, mg/dL	158.3 (44.0)	161.2 (49.3)	158.5 (46.5)	159.3 (46.6)
Fasting glucose, mmol/L	8.8 (2.4)	9.0 (2.7)	8.8 (2.6)	8.8 (2.6)

LDL= low-density lipoprotein.
Data are mean (standard deviation [SD]) or n (%) and include all randomised participants unless otherwise stated.
[a]Sex and race were self-reported.

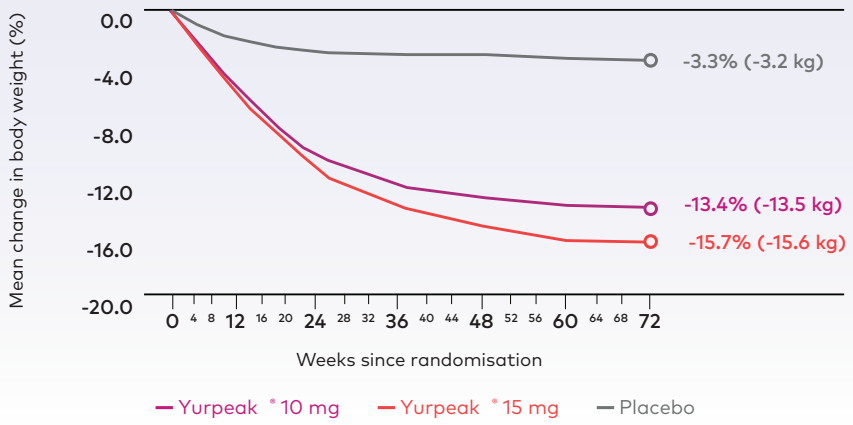
Efficacy

The results shown below align with the Efficacy estimand, representing the average treatment effect of Yurpeak® (tirzepatide) relative to placebo for all participants who had undergone randomisation, if the treatment was administered as intended.[1,5]

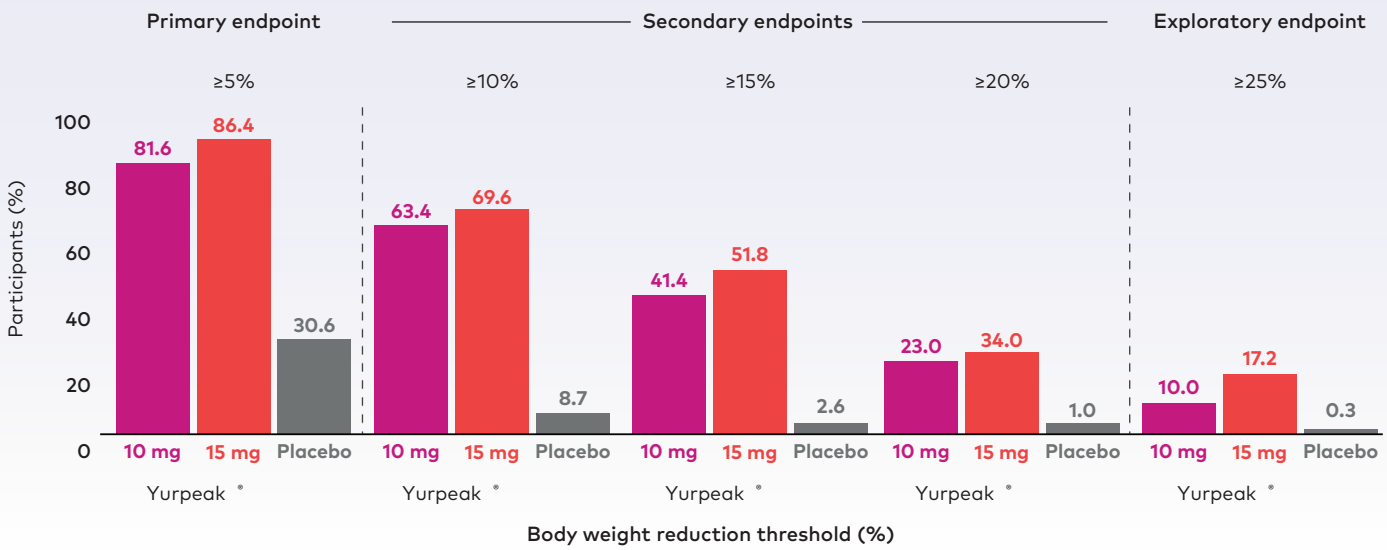
Primary outcome measures

In SURMOUNT-2, participants taking the Yurpeak® 10 mg and 15 mg doses saw means of 13.4% and 15.7% in body weight reduction, respectively. The placebo group saw a mean of 3.2% in weight reduction.[1,5] The European Association for the Study of Obesity (EASO) considers a reduction target of ≥5% to be clinically meaningful and recommends weight loss goals of 5% to 15% over 6 months and a cumulative weight reduction of ≥20% for participants with BMI ≥35 kg/m^2.[1,5]

Percentage Change in Body Weight From Baseline Over Time
(Mean Body Weight at Week 72)[a,1,5]



Percentage of Participants Who Achieved Body Weight Reduction Targets at 72 Weeks[b,1,5]



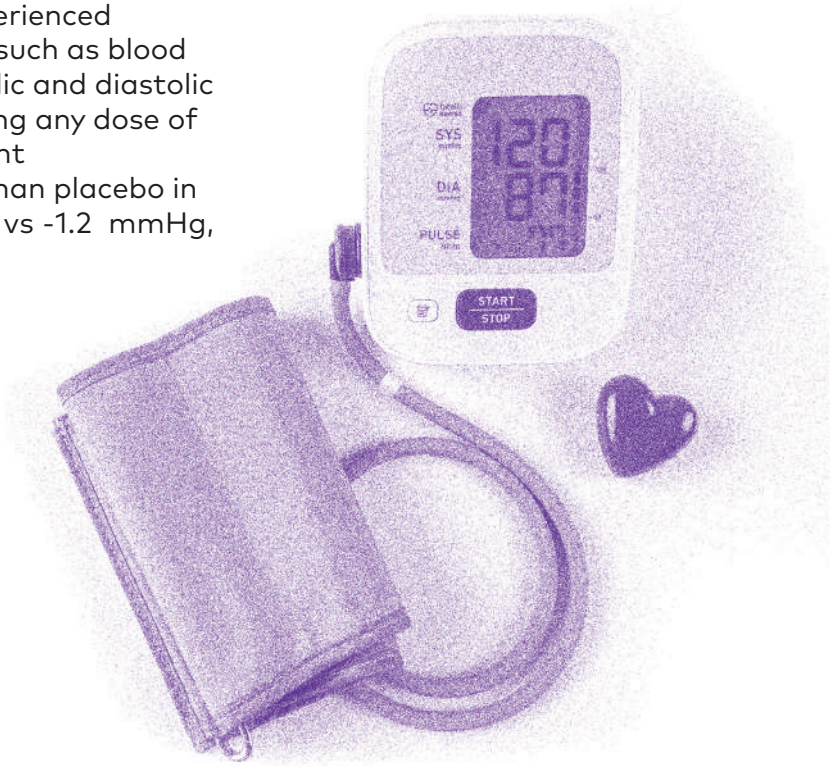
Least-squares mean data are presented, unless otherwise noted.
[a]Percentage change in body weight over time from baseline to 72 weeks, derived from a mixed-model-for-repeated-measures analysis for the efficacy estimand.[5]
[b]Percentage of participants reaching weight-reduction thresholds (efficacy estimand) was obtained by logistic regression with missing value at week 72 imputed from mixed-model-for-repeated-measures analysis.[5]

Select secondary endpoints

Cardiometabolic parameters[1,5]

Participants taking Yurpeak® (tirzepatide) experienced improvements in cardiometabolic parameters such as blood pressure and lipid levels vs placebo. Both systolic and diastolic blood pressure decreased for participants taking any dose of Yurpeak®. Improvements with Yurpeak® treatment (10 mg and 15 mg) were significantly greater than placebo in terms of systolic blood pressure (-5.9 and -7.7 vs -1.2 mmHg, respectively) and diastolic blood pressure (-2.1 and -2.9 vs -0.3 mmHg respectively)[1,5].

Additional cardiometabolic parameters measured included lipid levels: triglycerides, HDL cholesterol, LDL cholesterol, and total cholesterol. Across both doses of Yurpeak®, there were decreases in triglyceride levels. There were increases in HDL cholesterol across both Yurpeak® groups. Finally, there were decreases in total cholesterol across both Yurpeak® groups.[1,5]



Change From Baseline in Secondary Endpoints for Yurpeak® Groups vs Placebo at Week 7[1,5]

	Yurpeak®		Placebo
Secondary endpoint	**10 mg** (n=312)	**15 mg** (n=311)	(n=315)
Percent change in fasting:			
Triglycerides	-26.8 (p<0.0001)	-30.6 (p<0.0001)	-5.8
HDL cholesterol	6.9 (p=0.0001)	9.6 (p=0.0001)	1.1
LDL cholesterol	2.3 (p=0.12)	3.2 (p=0.23)	6.3
Total cholesterol	-3.0 (p=0.0010)	-2.2 (p=0.0065)	2.1
Glucose, mg/dL	-42.9 (p<0.0001)	-51.7 (p<0.0001)	-2.4
Glucose, mmol/L	-2.7 (p<0.0001)	-2.9 (p<0.0001)	-0.1
Change in:			
Body weight, kg	-13.5 (p<0.0001)	-15.6 (p<0.0001)	-3.2
BMI, kg/m^2	-4.9 (p<0.0001)	-5.7 (p<0.0001)	-1.2
Waist circumference, cm	-11.2 (p<0.0001)	-13.8 (p<0.0001)	-3.4
HbA1c, %	-2.14 (p<0.0001)	-2.22 (p<0.0001)	-0.16

Data are from the efficacy analysis set. All changes are from baseline to week 72. P values are treatment comparison vs placebo.[5]

In SURMOUNT-2, the most frequently reported AEs with Yurpeak® (tirzepatide) were gastrointestinal (nausea, diarrhoea, constipation). Most of these events occurred during dose escalation, were mild to moderate in severity, and decreased over time. Serious AEs were reported by 7% of the participants overall, with no significant differences in reporting across the groups.

GI AEs leading to discontinuation were nausea, diarrhoea, and vomiting. AEs leading to discontinuation, including both GI AEs and other AEs, occurred in 4% of participants taking Yurpeak® 10 mg, 7% of those taking Yurpeak® 15 mg, and 4% of those taking placebo.[1,5]

Adverse Events (Intention-to-Treat Population)[a,1,5]

	Yurpeak®		Placebo
	10 mg (n=312)	**15 mg** (n=311)	(n=315)
Participants with ≥1 TEAE	242 (78%)	222 (71%)	239 (76%)
Serious AEs[b]	18 (6%)	27 (9%)	23 (7%)
Deaths[b]	2 (1%)	0	0
AEs leading to discontinuation of study drug	**12 (4%)**	**23 (7%)**	**12 (4%)**
Diarrhoea	0	5 (2%)	0
Nausea	1 (<1%)	4 (1%)	0
Vomiting	2 (1%)	0	0
Elevated blood calcitonin	2 (1%)	0	0
Elevated pancreatic enzymes	2 (1%)	0	0
TEAEs occurring in ≥5% of participants in any treatment group			
Diarrhoea	62 (20%)	67 (22%)	28 (9%)
Nausea	63 (20%)	68 (22%)	20 (6%)
COVID-19	53 (17%)	33 (11%)	53 (17%)
Vomiting	34 (11%)	41 (13%)	10 (3%)
Decreased appetite	30 (10%)	31 (10%)	7 (2%)
Constipation	25 (8%)	28 (9%)	13 (4%)
Dyspepsia	23 (7%)	22 (7%)	10 (3%)
Hyperglycaemia	6 (2%)	4 (1%)	45 (14%)
Upper respiratory tract infection	10 (3%)	12 (4%)	21 (7%)
Abdominal pain	12 (4%)	23 (7%)	7 (2%)
Headache	16 (5%)	15 (5%)	9 (3%)
Nasopharyngitis	9 (3%)	10 (3%)	17 (5%)
Eructation	19 (6%)	13 (4%)	2 (1%)
Dizziness	17 (5%)	8 (3%)	5 (2%)

TEAE= treatment emergent adverse event.
[a]AEs are listed according to the Medical Dictionary for Regulatory Activities, version 24.1, preferred terms; only preferred terms with n ≥2 in at least 1 group are presented.[1]
[b]Deaths were also included as serious AEs; all deaths were adjudicated by an external committee of physicians as to whether the death was a cardiovascularrelated death or not.[1]

SURMOUNT-3:

Yurpeak® (tirzepatide) vs placebo in participants with overweight or obesity after an intensive lifestyle programme

Summary

SURMOUNT-3 was a multicentre, randomised, double-blind, 84-week study that evaluated the efficacy and safety of Yurpeak® among participants with obesity or overweight without type 2 diabetes (T2D) who achieved ≥5% weight reduction after a 12-week intensive lifestyle intervention. The study enrolled 806 participants in the intensive lifestyle intervention, and 579 participants achieved ≥5% weight reduction at the end of the lead-in period. In this study, Yurpeak® demonstrated additional weight reductions in participants who had achieved ≥5% weight reduction after an intensive lifestyle programme. At week 72, participants taking the maximum tolerated dose (MTD) of Yurpeak® (10 mg or 15 mg) saw an overall mean change in body weight of -21.1% and 3.3% with placebo. Additionally, 94.4% of participants given the MTD of Yurpeak® had an additional weight reduction of ≥5% from randomisation. Compared to those taking placebo, participants taking Yurpeak® saw improvements in cardiometabolic parameters such as blood pressure and lipid levels. The most common adverse events (AEs) were gastrointestinal and mild to moderate in severity. These occurred most often during dose escalation.6

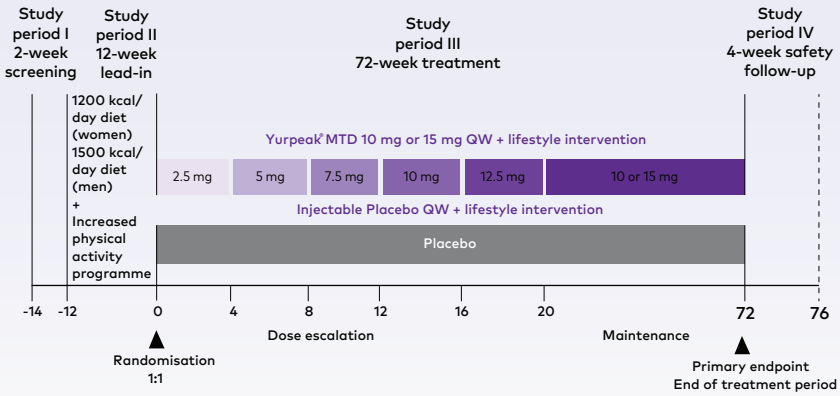
SURMOUNT-3 study

SURMOUNT-3 was designed to compare the Efficacy and safety of Yurpeako® (10 mg or 15 mg) in adults with obesity or overweight but not T2D who successfully lost ≥5% of baseline weight during a 12-week intensive lifestyle programme.[6] The treatment study period lasted 72 weeks and concluded in May 2023.[6] Key inclusion criteria were body mass index (BMI) of ≥30 kg/m² or ≥27 kg/m² and previously diagnosed with 1 or more weight-related complication, having 1 or more unsuccessful dietary attempts to lose weight, and achievement of ≥5% weight reduction at the end of the lead-in period. The study excluded patients with T2D.[6]

Study Design[6]

SURMOUNT-3 was a phase 3 trial that enrolled 806 participants in a 12-week intensive lifestyle intervention lead-in period. The intensive lifestyle intervention included 8 in-person lifestyle counselling sessions over 12 weeks, low-calorie diet of 1200 kcal/day for women, 1500 kcal/day for men, and 150 minutes of moderateintensity physical activity per week. Of the 806 participants enrolled, 579 participants achieved ≥5% weight reduction at the end of the lead-in period. Participants were randomised in a 1:1 ratio to receive the MTD of Yurpeak® (tirzepatide) 10 mg or 15 mg or placebo. This included a dose escalation period of up to 20 weeks. Participants started at Yurpeak® 2.5 mg, and doses increased every 4 weeks by 2.5 mg until a MTD of 10 mg or 15 mg was reached.[6]

SURMOUNT-3 Study Design[6]



All participants received lifestyle intervention, which included counselling every 12 weeks to help them adhere to a healthful balanced diet (with a deficit of 500 calories per day) and continuation of physical activity (at least 150 minutes per day).[6]

The 2 coprimary endpoints were a reduction in weight of ≥5% from baseline at week 72 and percent change in body weight from baseline at week 72. The secondary endpoints included weight reduction of ≥10%, ≥15%, or ≥20% at week 72; proportion of participants who maintained ≥80% of the weight reduction achieved during the 12-week lead-in period at week 72; and change from baseline in waist circumference at week 72.[6]

Coprimary endpoints[6]

Percentage change in body weight from baseline to week 72

Weight reduction of ≥5% at week 72

Key inclusion criteria[6]

- ≥18 years
- BMI ≥30 kg/m², or BMI ≥27 kg/m² and at least 1 weight-related complication (hypertension, dyslipidemia, obstructive sleep apnea, or cardiovascular disease)
- One or more unsuccessful dietary efforts to lose weight
- Achieved ≥5% weight reduction at the end of the lead-in period

QW= once weekly
MTD= maximum tolerated dose.

Participant demographics

Participants enrolled in SURMOUNT-3 had obesity or overweight and had ≥5% weight reduction after a 12-week intensive lifestyle intervention. People with T2D were not included in the study. The average duration of obesity was 15.1 years and 66.1% had one or more weight-related complication. The mean baseline weight decreased from 109.5 kg to 101.9 kg, and the mean baseline BMI decreased from 38.6 kg/m^2 to 35.9 kg/m^2 across all study groups from the start of the lead-in period to randomisation, respectively. The mean age of participants across all groups was 45.6 years. Among the Yurpeak® (tirzepatide)-treated participants, 86.4% had a MTD of 15 mg for Yurpeak®.[6]

Baseline Characteristics[6]

Characteristics	Yurpeak® MTD* (n=287)	Placebo (n=292)	Total (N=579)
Age, years	45.4 (12.6)	45.7 (11.8)	45.6 (12.2)
Duration of obesity, years[a]	15.4 (11.6)	14.8 (10.8)	15.1 (11.2)
Body weight (lead-in period), kg	110.1 (23.9)	108.9 (22.2)	109.5 (23.0)
Body weight (at randomisation), kg	102.5 (22.1)	101.3 (20.7)	101.9 (21.4)
Body mass index (lead-in period), kg/m^2	38.7 (6.6)	38.4 (6.8)	38.6 (6.7)
Body mass index (at randomisation), kg/m^2	36.1 (6.1)	35.7 (6.4)	35.9 (6.3)
Waist circumference (lead-in period), cm	115.9 (15.6)	116.3 (15.3)	116.1 (15.4)
Waist circumference (randomisation), cm	109.3 (15.2)	109.6 (15.1)	109.4 (15.0)
Sex, n (%)			
Female	181 (63.1)	183 (62.7)	364 (62.9)
Male	106 (36.9)	109 (37.3)	215 (37.1)
Race, n (%)[b]			
Asian	2 (0.7)	2 (0.7)	4 (0.7)
Black or African American	31 (10.8)	32 (11.0)	63 (10.9)
American Indian or Alaskan	2 (0.7)	4 (1.4)	6 (1.0)
White	246 (85.7)	252 (86.3)	498 (86.0)
Multiple	6 (2.1)	2 (0.7)	8 (1.4)
Ethnicity, n (%)[b]			
Hispanic or Latino	151 (52.6)	161 (55.1)	312 (53.9)
Not Hispanic or Latino	132 (46.0)	129 (44.2)	261 (45.1)
Not reported	4 (1.4)	2 (0.7)	6 (1.0)
Country			
Argentina	43 (15.0)	44 (15.1)	87 (15.0)
Brazil	59 (20.6)	60 (20.5)	119 (20.6)
USA	185 (64.5)	188 (64.4)	373 (64.4)
Body mass index category, n (%)			
<27	5 (1.7)	12 (4.1)	17 (2.9)
≥27-<30	32 (11.1)	38 (13.0)	70 (12.1)
≥30-<35	100 (34.8)	107 (36.6)	207 (35.8)
≥35-<40	95 (33.1)	79 (27.1)	174 (30.1)
≥40	55 (19.2)	56 (19.2)	111 (19.2)
Number of weight-related complications, n (%)[c]			
0	96 (33.4)	100 (34.2)	196 (33.9)
1	102 (35.5)	81 (27.7)	183 (31.6)
2	48 (16.7)	54 (18.5)	102 (17.6)
3	22 (7.7)	36 (12.3)	58 (10.0)
4	14 (4.9)	14 (4.48)	28 (4.8)
≥5	5 (1.7)	7 (2.4)	12 (2.1)

[a]Duration of obesity was assessed by self-report.[6]
[b]Race and ethnicity were determined by the participant according to fixed selection categories.[6]
[c]Baseline medical conditions were assessed through a review of participants' medical history.[6]
*MTD= maximum tolerated dose for Yurpeak® - 10 mg or 15 mg.

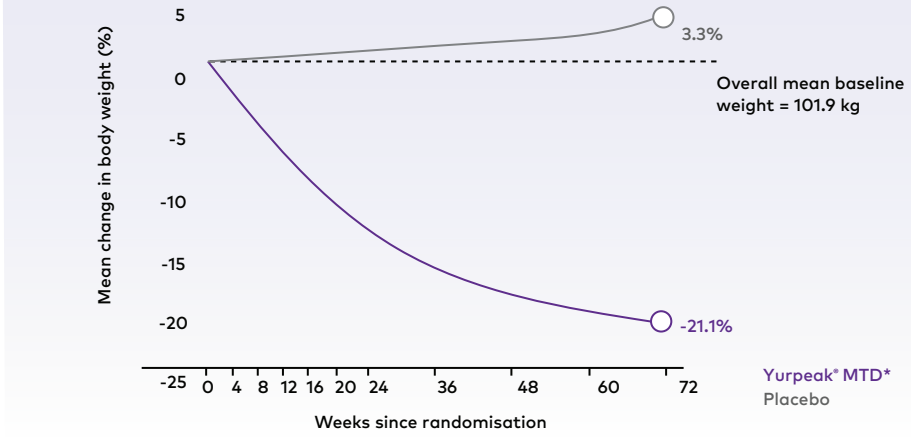
Efficacy

The results shown below align with the Efficacy estimand, representing the average treatment effect of Yurpeak® (tirzepatide) relative to placebo for all participants who had undergone randomisation, if the treatment was administered as intended.[6]

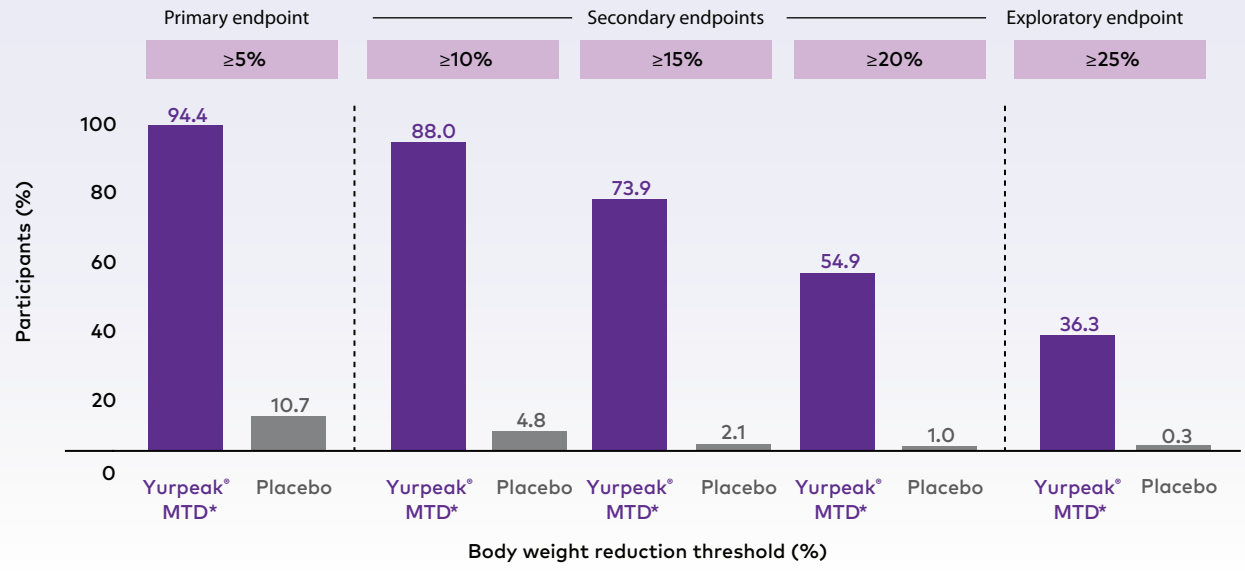
Primary outcome measures

In SURMOUNT-3, the mean change in body weight for participants taking the MTD of Yurpeak® was -21.1% and for participants in the placebo group was 3.3%.[6] The European Association for the Study of Obesity (EASO) considers a reduction target of ≥5% to be clinically meaningful and recommends weight loss goals of 5% to 15% over 6 months and a cumulative weight reduction of ≥20% for participants with BMI ≥35 kg/m^2.[6]

Percentage Change in Body Weight From Randomisation at Week 72 (Mean Body Weight at Week 72)[a,6]



Percentage of Participants Who Achieved Body Weight Reduction Targets at 72 Weeks[b,6]



Least-squares mean data are presented, unless otherwise noted.
[a]Percentage change in body weight over time from randomisation to 72 weeks, derived from a mixed-model-for-repeated-measures analysis for the efficacy estimand.[6]
[b]Percentage of participants reaching weight-reduction thresholds (efficacy estimand) was obtained by logistic regression with missing values at week 72 imputed from mixed-model-for-repeated-measure analysis.[6]
*MTD= maximum tolerated dose for Yurpeak - 10 mg or 15 mg.

Select secondary endpoints

Cardiometabolic parameters

Participants taking Yurpeak® (tirzepatide) experienced improvements in cardiometabolic parameters such as blood pressure and lipid levels vs placebo. Both systolic and diastolic blood pressure decreased for participants taking the MTD of Yurpeak® . Improvements with Yurpeak® MTD were greater than placebo in terms of systolic blood pressure (-5.1 mm Hg vs 4.1 mm Hg) and diastolic blood pressure (-3.2 mm Hg vs 2.3 mm Hg).[6]

Additional cardiometabolic parameters measured included lipid levels (triglycerides, HDL cholesterol, LDL cholesterol, and total cholesterol) and glycaemic control (HbA1c). There were decreases in triglyceride levels, total cholesterol, and LDL cholesterol. There was an increase in HDL cholesterol in the Yurpeak® group.[6]

Change From Randomisation for Secondary Endpoints at Week 72[6]

Secondary endpoints	Yurpeak® MTD (n=287)	Placebo (n=292)
Percent change in fasting:		
Total cholesterol[a]	-3.0	5.2
HDL cholesterol[a]	15.4	3.6
LDL cholesterol[a]	-6.1	6.1
Triglycerides[a]	-25.8	3.0
Glucosea, mg/dL	-8.8	2.4
Change in:		
Body weight,[a] kg	-21.5	3.5
Body mass index,[a] kg/m^2	-7.7	1.2
Waist circumference,[b] cm	-16.8	1.1
HbA1c, %	-0.5	0.0
Systolic blood pressure, mm Hg	-5.1	4.1
Diastolic blood pressure, mm Hg	-3.2	2.3

[a]P values are not reported for additional secondary endpoints because these were not controlled for type I error.[6]
[b]Key secondary endpoint was controlled for type I error; p<0.001.[6]

Waist circumference

Waist circumference is associated with cardiovascular risk and should be considered in conjunction with BMI to assess obesity-related health risks.[6t] In SURMOUNT-3, the mean decrease in waist circumference from randomisation to week 72 was 16.8 cm for participants in the Yurpeak® MTD group and 1.1 cm increased in participants taking placebo. The mean waist circumference across all groups at randomisation was 109.4 cm.[6]

Physical Functioning scores

In SURMOUNT-3 participants reported improvements in physical functioning. The improvements were greater in participants taking Yurpeak® than in those taking placebo from randomisation to week 72. The change in SF-36v2® Physical Functioning domain score was 3.3 in the Yurpeak® MTD group and -0.6 for the placebo group. The change in IWQOL-Lite-CT physical function composite score was 13.9 in the Yurpeak® MTD group and 1.1 for the placebo group.[6]

HDL= high-density lipoprotein; IWQOL-Lite-CT= Impact of Weight on Quality of Life-Lite-Clinical Trials Version; LDL= low-density lipoprotein; SF-36v2=36-Item Short Form Health Survey, version 2, acute form.
SF-36v2 is a registered trademark of Quality Metric.

SAFETY AND TOLERABILITY

In SURMOUNT-3, the most frequently reported AEs with Yurpeak® (tirzepatide) were gastrointestinal (nausea, diarrhoea, and constipation). Most of these events occurred during dose escalation and were mild to moderate in severity. Serious AEs were reported by 5.4% of the participants overall, with similar occurrence across the 2 groups.[6]

Adverse Events[a,6]

	Yurpeak® MTD (n=287) n (%)	Placebo (n=292) n (%)
Participants with ≥1AE	250 (87.1)	224 (76.7)
Serious AEs	17 (5.9)	14 (4.8)
Death[b]	1 (0.3)	1 (0.3)
Adverse events leading to discontinuation[c]		
Nausea	24 (8.4)	4 (1.4)
Vomiting	6 (2.1)	0
Diarrhoea	3 (1.0)	0
Dyspepsia	3 (1.0)	0
Constipation	2 (0.7)	0
Adverse events occurring in ≥ 5% of participants in any treatment group		
Nausea	114 (39.7)	41 (14.0)
Diarrhoea	89 (31.0)	27 (9.2)
Constipation	66 (23.0)	20 (6.8)
COVID-19	66 (23.0)	74 (25.3)
Vomiting	52 (18.1)	4 (1.4)
Injection-site reaction	32 (11.1)	3 (1.0)
Abdominal pain	30 (10.5)	7 (2.4)
Decreased appetite	27 (9.4)	12 (4.1)
Dyspepsia	27 (9.4)	9 (3.1)
Headache	27 (9.4)	22 (7.5)
Upper respiratory tract infection	25 (8.7)	21 (7.2)
Alopecia	20 (7.0)	4 (1.4)
Dizziness	20 (7.0)	6 (2.1)
Fatigue	20 (7.0)	9 (3.1)
Flatulence	19 (6.6)	8 (2.7)
Gastroesophageal reflux disease	19 (6.6)	7 (2.4)
Back pain	17 (5.9)	15 (5.1)
Eructation	16 (5.6)	3 (1.0)
Influenza	12 (4.2)	25 (8.6)
Urinary tract infection	11 (3.8)	15 (5.1)
Anxiety	9 (3.1)	19 (6.5)
Arthralgia	7 (2.4)	15 (5.1)
Sinusitis	6 (2.1)	16 (5.5)

[a]Adverse events are listed according to the Medical Dictionary for Regulatory Activities, version 26.0, preferred terms.[6]
[b]Deaths are also included as serious adverse events and discontinuations due to adverse events.[6]
[c]Only adverse events occurring in ≥2 participants in any treatment group are presented.[6]

SURMOUNT-4:

Yurpeak® (tirzepatide) vs placebo in participants with overweight or obesity for the maintenance of weight reduction

Summary

SURMOUNT-4 was a randomised 88-week withdrawal study that evaluated the efficacy and safety of continued treatment with Yurpeak® compared with placebo on the maintenance of weight reduction among participants with obesity or overweight without type 2 diabetes (T2D). The study consisted of a 36-week, open-label Yurpeak® lead-in period followed by a 52-week, double-blind, placebo-controlled period. The study enrolled 783 participants in the 36-week open-label period, among which 113 participants discontinued Yurpeak®. A total of 670 participants were randomised to continue treatment with the maximum tolerated dose (MTD) of Yurpeak® (10 mg or 15 mg) or switch to receiving placebo up to week 88.[7]

At the end of 36-week lead-in period, participants taking Yurpeak® achieved a mean weight reduction of 20.9%. From week 36 to week 88, those who continued taking Yurpeak® experienced a mean change in body weight of -6.7% compared with 14.8% in the placebo group. The overall mean change in body weight from week 0 to week 88 was -26.0% in the Yurpeak® group versus -9.5% in the placebo group. At week 88, 93.4% of participants who continued taking Yurpeak® maintained ≥80% of the body weight lost during the lead-in period versus 13.5% of participants in the placebo group. Compared to those taking placebo, participants taking Yurpeak® saw improvements in body weight, body mass index (BMI), and cardiometabolic parameters such as blood pressure and lipid levels. The most common adverse events (AEs) were gastrointestinal and mild to moderate in severity.[7]

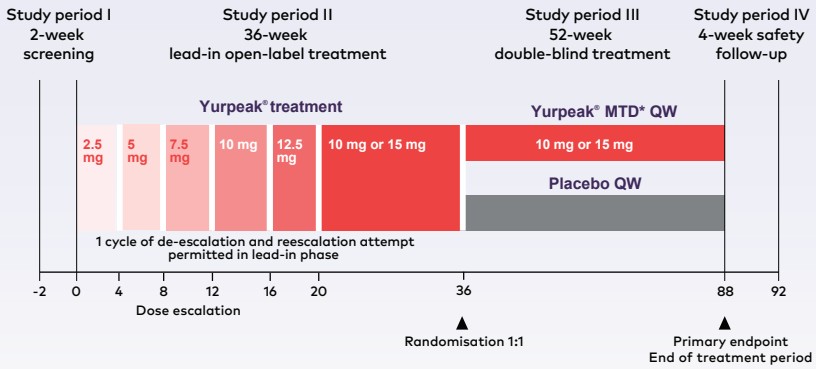
SURMOUNT-4 study

SURMOUNT-4 was designed to assess the effect of continued treatment with Yurpeak® (10 mg or 15 mg) on maintaining initial weight reduction in adults with obesity or overweight. Patients with T2D were excluded from the trial. The treatment study period lasted 88 weeks and concluded in May 2023. Key inclusion criteria were BMI of ≥30 kg/m^2 or ≥27 kg/m^2, previously diagnosed with 1 or more weight-related complications, and having 1 or more unsuccessful dietary attempts to lose weight.[7]

Study Design

SURMOUNT-4 was a phase 3 trial that enrolled 783 participants in a 36-week lead-in period, where participants received the maximum tolerated dose of Yurpeak® (tirzepatide) 10 mg or 15 mg. During this 36-week period, participants started at Yurpeak® 2.5 mg, and Yurpeak® doses increased every 4 weeks by 2.5 mg until a MTD of 10 or 15 mg was reached. During the lead-in period, 113 participants discontinued due to an AE or participant withdrawal. After completing the 36-week lead-in period, 670 participants were randomised in a 1:1 ratio to continue receiving the MTD of Yurpeak® (10 mg or 15 mg) or placebo for 52 weeks. Most participants (92.7%) had a MTD of 15 mg.[7]

SURMOUNT-4 Study Design[7]



All participants received lifestyle intervention, which included counselling to help them adhere to a healthful balanced diet (with a deficit of 500 calories per day) and at least 150 minutes of physical activity per week.[7]

The primary endpoint was the percent change in body weight from randomisation (week 36) to week 88. NThe key secondary endpoints included the proportion of participants who maintained ≥80% of the weight reduction achieved during the 36-week lead-in period at week 88; change in body weight from week 36 to week 88; and change in waist circumference from week 36 to week 88.[7]

Primary endpoints[7]

Percentage change in body weight from randomisation (week 36) to week 88

Key inclusion criteria[7]

≥18 years

BMI ≥30 kg/m^2 , or BMI ≥27 kg/m^2 and at least 1 weight-related complication (hypertension, dyslipidemia, obstructive sleep apnea, or cardiovascular disease)

One or more unsuccessful dietary efforts to lose weight

QW= once weekly
*MTD= maximum tolerated dose for Yurpeak® - 10 mg or 15 mg.

Participant demographics

Participants enrolled in SURMOUNT-4 had obesity or overweight and either continued treatment with Yurpeak ® (tirzepatide) or switched to placebo to assess the impact on maintaining weight reduction. People with T2D were not included in the study. The average duration of obesity was 15.5 years, and 69.4% had 1 or more weight-related complications. At the start of the Yurpeak ® lead-in treatment period (week 0), the mean body weight was 107.3 kg, the mean baseline BMI was 38.4 kg/m^2, and the mean waist circumference was 115.2 cm. At randomisation (week 36), the mean body weight was 85.2 kg, the mean baseline BMI was 30.5 kg/m^2, and the mean waist circumference was 97.5 cm across Yurpeak ® and placebo groups. The mean age of participants across all groups was 48 years. Among the Yurpeak ®-treated participants at randomization, 92.7% had a MTD of 15 mg for Yurpeak ®.[7]

Baseline Characteristics[7]

	Week 0 (start of lead-in period)	Week 36 (randomisation)	
	Yurpeak ®	Yurpeak ® MTD*	Placebo
Characteristics	(n=670)	(n=335)	(n=335)
Age, years	48 (13)	49 (13)	48 (12)
Duration of obesity, years[a]	15.5 (11.8)	15.9 (12.1)	15.2 (11.4)
Body weight, kg	107.3 (22.3)	84.6 (19.8)	85.8 (22.3)
Body mass index, kg/m^2	38.4 (6.6)	30.3 (6.0)	30.7 (6.8)
Waist circumference, cm	115.2 (14.5)	96.8 (14.1)	98.2 (16.0)
Sex, n (%)			
Female	473 (70.6)	236 (70.4)	237 (70.7)
Male	197 (29.4)	99 (29.6)	98 (29.3)
Race, or ethnic group, n (%)[b]			
Asian	48 (7.2)	26 (7.8)	22 (6.6)
Black or African American	75 (11.2)	39 (11.6)	36 (10.7)
Native Hawaiian or other Pacific Islander	2(0.3)	1 (0.3)	1 (0.3)
White	537 (80.1)	264 (78.8)	273 (81.5)
Multiple	8 (1.2)	5 (1.5)	3 (0.9)
Hispanic or Latino	296 (44.2)	141 (42.1)	155 (46.3)
Body mass index category, n (%)			
<25	0	59 (17.6)	63 (18.8)
≥25-<30	18 (2.7)	122 (36.4)	120 (35.8)
≥30-<35	212 (31.6)	88 (26.3)	75 (22.4)
≥35-<40	215 (32.1)	41 (12.2)	43 (12.8)
≥40	225 (33.6)	25 (7.5)	34 (10.1)
Blood pressure, mm Hg			
Systolic	126 (13)	115 (13)	115 (12)
Diastolic	81 (8)	75 (9)	76 (9)
Lipid levels, mg/dL (%)			
Total cholesterol	192.3 (39.6)	179.9 (36.8)	180.2 (37.3)
HDL cholesterol	51.5 (13.1)	49.1 (11.6)	48.8 (11.5)
LDL cholesterol	113.8 (32.9)	111.0 (32.4)	113.2 (33.6)
Triglycerides	136.2 (80.9)	99.1 (45.1)	93.0 (44.3)

HDL=high-density lipoprotein; LDL=low-density lipoprotein.
[a]Duration of obesity was self-reported by participants.[7]
[b]Race and ethnicity were determined by the participant according to fixed selection categories.[7]
*MTD= maximum tolerated dose for Yurpeak® - 10 mg or 15 mg.

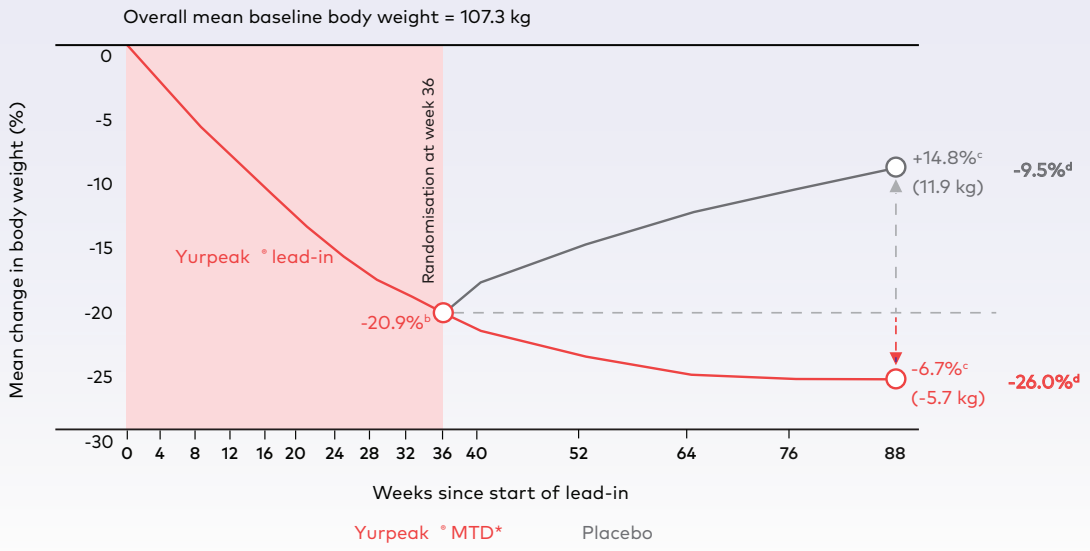
Efficacy

The results shown below align with the Efficacy estimand, representing the average treatment effect of Yurpeak® (tirzepatide) relative to placebo for all participants who had undergone randomisation, if the treatment was administered as intended.[7]

Primary outcome measures

In SURMOUNT-4, at randomisation (week 36), participants who started on Yurpeak® had already experienced a mean weight reduction of 20.9%. From week 36 to week 88, participants who continued taking the MTD of Yurpeak® experienced an additional 6.7% weight loss versus 14.8% weight gain in the placebo group. Overall, participants who continued taking Yurpeak® achieved a mean change in body weight of -26.0% from week 0 to week 88 versus -9.5% for participants in the placebo group. At baseline, the average BMI for participants was 38.4 kg/m^2.[7] While the European Association for the Study of Obesity (EASO) considers a reduction target of ≥5% over a period of 6 months to be clinically meaningful, for participants with BMI ≥35 kg/m^2 the cumulative weight reduction goal is >20%.[7]

Percentage Change in Body Weight Over Time From Baseline to Week 88[a,7]



[a]Least-squares mean data are presented, unless otherwise noted.[7]
[b]Percent change in body weight from week 0 to week 36 in participants taking the MTD of Yurpeak * during the lead-in period.[7]
[c]Percent change in body weight from week 36 to week 88.[7]
[d]Percent change in body weight from week 0 to week 88.[7]
*MTD= maximum tolerated dose for Yurpeak® - 10 mg or 15 mg.

Select secondary endpoints

In SURMOUNT-4, 93.4% of participants taking Yurpeak® (tirzepatide) maintained ≥80% of the body weight lost during the 36-week lead-in period versus 13.5% in the placebo group. From week 36 to week 88, participants taking Yurpeak® experienced -5.7 kg weight loss while those taking placebo experienced 11.9 kg weight regain. The mean change in waist circumference from week 36 to week 88 for participants taking Yurpeak® was -4.6 cm versus 8.3 cm in the placebo group. In SURMOUNT-4, only participants who continued taking Yurpeak® maintained improvements in cardiometabolic health, including systolic blood pressure, diastolic blood pressure, and lipid levels.[7]

Change From Week 36 to Week 88[a,7]

Secondary endpoints	Yurpeak® MTD* (n=335)	Placebo (n=335)
Percent change in lipid levels:		
Total cholesterol	2.3	8.3
HDL cholesterol	18.3	14.6
LDL cholesterol	-3.4	3.4
Triglycerides	-8.2	15.6
Change in:		
Body weight, kg	-5.7	11.9
BMI, kg/m^2	-2.1	4.3
Waist circumference, cm	-4.6	8.3
Systolic blood pressure, mm Hg	2.1	8.4
Diastolic blood pressure, mm Hg	-0.4	3.2

[a]Tested for significant difference, not controlled for Type 1 error.[7]
*MTD= maximum tolerated dose for Yurpeak® - 10 mg or 15 mg.

In SURMOUNT-4, the most frequently reported AEs with Yurpeak ® (tirzepatide) were gastrointestinal (nausea, diarrhoea, constipation, and vomiting). In the double-blind period, participants also commonly reported COVID-19 as an AE. Most of the gastrointestinal events were mild to moderate in severity and the incidence of new events decreased over time. Serious AEs were reported by 2.0% of the participants during the lead-in period and 3.0% of participants during the double-blind period, with no significant difference in reporting across groups. During the lead-in period, treatment discontinuation due to an AE occurred in 7.0% of enrolled participants, mainly due to gastrointestinal events.[7]

Adverse Events From Week 36 to Week 88[7]

	Yurpeak® MTD* (n=335) n (%)	Placebo (n=335) n (%)
Participants with ≥1AE	202 (60.3)	187 (55.8)
Serious AEs	10 (3.0)	10 (3.0)
Death	1 (0.3)	1 (0.3)
Adverse events leading to discontinuation		
Diarrhoea	2 (0.6)	0
Cardiac failure congestive	1 (0.3)	0
Abdominal pain	1 (0.3)	0
Vomiting	1 (0.3)	0
Pancreatic enzymes increased	1 (0.3)	0
Adenocarcinoma of colon	0	1 (0.3)
Colorectal cancer	0	1 (0.3)
Non-Hodgkin lymphoma	0	1 (0.3)
Adverse events occurring in ≥5% of participants in any treatment group		
COVID-19	47 (14.0)	50 (14.9)
Diarrhoea	36 (10.7)	16 (4.8)
Nausea	27 (8.1)	9 (2.7)
Vomiting	19 (5.7)	4 (1.2)
Upper respiratory tract infection	8 (2.4)	18 (5.4)

*MTD= maximum tolerated dose for Yurpeak® - 10 mg or 15 mg.

SURMOUNT-5:

Yurpeak® (tirzepatide) as compared with semaglutide for the treatment of obesity

Summary

SURMOUNT-5 was a 72-week, Phase 3b, multicenter, randomized, parallel-arm, open-label, comparator-controlled study that evaluated the efficacy and safety of Yurpeak® (tirzepatide) at the maximum tolerated dose (MTD) compared with semaglutide at its MTD in adults with obesity (body mass index [BMI] ≥30 kg/m²) or overweight (BMI ≥27 kg/m²) with at least one obesity-related complication (e.g., hypertension, dyslipidemia), excluding diabetes.
A total of 750 participants were enrolled and randomized in a 1:1 ratio to receive either Yurpeak® (10 mg or 15 mg) or semaglutide (1.7 mg or 2.4 mg) administered subcutaneously once weekly for 72 weeks.
Participants in the Yurpeak® group were more likely to achieve weight reductions of at least 10%, 15%, 20%, and 25% compared to those in the semaglutide group.
By week 72, participants demonstrated reductions in both weight and waist circumference. Notably, approximately one in three participants receiving Yurpeak® at MTD achieved a ≥25% reduction in body weight. The mean percent change in body weight was −21.6% with Yurpeak® and −15.4% with semaglutide. The mean change in waist circumference was −20.0 cm with Yurpeak® and −14.7 cm with semaglutide.
The most common adverse events in both treatment groups were gastrointestinal in nature. These events were predominantly mild to moderate in severity and occurred primarily during the dose-escalation phase.[3]

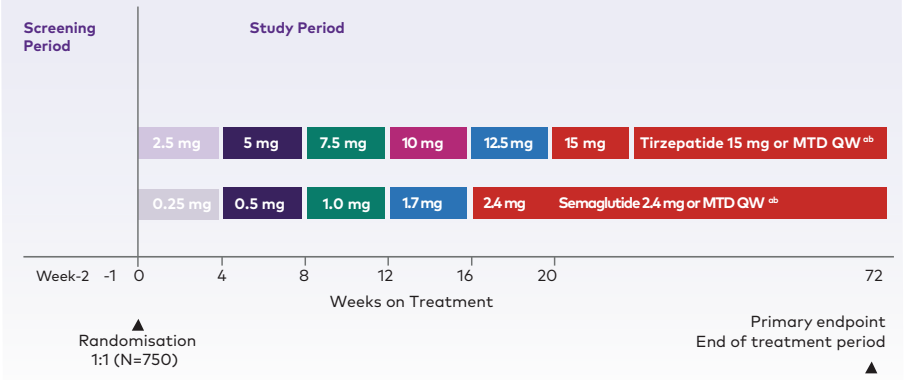
SURMOUNT-5 study

SURMOUNT-5 was designed to evaluate the Efficacy and safety of Yurpeak®(tirzepatide) at the maximum tolerated dose (MTD) compared with semaglutide at its MTD in adults having obesity (body mass index (BMI) ≥30 kg/m²) or overweight (BMI ≥27 kg/m²) with at least one obesity-related complication (e.g., hypertension, dyslipidemia), excluding diabetes.

Study Design

The SURMOUNT-5 trial included 750 participants. The mean age was 44.7 years; 64.7% were female, and 76.1% were white. At baseline, the mean body weight and mean waist circumference were 113.0 kg and 118.3 cm, respectively, and most participants (75.9%) had one or more Obesity-related complications.[3]
Overall, 85.0% of participants completed the trial (85.1% in the Yurpeak ® group and 84.8% in the semaglutide group) and 80.2% completed the 72 weeks of study treatment.[3]

SURMOUNT-5 Study Design[3]



[a]Treatment received as an adjunct to a reduced-calorie diet and increased physical activity.[1]
[b]Tirzepatide MTD was 10 mg or 15 mg; Semaglutide MTD was 1.7 mg or 2.4 mg.[1]
MTD= maximum tolerated dose; QW, once weekly.

At 72 weeks, participants taking Yurpeak ® MTD (10 mg or 15 mg) experienced a superior mean percentage body weight reduction of -21.6%[a] vs -15.4%[a] in those taking semaglutide MTD (1.7 mg or 2.4 mg).[3]

Primary endpoints[3]

Mean percentage change in body weight from baseline to 72 weeks

Week 72

Key inclusion criteria[3]

(BMI) of ≥30 kilogram per square meter (kg/m²) or ≥27 kg/m²

Previously diagnosed with at least one of the following weight related comorbidities: hypertension, dyslipidemia, obstructive sleep apnea, cardiovascular disease

Have a history of at least 1 unsuccessful dietary effort to lose body weight

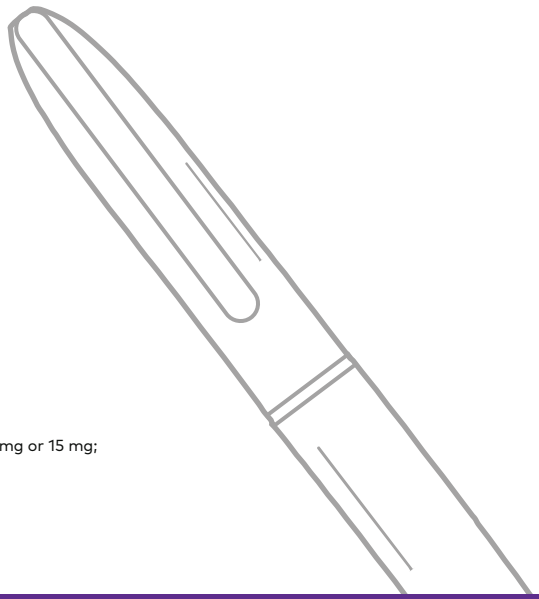
QW= once weekly

Participant demographics

The SURMOUNT-5 trial included 750 participants. The mean age was 44.7 years; 64.7% were female, and 76.1% were white. At baseline, the mean body weight and mean waist circumference were 113.0 kg and 118.3 cm, respectively, and most participants (75.9%) had one or more Obesity-related complications.[3]

Baseline Demographics and Clinical Characteristics[3]

Characteristics	Tirzepatide MTD (n=374)	Semaglutide MTD (n=376)
Age, years	45.0±12.9	44.4±12.7
Female sex, no. (%)	242 (64.7)	243 (64.6)
Age (<65), no. (%)	342 (91.4)	349 (92.8)
Age (≥ 65), no. (%)	32 (8.6)	27 (7.2)
Pre-diabetes at randomization, no. (%)	215 (57.5)	210 (55.9)
Duration of Obesity, years	16.4±11.58	14.7±10.99
Body weight, kg	112.7±24.81	113.4±26.33
BMI	39.4±7.42	39.4±7.72
Walst circumference, cm	117.7±16.14	118.8±17.56
Systolic blood pressure, mmHg	125.6±13.56	125.8±12.48
Diastolic blood pressure, mmHg	81.1±8.48	81.6±8.04
Glycated hemoglobin, %	5.6±0.35	5.6±0.38
Fasting serum glucose, mg/dL	94.4±10.43	94.9±9.83
Triglycerides, mg/dL	127.0±66.2	133.5±105.1
HDL cholesterol, mg/dL	49.9±13.1	49.9±13.5
Non-HDL cholesterol, mg/dL	138.9±36.2	141.0±35.3



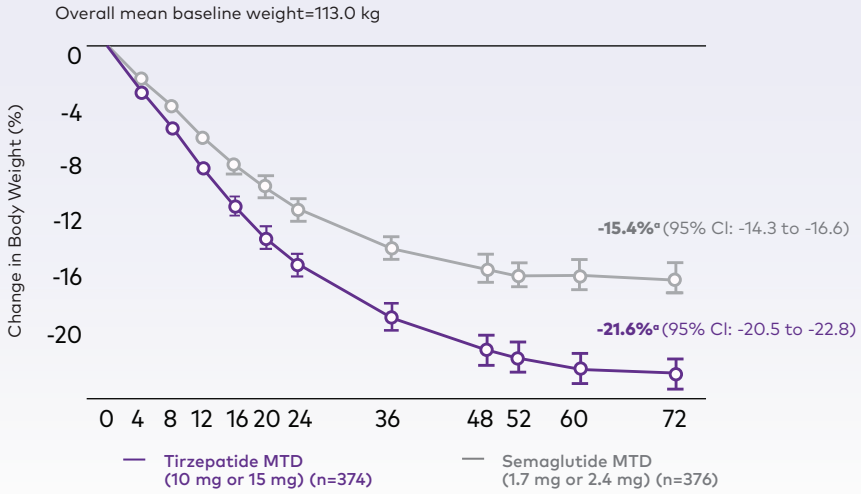
[a]Plus–minus values are mean±SD.[3]
HDL= high-density lipoprotein; *MTD= maximum tolerated dose for Yurpeak® - 10 mg or 15 mg;
#MTD= maximum tolerated dose for Semaglutide - 1.7 mg or 2.4 mg.
SD= standard deviation.

Efficacy

Primary Endpoint

Tirzepatide demonstrated superior reduction in body weight compared to semaglutide.[3] At 72 weeks, participants taking tirzepatide MTD (10 mg or 15 mg) experienced a superior mean percentage body weight reduction of -21.6%[a] vs -15.4%[a] in those taking semaglutide MTD (1.7 mg or 2.4 mg).[3]

Mean Percentage Change in Body Weight Over Time From Randomization to Week 72[3]

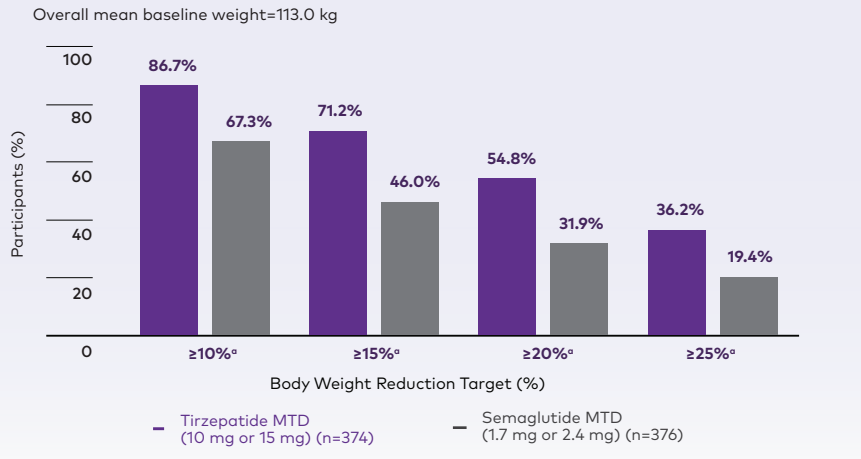


[a]Data are least-squares mean with 95% confidence intervals or no. (%). Only the Week 72 timepoint was pre-specified and controlled for multiplicity.[3]

Key Secondary Endpoints

1 in 3 participants taking tirzepatide 15 mg or MTD (10 mg or 15 mg) achieved ≥25% mean reduction in body weight vs 1 in 5 taking semaglutide 2.4 mg or MTD (1.7 mg or 2.4 mg) at Week 72.[3] More participants in the tirzepatide group attained body weight reduction targets of ≥10%, ≥15%, ≥20%, and ≥25% from baseline compared to the semaglutide group.[3]

Percentage of Participants Who Achieved Weight Reduction Targets At Week 72[3]

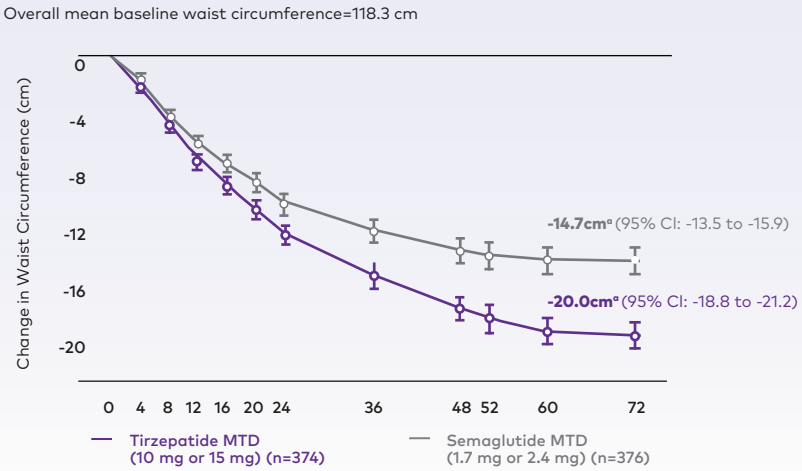


[a]Data are least squares mean with 95% confidence intervals or no. (%).[3]
MTD= maximum tolerated dose.

Tertiary Endpoints

Tirzepatide was superior to semaglutide with respect to waist circumference.[3]
Participants taking tirzepatide experienced superior reduction in waist circumference (cm) vs participants taking semaglutide at Week 72.[3]

Change in Waist Circumference (cm) From Randomization to Week 72[3]



[a]Data are least squares mean with 95% confidence intervals or no. (%).[3]

In addition to weight reduction and decreases in waist circumference, improvements in systolic and diastolic blood pressure were seen in participants taking both tirzepatide and semaglutide.[3]
In addition, consistent with previous trials, improvements were seen in HbA1c and lipids with both study treatments.[3]

Tertiary Endpoints[3]

Endpoint	Tirzepatide MTD*	Semaglutide MTD*
Change in systolic blood pressure, mmHg[a]	**-10.2** (-11.4 to -8.9)	-7.7 (-8.9 to -6.4)
Change in diastolic blood pressure, mmHg[a]	**-4.6** (-5.5 to -3.8)	-3.2 (-4.0 to -2.3)
Change in HbA1c, %[a]	**-0.50** (-0.53 to-0.47)	-0.39 (-0.42 to -0.36)
Change in triglycerides, mg/dL[b]	**-34.9** (-38.0 to -31.8)	-27.5 (-30.9 to -24.1)
Change in non-HDL cholesterol, mg/dL[b]	**-15.6** (-18.4 to-12.7)	-12.8 (-15.7 to -9.9)
Change in HDL cholesterol, mg/dL[b]	**5.7** (4.8 to 6.7)	2.9 (2.0 to 3.8)

[a]Data are least squares mean with 95% confidence intervals. The confidence intervals have not been adjusted for multiplicity and should not be used to make inferences[3]

[b]Estimate 95% confidence intervals. The confidence intervals have not been adjusted for multiplicity and should not be used to make inferences.[3]

HbA1c= glycated hemoglobin; HDL= high-density lipoprotein;
*MTD= maximum tolerated dose for Yurpeak® - 10 mg or 15 mg.
MTD= maximum tolerated dose for Semaglutide - 1.7 mg or 2.4 mg.

The overall safety profile of tirzepatide in SURMOUNT-5 was similar to previously reported SURMOUNT trials.[3] In SURMOUNT-5, the most frequently reported adverse events were gastrointestinal (e.g. nausea, constipation, diarrhea, and vomiting). Most were mild to moderate in severity and occurred primarily during dose escalation, with some pattern variation for incidence and prevalence between the two study treatments.[3]

Adverse Reactions that Occurred in ≥5% of Total Participants in both Treatment Groups.

	Tirzepatide MTD (10 mg or 15 mg) (n=374)	Semaglutide MTD (1.7 mg or 2.4 mg) (n=376)
Nausea	43.6%	44.4%
Constipation	27.0%	28.5%
Diarrhea	23.5%	23.4%
Vomiting	15.0%	21.3%
COVID-19	13.6%	12.5%
Fatigue	10.4%	12.2%
Eructation	9.9%	7.7%
Injection site reaction	8.6%	0.3%
Upper respiratory tract Infection	8.6%	11.4%
Hair loss	8.3%	6.1%
Abdominal distention	7.2%	6.4%
Headache	7.2%	7.2%
Abdominal pain	6.4%	6.9%
Dizziness	6.4%	4.8%
Gastroesophageal reflux disease	6.1%	10.6%
Dyspepsia	5.9%	7.4%
Decreased appetite	4.5%	5.1%
Nasopharyngitis	4.5%	6.1%
Sinusitis	2.9%	5.6%

MTD= maximum tolerated dose.

once weekly
yurpeak®
(tirzepatide) injection

Reference: 1. Yurpeak® (tirzepatide). prescribing information, India: Updated on July 2025 **2.**Le Roux CW, Zhang S, Aronne LJ, et al. Tirzepatide for the treatment of obesity: trationale and design of the SURMOUNT clinical development program. Obesity (Silver Spring). 2023;31(1):96-110. doi:10.1002/oby.23612 **3.**Louis A et al. Tirzepatide as Compared with Semaglutide for the Treatment of Obesity. New England Journal of Medicine doi: 10.1056/NEJMoa2416394 **4.**Jastreboff AM, Aronne LJ, Ahmad NN, et al; SURMOUNT-1 Investigators. Tirzepatide once weekly for the treatment of obesity. N Engl J Med. 2022;387(3):205-216 and Supplementary Appendix. doi:10.1056/NEJMoa2206038 **5.**Garvey WT, Frias JP, Jastreboff AM, et al. Tirzepatide once weekly for the treatment of obesity in people with type 2 diabetes (SURMOUNT-2): a doubleblind, randomised, multicentre, placebo-controlled, phase 3 trial. Lancet. 2023;402(10402):613-626. doi:10.1016/S0140-6736(23)01200-X2 **6.**Wadden TA, Chao AM, Machineni S, et al. Tirzepatide after intensive lifestyle intervention in adults with overweight or obesity: the SURMOUNT-3 phase 3 trial. Nat Med. 2023;29(11):2909-2918. doi:10.1038/s41591-023-02597-w **7.**Aronne LJ, Sattar N, Horn DB, et al; SURMOUNT-4 Investigators. Continued treatment with tirzepatide for maintenance of weight reduction in adults with obesity: The SURMOUNT-4 randomized clinical trial. JAMA. 2024;331(1)38-48. doi:10.1001/jama.2023.24945 **8.**Jastreboff AM, Aronne LJ, Ahmad NN, et al; SURMOUNT-1 Investigators. Tirzepatide once weekly for the treatment of obesity. Protocol. N Engl J Med. 2022;387(3):205-216 and Supplementary Appendix. https://www.nejm.org/doi/suppl/10.1056/NEJMoa2206038/suppl_file/nejmoa2206038_protocol.pdf

For Tirzepatide Prescribing Information, Please Scan QR Code.

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