TIRZEPATIDE: REAL LIFE EVIDENCE

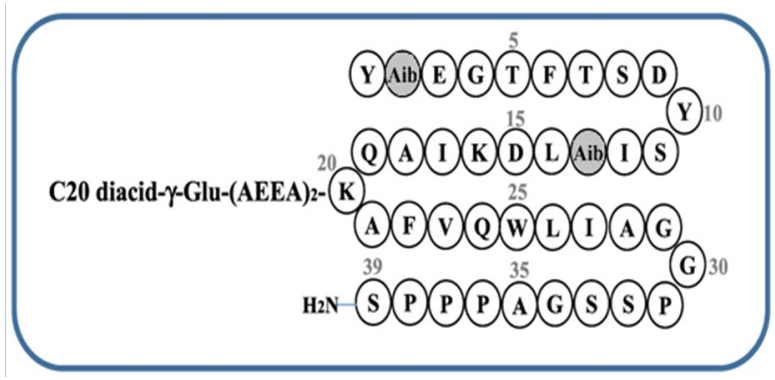
Giovanna Muscogiuri

Università degli studi di Napoli "Federico II "

Tirzepatide: A Novel GIP and GLP-1 Receptor Agonist

Molecular Attributes

- Tirzepatide is a multi-functional peptide engineered from the native GIP peptide sequence, modified to bind to both GIP and GLP-1 receptors
- 39 amino acid linear peptide and includes a C20 fatty diacid moiety
- Conjugated to a C20 fatty diacid moiety via a hydrophilic linker connected to the lysine residue at position 20. (This allows the binding of the molecule to albumin and prolongation of its half-life)
- Contains two non-coded amino acid residues at positions 2 and 13 (Aib, a-amino isobutyric acid)
- the C-terminus is amidated (this removes the charge form the C-terminus, more closely mimics the native protein, and therefore may increase the biological activity of a peptide. It also tends to increase the stability and prolongs their shelf life)
- The molecular weight is 4.8 kD (dula 63 kD, sema 4.11 kD)



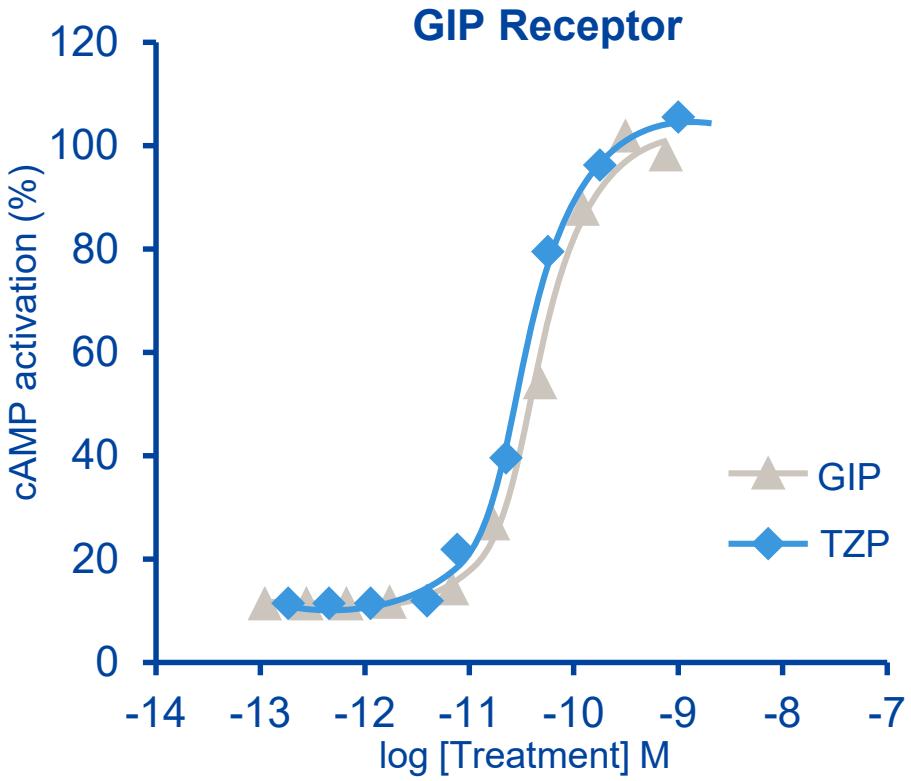
Tirzepatide molecule structure
Shading indicates non-coded amino acids

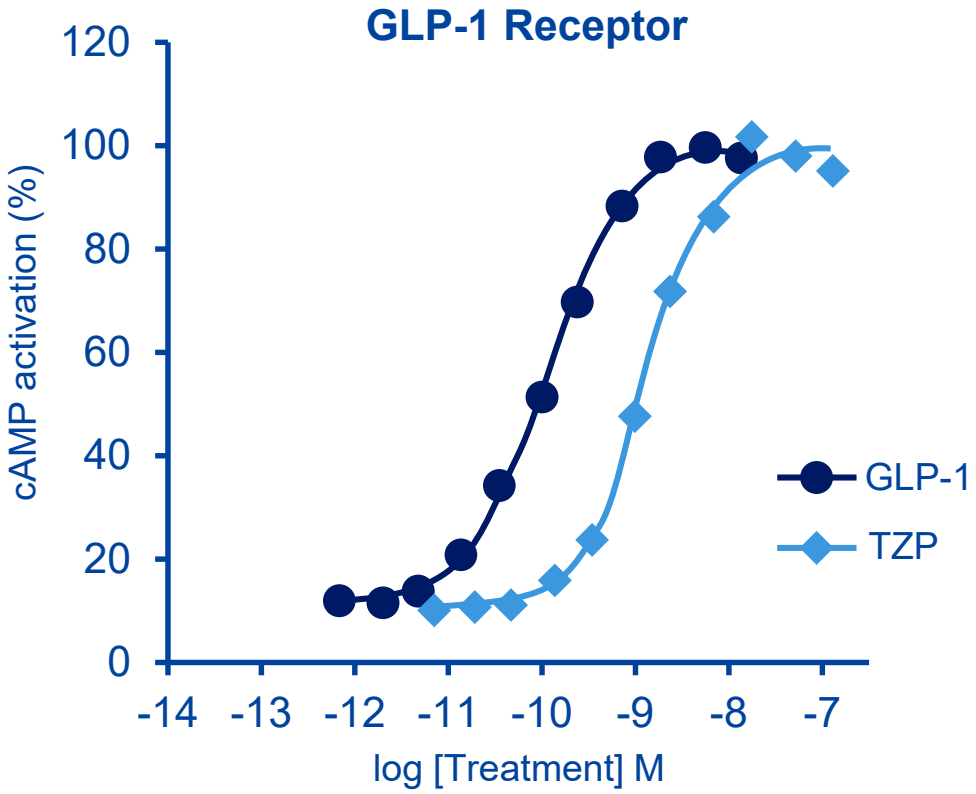
GIP = glucose-dependent insulinotropic polypeptide; GLP-1R = glucagon-like peptide-1

1. Coskun T, et al. *Mol Metab*. 2018;18:3-14. 2. Urva S, et al. *Diabetes*. 2020;69(Suppl. 1):Abstract 971-P.

Tirzepatide Potency and Affinity for GIP and GLP-1 Receptors

- In vitro, tirzepatide has a potency/affinity for the GIP receptor similar to native GIP
- Potency/affinity for the GLP-1 receptor is slightly weaker compared with native GLP-1





cAMP = cyclic adenosine monophosphate; TZP = tirzepatide.

Coskun T, et al. *Mol Metab.* 2018;18:3-14.

Can next generation incretin therapies combine GLP-1R and GIPR-mediated actions?

GLP-1 Receptor Agonism

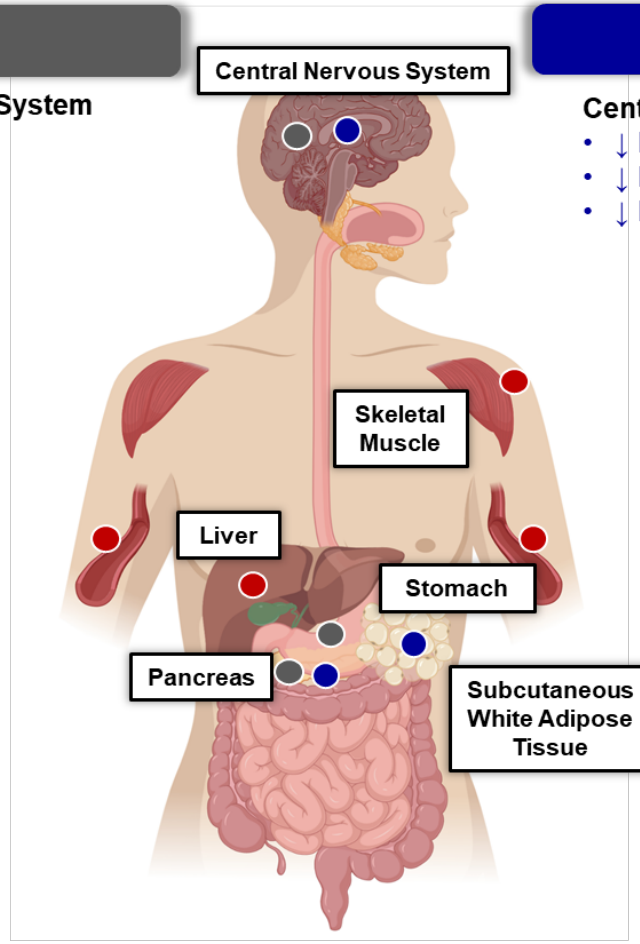
Central Nervous System
- ↑ Satiety
- ↓ Food Intake
- ↑ Nausea
- ↓ Body Weight

Pancreas
- ↑ Insulin
- ↓ Glucagon

Stomach
- ↓ Gastric Emptying

Systemic
- ↓ Hyperglycemia

Liver
- ↑ Insulin Sensitivity
- ↓ Hepatic Glucose Production
- ↓ Ectopic Lipid Accumulation



GIP Receptor Agonism

Central Nervous System
- ↓ Food intake
- ↓ Nausea
- ↓ Body weight

Pancreas
- ↑ Insulin
- ↑ Glucagon

Subcutaneous White Adipose Tissue
- ↑ Insulin Sensitivity
- ↑ Lipid Buffering Capacity
- ↑ Blood Flow
- ↑ Storage Capacity
- ↓ Proinflammatory Immune Cell Infiltration

Systemic
- ↓ Hyperglycemia, Dietary Triglyceride

Skeletal Muscle
- ↑ Insulin Sensitivity
- ↑ Metabolic Flexibility
- ↓ Ectopic Lipid Accumulation

GLP-1 Receptor Agonism
GIP Receptor Agonism
Indirect Action

Adapted from: Samms RJ, et al. *Trends Endocrinol Metab*. 2020;31(6):410-421

SURMOUNT: Tirzepatide in People With Obesity

- Phase 3 Global Clinical Trials Overview

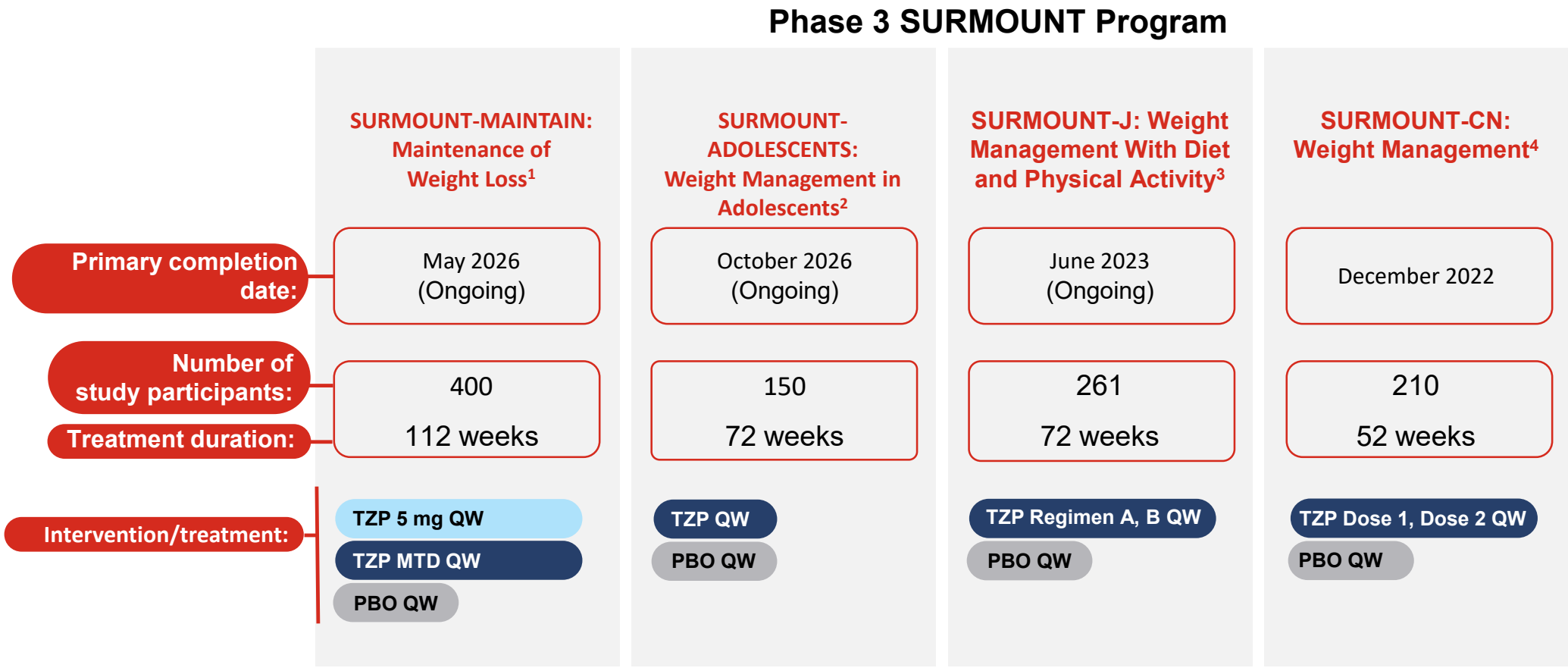
Phase 3 SURMOUNT Program

	SURMOUNT-1: Weight Management[1]	SURMOUNT-2: Weight Management in T2D[2]	SURMOUNT-3: Weight Management After Intensive Lifestyle Intervention[3]	SURMOUNT-4: Maintenance of Weight Loss[4]	SURMOUNT-5: Weight Management in Participants With Weight-Related Comorbidities[5]
Primary completion date:	April 2022	April 2023	May 2023	May 2023	November 2024 (Ongoing)
Number of study participants:	2539	938	806	783	700
Treatment duration:	72 weeks → Prediabetes Extension to 176 Weeks	72 weeks	72 weeks	88 weeks (36 weeks open-label treatment followed by 52 weeks double-blind treatment)	72 weeks
Intervention/treatment:	TZP 5, 10, 15 mg QW; PBO QW	TZP 10, 15 mg QW; PBO QW	TZP MTD (10 or 15 mg) QW; PBO QW	TZP MTD (10 or 15 mg) QW; PBO QW	TZP QW; SEMA QW

- Abbreviations and references are listed in speaker notes section below.

SURMOUNT: Tirzepatide in People With Obesity

- Phase 3 Global Clinical Trials Overview



- Abbreviations and references are listed in speaker notes section below.

SURMOUNT: Tirzepatide in People With Obesity

- Phase 3 Global Clinical Trials Overview

Phase 3 SURMOUNT Program

	SURMOUNT-1: Weight Management[1]	SURMOUNT-2: Weight Management in T2D[2]	SURMOUNT-3: Weight Management After Intensive Lifestyle Intervention[3]	SURMOUNT-4: Maintenance of Weight Loss[4]	SURMOUNT-5: Weight Management in Participants With Weight-Related Comorbidities[5]
Primary completion date:	April 2022	April 2023	May 2023	May 2023	November 2024 (Ongoing)
Number of study participants:	2539	938	806	783	700
Treatment duration:	72 weeks → Prediabetes Extension to 176 Weeks	72 weeks	72 weeks	88 weeks (36 weeks open-label treatment followed by 52 weeks double-blind treatment)	72 weeks
Intervention/treatment:	TZP 5, 10, 15 mg QW; PBO QW	TZP 10, 15 mg QW; PBO QW	TZP MTD (10 or 15 mg) QW; PBO QW	TZP MTD (10 or 15 mg) QW; PBO QW	TZP QW; SEMA QW

- Abbreviations and references are listed in speaker notes section below.

Tirzepatide in Obesity Management: Real-World Multicenter Study by the Italian Society of Obesity Campania Region

- The aim was to evaluate the short-term effects of tirzepatide 2.5 mg and 5.0 mg on weight changes and modifications in metabolic parameters in adults with obesity, in a real-world outpatient setting, and to assess its tolerability profile at these initial doses

Tirzepatide in Obesity Management: Real-World Multicenter Study by the Italian Society of Obesity Campania Region

- Methods: Retrospective, multicenter study included adults with obesity and without T2DM who were prescribed tirzepatide for weight management. Data were collected retrospectively from multiple outpatient clinics across Italy between January and June 2025.

Tirzepatide in Obesity Management: Real-World Multicenter Study by the Italian Society of Obesity Campania Region

- BMI
- WC
- Prediabetes
- Lipid profile
- AST, ALT
- Fasting plasma glucose, fasting insulin, HOMA – IR
- Side effects

Italian Society of Obesity – Campania Region Study Group

Luigi Barrea*, Ludovica Verde*, Martina Galasso*, Renato Patrone, Lucia Digitale, Alessandro Limardi, Marcello Orio, Ragozzino Giovanni, Luigi Digitale, Vittorio Salvatore, Antonella Savoia, Silvia Savastano, Annamaria Colao, Giovanna Muscogiuri

Changes in anthropometric and laboratory parameters from baseline to Tirzepatide 2.5 mg and 5.0 mg

Characteristic	Baseline	Tirzepatide 2.5 mg	p-value	Tirzepatide 5.0 mg	p-value	p-value*
Body weight – kg (N=70)	105.9 ± 23.6	100.9 ± 22.6	<0.001	92.6 ± 22.2	<0.001	<0.001
Mean BMI – kg/m² (N=70)	37.5 ± 6.8	35.7 ± 6.5	<0.001	32.7 ± 6.4	<0.001	<0.001
BMI category – no. (%)						
< 25.0 kg/m² (N=70)	0	0	-	6 (8.6)	χ^2=4.35, p=0.037	χ^2=4.35, p=0.037
≥ 25.0 to < 30.0 kg/m² (N=70)	8 (11.4)	13 (18.6)	χ^2=0.90, p=0.344	17 (24.3)	χ^2=3.12, p=0.075	χ^2=0.38, p=0.537
≥ 30.0 to < 35.0 kg/m² (N=70)	21 (30.0)	22 (31.4)	χ^2=0.00, p=1.00	26 (37.1)	χ^2=0.51, p=0.474	χ^2=0.53, p=0.045
≥ 35.0 to < 40.0 kg/m² (N=70)	20 (28.6)	18 (25.7)	χ^2=0.04, p=0.849	12 (17.1)	χ^2=1.99, p=0.159	χ^2=1.06, p=0.303
≥ 40.0 kg/m² (N=70)	21 (30.0)	17 (24.3)	χ^2=0.33, p=0.569	9 (12.9)	χ^2=5.13, p=0.024	χ^2=2.31, p=0.128
WC – cm (N=59)	117.8 ± 16.1	113.1 ± 16.7	<0.001	104.8 ± 15.7	<0.001	<0.001
Total cholesterol – mg/dl (N=34)	201.3 ± 40.7	189.2 ± 33.2	0.001	179.1 ± 28.3	<0.001	0.006
LDL cholesterol – mg/dl (N=32)	129.8 ± 31.0	115.3 ± 27.5	<0.001	102.6 ± 21.7	<0.001	0.001
HDL cholesterol – mg/dl (N=33)	47.4 ± 13.6	50.3 ± 13.4	0.001	52.2 ± 11.7	<0.001	0.032
Triglycerides – mg/dl (N=34)	153.4 ± 51.4	139.8 ± 40.9	0.002	124.4 ± 34.8	<0.001	<0.001
Prediabetes, yes – no. (%) (N=35)	17 (48.6)	11 (31.4)	<0.001	4 (11.4)	0.029	0.002
Fasting plasma glucose – mg/dl (N=36)	103.6 ± 14.1	95.6 ± 14.4	<0.001	90.2 ± 12.1	<0.001	<0.001
Fasting insulin – mIU/ml (N=34)	27.8 ± 11.8	20.8 ± 8.4	<0.001	15.7 ± 6.8	<0.001	<0.001
HOMA-IR (N=33)	7.3 ± 3.2	5.1 ± 2.1	<0.001	3.6 ± 1.6	<0.001	<0.001

p-values from paired t-test or chi-square test as appropriate

* comparing Tirzepatide 2.5 mg and Tirzepatide 5.0 mg

Percentage change in body weight after treatment with tirzepatide 2.5 mg and 5 mg

% change in body weight	Tirzepatide 2.5 mg (n=70)	Tirzepatide 5.0 mg (n=70)	p-value
Mean (%)	-4.7 ± 2.6	-12.7 ± 5.4	<0.001
< 5 no. (%)	43 (61.4)	2 (2.9)	χ^2=52.40, p<0.001
> 5 no. (%)	27 (28.6)	68 (97.1)	
> 10 no. (%)	3 (4.3)	48 (68.6)	χ^2=59.71, p<0.001
> 15 no. (%)	1 (1.4)	19 (27.2)	χ^2=16.86, p<0.001

p-values from paired t-test or chi-square test as appropriate between Tirzepatide 2.5 mg and Tirzepatide 5.0 mg

Changes in laboratory parameters from baseline to Tirzepatide 2.5 mg and 5.0 mg

Characteristic	Baseline	Tirzepatide 2.5 mg	p-value	Tirzepatide 5.0 mg	p-value	p-value*
Amylase – U/L (N=44)	52.0 ± 15.8	55.0 ± 16.7	0.112	56.5 ± 18.7	0.016	0.717
Lipase – U/L (N=43)	36.3 ± 13.9	38.5 ± 17.5	0.081	40.3 ± 17.4	0.064	0.382
AST– U/L (N=48)	34.6 ± 11.5	31.1 ± 10.1	0.012	28.9 ± 9.5	<0.001	0.006
ALT – U/L (N=44)	41.6 ± 15.7	36.0 ± 12.5	0.055	32.1 ± 10.3	<0.001	0.007
Estimated GFR – ml/min/1.73 m^2 (N=27)	83.2 ± 13.2	84.6 ± 12.0	0.025	85.6 ± 11.6	0.005	0.064

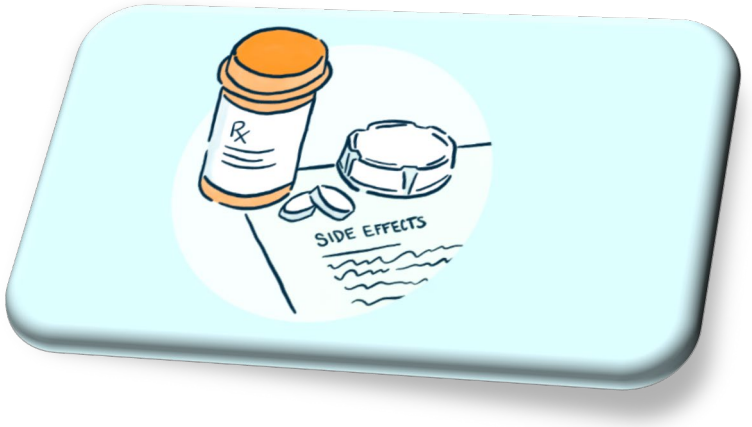
p-values from paired t-test

* comparing Tirzepatide 2.5 mg and Tirzepatide 5.0 mg

Gastrointestinal side effects in participants treated with Tirzepatide 2.5 mg and 5 mg

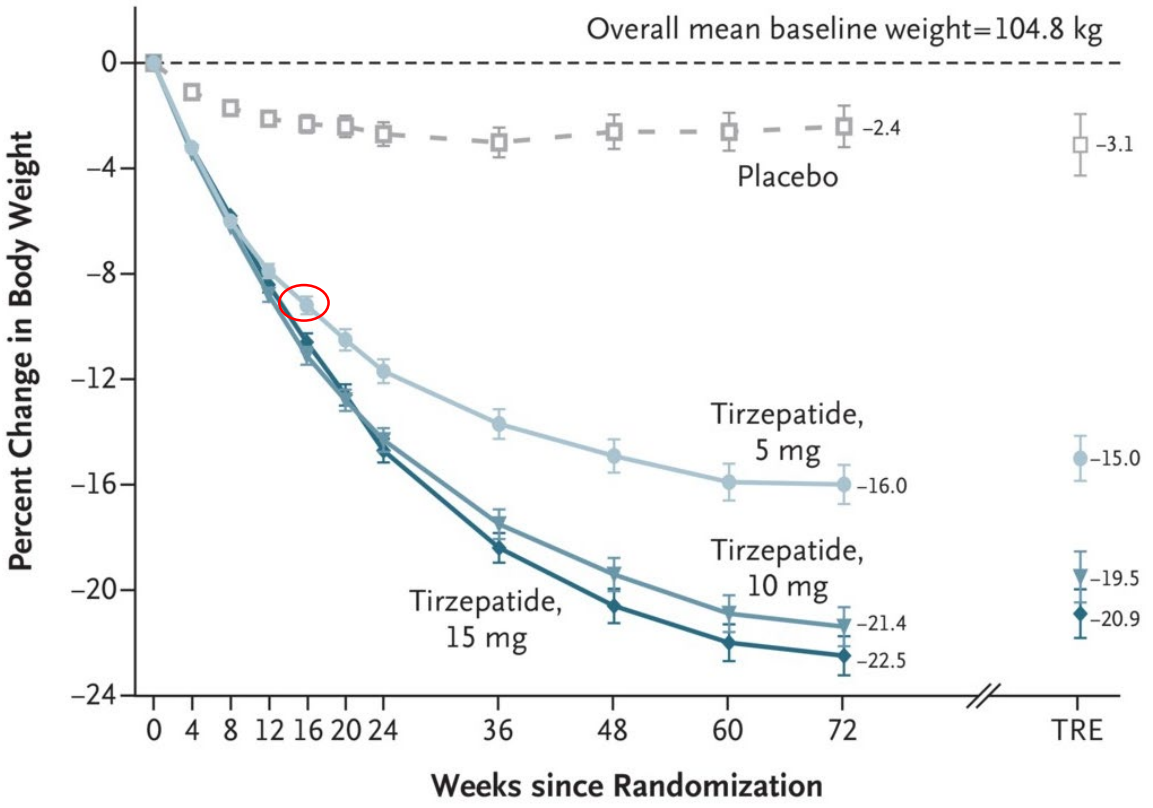
Gastrointestinal side effects	Tirzepatide 2.5 mg (N=70)	Tirzepatide 5.0 mg (N=70)	p-value
Diarrhea yes – no. (%)	5 (7.1)	6 (8.6)	χ^2=0.00, p=1.000
Constipation yes – no. (%)	19 (27.1)	17 (24.3)	χ^2=0.04, p=0.847
Nausea yes – no. (%)	14 (20.0)	9 (12.9)	χ^2=0.83, p=0.362
Abdominal colic yes – no. (%)	2 (2.9)	2 (2.9)	χ^2=0.00, p=1.000

p-values from chi-square test between Tirzepatide 2.5 mg and Tirzepatide 5.0 mg



From Trials to Real Life

End Points	Tirzepatide, 5 mg (N=630) SURMOUNT-1 72w	Tirzepatide, 5 mg (N=630) REAL WORLD 17w
Percentage change in body weight	- 15.0 (-15.9 to – 14.2)	- 11.03
Weight reduction of 5% or more at week 72- percentage of partecipants	85.1 (81.6 to 88.6)	97.1
Weight reduction of 10% or more at week 72- percentage of partecipants	68.5 (64.5 to 72.5)	68.6
Weight reduction of 15% or more at week 72- percentage of partecipants	48.0 (43.9 to 52.1)	27.2
Change in waist circumference - cm	- 14.0 (-14.9 to -13.1)	- 13.0



- I dati del nostro studio real-time sono in linea con I dati riportati nel trial Surmount 1;

- I miglioramenti dei parametri antropometrici e cardiometabolici si verificano già dopo le prime settimane di trattamento ;

- Tirzepatide si conferma un farmaco efficace e sicuro per il trattamento dell'obesità


Grazie