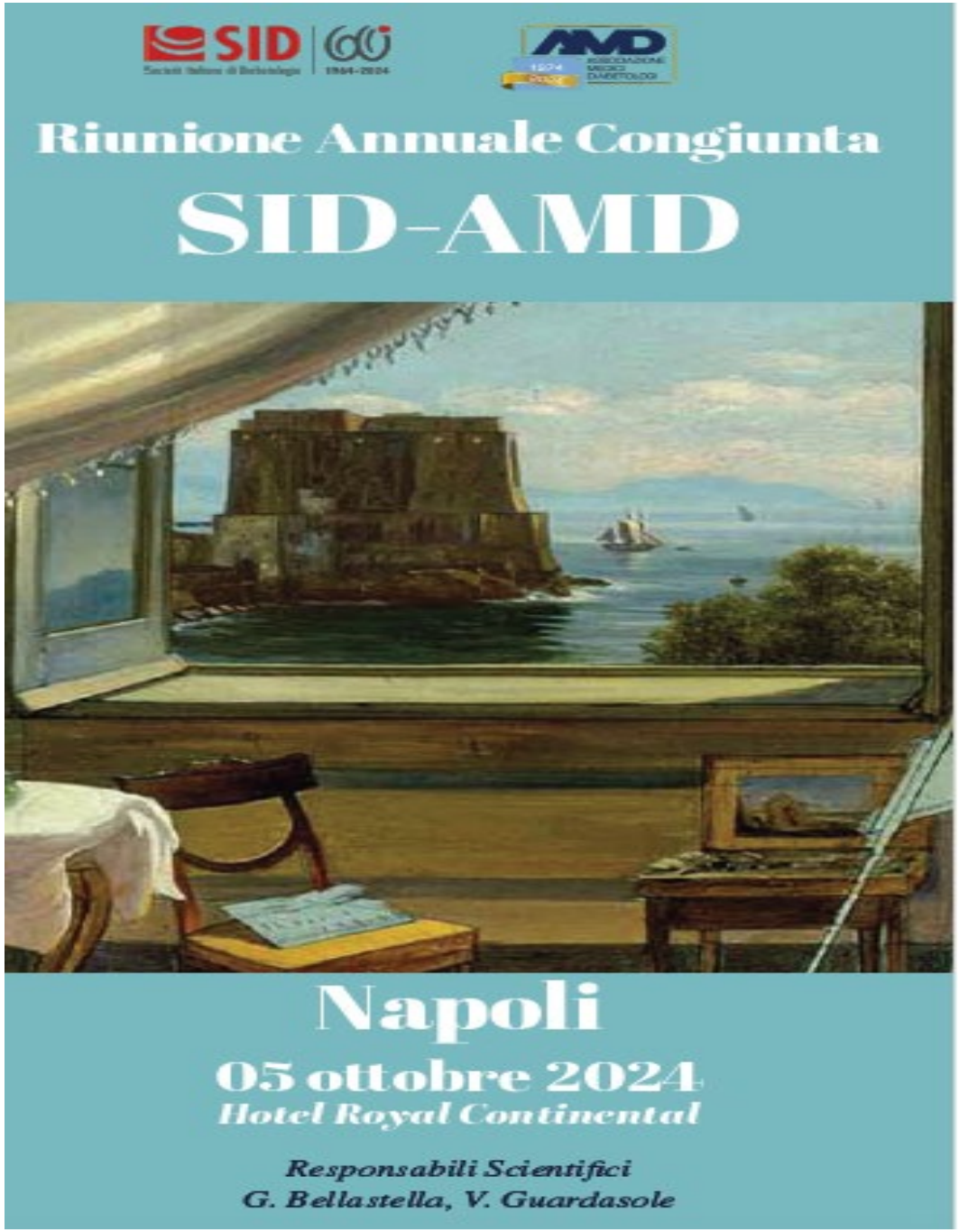
AGONISTI E COAGONISTI

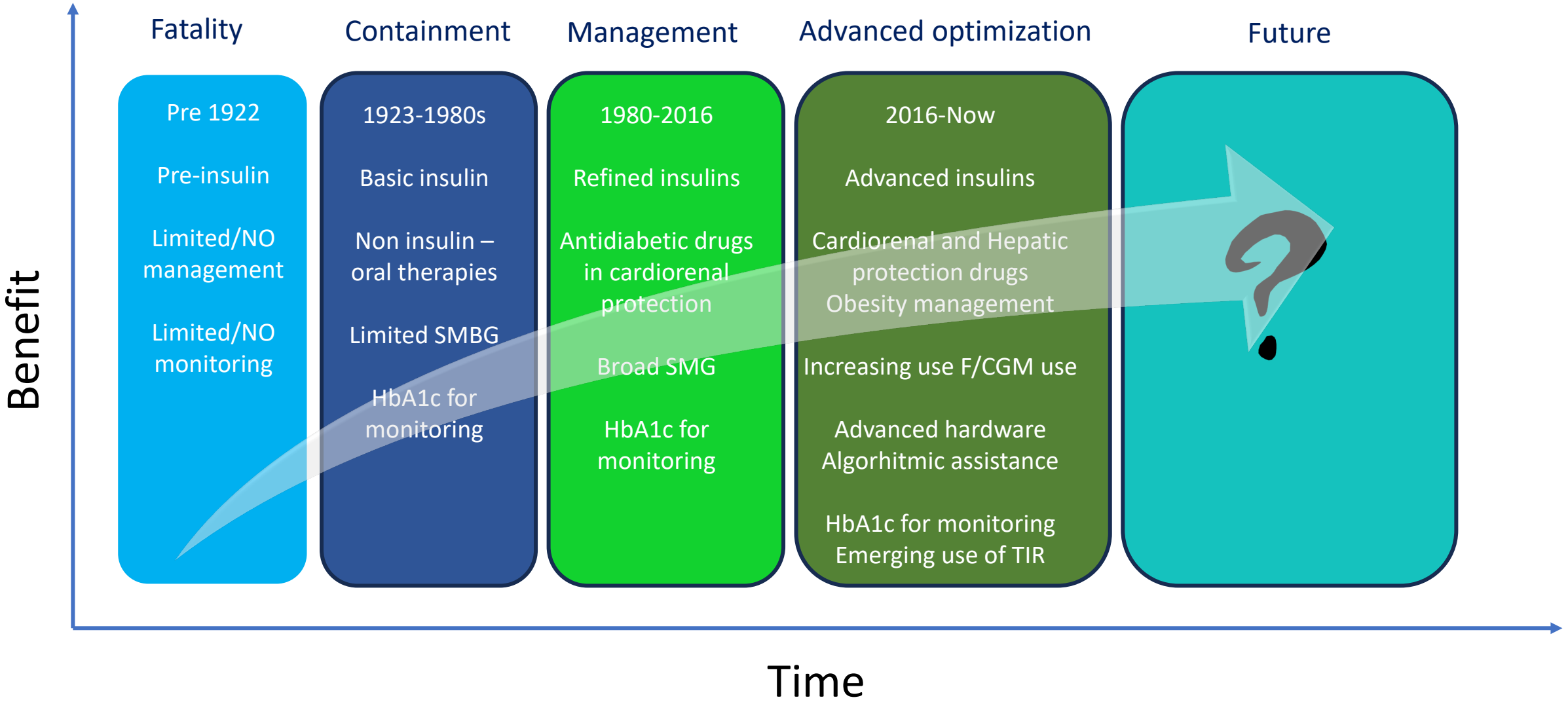
Giuseppe Memoli
CAD San Luca
Ariano Irpino (AV)



AGONISTI, COAGONISTI, ANTAGONISTI, PROTAGONISTI DI NUOVA ERA IN DIABETOLOGIA

Giuseppe Memoli
CAD San Luca
Ariano Irpino (AV)

ERAS OF DIABETES



TREAT TO TARGET

TREAT TO SATISFACTION

TREAT TO BENEFIT

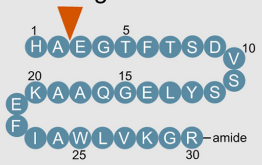
TREAT TO PREVENT

TREAT TO REMISSION

GLP-1Ras

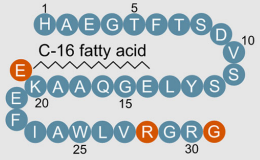
Native GLP-1 (7-36) amide

DPP-IV recognition site

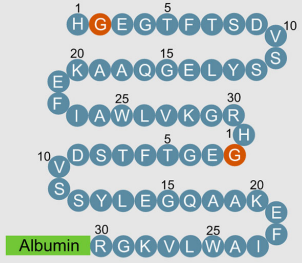


Exenatide

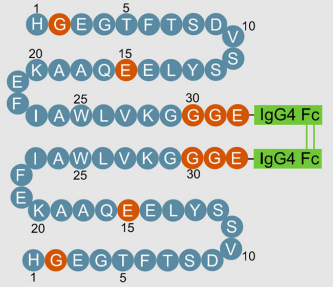
Liraglutide



Albiglutide

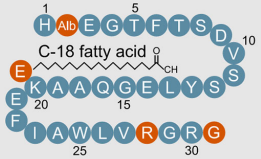


Dulaglutide

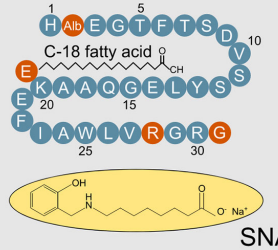


Lixisenatide

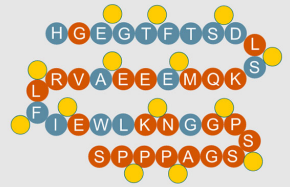
Semaglutide



Oral semaglutide

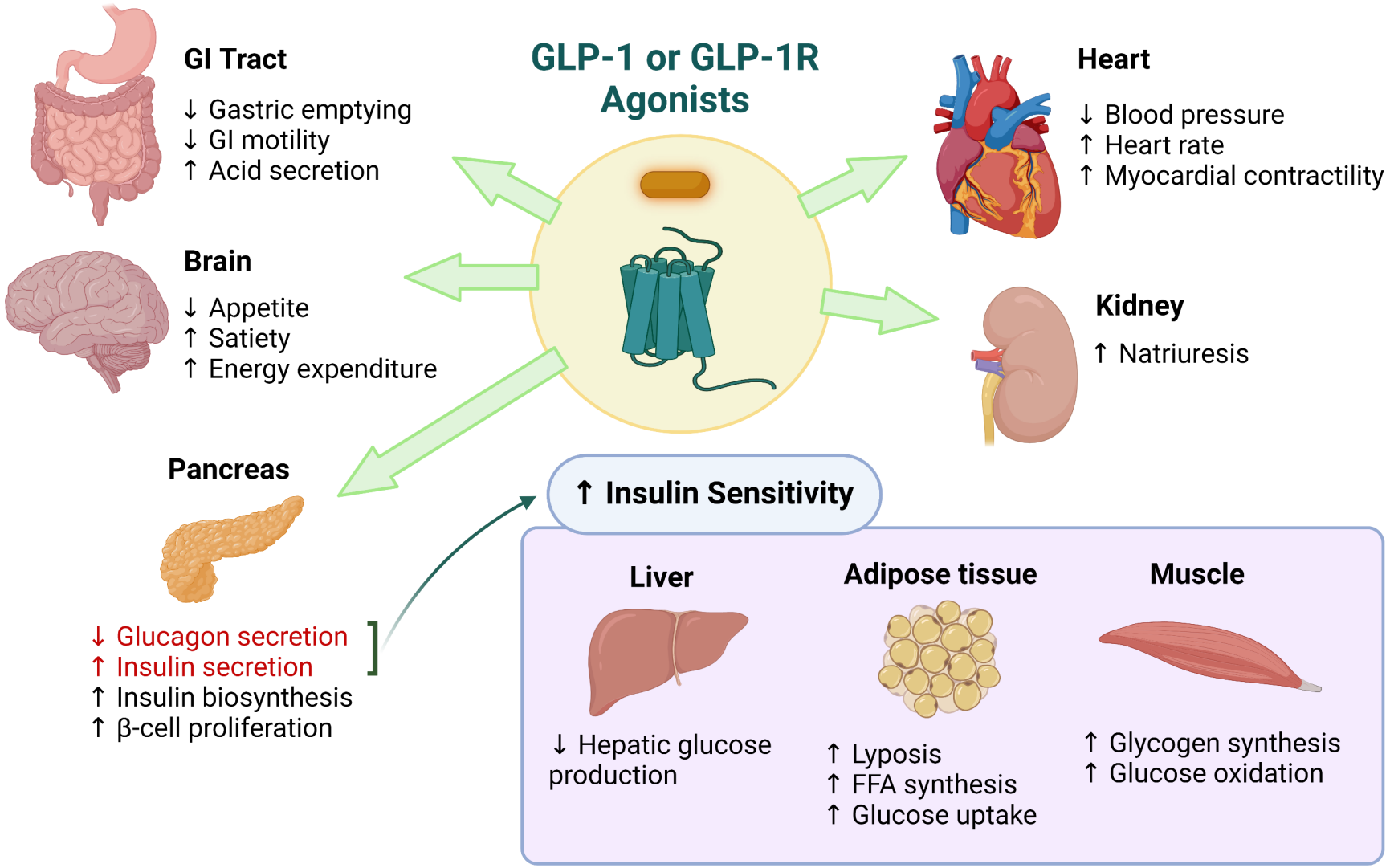


Extended-release formulation of exenatide



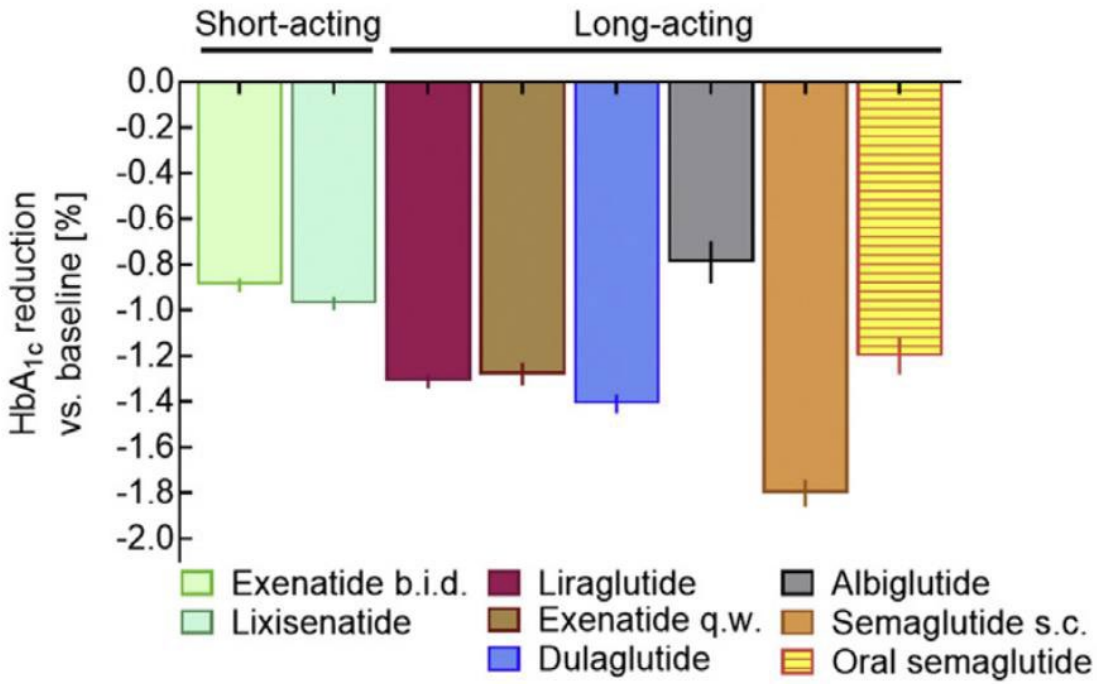
poly(D,L-lactide-co-glycolide) polymer

Pleiotropic effects of GLP-1 RAS

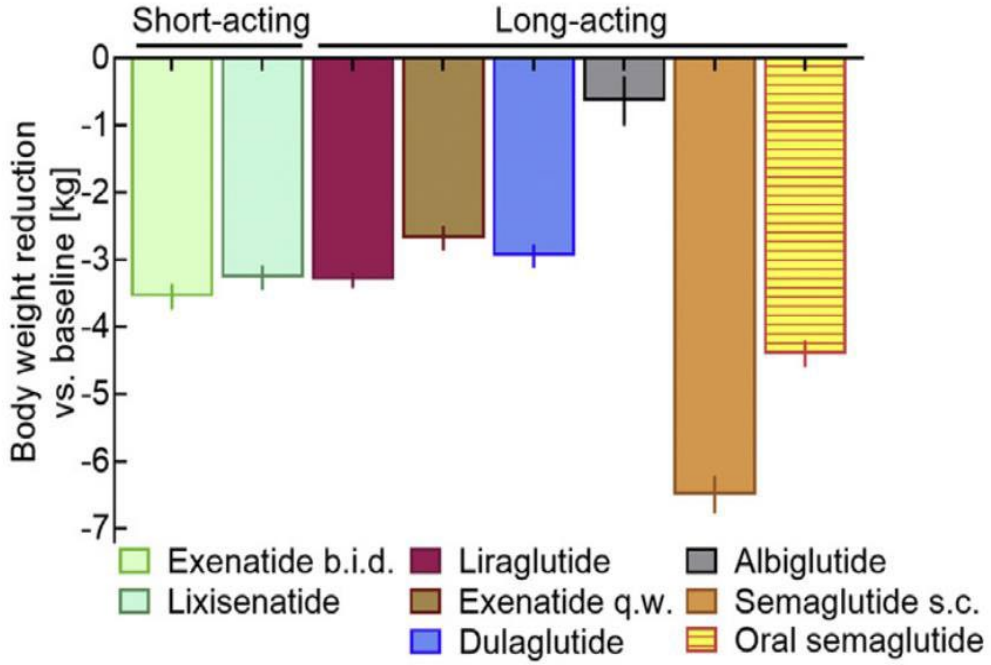


GLP-1Ras EFFICACY

⊗HbA1c vs Baseline (%)

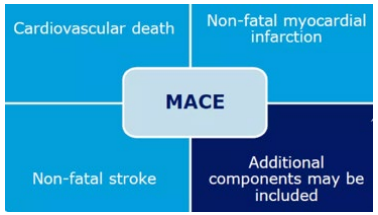


⊗BodyWeight vs Baseline (kg)

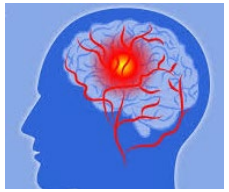


Nauck MA et al, Mol Met 2021

GLP-1RA MIGLIORANO GLI ESITI NELLE PERSONE CON DM TIPO 2



-14% RRR



Fatal non fatal stroke

-17% RRR

Fatal non fatal MI

-10% RRR

All-cause mortality

-12% RRR

GLP1 AGONISTS

Cardiovascular death

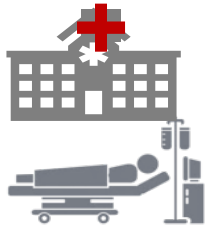
-13% RRR

Kidney outocomes + macroalbuminuria

-21% RRR

Worsening Kidney function

-14% RRR



Hospitalisation for heart failure

-11% RRR

Sattar N et al ***Lancet Diabetes Endocrinol*** 2021; 9:653-662

FLOW

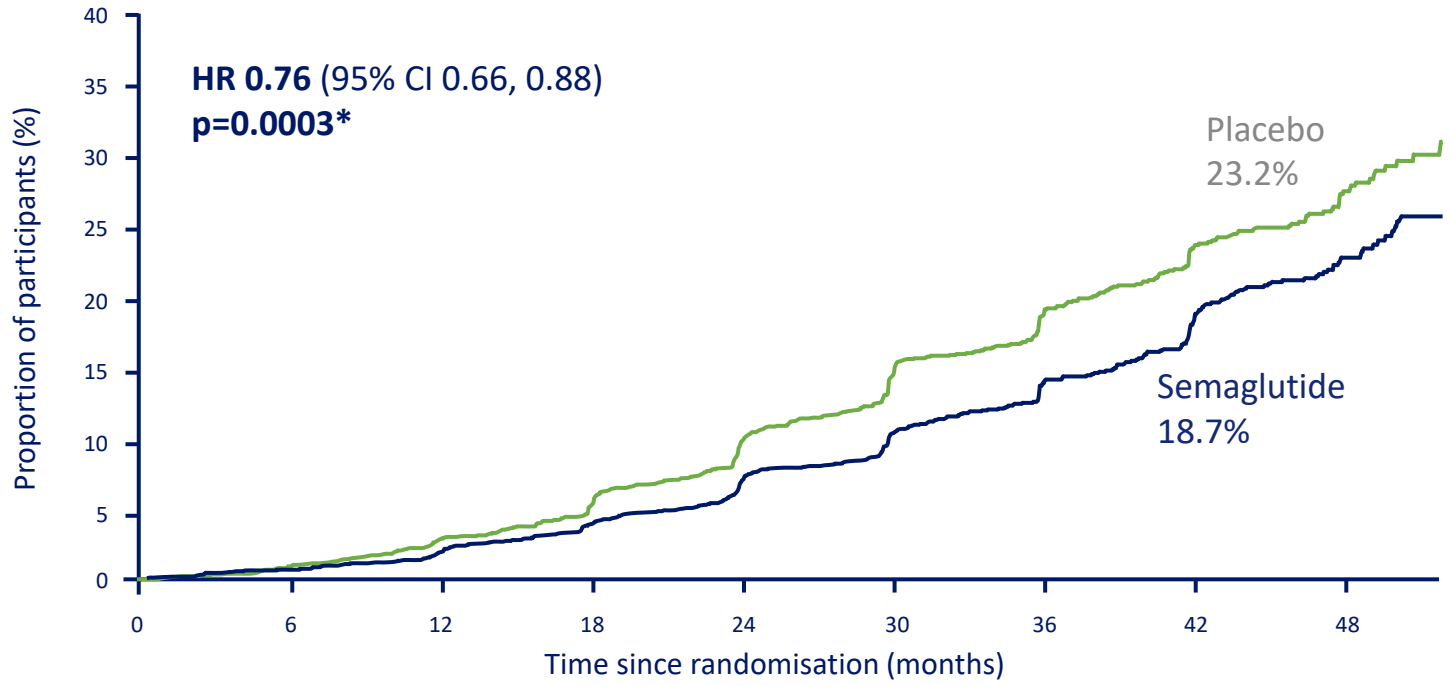
Semaglutide demonstrated a 24% risk reduction of a composite outcome, incl. kidney disease progression, CV and kidney death in people with CKD and T2D

Primary kidney endpoint

Time to first occurrence of a composite endpoint consisting of:

- Onset of persistent ≥50% reduction in eGFR compared with baseline
- Onset of persistent eGFR <15 mL/min/1.73 m^2
- Initiation of chronic renal replacement therapy (dialysis or kidney transplantation)
- Renal death
- CV death

First composite kidney event: Primary outcome



Semaglutide	1,767	1,738	1,693	1,640	1,572	1,489	1,131	742	392
Placebo	1,766	1,736	1,682	1,605	1,516	1,408	1,048	660	354

*Full analysis set. Data from the in-trial period. * Superiority if p value <0.0322*
Numbers shown in the lower panels represent the number of participants at risk. CI, confidence interval; CV, cardiovascular; eGFR, estimated glomerular filtration rate; HR, hazard ratio. Perkovic V, et al. N Engl J Med. 2024: DOI: 10.1056/NEJMoa2403347

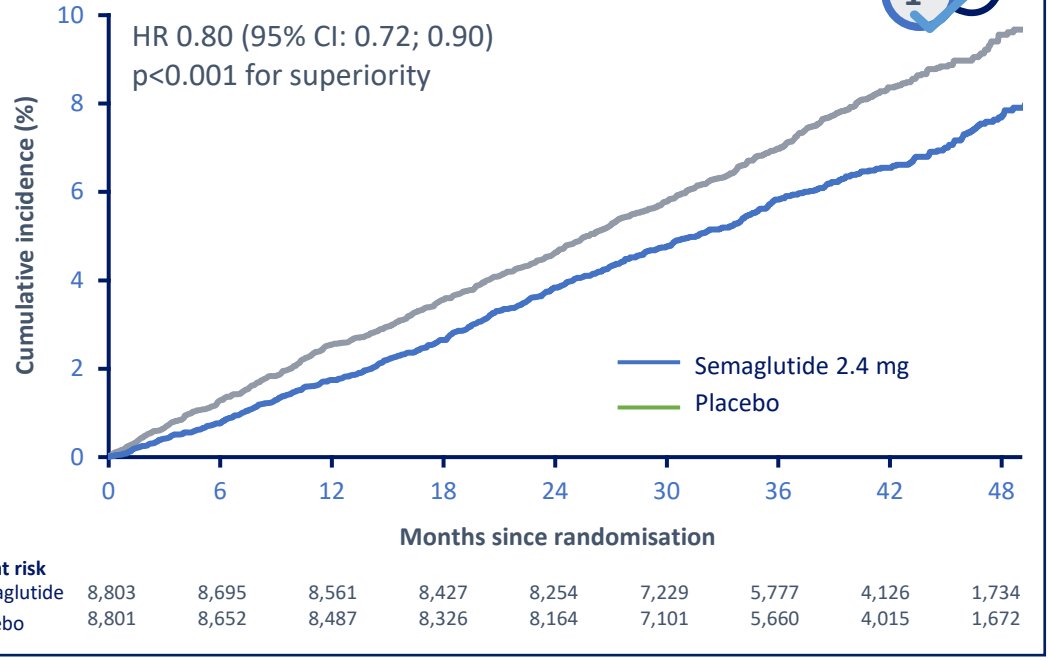
FLOW semaglutide | renal outcomes trial

SELECT: Key trial results

Lincoff AM et al. N Engl J Med 2023;DOI:10.1056/NEJMoa2307563

Primary endpoint

Semaglutide 2.4 mg **reduced the risk of MACE by 20%** vs placebo[1]



Confirmatory secondary endpoints

HRs (95% CI) for the confirmatory secondary endpoints were[1]:

- Death from CV causes: 0.85 (0.71; 1.01); p=0.07*
- HF composite†: 0.82 (0.71; 0.96)
- Death from any cause: 0.81 (0.71; 0.93)

Safety and tolerability

The safety and tolerability profile of semaglutide 2.4 mg in people with established CVD and overweight or obesity was consistent with previous semaglutide 2.4 mg trials[1]

**p-value did not meet statistical significance required for hierarchical testing and so superiority testing was not performed for the remaining confirmatory secondary endpoints. †HF hospitalisation, urgent HF visit or CV-related death.*

CI, confidence interval; CV, cardiovascular; CVD, cardiovascular disease; GI, gastrointestinal; HF, heart failure; HR, hazard ratio; MACE, major adverse cardiovascular event.

GLP-1RA: not only glycemic control…

Review > J Clin Endocrinol Metab. 2020 Aug 1;105(8):e2695-e2709. doi: 10.1210/clinem/dgaa285.

Obesity, Polycystic Ovary Syndrome, and Infertility: A New Avenue for GLP-1 Receptor Agonists

Hellas Cena [1 2], Luca Chiovato [3 4], Rossella E Nappi [5 6]

> Andrology. 2024 Mar;12(3):633-642. doi: 10.1111/andr.13519. Epub 2023 Aug 24.

Long-acting glucagon-like peptide 1 receptor agonists boost erectile function in men with type 2 diabetes mellitus complaining of erectile dysfunction: A retrospective cohort study

Giuseppe Lisco [1], Nicola Bartolomeo [1], Anna De Tullio [1], Giovanni De Pergola [2], Edoardo Guastamacchia [1], Emilio Jirillo [3], Giuseppina Piazzolla [1], Vincenzo Triggiani [1], Vito Angelo Giagulli [1 4]

Review > Drug Des Devel Ther. 2022 Mar 14:16:665-684. doi: 10.2147/DDDT.S348055. eCollection 2022.

The Role of Glucagon-Like Peptide-1 Receptor Agonists (GLP-1 RA) in Diabetes-Related Neurodegenerative Diseases

Dihe Cheng [1], Shuo Yang [1], Xue Zhao [1], Guixia Wang [1]

Review > Pharmacy (Basel). 2024 Jan 8;12(1):11. doi: 10.3390/pharmacy12010011.

The Impact of Glucagon-like Peptide 1 Receptor Agonists on Obstructive Sleep Apnoea: A Scoping Review

Khang Duy Ricky Le [1 2 3 4], Kelvin Le [5], Felicia Foo [6]

> Endocr Rev. 2023 Jan 12;44(1):14-32. doi: 10.1210/endrev/bnac018.

Glucagon-like Peptide-1 Receptor-based Therapeutics for Metabolic Liver Disease

Julian M Yabut [1], Daniel J Drucker [1]

Review > Front Endocrinol (Lausanne). 2022 Nov 17:13:1033479. doi: 10.3389/fendo.2022.1033479. eCollection 2022.

The mechanism and efficacy of GLP-1 receptor agonists in the treatment of Alzheimer's disease

Haiyang Du [1], Xiaoyu Meng [2 3], Yu Yao [1], Jun Xu [1]

> JCI Insight. 2023 Jun 22;8(12):e170671. doi: 10.1172/jci.insight.170671.

The glucagon-like peptide-1 (GLP-1) analogue semaglutide reduces alcohol drinking and modulates central GABA neurotransmission

Vicky Chuong [1 2], Mehdi Farokhnia [1], Sophia Khom [3 4], Claire L Pince [1 2], Sophie K Elvig [2], Roman Vlkolinsky [3], Renata Cn Marchette [2], George F Koob [2], Marisa Roberto [3], Leandro F Vendruscolo [5], Lorenzo Leggio [1]

Review > J Dermatolog Treat. 2022 May;33(3):1299-1305. doi: 10.1080/09546634.2021.1882658. Epub 2021 May 3.

Efficacy of GLP-1rA, liraglutide, in plaque psoriasis treatment with type 2 diabetes: a systematic review and meta-analysis of prospective cohort and before-after studies

Guizhen Chang [1], Baojiang Chen [1], Litao Zhang [2]

> Mech Ageing Dev. 2023 Dec 29:111898. doi: 10.1016/j.mad.2023.111898. Online ahead of print.

A feasibility study of the combination of intranasal insulin with oral semaglutide for cognition in older adults with metabolic syndrome at high dementia risk- Study rationale and design

Tal Davidy [1], Iscka Yore [2], Tali Cukierman-Yaffe [3], Ramit Ravona-Springer [4], Abigail Livny [5], Orit H Lesman-Segev [5], Yossi Azuri [6], Owen Carmichael [7], Dimitrios Kapogiannis [8], Henrik Zetterberg [9], HungMo Lin [10], Mary Sano [11], Michal Schnaider Beeri [12]

News

GLP-1 shortages will not resolve this year, EMA warns, amid concern over off-label use

BMJ 2024 ; 385 doi: https://doi.org/10.1136/bmj.q1448 (Published 28 June 2024)

quotidianosanità.it Scienza e Farmaci Quotidiano on line di informazione sanitaria Venerdì 27 SETTEMBRE 2024 QS

Farmaci. Ema lancia raccomandazioni per affrontare la carenza di agonisti dei recettori GLP-1: "Uso estetico sta mettendo a rischio forniture"

Prescrivere un GLP-1 RA oggi fra carenze, linee-guida e necessità dei pazienti… ovvero fare di necessità virtù

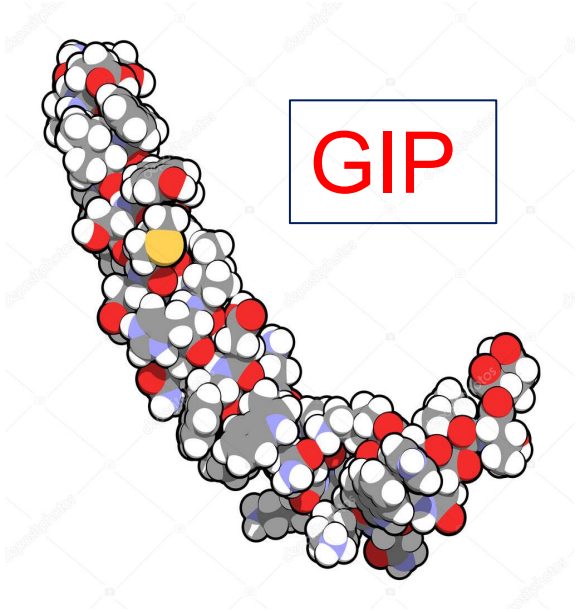
A cura di Fabrizio Diacono

27 marzo 2023 (Gruppo ComunicAzione) – Fra crisi economiche e geopolitiche, in questi anni il sistema produttivo industriale in generale ha raggiunto una soglia critica per cui l'offerta non riesce sempre a soddisfare la domanda. Realtà ormai vera anche per il settore salute, ove la carenza di taluni farmaci – ad esempio, i GLP-1 RA – impone comunque al diabetologo il rispetto ma anche all'obbligo di riuscire a trovare sempre le strategie terapeutiche migliori per garantire ai propri pazienti una corretta prospettiva di cura.

CORRIERE Salute

Semaglutide, allerta dell'Oms per tre lotti contraffatti venduti in Brasile, Regno Unito e Stati Uniti

EMERGING ROLE OF GIP IN GLUCOSE HOMEOSTASIS: BEYOND GLP-1 IN DIABETES AND METABOLIC DISORDERS



Review > Trends Endocrinol Metab. 2020 Jun;31(6):410-421. doi: 10.1016/j.tem.2020.02.006. Epub 2020 Mar 16.

How May GIP Enhance the Therapeutic Efficacy of GLP-1?

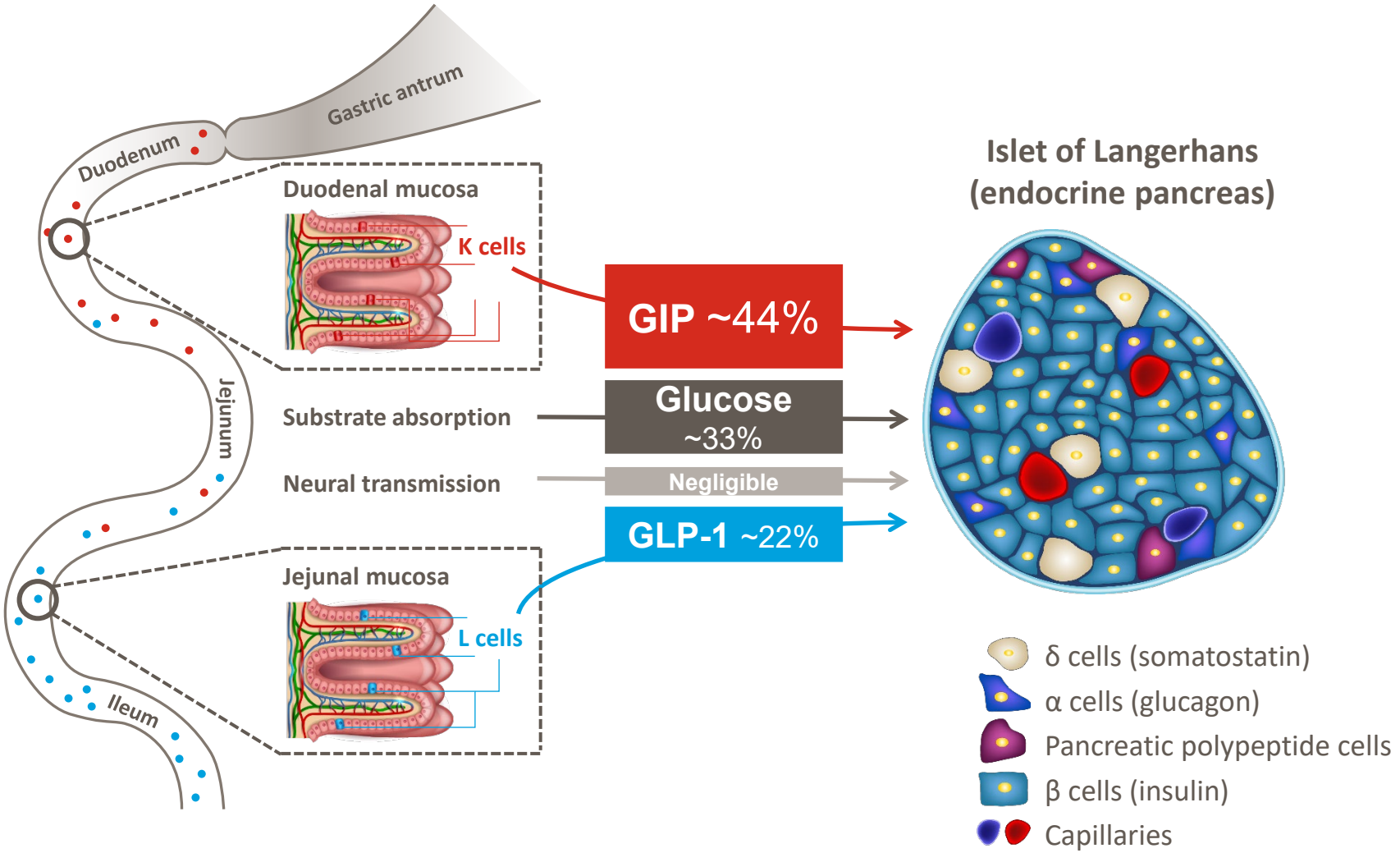
Ricardo J Samms [1], Matthew P Coghlan [1], Kyle W Sloop [2]

Comment > Diabetes. 2019 May;68(5):897-900. doi: 10.2337/dbi19-0005.

GIP and GLP-1: Stepsiblings Rather Than Monozygotic Twins Within the Incretin Family

Michael A Nauck [1], Juris J Meier [2]

IN HEALTHY SUBJECTS, GIP ACCOUNTS FOR THE MAJORITY OF INSULIN SECRETION



Nauck MA and Meier JJ -Diabetes 2019; 68:897-90

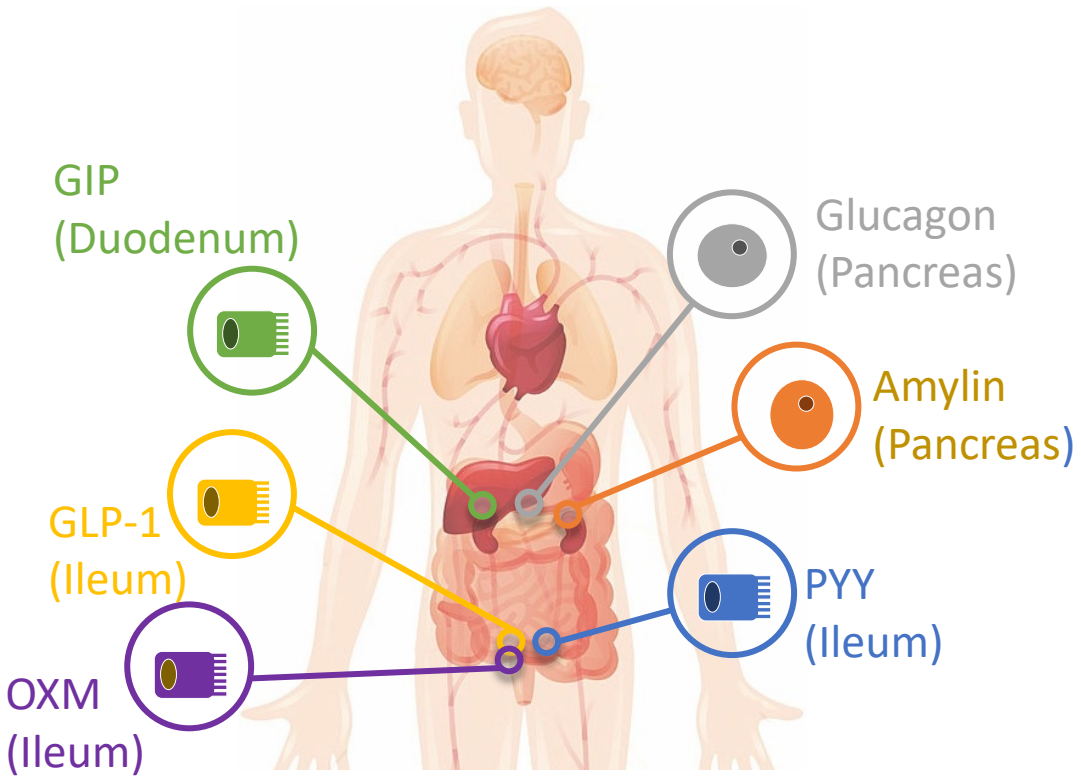
Secretion and Main Actions of Gut Hormones

GIP

- ↓ appetite ↓ nausea
- ↑ insulin ↑ glucagon
- ↓ gastric acid secretion
- ↑ lipid deposition
  ↑ lipogenesis
- ↓ bone resorption

GLP-1

- ↓ appetite ↑ nausea
  ↓ food intake
- ↑ insulin ↓ glucagon
- ↓ gastric emptying
- ↑ lipolysis
- ↑ cardioprotection
  ↓ heart rate



OXM

- ↓ appetite ↑ nausea
  ↓ food intake
- ↑ insulin
- ↓ gastric emptying
- ↑ energy expenditure

PYY

- ↓ appetite ↑ nausea
  ↓ food intake
- ↓ gastric emptying
- ↑ energy expenditure

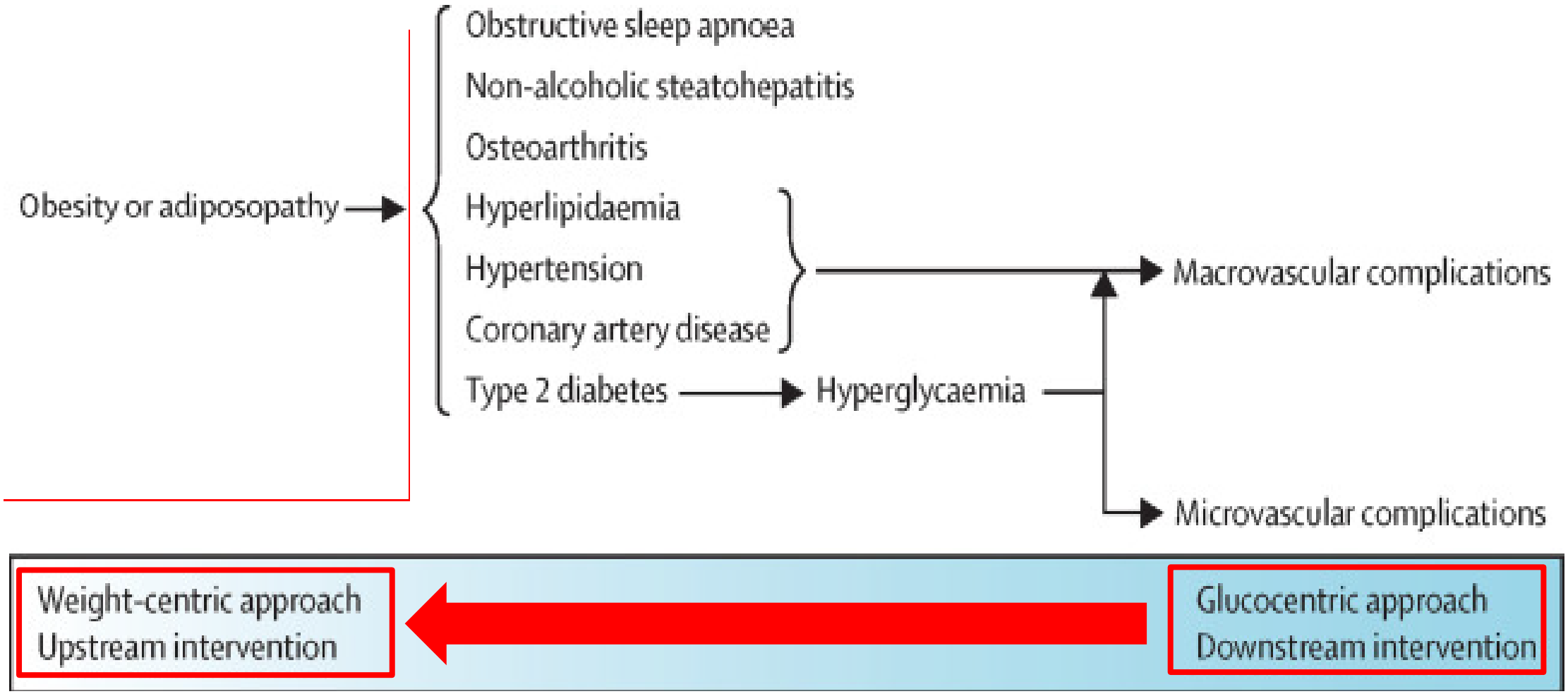
Glucagon

- ↓ appetite ↑ nausea
  ↓ food intake
- ↑ insulin
- ↑ hepatic glucose production
  ↑ lipid oxidation
  ↓ hepatic lipid synthesis
- ↓ gastric emptying
- ↑ energy expenditure
- ↑ heart rate

Amylin

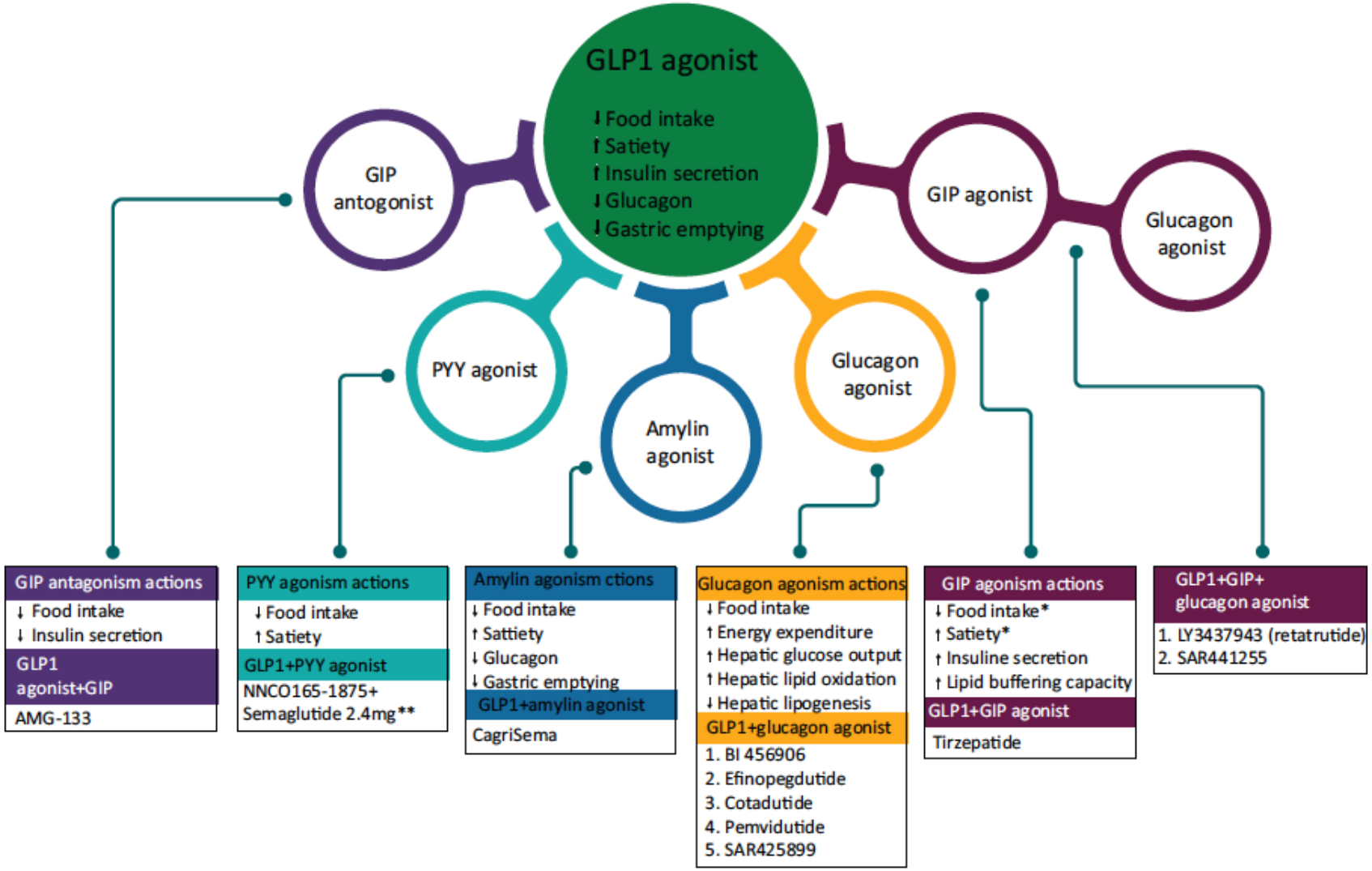
- ↓ appetite ↓ food intake
- ↓ glucagon
- ↑ energy expenditure
- ↓ gastric emptying
- ↓ osteoclast activity
  ↑ osteoblast activity

PARADIGM SHIFT FROM GLUCOCENTRIC TO WEIGHT APPROACH



Obesity management as a primary treatment goal for type 2 diabetes: time to reframe the conversation
LINGVAY L LANCET 2021

FUTURE THERAPIES FOR OBESITY



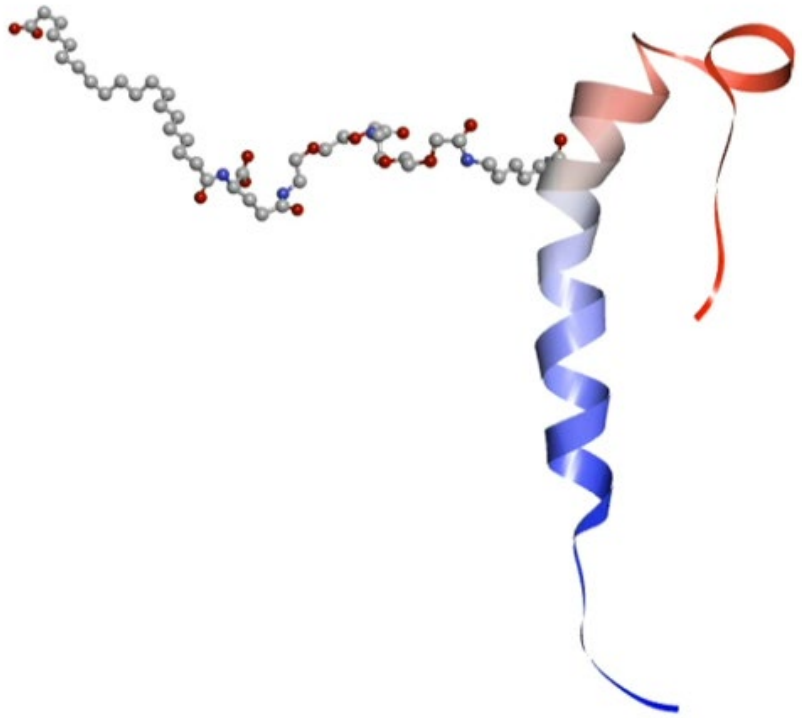
Eka Melson,A Alexander Dimitri MirasB and Dimitris Papamargaritis CClinical Medicine 2023 Vol 23, No 4: 337–46

MOLECOLE AD AZIONE MULTITARGET: DOPPIO, TRIPLO…

	GLP1-RA	GIP-RA	GIP-RA antagonism	GLUCAGONE RA	OSSINTOMODULINA	AMILINA	PYY AGONISM
TIRZEPATIDE	✓	✓					
AMG 133	✓		✓				
SERVODUTIDE-EFINOPEGDUTIDE - PEMVIDUTIDE	✓			✓			
MAZTUDITE - PEGAPAMODUTIDE	✓			✓	✓		
CAGRISEMA	✓					✓	
NNC0165-1875	✓						✓
RETATRUDITE	✓	✓		✓			

Tirzepatide is a unimolecular dual GIPR / GLP-1R agonist

- Tirzepatide is a multi-functional peptide based on the native GIP peptide sequence, modified to bind to both GIPR and GLP-1R
- Tirzepatide is a 39 amino acid linear peptide and includes a C20 fatty diacid moiety
- Tirzepatide has a mean half-life of approximately 5 days (116.7 hours), enabling once-weekly dosing



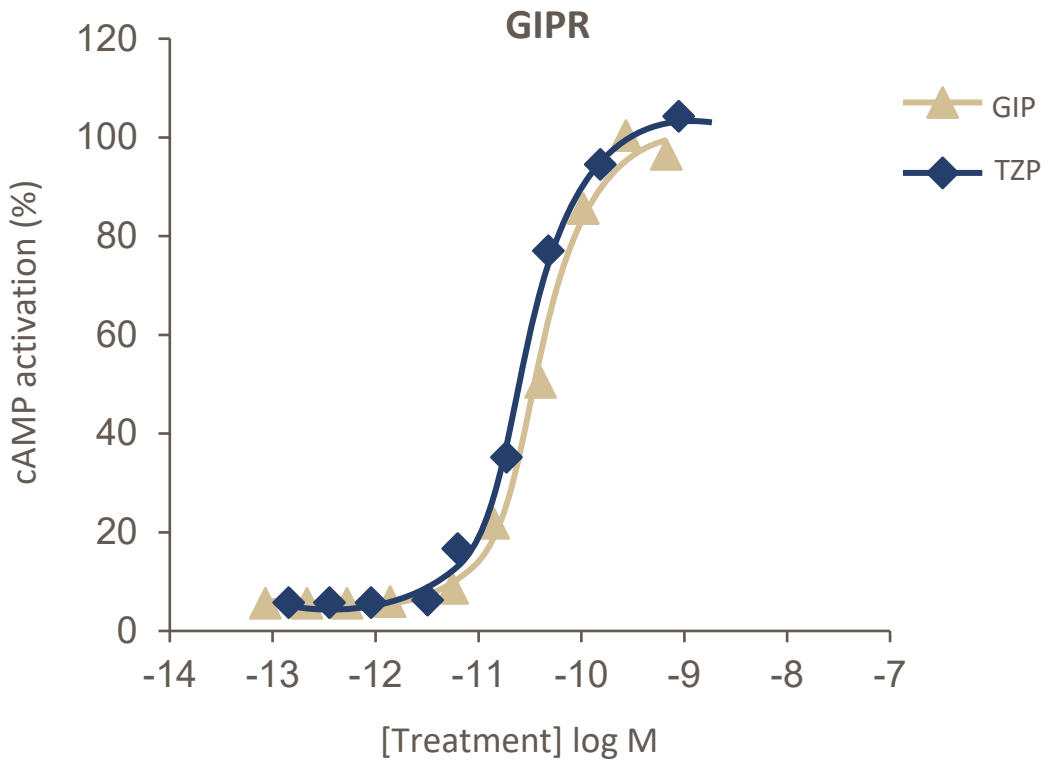
Tirzepatide is not the sum of GIP and GLP-1. It is a single molecule

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

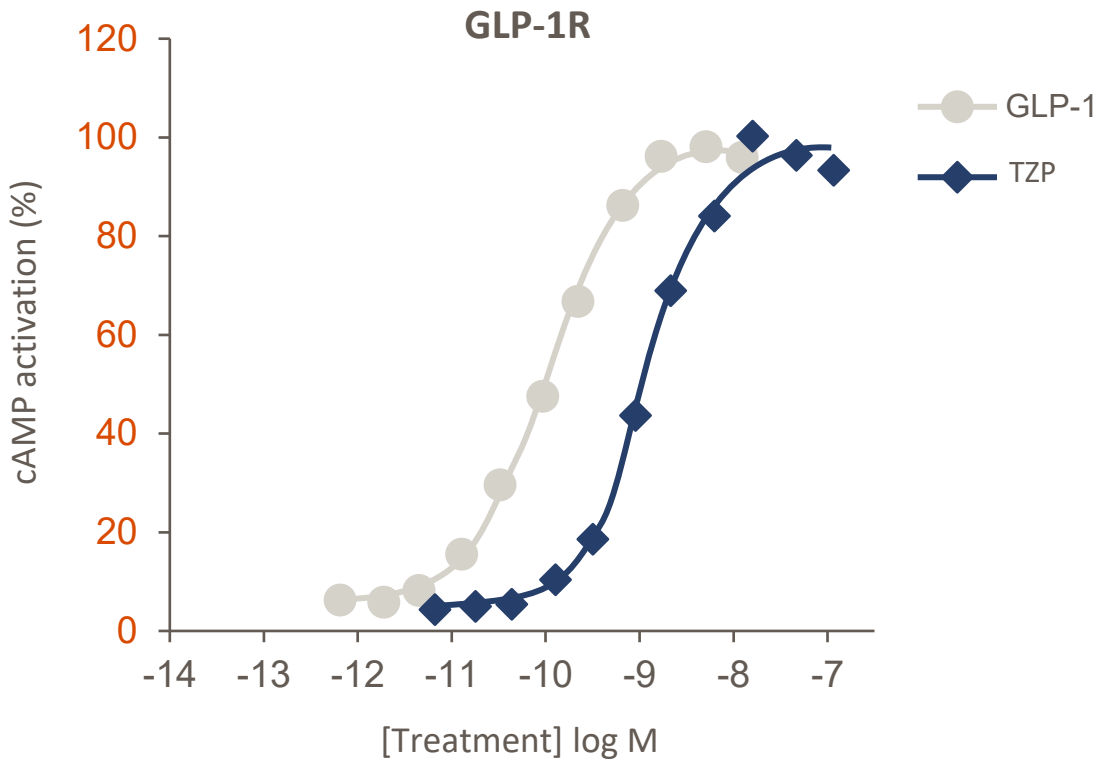
Coskun T, et al. *Mol Metab*. 2018;18:3-14.

Tirzepatide is a potent activator of both GIP and GLP-1 receptors

In vitro, tirzepatide has a potency for the GIPR similar to native GIP.*



Potency for the GLP-1R is weaker than native GLP-1.*



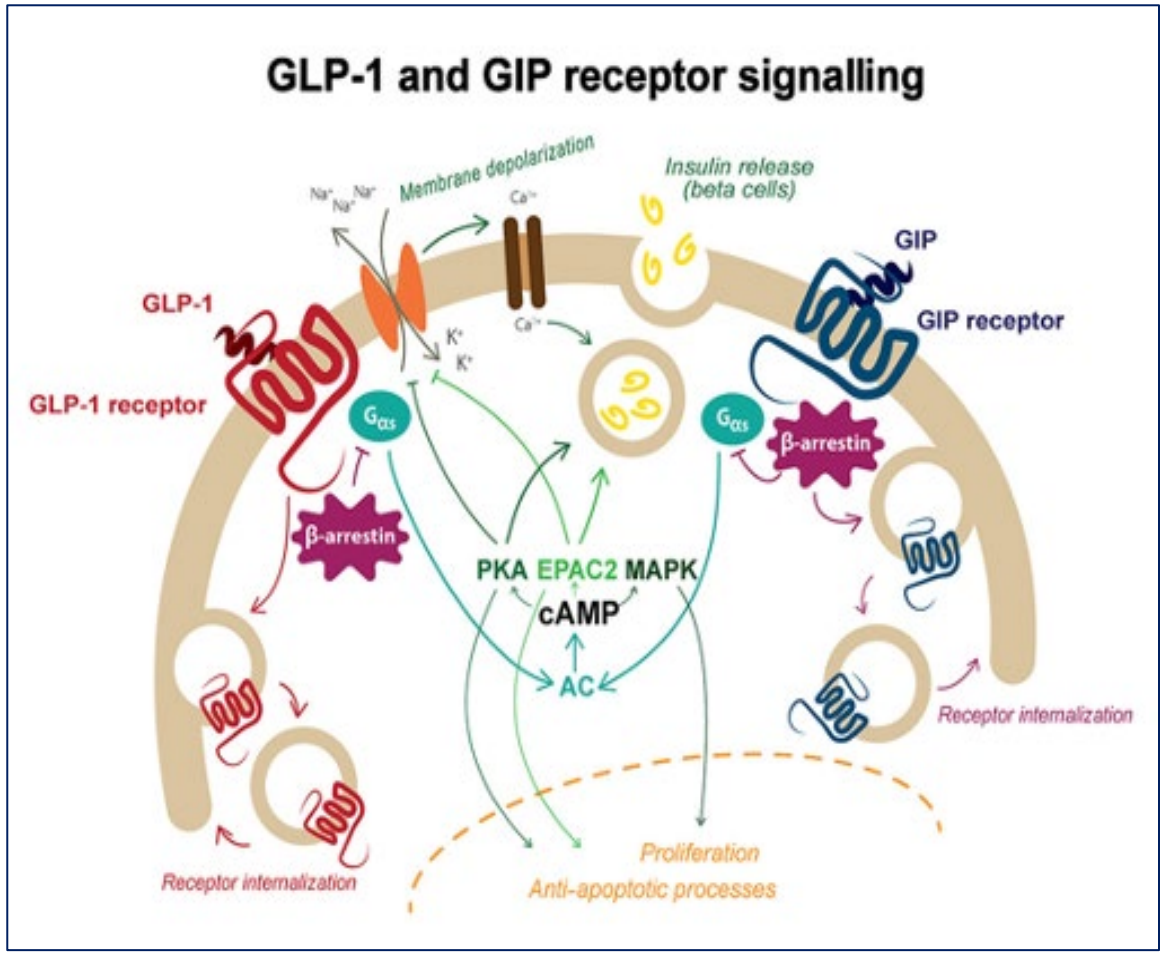
*In overexpressed HEK cells.
cAMP = cyclic adenosine monophosphate; GIP = glucose-dependent insulinotropic polypeptide; GIPR = glucose-dependent insulinotropic polypeptide receptor; GLP-1 = glucagon-like peptide-1; GLP-1R = glucagon-like peptide-1 receptor; HEK = human endometrial adenocarcinoma; TZP = tirzepatide.
Coskun T, et al. *Mol Metab*. 2018;18:3-14.

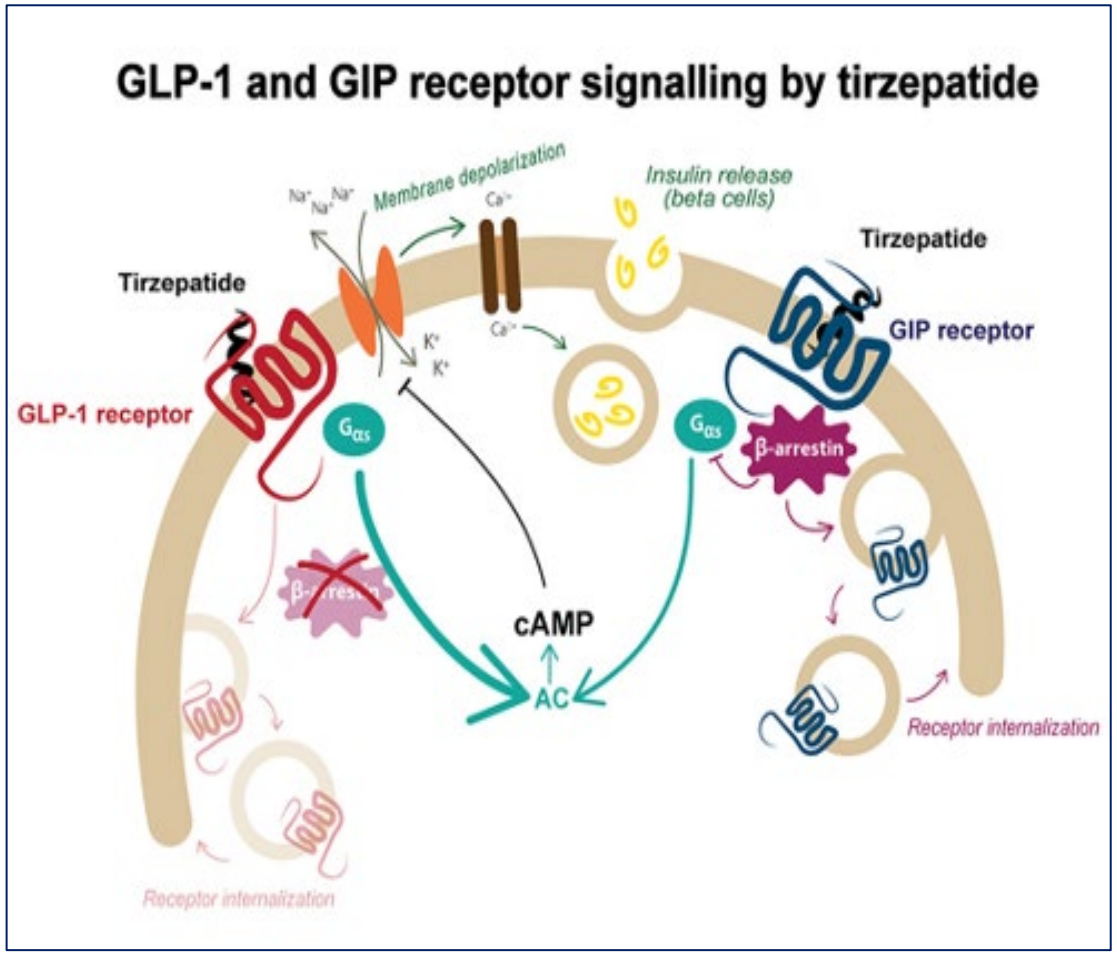
DIABETES, OBESITY AND METABOLISM
A JOURNAL OF PHARMACOLOGY AND THERAPEUTICS

The importance of glucose-dependent insulinotropic polypeptide receptor activation for the effects of tirzepatide

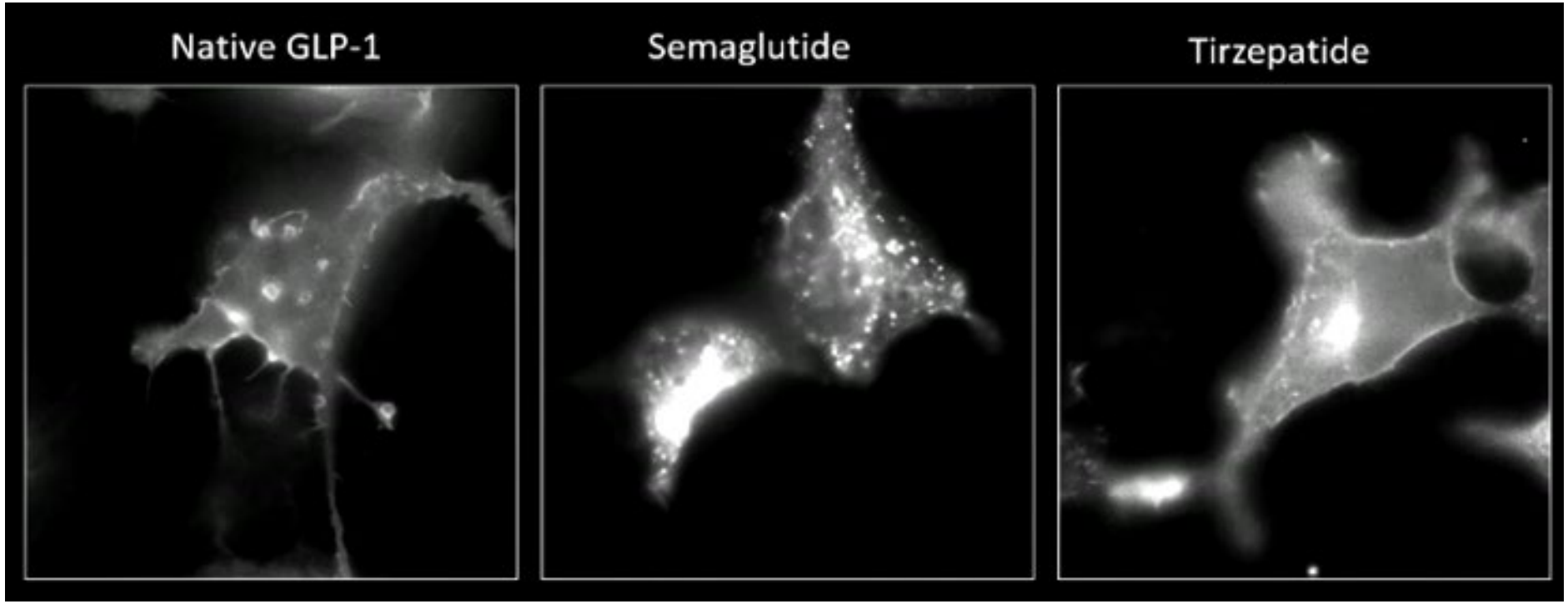
Lærke S. Gasbjerg MD, Mette M. Rosenkilde MD, Juris J. Meier MD, Jens J. Holst MD, Filip K. Knop MD

First published: 08 August 2023





TIRZEPATIDE CAUSES FASTER RECYCLING OF INTERNALIZAED GLP-1R IN HEK293T CELLS



GLP-1 and semaglutide cause internalization of GLP-1 receptor → limits the effect

TZP increases membrane GLP-1 receptor → potentiates the effect

Mol Metab. 2021 Jul;49:101181

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

GLP-1 Receptor Agonism

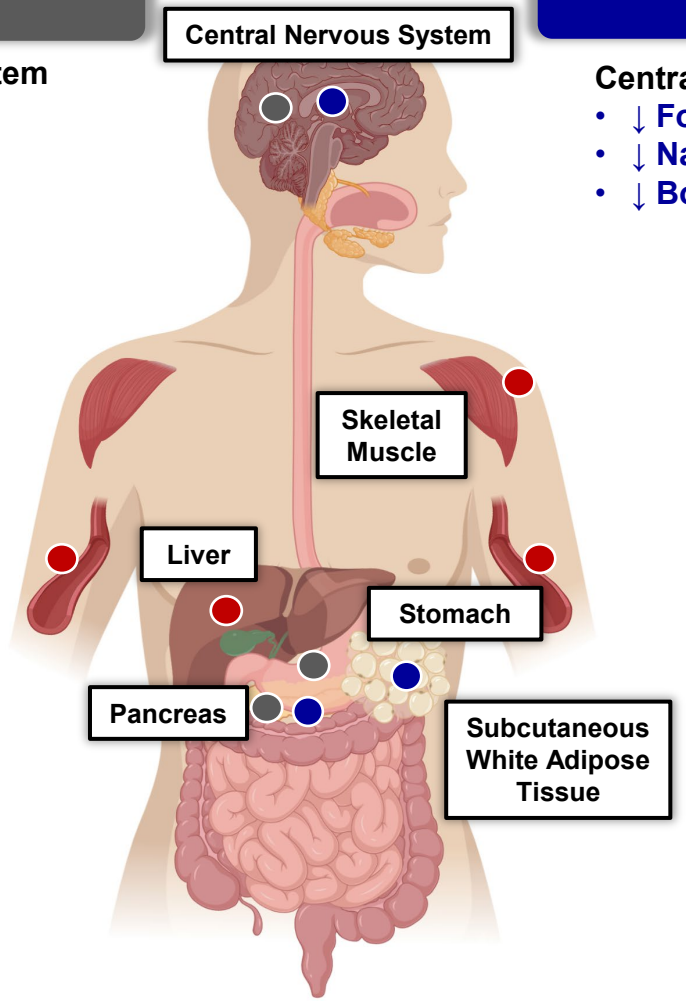
Central Nervous System
- ↑ Satiety
- ↓ Food Intake
- ↑ Nausea
- ↓ Body Weight

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

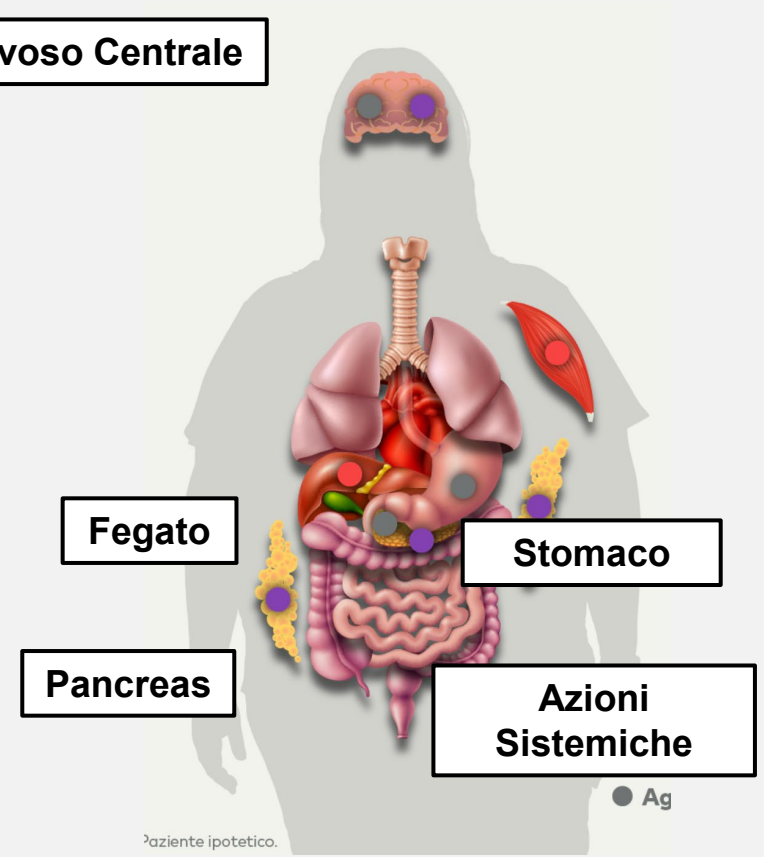
Systemic
- ↓ Hyperglycemia, Dietary Triglyceride

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

Meccanismo d'azione di Tirzepatide



Sistema Nervoso Centrale[1]

- ↓ Appetito
- ↓ Assunzione di cibo

Fegato[2]

- ↓ Contenuto di grassi nel fegato

Pancreas[2]

- Migliora la sensibilità al glucosio delle cellule β
- ↑ Secrezione di Insulina
- ↓ Secrezione di Glucagone

Stomaco[3]

- ↓ Svuotamento gastrico

Azione sistemica[4]

- ↑ sensibilità all'insulina

1. Heise T, et al. Oral presentation at: *ADA 2022*. Abstract 338-OR. 2. Gastaldelli A, et al. *Lancet Diabetes Endocrinol*. 2022;10(6):393-406. 3. Heise T, et al. *Lancet Diabetes Endocrinol*. 2022;10(6):418-429. 4. Samms RJ, et al. *Trends Endocrinol Metab*. 2020;31(6):410-421.

SURPASS Program:
Clinical Trials Across the T2D Spectrum

Total studied population: 7699 T2 diabetic patients

Monotherapy	2-Drug Combination	2-3 Drug Combinations	2-4 Drug Combinations	Combination With Insulin
SURPASS-1 **vs. placebo[1]** Drug-naïve or washout from any OAM	**SURPASS-2** **vs. semaglutide[2]** Add-on to metformin	**SURPASS-3** **vs. insulin degludec[3]** Add-on to metformin with or without SGLT-2i	**SURPASS-4** **vs. insulin glargine[4]** Add-on to ≥1 and ≤3 OAMs (metformin, SGLT-2i, or SU)	**SURPASS-5** **vs. placebo[5]** Both with insulin glargine with or without metformin **SURPASS-6** **vs. insulin lispro[6] (TID)** Both with insulin glargine with or without metformin (ongoing)

SURPASS-CVOT[7]
H2H comparing TZP vs. dulaglutide
>12,000 participants (ongoing)

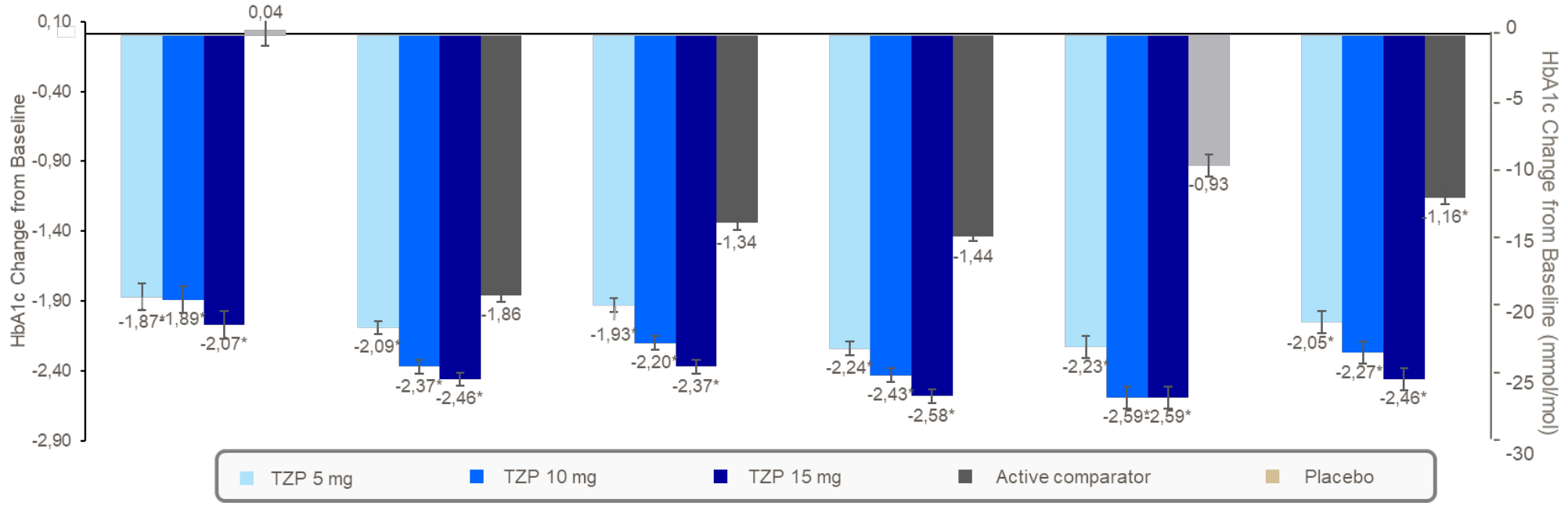
SURPASS-EARLY
to understand the effect of TZP when used early in the treatment paradigm compared to Intensified Conventional Care for the treatment of T2D (ongoing)

CVOT = cardiovascular outcomes trial; H2H = head-to-head; OAM = oral antihyperglycemic medication; SGLT2i = sodium-glucose co-transporter-2 inhibitor; SU = sulfonylurea; TID = three times daily; T2D = type 2 diabetes; TZP = tirzepatide.

1. Rosenstock J, et al. *Lancet*. 2021;398(10295):143-155. 2. Frias JP, et al. *N Eng J Med*. 2021;385(6):503-515. 3. Ludvik B, et al. *Lancet*. 2021;398(10300):583-598. 4. Del Prato S, et al. *Lancet*. 2021;398(10313):1811-1824. 5. Dahl D, et al. *JAMA*. 2022;327(6):534-545. 6. https://clinicaltrials.gov/ct2/show/NCT04537923 (Accessed May 06, 2022). 7. https://clinicaltrials.gov/ct2/show/NCT04255433 (Accessed May 06, 2022).

Tirzepatide All Doses Are Associated To Superior Hba1c Reduction Vs Comparators

Study	SURPASS-1[1]	SURPASS-2[2]	SURPASS-3[3]	SURPASS-4[4]	SURPASS-5[5]	SURPASS-6[6]
Duration	40 Weeks	40 Weeks	52 Weeks	52 Weeks	40 Weeks	52 Weeks
Baseline HbA1c	7.9%	8.3%	8.2%	8.5%	8.3%	8.8%
N	478	1879	1444	2002	475	1425



Superiority vs.	Placebo	SEMA 1 mg	Insulin degludec	Insulin glargine	Placebo	Insulin lispro
Background therapy	Monotherapy	Add-on to MET	Add-on to MET or MET + SGLT2i	Add-on to MET, SGLT2i, or SU	Add-on to insulin glargine ± MET	Add-on to insulin glargine ± MET

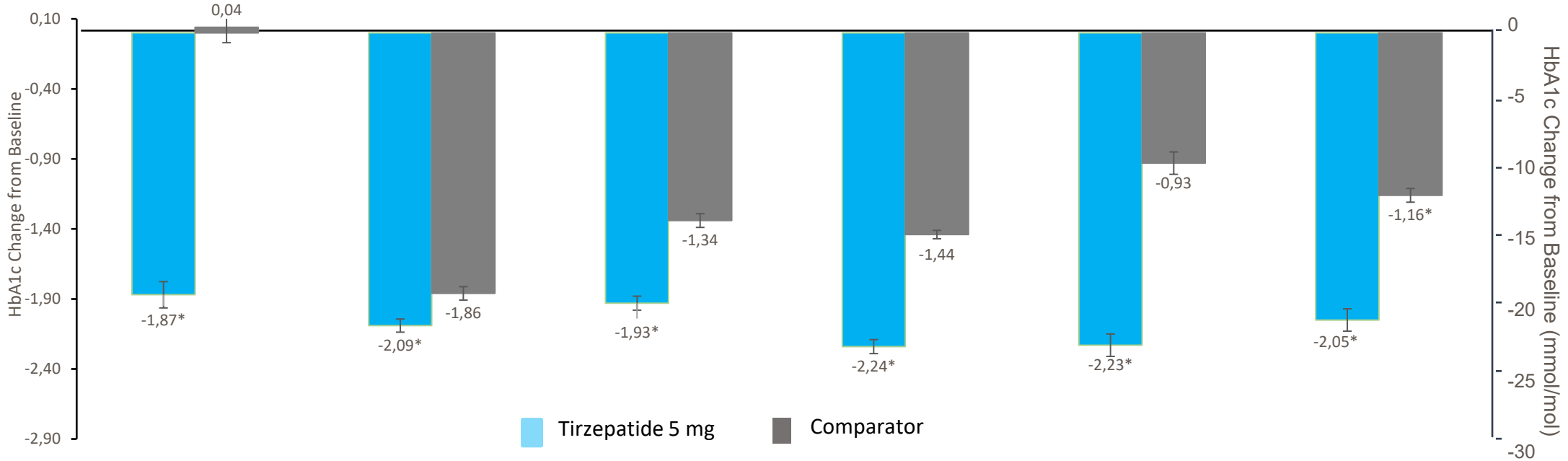
*p<0.001 vs. placebo or active comparator.

Data are LSM (SE). mITT population (efficacy analysis set). MMRM analysis. Data labels are % HbA1c. Number of participants (N) mentioned is randomized participants.

1. Rosenstock J, et al. *Lancet*. 2021;398(10295):143-155. 2. Frias JP, et al. *N Eng J Med*. 2021;385(6):503-515. 3. Ludvik B, et al. *Lancet*. 2021;398(10300):583-598. 4. Del Prato S, et al. *Lancet*. 2021;398(10313):1811-1824. 5. Dahl D, et al. *JAMA*. 2022;327(6):534-545. 6. 6. Rosenstock J, et al. JAMA. 2023;330(17):1631–1640

Tirzepatide already at 5 mg provide clinically relevant HbA1c reduction superior both to placebo and active comparators

Study	SURPASS-1[1]	SURPASS-2[2]	SURPASS-3[3]	SURPASS-4[4]	SURPASS-5[5]	SURPASS-6[6]
Duration	40 Weeks	40 Weeks	52 Weeks	52 Weeks	40 Weeks	52 Weeks
Baseline HbA1c	7.9%	8.3%	8.2%	8.5%	8.3%	8.8%
N	478	1879	1444	2002	475	1425



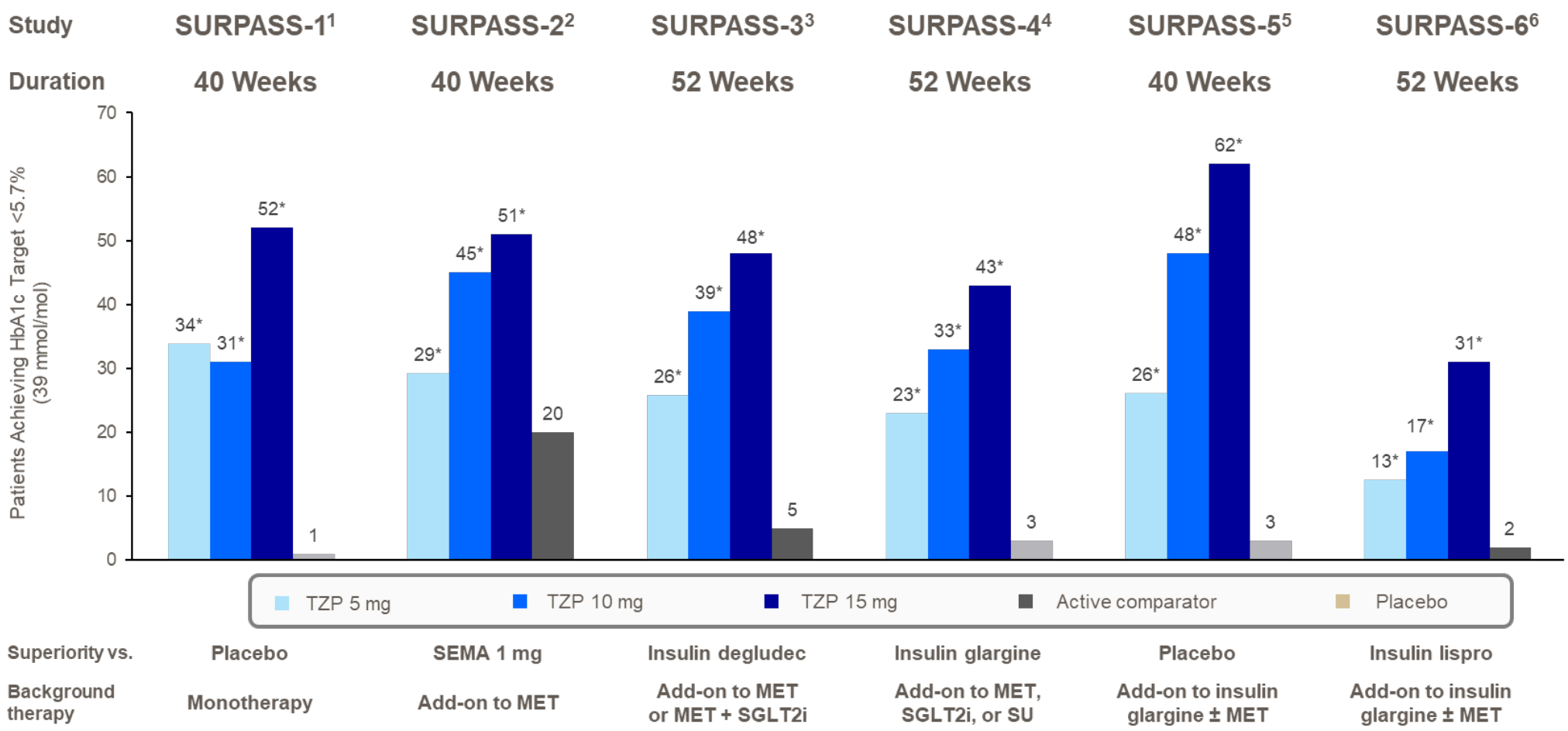
Superiority vs.	Placebo	SEMA 1 mg	Insulin degludec	Insulin glargine	Placebo	Insulin lispro
Background therapy	Monotherapy	Add-on to MET	Add-on to MET or MET + SGLT2i	Add-on to MET, SGLT2i, or SU	Add-on to insulin glargine ± MET	Add-on to insulin glargine ± MET

*p<0.001 vs. placebo or active comparator.

Data are LSM (SE). mITT population (efficacy analysis set). MMRM analysis. Data labels are % HbA1c. Number of participants (N) mentioned is randomized participants.

1. Rosenstock J, et al. *Lancet*. 2021;398(10295):143-155. 2. Frias JP, et al. *N Eng J Med*. 2021;385(6):503-515. 3. Ludvik B, et al. *Lancet*. 2021;398(10300):583-598. 4. Del Prato S, et al. *Lancet*. 2021;398(10313):1811-1824. 5. Dahl D, et al. *JAMA*. 2022;327(6):534-545. 6. 6. Rosenstock J, et al. JAMA. 2023;330(17):1631–1640

Higher Percentages Of Tirzepatide Treated Subjects Achieved Normal Hba1c Level (< 5,7%)

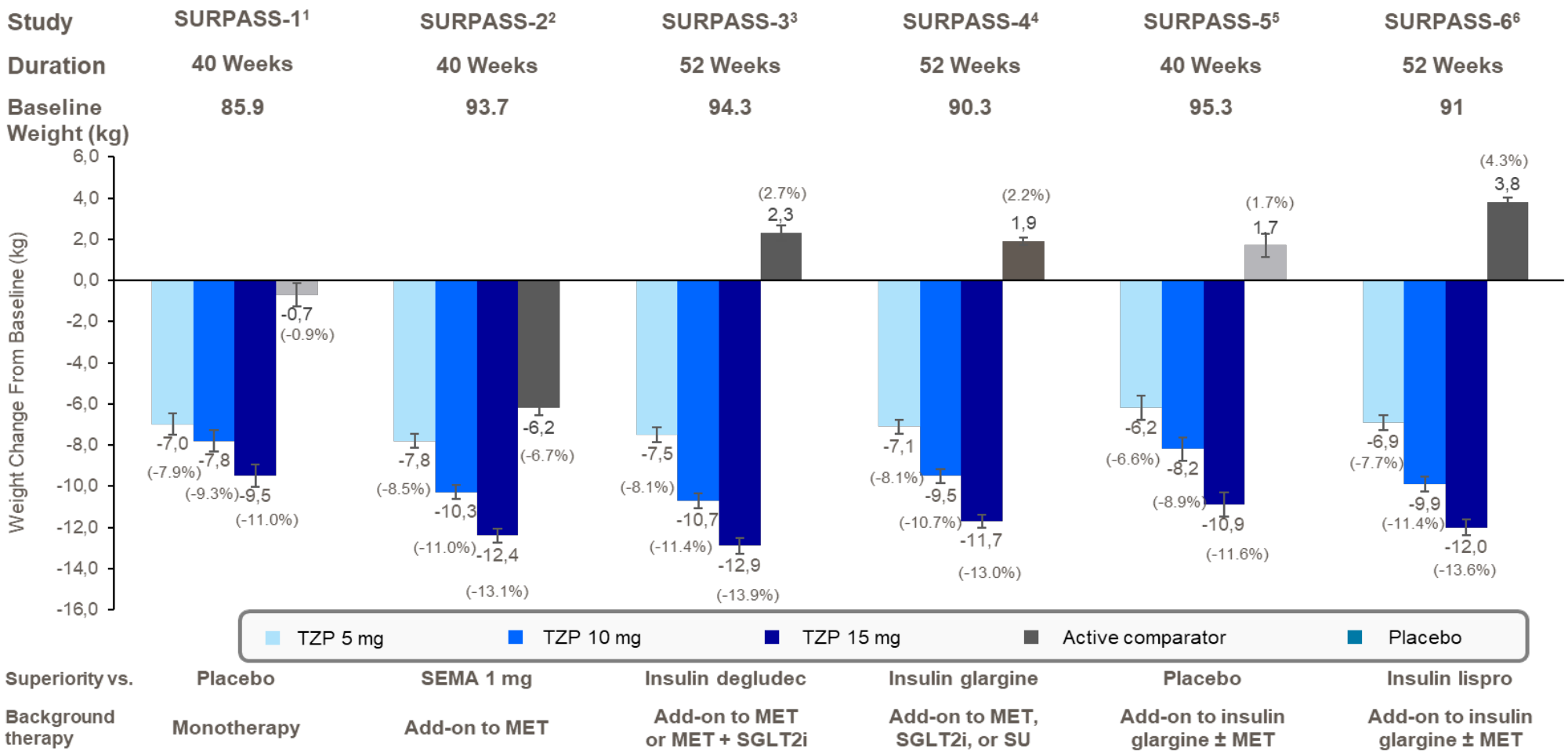


***p<0.001 vs. placebo or active comparator.**

Data are estimated mean; mITT population (efficacy analysis set). Logistic regression.

1. Rosenstock J, et al. *Lancet*. 2021;398(10295):143-155. 2. Frias JP, et al. *N Eng J Med*. 2021;385(6):503-515. 3. Ludvik B, et al. *Lancet*. 2021;398(10300):583-598. 4. Del Prato S, et al. *Lancet*. 2021;398(10313):1811-1824. 5. Dahl D, et al. *JAMA*. 2022;327(6):534-545. 6. 6. Rosenstock J, et al. JAMA. 2023;330(17):1631–1640

Tirzepatide Produces Clinically Significant Weight Reductions Versus Placebo and Active Comparators

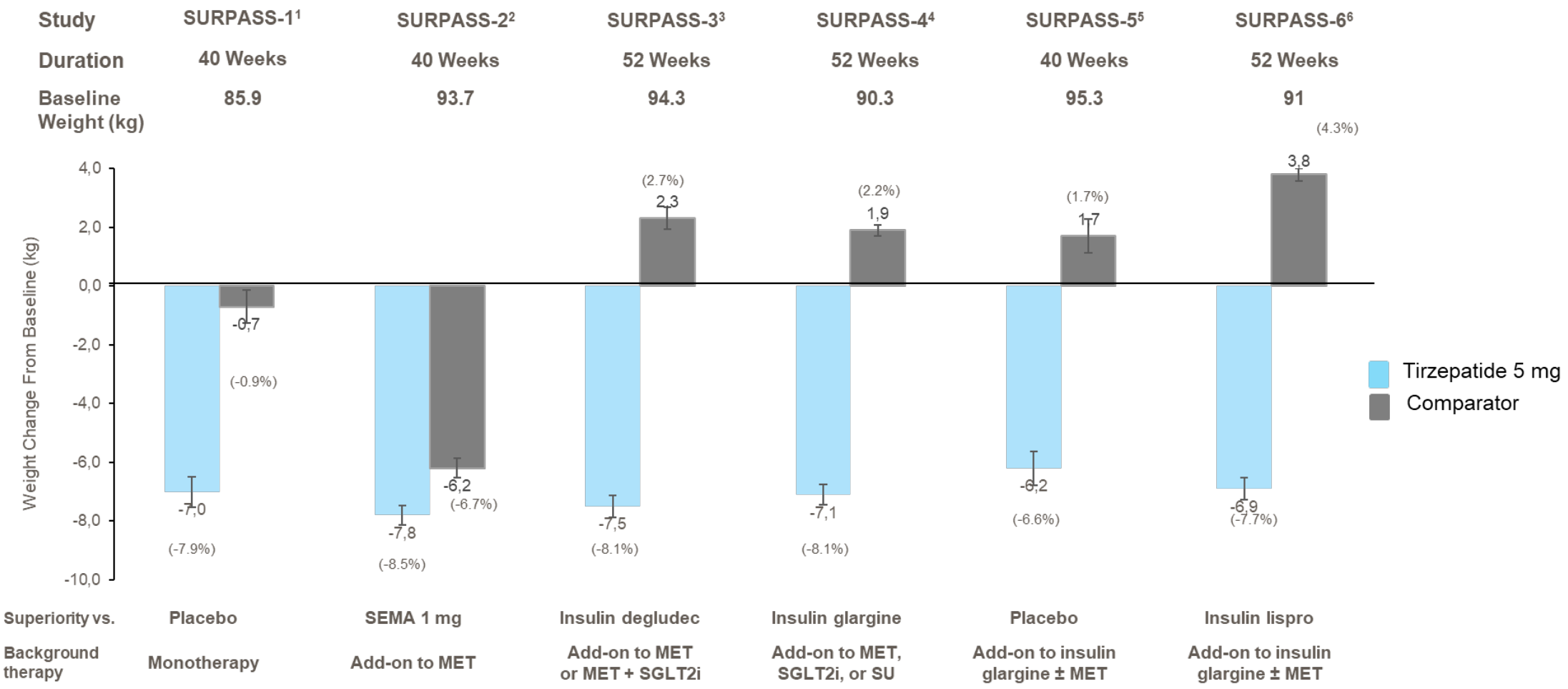


*p<0.001 vs. placebo or active comparator.

Data are LSM (SE); mITT population (efficacy analysis set). MMRM analysis.

1. Rosenstock J, et al. *Lancet*. 2021;398(10295):143-155. 2. Frias JP, et al. *N Eng J Med*. 2021;385(6):503-515. 3. Ludvik B, et al. *Lancet*. 2021;398(10300):583-598. 4. Del Prato S, et al. *Lancet*. 2021;398(10313):1811-1824. 5. Dahl D, et al. *JAMA*. 2022;327(6):534-545. 6. 6. Rosenstock J, et al. JAMA. 2023;330(17):1631–1640.

Tirzepatide Already at 5 mg Produces Clinically Significant Weight Reductions Versus Placebo and Active Comparators

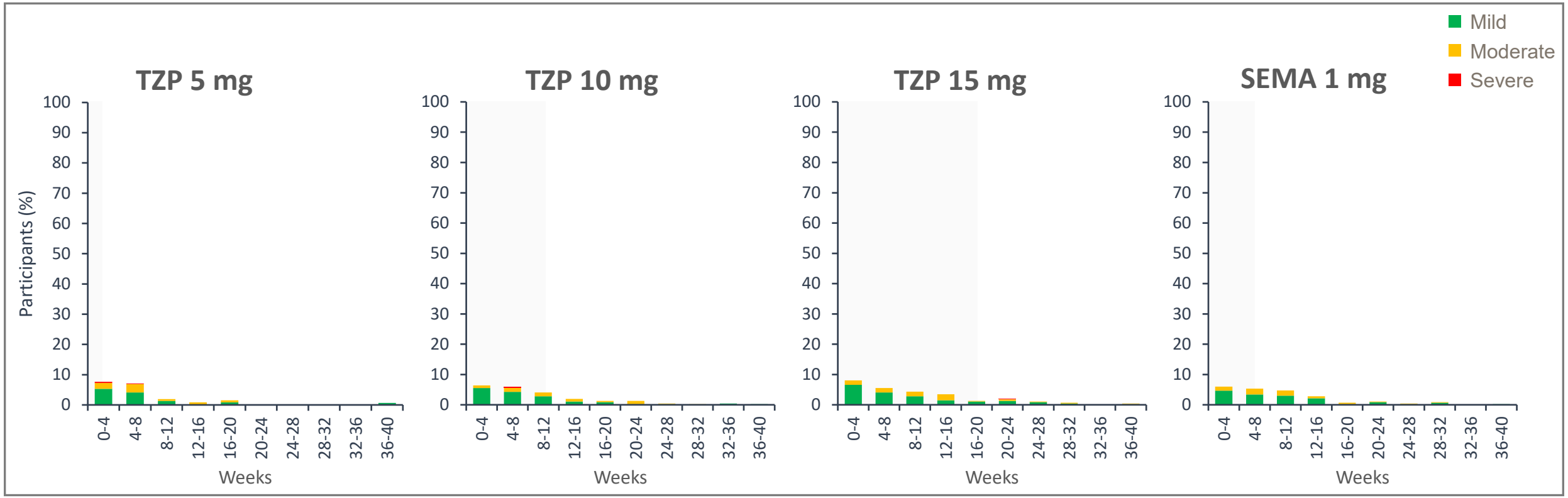


***p<0.001 vs. placebo or active comparator.**

Data are LSM (SE); mITT population (efficacy analysis set). MMRM analysis.

1. Rosenstock J, et al. *Lancet*. 2021;398(10295):143-155. 2. Frias JP, et al. *N Eng J Med*. 2021;385(6):503-515. 3. Ludvik B, et al. *Lancet*. 2021;398(10300):583-598. 4. Del Prato S, et al. *Lancet*. 2021;398(10313):1811-1824. 5. Dahl D, et al. *JAMA*. 2022;327(6):534-545. 6. 6. Rosenstock J, et al. JAMA. 2023;330(17):1631–1640.

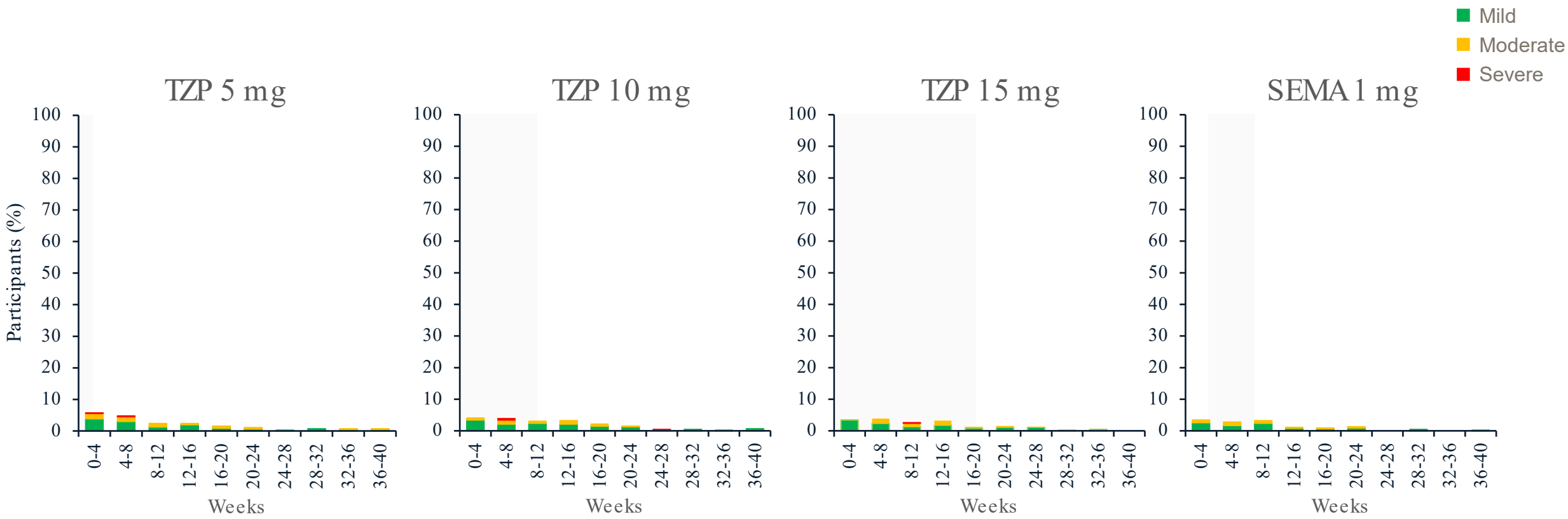
Incidence of Nausea Over Time Through 40 Weeks
SURPASS-2 (Tirzepatide versus Semaglutide)



Most cases of nausea were mild to moderate, transient, and occurred during the dose-escalation period in all groups

Data are percentage of participants who reported a new event relative to participants at risk during a time interval; mITT population (safety analysis set). Shaded areas indicate the period of time before reaching the maintenance dose of the study treatments. Incidence refers to the proportion of participants who have a new event during a time interval.
mITT = modified intent-to-treat; SEMA = semaglutide; TZP = tirzepatide.
Frias JP, et al. *N Eng J Med*. 2021;385(6):503-515.

Incidence of Diarrhea Over Time Through 40 Weeks SURPASS-2 (Tirzepatide versus Semaglutide)



Most cases of diarrhea were mild to moderate, transient, and occurred during the dose-escalation period in all groups

Data are percentage of participants who reported a new event relative to participants at risk during a time interval. mITT population (safety analysis set). Shaded areas indicate the period of time before reaching the maintenance dose of the study treatments. Incidence refers to the proportion of participants who have a new event during a time interval.
mITT = modified intent-to-treat; SEMA = semaglutide; TZP = tirzepatide.
Frias JP, et al. *N Eng J Med*. 2021;385(6):503-515.

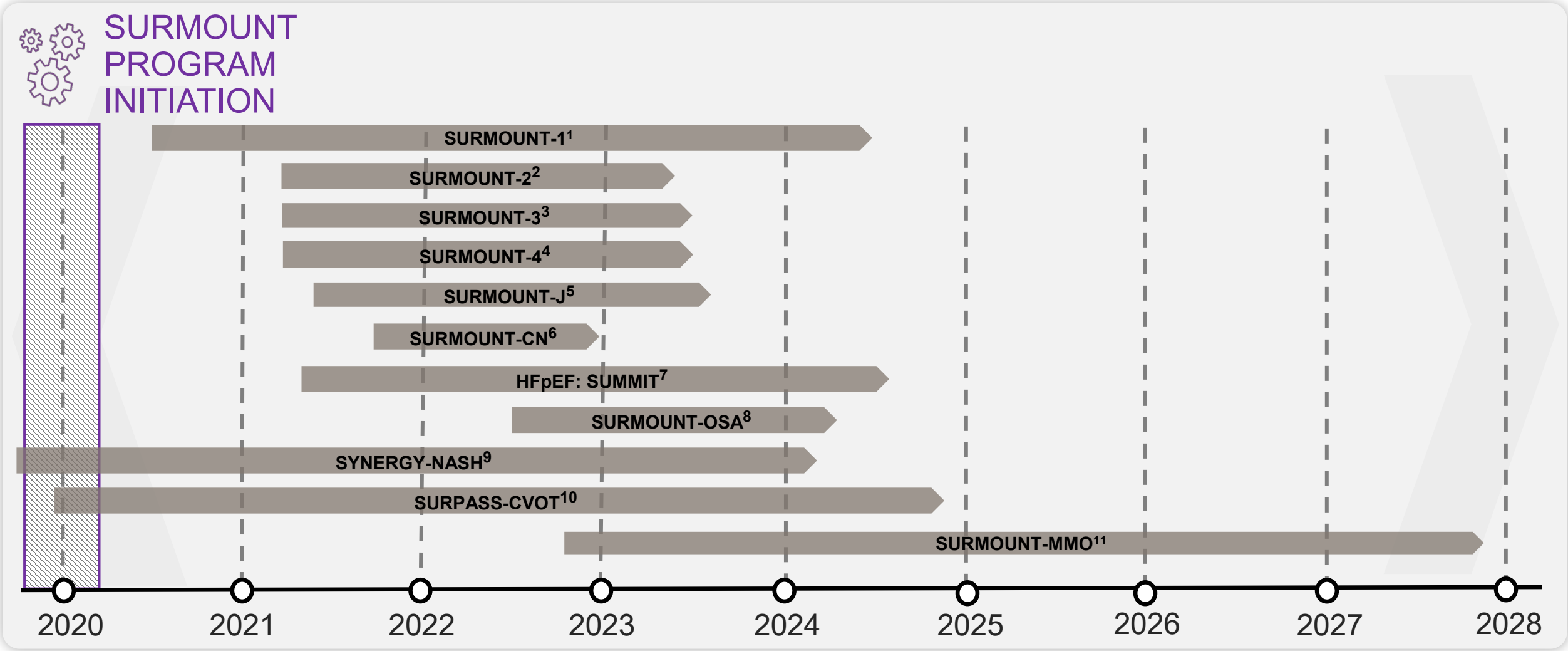
Other Adverse Events of Interest

Parameters	SURPASS-1[1]	SURPASS-2[2]	SURPASS-3[3]	SURPASS-4[4]	SURPASS-5[5]
Pancreatitis[a]	**0**	**2** (TZP 10 mg) **2** (TZP 15 mg) **3** (SEMA 1 mg)	**0**	**3** (TZP 5 mg) **2** (TZP 10 mg) **1** (TZP 15 mg) **1** (Insulin Glargine)	**0**
Cholelithiasis	**1** (TZP 5 mg)	**4** (TZP 5 mg) **4** (TZP 10 mg) **4** (TZP 15 mg) **2** (SEMA 1 mg)	**2** (TZP 5 mg) **1** (TZP 10 mg) **1** (TZP 15 mg)	**3** (TZP 5 mg) **1** (TZP 10 mg) **1** (TZP 15 mg) **4** (Insulin Glargine)	**1** (TZP 5 mg)
Medullary Thyroid Carcinoma	**0**	**0**	**0**	**0**	**0**
Diabetic Retinopathy	**0**	**2** (TZP 10 mg)	**2** (TZP 5 mg) **1** (TZP 15 mg)	**2** (TZP 5 mg) **1** (TZP 10 mg) **1** (TZP 15 mg) **1** (Insulin Glargine)	**0**

[a]Adjudication-Confirmed.

1. Rosenstock J, et al. *Lancet*. 2021;398(10295):143-155. 2. Frias JP, et al. *N Eng J Med*. 2021;385(6):503-515. 3. Ludvik B, et al. *Lancet*. 2021;398(10300):583-598. 4. Del Prato S, et al. *Lancet*. 2021;398(10313):1811-1824. 5. Dahl D, et al. *JAMA*. 2022;327(6):534-545.

Tirzepatide in Cronich Weight Management

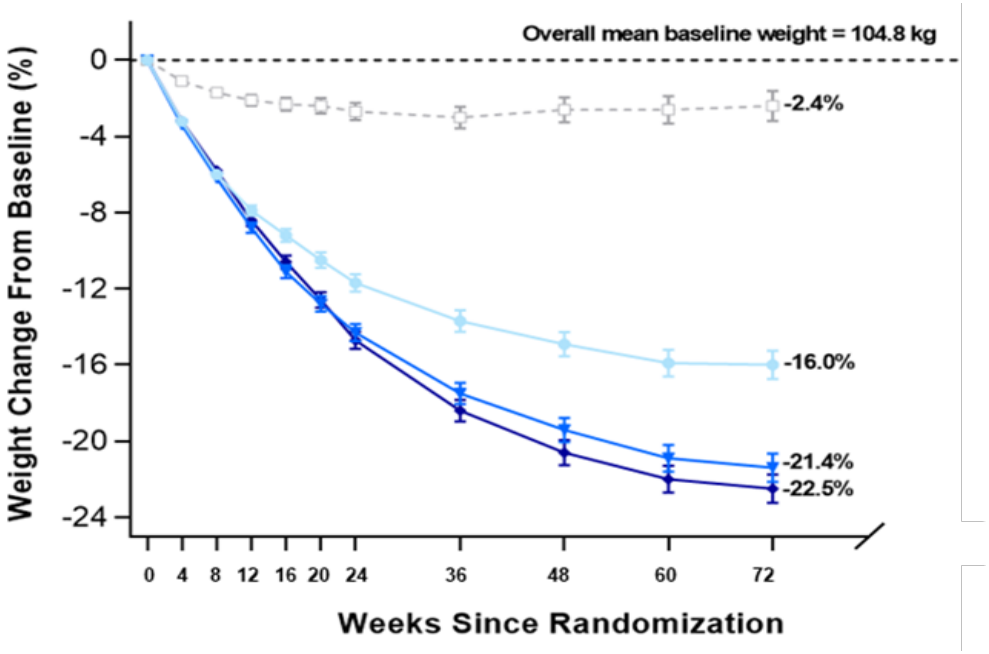


Note: Abbreviations and References are mentioned in the speaker note section.

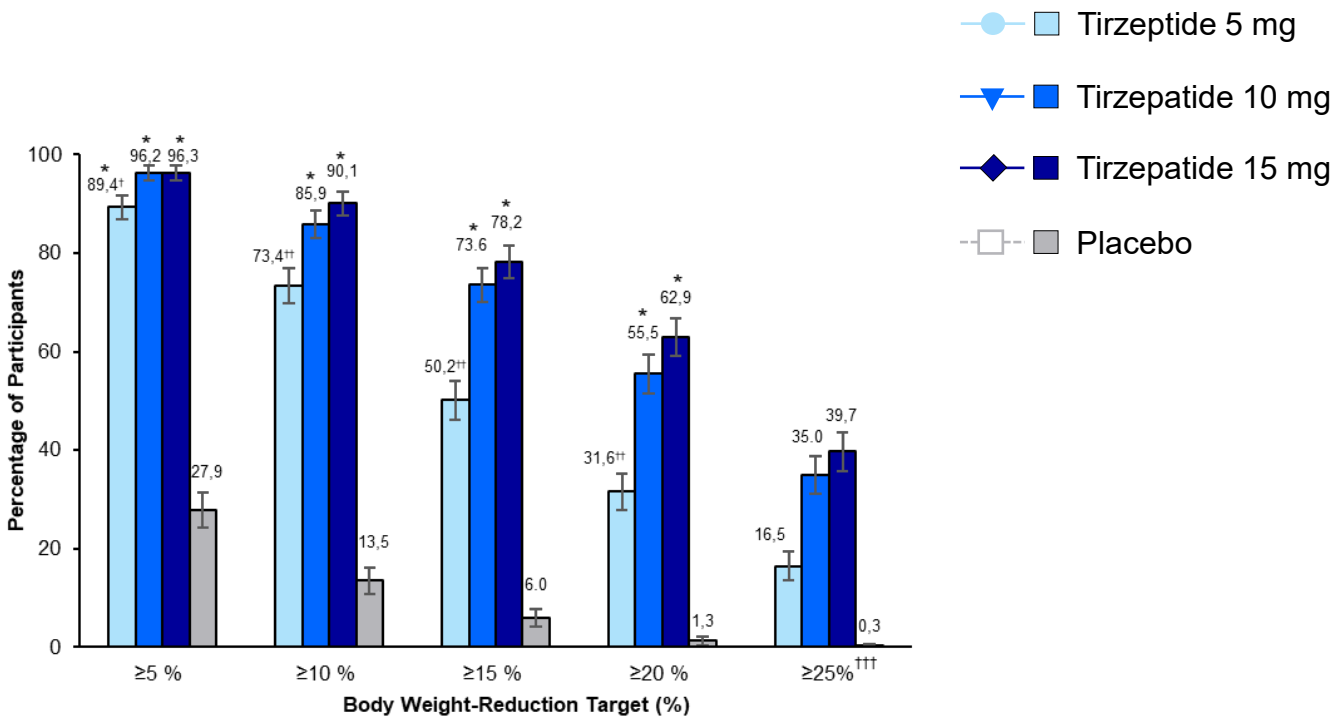
SURMOUNT-1: primary and main secondary end point in subjects with obesity

% body weight reduction from baseline

	TZP 5 mg vs PBO*	TZP 10 mg vs PBO	TZP 15 mg vs PBO
ETD (%) (95% CI)	−13.5 (−14.6 to −12.5)	−18.9 (−20.0, −17.8)	−20.1 (−21.2, −19.0)
P value		<.001	



% of subjects achieving different targets of body weight reduction

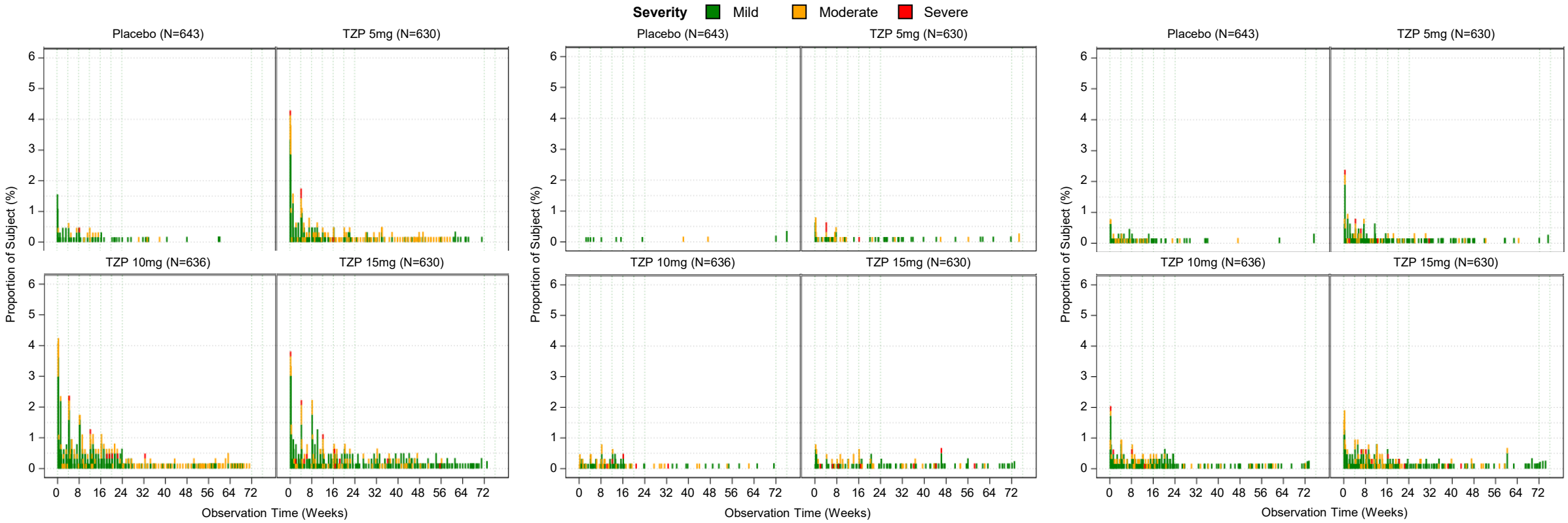


From – 14,6 cm (TZP 5 mg) up to -19,9 cm (TZP 15 mg) of **Waist Circumference** reduction respect to baseline

ETD = Estimated Treatment Difference;
Jastreboff AM, et al. *N Engl J Med*. 2022;387(3):205-216.

Incidence of Nausea, Vomiting, and Diarrhea Over Time in subject with obesity: SURMOUNT 1 Study

Most gastrointestinal events were transient, occurring primarily during the dose-escalation period, and were mostly mild to moderate in severity



Note: Percentages are based on number of participants at risk at specific observation time

TZP = Tirzepatide.

Jastreboff AM, et al. *New Engl. J. Med.* 2022; doi: 10.1056/NEJMoa2206038 (Online ahead of print).

Journal of Endocrinological Investigation
https://doi.org/10.1007/s40618-024-02441-z

ORIGINAL ARTICLE

The real-world safety profile of tirzepatide: pharmacovigilance analysis of the FDA Adverse Event Reporting System (FAERS) database

I. Caruso[1] · L. Di Gioia[1] · S. Di Molfetta[1] · M. Caporusso[1] · A. Cignarelli[1] · G. P. Sorice[1] · L. Laviola[1] · F. Giorgino[1]

Received: 24 May 2024 / Accepted: 2 August 2024

In sintesi, le prove del mondo reale del database FAERS descrivono un profilo di sicurezza rassicurante per TZP.
Pur mostrando un'efficacia impressionante, la TZP mantiene una tollerabilità gastrointestinale simile rispetto alla classe ampiamente utilizzata di GLP-1RA senza aumentare il rischio di pancreatite, retinopatia diabetica e carcinoma midollare della tiroide.

ERAS OF DIABETES