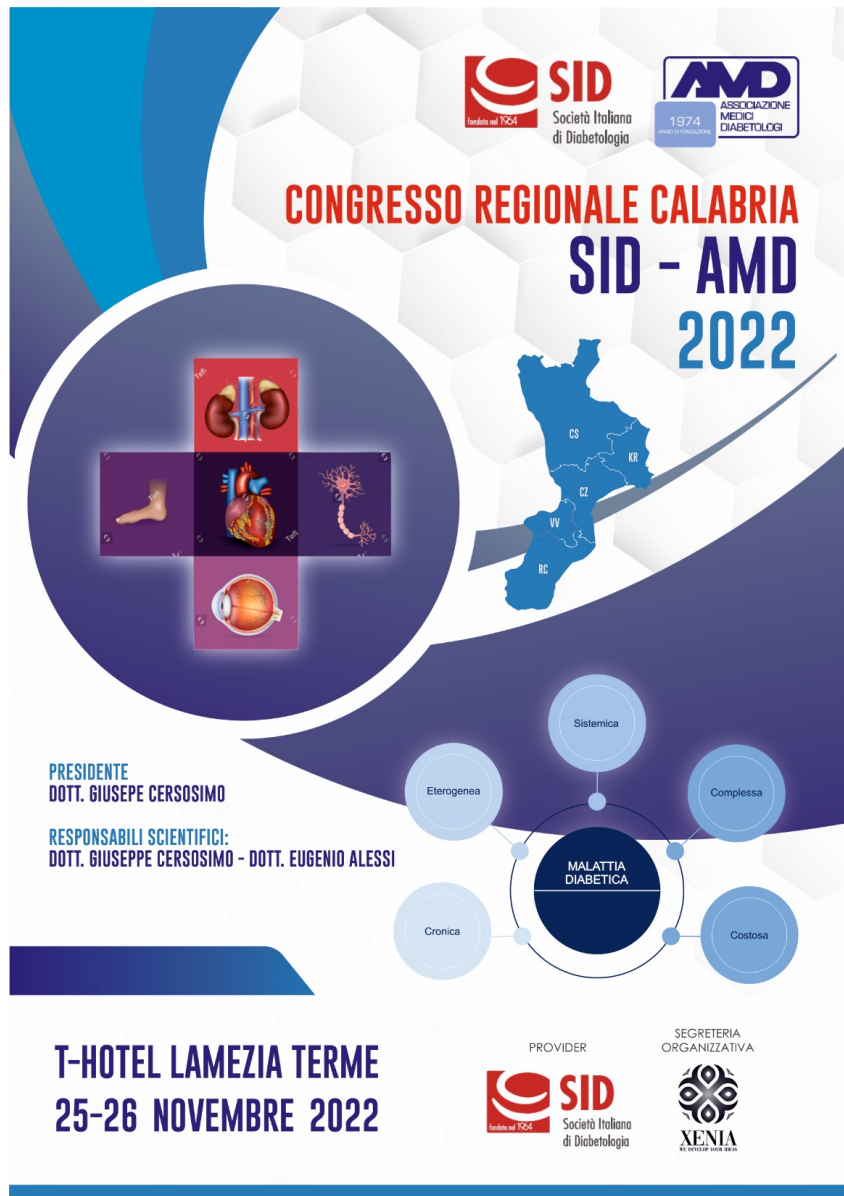




The poster for the Calabria Regional Congress SID - AMD 2022 features a central graphic of a cross with medical icons (kidneys, heart, foot, pancreas) and a map of Calabria. Logos for SID (founded 1954) and AMD (founded 1974) are at the top. A diagram at the bottom shows 'MALATTIA DIABETICA' at the center, surrounded by 'Sistemica', 'Eterogenea', 'Cronica', 'Complessa', and 'Costosa'. The event is held at T-Hotel Lamezia Terme on November 25-26, 2022, with Dott. Giuseppe Cersosimo as President and Dott. Giuseppe Cersosimo and Dott. Eugenio Alessi as Scientific Responsible. Logos for SID, XENIA, and the organizing committee are at the bottom.

SID Società Italiana di Diabetologia
AMD ASSOCIAZIONE MEDICI DIABETOLOGI

**CONGRESSO REGIONALE CALABRIA
SID - AMD
2022**

PRESIDENTE
DOTT. GIUSEPPE CERSOSIMO

RESPONSABILI SCIENTIFICI:
DOTT. GIUSEPPE CERSOSIMO - DOTT. EUGENIO ALESSI

**T-HOTEL LAMEZIA TERME
25-26 NOVEMBRE 2022**

PROVIDER
SID Società Italiana di Diabetologia

SEGRETERIA ORGANIZZATIVA
XENIA

**Nuove opportunità terapeutiche: le
nuove incretine**

Elena Succurro



Università degli Studi “Magna Graecia” di Catanzaro
Dipartimento di Scienze Mediche e Chirurgiche
U.O.C. di Medicina Interna



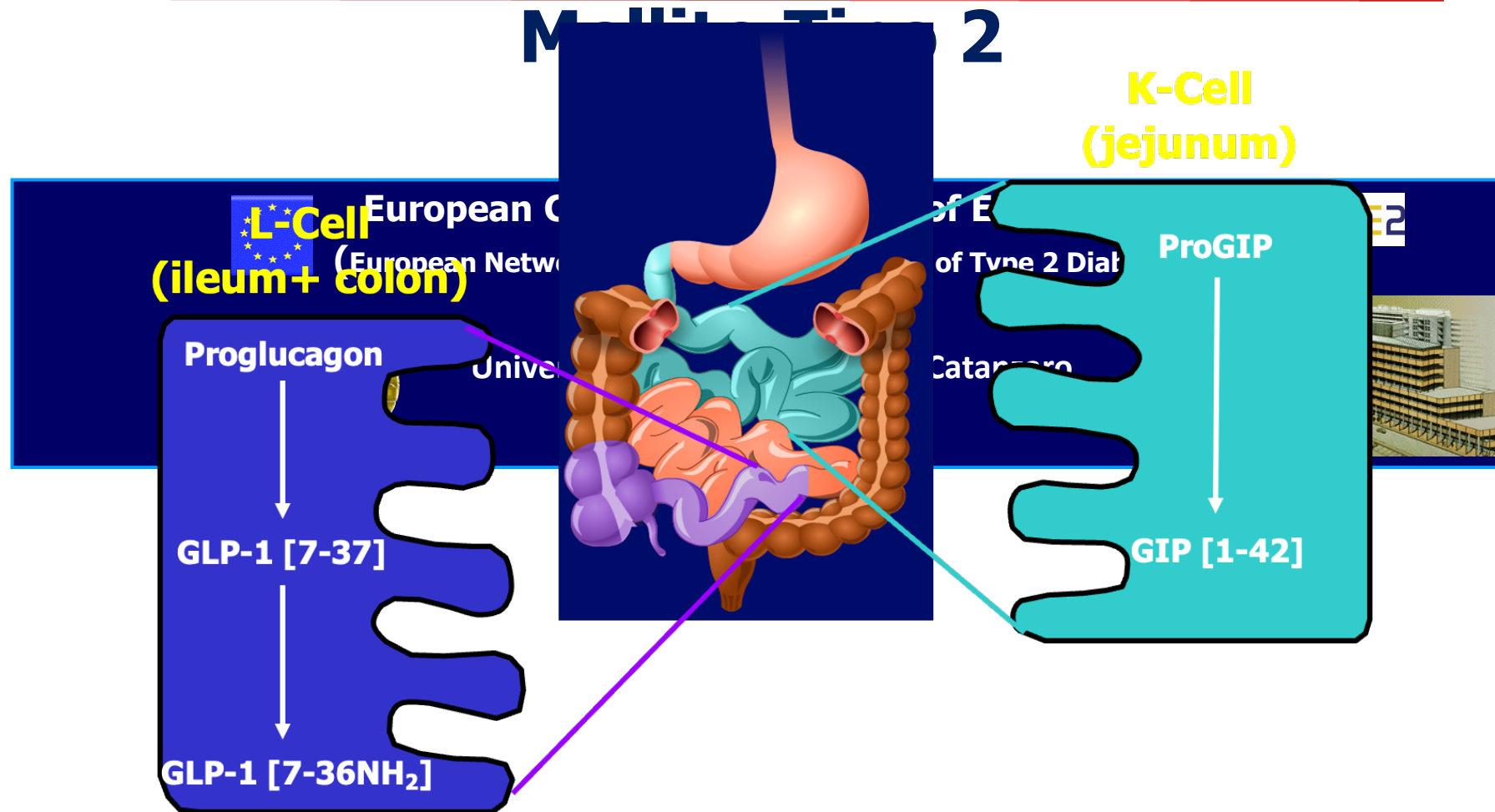
La Prof.ssa Succurro Elena dichiara di aver ricevuto negli ultimi due anni compensi o finanziamenti dalle seguenti Aziende Farmaceutiche e/o Diagnostiche:

Eli Lilly, Novo Nordisk, MSD Italia, Mundipharma, Medtronic (per eventi, advisory board e consulenza per formazione dipendenti)

Dichiara altresì il proprio impegno ad astenersi, nell'ambito dell'evento, dal nominare, in qualsivoglia modo o forma, aziende farmaceutiche e/o denominazione commerciale e di non fare pubblicità di qualsiasi tipo relativamente a specifici prodotti di interesse sanitario (farmaci, strumenti, dispositivi medico-chirurgici, ecc.).

Nuove Opportunita' Nella Terapia Del Diabete

Synthesis and Secretion of GLP-1 and GIP



GLP-1 Effects in Humans: Understanding Development of Exenatide: An Incretin Mimetic

Exenatide (Exendin-4)

- Synthetic version of salivary protein found in the Gila monster
- Approximately 50% identity with human GLP-1
 - Binds to known human GLP-1 receptors on β cells *in vitro*
 - Resistant to DPP-IV inactivation



Exenatide H G E G T F T S D L S K Q M E E E A V R L F I E W L K N G G P S S G A P P P S - N H₂

GLP-1 H A E G T F T S D V S S Y L E G Q A A K E F I A W L V K G R - N H₂
Human

Site of DPP-IV Inactivation

Adapted from Nielsen LL, et al. *Regulatory Peptides*. 2004;117:77-88.; Fineman MS, et al. *Diabetes Care*. 2003;26:2370-2377. Reprinted from *Regulatory Peptides*, 117, Nielsen LL, et al, Pharmacology of exenatide (synthetic exendin-4): a potential therapeutic for improved glycemic control of type 2 diabetes, 77-88, 2004, with permission from Elsevier.



+ASCVD/Indicators of High Risk

Glycaemic Management: Choose approaches that provide the efficacy to achieve goals:

Metformin OR Agent(s) including COMBINATION therapy that provide adequate EFFICACY to achieve and maintain treatment goals
Consider avoidance of hypoglycaemia a priority in high-risk individuals

In general, higher efficacy approaches have greater likelihood of achieving glycaemic goals
Efficacy for glucose lowering

Very High:

Dulaglutide (high dose),
Semaglutide, Tirzepatide

Insulin

Combination Oral, Combination
Injectable (GLP-1 RA/Insulin)

High:

GLP-1 RA (not listed above), Metformin,
SGLT2i, Sulfonylurea, TZD

Intermediate:

DPP-4i

Achievement and Maintenance of Weight Management Goals:

Set individualised weight management goals

When choosing glucose-lowering therapies:

Consider regimen with high-to-very-high dual glucose and weight efficacy

Efficacy for weight loss

Very High:

Semaglutide, Tirzepatide

High:

Dulaglutide, Liraglutide

Intermediate:

GLP-1RA (not listed above), SGLT2i

Neutral:

DPP-4i, Metformin

Evidence from CVOTs has shown that some glucose-lowering agents have beneficial effects on CV outcomes

3P-MACE	LEADER ⁴ (liraglutide)	SUSTAIN-6 ⁵ (semaglutide)	Harmony Outcomes ⁶ (albiglutide)
CV death	HR 0.87 (95% CI 0.78, 0.97) <i>p</i> =0.01	HR 0.74 (95% CI 0.58, 0.95) <i>p</i> =0.02 [§]	HR 0.78 (95% CI 0.68, 0.90) <i>p</i> =0.0006
HHF	HR 0.78 (95% CI 0.66, 0.93) <i>p</i> =0.007*	HR 0.98 (95% CI 0.65, 1.48) <i>p</i> =0.92*	HR 0.93 (95% CI 0.73, 1.19) <i>p</i> =0.578*
CV death or HHF	HR 0.87 (95% CI 0.73, 1.05) <i>p</i> =0.14*	HR 1.11 (95% CI 0.77, 1.61) <i>p</i> =0.57*	N/R
Non-fatal stroke	N/R	N/R	HR 0.85 (95% CI 0.70, 1.04) <i>p</i> =0.113*
Fatal/non-fatal MI	HR 0.89 (95% CI 0.72, 1.11) <i>p</i> =0.30*	HR 0.61 (95% CI 0.38, 0.99) <i>p</i> =0.04*	N/R
3P-MACE	HR 0.88 (95% CI 0.75, 1.03) <i>p</i> =0.11*	HR 0.74 (95% CI 0.51, 1.08) <i>p</i> =0.12*	HR 0.75 (95% CI 0.61, 0.90) <i>p</i> =0.003*

Comparison of trials should be interpreted with caution due to differences in study design, populations and methodology. *p*-values are for superiority

*Nominal *p*-value; †Testing for superiority for 3P-MACE was part of the statistical analysis plan, but was not part of the hierarchical testing strategy; ‡Exploratory outcome, no *p*-value is reported – only nominal effect estimate is given; §Testing for superiority was neither pre-specified nor adjusted for multiplicity. See slide notes for abbreviations

1. Zinman B *et al. N Engl J Med* 2015;373:2117; 2. Neal B *et al. N Engl J Med* 2017;377:644; 3. Wiviott S *et al. N Engl J Med* 2019;380:347; 4. Marso SP *et al. N Engl J Med* 2016;375:1834;

5. Marso SP *et al. N Engl J Med* 2016;375:311; 6. Hernandez AF *et al. Lancet* 2018;392:1519

ORIGINAL INVESTIGATION

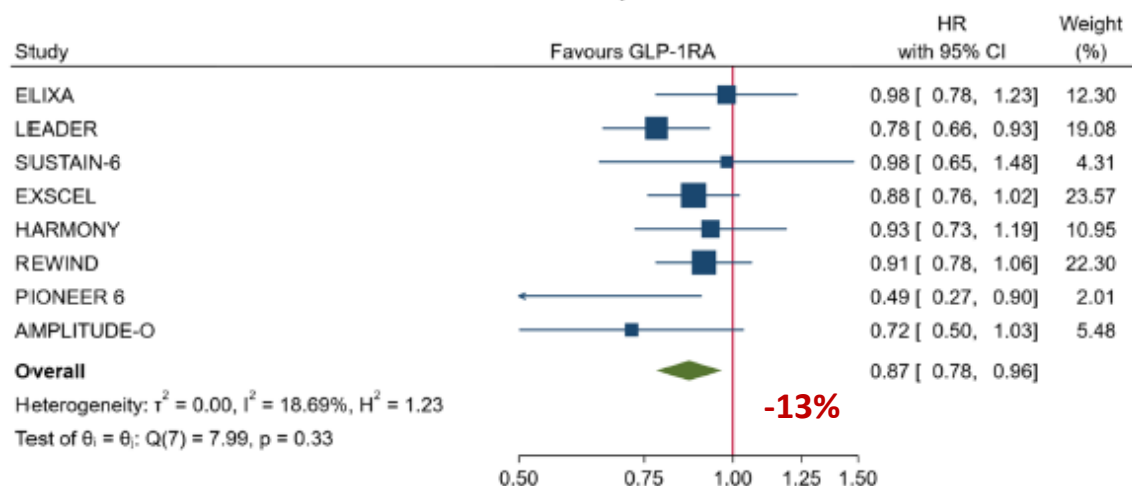
Open Access

GLP-1 receptor agonists and cardiorenal outcomes in type 2 diabetes: an updated meta-analysis of eight CVOTs

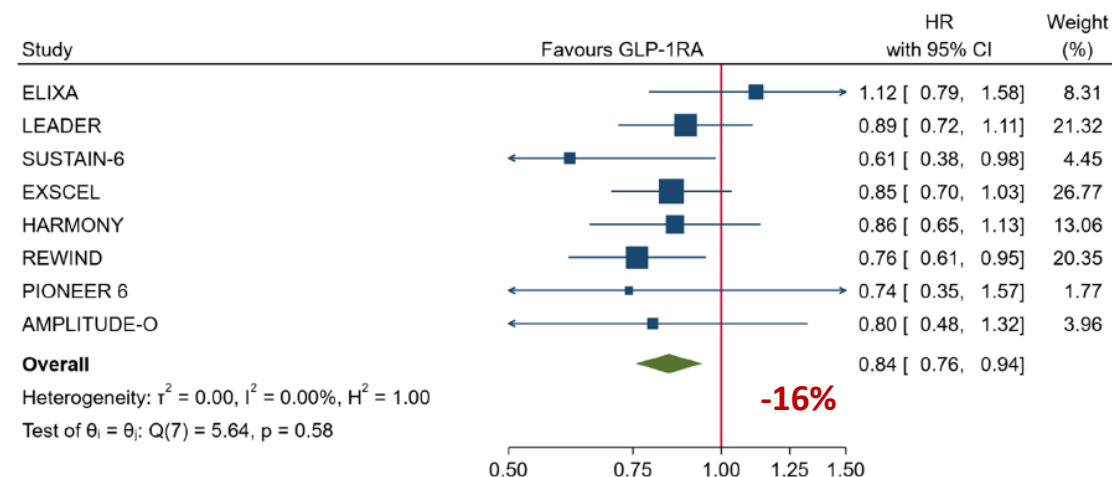
Dario Giugliano^{1,2†}, Lorenzo Scappaticcio^{1,2†}, Miriam Longo^{1,2†}, Paola Caruso^{1,2}, Maria Ida Maiorino³, Giuseppe Bellastella¹, Antonio Ceriello⁴, Paolo Chiodini⁵ and Katherine Esposito^{2,3}



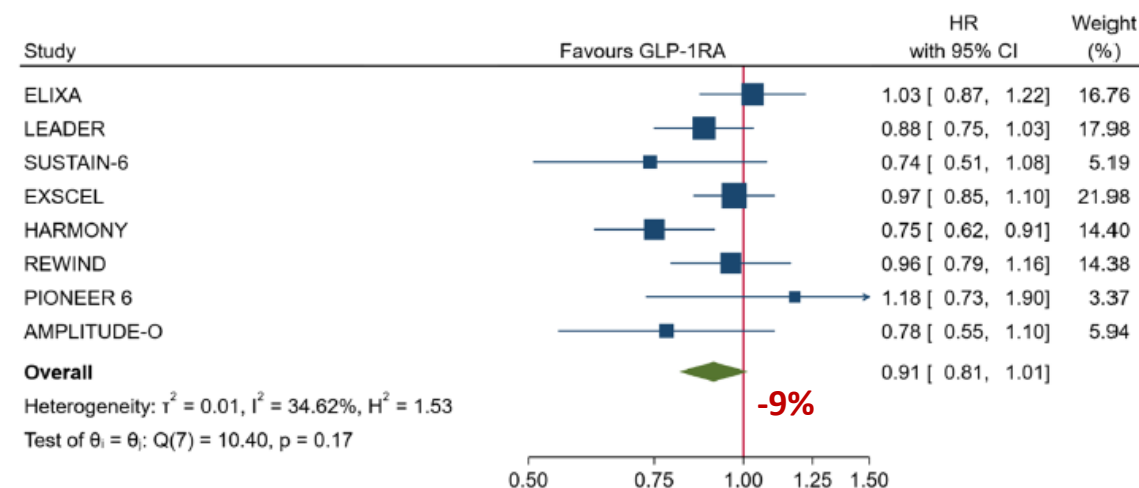
CV mortality



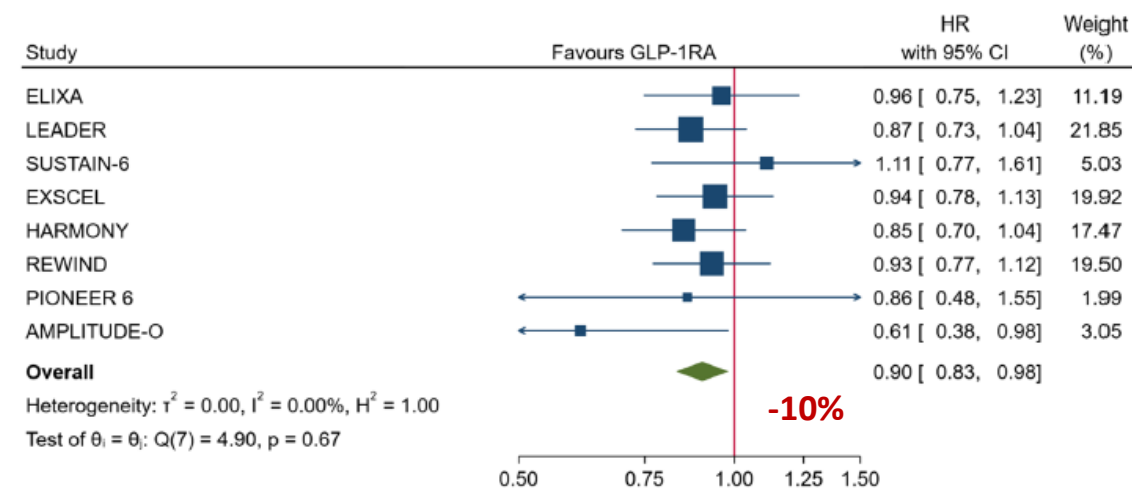
Non-fatal stroke

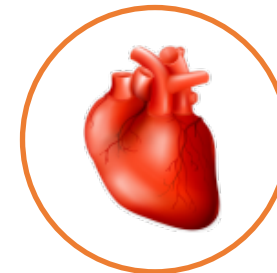


Non-fatal MI

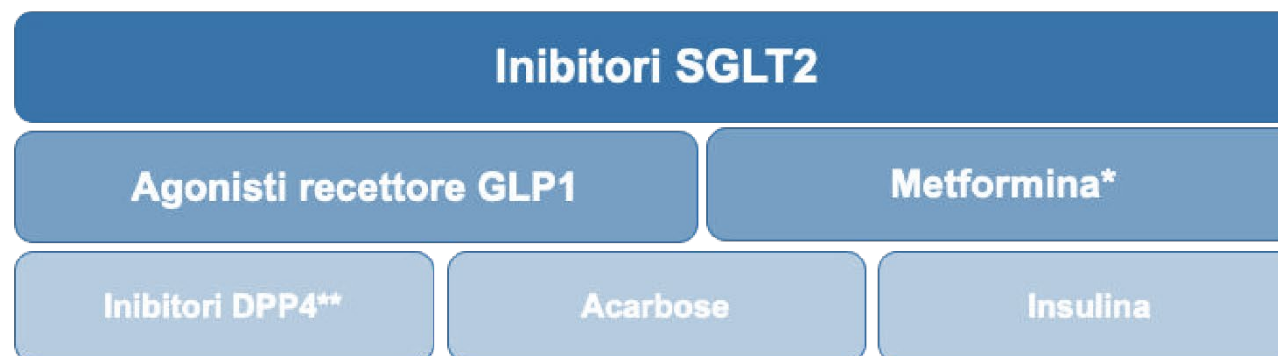


Heart failure



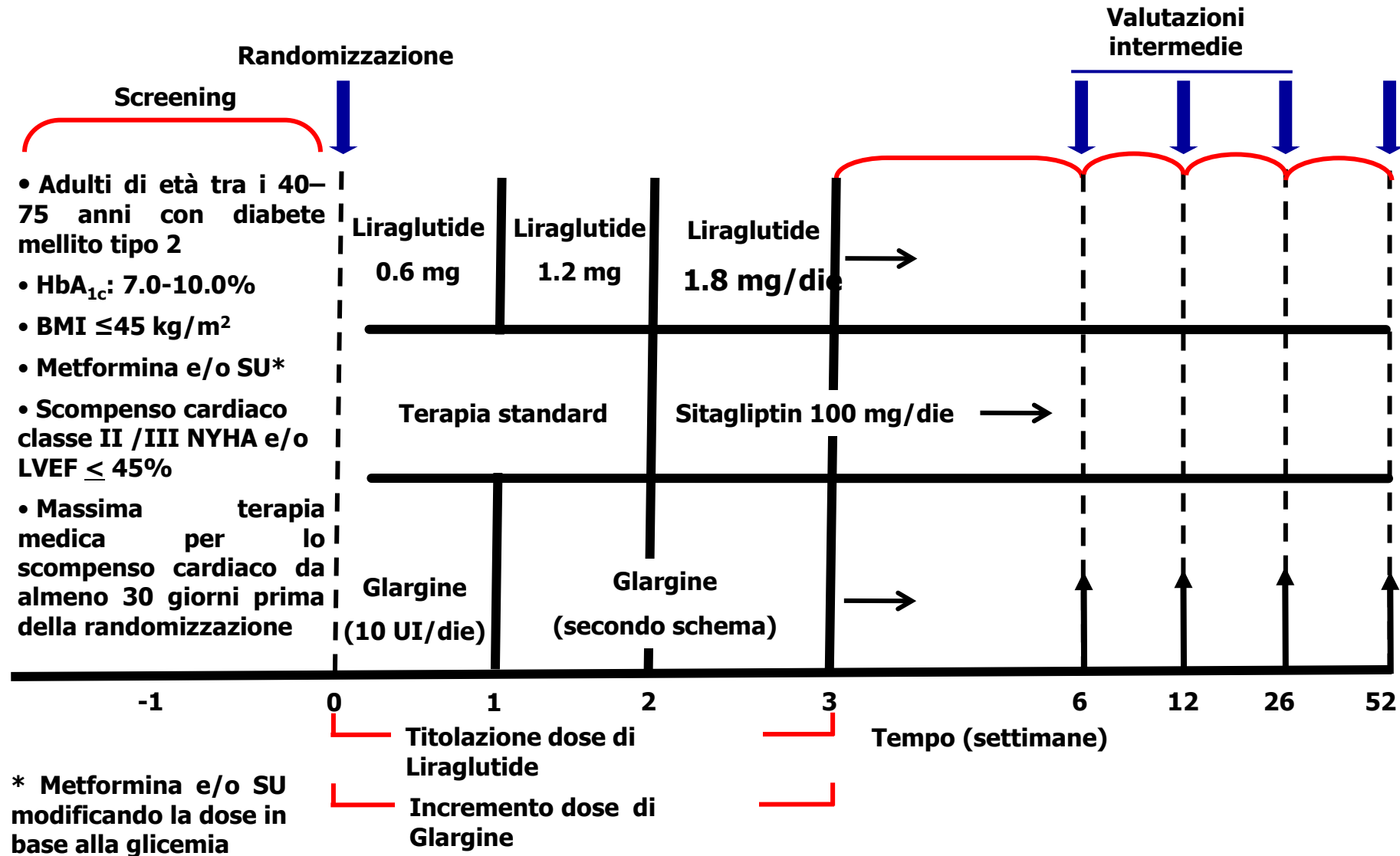


5.2.2. Si raccomanda l'uso di SGLT-2i come farmaci di prima scelta per il trattamento a lungo termine di pazienti con diabete di tipo 2 con scompenso cardiaco. I GLP-1 RA e metformina dovrebbero essere considerati come farmaci di seconda scelta, mentre DPP-4i, acarbose ed insulina come farmaci di terza scelta.

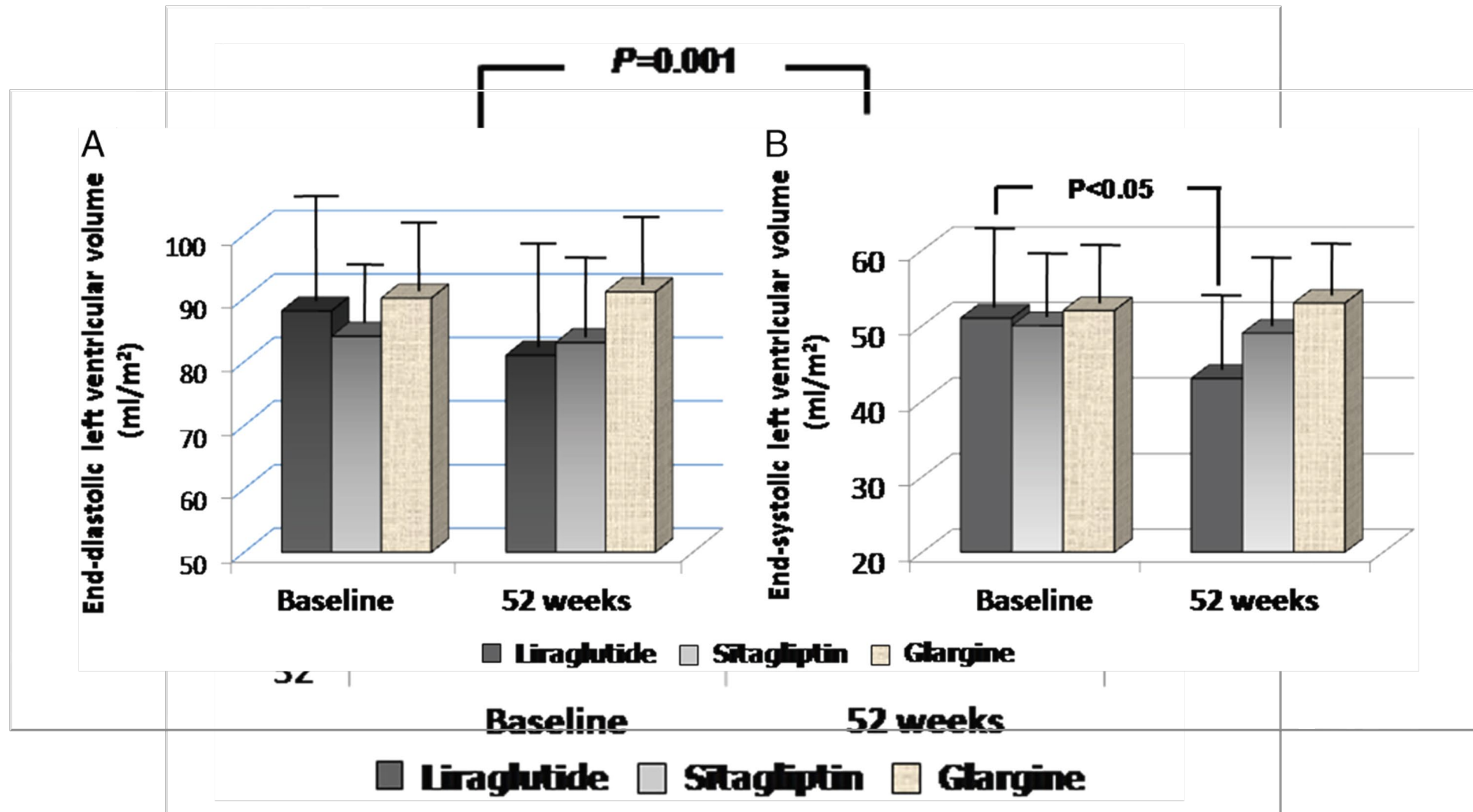




Liraglutide improves cardiac function in patients with type 2 diabetes and HF

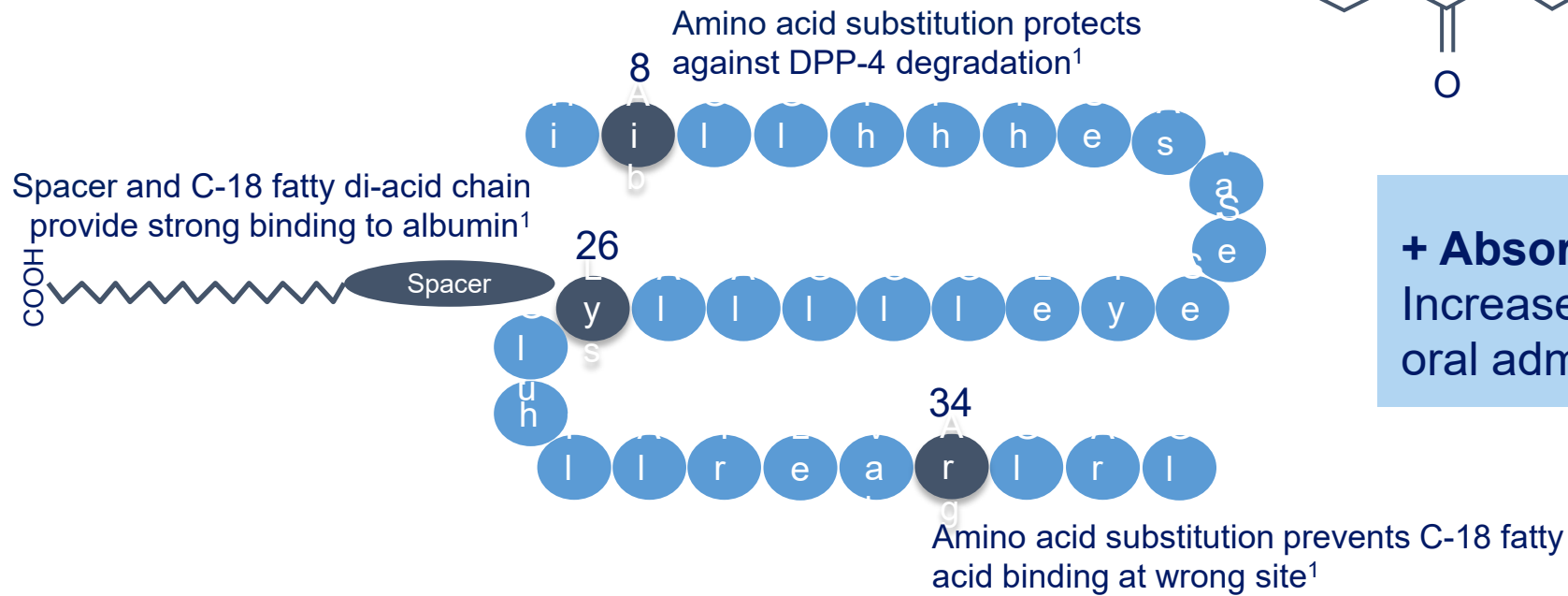


Liraglutide improves cardiac function in patients with type 2 diabetes and HF

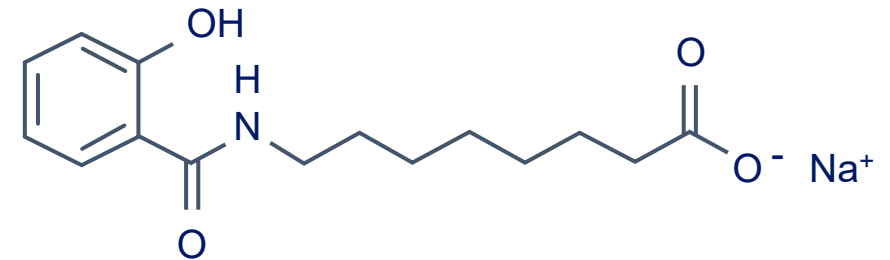


Semaglutide

94% homology to human GLP-1¹
 $t_{1/2}$ of approximately 1 week²⁻⁴



Sodium N-(8-(2-hydroxybenzoyl) Amino) Caprylate

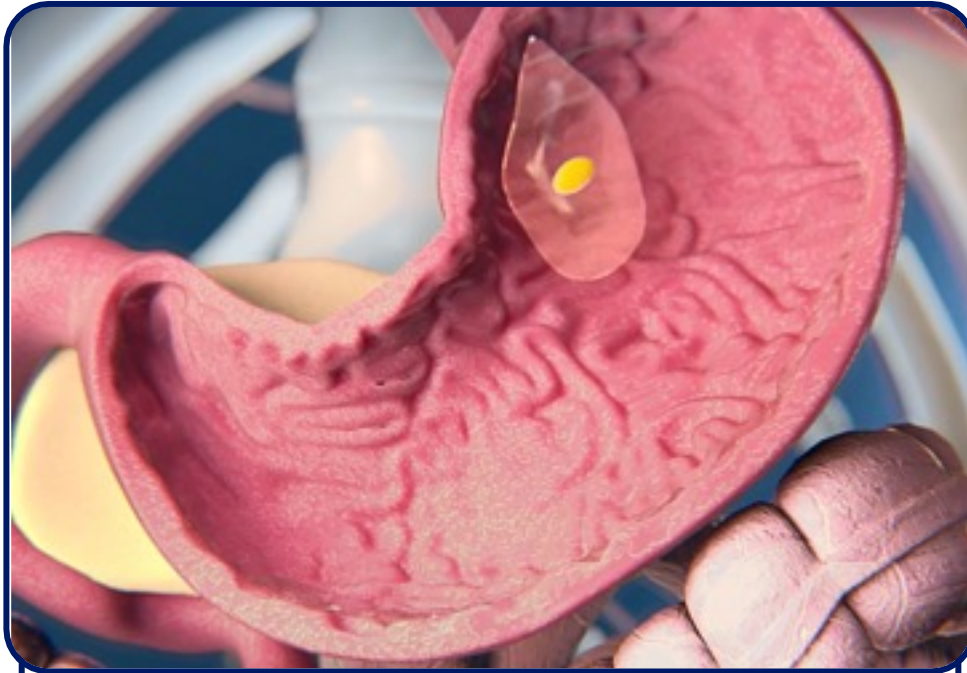


+ Absorption enhancer (SNAC)
 Increases bioavailability of oral administration⁵

DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; SNAC, Sodium N-(8-(2-hydroxybenzoyl) amino) caprylate; $t_{1/2}$, half-life.

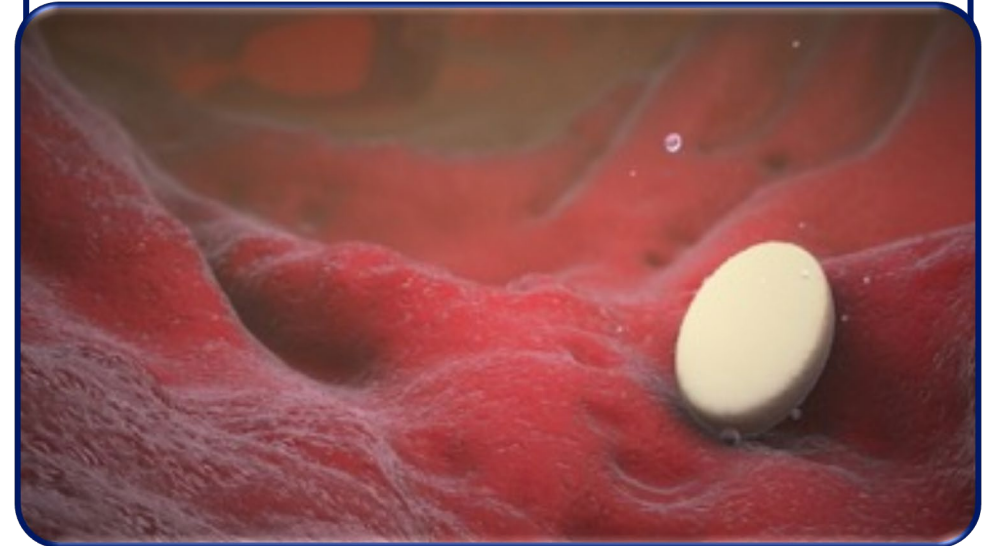
1. Lau J et al. *J Med Chem* 2015;58:7370-80; 2. Kapitza C et al. *J Clin Pharmacol* 2015;55:497-504; 3. Marbury TC et al. *Diabetologia* 2014;57:S358; 4. Connor et al. Poster 1195-P. ADA 77th Scientific Sessions. June 9-13, 2017; 5. Buckley ST et al. *Sci Transl Med* 2018;10:eaar7047.

Absorption of oral Semaglutide occurs in the stomach



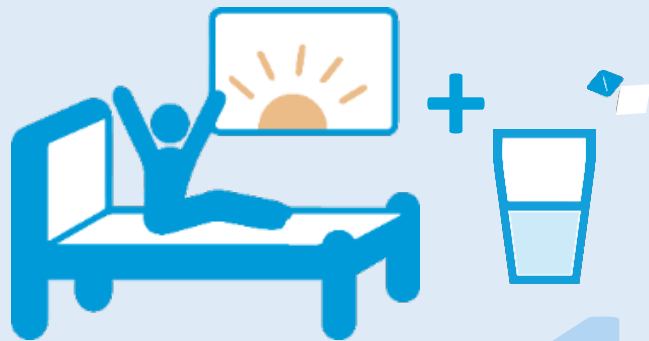
Gastric absorption of Semaglutide due to co-formulation with SNAC

SNAC determines a local increase in pH which favors greater solubility of the tablet and protects against proteolytic degradation



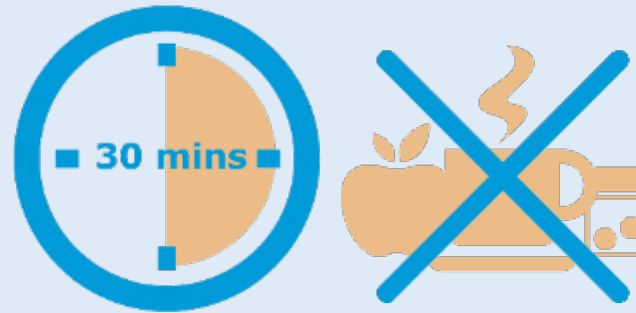
Dosing instructions for oral semaglutide

Wake up fasting and take your semaglutide tablet with up to half a glass of water (approximately 120 mL/4 fl oz)



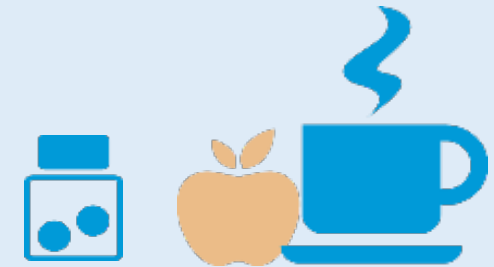
1

Wait at least **30 minutes** before eating, drinking or taking any other oral medication



2

Have your first meal and drink of the day and take any other medications you need



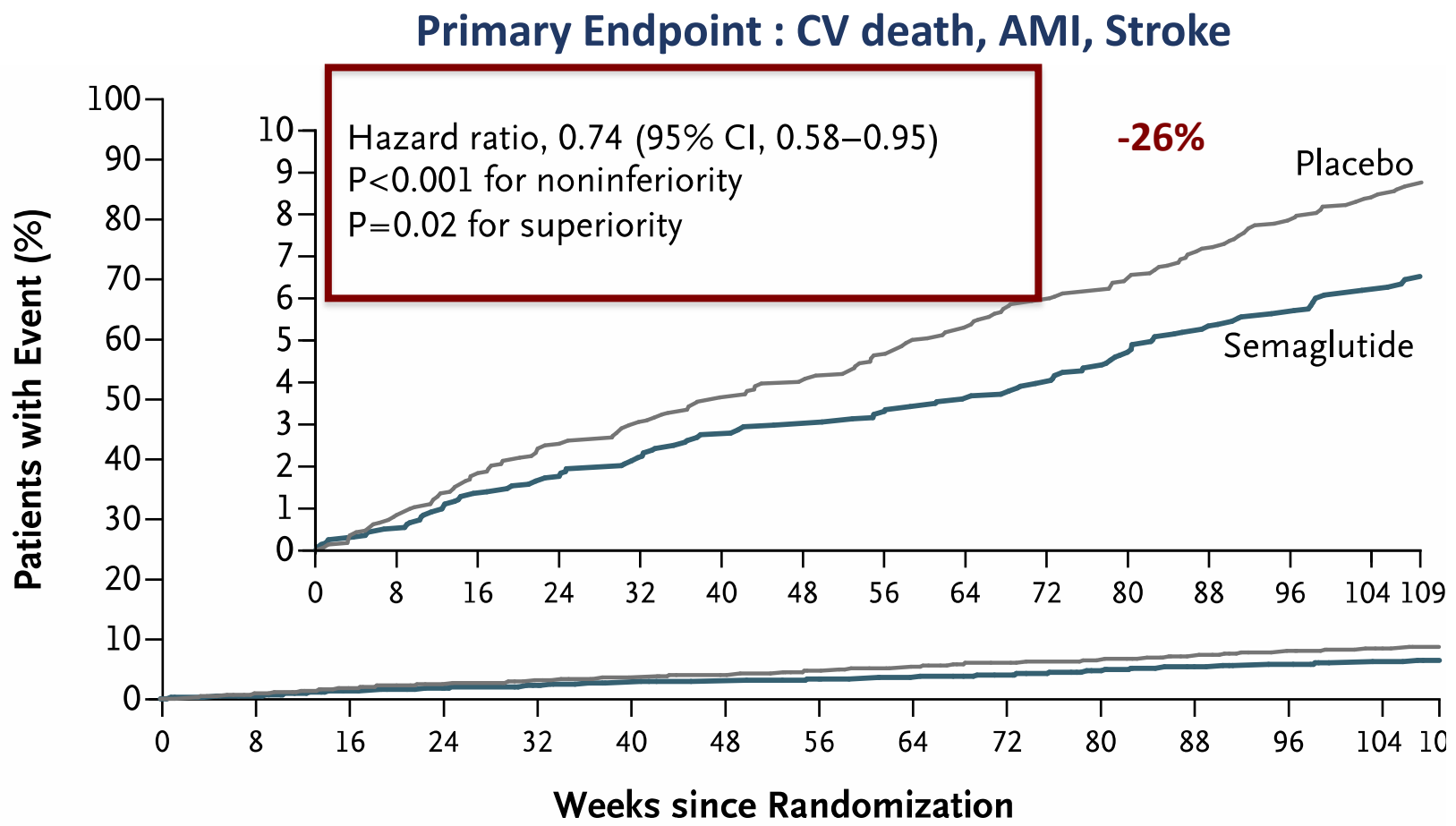
3

Used in Phase 2 and Phase 3a (PIONEER) programme.

1. Buckley ST et al. *Sci Transl Med* 2018;10(467); 2. Bækdal TA et al. *Clin Pharmacokinet* 2019;58:1193–1203.

Semaglutide reduces MACE in type 2 diabetic subjects at high CV risk

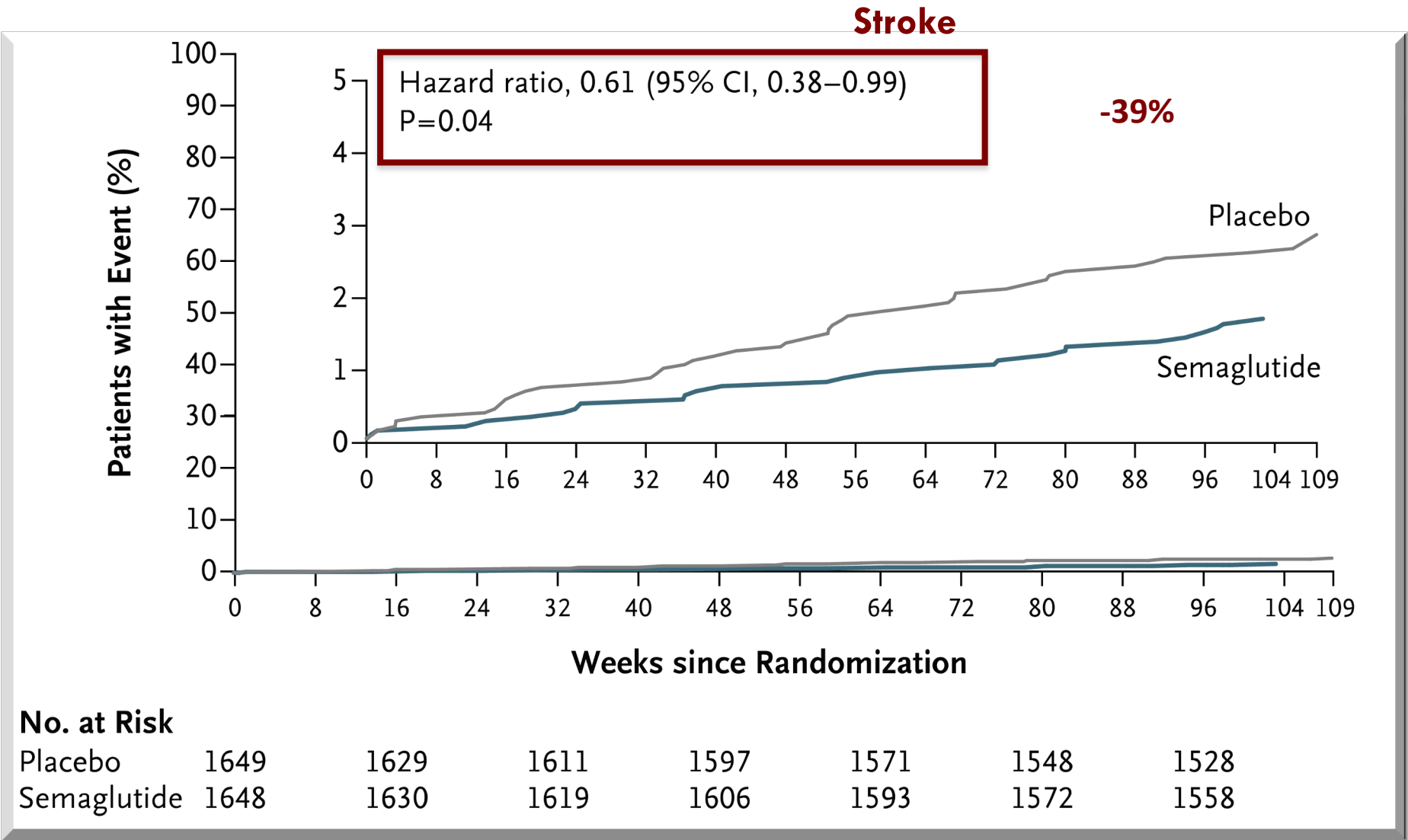
SUSTAIN 6



No. at Risk							
Placebo	1649	1616	1586	1567	1534	1508	1479
Semaglutide	1648	1619	1601	1584	1568	1543	1524

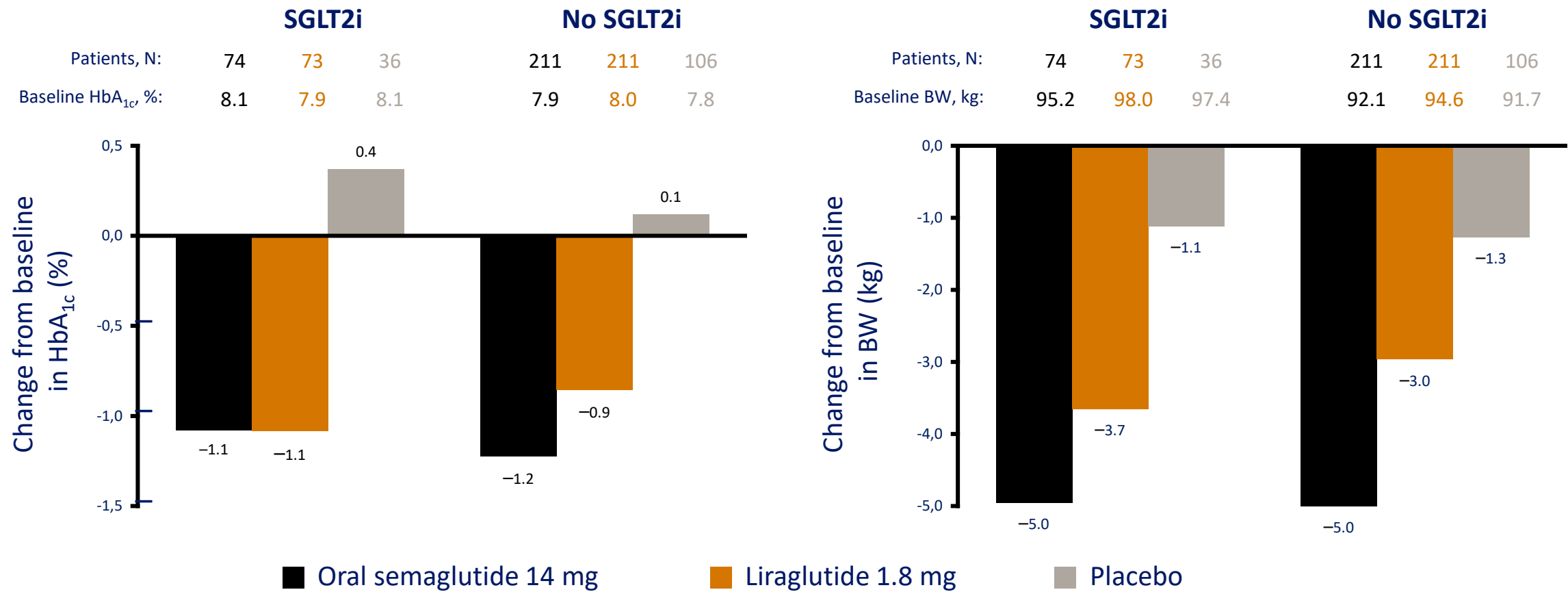
Semaglutide reduces Stroke in type 2 diabetic subjects at high CV risk

SUSTAIN 6



In addition to SGLT2i therapy, oral semaglutide further reduced HbA_{1c} and body weight

PIONEER 4 patient subgroup with Met + SGLT2i at baseline Results at 52 weeks



• Data are estimated means for the trial product estimand (on trial product without rescue medication use). Changes from baseline were analyzed using a mixed model for repeated measurements model with treatment, region, baseline glucose-lowering background and interaction between treatment and baseline glucose-lowering background as categorical fixed effects and baseline value as covariate, all nested within visit, and an unstructured residual covariance matrix. ADA, American Diabetes Association; BW, body weight. Pratley R, et al. Poster 927-P. ADA 80th Scientific Sessions Virtual Meeting. June 12–16, 2020.

Semaglutide reduces endpoints related to cardiovascular risk

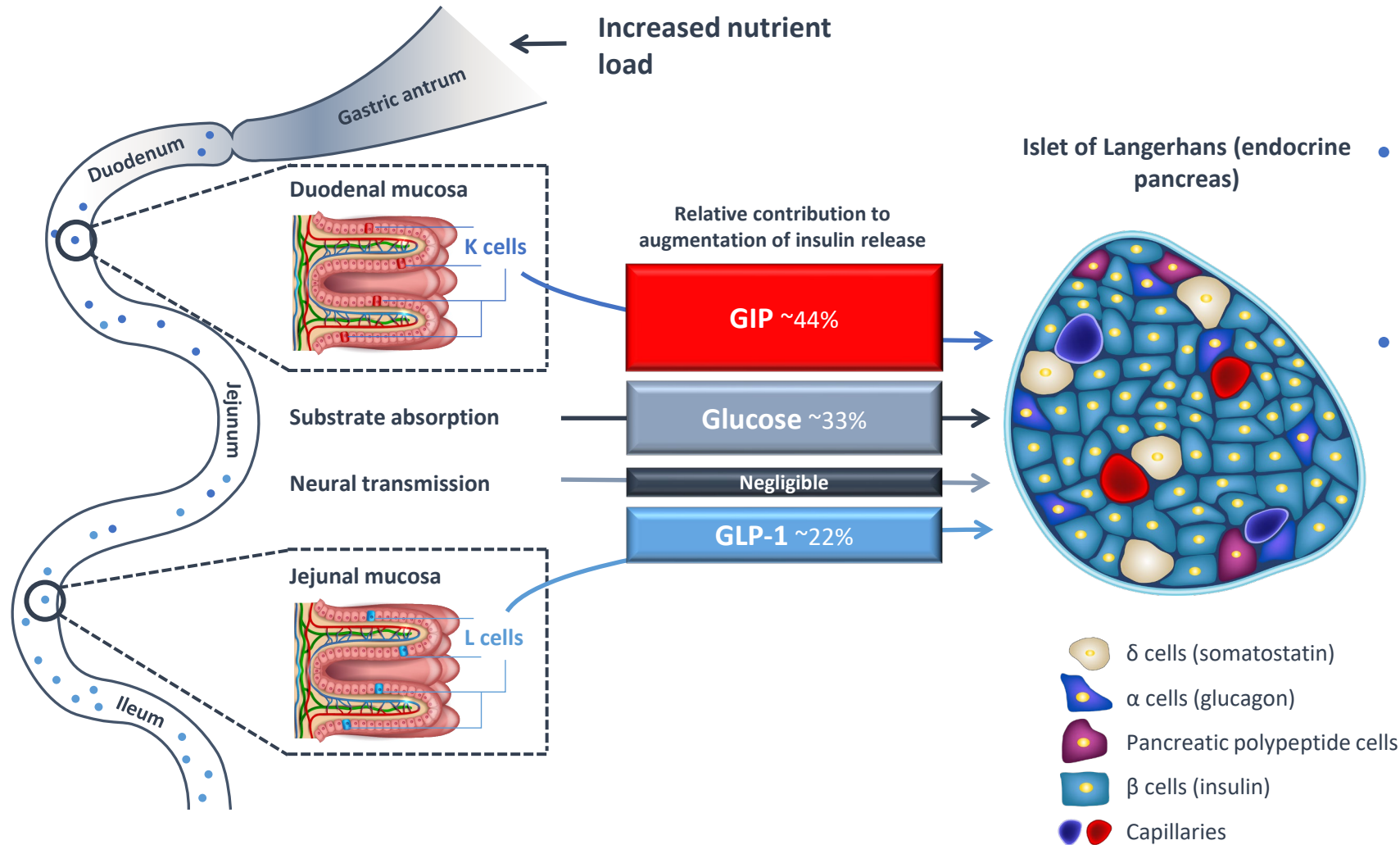
Change at Week 26 in*:		 HbA1c (%)	 Body Weight (kg)	 Systolic Blood Pressure (mmHg)	 Lipid Profile ^{††}	 hsCRP (Ratio to baseline)	 Waist Circumference (cm)
PIONEER 2 (vs empagliflozin)	Sema	-1.3 [†]	-3.8	-5	TC↓, LDL↓	0.67 [†]	-3.7 [†]
	Empa	-0.9	-3.7	-5		0.74	-3.0
PIONEER 3 (vs sitagliptin)	Sema	-1.3 [†]	-3.1 [†]	-3	TC↓, LDL↓, TG↓	n/a	-2.3 [†]
	Sita	-0.8	-0.6	-2			-0.6
PIONEER 4 (vs placebo & liraglutide)	Sema	-1.2	-4.4 [†]	-4	TG↓	n/a	-4.2 [†]
	Lira	-1.1	-3.1	-3			-2.9
PIONEER 7 (vs sitagliptin)	Sema	-1.3 [†]	-2.6 [†]	-4	TC↓, LDL↓	n/a	n/a
	Sita	-0.8	-0.7	-2			

*Treatment policy estimands; change from baseline at Week 26. † p <0.05; † †Up arrow indicates significantly greater increase vs. comparator; down arrow indicates significantly greater decrease
Sema, semaglutide; PBO, placebo; empa, empagliflozin; sita, sitagliptin; lira, liraglutide; BMI, body mass index; n/a, not applicable; TC, total cholesterol; LDL, low-density lipoprotein cholesterol; TG, triglycerides.
1. Rodbard HW et al. Diabetes Care 2019;42:2272–2281; 2. Rosenstock J et al. JAMA 2019;321:1466–80; 3. Pratley R et al. Lancet 2019;394:39–50. Pieber TR et al. Lancet Diabetes Endocrinol 2019;7:528–39.

GLP-1 and GIP are the two major incretins

GLP-1	GIP
▪ Released from L cells in ileum and colon, -NH₂ term inactivation by DPP-IV ▪ Stimulates insulin secretion from β-cell in response to meal ▪ Inhibition of gastric emptying ▪ Inhibits glucagon secretion ▪ Reduction of food intake and body weight ▪ Promotes expansion of β-cell mass – differentiation, $\downarrow$apoptosis	▪ 42 aa peptide, from K cells in duodenum, -NH₂ term inactivation by DPP-IV ▪ Stimulates insulin secretion from β-cell in response to meal ▪ Minimal effects on gastric emptying ▪ Stimulates glucagon secretion at euglycemia during fasting ▪ No significant effects on satiety or body weight ▪ Promotes expansion of β-cell mass in vitro

The Incretin Hormones GIP and GLP-1 Signal to the Pancreas

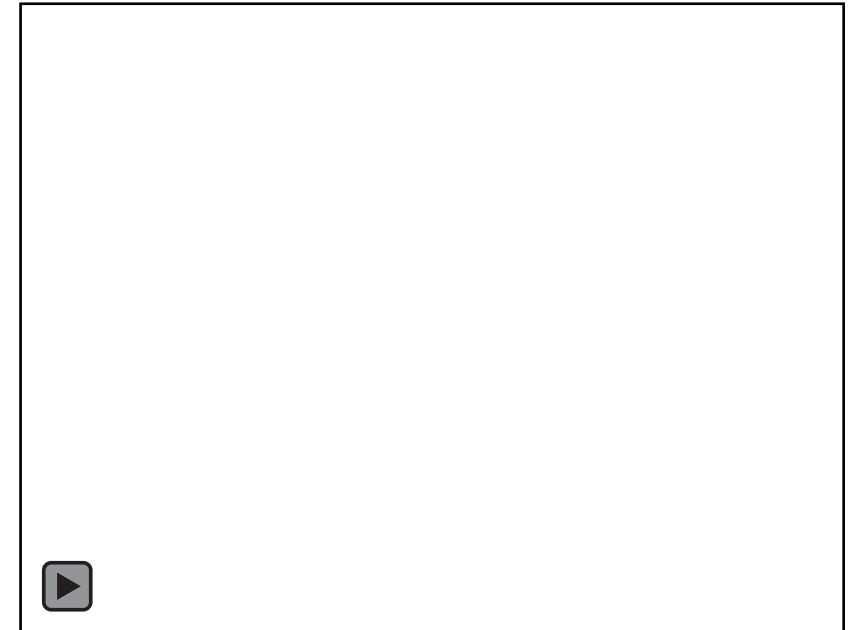


- **Nutrient load in the gut stimulates release of the incretin hormones GIP and GLP-1**
- **GIP and GLP-1 signal to pancreatic islets to enhance glucose-dependent insulin secretion and subsequent PPG clearance in healthy people**

GIP = gastric inhibitory polypeptide; GLP-1 = glucagon-like peptide-1; PPG = postprandial glucose.

Tirzepatide

- **Structure: linear peptide, 39 amino acids based on the GIP sequence¹**
 - **Binds to both GIPR and GLP-1R**
 - **Includes a C20 fatty diacid moiety**
- **Mean half-life: approximately 5 days¹**
- **Plasma concentrations in people with renal impairment do not differ vs healthy people²**



This 3-dimensional rendering of tirzepatide is not an exact reproduction of the molecule and should be used for representative purposes only.
GIP = glucose-dependent insulintropic polypeptide; GIPR = glucose-dependent insulintropic polypeptide receptor; GLP-1R = glucagon-like peptide-1 receptor.

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

SURPASS Clinical Trial Programme

Monotherapy		Combination With OAMs			Combination With Insulin
SURPASS-1 vs placebo¹ (mean T2D duration: 4.7 y)	SURPASS-2 vs semaglutide² Add-on to metformin (mean T2D duration: 8.6 y)	SURPASS-3 vs insulin degludec³ Add-on to metformin with or without SGLT2i (mean T2D duration: 8.4 y)	SURPASS-4 vs insulin glargine⁴ Add-on to ≥1 and ≤3 OAMs (metformin, SGLT2i, or SU) (mean T2D duration: 11.8 y)	SURPASS-5 vs placebo⁵ Add-on to insulin glargine with or without metformin (mean T2D duration: 13.3 y) SURPASS-6⁷ vs insulin lispro (TID) Add-on to insulin glargine with or without metformin (ongoing)	

SURPASS-CVOT vs dulaglutide (ongoing)⁶

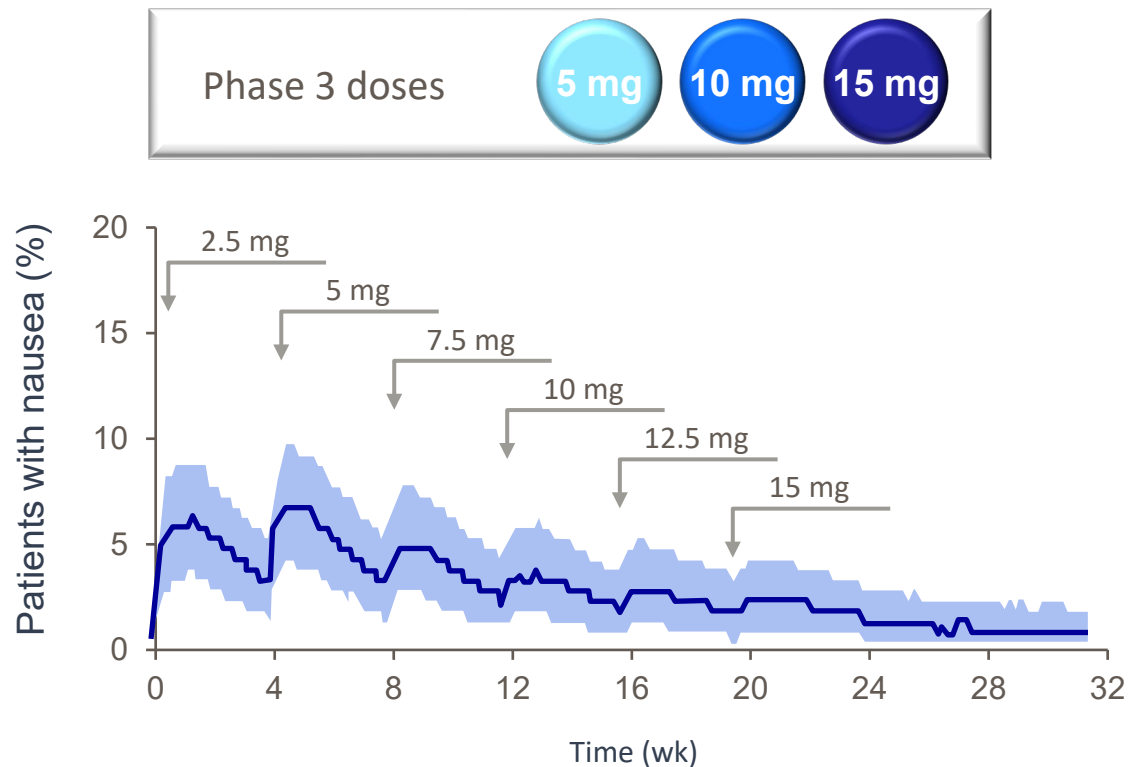
OAM = oral antihyperglycaemic medication; SGLT2i = sodium-glucose co-transporter-2 inhibitor; SU = sulphonylurea; TID = thrice daily; T2D = type 2 diabetes.

1. Rosenstock J, et al. *Lancet*. Published online June 26, 2021. 2. Frias JP, et al. *N Engl J Med*. Published online June 25, 2021. 3. Ludvik B, et al. *Lancet*. 2021; In press. 4. Eli Lilly and Company, 2021. Accessed 5 June 2021. <https://investor.lilly.com/news-releases/news-release-details/lillys-tirzepatide-achieves-all-primary-and-key-secondary-study> 5. Dahl D, et al. Presented at the 81st Scientific Sessions of the ADA. 2021. 6. SURPASS-CVOT. Accessed 1 April 2021. Available at: <https://clinicaltrials.gov/ct2/show/NCT04255433> 7. SURPASS-6. Accessed 1 April 2021. Available at: <https://clinicaltrials.gov/ct2/show/NCT04537923>

Tirzepatide: Dosing in Phase 3 SURPASS Clinical Trial Programme

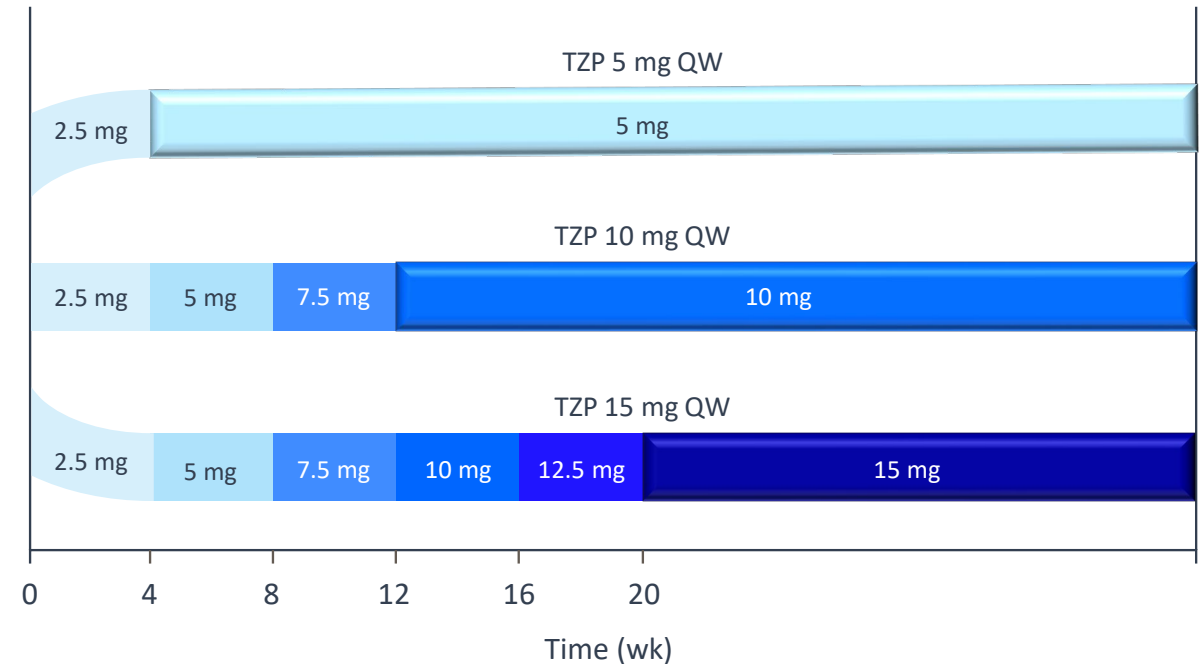
Simulation of dose escalation¹

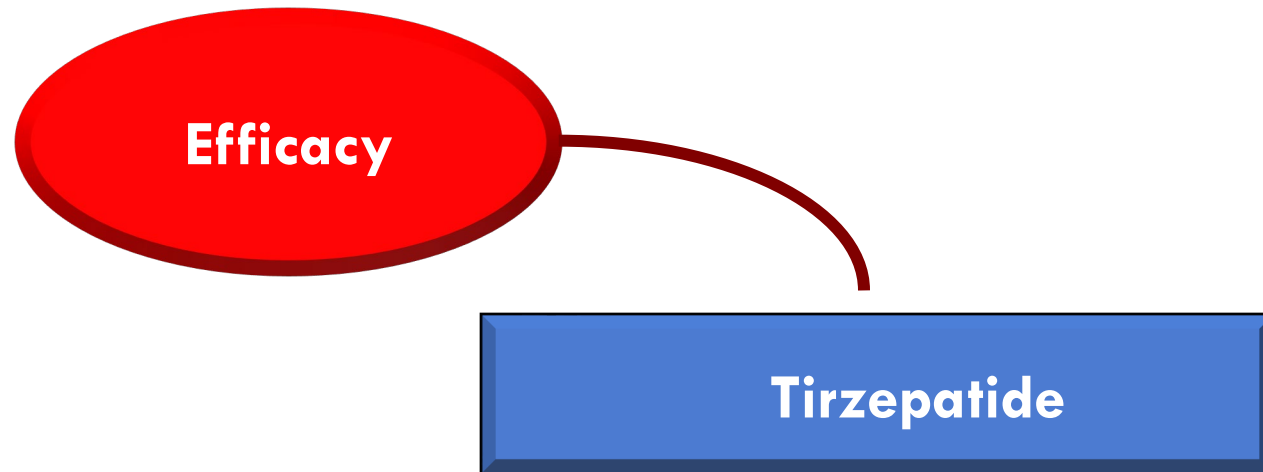
- Model predicts incidence of nausea with slow, step-wise escalation and supports improved tolerability profile from phase 2 to phase 3^{1,2}



QW = once-weekly; TZP = tirzepatide.

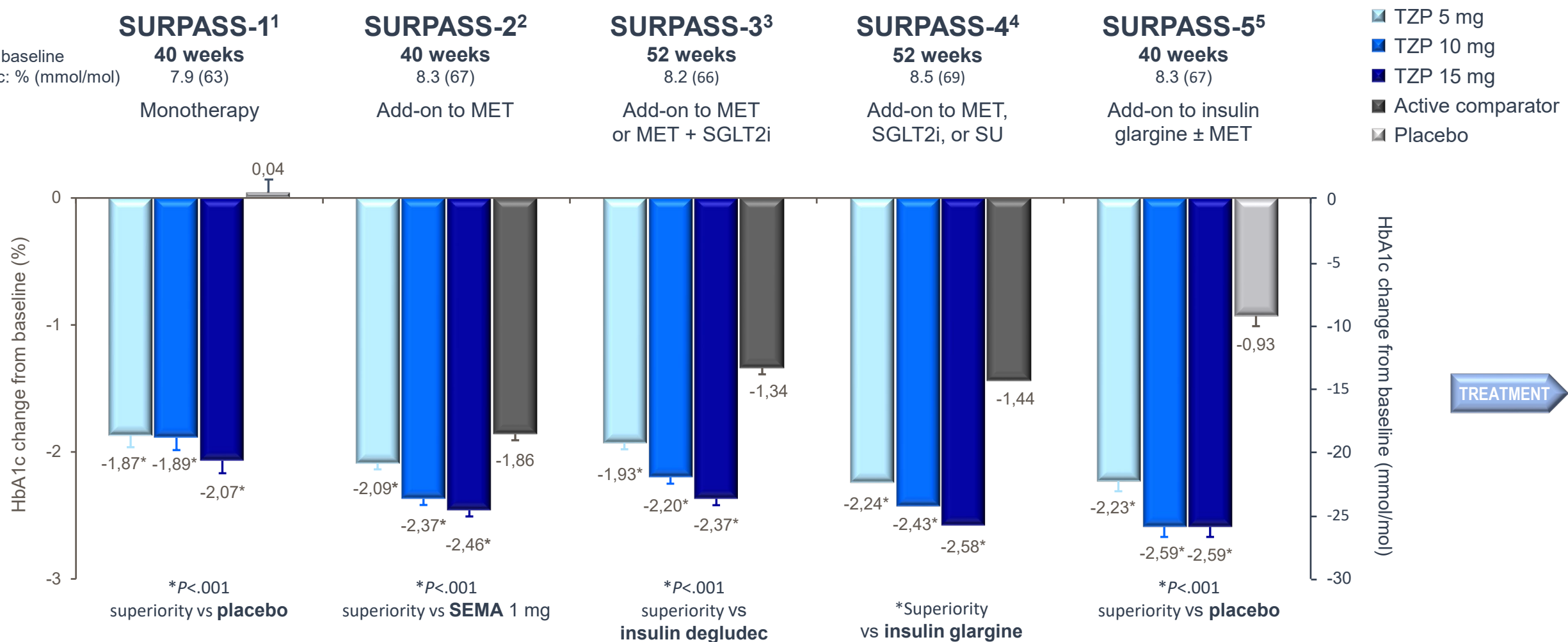
- 2.5-mg increments allow gradual introduction and improved tolerability profile
- Dosing was informed by phase 2 studies and exposure modelling





Tirzepatide: HbA1c Change From Baseline to Primary Endpoint

Efficacy Estimand



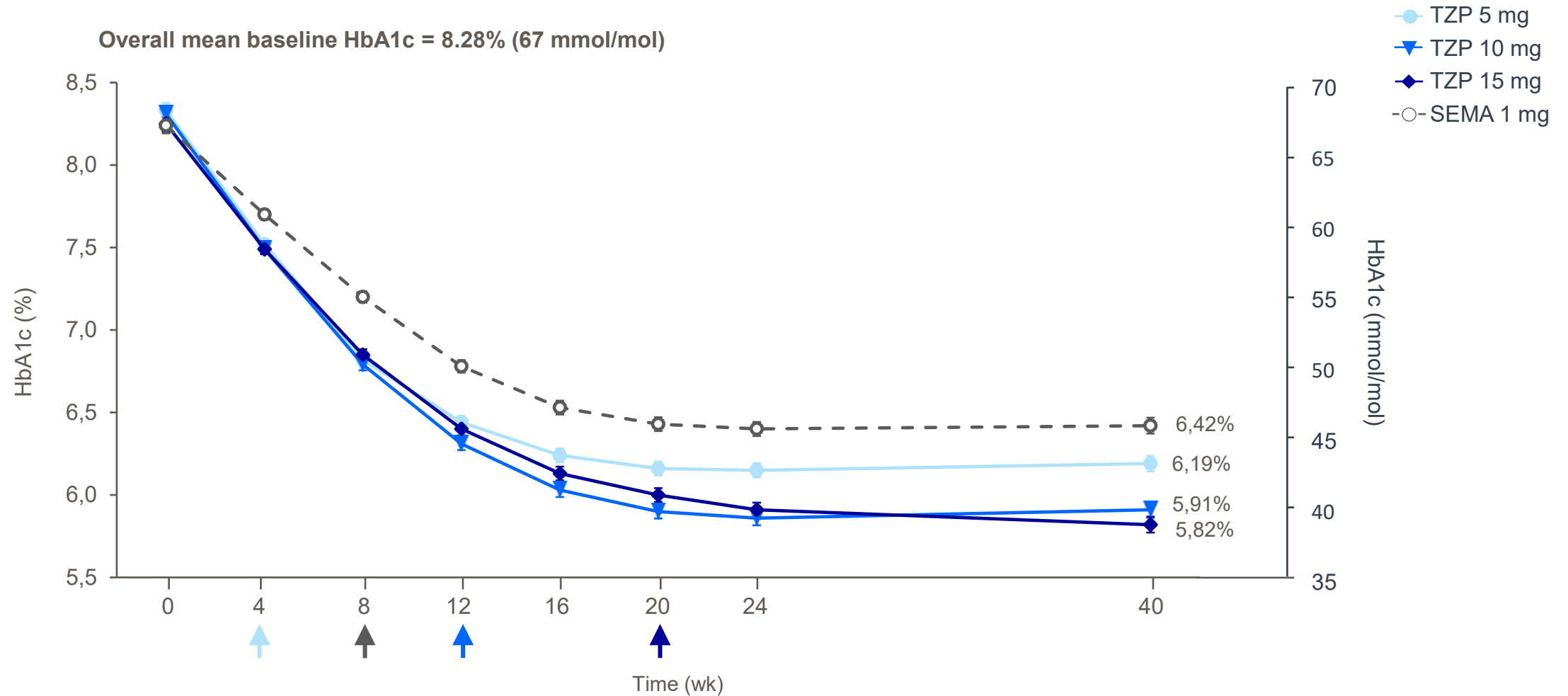
Data are LSM (SE). mITT population (efficacy analysis set). MMRM analysis. Data labels are % HbA1c.

HbA1c = glycated haemoglobin; LSM = least squares mean; MET = metformin; mITT = modified intent-to-treat; MMRM = mixed model repeated measures; SGLT2i = sodium-glucose co-transporter-2 inhibitor; SEMA = semaglutide; SU = sulphonylurea; TZP = tirzepatide.

1. Rosenstock J, et al. *Lancet*. Published online June 26, 2021. 2. Frias JP, et al. *N Engl J Med*. Published online June 25, 2021. 3. Ludvik B, et al. *Lancet*. 2021; In press. 4. Eli Lilly and Company, 2021. Accessed 5 June 2021. <https://investor.lilly.com/news-releases/news-release-details/lillys-tirzepatide-achieves-all-primary-and-key-secondary-study> 5. Dahl D, et al. Presented at the 81st Scientific Sessions of the ADA. 2021.

Tirzepatide: HbA1c Over Time (SURPASS-2)

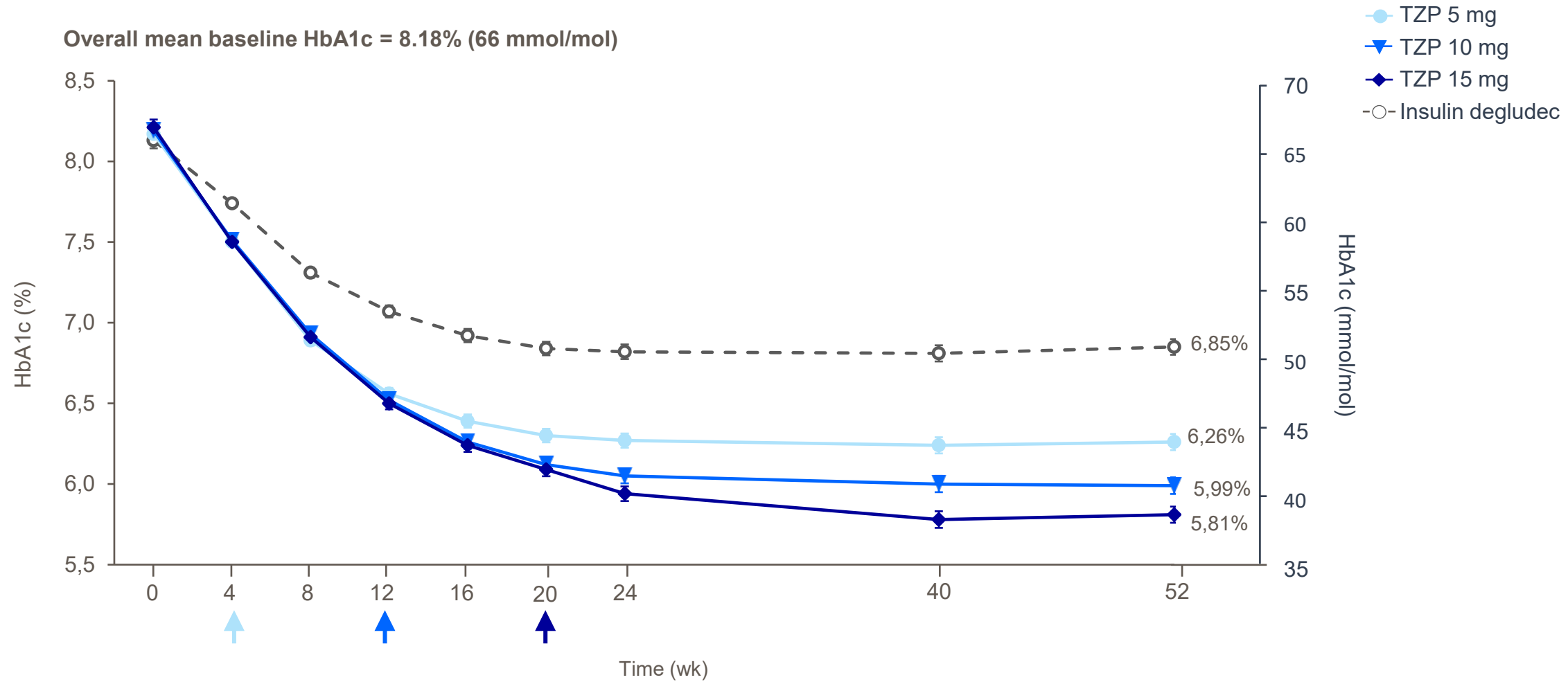
Efficacy Estimand



Data are LSM (SE); mITT population (efficacy analysis set). ANOVA analysis (week 0) and MMRM analysis (week 40). Arrows indicate when the dose of TZP 5 mg, 10 mg, 15 mg, and SEMA 1 mg were achieved. Data labels are % HbA1c. ANOVA = analysis of variance; HbA1c = glycated haemoglobin; LSM = least squares mean; mITT = modified intent-to-treat; MMRM = mixed model repeated measures; SEMA = semaglutide; TZP = tirzepatide. Frias JP, et al. *N Engl J Med*. Published online June 25, 2021.

Tirzepatide: HbA1c Over Time (SURPASS-3)

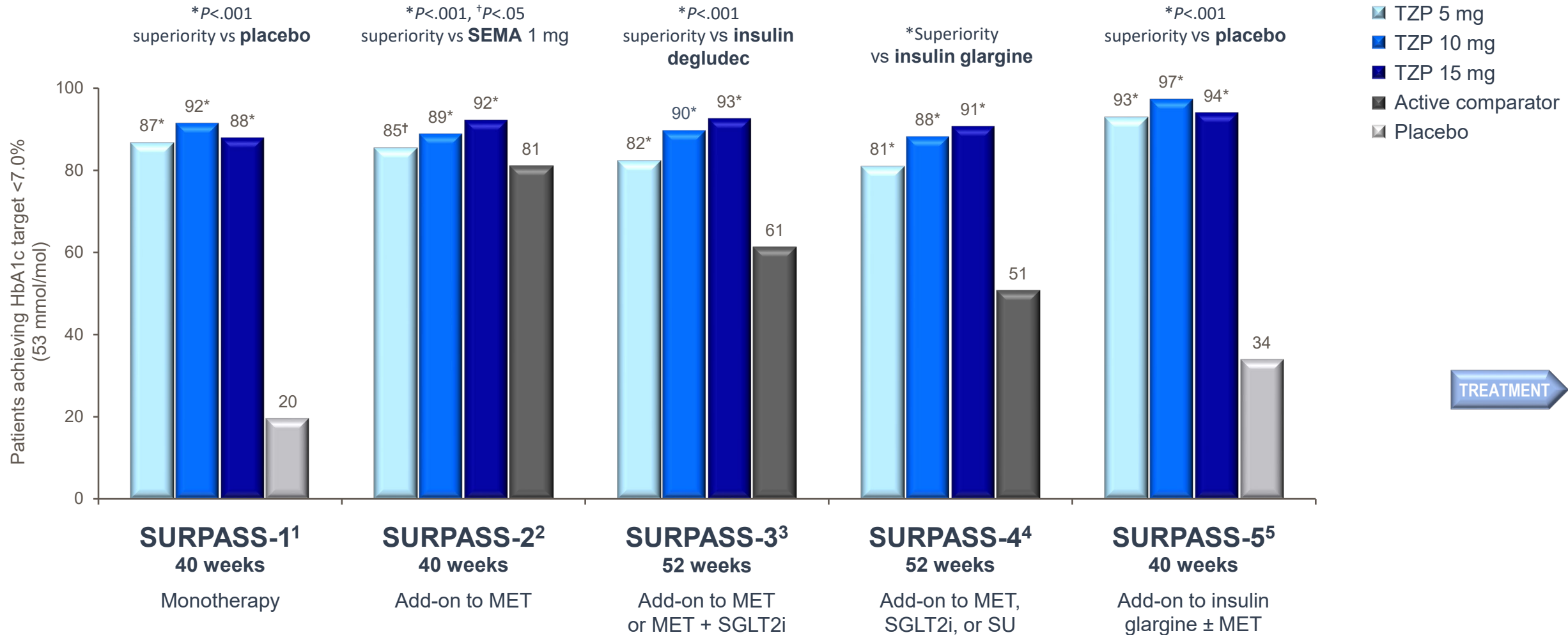
Efficacy Estimand



Data are LSM (SE); mITT population (efficacy analysis set). MMRM analysis (week 52). Arrows indicate when the dose of TZP 5 mg, 10 mg, and 15 mg were achieved. Data labels are % HbA1c.
HbA1c = glycated haemoglobin; LSM = least squares mean; mITT = modified intent-to-treat; MMRM = mixed model repeated measures; TZP = tirzepatide.
Ludvik B, et al. *Lancet*. 2021; In press.

Proportion of Patients Achieving HbA1c <7.0%

Efficacy Estimand



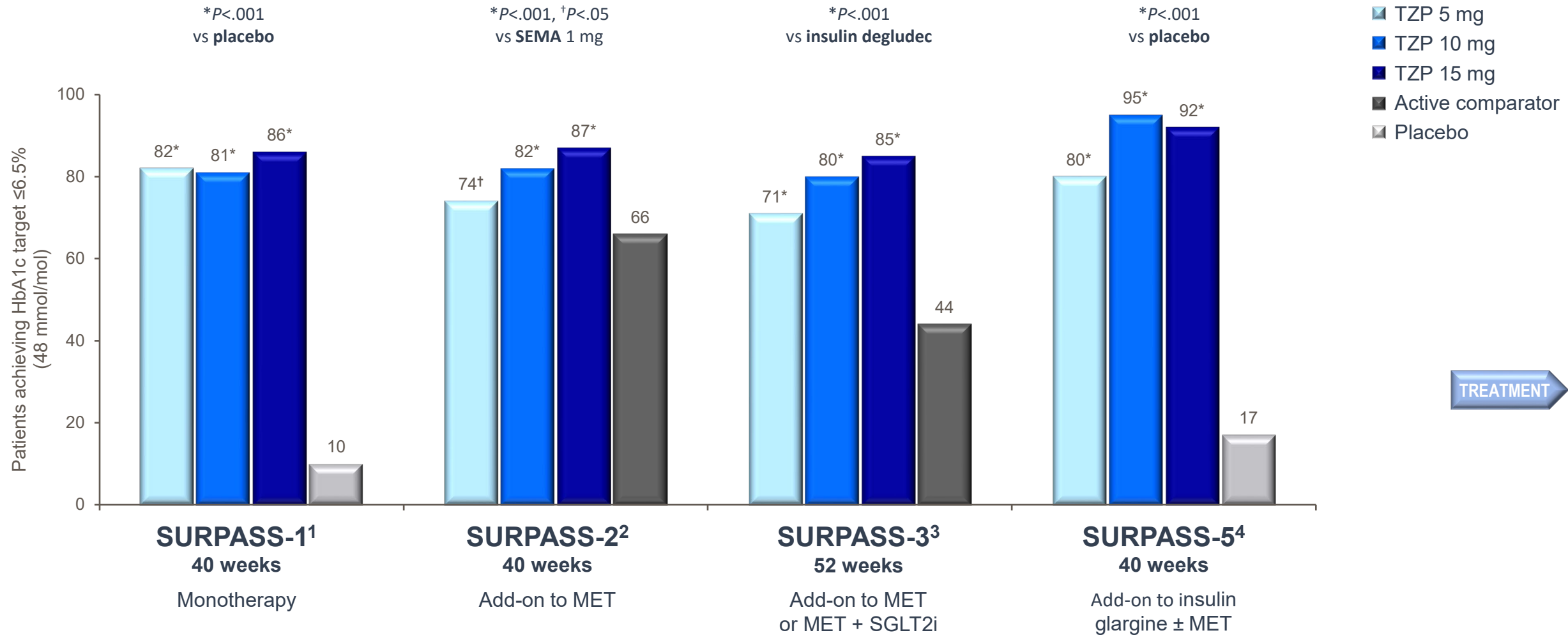
Data are estimated mean; mITT population (efficacy analysis set). Logistic regression.

HbA1c = glycated haemoglobin; MET = metformin; mITT = modified intent-to-treat; SGLT2i = sodium-glucose co-transporter-2 inhibitor; SEMA = semaglutide; SU = sulphonylurea; TZP = tirzepatide.

1. Rosenstock J, et al. *Lancet*. Published online June 26, 2021. 2. Frias JP, et al. *N Engl J Med*. Published online June 25, 2021. 3. Ludvik B, et al. *Lancet*. 2021; In press. 4. Eli Lilly and Company, 2021. Accessed 5 June 2021. <https://investor.lilly.com/news-releases/news-release-details/lillys-tirzepatide-achieves-all-primary-and-key-secondary-study> 5. Dahl D, et al. Presented at the 81st Scientific Sessions of the ADA. 2021.

Proportion of Patients Achieving HbA1c ≤6.5%

Efficacy Estimand



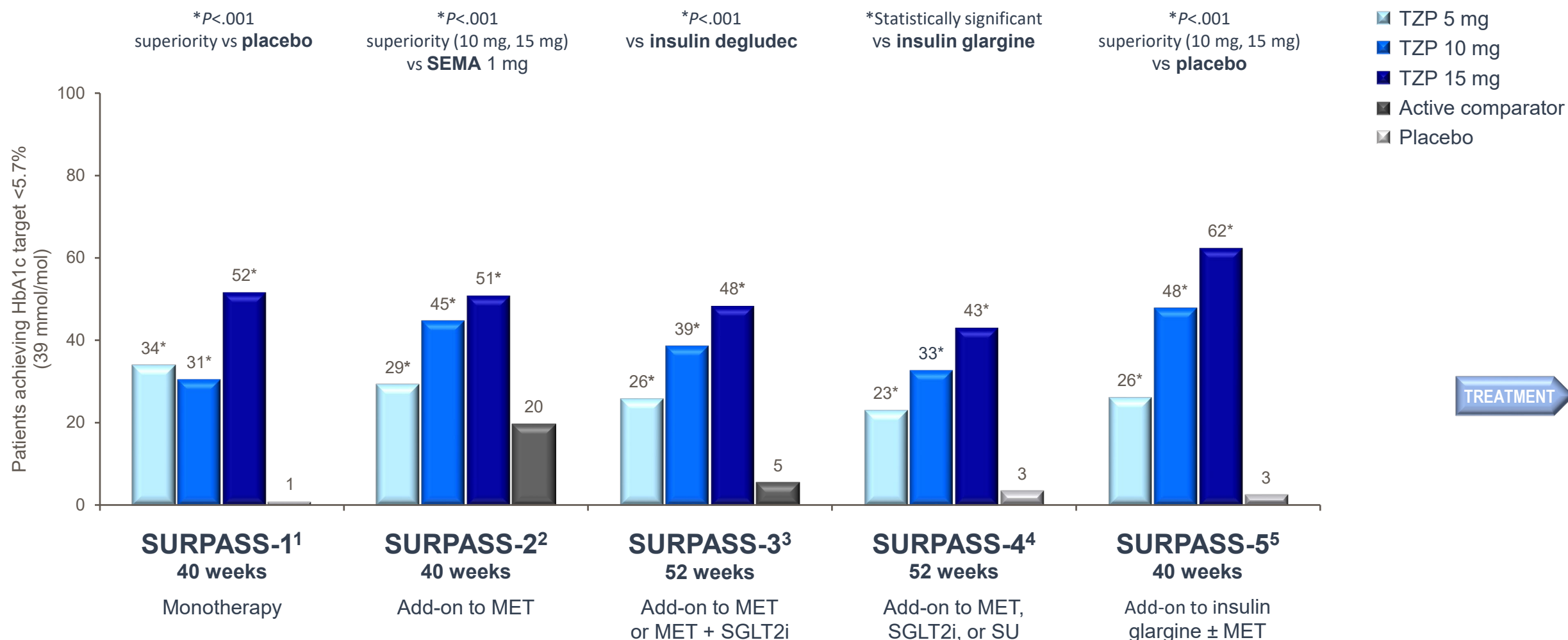
Data are estimated mean; MITT population (efficacy analysis set). Logistic regression.

HbA1c = glycated haemoglobin; MET = metformin; MITT = modified intent-to-treat; SGLT2i = sodium-glucose co-transporter-2 inhibitor; SEMA = semaglutide; TZP = tirzepatide.

1. Rosenstock J, et al. *Lancet*. Published online June 26, 2021. 2. Frias JP, et al. *N Engl J Med*. Published online June 25, 2021. 3. Ludvik B, et al. *Lancet*. 2021; In press. 4. Dahl D, et al. Presented at the 81st Scientific Sessions of the ADA. 2021.

Proportion of Patients Achieving HbA1c <5.7%

Efficacy Estimand



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

HbA1c = glycated haemoglobin; MET = metformin; mITT = modified intent-to-treat; SGLT2i = sodium-glucose co-transporter-2 inhibitor; SEMA = semaglutide; SU = sulphonylurea; TZP = tirzepatide.

1. Rosenstock J, et al. *Lancet*. Published online June 26, 2021. 2. Frias JP, et al. *N Engl J Med*. Published online June 25, 2021. 3. Ludvik B, et al. *Lancet*. 2021; In press. 4. Eli Lilly and Company, 2021. <https://investor.lilly.com/news-releases/news-release-details/lillys-tirzepatide-achieves-all-primary-and-key-secondary-study>. Accessed 5 June 2021. 5. Dahl D, et al. Presented at the 81st Scientific Sessions of the ADA. 2021.

FSG Change From Baseline to Primary Endpoint

Treatment Regimen Estimand

SURPASS-1¹

40 weeks

154 (8.5)

Monotherapy

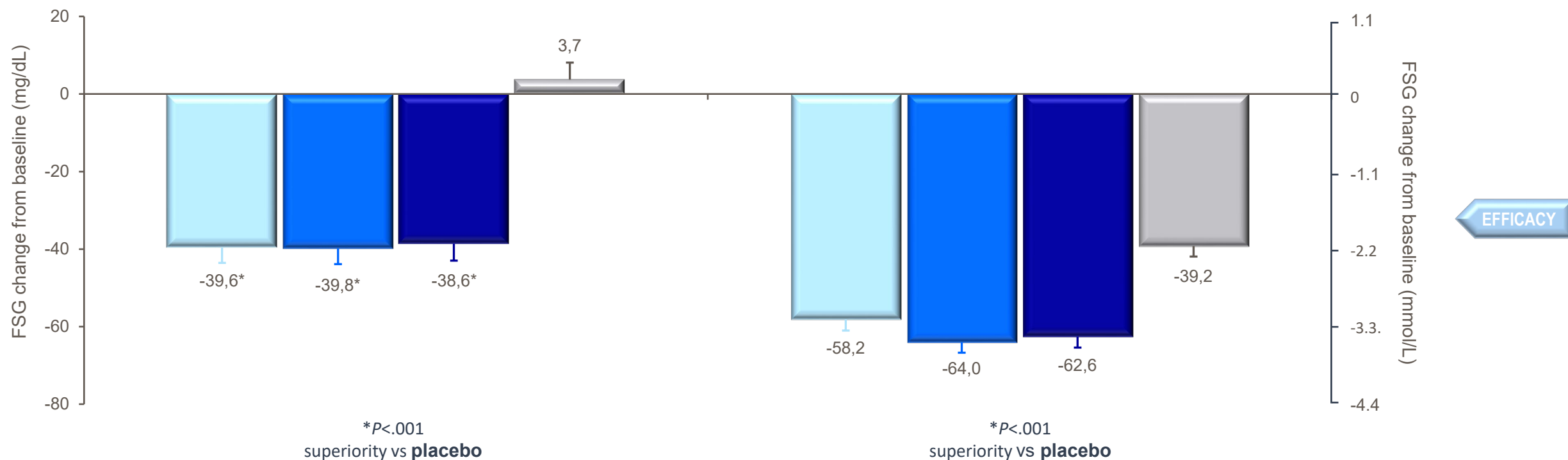
SURPASS-5⁴

40 weeks

163 (9.1)

Add-on to insulin
glargine ± MET

- TZP 5 mg
- TZP 10 mg
- TZP 15 mg
- Active comparator
- Placebo

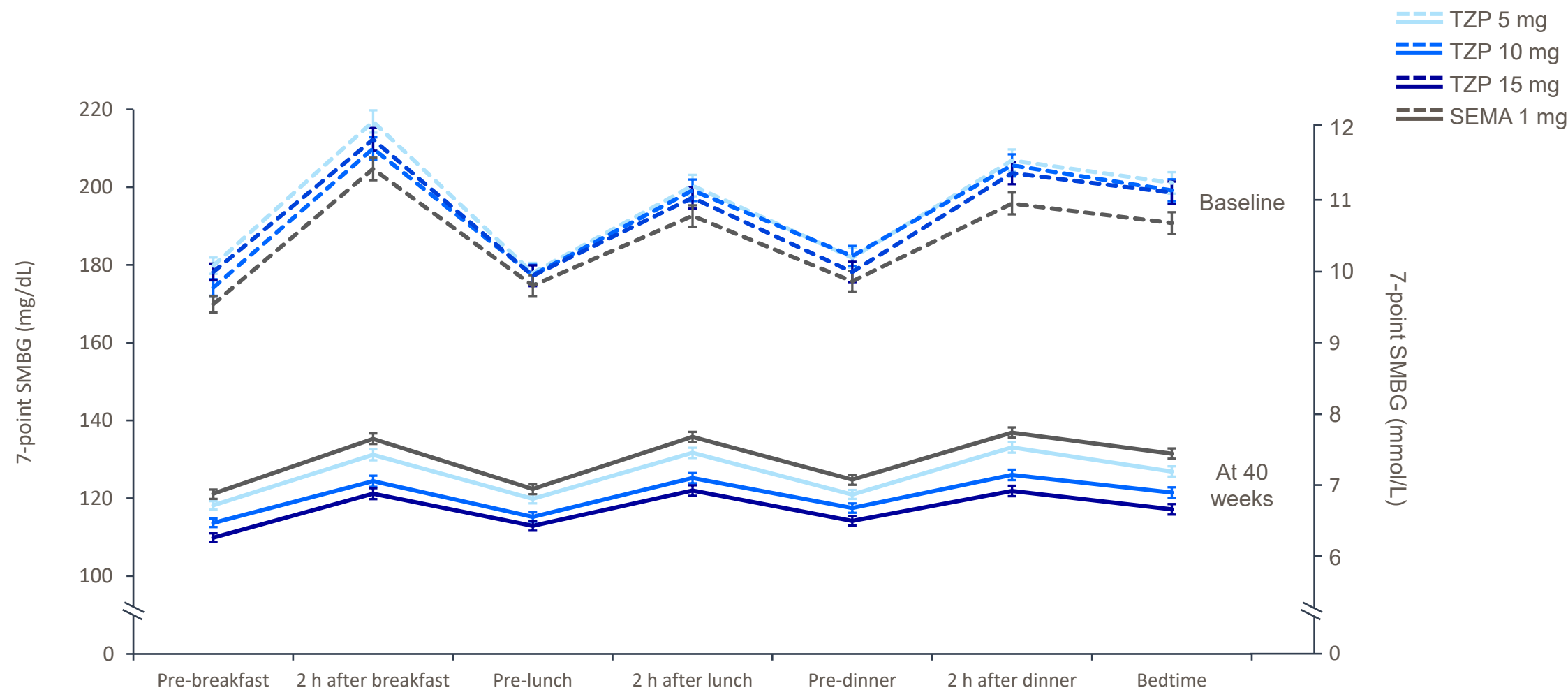


Data are LSM (SE); mITT population (full analysis set) MMRM analysis. Data labels are in mg/dL.

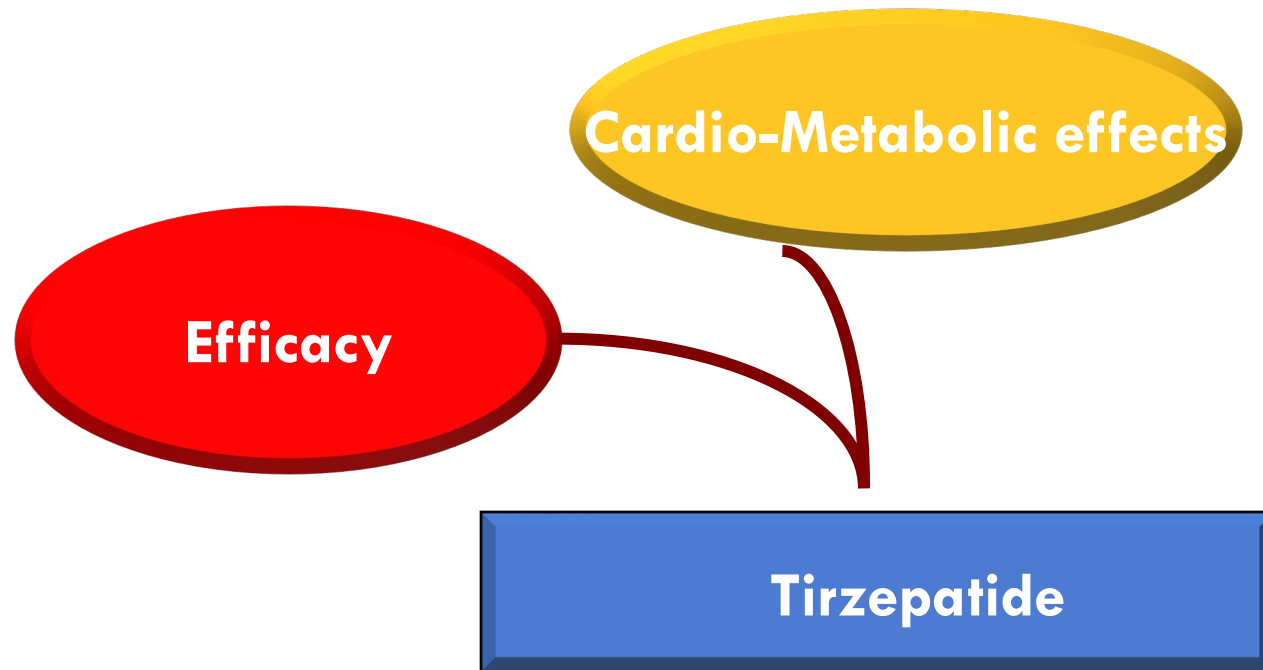
FSG = fasting serum glucose; LSM = least squares mean; MET = metformin; mITT = modified intent-to-treat; MMRM = mixed model repeated measures; TZP = tirzepatide.

1. Rosenstock J, et al. *Lancet*. Published online June 26, 2021. 2. Dahl D, et al. Presented at the 81st Scientific Sessions of the ADA. 2021.

7-Point SMBG at Baseline and at 52 Weeks (SURPASS-3)

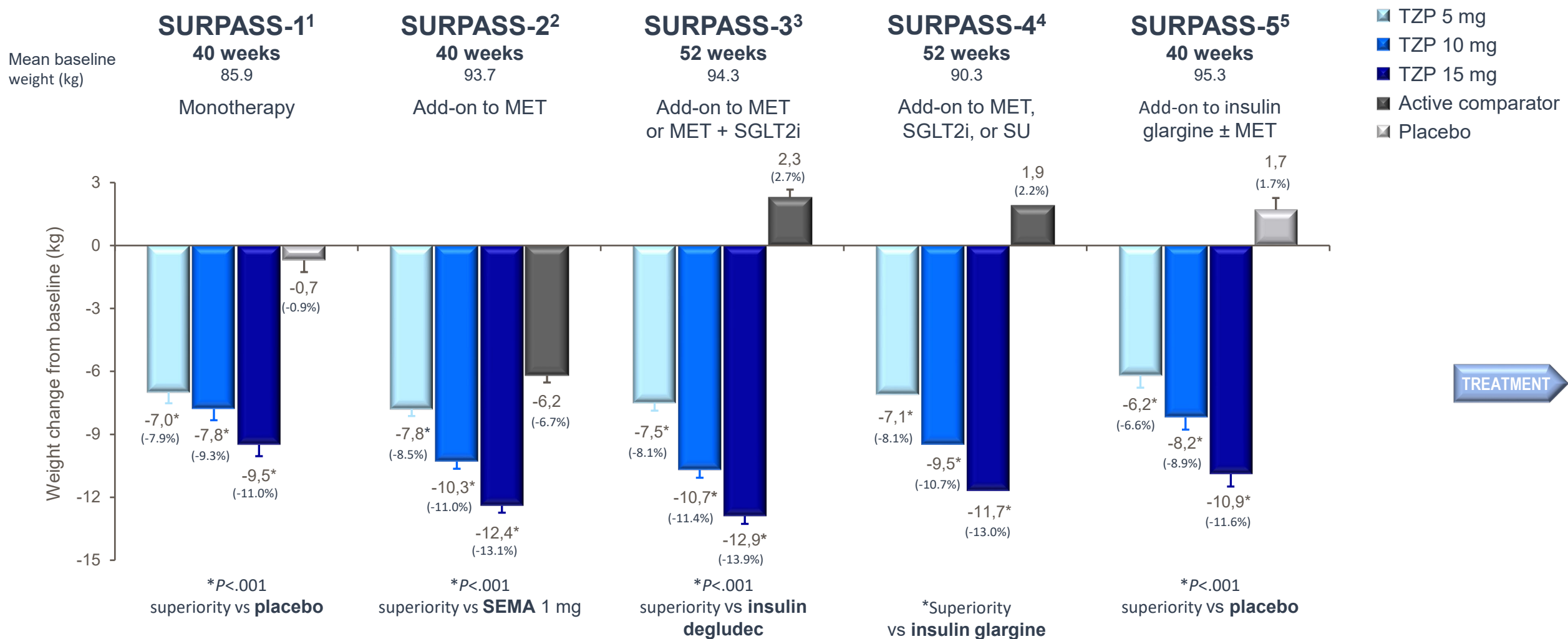


Data are LSM (SE); mITT population (efficacy analysis set) ANOVA analysis (baseline) and MMRM analysis (week 40). Data labels are in mg/dL.
ANOVA = analysis of variance; LSM = least squares mean; mITT = modified intent-to-treat; MMRM = mixed model repeated measures; SMBG = self-monitored blood glucose; SEMA = semaglutide; TZP = tirzepatide.
Frias JP, et al. *N Engl J Med*. Published online June 25, 2021.



Body Weight Change From Baseline to Primary Endpoint

Efficacy Estimand



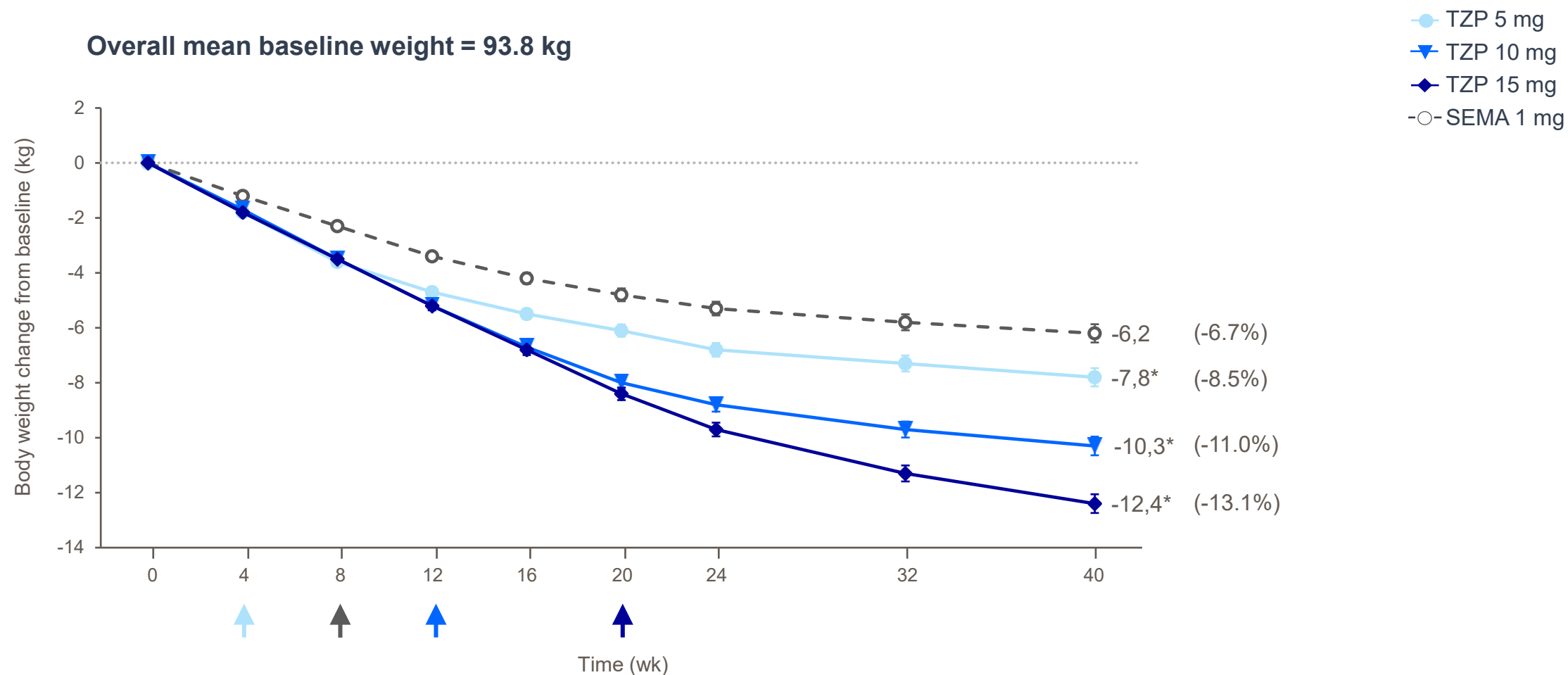
Data are LSM (SE); mITT population (efficacy analysis set). MMRM analysis.

LSM = least squares mean; MET = metformin; mITT = modified intent-to-treat; MMRM = mixed model repeated measures; SGLT2i = sodium-glucose co-transporter-2 inhibitor; SEMA = semaglutide; SU = sulphonylurea; TzEP = tirzepatide.

1. Rosenstock J, et al. *Lancet*. Published online June 26, 2021. 2. Frias JP, et al. *N Engl J Med*. Published online June 25, 2021. 3. Ludvik B, et al. *Lancet*. 2021; In press. 4. Eli Lilly and Company, 2021. Accessed 5 June 2021. <https://investor.lilly.com/news-releases/news-release-details/lillys-tirzepatide-achieves-all-primary-and-key-secondary-study>. 5. Dahl D, et al. Presented at the 81st Scientific Sessions of the ADA. 2021.

Body Weight Change Over Time (SURPASS-2)

Efficacy Estimand



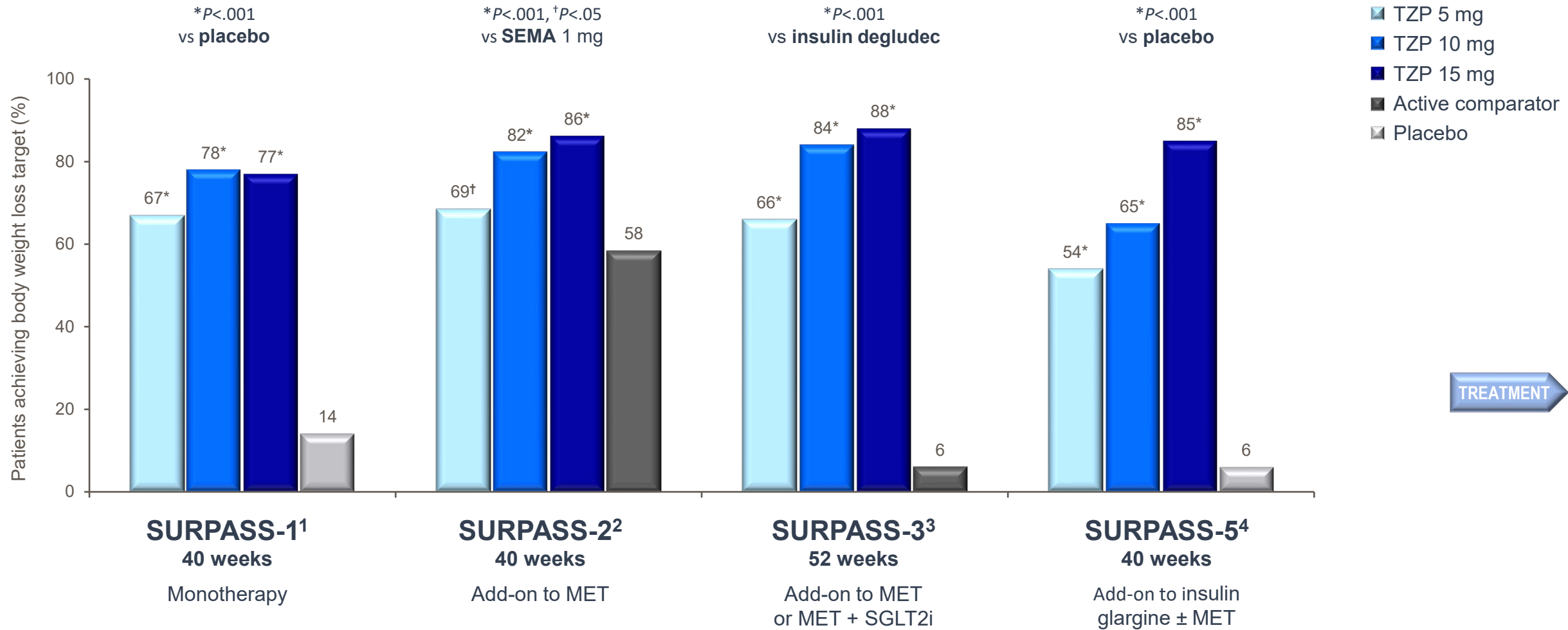
Data are LSM (SE); mITT population (efficacy analysis set). ANOVA analysis (week 0) and MMRM analysis (week 40). Arrows indicate when the dose of TZP 5 mg, 10 mg, 15 mg, and SEMA 1 mg were achieved. Data labels are weight in kg (% change from baseline).

* $P < .001$ vs SEMA.

ANOVA = analysis of variance; LSM = least squares mean; mITT = modified intent-to-treat; MMRM = mixed model repeated measures; SEMA = semaglutide; TZP = tirzepatide.

Frias JP, et al. *N Engl J Med*. Published online June 25, 2021.

Proportion of Patients Achieving $\geq 5\%$ Weight Loss

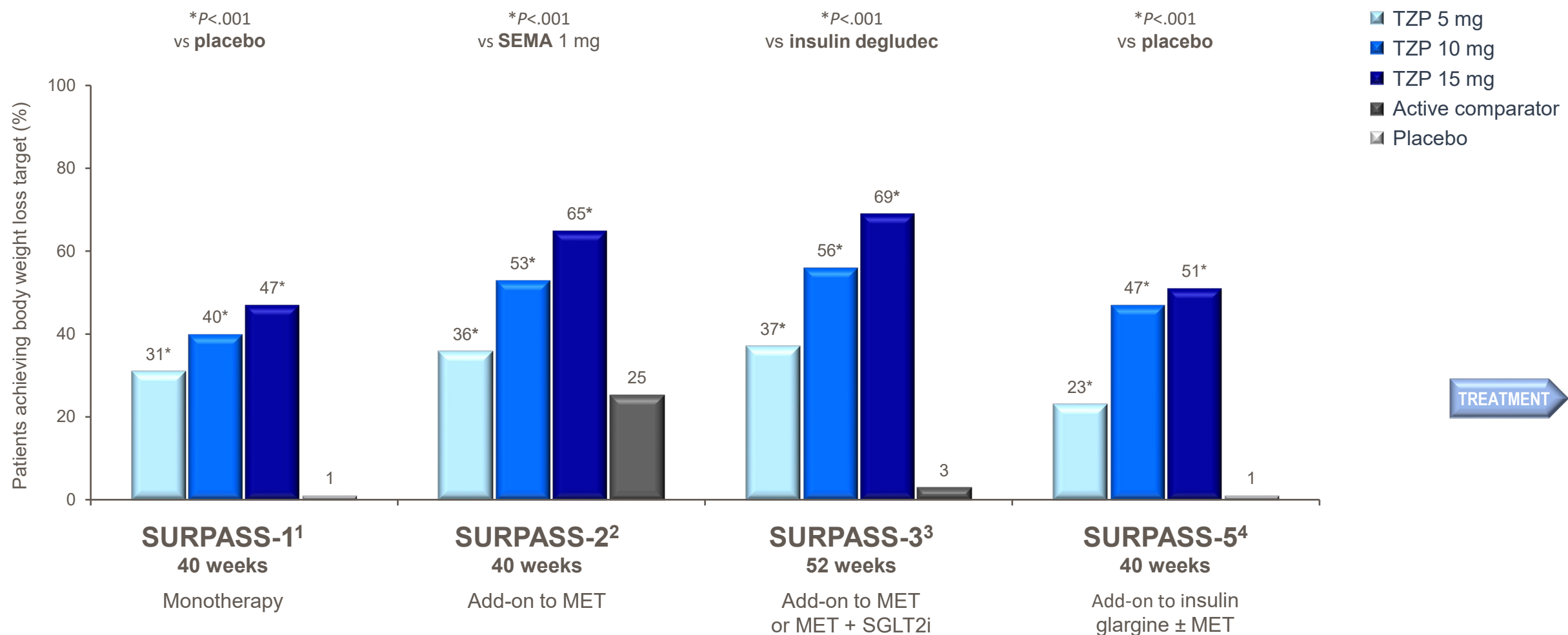


Data are estimated mean; mITT population (efficacy analysis set). Logistic regression.

MET = metformin; mITT = modified intent-to-treat; SGLT2i = sodium-glucose co-transporter-2 inhibitor; SEMA = semaglutide; TZIP = tirzepatide.

1. Rosenstock J, et al. *Lancet*. Published online June 26, 2021. 2. Frias JP, et al. *N Engl J Med*. Published online June 25, 2021. 3. Ludvik B, et al. *Lancet*. 2021; In press. 4. Dahl D, et al. Presented at the 81st Scientific Sessions of the ADA. 2021.

Proportion of Patients Achieving $\geq 10\%$ Weight Loss

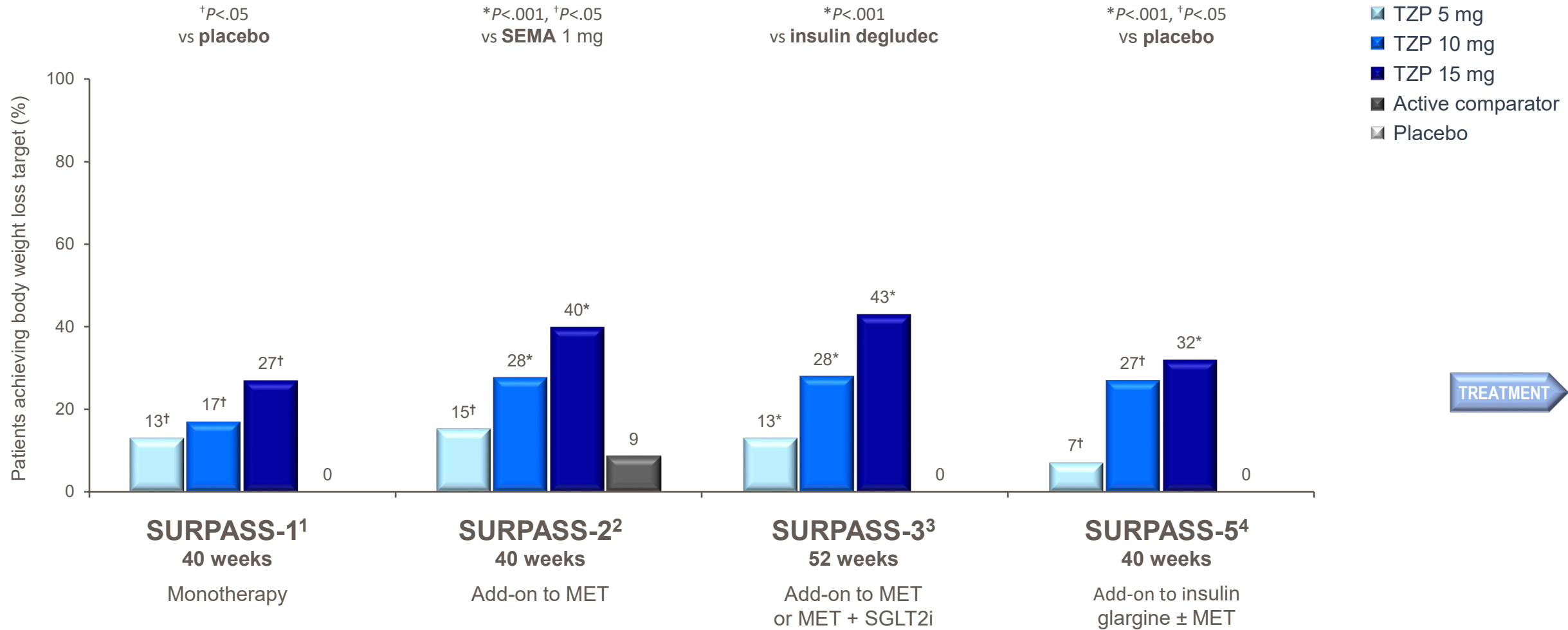


Data are estimated mean; mITT population (efficacy analysis set). Logistic regression.

MET = metformin; mITT = modified intent-to-treat; SGLT2i = sodium-glucose co-transporter-2 inhibitor; SEMA = semaglutide; TZP = tirzepatide.

1. Rosenstock J, et al. *Lancet*. Published online June 26, 2021. 2. Frias JP, et al. *N Engl J Med*. Published online June 25, 2021. 3. Ludvik B, et al. *Lancet*. 2021; In press. 4. Dahl D, et al. Presented at the 81st Scientific Sessions of the ADA. 2021.

Proportion of Patients Achieving $\geq 15\%$ Weight Loss



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

MET = metformin; mITT = modified intent-to-treat; SGLT2i = sodium-glucose co-transporter-2 inhibitor; SEMA = semaglutide; TZP = tirzepatide.

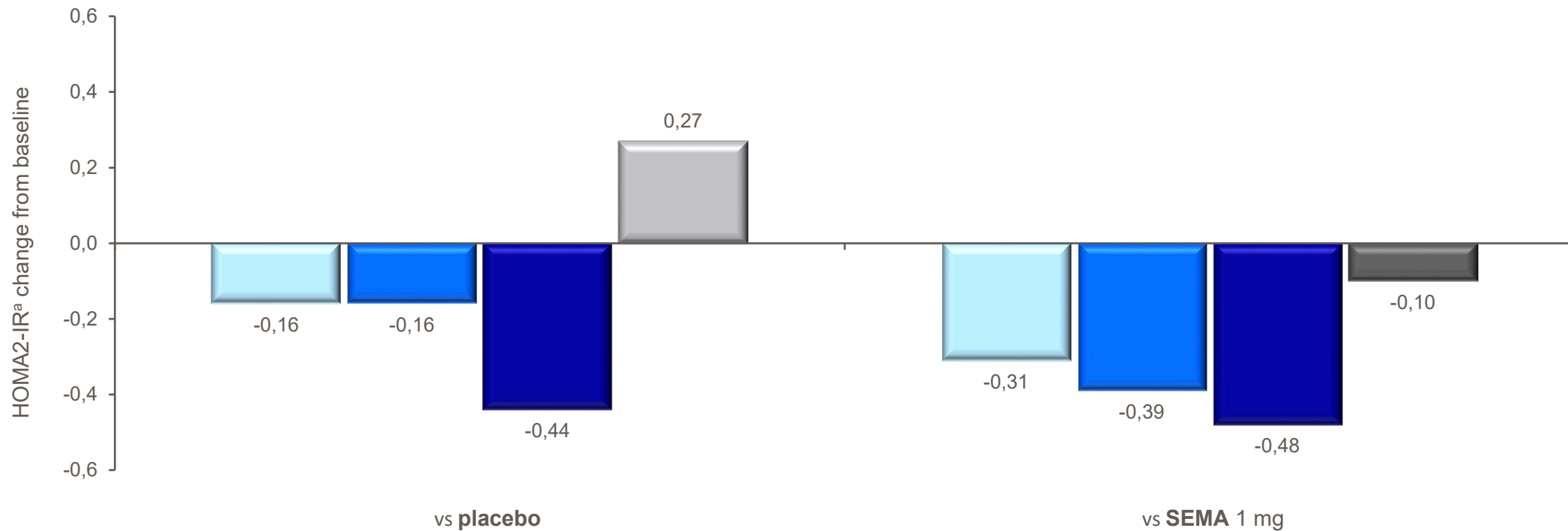
1. Rosenstock J, et al. *Lancet*. Published online June 26, 2021. 2. Frias JP, et al. *N Engl J Med*. Published online June 25, 2021. 3. Ludvik B, et al. *Lancet*. 2021; In press. 4. Dahl D, et al. Presented at the 81st Scientific Sessions of the ADA. 2021.

Insulin-sensitizing effects of tirzepatide HOMA2-IR

SURPASS-1¹
40 weeks
Monotherapy

SURPASS-2²
40 weeks
Add-on to MET

- TZP 5 mg
- TZP 10 mg
- TZP 15 mg
- Active comparator
- Placebo



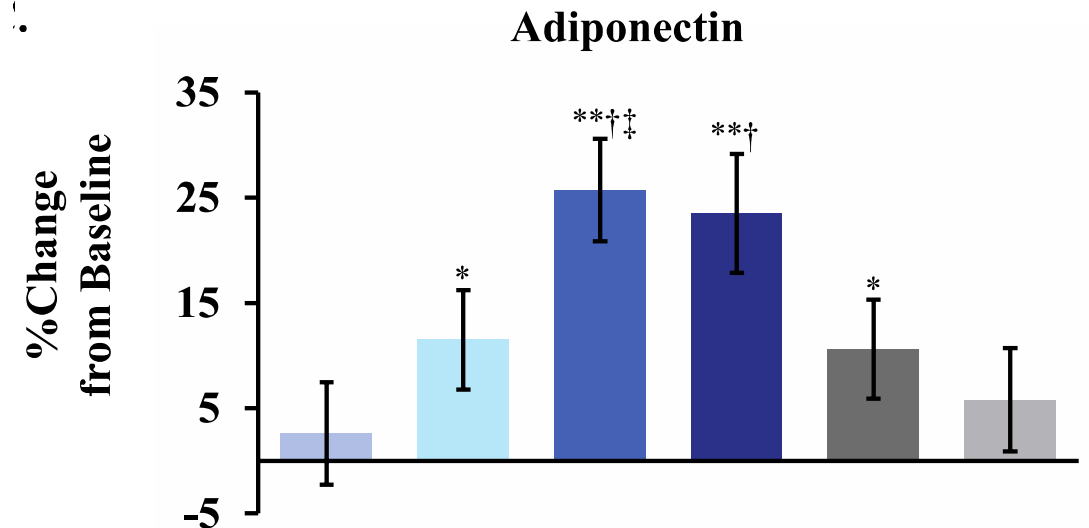
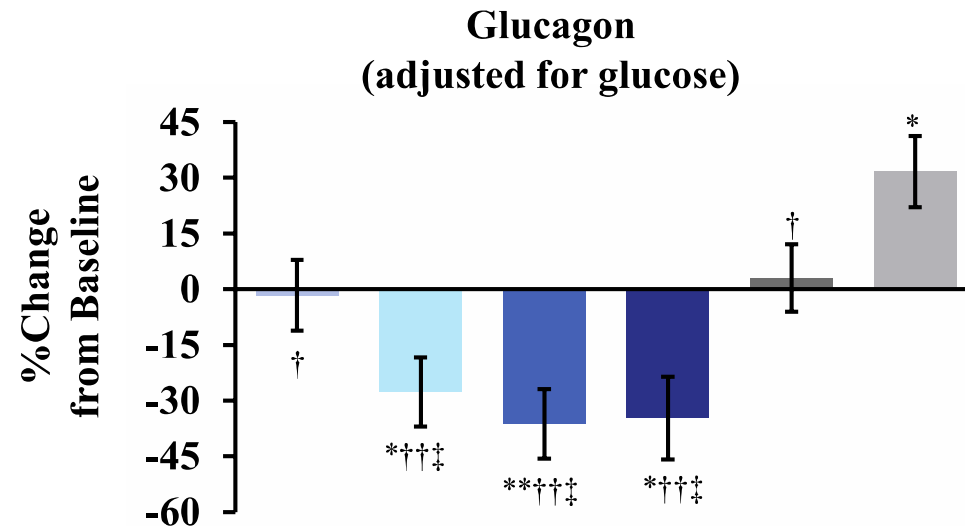
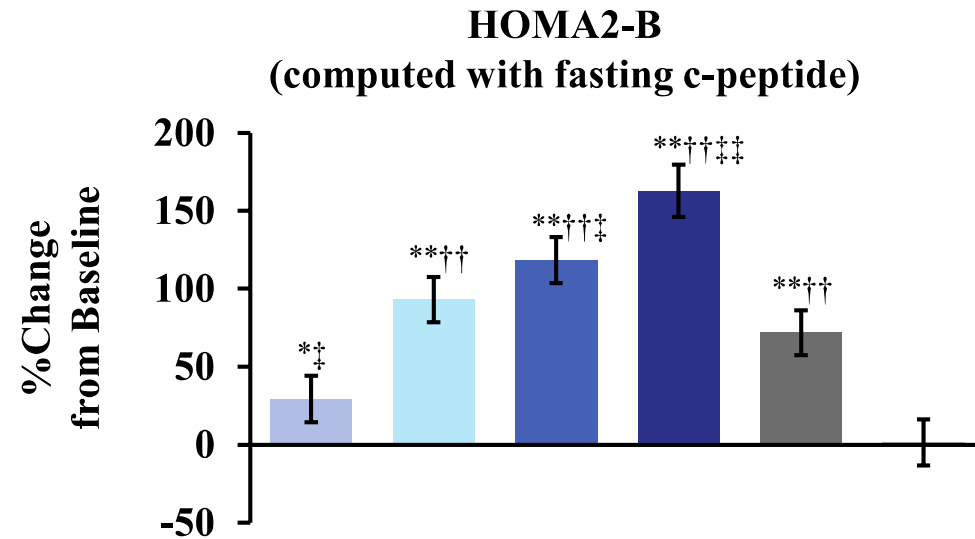
^aHOMA-IR measures were estimated using the HOMA2 calculator (licensed from Oxford University) that uses fasting insulin levels for the calculations.

Data are estimate (SE) from MMRM analysis using log transformation, mITT population (efficacy analysis set). Computed with fasting insulin.

HOMA2-IR = homeostasis model assessment of insulin resistance; MET = metformin; mITT = modified intent-to-treat; MMRM = mixed model repeated measures; SEMA = semaglutide; TZP = tirzepatide.

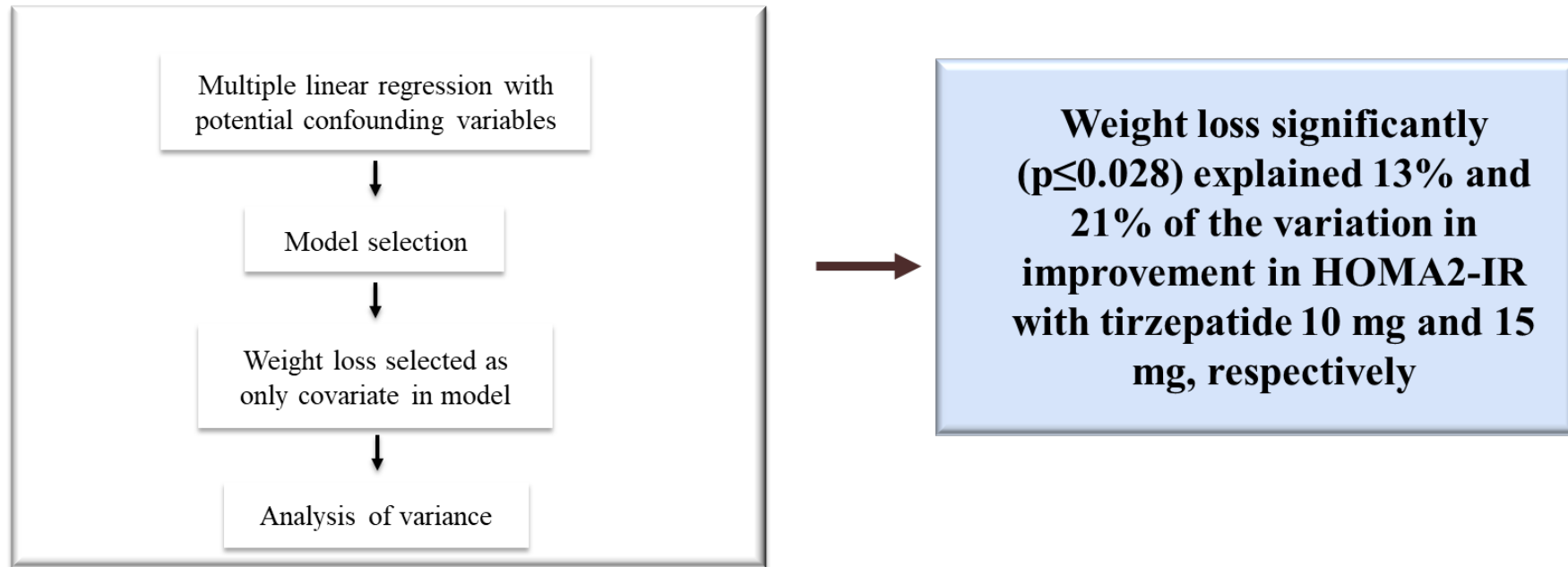
1. Rosenstock J, et al. *Lancet*. Published online June 26, 2021. 2. Frias JP, et al. *N Engl J Med*. Published online June 25, 2021.

Tirzepatide improves beta-cell function, increases adiponectin and decreases glucagon levels

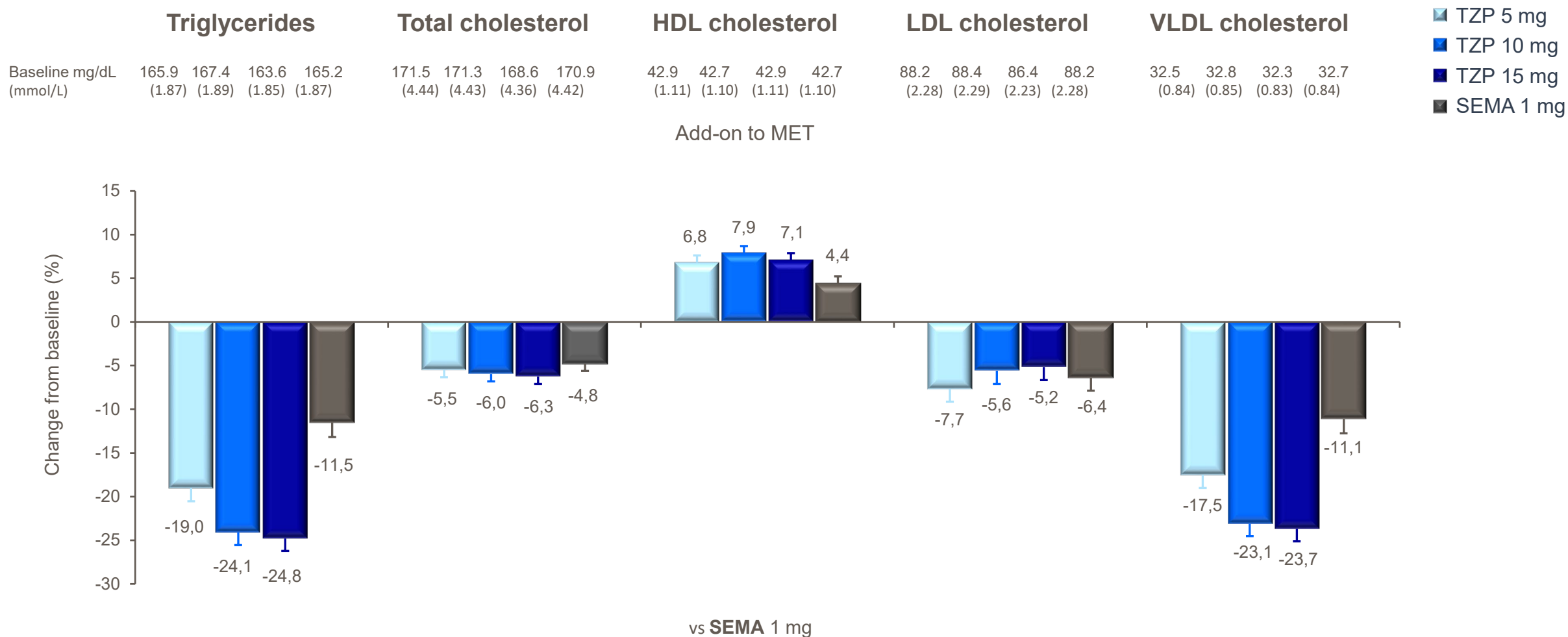


Insulin-sensitizing effects of tirzepatide

How much Tirzepatide-mediated improvement in HOMA2-IR at 26 weeks can be explained by weight loss?



Lipid Profile at 40 Weeks (SURPASS-2)



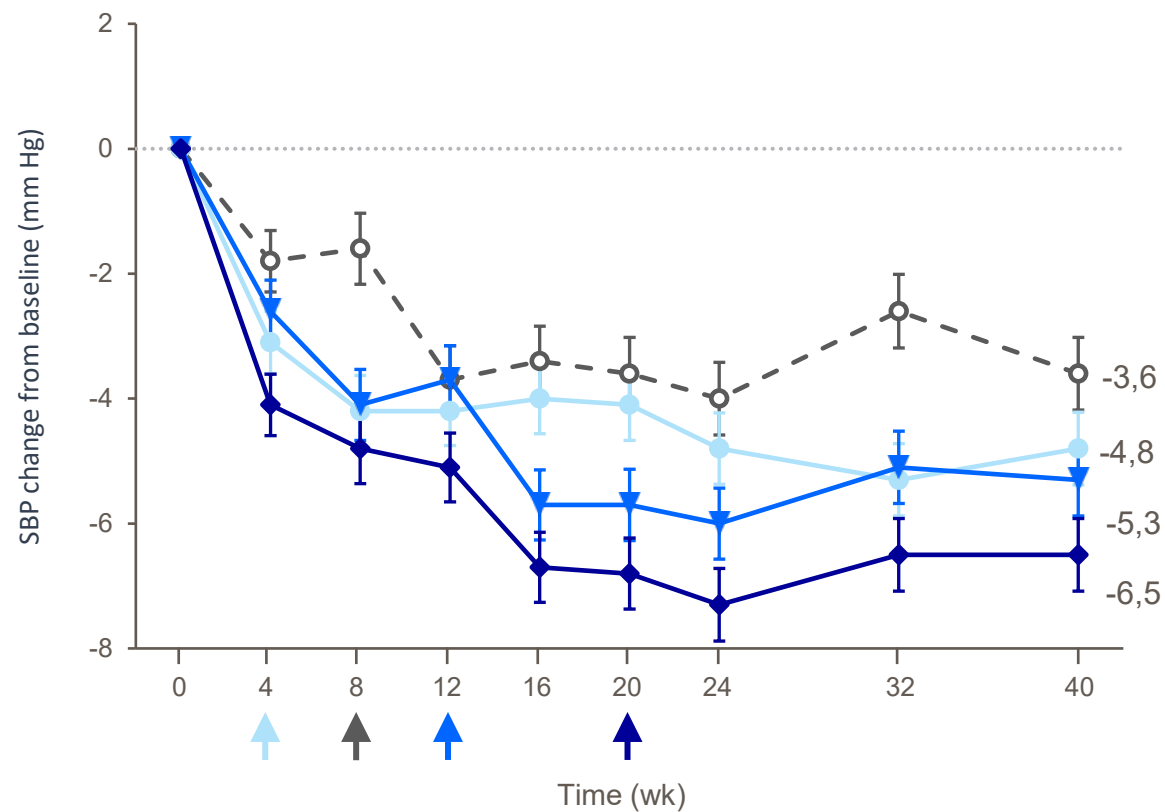
Data are estimated percentage means (SE) from MMRM analysis using log transformation; mITT population (efficacy analysis set).

HDL = high-density lipoprotein; LDL = low-density lipoprotein; MET = metformin; mITT = modified intent-to-treat; MMRM = mixed model repeated measures; SEMA = semaglutide; TZP = tirzepatide; VLDL = very-low-density lipoprotein.

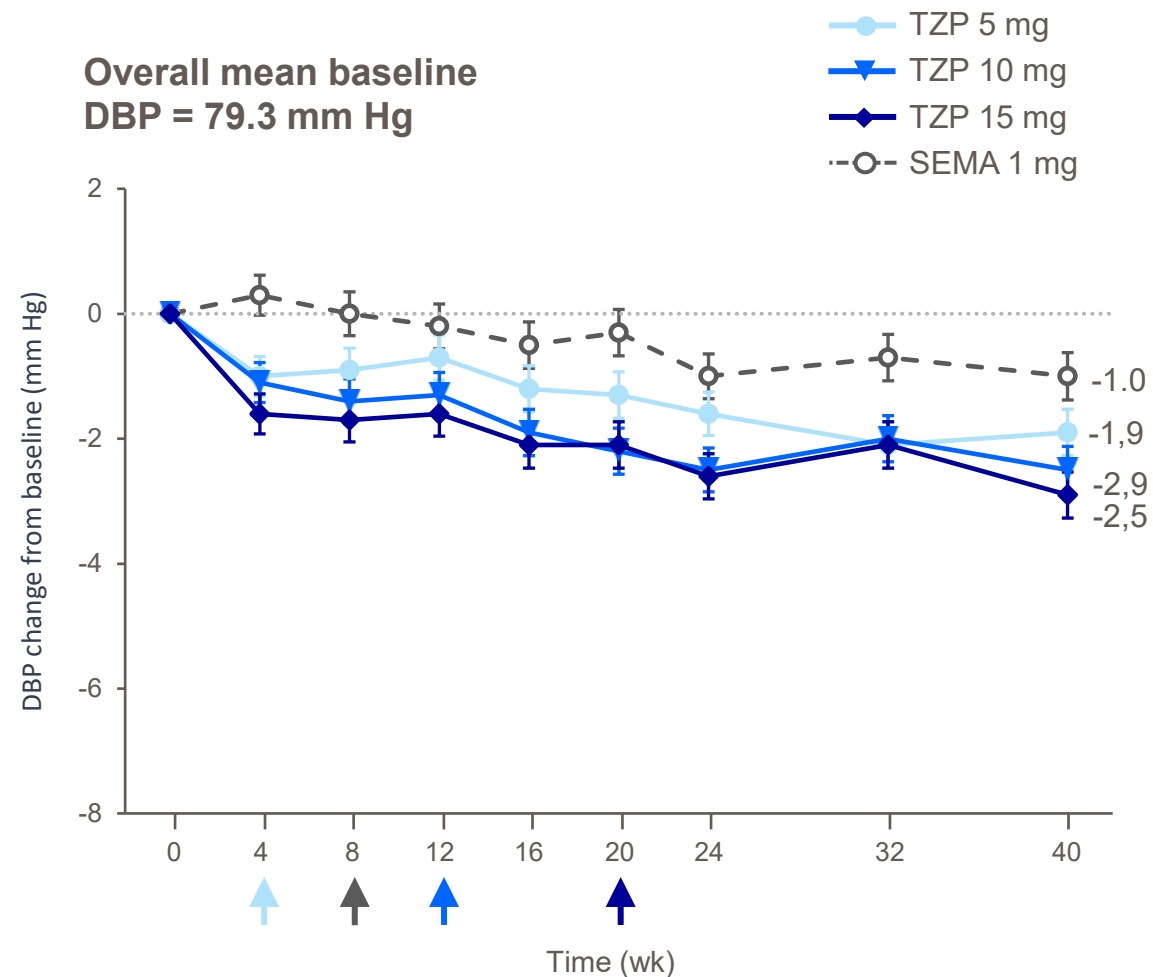
Frias JP, et al. *N Engl J Med*. Published online June 25, 2021.

Blood Pressure Over Time (SURPASS-2)

Overall mean baseline
SBP = 130.6 mm Hg

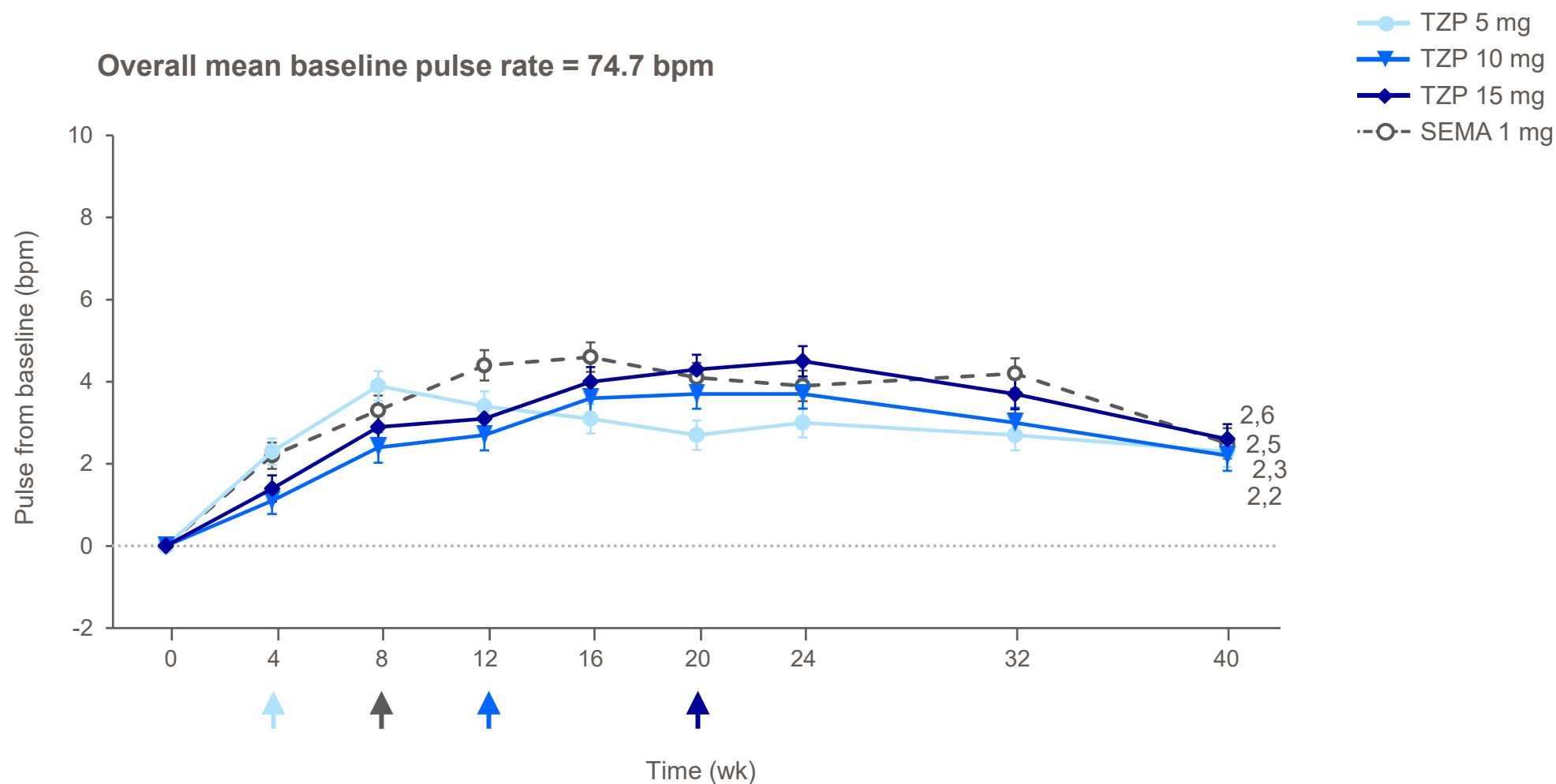


Overall mean baseline
DBP = 79.3 mm Hg

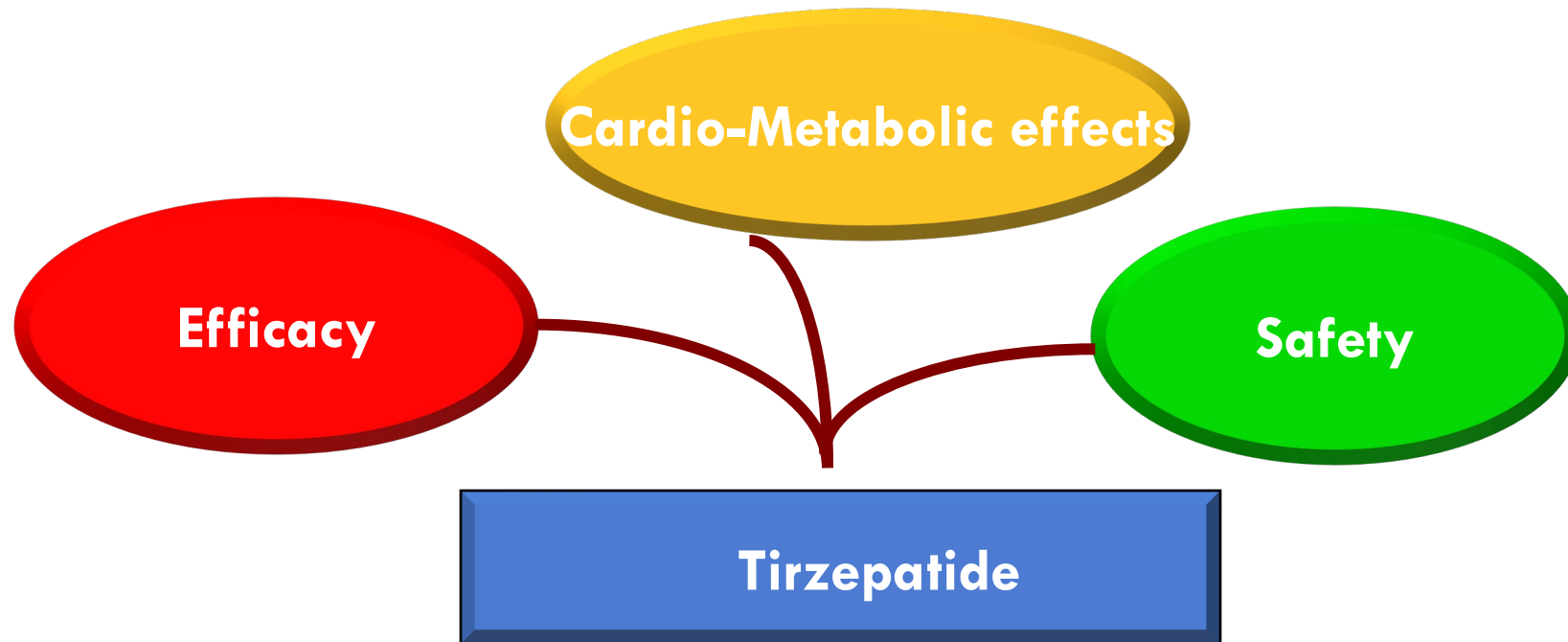


Data are LSM (SE); mITT population (safety analysis set). Arrows indicate when the dose of TZP 5 mg, 10 mg, 15 mg, and SEMA 1 mg were achieved. *Prevalence* refers to the proportion of subjects who have an event during a time interval. DBP = diastolic blood pressure; LSM = least squares mean; mITT = modified intent-to-treat; SBP = systolic blood pressure; SEMA = semaglutide; TZP = tirzepatide. Frias JP, et al. *N Engl J Med*. Published online June 25, 2021.

Pulse Rate Over Time (SURPASS-2)



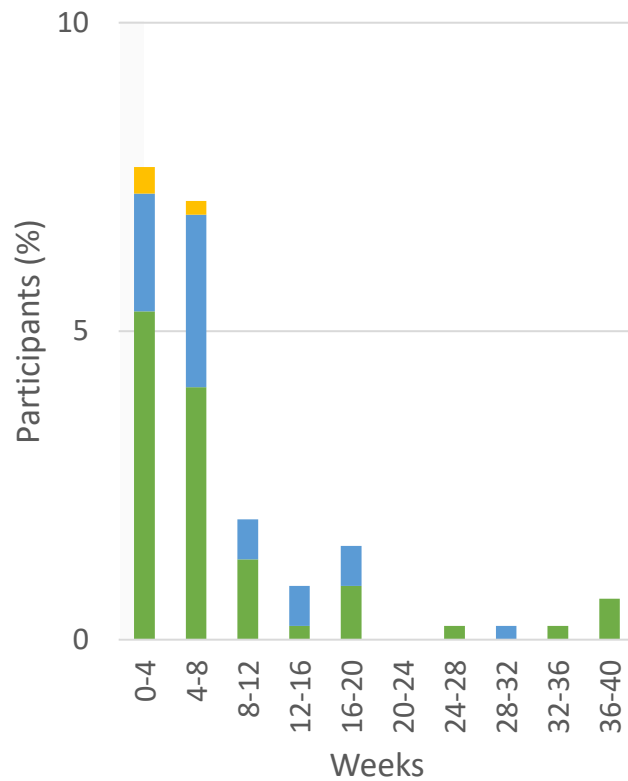
Data are LSM (SE); mITT population (safety analysis set). Arrows indicate when the dose of TZP 5 mg, 10 mg, 15 mg, and SEMA 1 mg were achieved. *Prevalence* refers to the proportion of subjects who have an event during a time interval. bpm = beats per minute; LSM = least squares mean; mITT = modified intent-to-treat; SEMA = semaglutide; TZP = tirzepatide. Frias JP, et al. *N Engl J Med*. Published online June 25, 2021.



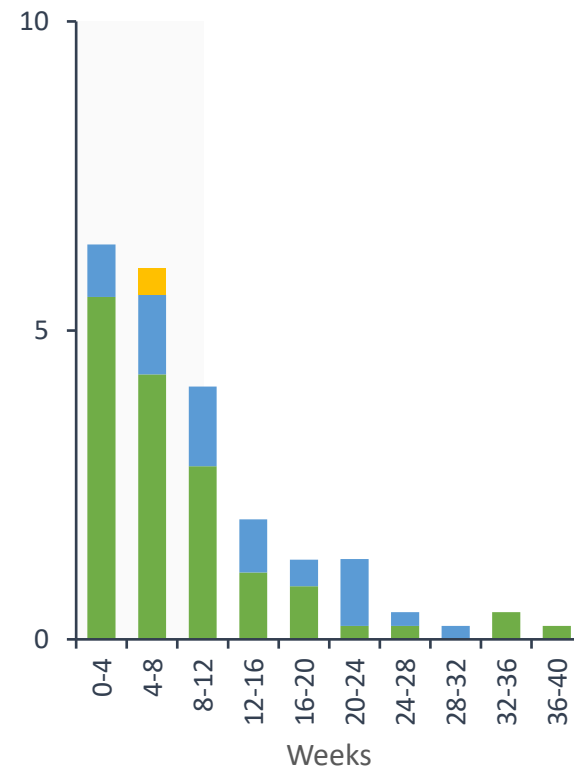
Incidence of Nausea Over Time Through 40 Weeks (SURPASS-2)

- Mild
- Moderate
- Severe

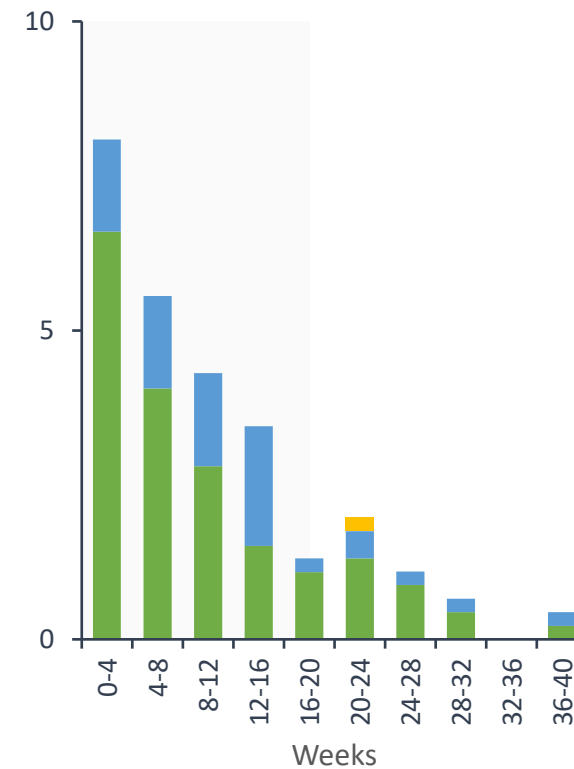
TZP 5 mg



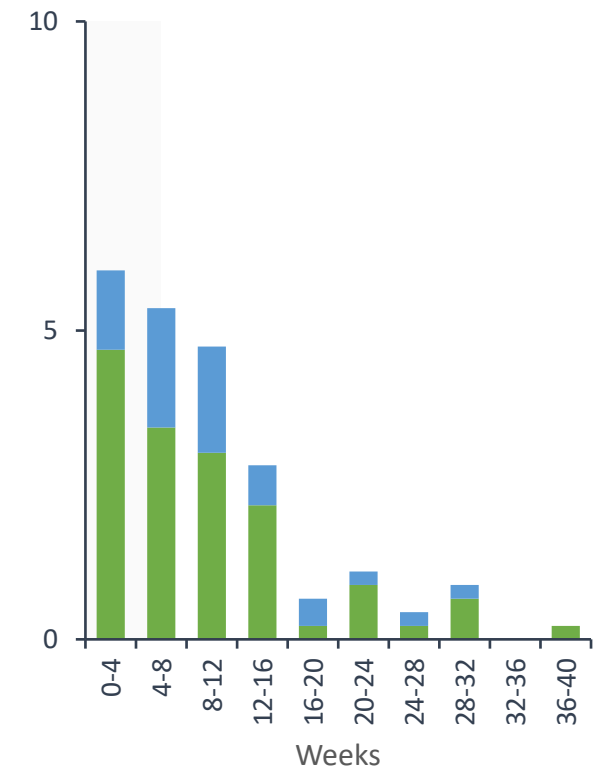
TZP 10 mg



TZP 15 mg



SEMA 1 mg



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.

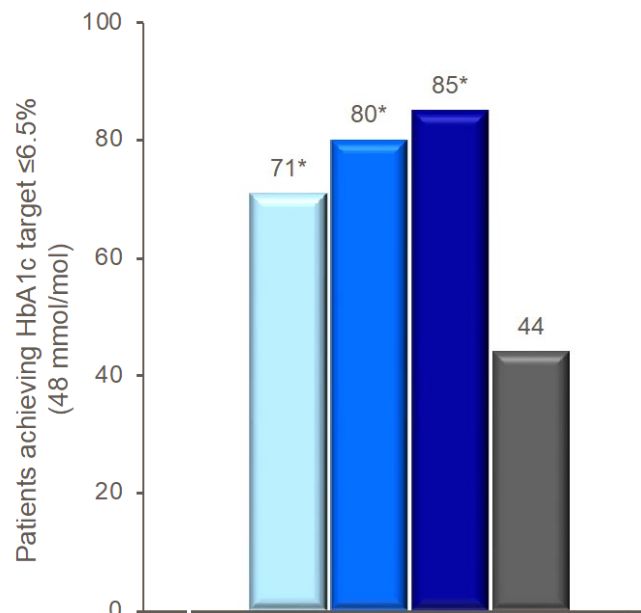
Incidence refers to the proportion of participants who have a new event during a time interval.

mITT = modified intent-to-treat; SEMA = semaglutide; TZP = tirzepatide.

Frias JP, et al. *N Engl J Med*. Published online June 25, 2021.

CV Safety SURPASS-4

Proportion of Patients Achieving HbA1c $\leq 6.5\%$

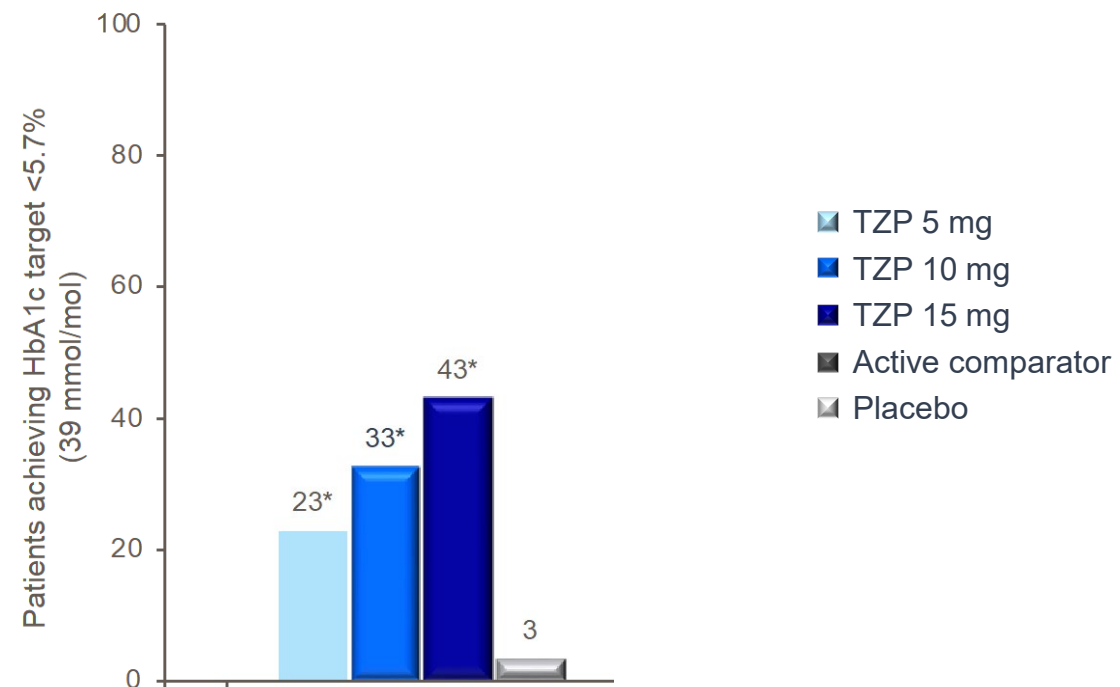


vs insulin glargine

SURPASS-4⁴
52 weeks

Add-on to MET,
SGLT2i, or SU

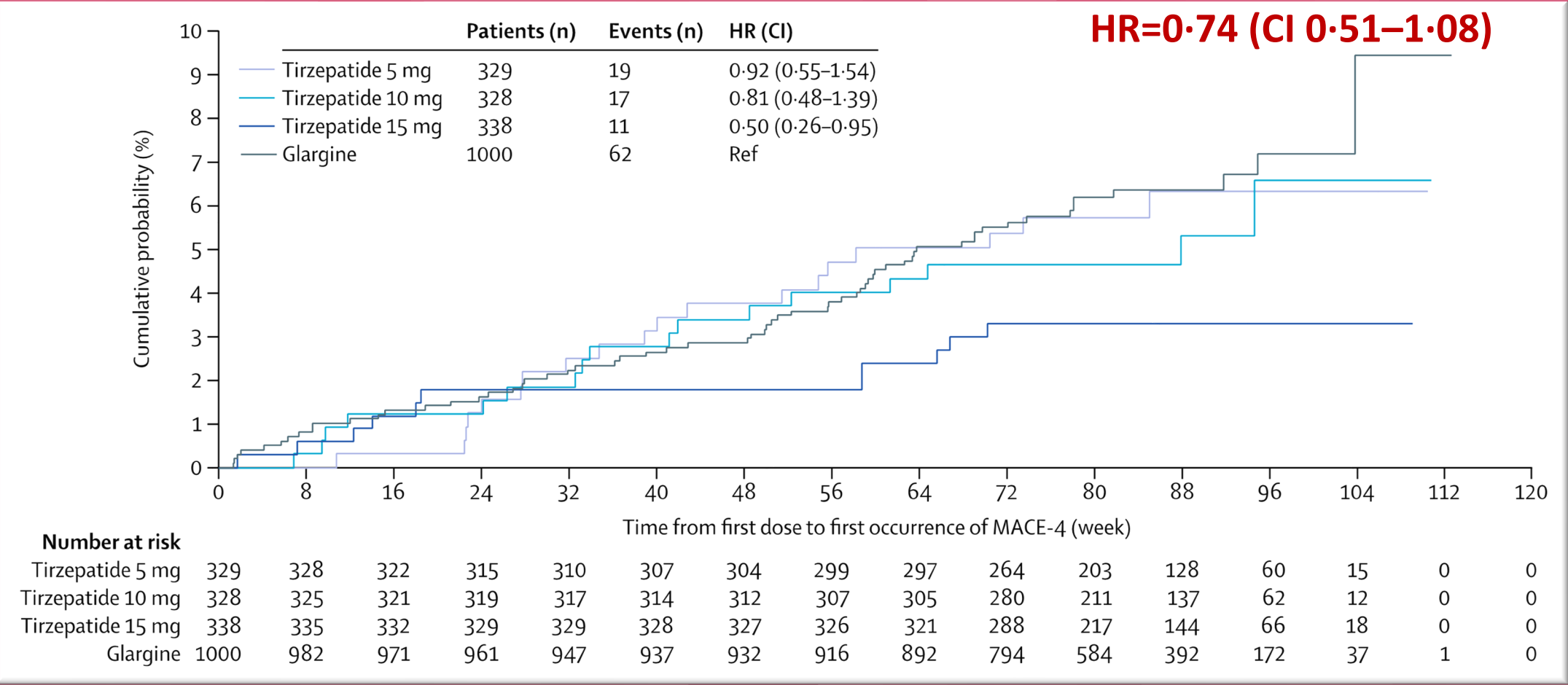
Proportion of Patients Achieving HbA1c $< 5.7\%$



Del Prato S et al Lancet 2021

CV Safety SURPASS-4

Time to first occurrence of MACE-4 nonfatal myocardial infarction, non-fatal stroke, cardiovascular death and hospital admission for angina



CV Safety Meta-Analysis

- Conducted across the clinical programme once a predefined number of MACE occurred
- Consisted of 116 participants with adjudicated MACE
 - **Composite endpoint of death from CV or undetermined causes, MI, stroke and hospitalisation for unstable angina**

HR=0.81 (97.85% CI, 0.52 to 1.26)
of pooled TZP vs pooled comparators

- The SURPASS clinical trial programme has now met regulatory submission requirements for evaluating CV risk

Hypoglycaemia

SURPASS-1¹	TZP 5 mg N=121	TZP 10 mg N=121	TZP 15 mg N=121	Placebo N=115
Hypoglycaemia (blood glucose <54 mg/dL [3.0 mmol/L])	0	0	0	1 (1)
Severe hypoglycaemia ^a	0	0	0	0
SURPASS-2²	TZP 5 mg N=470	TZP 10 mg N=469	TZP 15 mg N=470	SEMA 1 mg N=469
Hypoglycaemia (blood glucose <54 mg/dL [3.0 mmol/L])	3 (0.6)	1 (0.2)	8 (1.7)	2 (0.4)
Severe hypoglycaemia ^a	1 (0.2)	0	1 (0.2) ^b	0
SURPASS-3³	TZP 5 mg N=358	TZP 10 mg N=360	TZP 15 mg N=359	Insulin degludec N=360
Hypoglycaemia (blood glucose <54 mg/dL [3.0 mmol/L])	5 (1.4)	4 (1.1)	7 (1.9)	26 (7.3)
Severe hypoglycaemia ^a	0	0	1 (0.3) ^c	0
SURPASS-5⁴	TZP 5 mg N=116	TZP 10 mg N=119	TZP 15 mg N=120	Placebo N=120
Hypoglycaemia (blood glucose <54 mg/dL [3.0 mmol/L])	18 (15.5)	23 (19.3)	17 (14.2)	15 (12.5)
Severe hypoglycaemia ^a	0	2 (1.6)	1 (0.8)	0

Data are n (%); mITT population (safety analysis set). Note: Patients may be counted in more than 1 level. Data after initiation of new glucose lowering therapy are not included.

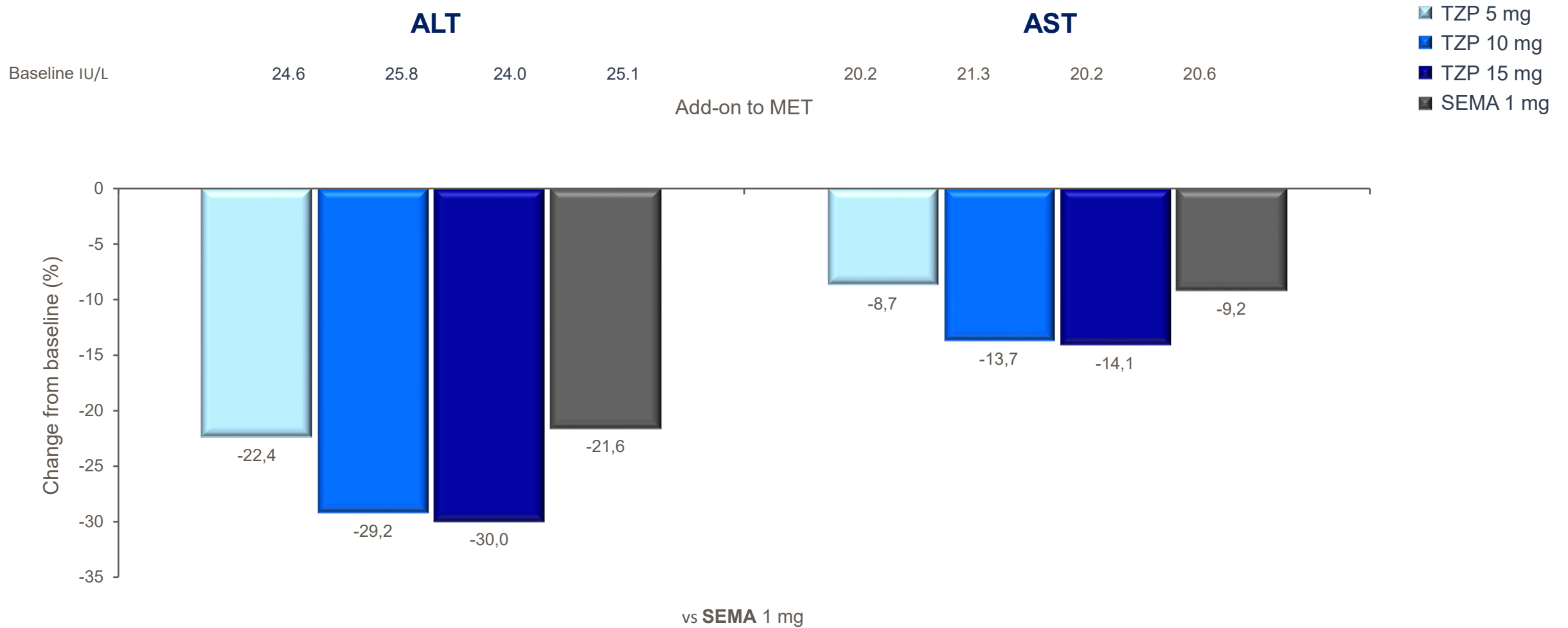
^aSevere event characterised by altered mental and/or physical status requiring assistance for treatment of hypoglycaemia; ^b1 patient randomised to TZP 15 mg had an event of hypoglycaemia that was not considered severe by the investigator but was reported as an SAE;

^c1 episode of severe hypoglycaemia was reported during the study for a patient assigned to the TZP 15-mg group during the escalation period (day 28).

mITT = modified intent-to-treat; SAE = severe adverse event; SEMA = semaglutide; TZP = tirzepatide.

1. Rosenstock J, et al. *Lancet*. Published online June 26, 2021. 2. Frias JP, et al. *N Engl J Med*. Published online June 25, 2021. 3. Ludvik B, et al. *Lancet*. 2021; In press. 4. Dahl D, et al. Presented at the 81st Scientific Sessions of the ADA. 2021.

Hepatic: ALT and AST at 40 Weeks (SURPASS-2)



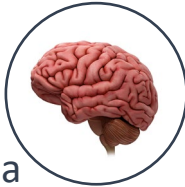
Analysis with log-transformation; mITT population (safety analysis set).

ALT = alanine transaminase; AST = aspartate aminotransferase; MET = metformin; mITT = modified intent-to-treat; SEMA = semaglutide; TZP = tirzepatide.

Potential MOAs of Tirzepatide Under Investigation

CNS

Appetite, feeding behaviour, energy expenditure, and nausea



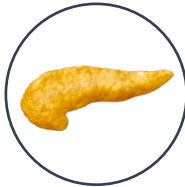
Liver

Insulin sensitivity, lipid metabolism, and energy expenditure



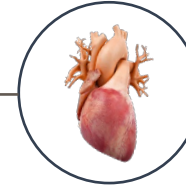
Pancreas: islets

Secretion of insulin and glucagon



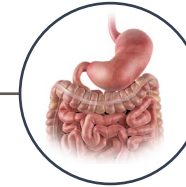
Cardiovascular

Plasma lipids, inflammation, and endothelial function



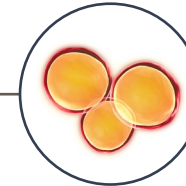
GI tract: stomach

Delayed gastric emptying



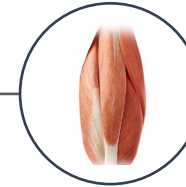
Adipose tissue

Lipid metabolism and insulin sensitivity



Skeletal muscle

Insulin sensitivity and glucose disposal



Increase insulin sensitivity
Improve β -cell function
Reduce food intake
Increase energy expenditure
Improve metabolic flexibility and nutrient partitioning
Alter adverse event profile vs GLP-1 RA

Glucagon-like Peptide-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

- Glucose-dependent Insulinotropic Polypeptide Receptor Agonism
- Glucagon-like Peptide 1 Receptor Agonism
- Indirect Action

Glucose-dependent Insulinotropic Polypeptide Receptor Agonism

Central Nervous System

- ↓ Food Intake
- ↓ Nausea
- ↓ Body Weight

Pancreas

- ↑ Insulin
- ↑ Glucagon

Subcutaneous White Adipose Tissue

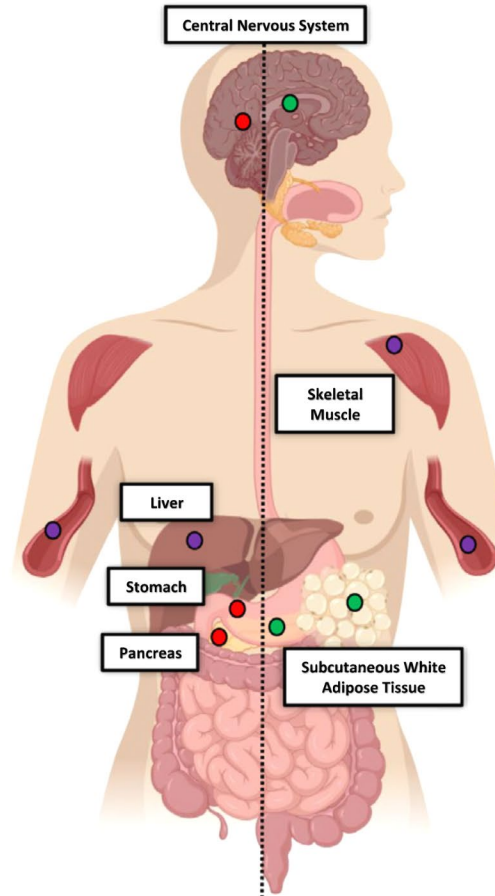
- ↑ Insulin Sensitivity
- ↑ Lipid Buffering Capacity
- ↑ Blood Flow
- ↑ Storage Capacity
- ↓ Proinflammatory Immune Cell Infiltration

Systemic

- ↓ Hyperglycemia
- ↓ Dietary Triglyceride

Skeletal Muscle

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



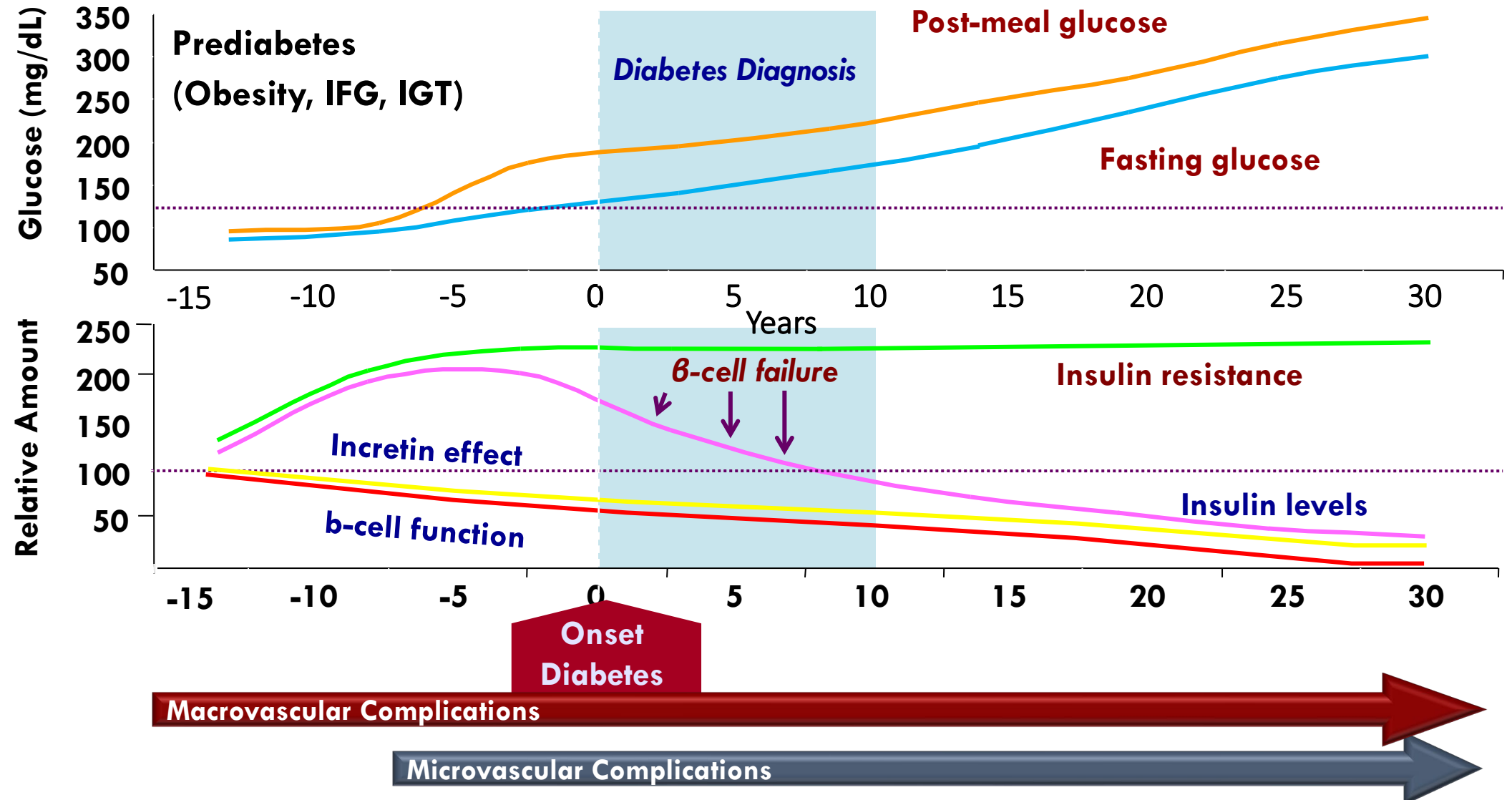


Take home messages

Outlook

Tirzepatide now is the first peptide dual agonist targeting GIP and GLP-1 receptors approved for the therapy of diabetes in the USA, Europe, and the UAE. Clinical trials employing this once-weekly injected compound impress with unprecedented effectiveness regarding glycaemic control (often resulting in normoglycaemia) and body weight reduction, in quantities that are likely to substantially change the underlying pathogenesis of type 2 diabetes [82] and have been associated with diabetes remission [83, 84]). The magnitude of the effects of tirzepatide on glycemia and weight loss opens a new era in diabetes therapy with the promise that a large percentage of patients can be treated to currently established targets. In addition, the clinical efficacy indicates large changes to diabetic physiology and should allow novel questions regarding pathogenesis to be addressed. For example, what does major weight loss added to excellent glycaemic control mean in terms of disease progression and long-term prognosis? And, what effect does the combination of weight loss and dramatic HbA_{1c} reduction have on micro- and macrovascular complications? The next important step will be more information on the cardiovascular consequences of using tirzepatide in type 2 diabetes. The SURPASS CVOT results are eagerly awaited, since there has not been any previous experience with long-term GIPR agonism in clinical medicine. GIP has been

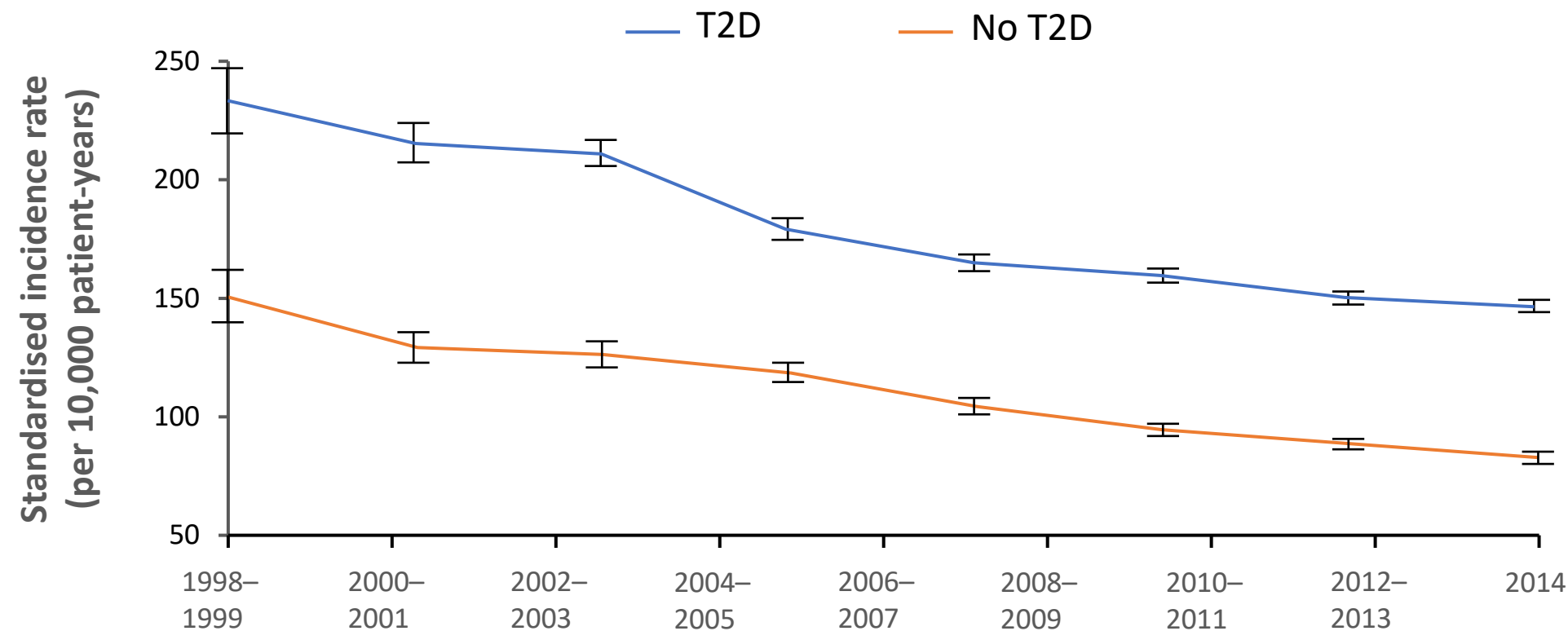
Natural history of type 2 diabetes





Despite falling mortality rates, patients with T2D remain at increased risk of CV mortality

Death from CV disease in patients with T2D versus matched controls*



Data from 457,473 patients with T2D from the Swedish National Diabetes Register. Bars represent 95% confidence intervals

*Controls were matched for age, sex and country

CV, cardiovascular; T2D, type 2 diabetes

Rawshani A et al. *N Engl J Med* 2017;376:1407

Grazie per l'attenzione!

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U.O.C. di Medicina Interna