SID Società Italiana di Diabetologia fondata nel 1964

AMD Associazione Medici Diabetologi 1974 Anno di fondazione

Università degli Studi della Campania Luigi Vanvitelli

AOV Azienda Ospedaliera Universitaria Luigi Vanvitelli

PreVen ENDO

TIWS Top Italian Women Scientists

RIUNIONE ANNUALE CONGIUNTA SID - AMD CAMPANIA 2022

IL *DIABETE* AL CENTRO DI *PERCORSI INNOVATIVI* DI *CURA*

NAPOLI
Via Ponte di Tappia, 25

HOTEL MEDITERRANEO RENAISSANCE

08 OTTOBRE 2022

Dual agonists GLP-1/GIP

Prof. Katherine Esposito

Prof. Ordinario di Endocrinologia
Direttore della U.O.C. di Endocrinologia e Malattie del Metabolismo
Direttore della Scuola di Specializzazione in Endocrinologia e Malattie del Metabolismo
Direttore della Scuola di Dottorato in Scienze della Vita
Coordinatore del Dottorato di Medicina Traslazionale
Membro delle Top Italian Woman Scientists (TWIS)
Delegata della Terza Missione del Dipartimento di Scienze Mediche e Chirurgiche Avanzate
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La Prof. Katherine Esposito dichiara di aver ricevuto negli ultimi due anni compensi o finanziamenti dalle seguenti Aziende Farmaceutiche e/o Diagnostiche:

- Ely Lilly
- Novo Nordisk
- Abbott

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.).

Panoramica sugli effetti biologici del polipeptide insulinotropico glucosio-dipendente (GIP) e del peptide glucagon-like di tipo 1 (GLP-1) a livello di organi/tessuti

Diabetes Obes Metab. 2021;23(Suppl. 3):5–29.

DIABETES OBESITY AND METABOLISM

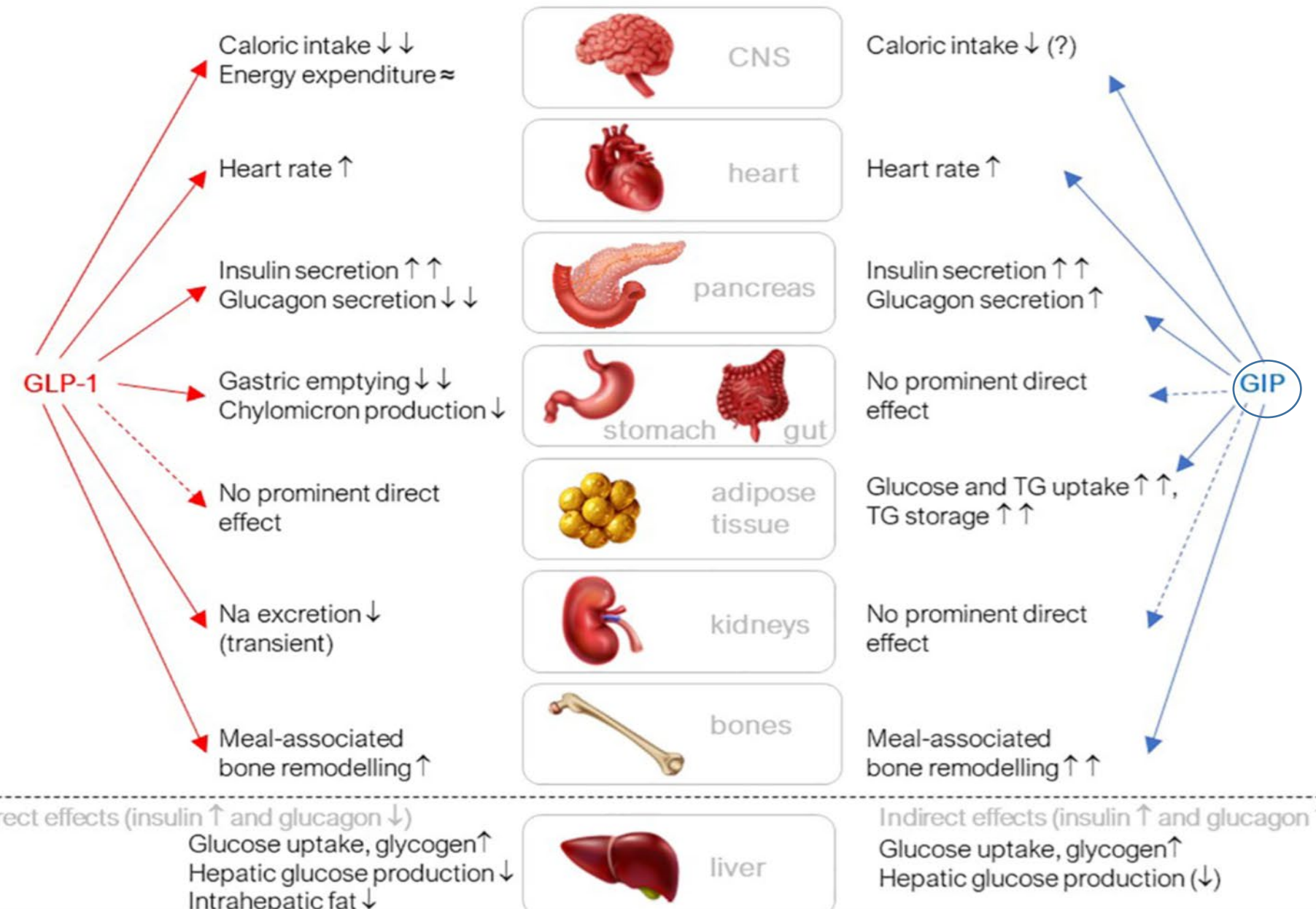
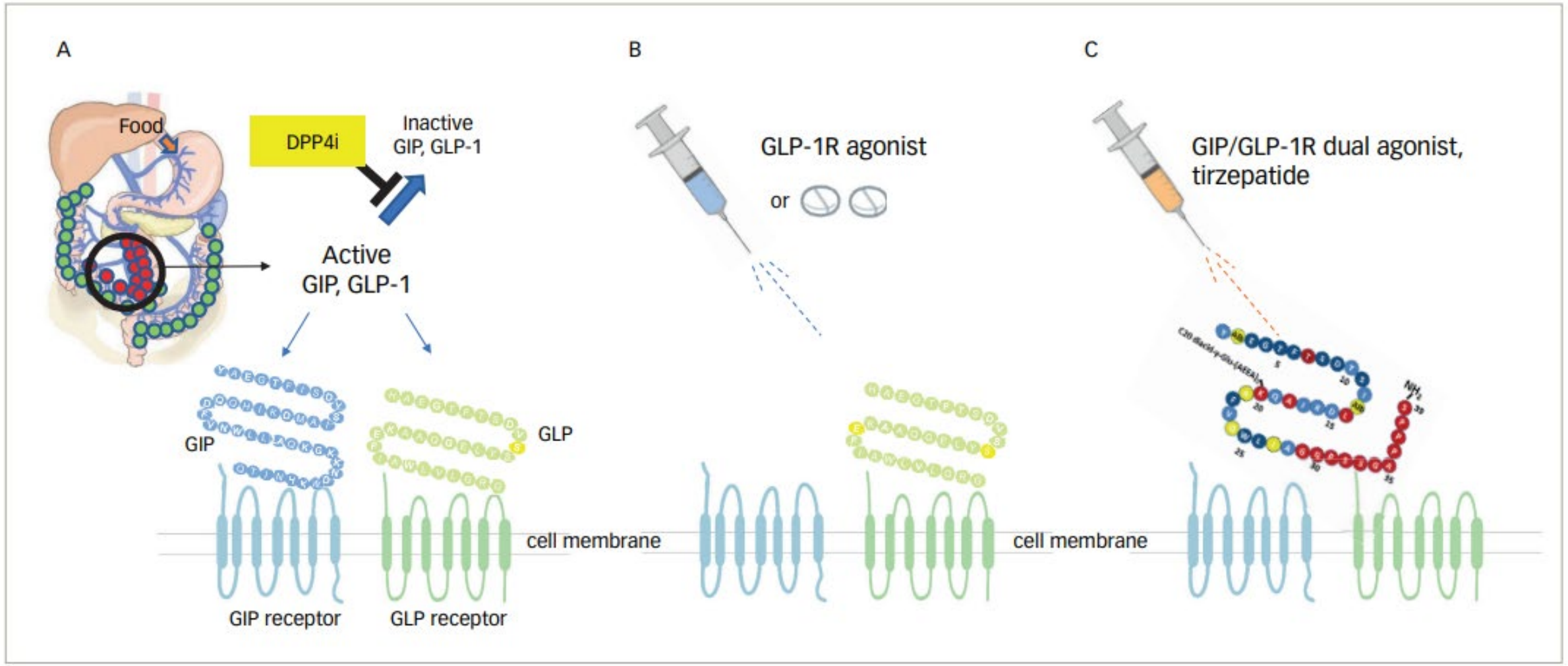


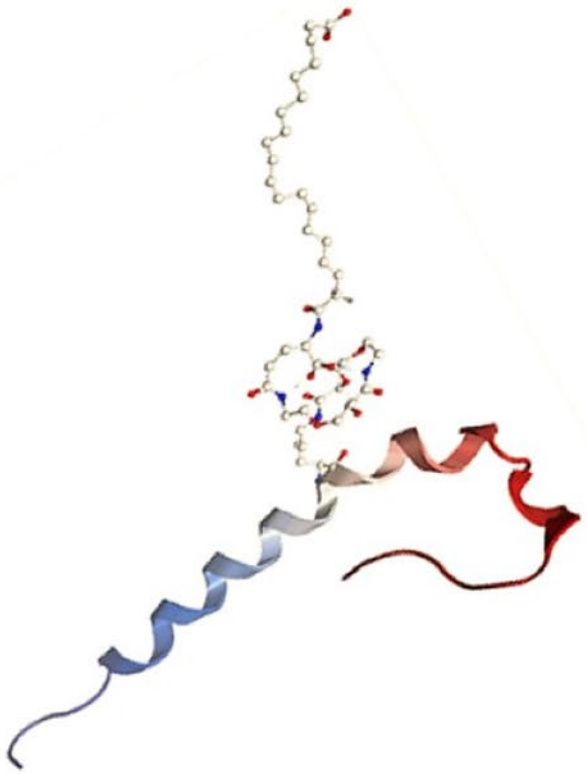
Figure 3: Gut activity in patients with T2D undergoing DPP-4 inhibitor therapy, GLP-1R agonist therapy or GIP/GLP-1R dual agonist therapy[64,66]



touchREV Endocrinol. 2022;18(1):10–19.

TIRZEPATIDE

Un nuovo doppio agonista GIP/GLP-1



Schematic illustration of tirzepatide

*Participants had T2D with inadequate glycemic control on diet and exercise alone or on a stable dose of metformin monotherapy.

HbA1c, glycated hemoglobin.

a. Coskun Tm, et al. *Molecular Metab*. 2018;18:3-14; b. Frias JP, et al. *Lancet*. 2018;392:2180-2193.

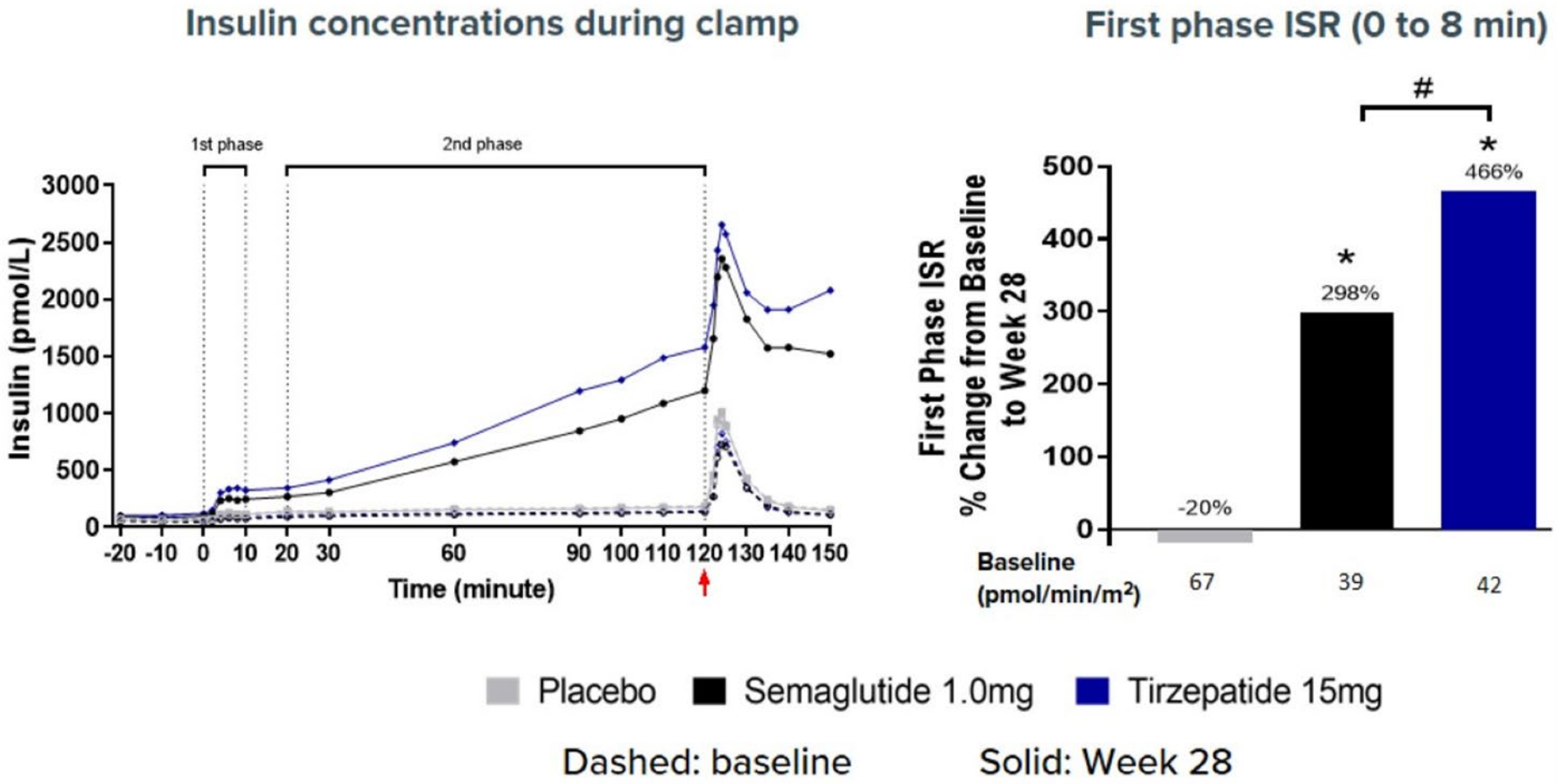
Caratteristiche della molecola[a]

- Tirzepatide è un peptide poli-funzionale, la cui sequenza amminoacidica deriva dal peptide GIP nativo, modificata in modo da legare sia i recettori di GIP che di GLP-1
- Tirzepatide è un peptide di 39 amminoacidi e include una porzione lipidica di 20 atomi di carbonio
- Tirzepatide ha una emivita di 5 giorni; pertanto è suscettibile di somministrazione settimanale

Studio di fase 2b (26 settimane)[b] – dose finding

- Tirzepatide (5 mg, 10 mg e 15 mg) riduce significativamente HbA1c e il peso corporeo rispetto al placebo o a un agonista recettoriale selettivo di GLP-1, Dulaglutide (1.5 mg)*

Modifiche della secrezione insulinica



ISR, insulin secretion rate.

Heise T, et al. Presented at: 57th Annual Meeting of the European Association for the Study of Diabetes 2021 Virtual; September 23-October 2, 2021.

- **Significativo aumento della secrezione insulinica**, sia con semaglutide che con tirzepatide, in prima e in seconda fase.

- **Incremento maggiore con tirzepatide**

SURPASS nel Diabete di tipo 2

SURPASS 1	SURPASS 2	SURPASS 3	SURPASS 4	SURPASS 5	SURPASS 6
Monotherapy[a]	2-Drug Combination[b]	2-Drug to 4-Drug Combination[c]	Open-Label RCT Phase 3[d]	Double-Blind Phase 3 RCT[e]	Combination With Insulin[f]
Tirzepatide (5 mg, 10 mg, 15 mg) weekly vs **Placebo** for 40 weeks	**Tirzepatide** (5 mg, 10 mg, 15 mg) weekly vs **Semaglutide (GLP-1 RA)** for 40 weeks (add-on to metformin)	**Tirzepatide** (5 mg, 10 mg, 15 mg) weekly vs **Insulin Degludec** for 52 weeks (add-on to metformin ± SGLT2 inhibitor)	**Tirzepatide** (5 mg, 10 mg, 15 mg) weekly vs **Insulin Glargine** for 52 weeks in patients at increased cardiovascular risk (add-on to ≥ 1 and ≤ 3 every morning metformin, SGLT2I, or SU)	**Tirzepatide** (5 mg, 10 mg, 15 mg) weekly vs **Placebo** for 40 weeks in patients inadequately controlled on insulin glargine ± metformin	**Tirzepatide** (5 mg, 10 mg, 15 mg) weekly vs **Insulin Lispro thrice daily** for 40 weeks in patients inadequately controlled on insulin glargine ± metformin **ONGOING**

GLP-1 RA, glucagon-like peptide-1 receptor agonist; OAM, oral antihyperglycemic medication, RCT, randomized controlled trial; SU, sulfonylurea.
a. Rosenstock J, et al. Lancet. 2021;398:143-155; b. Frías JP, et al. N Engl J Med. 2021;385:503-515; c. ClinicalTrials.gov. Accessed September 20, 2021. https://clinicaltrials.gov/ct2/show/NCT03882970; d. ClinicalTrials.gov. Accessed September 20, 2021. https://clinicaltrials.gov/ct2/show/NCT03730662; e. ClinicalTrials.gov. Accessed September 20, 2021. https://clinicaltrials.gov/ct2/show/NCT04039503; f. ClinicalTrials.gov. Accessed September 20, 2021. https://clinicaltrials.gov/ct2/show/NCT04537923.

SURPASS CVOT: sicurezza cardiovascolare nel diabete di tipo 2 - Criteri di Elegibilità

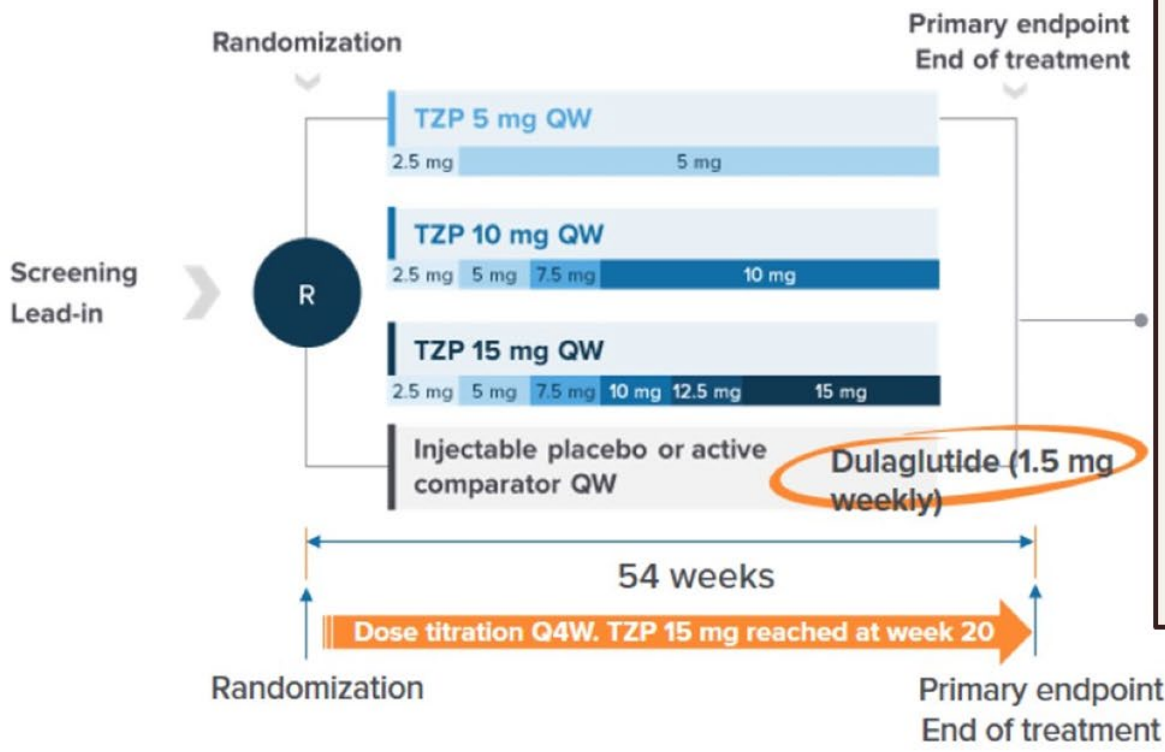
Trial clinico di fase 3, randomizzato, in doppio cieco, con outcomes cardiovascolari, per dimostrare la superiorità e la non inferiorità di Tirzepatide rispetto a Dulaglutide in 30 diversi paesi

Key Inclusion Criteria

- T2D
  - Aged 40 years
  - HbA1c ≥ 58 mmol/mol to ≤ 91 mmol/mol (≥ 7.5% to ≤ 10.5%)
  - BMI ≥ 25 kg/m^2
- Established ASCVD

Key Exclusion Criteria

- T1D
- 1 major CV event within the last 60 days
- GLP-1 RA or pramlintide in 3 months prior to screening visit and who discontinue treatment due to intolerability
- HF (NYHA lass 4)
- ESKD or dialysis



Outcome primario
- Tempo per l'evento: morte per cause cardiovascolari, infarto del miocardio non fatale o ictus non fatale (MACE-3)

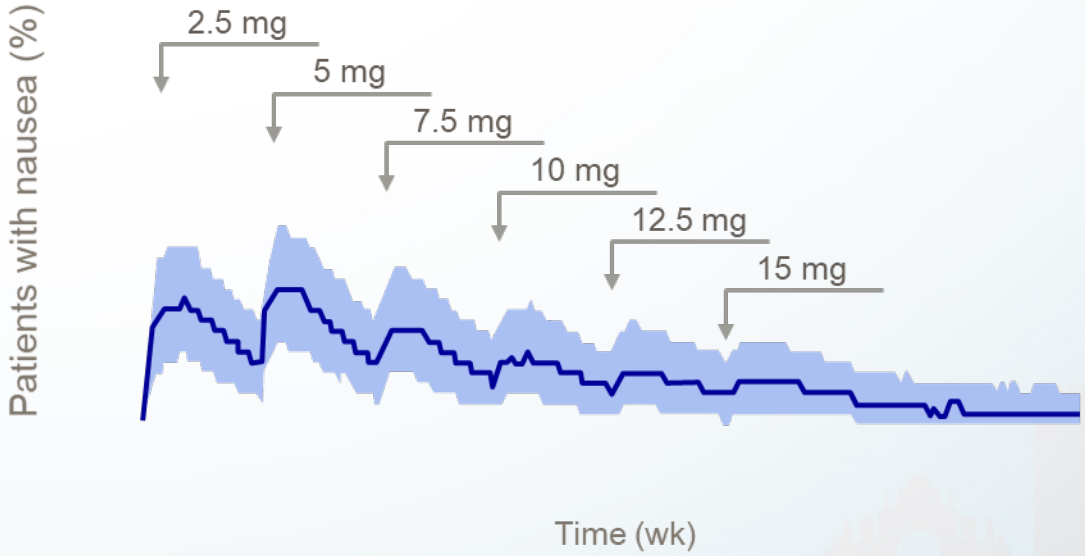
Outcomes secondari
- Tempo per morte per qualsiasi causa, tempo per l'insorgenza delle singole componenti del MACE, tempo per l'insorgenza di nefropatia o peggioramento di questa, modifiche del peso corporeo, dell'HbA1c, dell'UACR e del profilo lipidico

ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index, CV, cardiovascular; GLM, glucose-lowering medication; MACE, major adverse cardiovascular event; TZP tirzepatide.
ClinicalTrials.gov. Accessed September 20, 2021. https://clinicaltrials.gov/ct2/show/NCT04255433; Min T, Bain SC. Diabetes Ther. 2021;12:143-157.

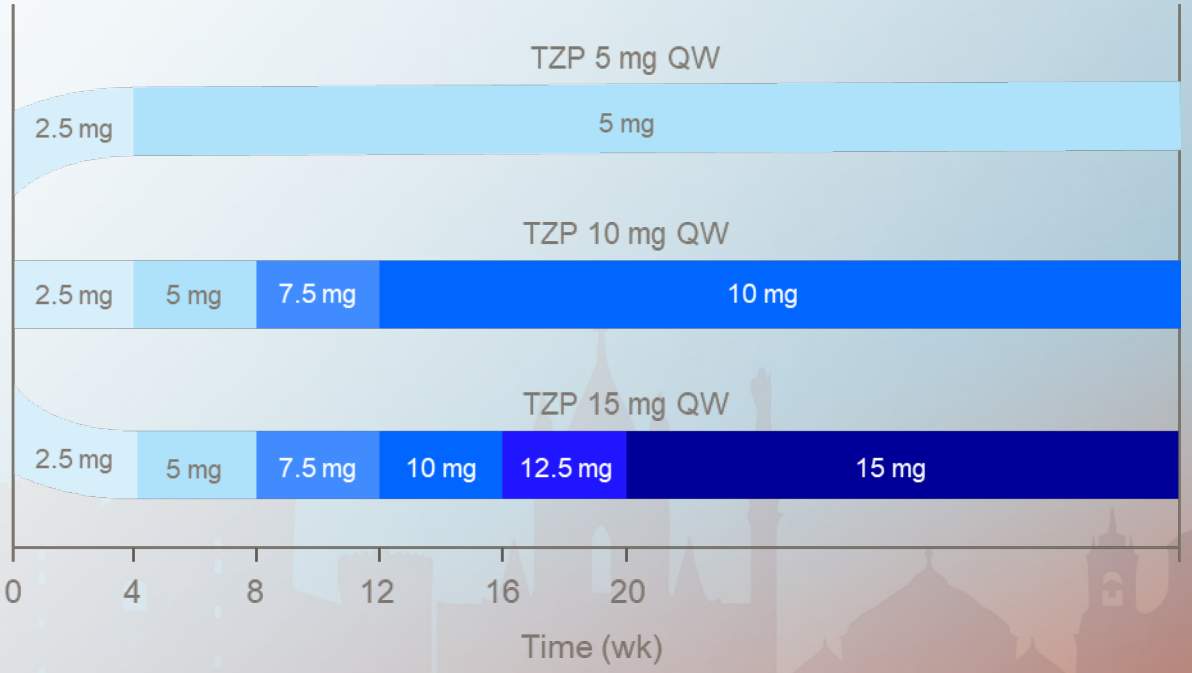
Tirzepatide: Dosaggio nel Programma del Trial clinico SURPASS di fase 3

Simulazione di un aumento di dose[1]

- Il modello prevede l'incidenza della nausea con una titolazione lenta e graduale e supporta un migliore profilo di tollerabilità dalla fase 2 alla fase 3[1,2]



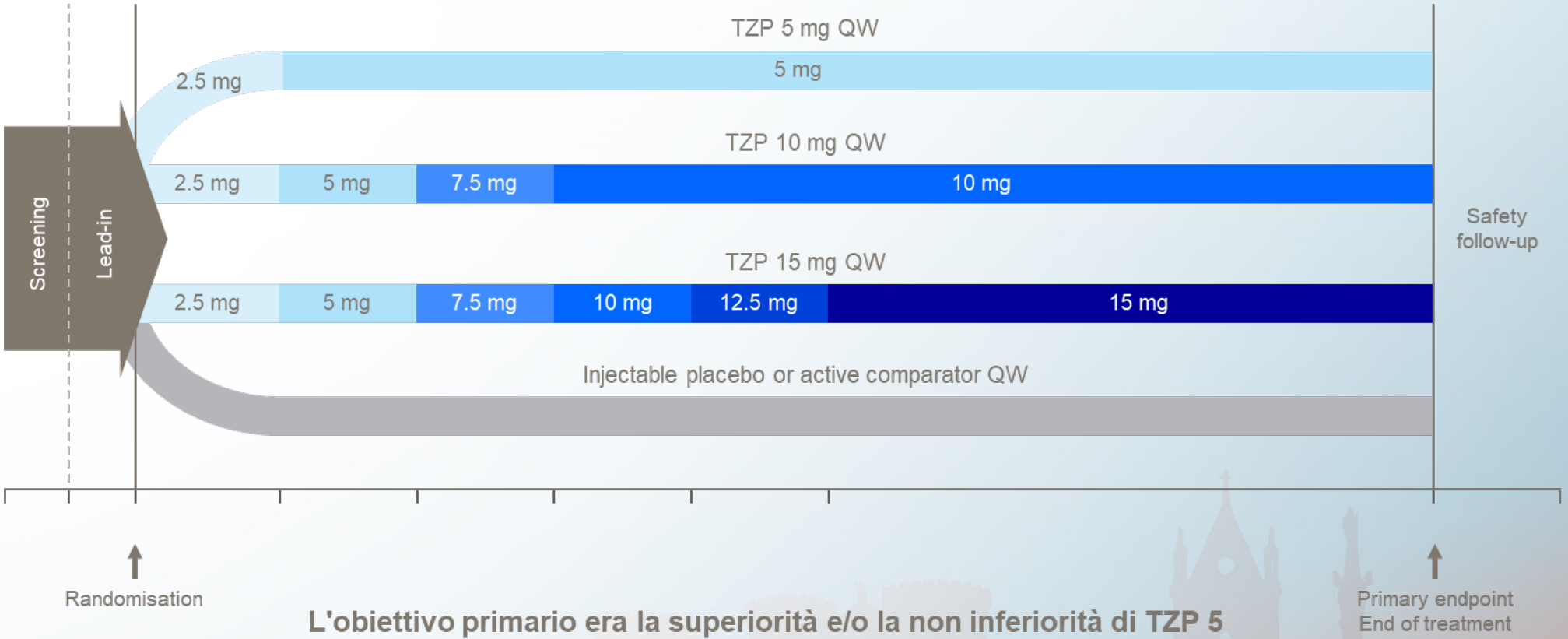
- Incrementi di 2.5 mg permettono una più graduale introduzione del farmaco e un migliorato profilo di tollerabilità
- Il dosaggio è basato su studi di fase 2 e modelli di esposizione



QW = once-weekly; TZP = tirzepatide.

1. Eli Lilly and Company. Diabetes – 2019 Business Update. 2. Frias JP, et al. *Diabetes Obes Metab.* 2020;22(6):938-946.

SURPASS: Disegno dello Studio 1-5



L'obiettivo primario era la superiorità e/o la non inferiorità di TZP 5 mg e/o 10 mg e/o 15 mg rispetto al placebo o al comparatore attivo nella variazione media dell'HbA1c rispetto al basale a 40 o 52 settimane.

HbA1c = glycated haemoglobin; QW = once weekly; 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.

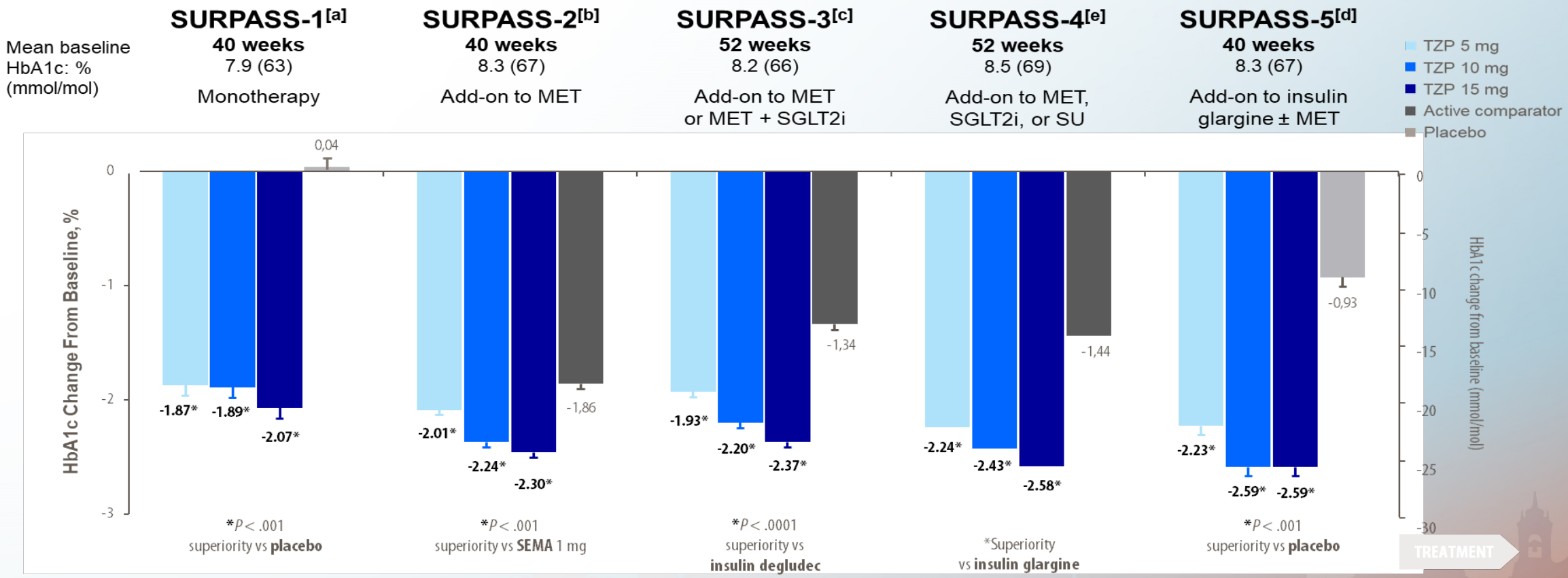
SURPASS: Caratteristiche al basale

Parameter	SURPASS-1[1]	SURPASS-2[2]	SURPASS-3[3]	SURPASS-4[4]	SURPASS-5[5]
N° subjects	478	1878	1437	1995	475
Mean T2D Duration (years)	4.7	8.6	8.4	11.8	13.3
Mean HbA1c (%)	7.9	8.3	8.2	8.5	8.3
Mean Weight (kg)	85.9	93.7	94.3	90.3	95.3
Mean BMI (kg/m^2)	32	34	34	33	33
Background T2D Medications	N/A	MET	MET ± SGLT2i	Any combination of MET/SGLT2i/ SU	Insulin glargine ± MET

BMI = body mass index; HbA1c = glycated hemoglobin; MET = metformin; QW = once weekly; SGLT2i = sodium-glucose co-transporter-2 inhibitor; SU = sulfonylurea; 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. Poster presented at: *ADA* 2021. Poster LB-20.

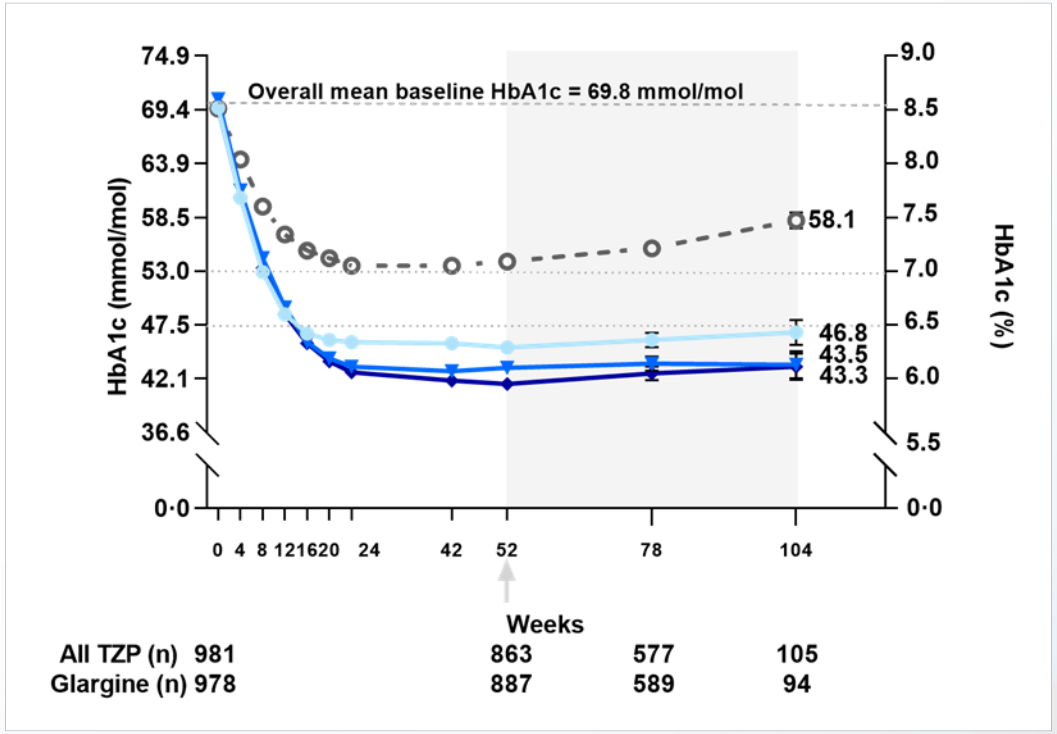
SURPASS: Modifiche di HbA1c dal Basale all'Endpoint primario



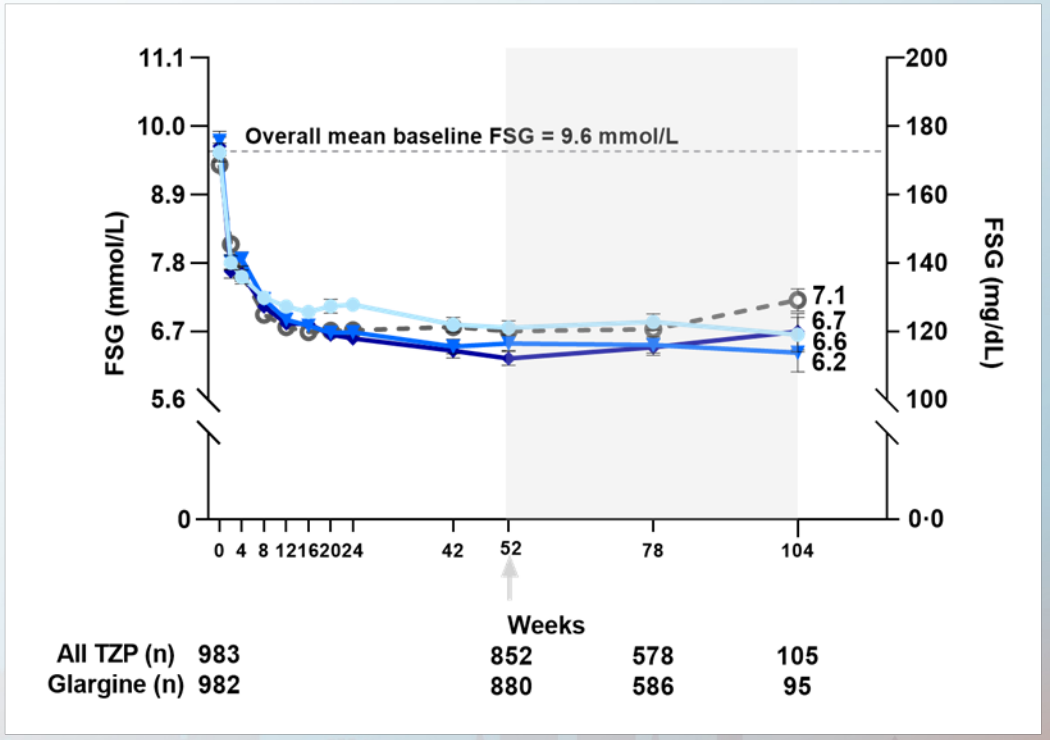
- Data are LSM (SE). mITT population (efficacy analysis set). MMRM analysis. Data labels are % HbA1c.
- LSM, least square mean; MET, metformin; mITT, modified intention to treat; MMRM, mixed-model repeated measures; SEMA, semaglutide; SGLT2i, sodium dependent glucose co-transporter 2 inhibitor.
- a. Rosenstock J, et al. Lancet. 2021;398:143-155; b. Frías JP, et al; SURPASS-2 Investigators. N Engl J Med. 2021;385:503-515; c. Ludvik B, et al. Lancet. 2021;398:583-598; d. Dahl D, et al. Presented at: 81st Scientific Sessions of the American Diabetes Association [virtual]; June 25-29, 2021. Poster 80-LB; e. Del Prato S, et al. Presented at: virtual EASD Annual Meeting 2021.

SURPASS 4: Efficacia Metabolica confermata per 104 settimane

HbA1c

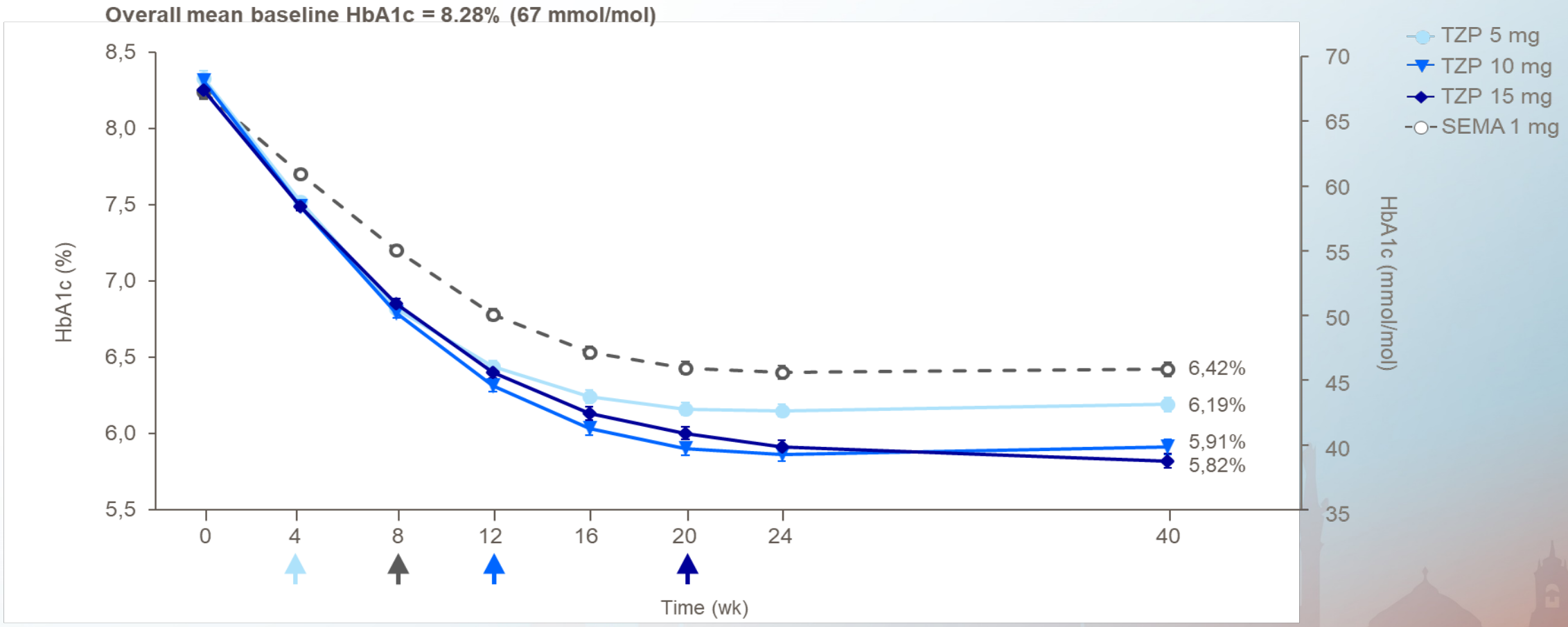


Fasting serum glucose



- mITT population (efficacy analysis set). Data are LSMean (SE)
- Del Prato S. et al. Lancet. 2021;398(10313):1811-24/suppl.

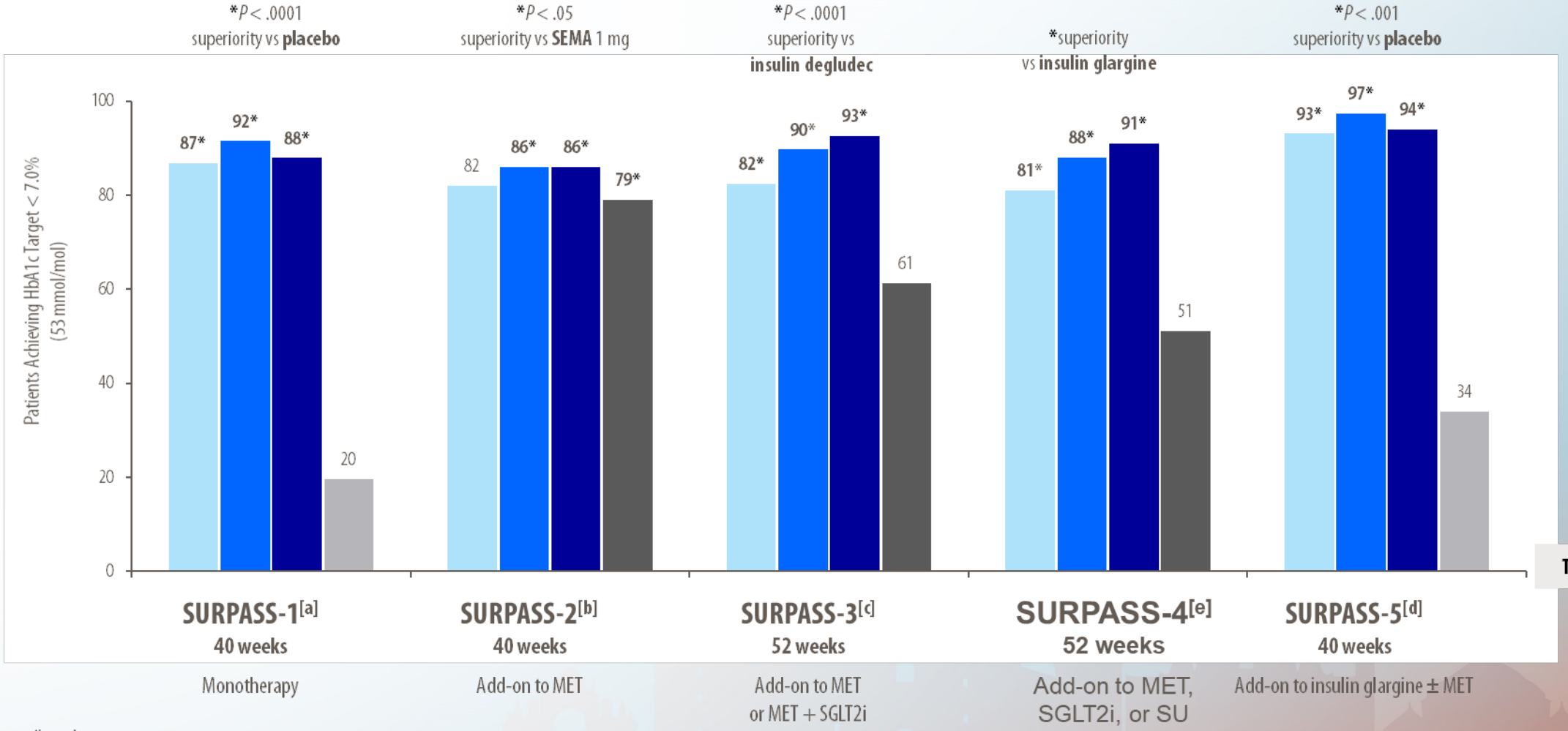
HbA1c nel tempo (SURPASS-2)
Stima dell'Efficacia



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, and 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.

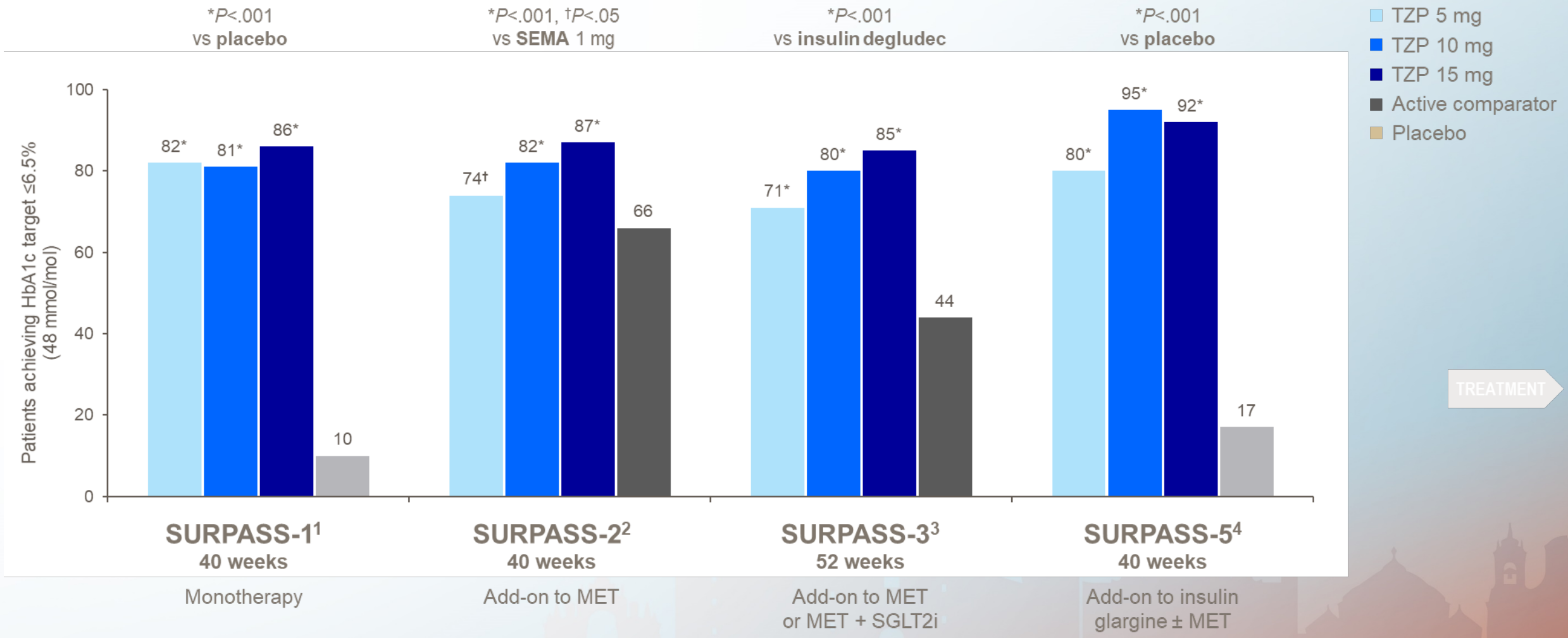
SURPASS

Proporzione di Pazienti che hanno raggiunto HbA1c < 7.0% (53 mmol/mol)*



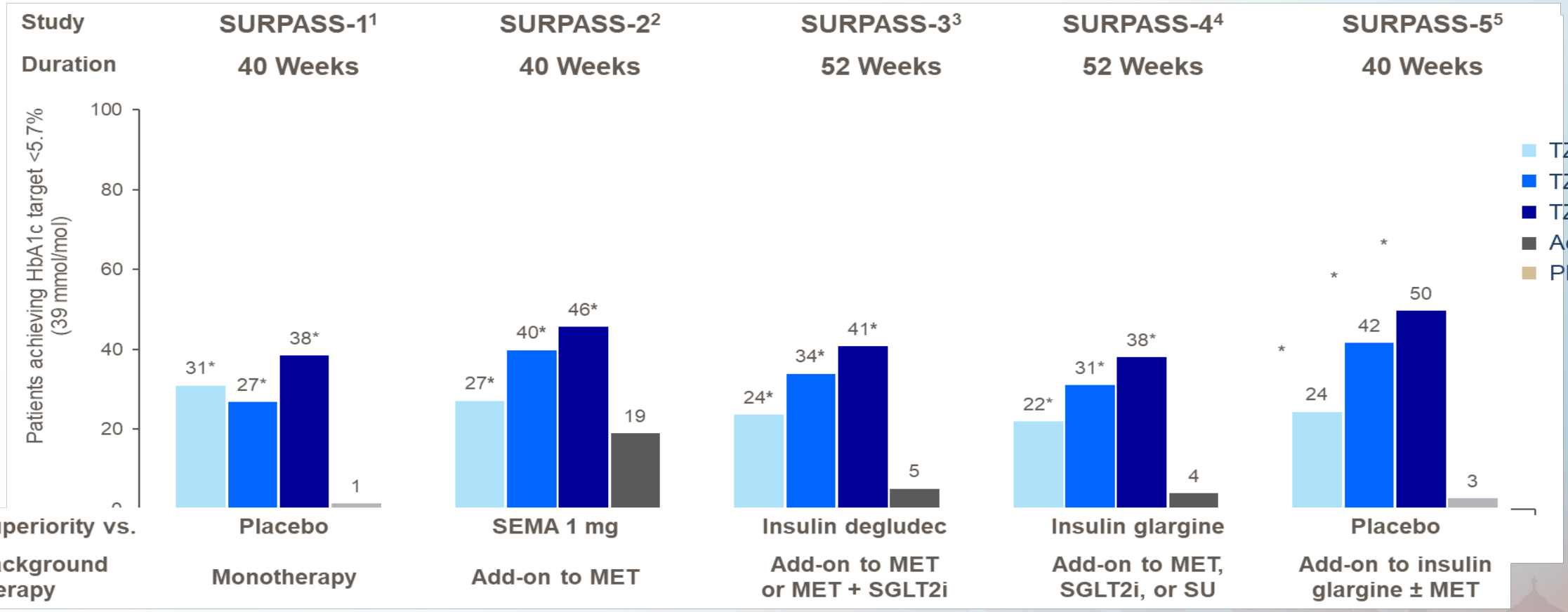
- †Efficacy estimand.
- Data are estimated mean; mITT population (efficacy analysis set). Logistic regression.
- a. Rosenstock J, et al. Lancet. 2021;398:143-155; b. Frías JP, et al; SURPASS-2 Investigators. N Engl J Med. 2021;385(6):503-515; c. Ludvik B, et al. Lancet. 2021;398:583-598; d. Dahl D, et al. Presented at: 81st Scientific Sessions of the American Diabetes Association [virtual]; June 25-29, 2021. Poster 80-LB; e. Del Prato S, et al. Presented at: virtual EASD Annual Meeting 2021

Proporzione di Pazienti che hanno raggiunto HbA1c ≤ 6.5%
Stima di Efficacia



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.

Proporzione di Pazienti che hanno raggiunto HbA1c < 5.7%
Stima del Regime di Trattamento

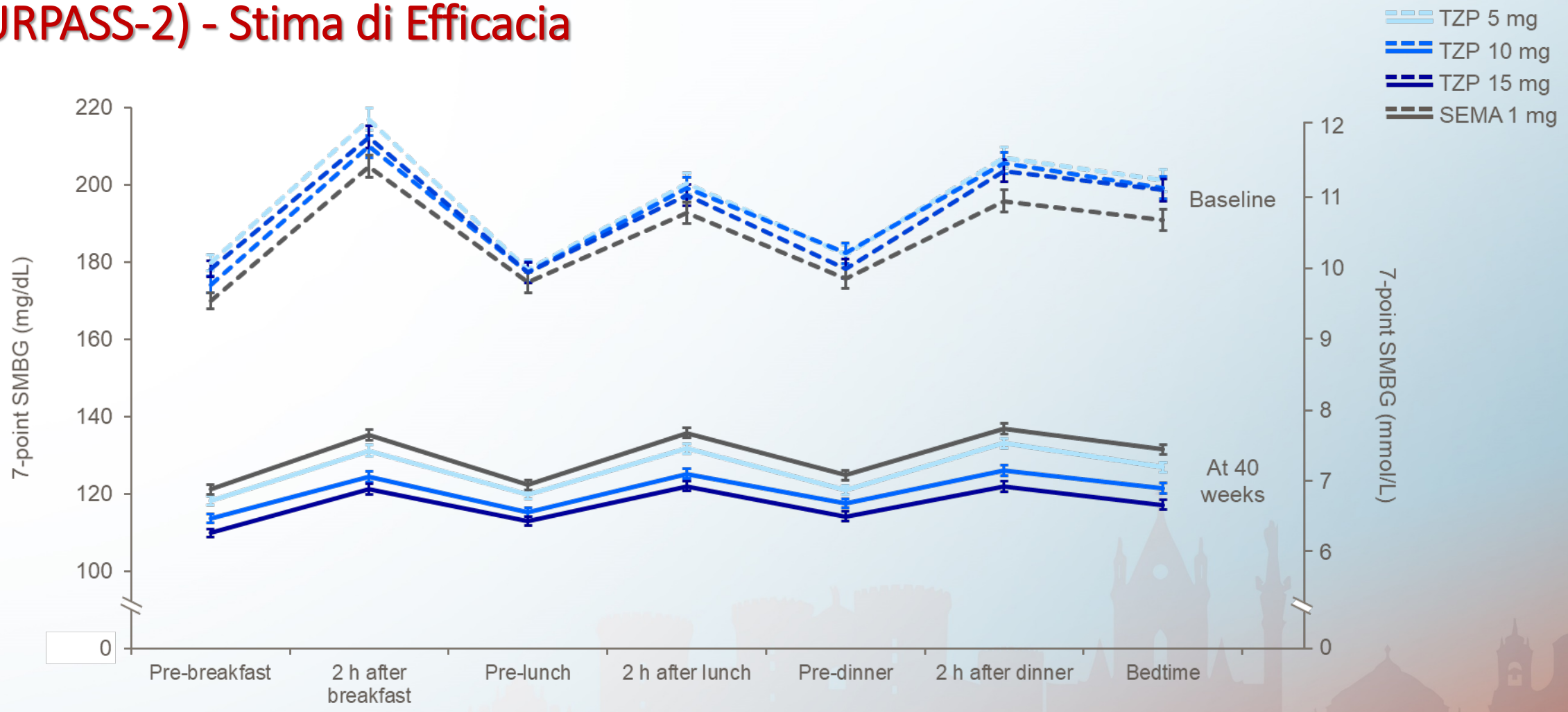


*P<.001 vs. placebo or active comparator.

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

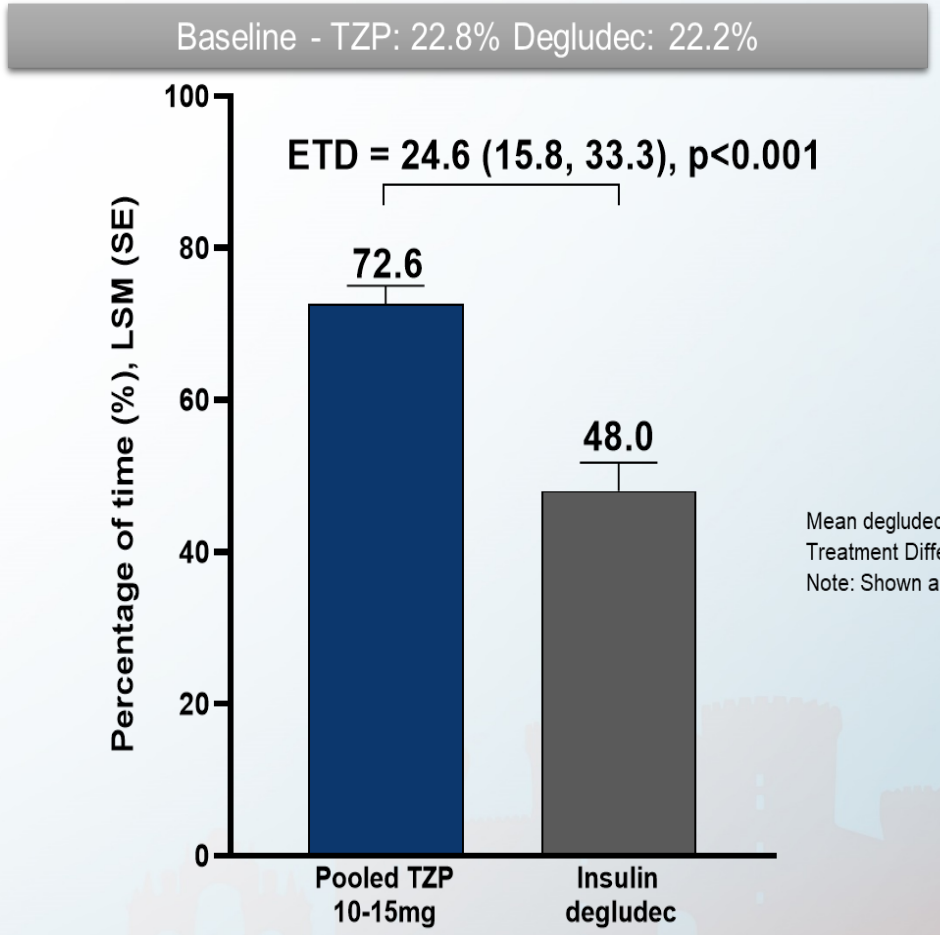
1. Rosenstock J, et al. *Lancet*. 2021;398(10295):143-155. 2. Frias JP, et al. *N Eng J Med*. 2021;385(6):503-515. 3. Ludvik B, et al. *Lancet*. 2021;398(10300):583-598. 4. Del Prato S, et al. *Lancet*. 2021;398(10313):1811-1824. 5. Dahl D, et al. Poster presented at: *ADA* 2021. Poster LB-20.

Automonitoraggio glicemico in 7 punti al Basale e a 40 Settimane (SURPASS-2) - Stima di Efficacia



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.

Percentuale del Tempo in Tight Target Range (71-140 mg/dL) a 52 Settimane

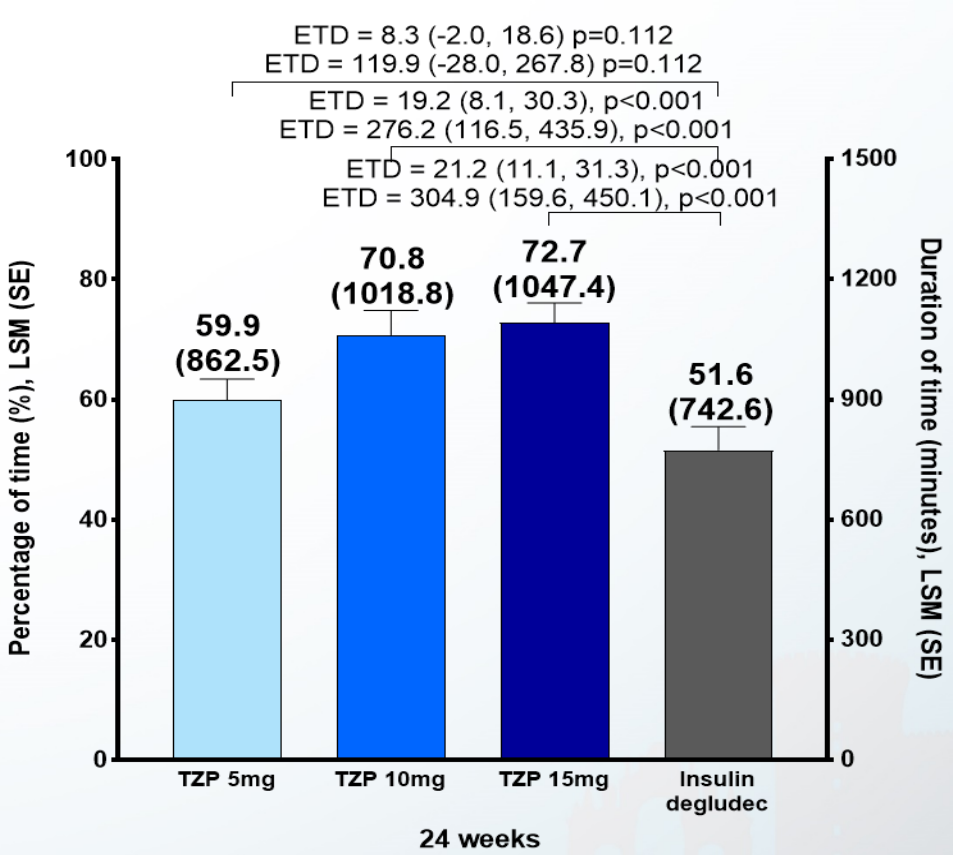


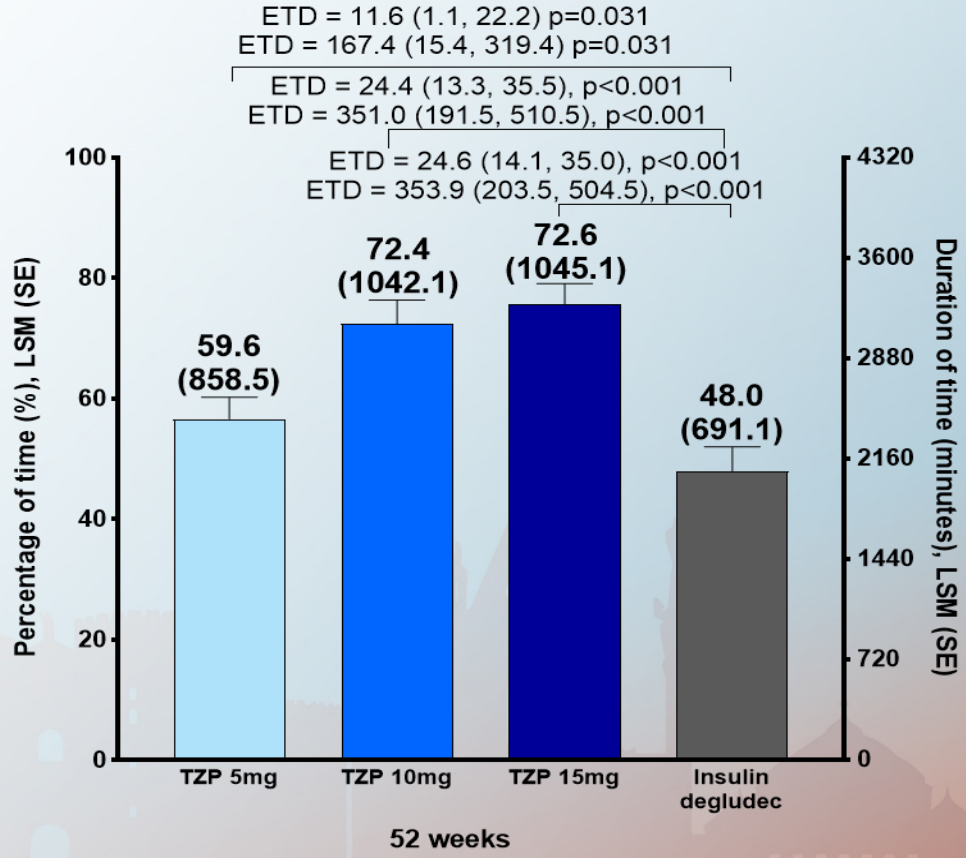
Mean degludec dose: 52.5 units (0.6 U/kg/day). ETD = Estimated Treatment Difference (95% confidence interval). TZP = tirzepatide.
Note: Shown are the least-squares means ± standard errors.

Battelino Tet al American Diabetes Association – 82nd Annual Scientific Sessions; Hybrid; 3-7 June 2022

Percentuale e Durata del Tempo in Tight Target Range a 24 e 52 Settimane

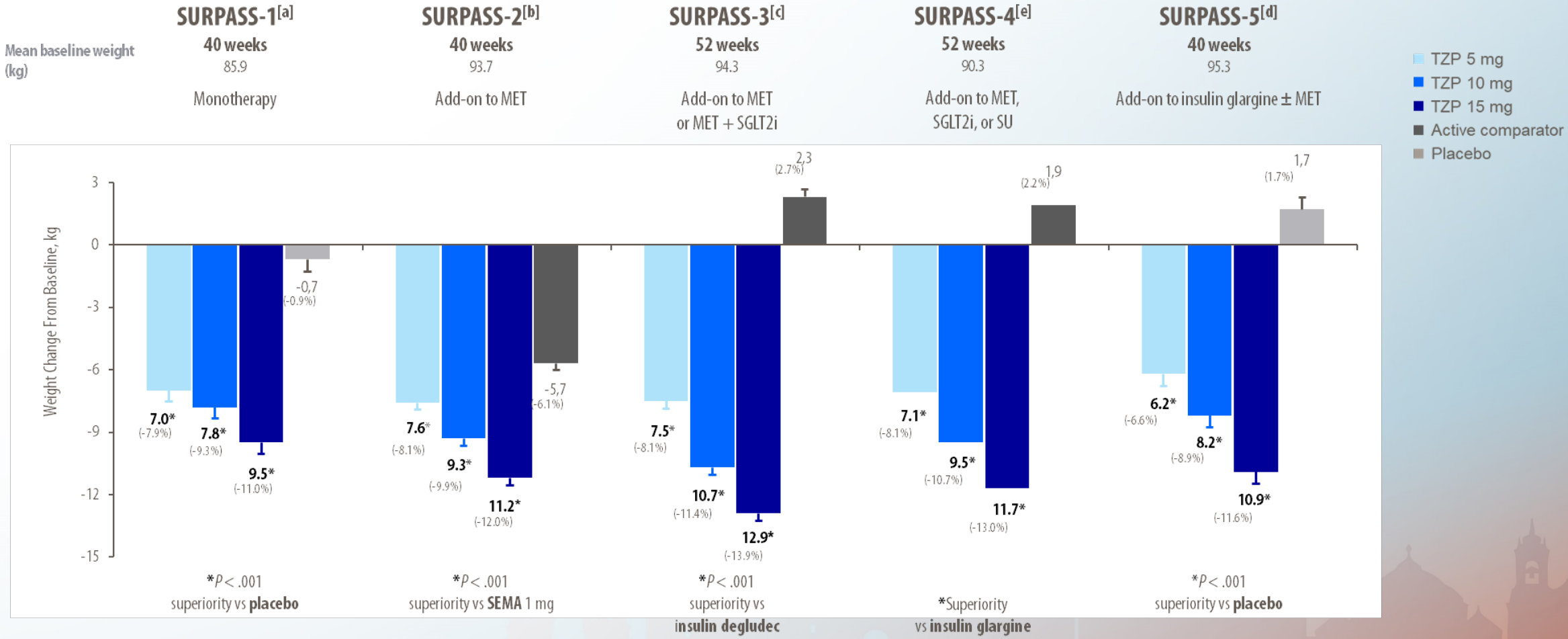
Baseline - TZP 5mg: 22.7%, 10 mg: 25.5%, 15 mg: 21.1%, Degludec: 22.2%





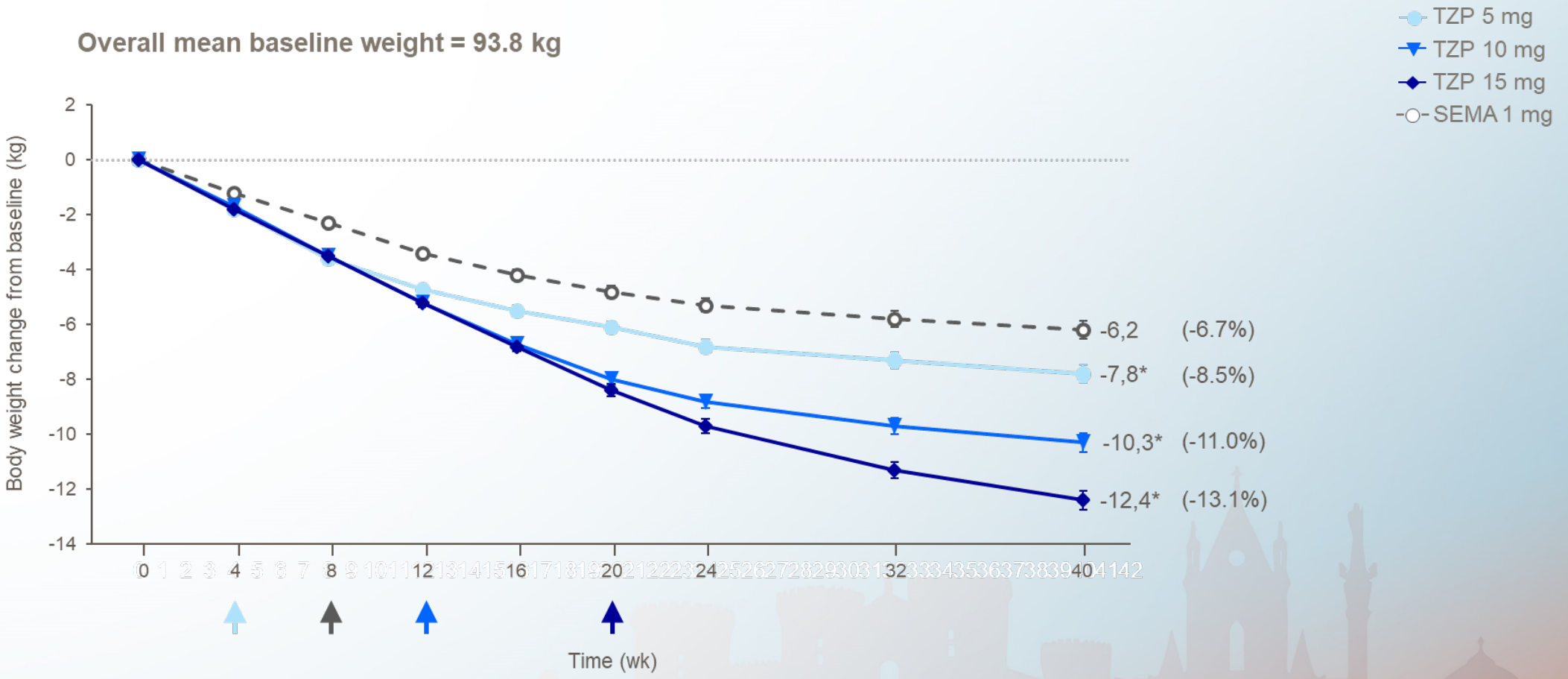
Battelino Tet al American Diabetes Association – 82nd Annual Scientific Sessions; Hybrid; 3-7 June 2022

SURPASS
Principali Risultati di Efficacia: Peso Corporeo



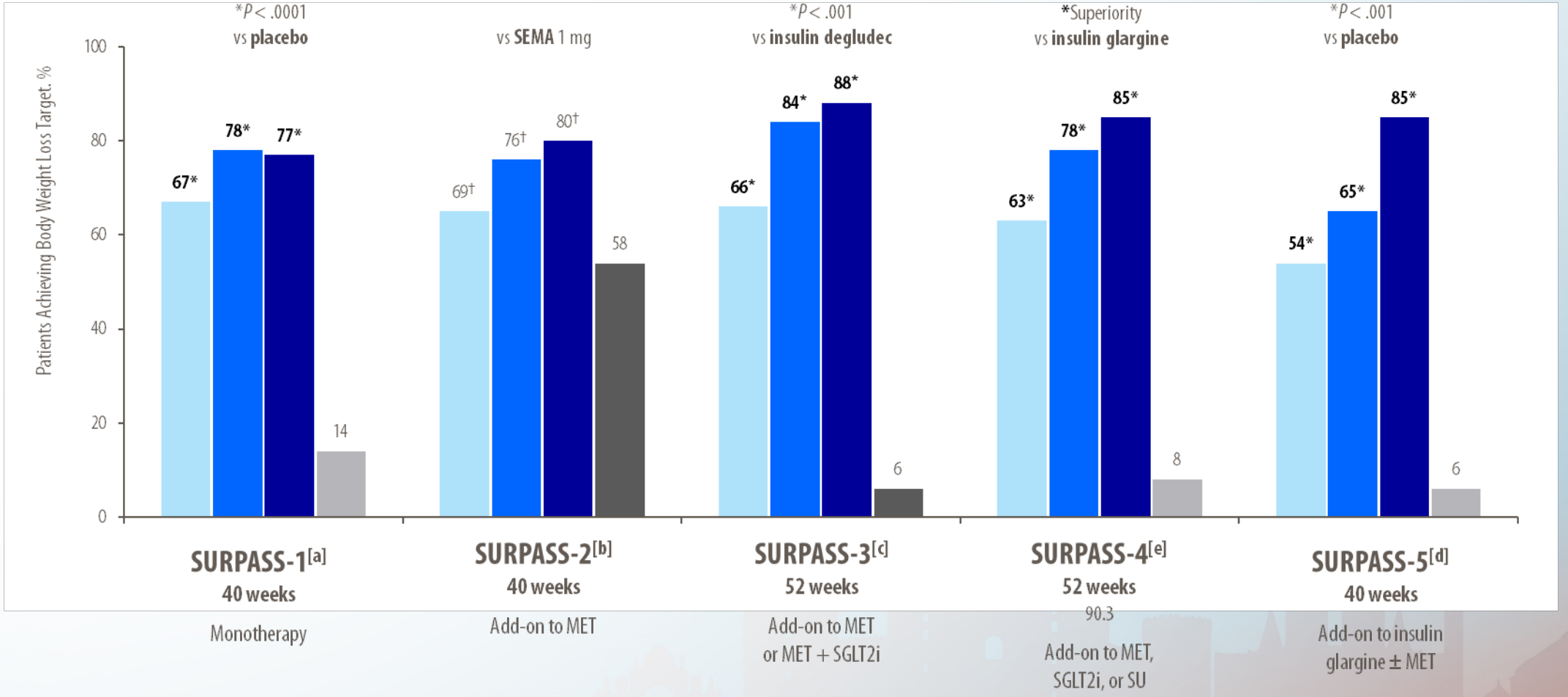
Data are LSM (SE); mITT population (efficacy analysis set). MMRM analysis.
a. Rosenstock J, et al. Lancet. 2021;398:143-155; b. Frías JP, et al; SURPASS-2 Investigators. N Engl J Med. 2021;385:503-515; c. Ludvik B, et al. Lancet. 2021;398:583-598; d. Dahl D, et al. Presented at: 81st Scientific Sessions of the American Diabetes Association [virtual]; June 25-29, 2021. Poster 80-LB; e. Del Prato S, et al. Presented at: virtual EASD Annual Meeting 2021.

Cambiamenti del Peso Corporeo nel Tempo (SURPASS-2) Stima di Efficacia



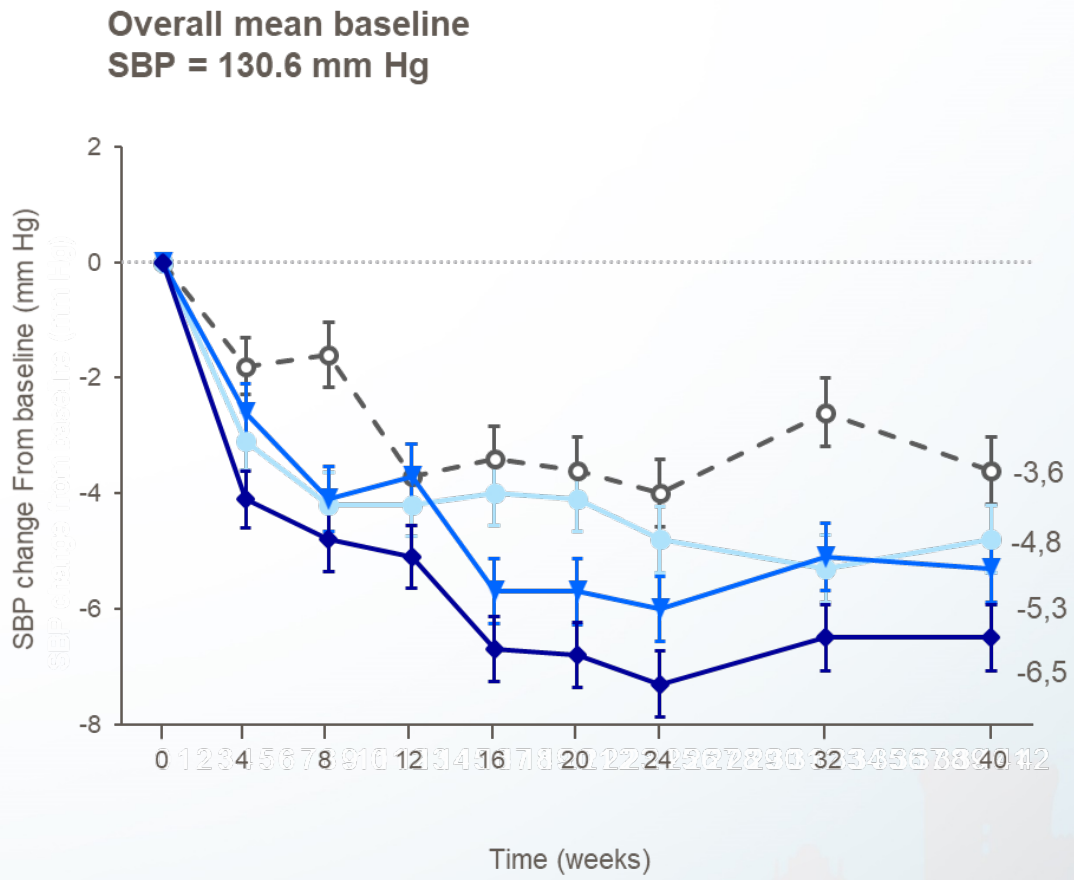
Data are LSM (SE); mITT population (efficacy analysis set). ANOVA analysis (week 0) and MMRM analysis (week 40). Arrows indicate when the dose of TZP 5 mg, 10 mg, 15 mg, and SEMA 1 mg were achieved. Data labels are weight in kg (% change from baseline).
*P<.001 vs SEMA.
ANOVA = analysis of variance; 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.

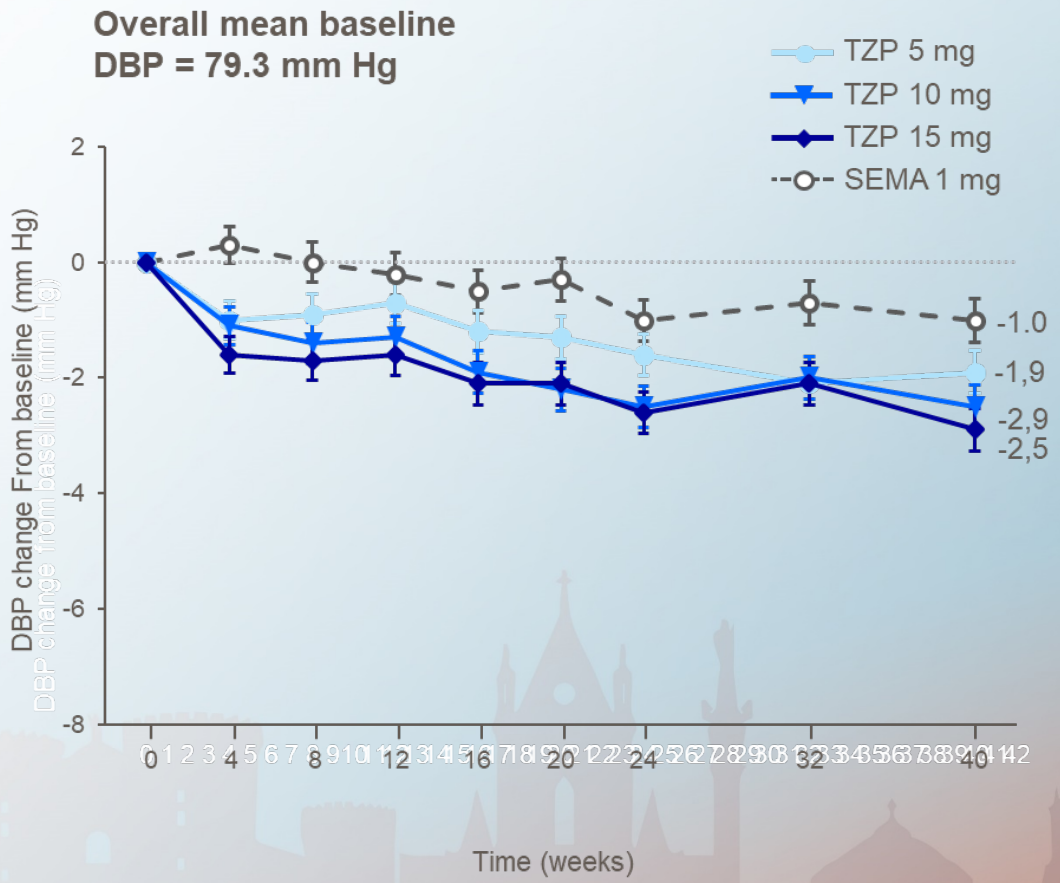
SURPASS
Proporzione di Pazienti che hanno perso ≥ 5% del Peso Corporeo*



Data are estimated mean; mITT population (efficacy analysis set). Logistic regression; †*P* not given.
a. Rosenstock J, et al. Lancet. 2021;398:143-155; b. Frías JP, et al; SURPASS-2 Investigators. N Engl J Med. 2021;385:503-515; c. Ludvik B, et al. Lancet. 2021;398:583-598; d. Dahl D, et al. Presented at: 81st Scientific Sessions of the American Diabetes Association [virtual]; June 25-29, 2021. Poster 80-LB; e. Del Prato S, et al. Presented at: virtual EASD Annual Meeting 2021.

Pressione Arteriosa nel Tempo (SURPASS-2)

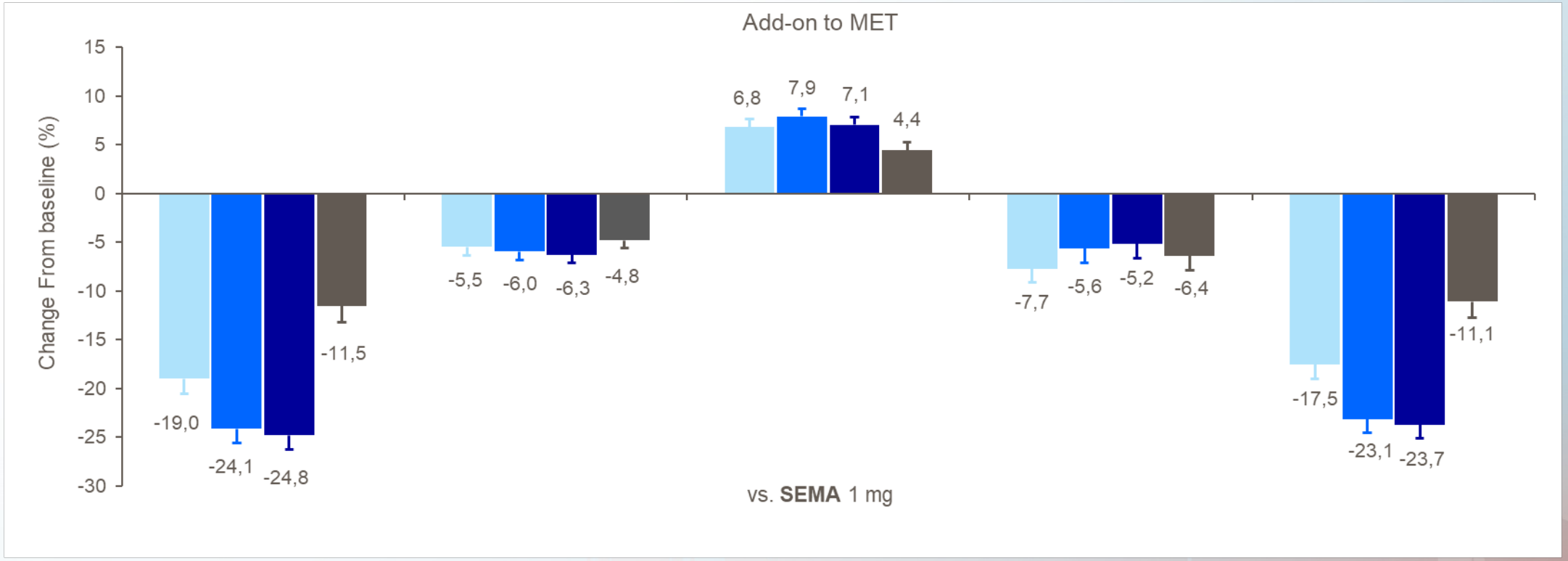




Data are LSM (SE); mITT population (safety analysis set). Arrows indicate when the dose of TZP 5 mg, 10 mg, 15 mg, and SEMA 1 mg were achieved. *Prevalence* refers to the proportion of subjects who have an event during a time interval.
DBP = diastolic blood pressure; LSM = least squares mean; mITT = modified intent-to-treat; SBP = systolic blood pressure; SE = standard error; SEMA = semaglutide; TZP = tirzepatide.
Frias JP, et al. *N Eng J Med*. 2021;385(6):503-515.

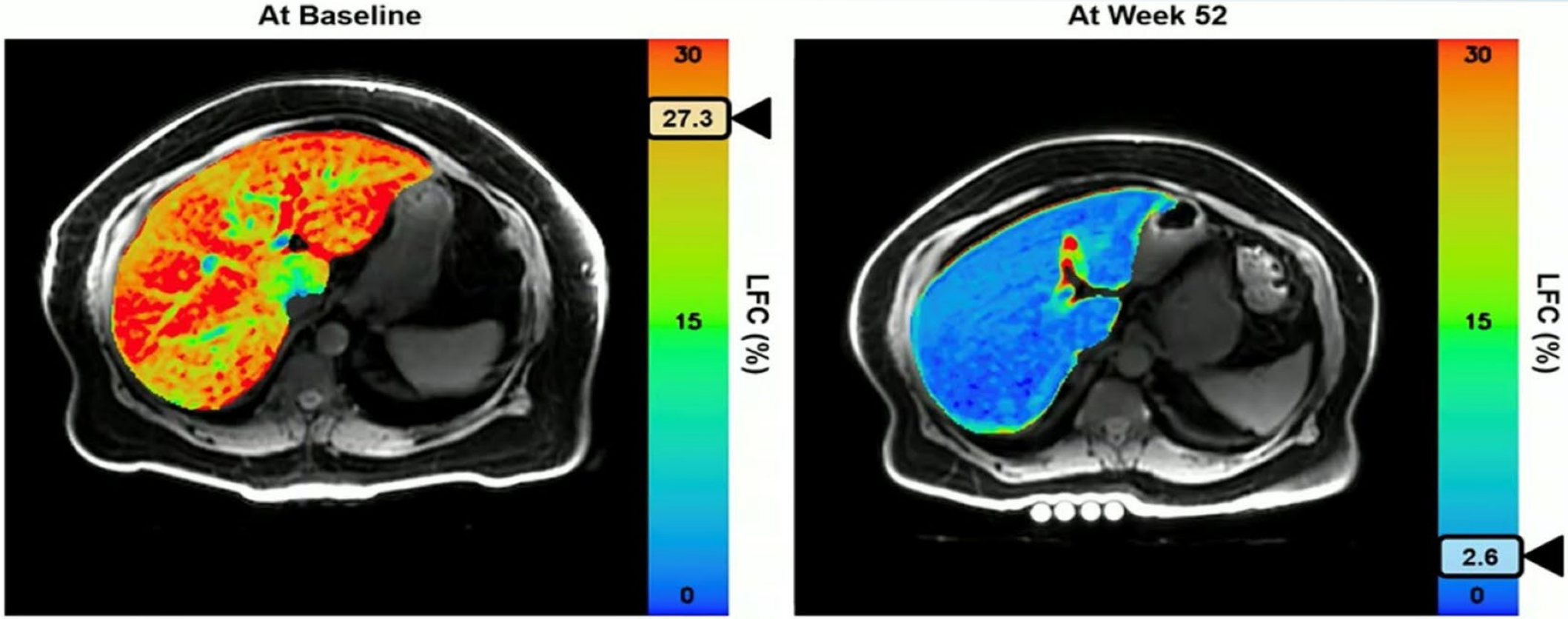
Profilo Lipidico a 40 Settimane (SURPASS-2)
Stima di Efficacia

	Triglycerides				Total cholesterol				HDL cholesterol				LDL cholesterol				VLDL cholesterol			
	40 weeks				40 weeks				40 weeks				40 weeks				40 weeks			
Baseline mg/dL (mmol/L)	165.9 (1.87)	167.4 (1.89)	163.6 (1.85)	165.2 (1.87)	171.5 (4.44)	171.3 (4.43)	168.6 (4.36)	170.9 (4.42)	42.9 (1.11)	42.7 (1.10)	42.9 (1.11)	42.7 (1.10)	88.2 (2.28)	88.4 (2.29)	86.4 (2.23)	88.2 (2.28)	32.5 (0.84)	32.8 (0.85)	32.3 (0.83)	32.7 (0.84)



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; SE = standard error; SEMA = semaglutide; TZP = tirzepatide; VLDL = very-low-density lipoprotein.
Frias JP, et al. *N Eng J Med.* 2021;385(6):503-515.

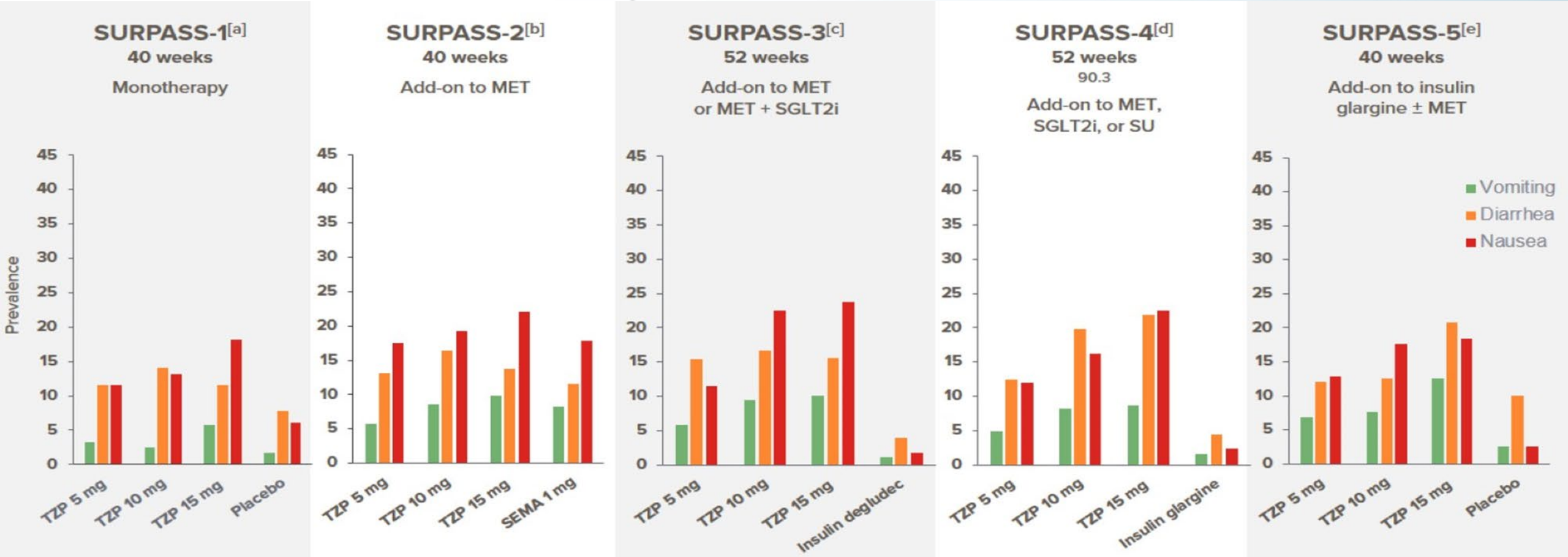
SURPASS-3
Immagini alla RM funzionale al basale e dopo 52 settimane



FSG, fasting serum glucose; LFC, liver fat content; WC, waist circumference.

Gastaldelli A, et al. Presented at: EASD Virtual Meeting; September 28-October 1, 2021. Presentation 426.

SURPASS
Prevalenza di vomito, diarrea e nausea



Data are percentage of TEAE with ≥ 5% frequency in any arm; mITT population (safety analysis set). Note: Patients may be counted in more than 1 category.
TEAE, treatment-emergent adverse event.
a. Rosenstock J, et al. Lancet. 2021;398:143-155; b. Frías JP, et al. N Engl J Med. 2021;385:503-515; c. Ludvik B, et al. Lancet. 2021;398:583-598; d. Del Prato S, et al. Lancet. 2021;398:1811-1824; e. Dahl D, et al. Diabetes. 2021;70(Suppl 1): Abstract 80-LB.

SURPASS
Altri eventi avversi

Pancreatite
4 casi di pancreatite sono stati imputati all'utilizzo di Tirzepatide (10 mg, n = 2; 15 mg, n= 2), ma nessuno di questi eventi è risultato severo

Anticorpi anti-farmaco
Nessuno dei pazienti che ha sviluppato anticorpi anti-farmaco durante il trattamento con Tirzepatide ha avuto reazioni di severa ipersensibilità o reazioni al sito di iniezione

Carcinoma midollare tiroideo
Non sono stati osservati cambiamenti rilevanti nelle concentrazioni medie di calcitonina, non è stato osservato nessun caso di carcinoma midollare tiroideo

Retinopatia diabetica
Sono stati evidenziati casi di retinopatia emersi durante il trattamento con Tirzepatide in SURPASS-2 (n=2) e in SURPASS-3 (n=3)

*These results do not yet include data from the SURPASS-4 or SURPASS-5 clinical trials.
a. Rosenstock J, et al. Lancet. 2021;398:143-155; b. Frías JP, et al. N Engl J Med. 2021;385:503-515; c. Ludvik B, et al. Lancet. 2021;398:583-598;
d. Dahl D, et al. Presented at: 81st Scientific Sessions of the American Diabetes Association, Virtual; June 25-29, 2021. Poster 80-LB.

Ipoglicemia

SURPASS-1[1]	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-2[2]	**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-3[3]	**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-5[4]	**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

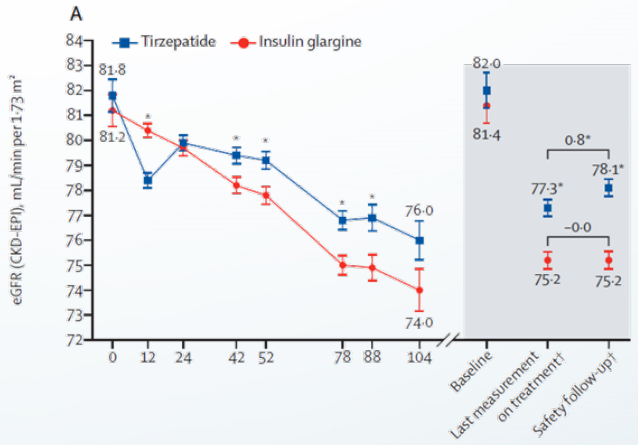
Data are n (%); mITT population (safety analysis set). Note: Patients may be counted in more than 1 level. Data after initiation of new glucose lowering therapy are not included.
[a]Severe event characterised by altered mental and/or physical status requiring assistance for treatment of hypoglycaemia; [b]1 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; [c]1 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.

Effects of tirzepatide versus insulin glargine on kidney outcomes in type 2 diabetes in the SURPASS-4 trial: post-hoc analysis of an open-label, randomised, phase 3 trial

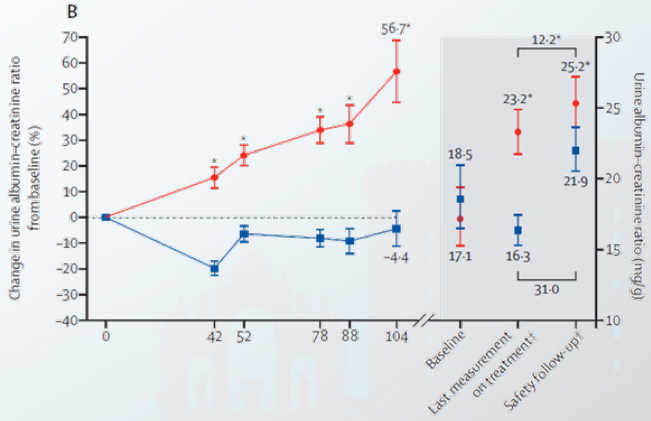
Endpoint renale: composito di declino del 40% dell'eGFR, morte per insufficienza renale, progressione alla malattia renale terminale, comparsa de novo di albuminuria

Analisi post-hoc dei dati di SURPASS-4, trial randomizzato open a gruppi paralleli in 187 siti in 14 paesi. **995 pazienti nel gruppo tirzepatide e 1000 con insulina glargine**
Declino medio di **eGFR–1·4 (SE 0·2) mL/min per 1·73 m²/anno nel Gruppo tirzepatide** e **–3·6 (0·2) mL/min per 1·73 m²/anno nel Gruppo insulina** (differenza tra gruppi 2·2 [95% CI 1·6 to 2·8]). UACR aumentata nel Gruppo glargine (36·9% [95% CI 26·0 to 48·7]) ma non in tirzepatide (–6·8% [–14·1 to 1·1]; between-group difference –31·9% [–37·7 to –25·7]). Pazienti del **Gruppo tirzepatide avevano minor incidenza di endpoint composito renale rispetto a quelli con glargine (HR 0·58 [95% CI 0·43 to 0·80]).**

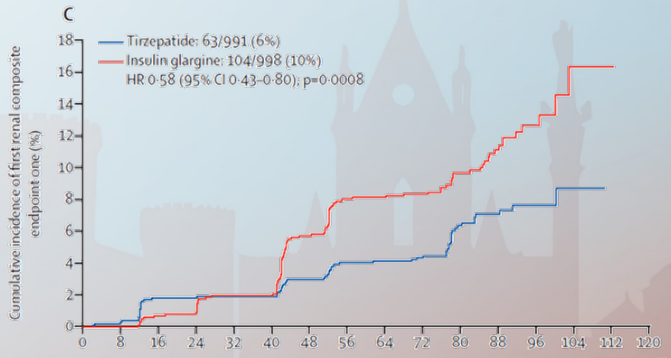
eGFR



UACR

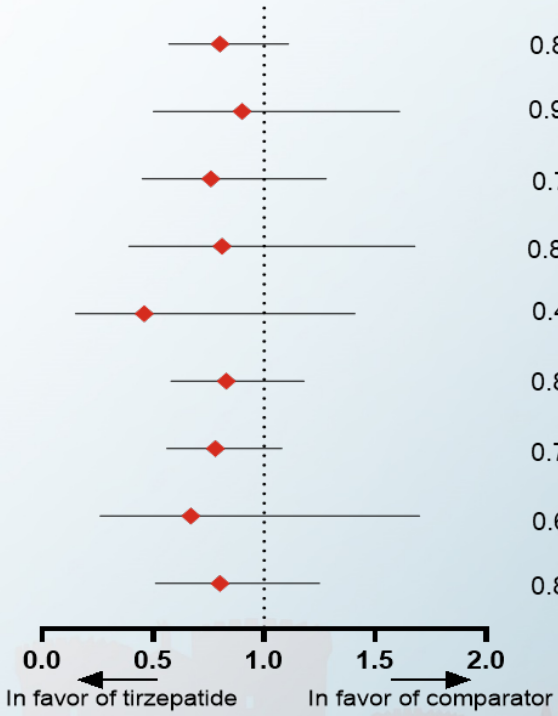


Endpoint composito renale



Outcome Cardiovascolari Primari e Secondari

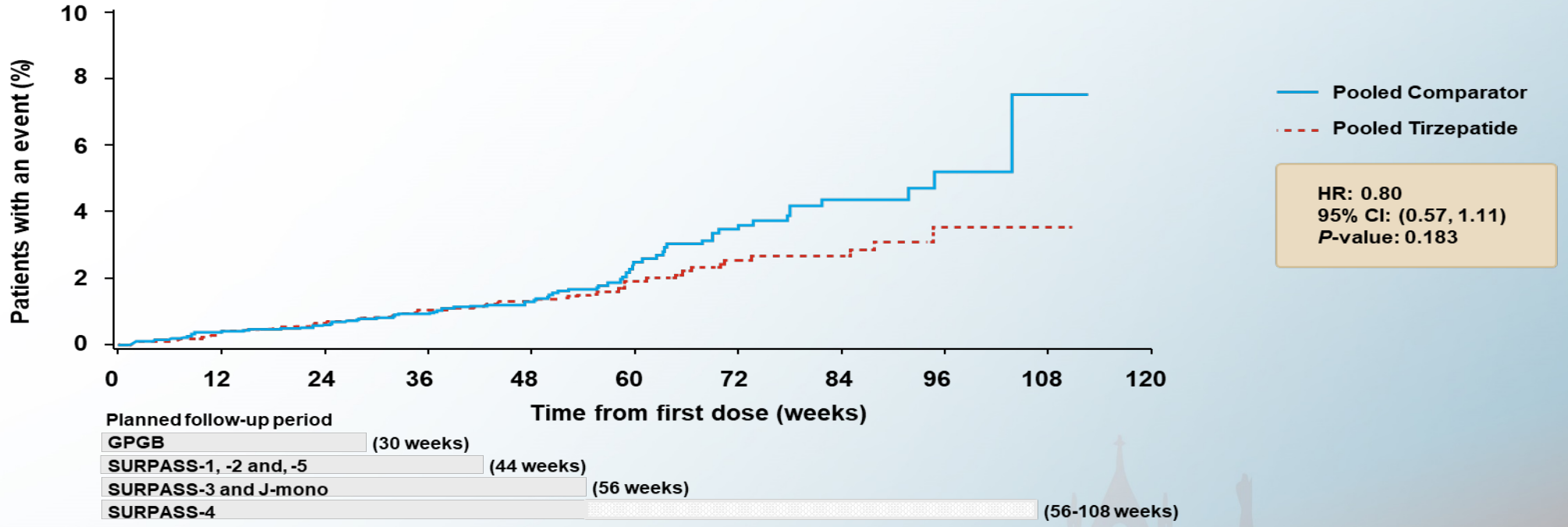
	All Tirzepatide N=4887 n (n/100 Person-Years[a])	All Comparator N=2328 n (n/100 Person-Years[a])	HR With 95% CI	HR (95% CI)	*P* Value
Composite MACE-4	72 (1.35)	70 (1.61)		0.80 (0.57, 1.11)	0.183
Death due to cardiovascular cause[b]	25 (0.46)	22 (0.43)		0.90 (0.50, 1.61)	
Myocardial infarction	30 (0.56)	30 (0.71)		0.76 (0.45, 1.28)	
Stroke	15 (0.27)	15 (0.35)		0.81 (0.39, 1.68)	
Hospitalization for unstable angina	5 (0.09)	9 (0.20)		0.46 (0.15, 1.41)	
Composite MACE-3[c]	67 (1.25)	62 (1.42)		0.83 (0.58, 1.18)	0.306
Composite MACE-3 or hospitalization for heart failure	74 (1.39)	71 (1.71)		0.78 (0.56, 1.08)	0.137
Hospitalization for heart failure	10 (0.19)	9 (0.29)		0.67 (0.26, 1.70)	
All-cause death	41 (0.76)	39 (0.86)		0.80 (0.51, 1.25)	



[a]Strata size adjusted estimate. Strata are defined as trial-level cardiovascular risk (SURPASS-4 forms one stratum, and all other trials form one stratum). [b]Death due to cardiovascular cause includes adjudication-confirmed deaths due to a cardiovascular or undetermined cause. [c]MACE-3 includes death due to cardiovascular or undetermined cause, myocardial infarction, or stroke.
Note: *P* values were based on the Wald Chi-square test. Data are point estimate of HR (illustrated by the diamond symbol) and range of 2-sided 95% CI of the HR.
HR=Hazard Ratio; CI=Confidence Interval; MACE=Major Adverse Cardiovascular Event.
Sattar N, et al. *Nat Med*. 2022; (Ahead of Print).

Metanalisi sul rischio cardiovascolare a partire dagli Studi SURPASS

Effect of Pooled Tirzepatide versus Pooled Comparator on Time to First Occurrence of Adjudication-Confirmed MACE-4 (Primary Outcome)



Cumulative number of events: Number of patients at risk

Pooled Tirzepatide:	0:4887	15:4813	28:4726	43:4477	53:2477	62:960	68:832	69:515	72:188	72:19	72:0
Pooled Comparator:	0:2328	13:2292	19:2250	28:2118	36:1438	52:914	62:794	67:496	69:172	70:14	70:0

Note: *P* values are based on the Wald Chi-square test. Gray bars represent the planned follow-up period for trials GPGB (30 weeks), SURPASS-1, SURPASS-2 and SURPASS-5 (44 weeks), SURPASS-3 and SURPASS J-mono (56 weeks), and SURPASS-4 (56-108 weeks).
HR=Hazard Ratio; CI=Confidence Interval; MACE=Major Adverse Cardiovascular Event.
Sattar N, et al. *Nat Med*. 2022;(Ahead of Print).

SURPASS
Tirzepatide in sintesi

- Robusta riduzione dell' HbA1c (da -1.87% a -2.59%)
- Alta percentuale di pazienti che hanno raggiunto il valore target di HbA1c inferiore a 7% (dall'81% al 97.4%)
- Maggiore percentuale di pazienti con valori di HbA1c ≤5.7% (dal 23% al 62.4%)
- Robusta riduzione di peso (da -6.2 kg a -12.9 kg)
- Efficacia confermata indipendentemente dalla terapia di background (naive, metformina, combinazione di antidiabetici orali, insulina basale) e dalla durata del diabete (4.7 anni, 8.4 anni, 8.6 anni, 11.8 anni, 13.3 anni)
- Basso rischio di ipoglicemie
- Tollerabilità gastrointestinale simile alla classe dei GLP-1RA

- ❖ **Miglior controllo glicemico**
- ❖ **Efficacia sia in diabete di breve durata che di lunga durata**
- ❖ **Possibile combinazione con antidiabetici orali e con insulina**
- ❖ **Da preferire per l'efficacia sul peso corporeo**

SURPASS
Tirzepatide in sintesi

- Non sono stati valutati gli effetti nei pazienti con eGFR inferiore a 45 ml/min/1.73 m^2 o inferiore a 30ml/min/1.73 m^2
- Riduzione della pressione arteriosa sistolica, miglioramenti nel profilo lipidico, riduzione di ALT e AST (informazioni sui MACE sono in corso di valutazione)
- Informazioni limitate su DKD/CKD
- Informazioni limitate a 52 settimane
- Informazioni limitate per pazienti con età superiore a 75 anni

- **No in pazienti con CKD (3b)/4/5**
- **Protezione dalla malattia aterosclerotica ?**
- **Protezione dall'insufficienza cardiaca ?**
- **Protezione da DKD/CKD ?**
- **Protezione da NAFLD/NASH ?**

CONSENSUS REPORT | SEPTEMBER 23 2022

Management of Hyperglycemia in Type 2 Diabetes, 2022. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) FREE

https://doi.org/10.2337/dci22-0034

USE OF GLUCOSE-LOWERING MEDICATIONS IN THE MANAGEMENT OF TYPE 2 DIABETES

HEALTHY LIFESTYLE BEHAVIOURS; DIABETES SELF-MANAGEMENT EDUCATION AND SUPPORT (DSMES); SOCIAL DETERMINANTS OF HEALTH (SDOH)

TO AVOID THERAPEUTIC INERTIA REASSESS AND MODIFY TREATMENT REGULARLY (3–6 MONTHS)

Goal: Cardiorenal Risk Reduction in High-Risk Patients with Type 2 Diabetes (In addition to comprehensive CV risk management)*

+ASCVD†
Defined differently across CVOTs but all included individuals with established CVD (e.g. MI, stroke, any revascularisation procedure). Variably included: conditions such as transient ischaemic attack, unstable angina, amputation, symptomatic or asymptomatic coronary artery disease.

+Indicators of high risk
While definitions vary, most comprise ≥ 55 years of age with two or more additional risk factors (including obesity, hypertension, smoking dyslipidaemia or albuminuria)

+ASCVD/Indicators of High Risk
GLP-1 RA# with proven CVD benefit — EITHER/OR — SGLT2i§ with proven CVD benefit
If HbA_{1c} above target
- For patients on a GLP-1 RA consider adding SGLT2i with proven CVD benefit or vice versa
- TZD^

+HF
Current or prior symptoms of HF with documented HFrEF or HFpEF

+HF
SGLT2i§ with proven HF benefit in this population

+CKD
eGFR < 60 ml/min per 1.73 m^2 OR albuminuria (ACR ≥ 3.0 mg/mmol (30mg/g)). These measurements may vary over time; thus, a repeat measure is required to document CKD.

+CKD (on maximally tolerated dose of ACEi/ARB)
PREFERABLY
SGLT2i§ with primary evidence of reducing CKD progression
Use SGLT2i in people with an eGFR ≥ 20 ml/min per 1.73 m^2; once initiated should be continued until dialysis or transplantation
OR
GLP-1 RA with proven CVD benefit if SGLT2i not tolerated or contraindicated
If HbA_{1c} above target, for patients on SGLT2i, consider incorporating a GLP-1 RA or vice versa

If additional cardiorenal risk reduction or glycaemic lowering needed

Goal: Achievement and Maintenance of Glycaemic and Weight Management Goals

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
- General lifestyle advice: medical nutrition therapy/eating patterns/physical activity
- Intensive evidence-based structured weight management programme
- Consider medication for weight loss
- Consider metabolic surgery

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

If HbA_{1c} above target

Identify barriers to goals:
- Consider DSMES referral to support self-efficacy in achievement of goals
- Consider technology (e.g. diagnostic CGM) to identify therapeutic gaps and tailor therapy
- Identify and address SDOH that impact on achievement of goals

* In people with HF, CKD, established CVD or multiple risk factors for CVD, the decision to use a GLP-1 RA or SGLT2i with proven benefit should be independent of background use of metformin; † A strong recommendation is warranted for people with CVD and a weaker recommendation for those with indicators of high CV risk. Moreover, a higher absolute risk reduction and thus lower numbers needed to treat are seen at higher levels of baseline risk and should be factored into the shared decision-making process. See text for details; ^ Low-dose TZD may be better tolerated and similarly effective; § For SGLT2i, CV/renal outcomes trials demonstrate their efficacy in reducing the risk of composite MACE, CV death, all-cause mortality, MI, HHF and renal outcomes in individuals with T2D with established/high risk of CVD; # For GLP-1 RA, CVOTs demonstrate their efficacy in reducing composite MACE, CV death, all-cause mortality, MI, stroke and renal endpoints in individuals with T2D with established/high risk of CVD.

PROGRAMMA - RIUNIONE CONGIUNTA SID - AMD CAMPANIA

Hotel Mediterraneo Renaissance - Napoli 8 Ottobre 2022

PreVen ENDO

Progetto di natura educativa e culturale della Prof.ssa Katherine Esposito sulla prevenzione e cura delle patologie endocrino-metaboliche e andrologiche per promuovere la salute

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