EVENTO TERRITORIALE SID/AMD LAZIO
Protezione cardio-renale nel Diabete di Tipo II (2):
L'integrazione tra Medici di Medicina generale e Specialisti nella cura del Diabete

Flash terapie innovative: TIRZEPATIDE

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SAPIENZA UNIVERSITÀ DI ROMA

Rieti, 17 Giugno 2023

AGENDA

Glycometabolic control

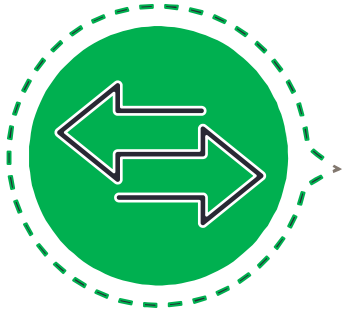
- Insulin secretion
- Glucagon
- Insulin sensitivity
- Lipids

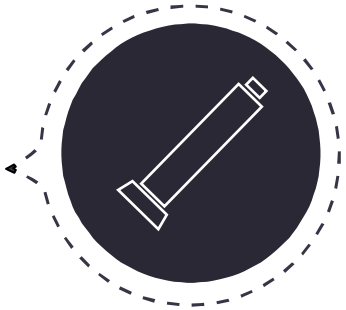
Adiposity

- Weight loss
- Lipid partitioning and adipose function

Receptor pharmacology

Dual agonism

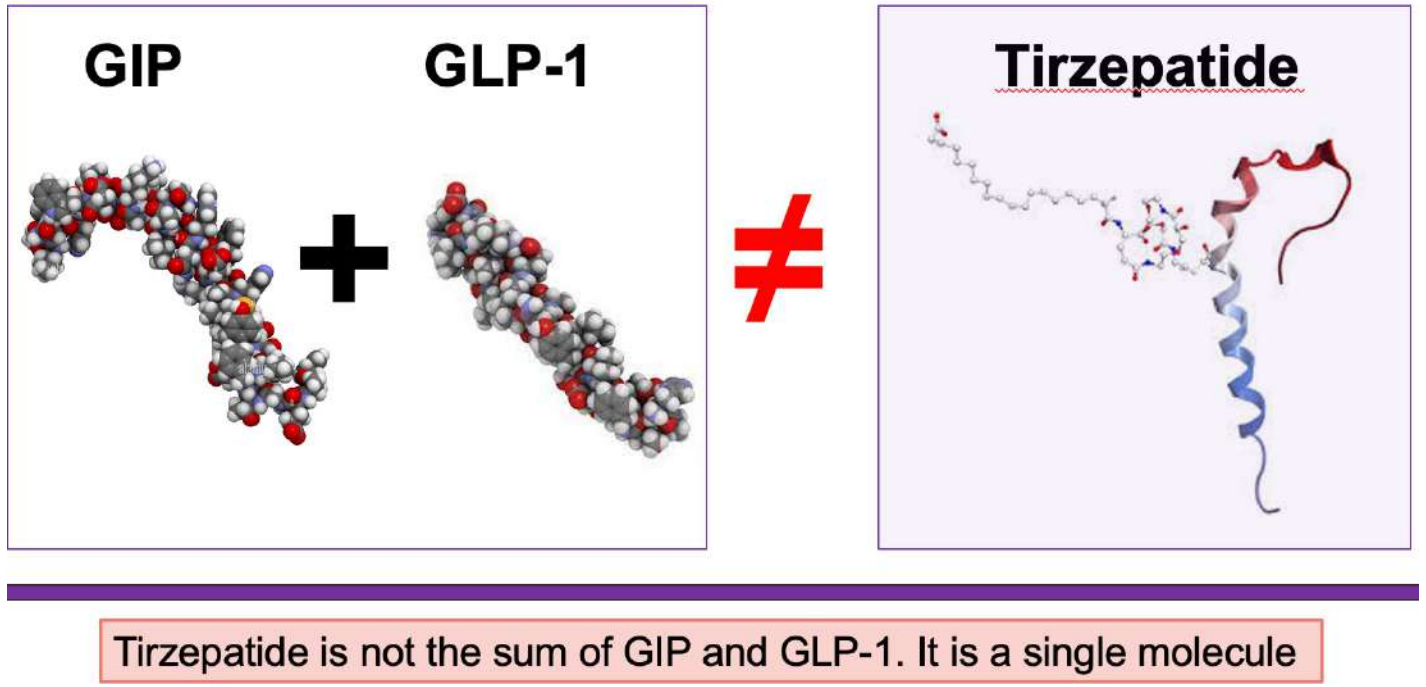




Dose escalation

Tirzepatide: a Dual GIP/GLP-1 Receptor agonist

- **Tirzepatide** is a multi-functional peptide based on the native GIP peptide sequence, modified to bind to both GIPR and GLP-1R

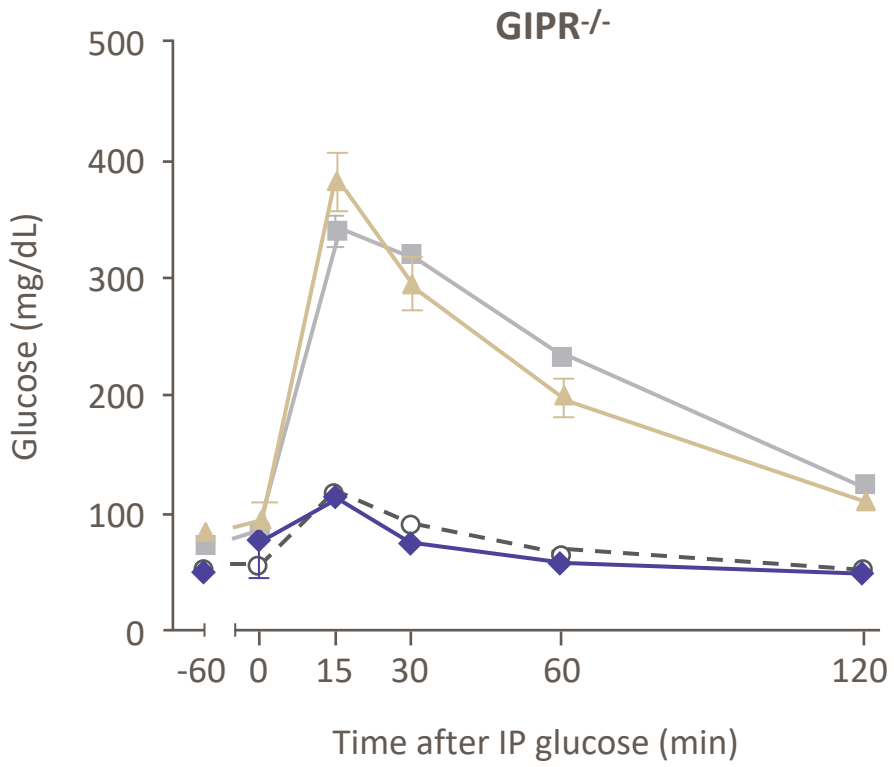


GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon like peptide-1

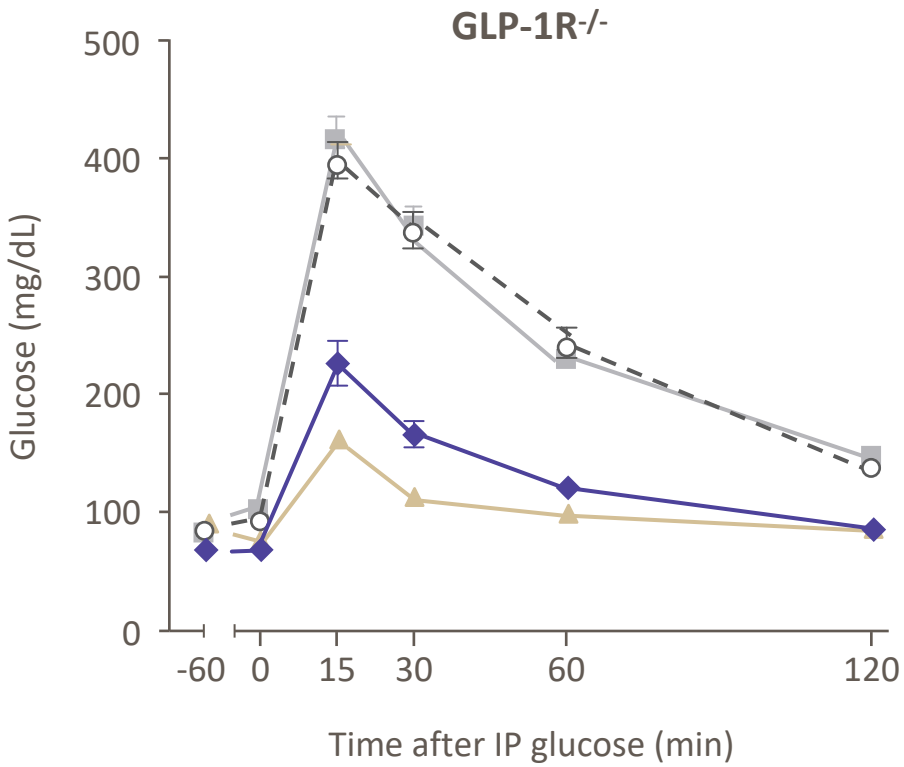
Coskun T, et al, Mol Metab 2018;18:3-14

Tirzepatide regulates glycemia acting on both receptors differently from a selective GLP1

GLP-1R–dependent glycemic control demonstrated in GIPR$^{-/-}$ mice IPGTT



GIPR-dependent glycemic control demonstrated in GLP-1R$^{-/-}$ mice IPGTT



*P<.05 using 1-way ANOVA vs vehicle treatment in high glucose.
ANOVA = analysis of variance; AUC = area under curve; GIP = glucose-dependent insulinotropic polypeptide; GIPR = glucose-dependent insulinotropic polypeptide receptor; GLP-1R = glucagon-like peptide-1 receptor; IP = intraperitoneal glucose; IPGTT = intraperitoneal glucose tolerance test; SEMA = semaglutide; TZP = tirzepatide.
Coskun T, et al. *Mol Metab*. 2018;18:3-14.

Tirzepatide: **Glycometabolic control**

Glycometabolic control

- Insulin secretion
- Glucagon
- Insulin sensitivity
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Adiposity

- Weight loss
- Lipid partitioning and adipose function

Receptor pharmacology

Dual agonism

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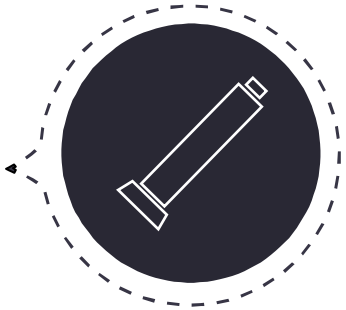
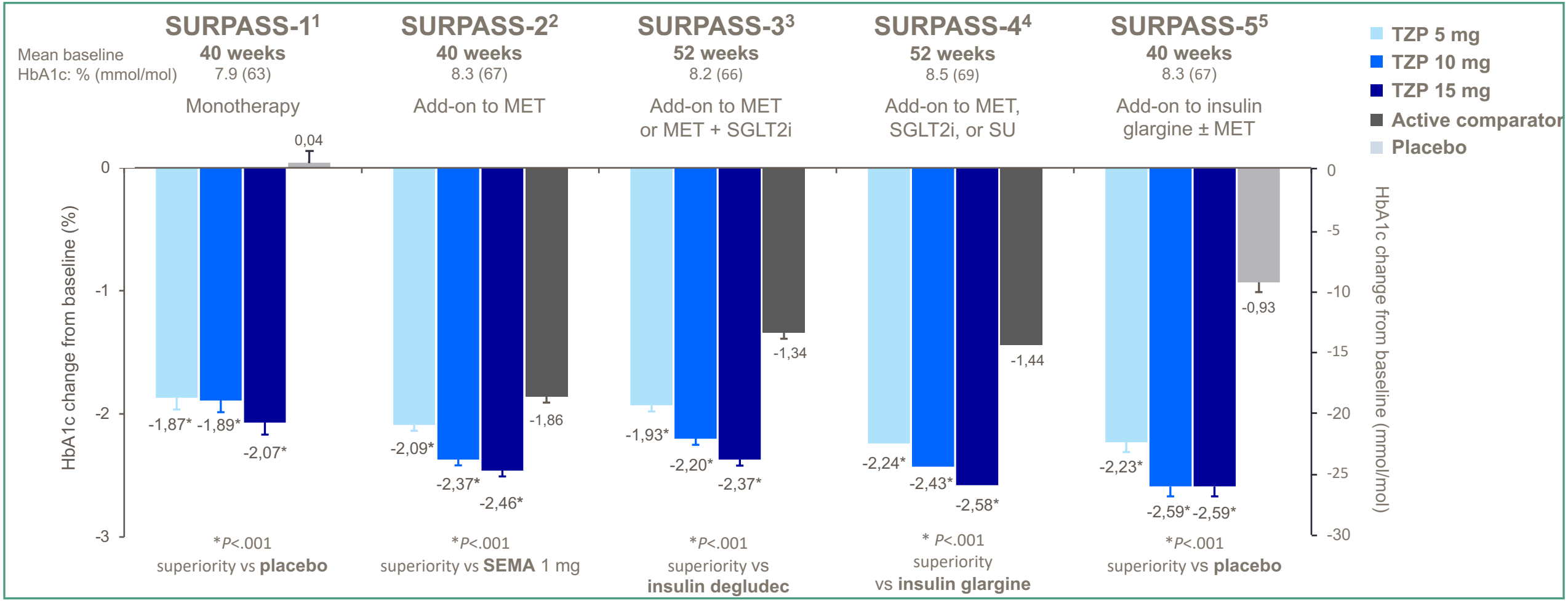


Unprecedented HbA1c reduction from baseline to primary endpoint

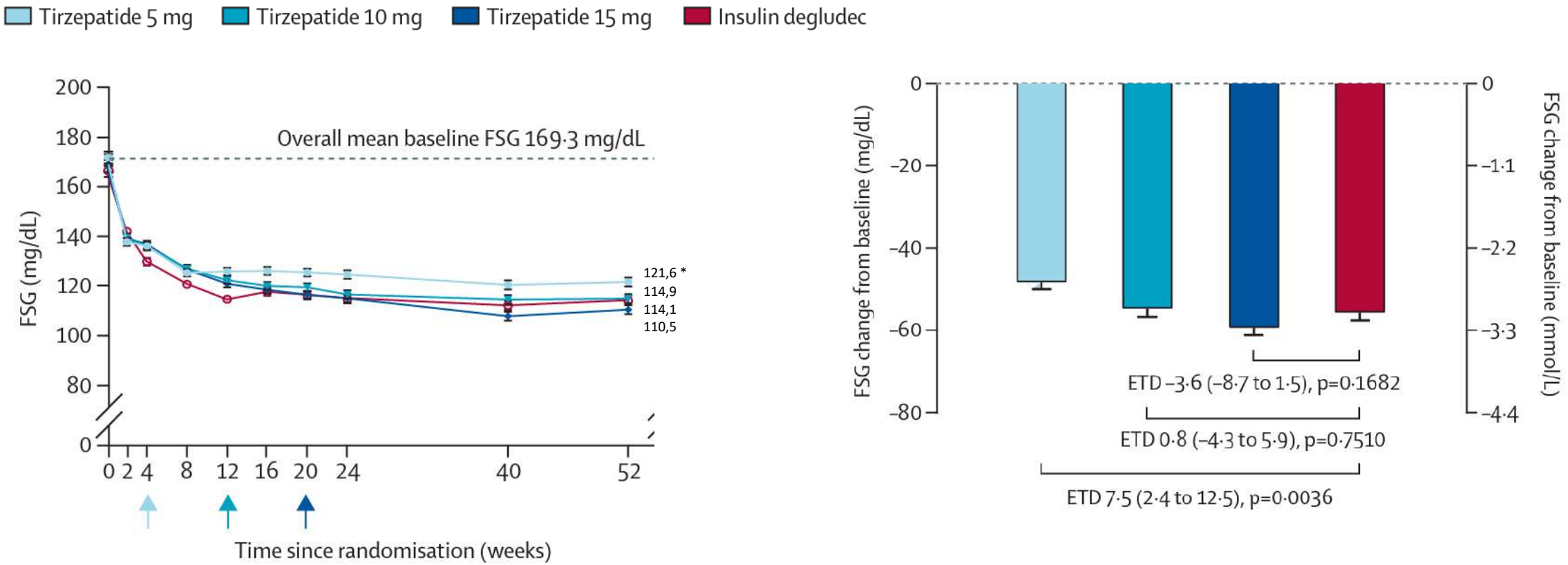


Data are LSM (SE). mITT population (efficacy analysis set). MMRM analysis. Data labels are % HbA1c.

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.

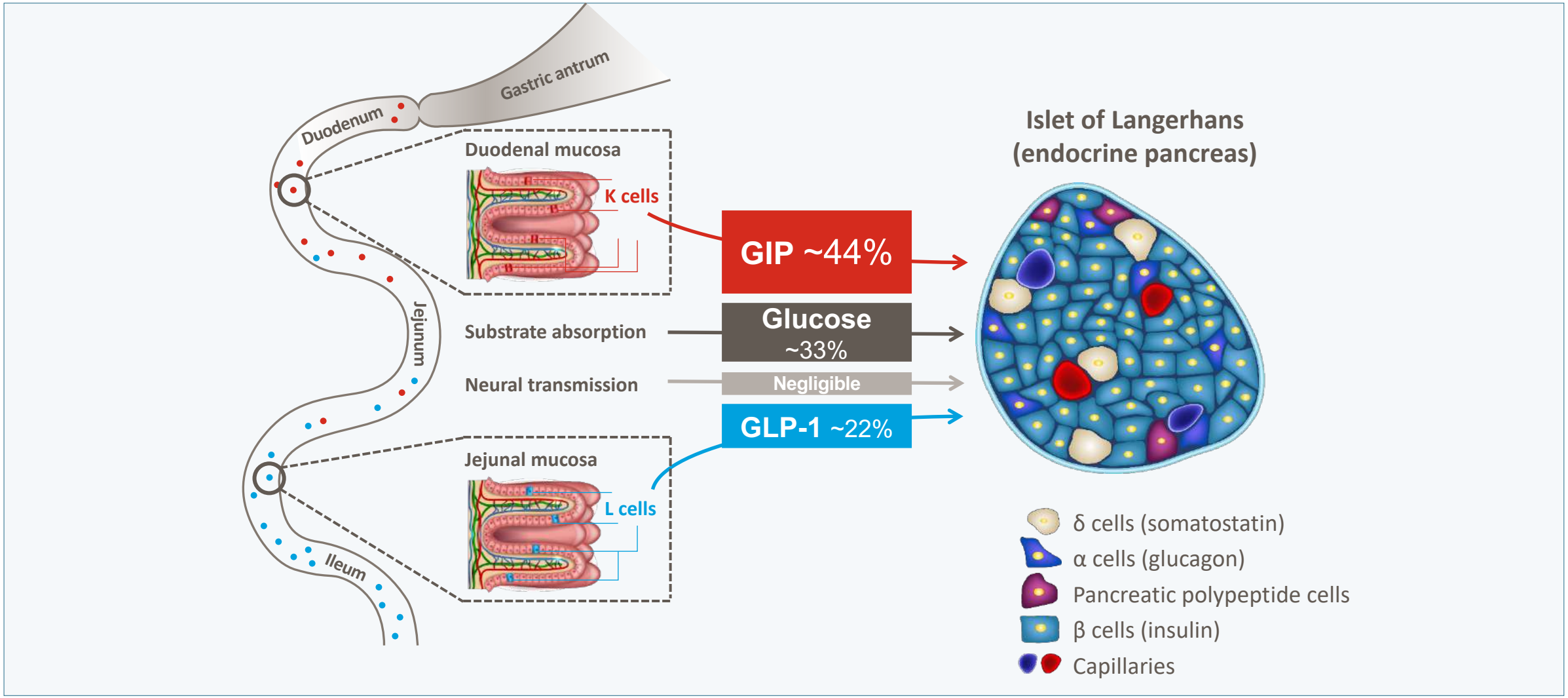
SURPASS-3: Fasting Serum Glucose Over Time and Change from Bseline at 52 Weeks



Data are LSM (SE) over time and 52 weeks. Estimated treatment differences at 52 weeks are LSM (95% CI); mITT (efficacy analysis set); MMRM analysis. Arrows indicate when the maintenance dose of tirzepatide 5 mg, 10 mg, 15 mg was initiated. *p=0,004 vs. insulin degludec

Ludvik B, Giorgino F, et al, Lancet 2021

In healthy subjects, GIP accounts for the majority of insulin secretion

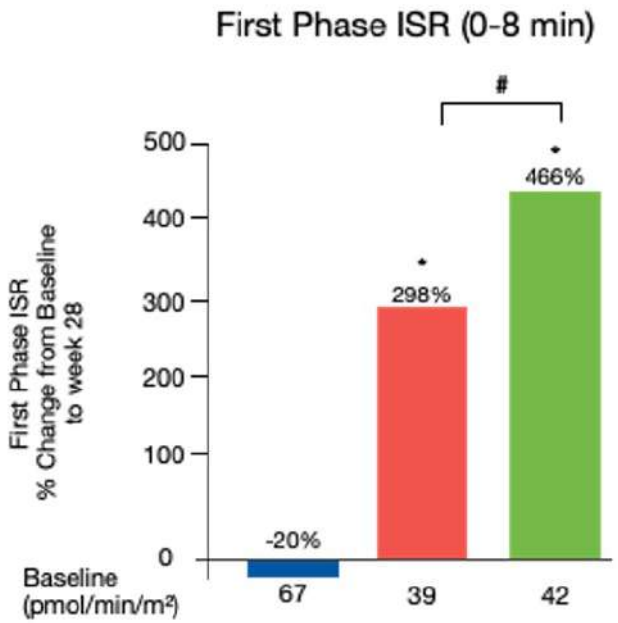


GIP = glucose-dependent insulinotropic polypeptide; GLP-1 = glucagon-like peptide-1; PPG = postprandial glucose.

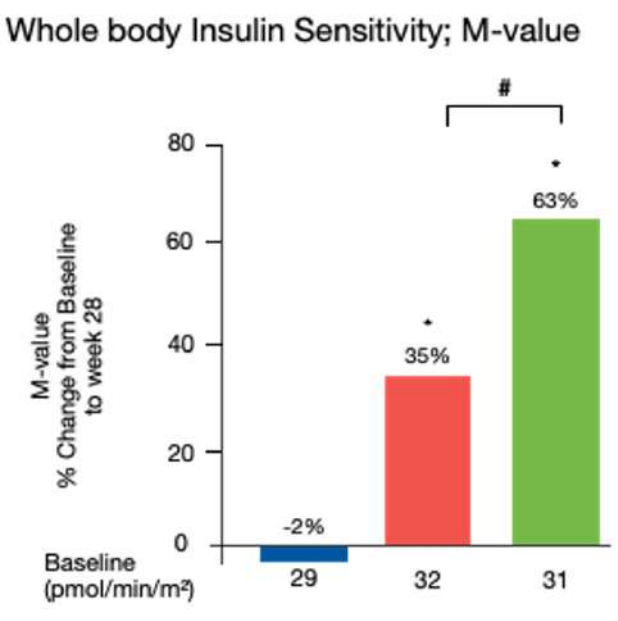
Nauck MA, Meier JJ. *Diabetes*. 2019;68(5):897-900.

Mechanism of glycemic control

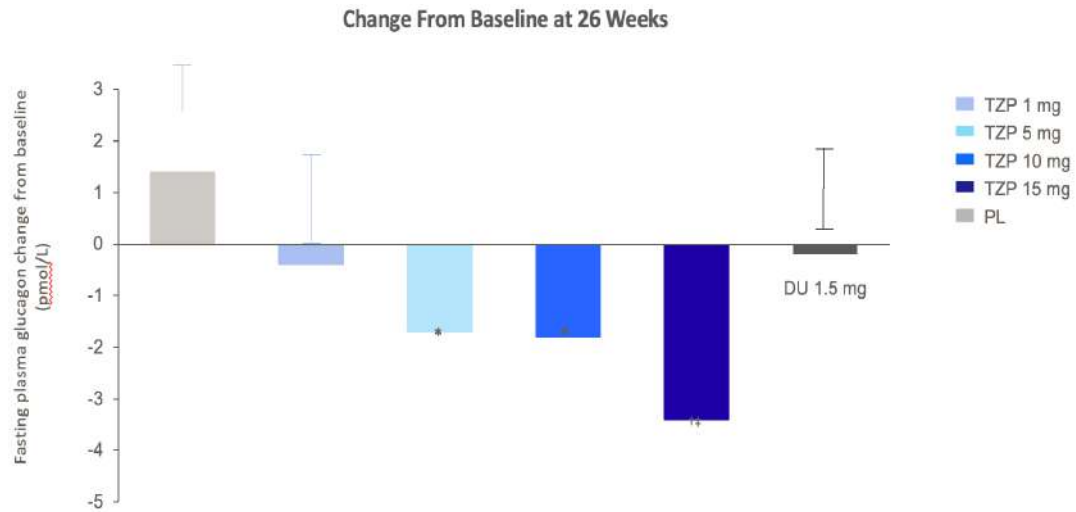
Enhanced insulin secretion



Improved insulin sensitivity



Reduced glucagon levels



Placebo Semaglutide 1.0mg Tirzepatide 15mg

Heise T et al, Lancet Diabetes Endocrinol 2022,
Frias JP, et al. *Lancet* 2018;392(10160):2180-2193

Tirzepatide: Adiposity

Glycometabolic control

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Adiposity

- Weight loss
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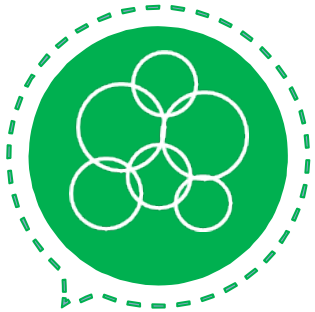
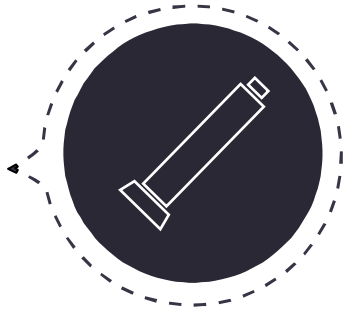


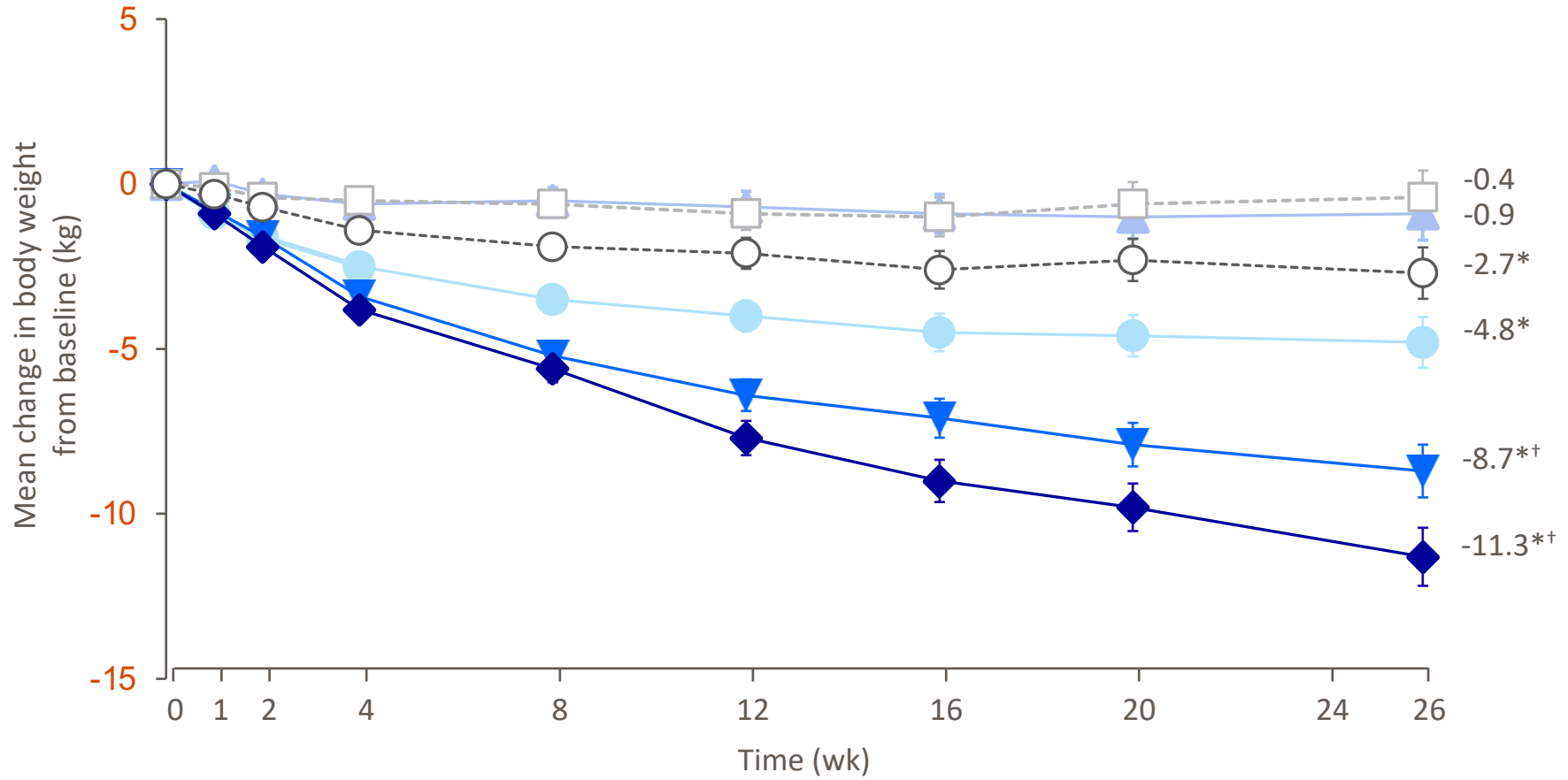
Receptor pharmacology

Dual agonism



Dose escalation

Tirzepatide reduces body weight vs selective GLP1-RA

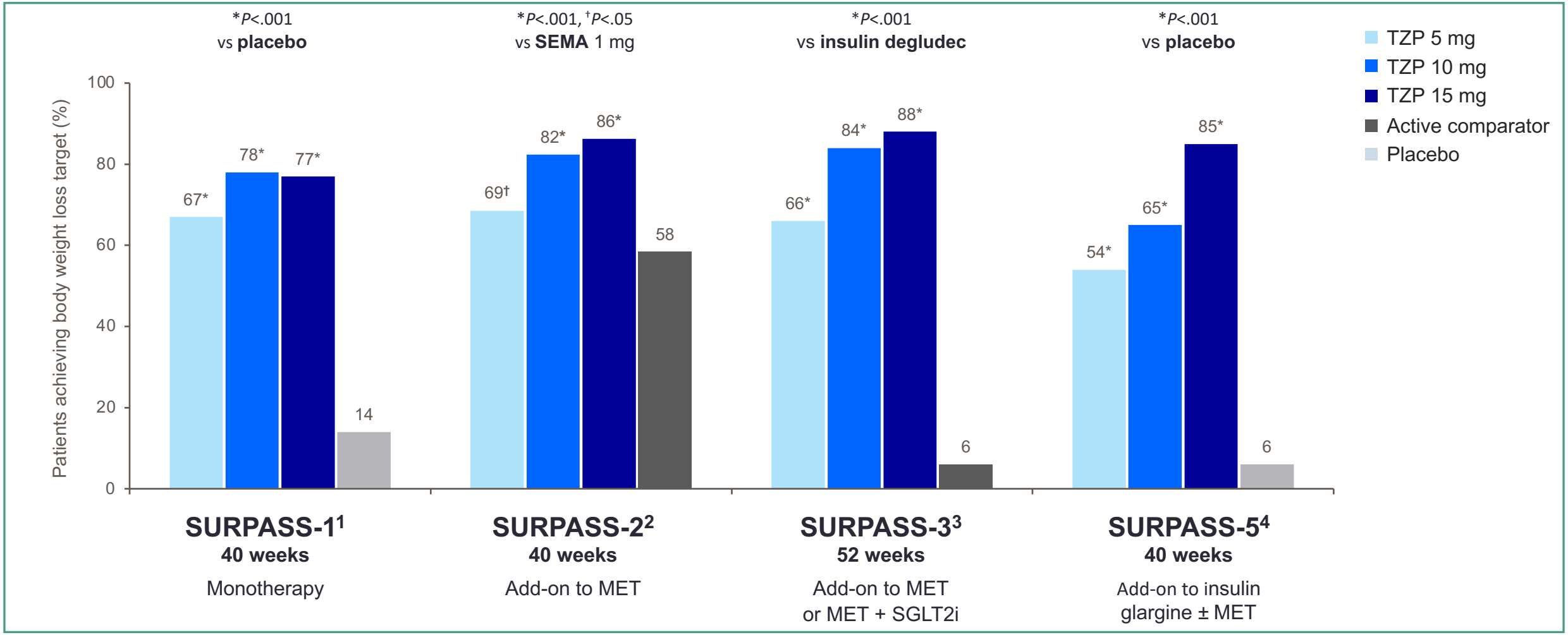


MMRM analysis, mITT on-treatment population. Values reported are LSM (SE).
*P<.05 vs PL; †P<.05 vs DU 1.5 mg.
DU = dulaglutide; HbA1c = glycated hemoglobin; LSM = least-squares mean; mITT = modified intention-to-treat; MMRM = mixed model repeated measures; PL = placebo; TZP = tirzepatide.

Frias JP, et al. *Lancet* 2018;392(10160):2180-2193

Up to 88% of Patients Achieving ≥5% Weight Loss

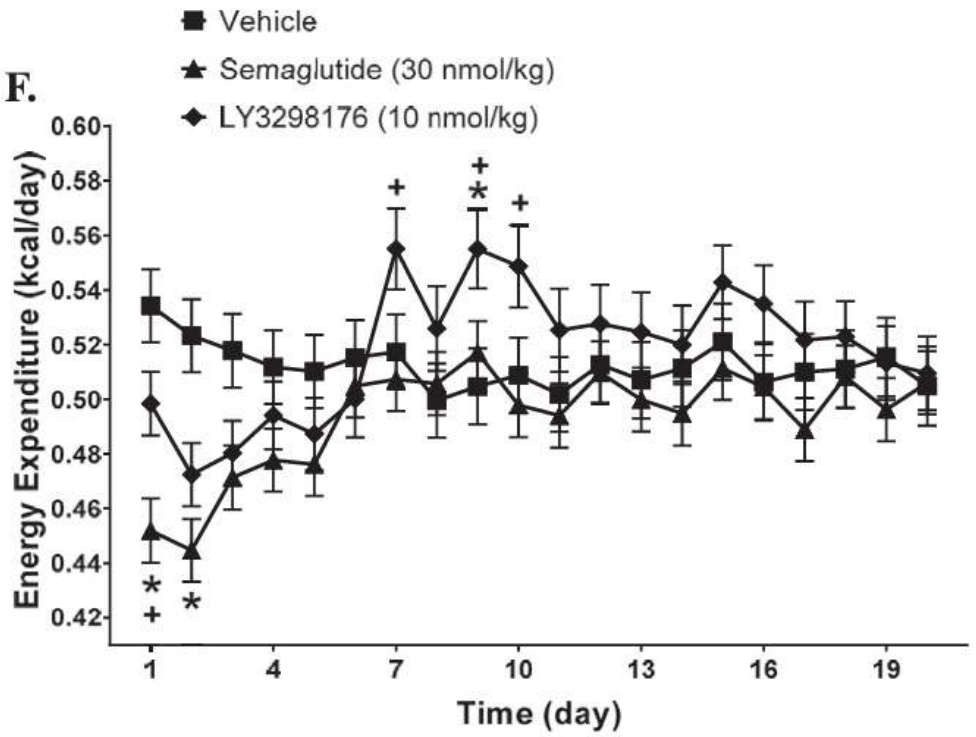
Efficacy Estimand



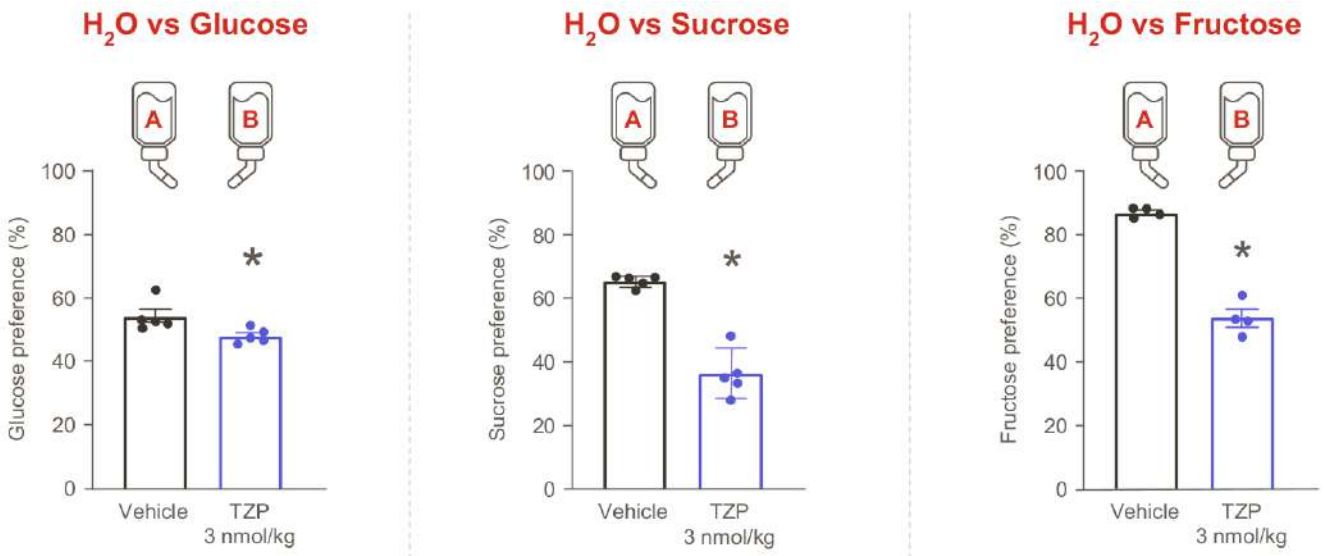
Data are estimated mean; mITT population (efficacy analysis set). Logistic regression.
MET = metformin; mITT = modified intent-to-treat; SGLT2i = sodium-glucose co-transporter-2 inhibitor; SEMA = semaglutide; TZP = tirzepatide.
1. Rosenstock J, et al. *Lancet*. Published online June 26, 2021. 2. Frias 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.

Mechanisms of weight loss

Tirzepatide demonstrated increased energy expenditure in obese mice.

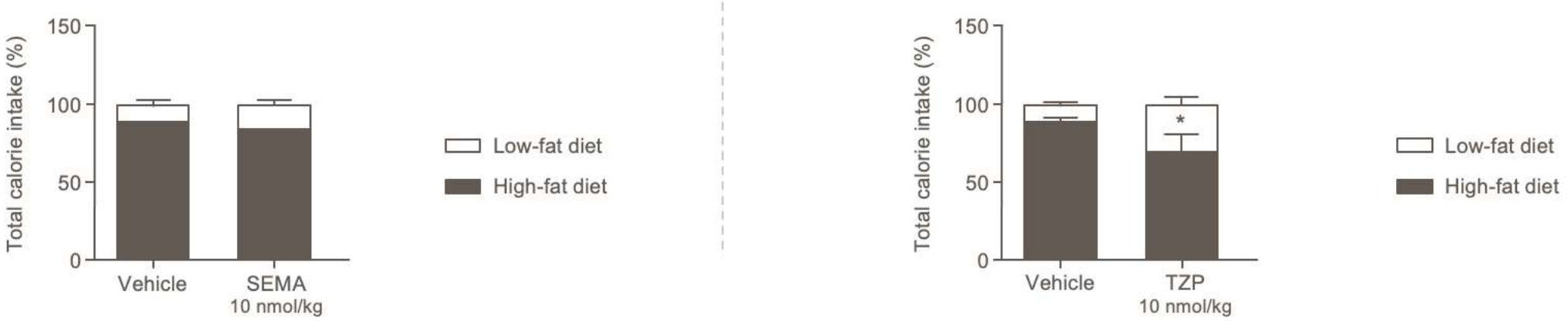


Tirzepatide reduced sweet-taste preference in mice



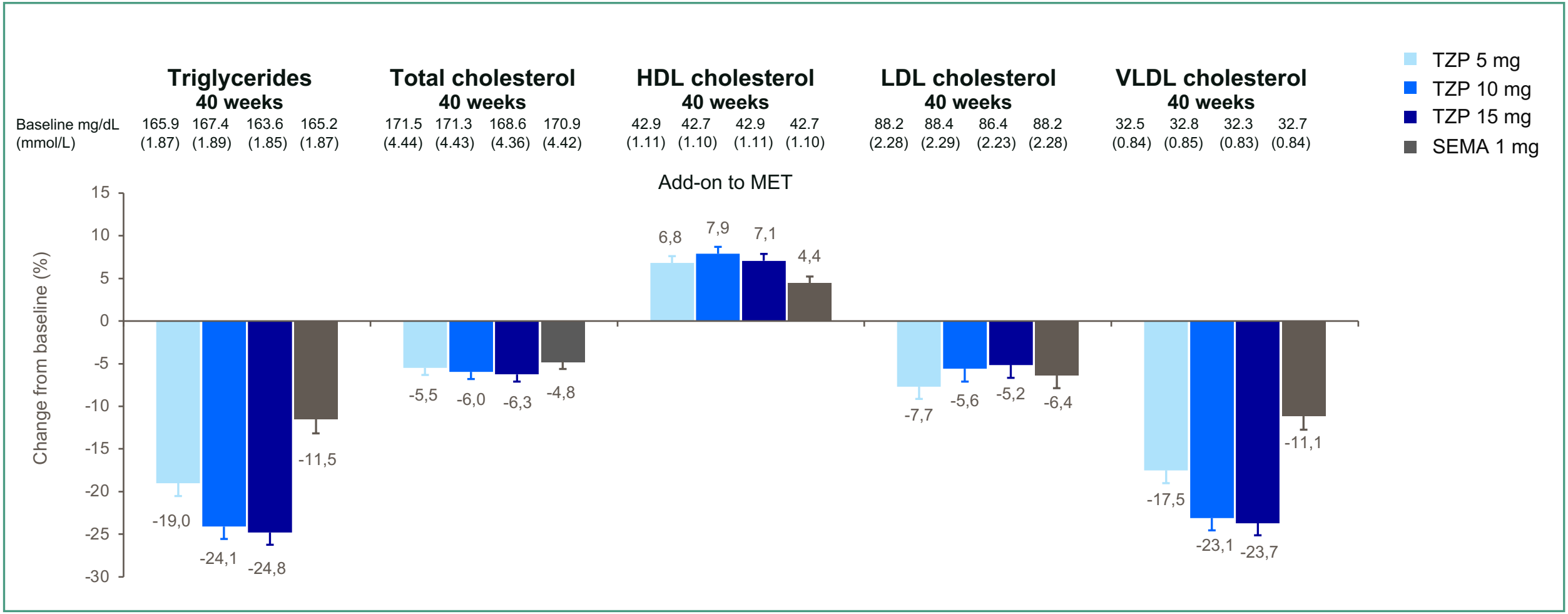
Coskun T, et al. Mol Metab. 2018;18:3-14
Cosgrove R, et al. Diabetes. 2020;69(suppl 1):-..

Tirzepatide induced low-fat diet preference in obese rats



Samms RJ, et al. Presented at: Obesity Week 2020; November 2-6, 2020; Atlanta, Georgia. Poster 450.

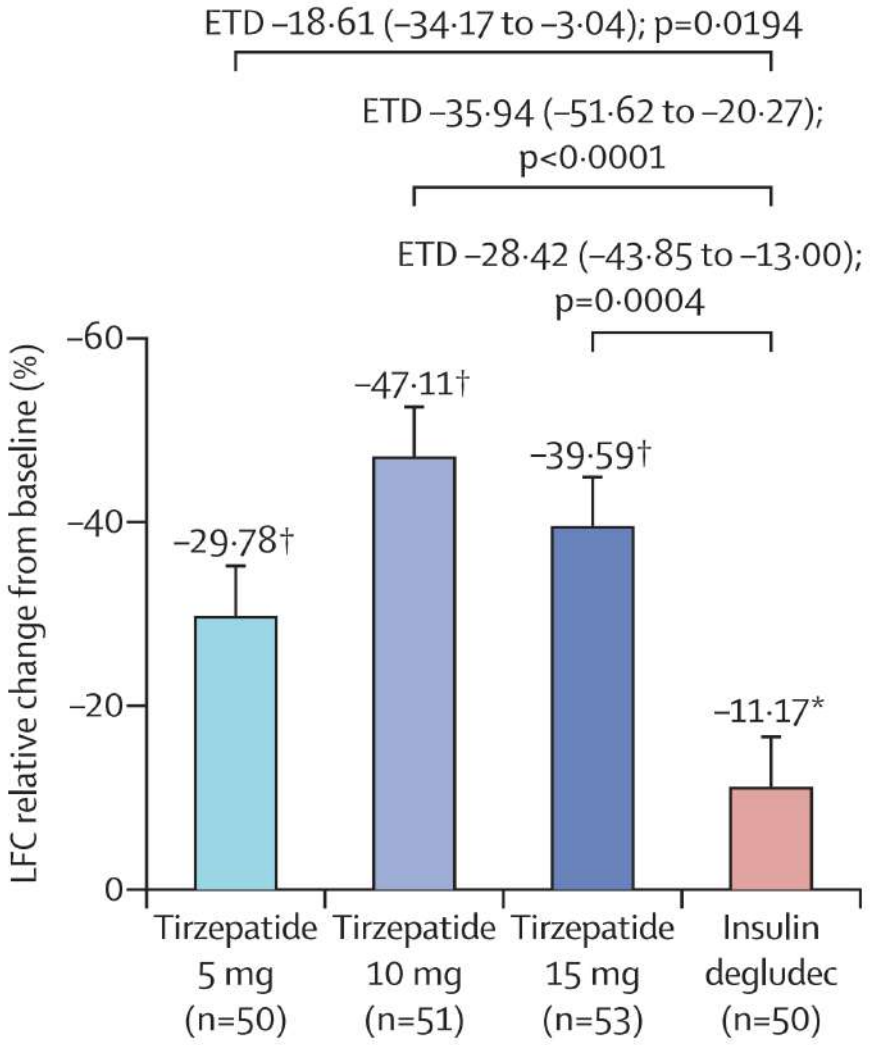
SURPASS-2: tirzepatide improves serum lipid profile at 40 Weeks vs semaglutide 1.0 mg

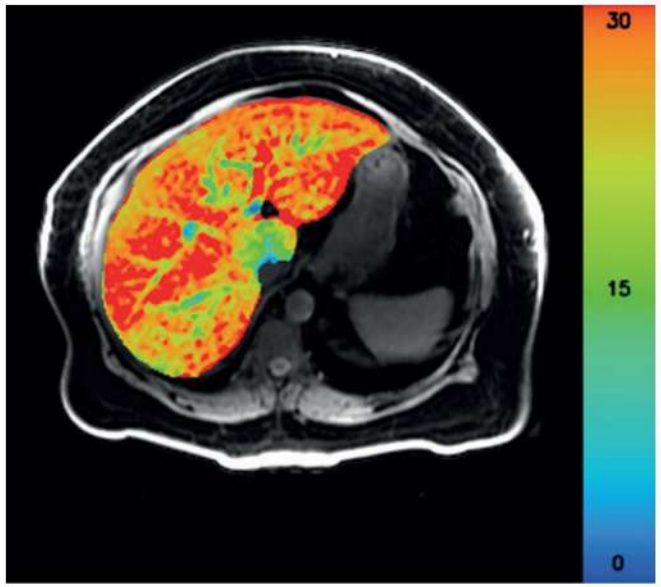


Data are estimated percentage means (SE) from MMRM analysis using log transformation; mITT population (efficacy analysis set).
HDL = high-density lipoprotein; LDL = low-density lipoprotein; MET = metformin; mITT = modified intent-to-treat; MMRM = mixed model repeated measures; SEMA = semaglutide; TZP = tirzepatide; VLDL = very-low-density lipoprotein.

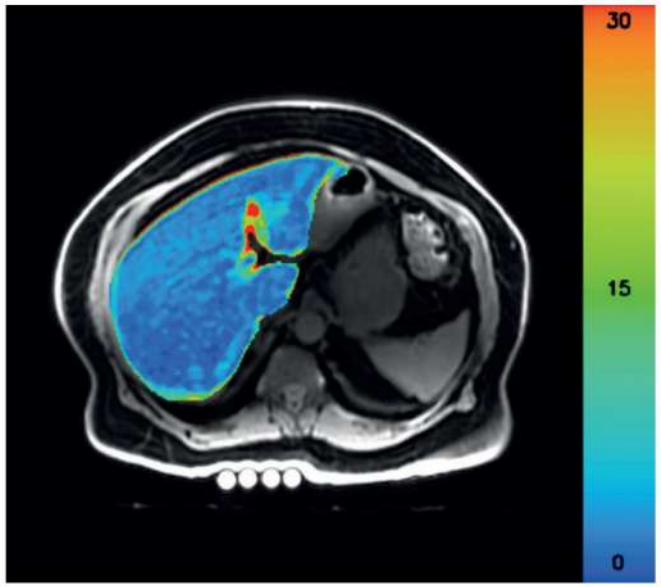
Frias JP, et al. *N Engl J Med*. 2021

SURPASS-3 MRI: Tirzepatide Reduces Fat Liver Content





LFC at baseline:27.3%



LFC at week 52: 2.6%

ETD, estimated treatment difference; LFC, liver fat content; * p<0·05; †p<0·0001; ‡ p<0·01, vs baseline.

Gastaldelli A, et al, Lancet Diabetes Endocrinol 2022

Systemic effects of GLP1 and GIP receptor Agonism

GLP-1 Receptor Agonism

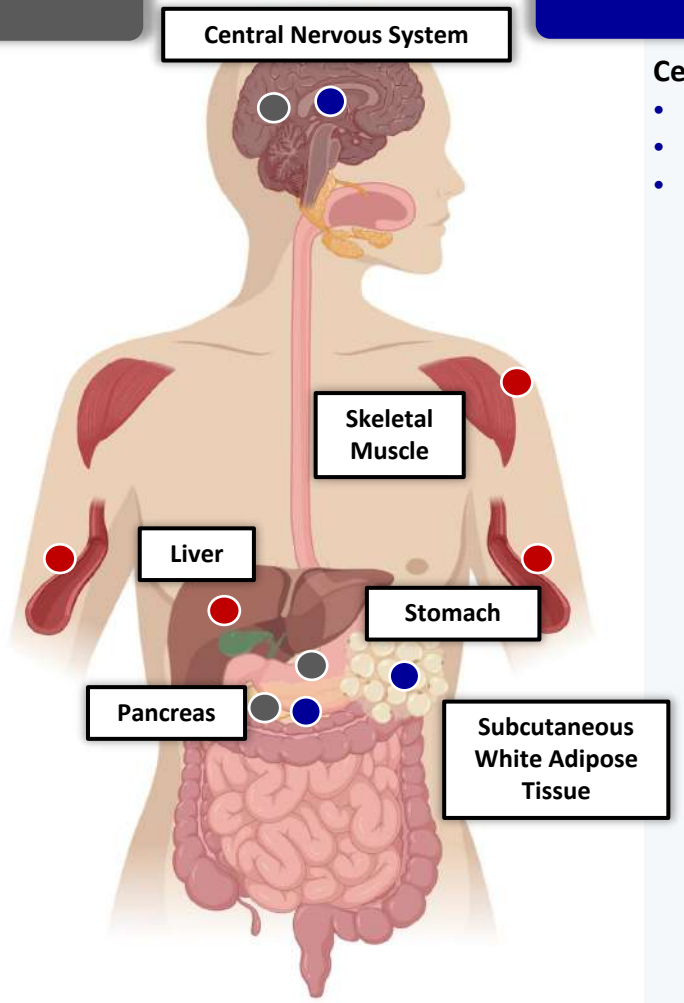
Central Nervous System
- ↑ Satiety
- ↓ Food Intake
- ↑ Nausea
- ↓ Body Weight

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

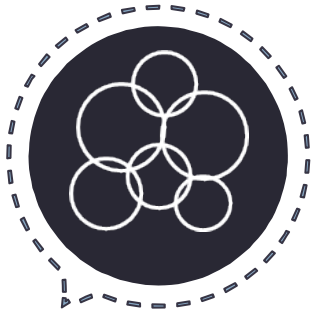
Tirzepatide: Dose escalation

Glycometabolic control

- Insulin secretion
- Glucagon
- Insulin sensitivity
- Lipids

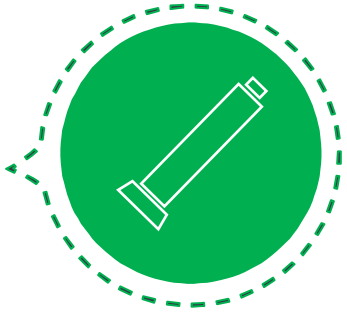
Adiposity

- Weight loss
- Lipid partitioning and adipose function



Receptor pharmacology

Dual agonism



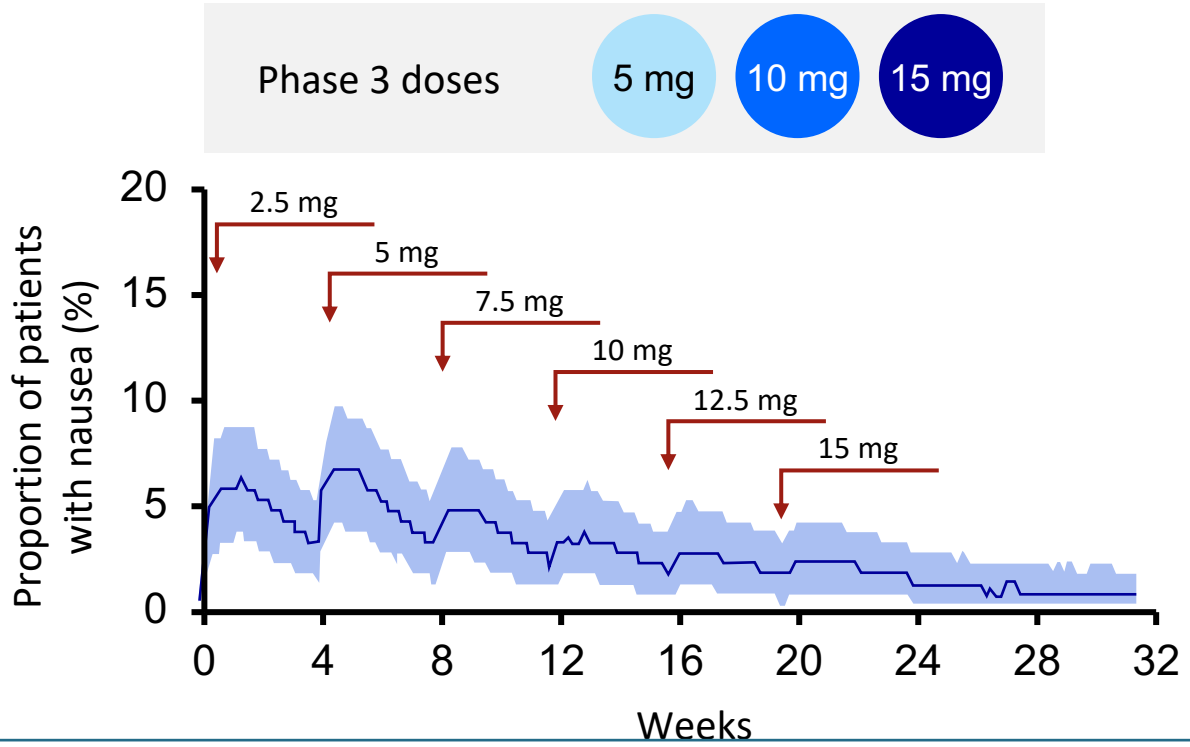
Dose escalation

Tirzepatide: choosing the dose

The availability of different dosages allows the clinician to personalize the therapy

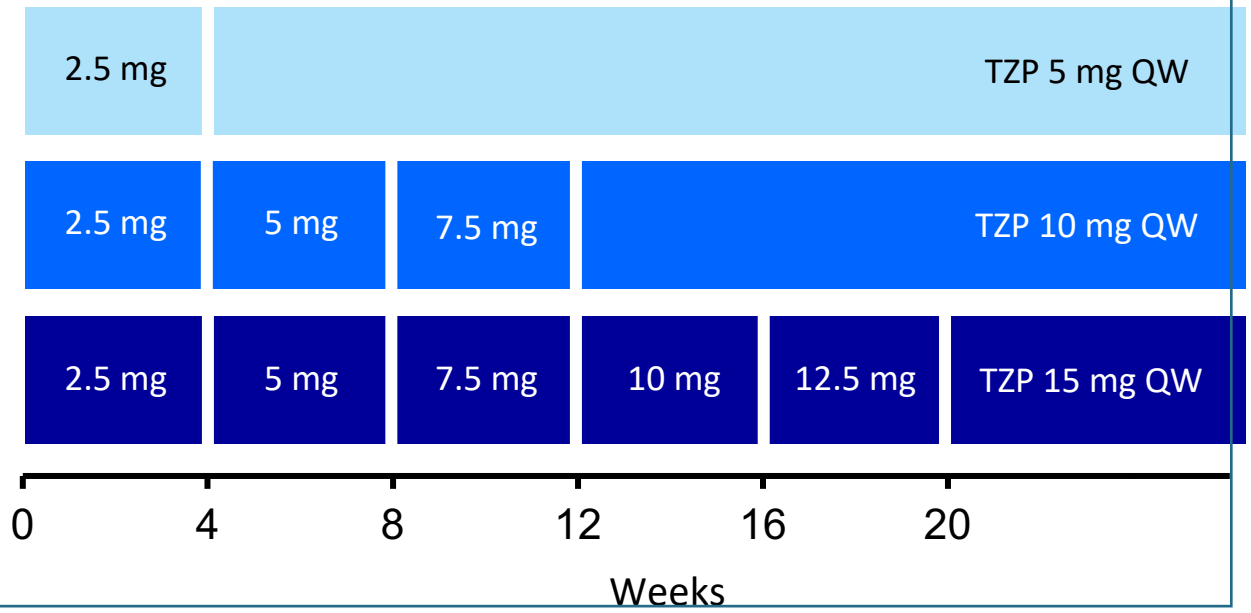
Simulation of Dose Escalation

- Model predicts incidence of nausea with slow, step-wise titration and supports improved tolerability profile from Phase 2 to Phase 3



Dosing in phase 3 clinical program

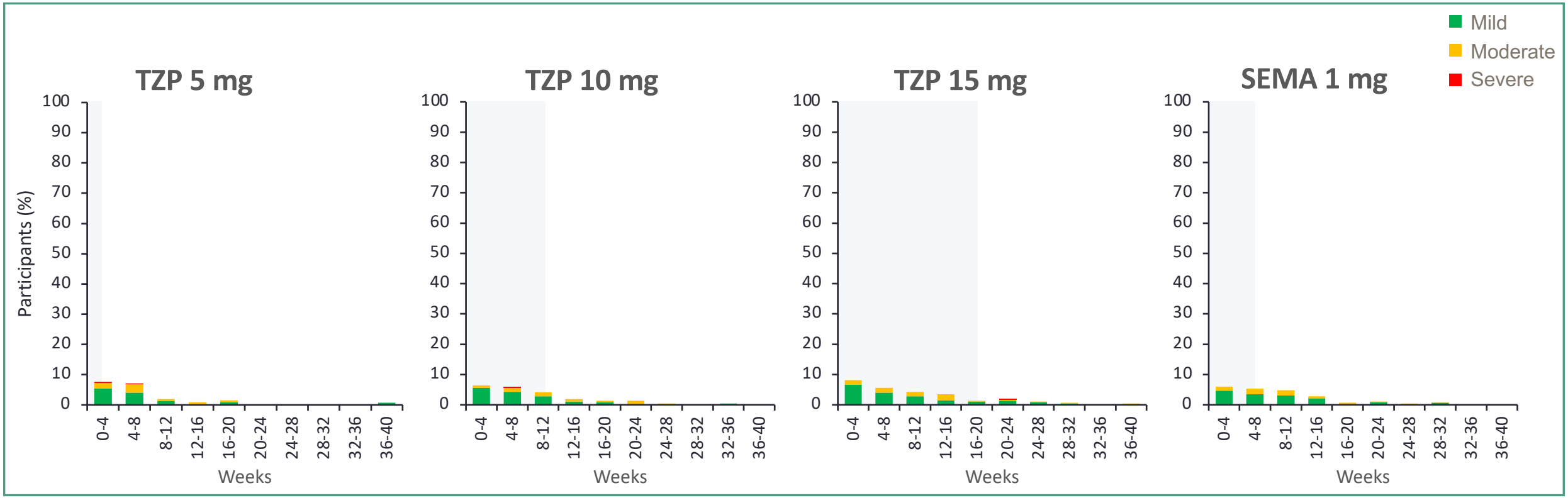
- Step through doses (2.5 mg increments) allow gradual introduction and improved tolerability profile
- Informed by Phase 2 studies and exposure modeling



Frias JP, et al. *Diabetes Obes Metab* 2020;22(6):938-946;

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.

The incidence of hypoglycaemia was low in tirzepatide (TZP) arms, and there was no increased risk of hypoglycaemia associated with TZP treatment

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.

Tirzepatide: take home messages

- Improvement of insulin sensitivity (more than GLP1-RA)
- Improvement of insulin secretion (more than GLP1-RA)
- Reduction of epatic fat
- Reduction of HbA1c, weight, and specific lipoproteins (more than GLP-1RA)
- Well-tollerated

- Grazie per l’attenzione