

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

Ernesto Maddaloni



AGENDA

Glycometabolic control

- Insulin secretion
- Glucagon
- Insulin sensitivity
- Lipids



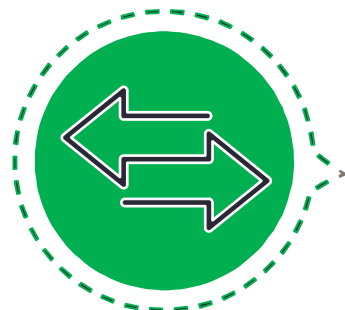
Adiposity

- Weight loss
- Lipid partitioning and adipose function

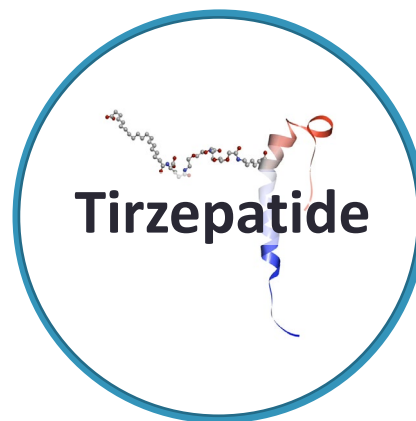


Receptor pharmacology

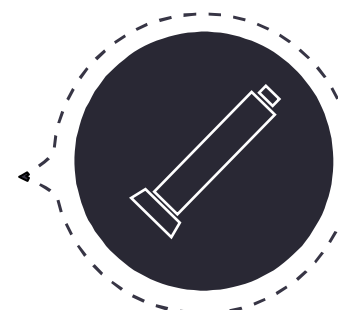
Dual agonism



Tirzepatide

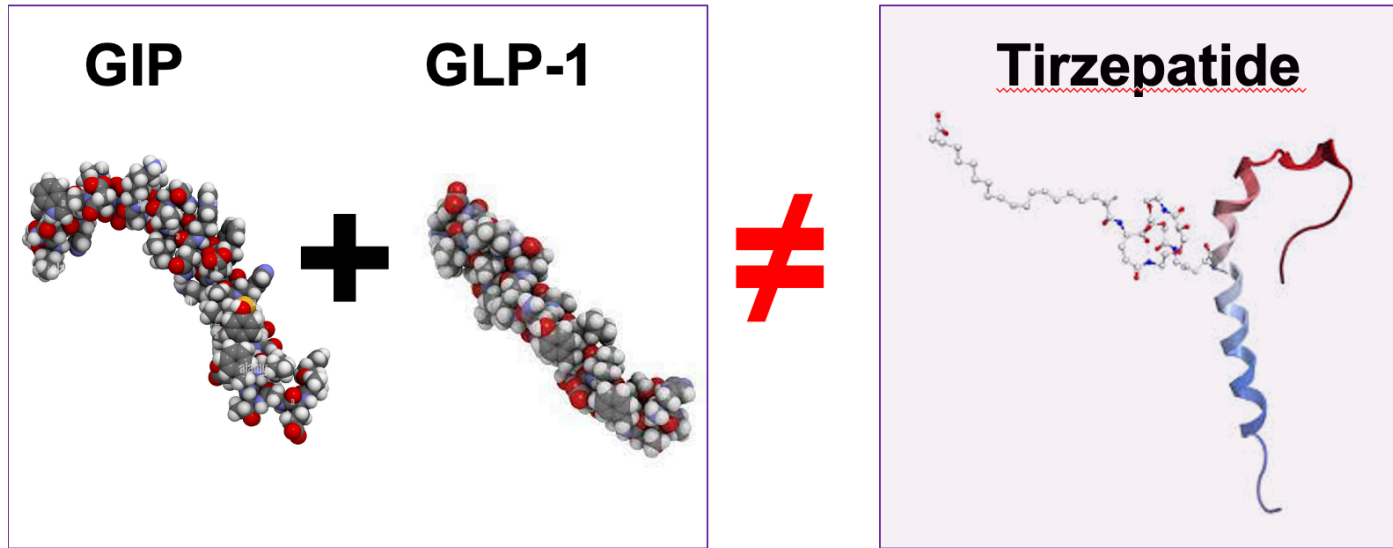


Dose escalation



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



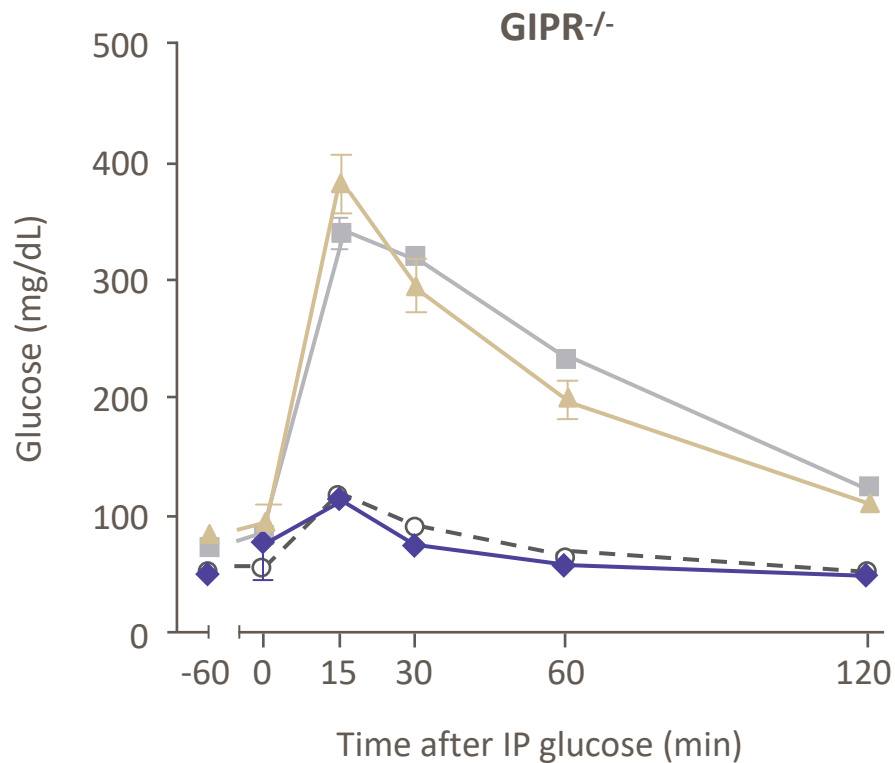
Tirzepatide is not the sum of GIP and GLP-1. It is a single molecule

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

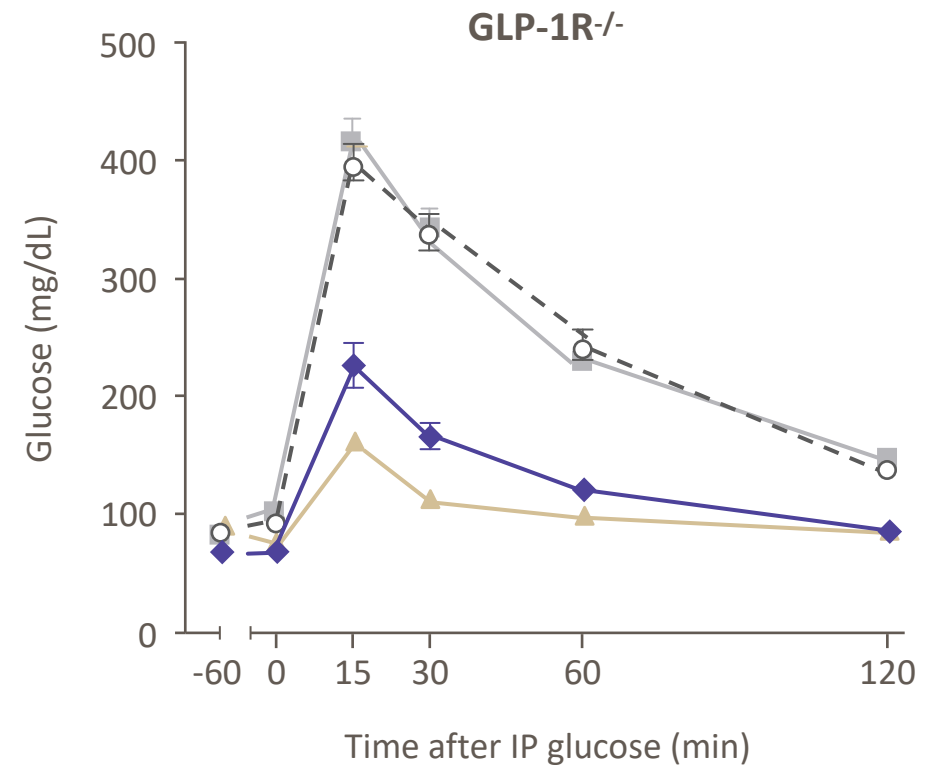
Tirzepatide regulates glycemia acting on both receptors differently from a selective GLP1



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

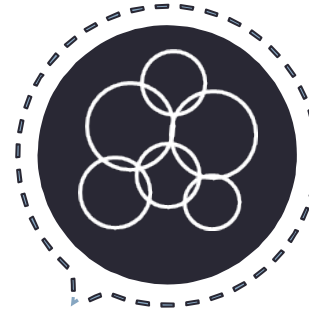
Glycometabolic control

- Insulin secretion
- Glucagon
- Insulin sensitivity
- Lipids



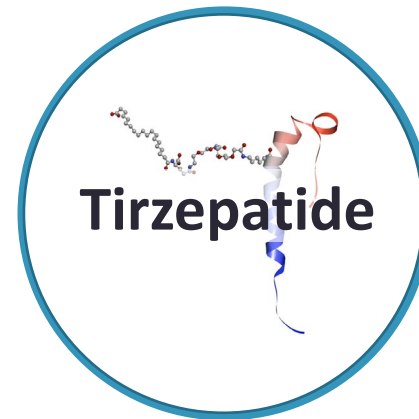
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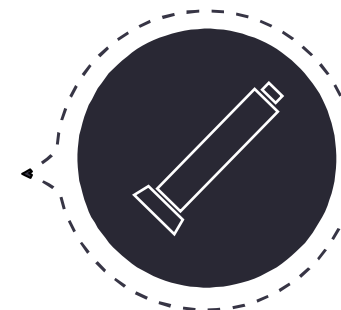


Receptor pharmacology

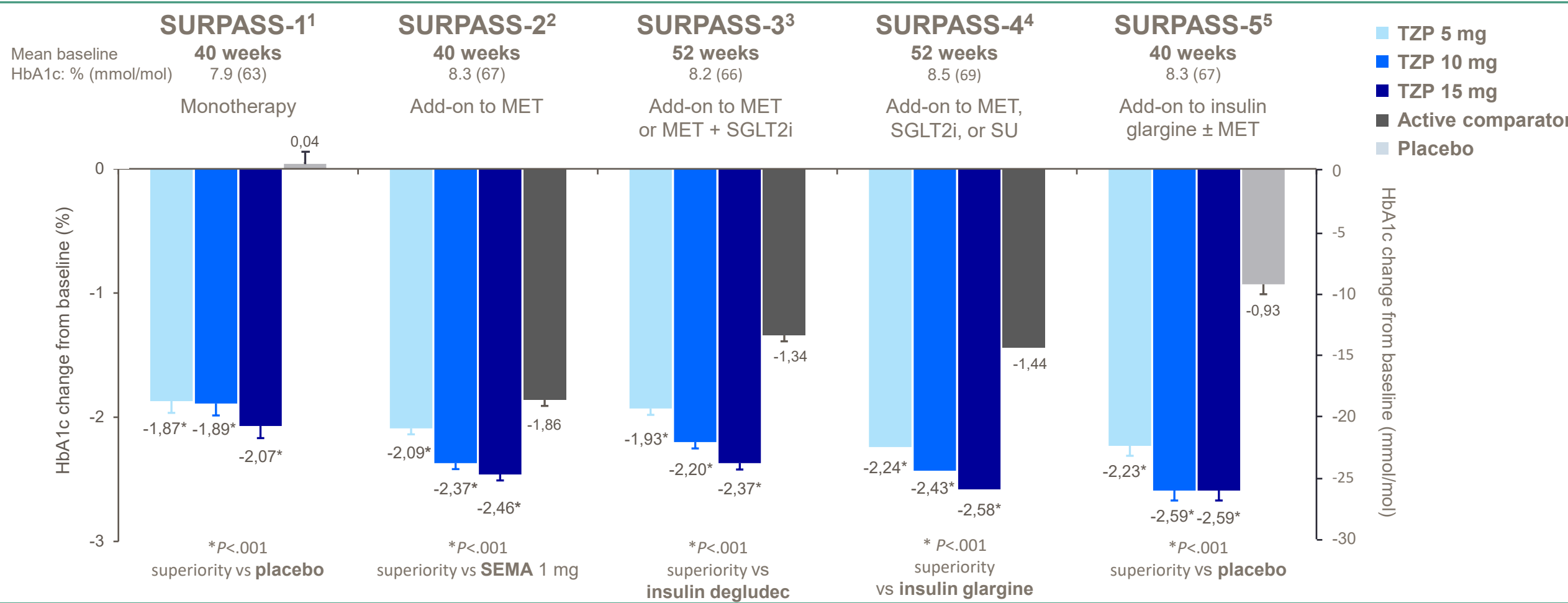
Dual agonism



Dose escalation



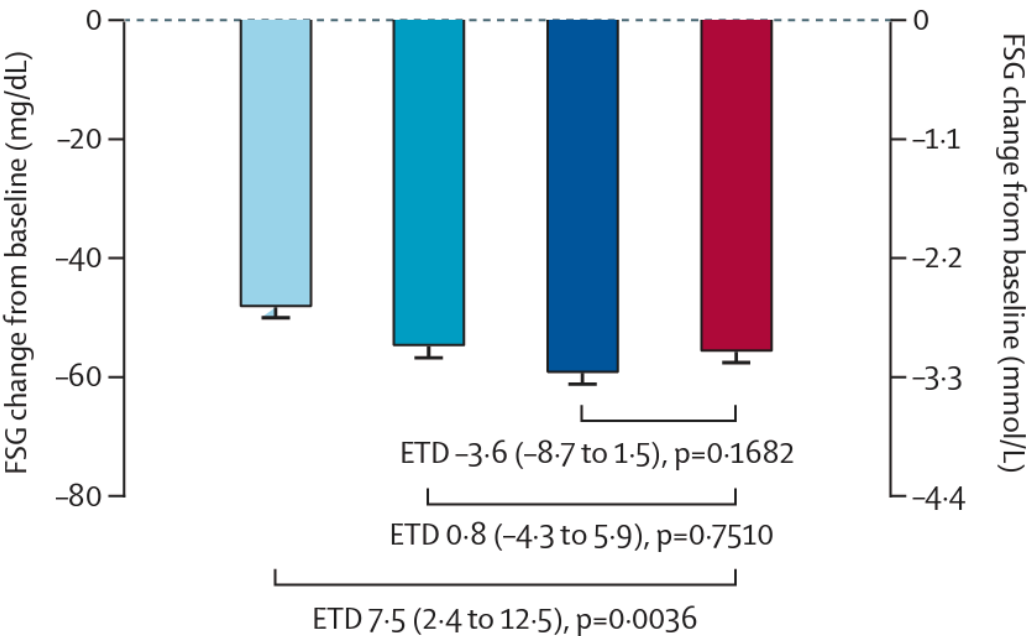
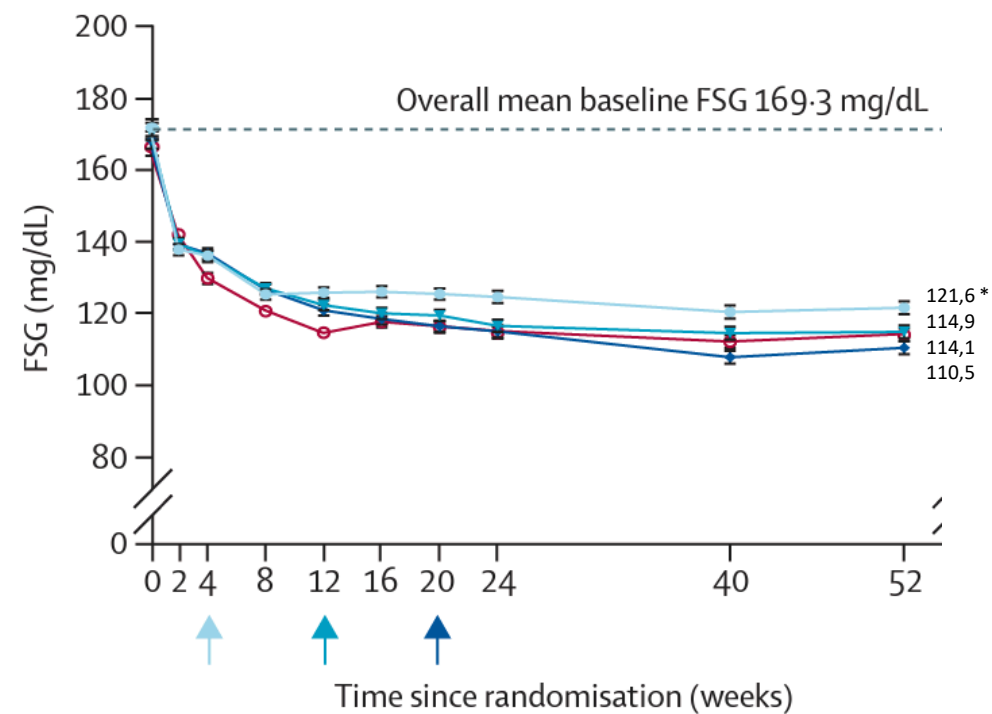
Unprecedented HbA1c reduction from baseline to primary endpoint



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.

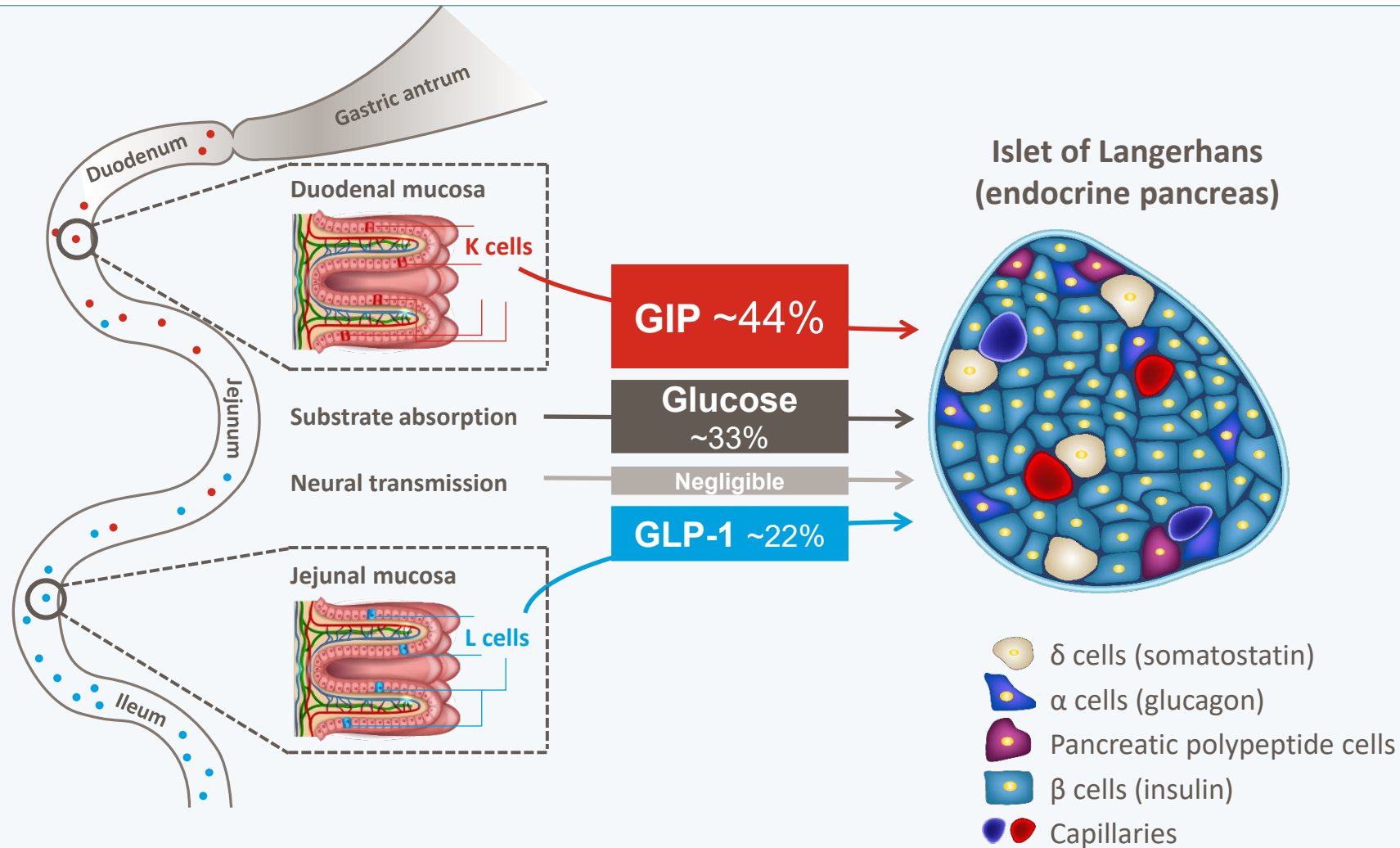
SURPASS-3: Fasting Serum Glucose Over Time and Change from Bseline at 52 Weeks

Tirzepatide 5 mg Tirzepatide 10 mg Tirzepatide 15 mg Insulin degludec



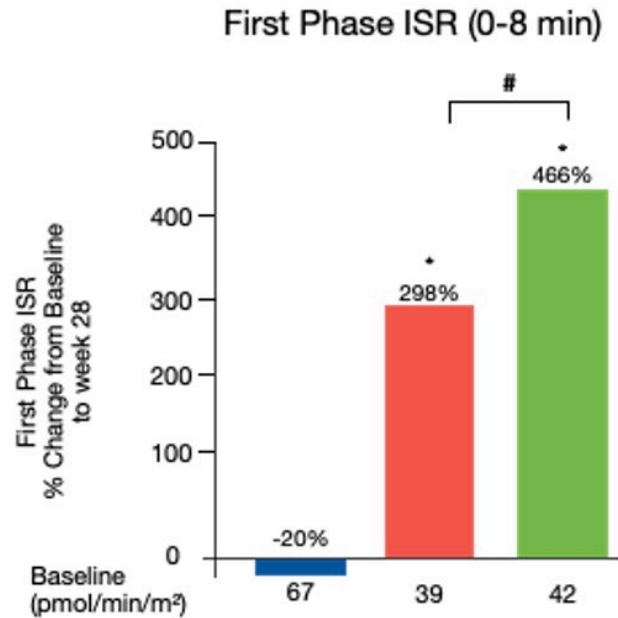
Data are LSM (SE) over time and 52 weeks. Estimated treatment differences at 52 weeks are LSM (95% CI); mITT (efficacy analysis set); MMRM analysis. Arrows indicate when the maintenance dose of tirzepatide 5 mg, 10 mg, 15 mg was initiated. *p=0,004 vs. insulin degludec

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

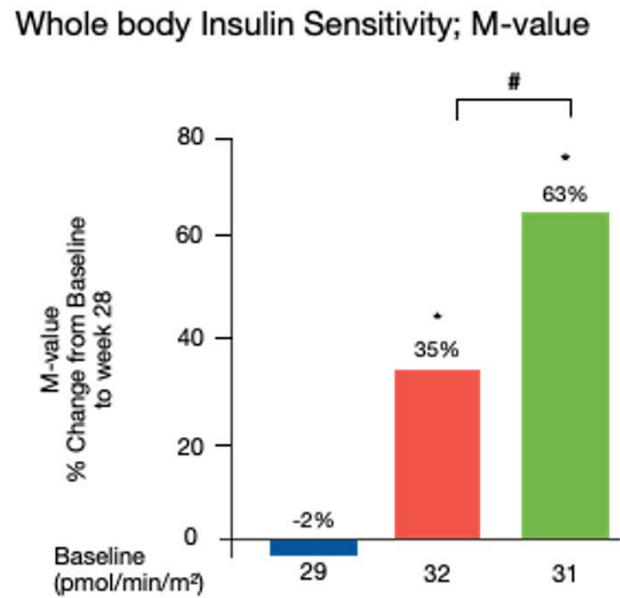


Mechanism of glycemic control

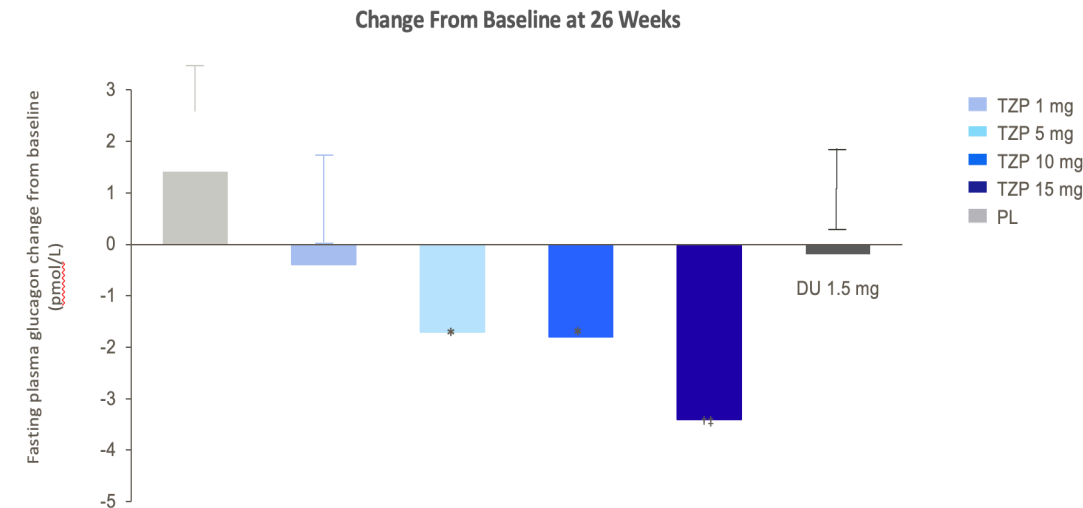
Enhanced insulin secretion



Improved insulin sensitivity



Reduced glucagon levels



■ Placebo ■ Semaglutide 1.0mg ■ Tirzepatide 15mg

Tirzepatide: Adiposity

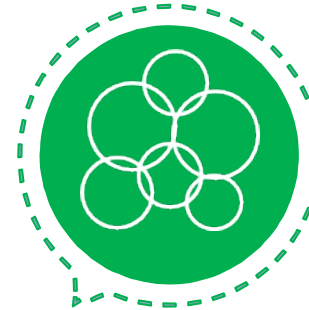
Glycometabolic control

- Insulin secretion
- Glucagon
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- Lipids



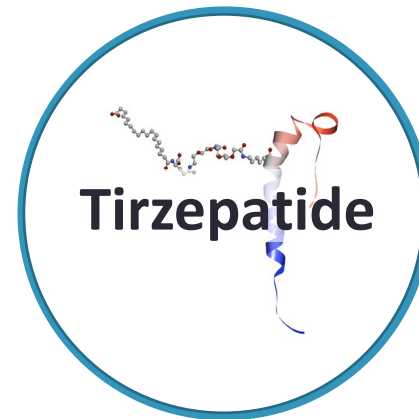
Adiposity

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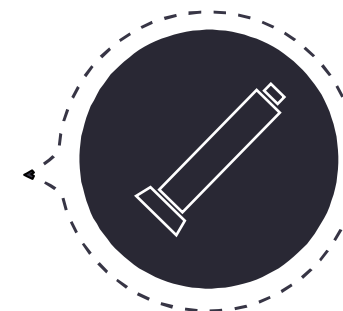


Receptor pharmacology

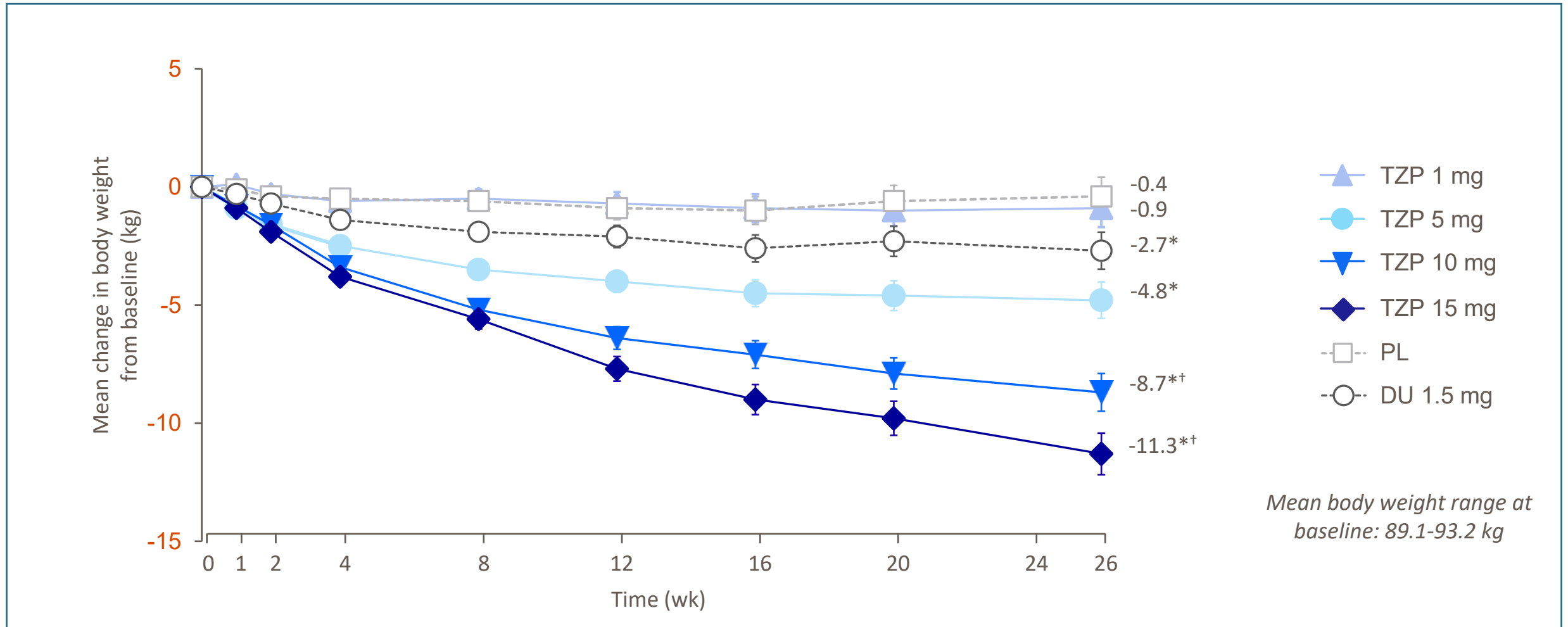
Dual agonism



Dose escalation



Tirzepatide reduces body weight vs selective GLP1-RA



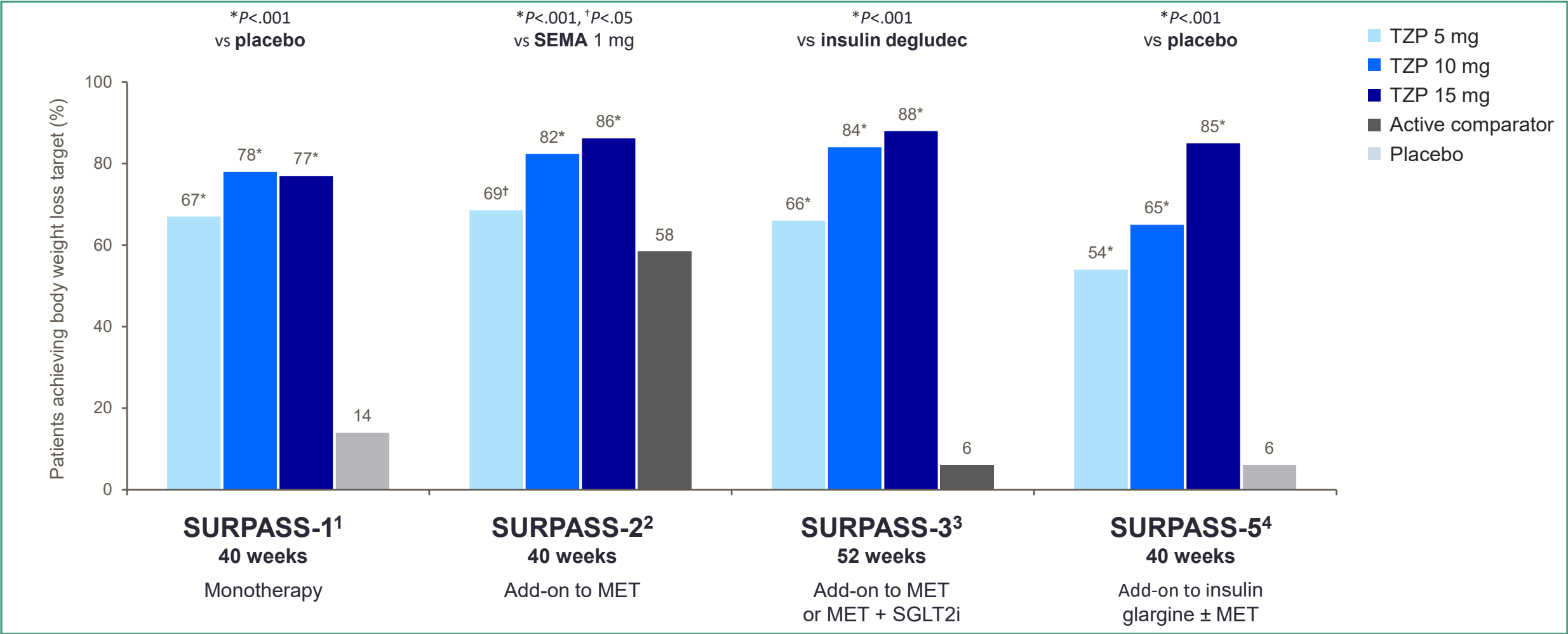
MMRM analysis, mITT on-treatment population. Values reported are LSM (SE).

* $P < .05$ 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.

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

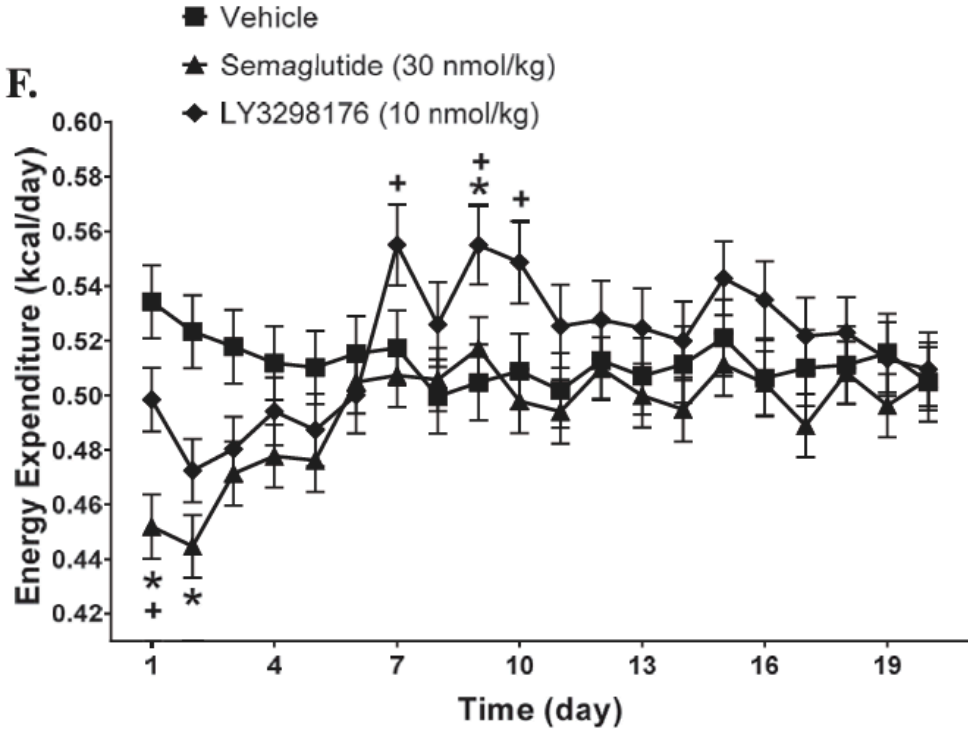
Efficacy Estimand



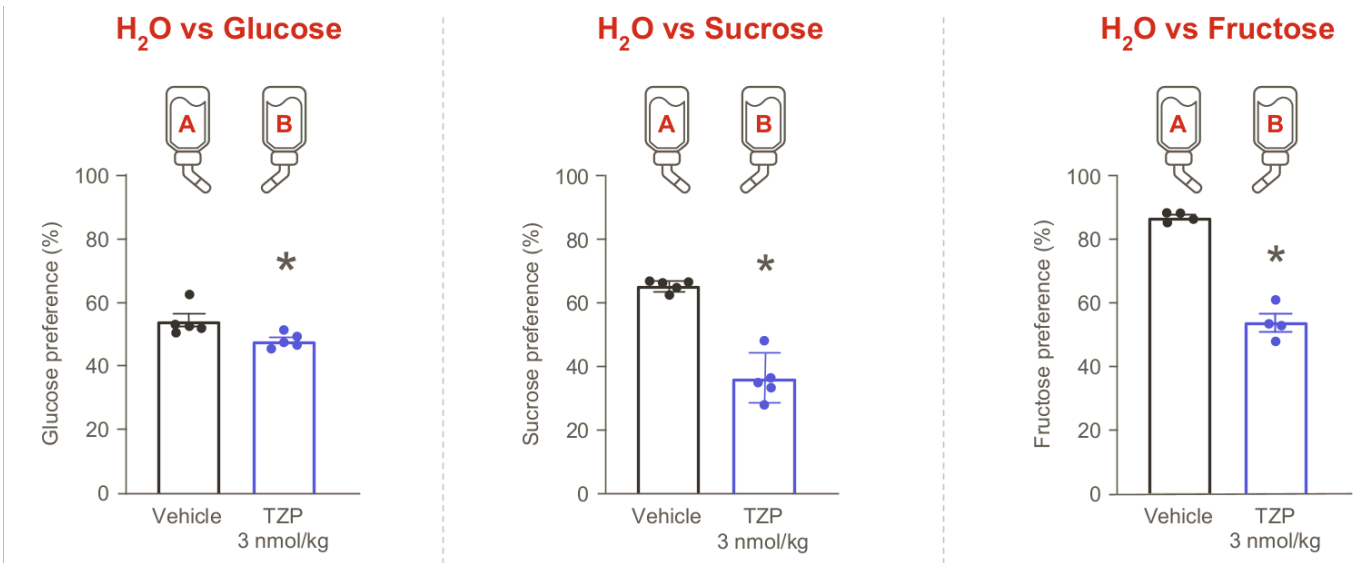
Data are estimated mean; mITT population (efficacy analysis set). Logistic regression.
MET = metformin; mITT = modified intent-to-treat; SGLT2i = sodium-glucose co-transporter-2 inhibitor; SEMA = semaglutide; TZP = tirzepatide.
1. Rosenstock J, et al. *Lancet*. Published online June 26, 2021. 2. Frias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

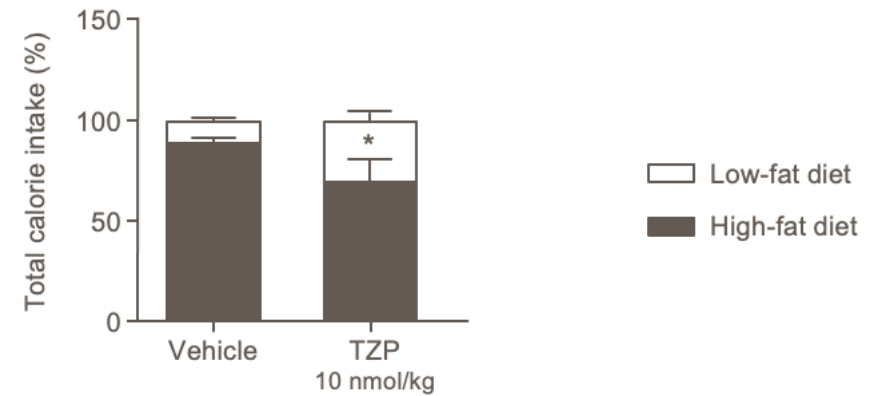
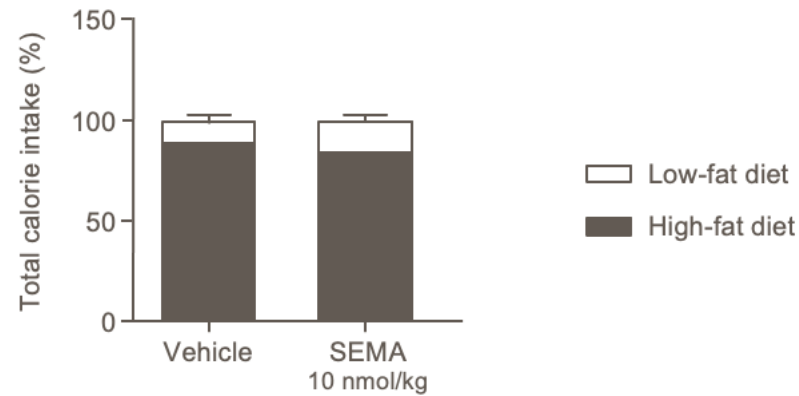
Tirzepatide demonstrated increased energy expenditure in obese mice.



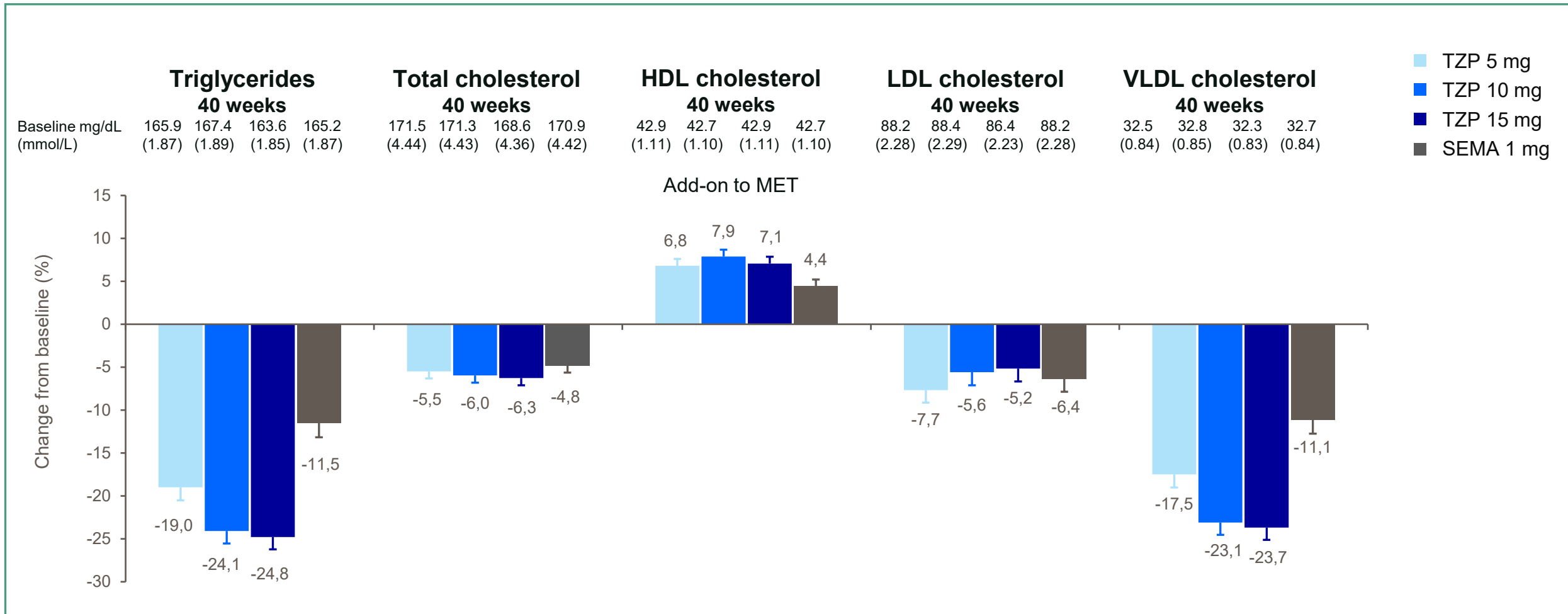
Tirzepatide reduced sweet-taste preference in mice



Tirzepatide induced low-fat diet preference in obese rats



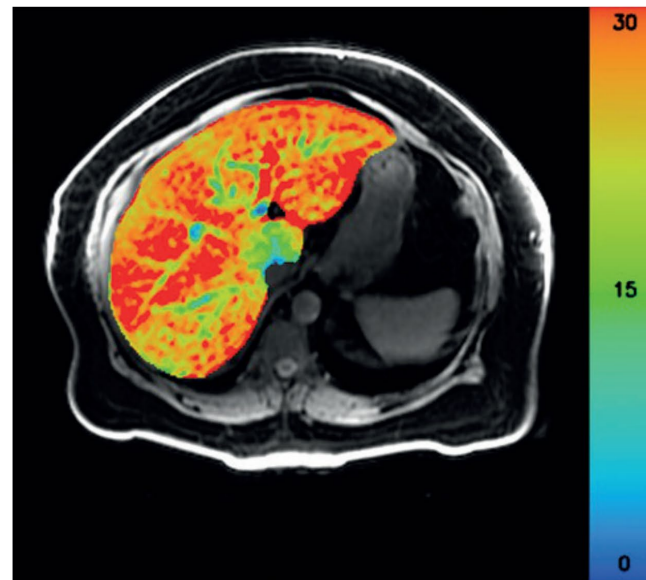
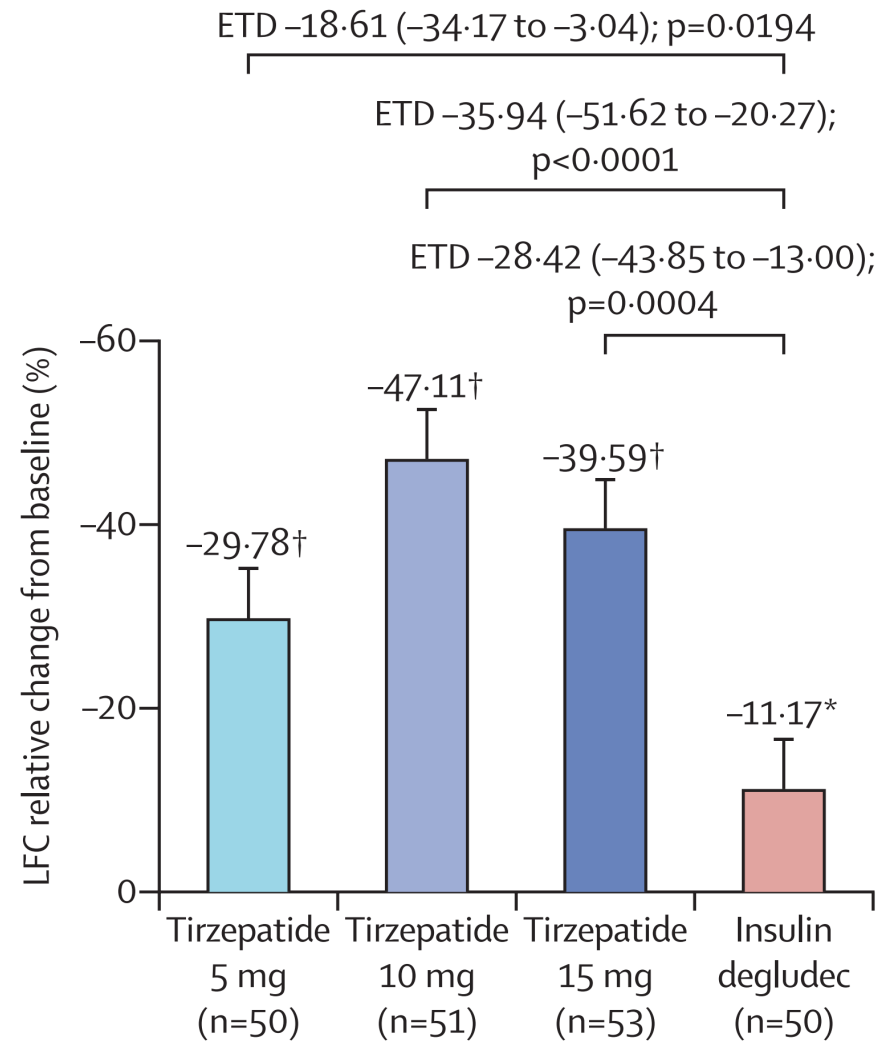
SURPASS-2: tirzepatide improves serum lipid profile at 40 Weeks vs semaglutide 1.0 mg



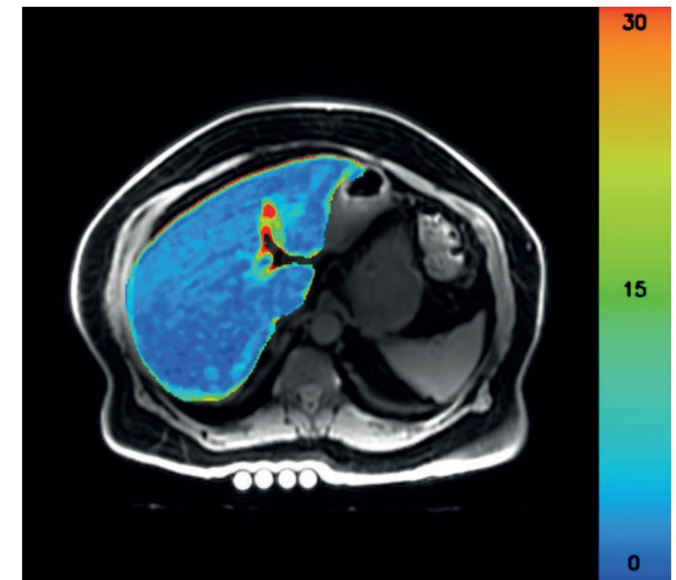
Data are estimated percentage means (SE) from MMRM analysis using log transformation; mITT population (efficacy analysis set).

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.

SURPASS-3 MRI: Tirzepatide Reduces Fat Liver Content



LFC at baseline: 27.3%



LFC at week 52: 2.6%

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**

Central Nervous System

GIP Receptor Agonism

Central Nervous System

- ↓ **Food intake**
- ↓ **Nausea**
- ↓ **Body weight**

Pancreas

- ↑ **Insulin**
- ↑ **Glucagon**

Subcutaneous White Adipose Tissue

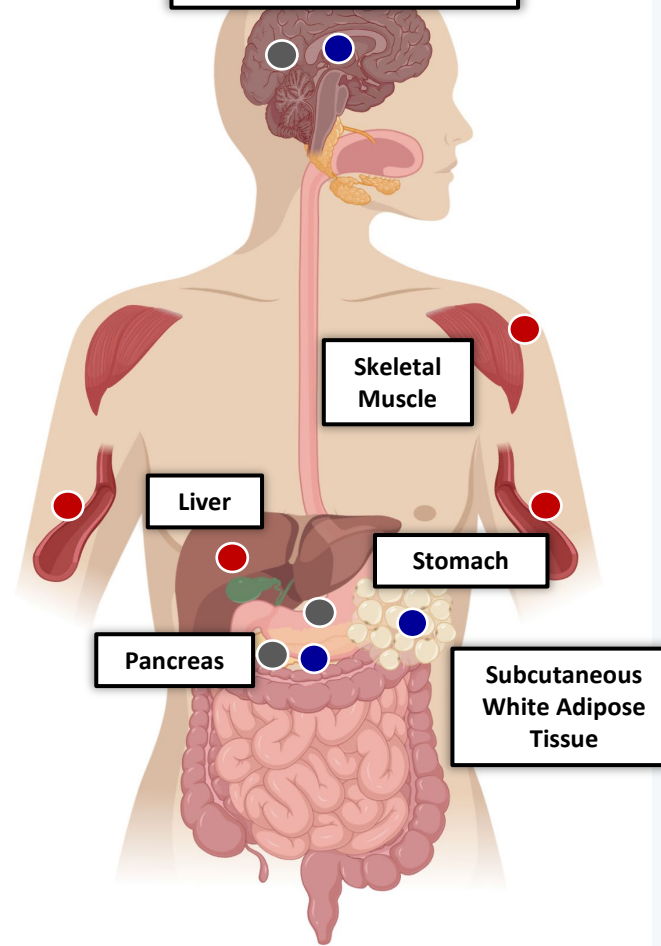
- ↑ **Insulin Sensitivity**
- ↑ **Lipid Buffering Capacity**
- ↑ **Blood Flow**
- ↑ **Storage Capacity**
- ↓ **Proinflammatory Immune Cell Infiltration**

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

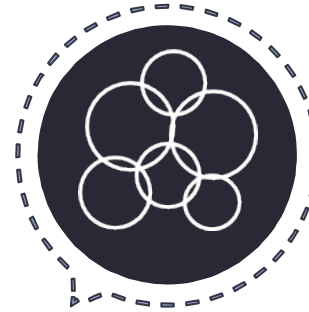
Glycometabolic control

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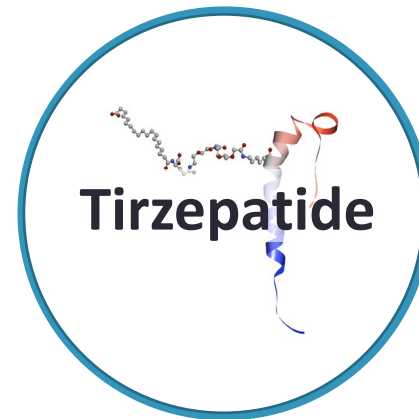
Adiposity

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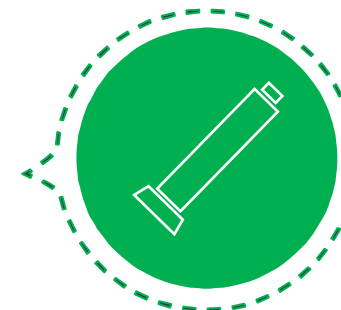


Receptor pharmacology

Dual agonism



Dose escalation

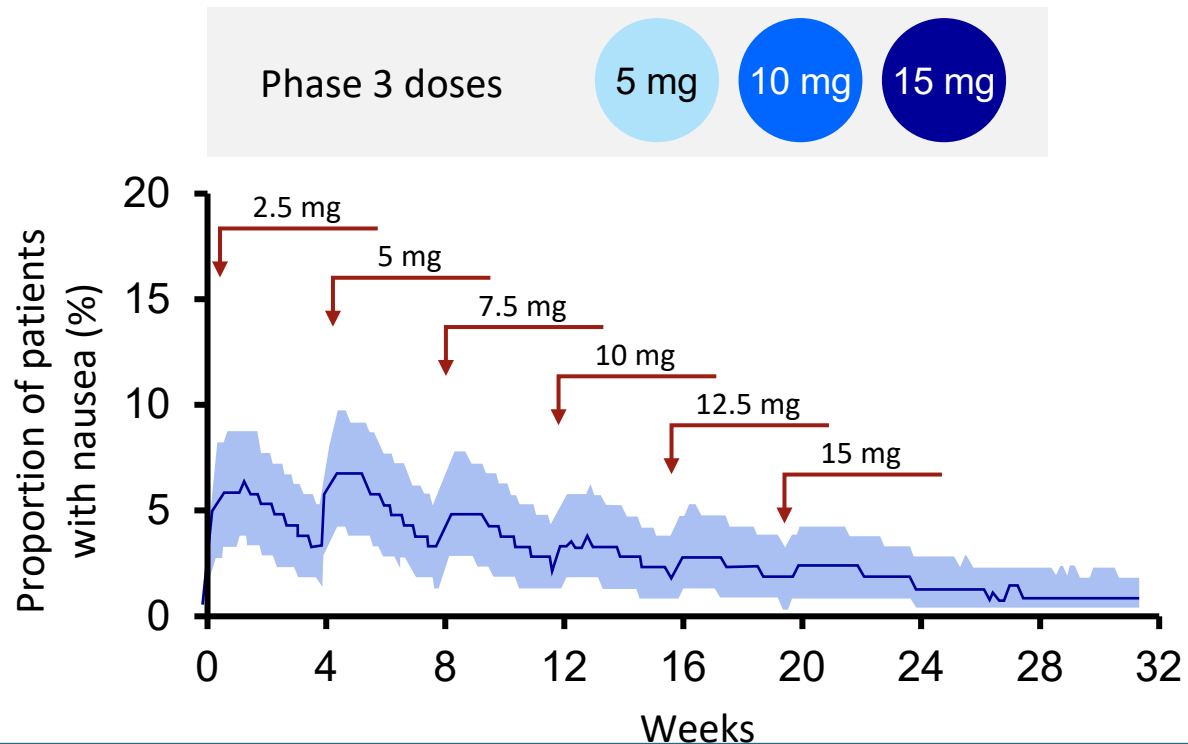


Tirzepatide: choosing the dose

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

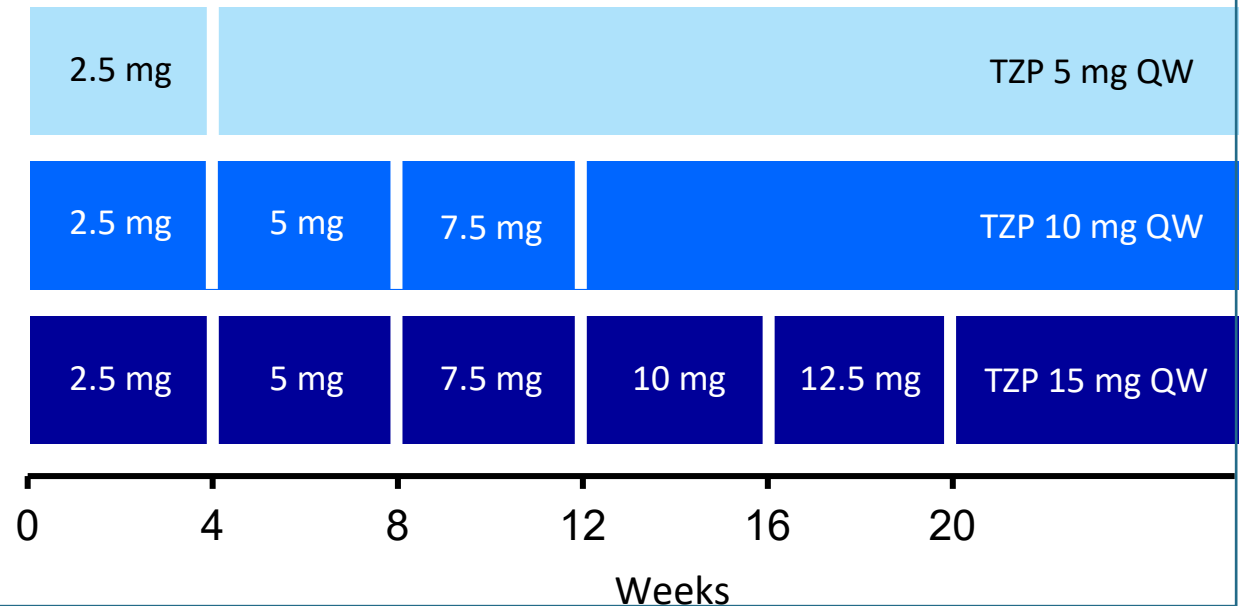
Simulation of Dose Escalation

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



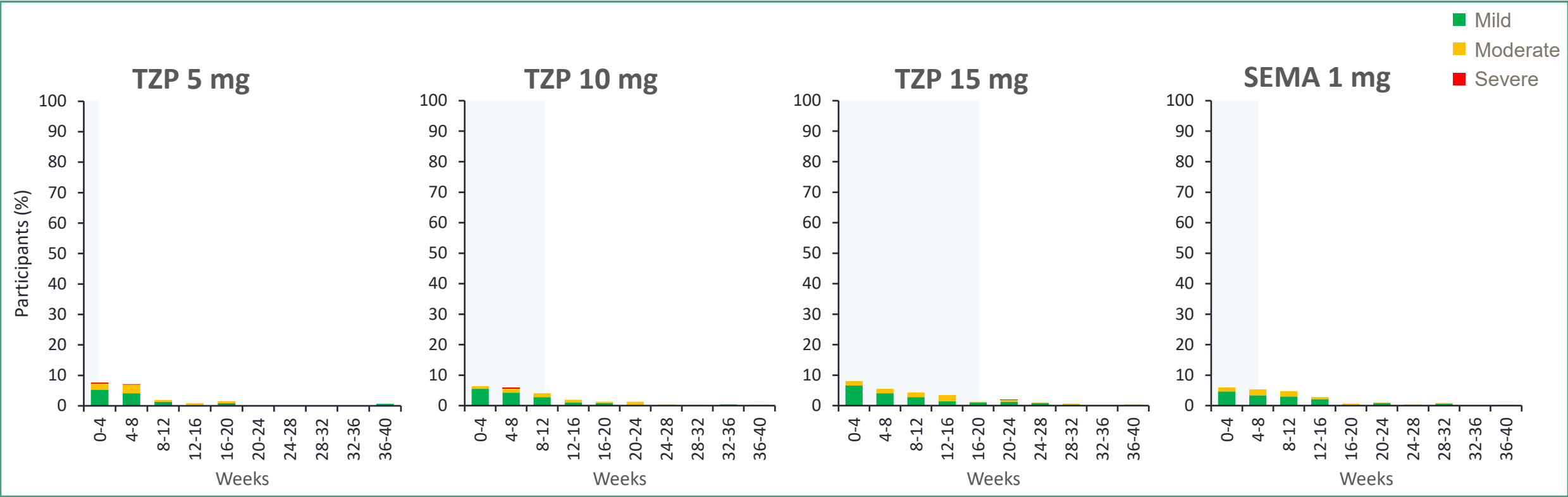
Dosing in phase 3 clinical program

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



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; TZIP = 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-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.

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