Futurs traitements médicaux de l'Obésité

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Socialement engagée

Hôpitaux Universitaires de Marseille | ap·hm

PACA
CENTRE SPÉCIALISÉ DE L'OBÉSITÉ

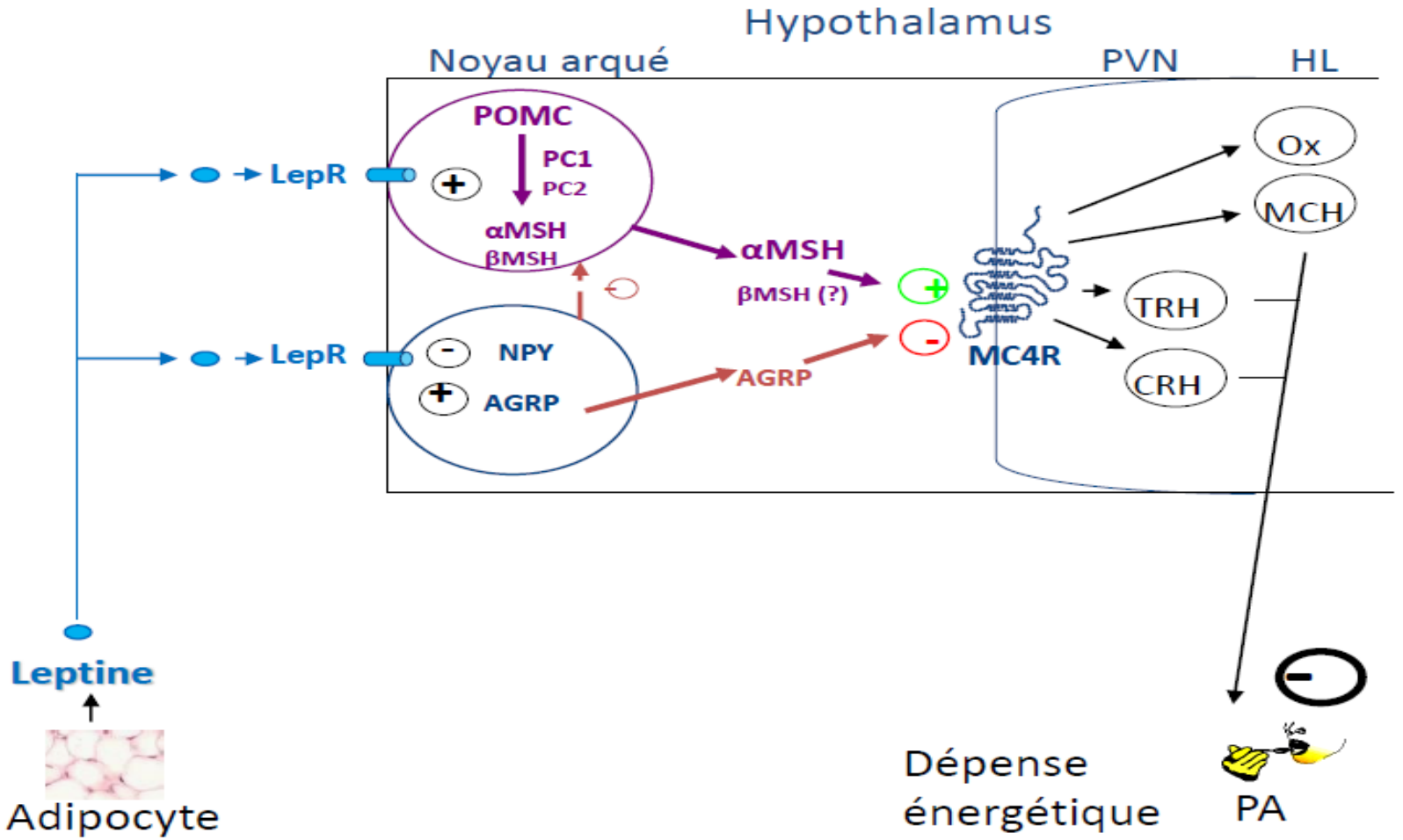
Futurs traitements médicaux de l’Obésité

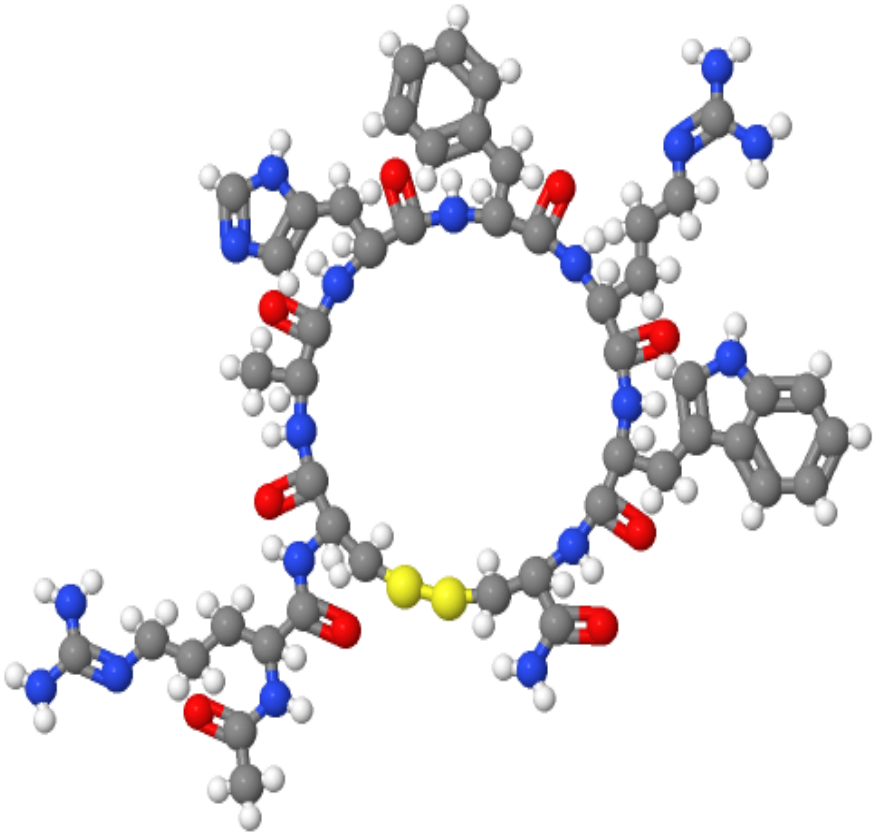
1 - Agoniste des récepteurs MC4R - Obésités génétiques

2- Agonistes des récepteurs au GLP-1

3- Double agoniste des récepteurs au GLP-1 et GIP

La voie leptine/mélanocortines



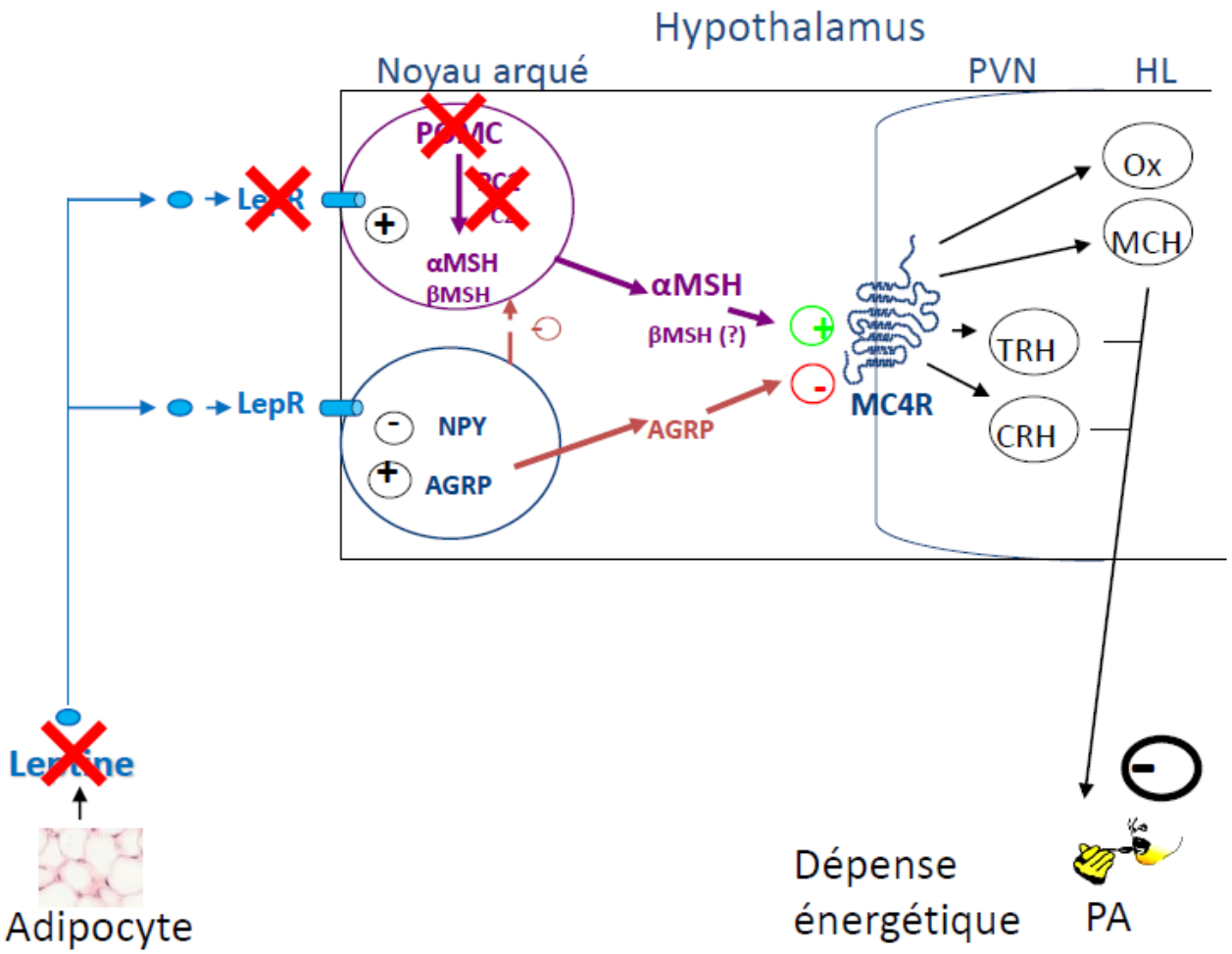


Setmelanotide

IMCIVREE®

(4R,7S,10S,13R,16S,19R,22R)-22-[[(2S)-2-acetamido-5-(diaminomethylideneamino)pentanoyl]amino]-13-benzyl-10-[3-(diaminomethylideneamino)propyl]-16-(1H-imidazol-5-ylmethyl)-7-(1H-indol-3-ylmethyl)-19-methyl-6,9,12,15,18,21-hexaoxo-1,2-dithia-5,8,11,14,17,20-hexazacyclotricosane-4-carboxamide

La voie leptine/mélanocortines



Approche gène candidat

Mutations sur les gènes de la voie leptine/mélanocortines

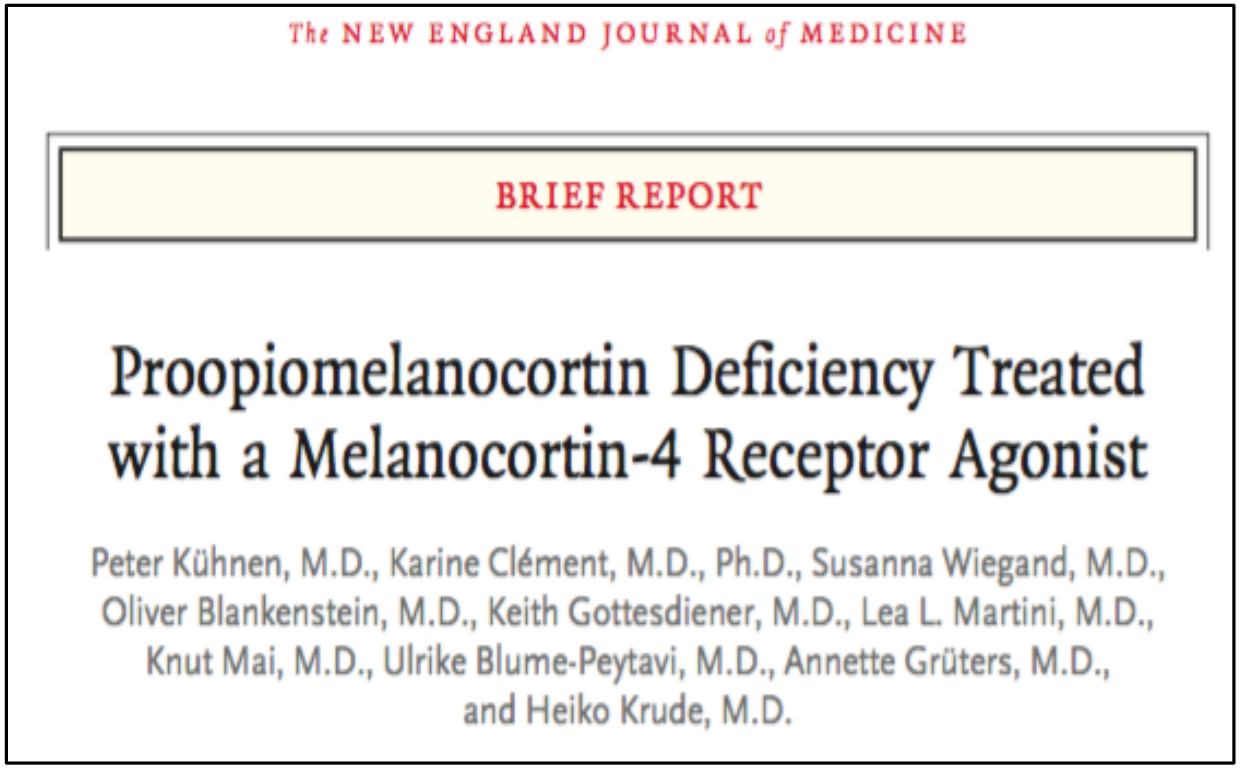
(Leptine, LepR, POMC, PC1)

Identifiées chez l'homme

Obésités rares
Phénotype extrême
Anomalies endocriniennes associées

Forme monogénique d'obésité Mutation de la POMC

- Phase 2
- Open label
- 2 patients
- Setmelanotide



The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

Proopiomelanocortin Deficiency Treated with a Melanocortin-4 Receptor Agonist

Peter Kühnen, M.D., Karine Clément, M.D., Ph.D., Susanna Wiegand, M.D., Oliver Blankenstein, M.D., Keith Gottesdiener, M.D., Lea L. Martini, M.D., Knut Mai, M.D., Ulrike Blume-Peytavi, M.D., Annette Grüters, M.D., and Heiko Krude, M.D.

Patiente 1

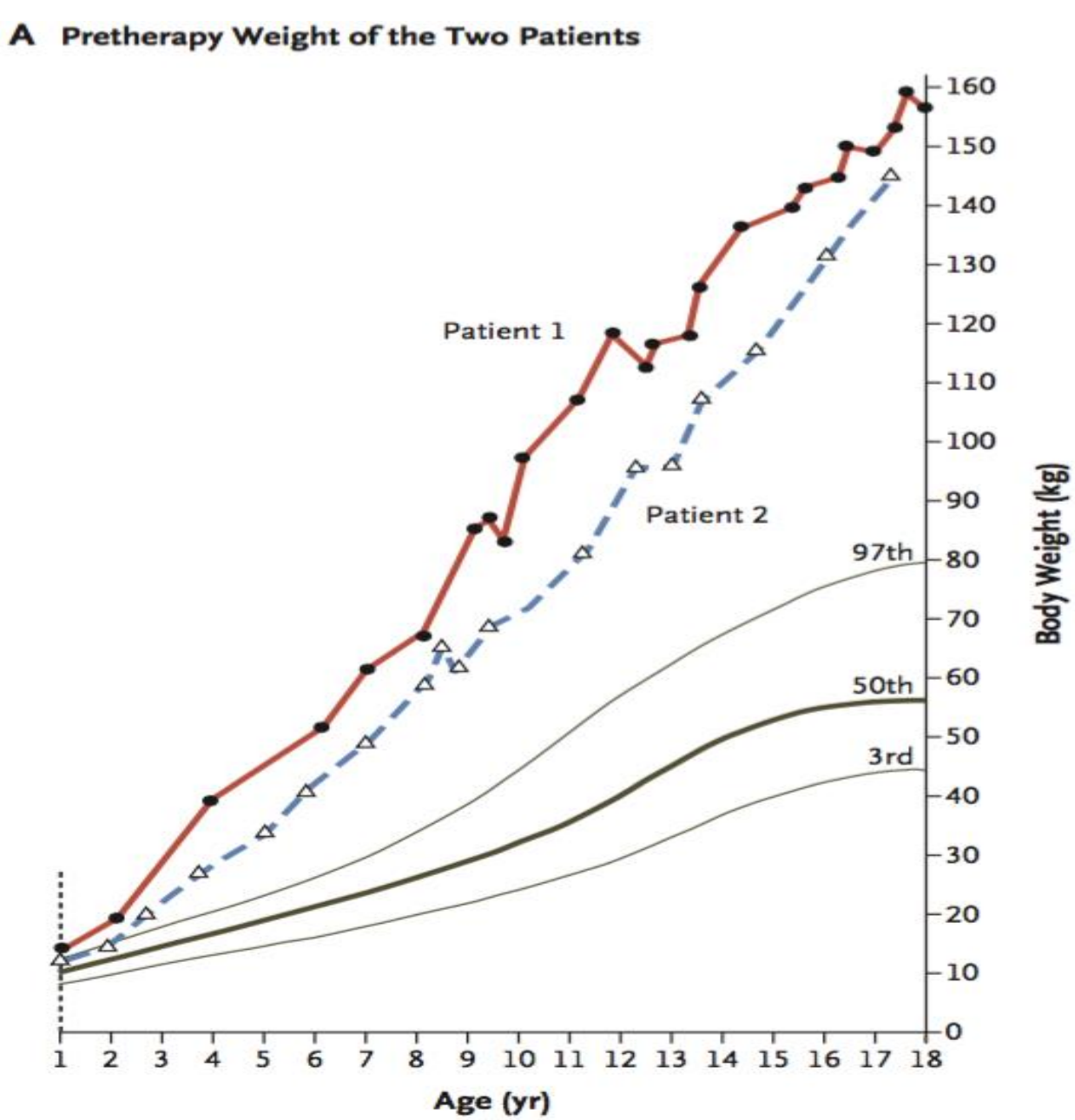
- Allemagne
- Insuffisance surrénale à la naissance
- 3 mois : Hyperphagie importante et prise de poids
- 4 ans : Mutation POMC hétérozygote compound : perte de fonction
- Adolescence: Hyperinsulinisme sans anomalie glucidique
- Retard pubertaire : Tanner S2 P1

Patiente 2

- Française de 26 ans
- 1 mois.: Insuffisance surrenalienne.
- 2 ans Hyperphagie importante

Unexpected Endocrine Features and Normal Pigmentation in a Young Adult Patient Carrying a Novel Homozygous Mutation in the POMC Gene> Karine Clement et al, JCEM 2008

- 13 ans retard pubertaire: Hypogonadism hypogonadotrope et deficit somatotrope
- 15 ans hypothyroidie centrale
- 18 ans: Diagnostique homozygote frameshift mutation POMC (perte de production)


A Pretherapy Weight of the Two Patients
Patient 1
Patient 2
97th
50th
3rd
Body Weight (kg)
Age (yr)
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18

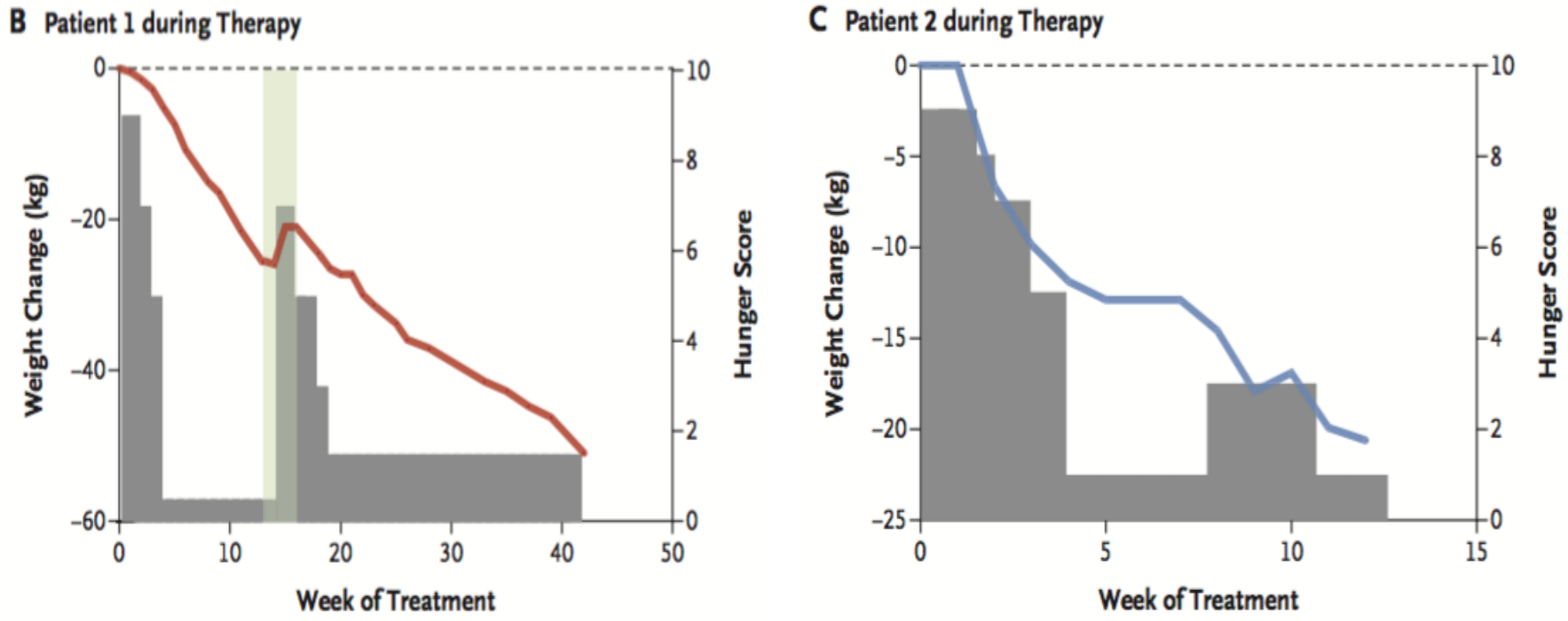
Setmelanotide en injection sous cutanée 1/jour

Patiente 1 : dose initiale 0,25 mg

Patiente 2 : dose initiale 0,5 mg

Majoration hebdomadaire jusqu’a 1,5 mg / jour

Poids et sensation de faim



Excellente efficacité du setmelanotide

Effets secondaires

- Pas d'effet cardiovasculaire

- Mélanodermie ++, l'agoniste active aussi MC1R
- Nécessité d'une surveillance à long terme de l'effet de l'hyperstimulation des mélanocytes

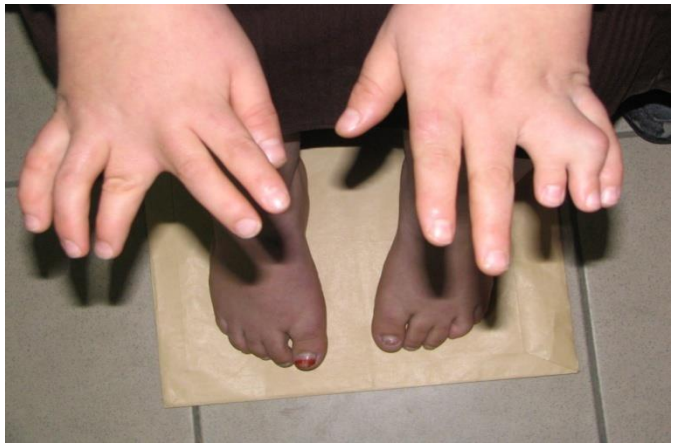
Etudes en cours

- Role therapeutique dans mutations de MC4R, LEPR, PCSK1, BBS?
- Role dans variants polymorphiques de POMC predisposants à l'obesite ?
- Role potential pour controler la +++ faim post perte importante de poids
- Role synergetique avec analogues de GLP-1 ? *Dual melanocortin-4 receptor and GLP-1 receptor agonism amplifies metabolic benefits in diet-induced obese mice*, EMBO Mol Med. 2015 Feb

Les obésités syndromiques

Le syndrome de Bardet-Biedl : autosomique récessive

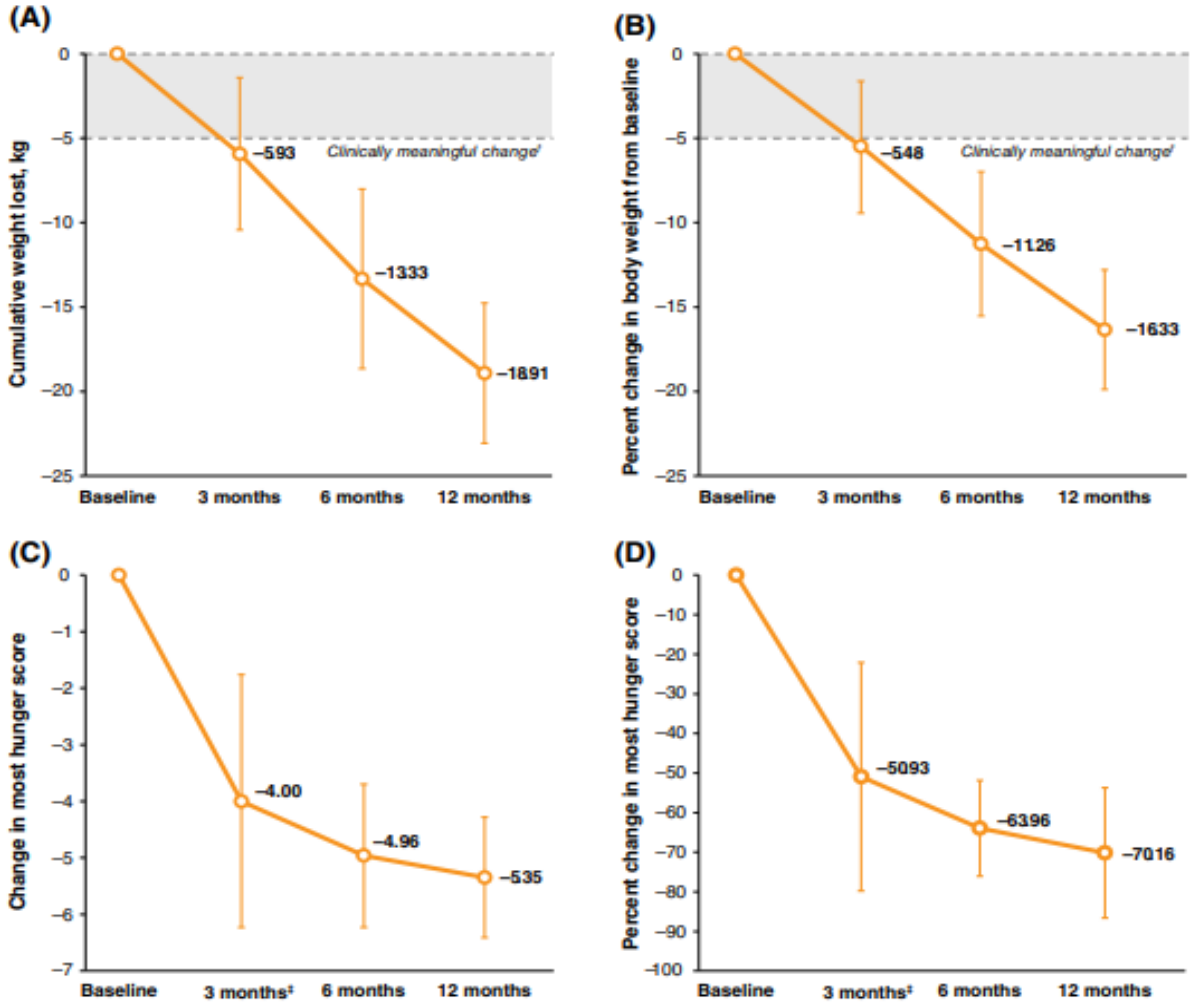
- Obésité très sévère
- Rétinite pigmentaire
- Hexadactylie
- Atteinte rénale variables
- Retard mental
- hypogonadisme



19 genes (BBS 1 à 19) sur des chromosomes différents tous liés au fonctionnement des cils primaires (protéine du centrosome impliquée dans la constitution du cil primitif, ou des chaperonines)

=> ciliopathie

Bonne efficacité du Setmelanotide chez les patients atteints de BBS



Effect of setmelanotide, a melanocortin-4 receptor agonist, on obesity in Bardet-Biedl syndrome
R Haws et al, DOM 2020

ObsGen

Un outil web d'aide au diagnostic

http://obsgen.nutriomics.org

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GLP-1RAs have multifactorial effects

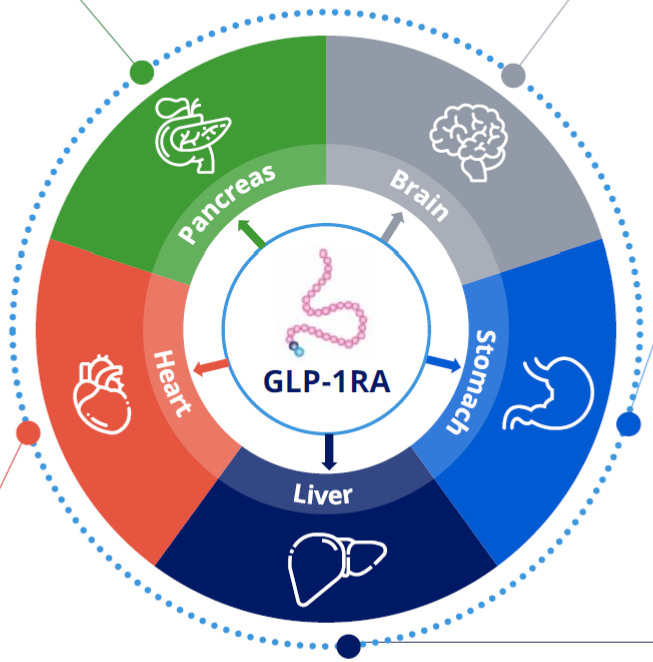
Pharmacological effects

Pancreas

- ↑ Beta-cell function[1]
- ↓ Beta-cell apoptosis[1]
- ↑ Insulin biosynthesis[1]
- ↑ Glucose-dependent insulin secretion[1]
- ↓ Glucose-dependent glucagon secretion[1]

Brain

- ↓ Body weight[5]
- ↓ Food intake[6]
- ↑ Satiety[7,8]



Stomach

- ↓ Gastric emptying[9]

Heart

- ↓ Cardiovascular risk[2]
- ↓ Fatty acid metabolism[3]
- ↑ Cardiac function[3]
- ↓ Systolic blood pressure[3]
- ↓ Inflammation[4]

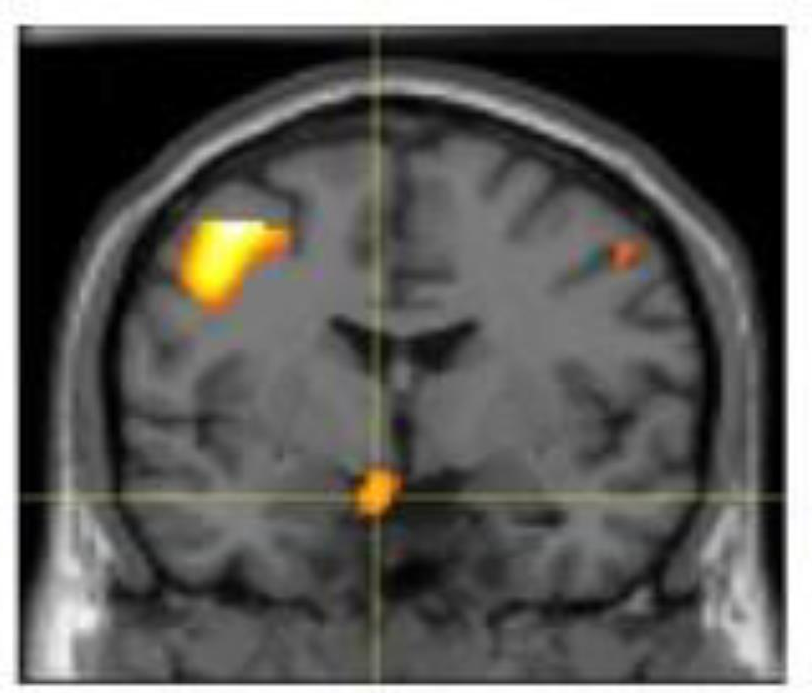
Liver

- ↓ Endogenous glucose production[10]
- ↑ Hepatic insulin sensitivity[10]
- ↓ *De novo* lipogenesis[10]
- ↓ Lipotoxicity[10]
- ↓ Steatosis[11]

GLP-1RA, glucagon-like peptide-1 receptor agonist

Adapted from 1. Campbell JE, DJ Drucker. Cell Metab 2013;17:819–37; 2. Marso SP et al. N Engl J Med 2016;375:311–22; 3. Ryan D, Acosta A. Obesity 2015;23:1119–29; 4. Hogan AE et al. Diabetologia 2014;57:781–4; 5. Baggio LL, Drucker DJ. J Clin Invest 2014;124:4223–6; 6. Bagger JI et al. Clin Endocrinol Metab 2015;100:4541–52; 7. Flint A et al. J Clin Invest 1998;101:515–20; 8. Blundell J et al. Diabetes Obes Metab. 2017;19(9):1242–51; 9. Tong J, D'Alessio D. Diabetes 2014;63:407–9; 10. Armstrong MJ et al. J Hepatol 2016;64:399–408; 11. Armstrong MJ et al. Lancet 2016;387:679–90.

GLP-1 activates areas of brain involved in appetite regulation

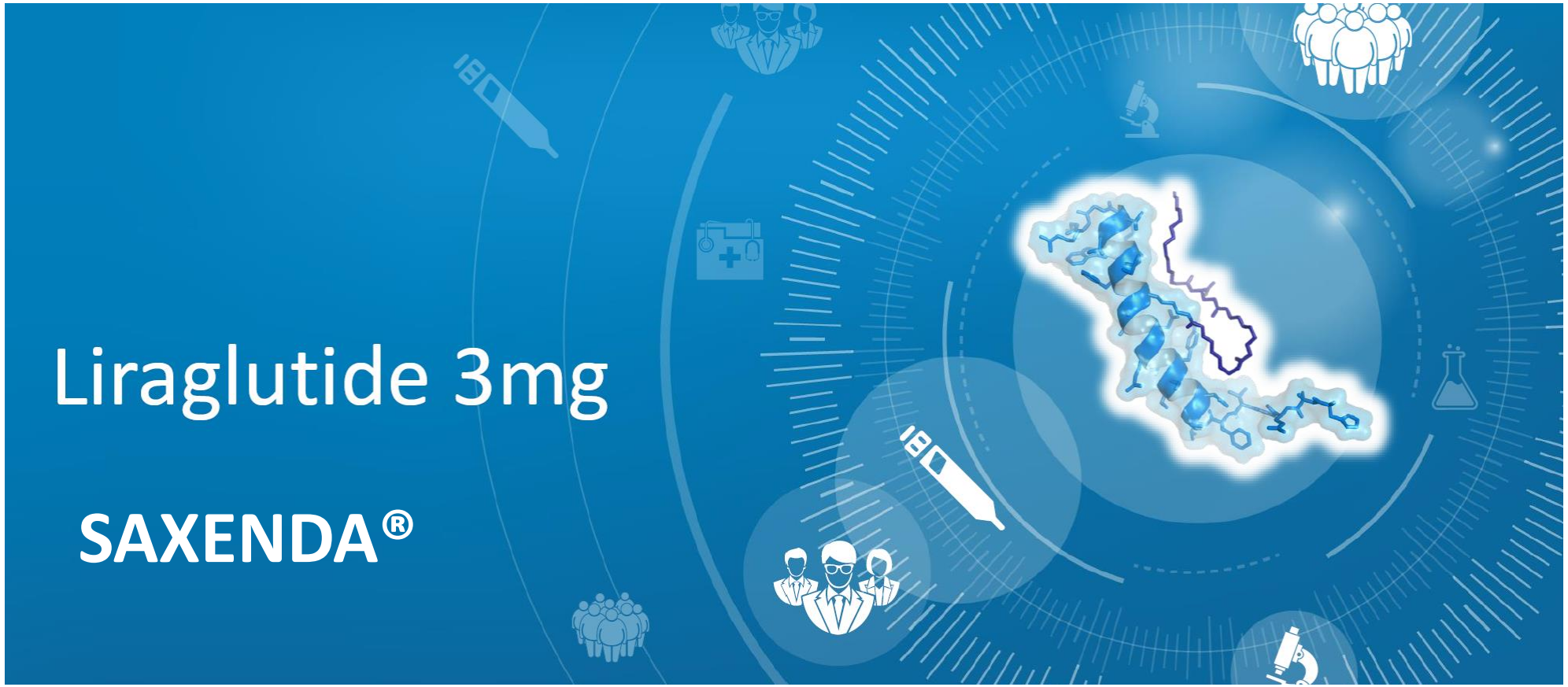


- The postprandial GLP-1 response is associated with **activation of areas of the human implicated in regulation of appetite and food intake**
- Peak postprandial increases in plasma GLP-1 concentrations are correlated with increases in regional cerebral blood flow in the **left dorsolateral prefrontal cortex and the hypothalamus**

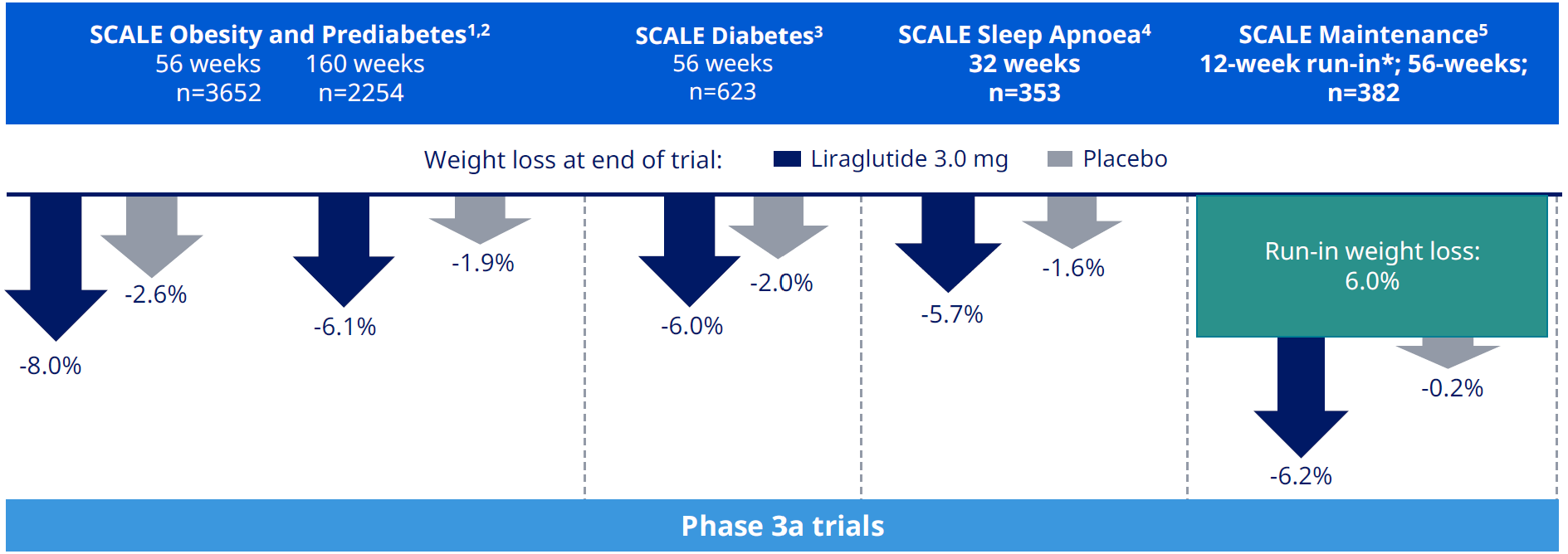
GLP-1, glucagon-like peptide-1; PET, positron emission tomography
Pannacciulli et al. Neuroimage 2007;35:511–17

Liraglutide 3mg

SAXENDA®



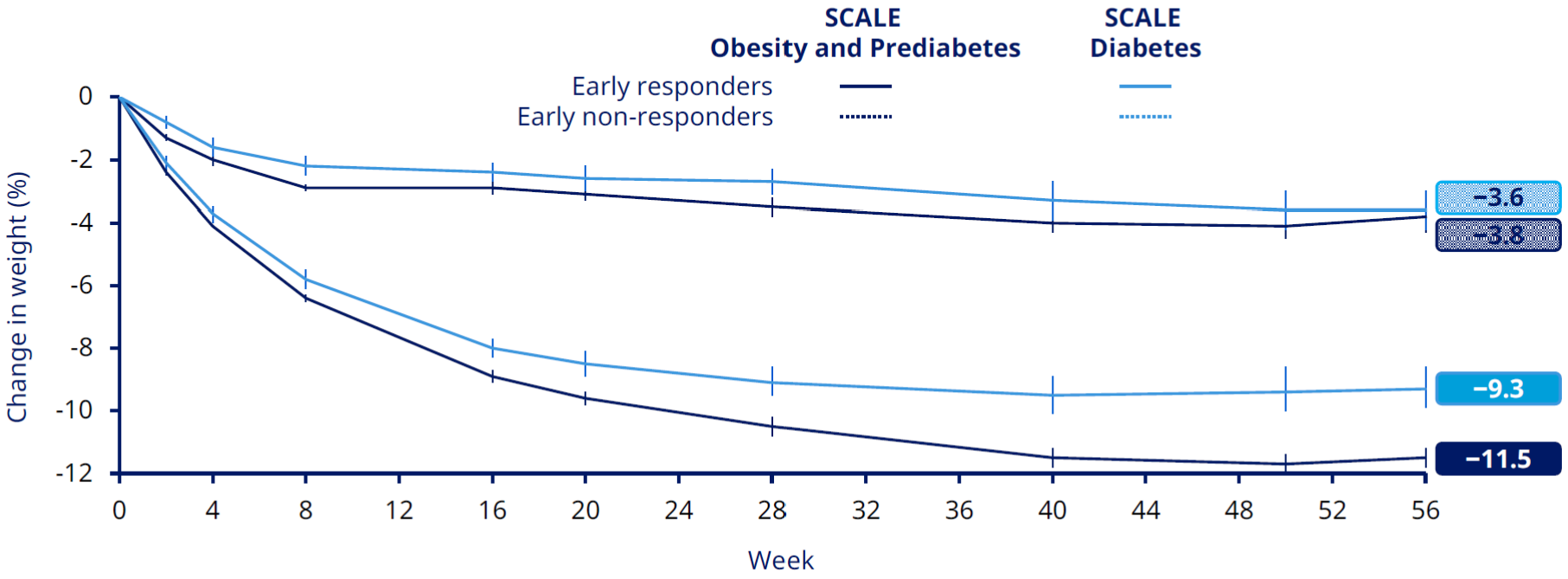
Weight loss across Phase 3a trials



Data are observed means; last observation carried forward at end of trial; N, number of individuals contributing to the analysis
**Low calorie diet (total energy intake 1200–1400 kcal/day)*
1. Pi-Sunyer et al. N Engl J Med 2015;373:11–22; 2. le Roux CW et al. Lancet. 2017;389:1399–1409; 3. Davies et al. JAMA 2015;314:687–99; 4. Blackman et al. Int J Obes (Lond) 2016;40:1310–19; 5. Wadden et al. Int J Obes (Lond) 2013;37:1443–51

Change in body weight (%)

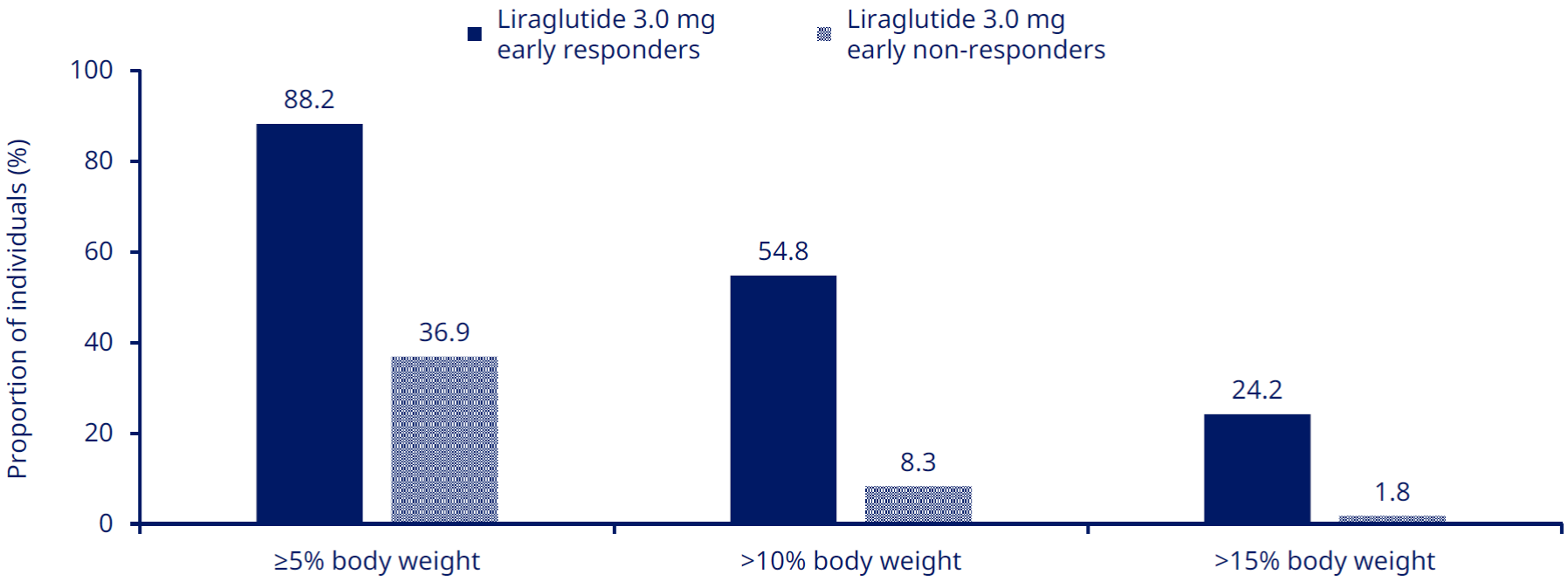
Early responders and non-responders: 0–56 weeks



Early responders, individuals who achieved ≥5% weight loss from baseline at 16 weeks; early non-responders, individuals who achieved <5% weight loss from baseline at 16 weeks. Week 56 completers, FAS, fasting visit data only. Line graphs are observed means (±95% CI).
CI, confidence interval; FAS, full analysis set
Blüher et al. IDF 2015. 30 November–4 December 2015, Vancouver, Canada. Poster 0208-P

Categorical weight loss achievers at week 56

Completers: SCALE Obesity and Prediabetes



Early responders, individuals who achieved ≥5% weight loss from baseline at 16 weeks; early non-responders, individuals who achieved <5% weight loss from baseline at 16 weeks. Values are estimated proportions from a logistic regression model. Week 56 completers
Blüher et al. IDF 2015. 30 November–4 December 2015, Vancouver, Canada. Poster 0208-P

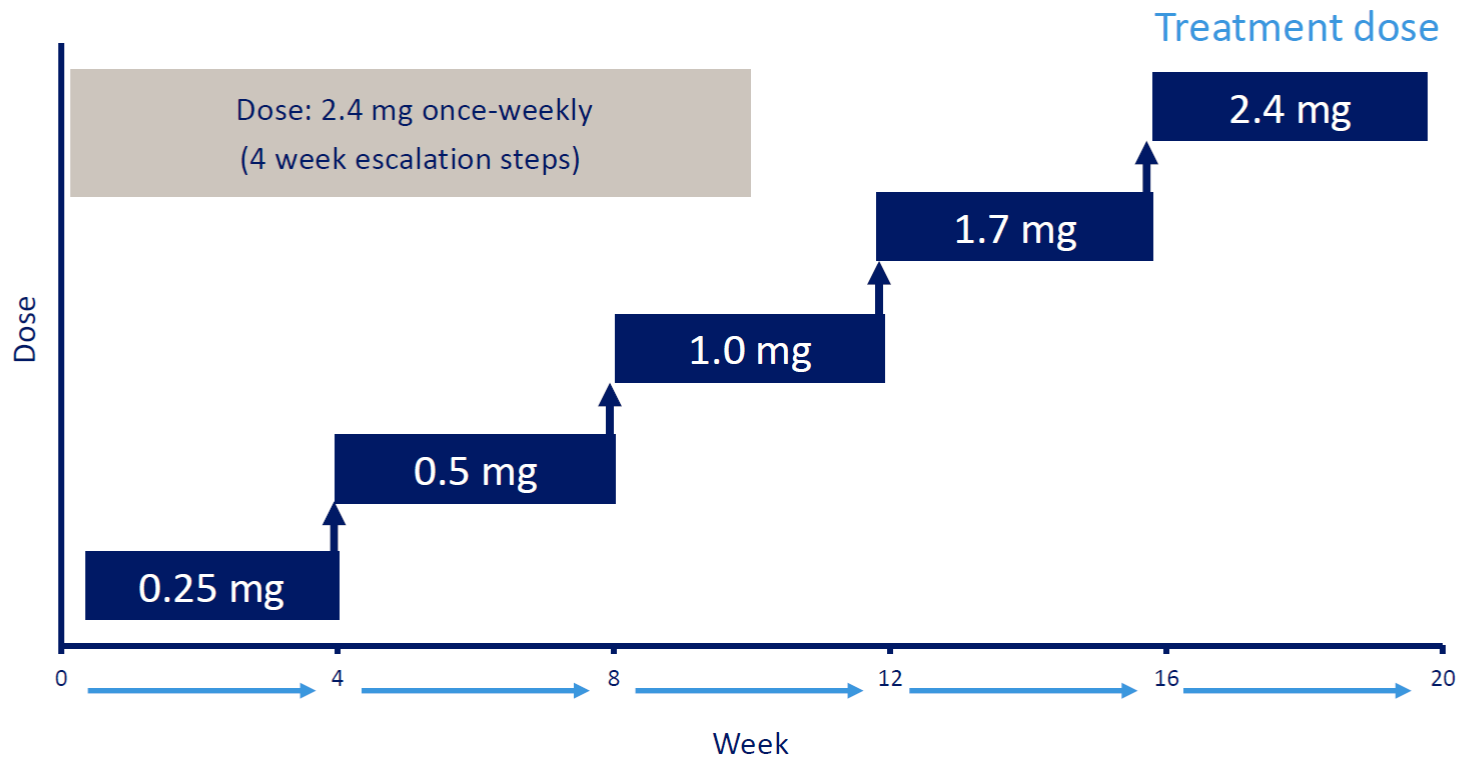
Les solutions existantes en France

Compléments alimentaires OTC : produits disponibles aux pharmacies sans ordonnance pour perdre du poids

Semaglutide 2.4 mg

WEGOVY®

Semaglutide obesity dose escalation

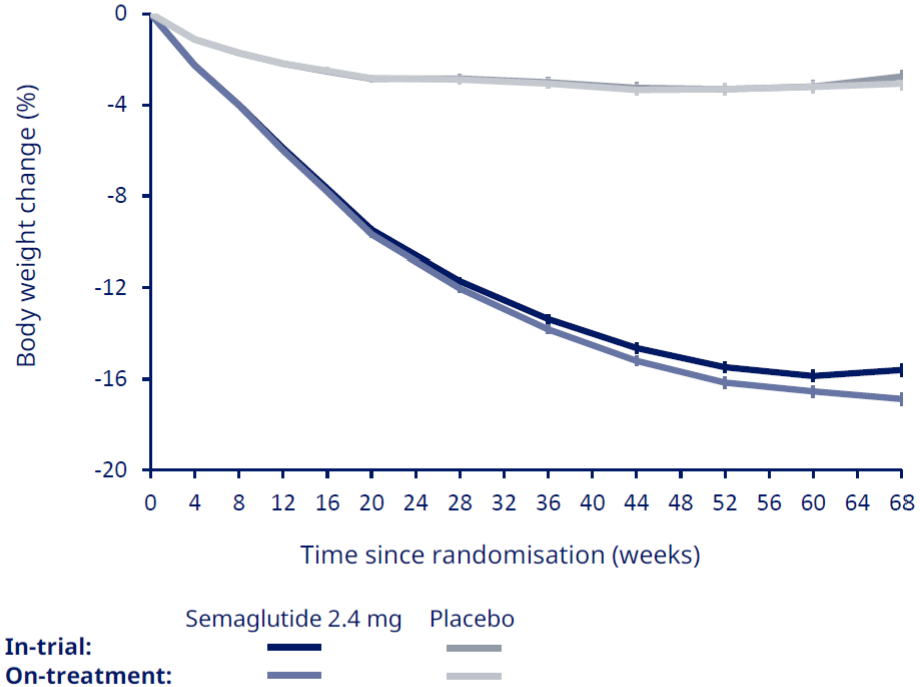


Semaglutide is not approved for treatment of obesity

STEP 1: Body weight change

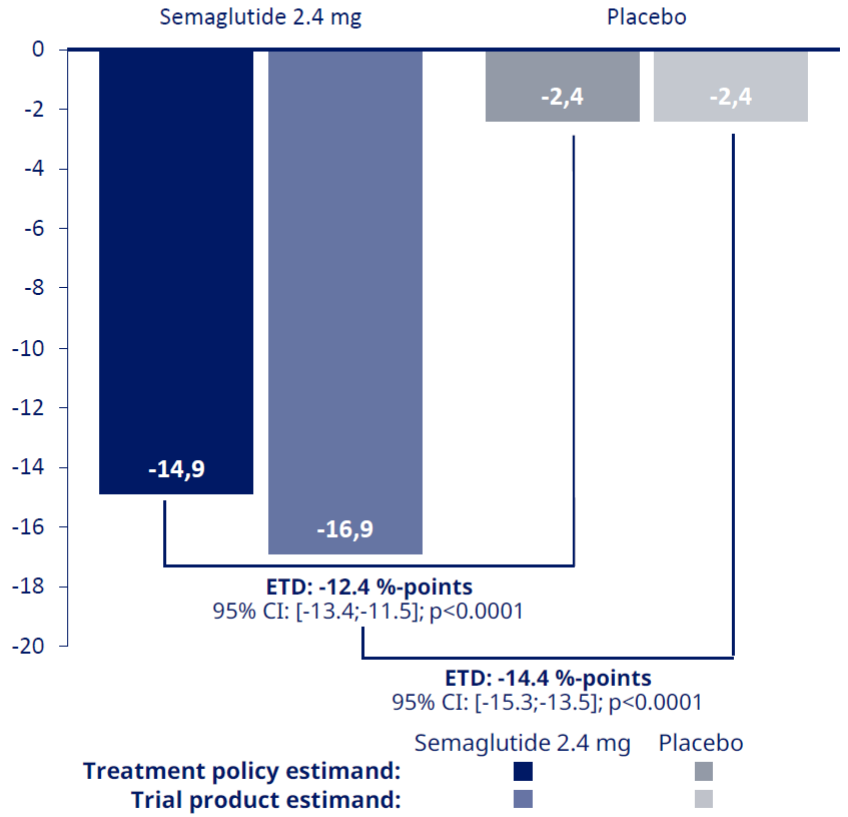
Observed body weight change over time

(Mean at baseline: 105.8 kg)



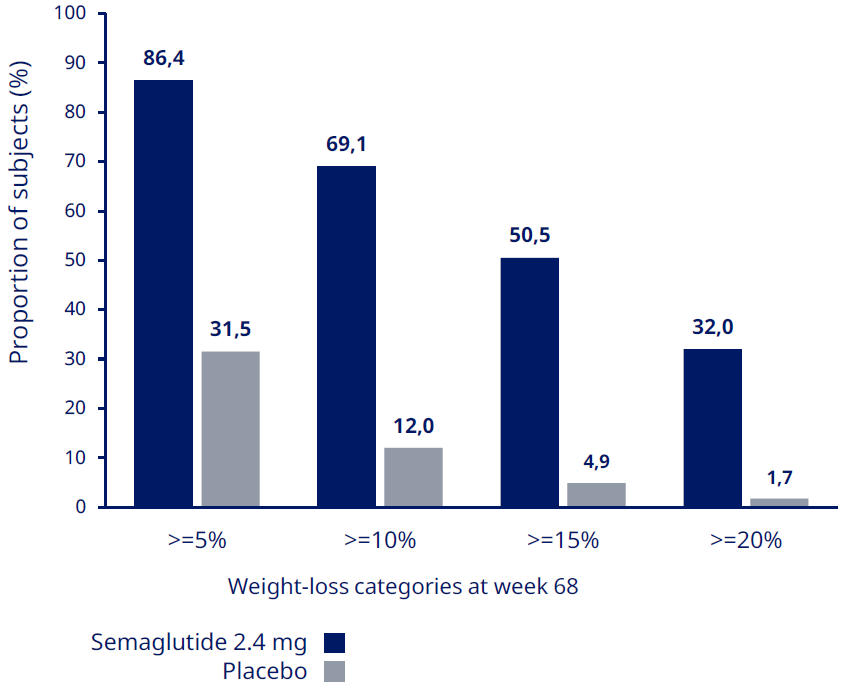
Error bars are +/- standard error of the mean.
CI, confidence interval; ETD, estimated treatment difference.
Wilding JPH et al. NEJM 2021; doi: 10.1056/NEJMoa2032183. Online ahead of print.

Estimated change from baseline to week 68

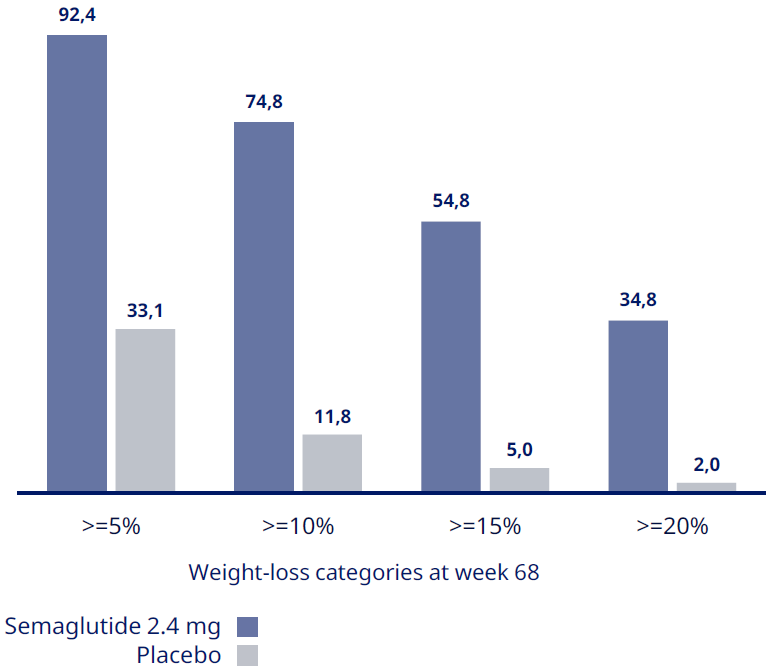


STEP 1: Categorical body weight loss

In-trial

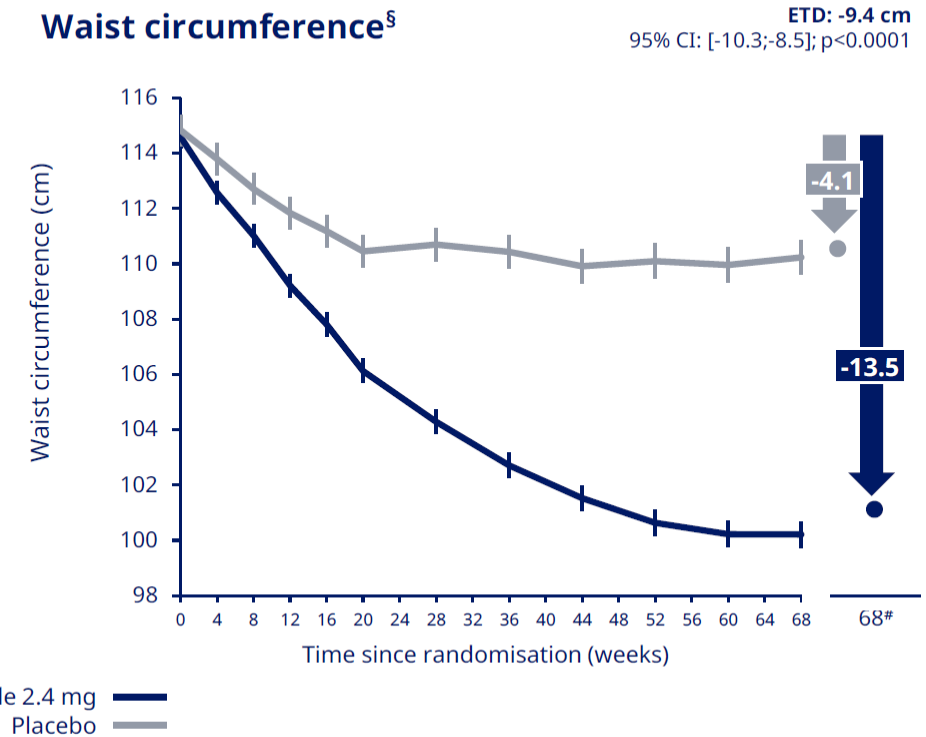


On-treatment



§ Proportions are based on observed data.
Wilding JPH et al. NEJM 2021; doi: 10.1056/NEJMoa2032183. Online ahead of print.

STEP 1: Waist circumference



§ Means are based on observed data from the in-trial period and the ETD is for the treatment policy estimand. Error bars are +/- standard error of the mean.
BMI, body mass index; CI, confidence interval; ETD, estimated treatment difference.
Wilding JPH et al. NEJM 2021; doi: 10.1056/NEJMoa2032183. Online ahead of print.

Semaglutide for the treatment of obesity

Semaglutide is a human GLP-1 analogue[1–3]

94% homology to human GLP-1

t½ of approx.
1 week

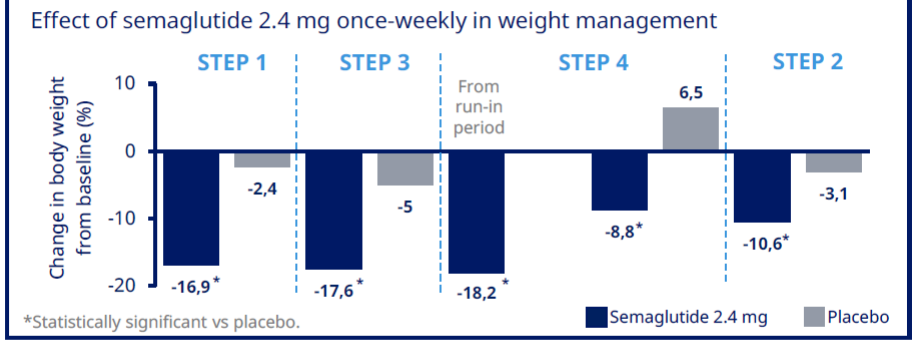
Semaglutide: mechanism of action[4,5]

Reduced appetite and cravings, improved control of eating

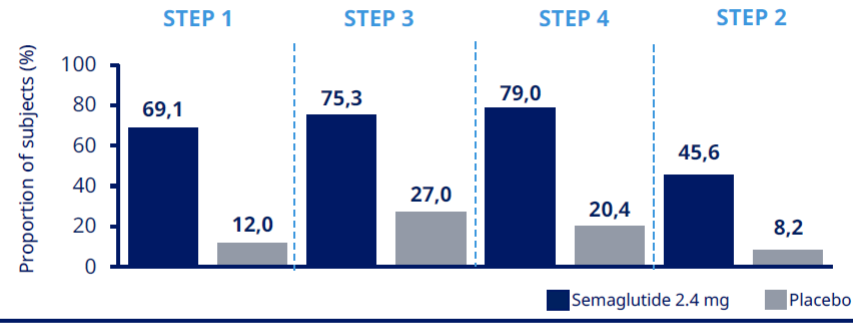
Reduced energy intake

Reduced body weight

STEP: change in body weight from baseline[6–8]



STEP: subjects achieving ≥10% weight loss[6–8]



[a] *Results according to trial product estimand*

GLP-1, glucagon-like peptide-1.

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. Clin Pharmacokinet 2017;56:1381–90; 4. Blundell J et al. Diabetes Obes Metab 2017;19:1242–51; 5. Skovgaard D et al. Presented at the 56th European Association for the Study of Diabetes (EASD) virtual meeting, 22–25 September 2020. Poster Number: 555; 6. Wilding JPH et al. NEJM 2021; doi: 10.1056/NEJMoa2032183. Online ahead of print; 7. Davies M et al. Lancet 2021; doi: 10.1016/S0140-6736(21)00213-0. Online ahead of print; 8. Wadden TA et al. JAMA 2021; doi: 10.1001/jama.2021.1831. Online ahead of print.

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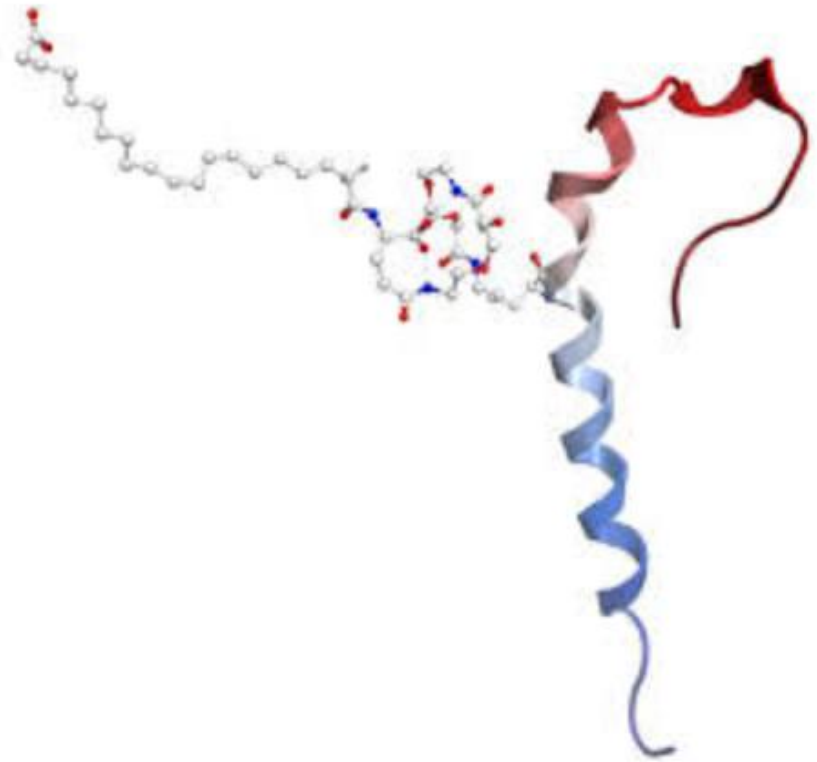


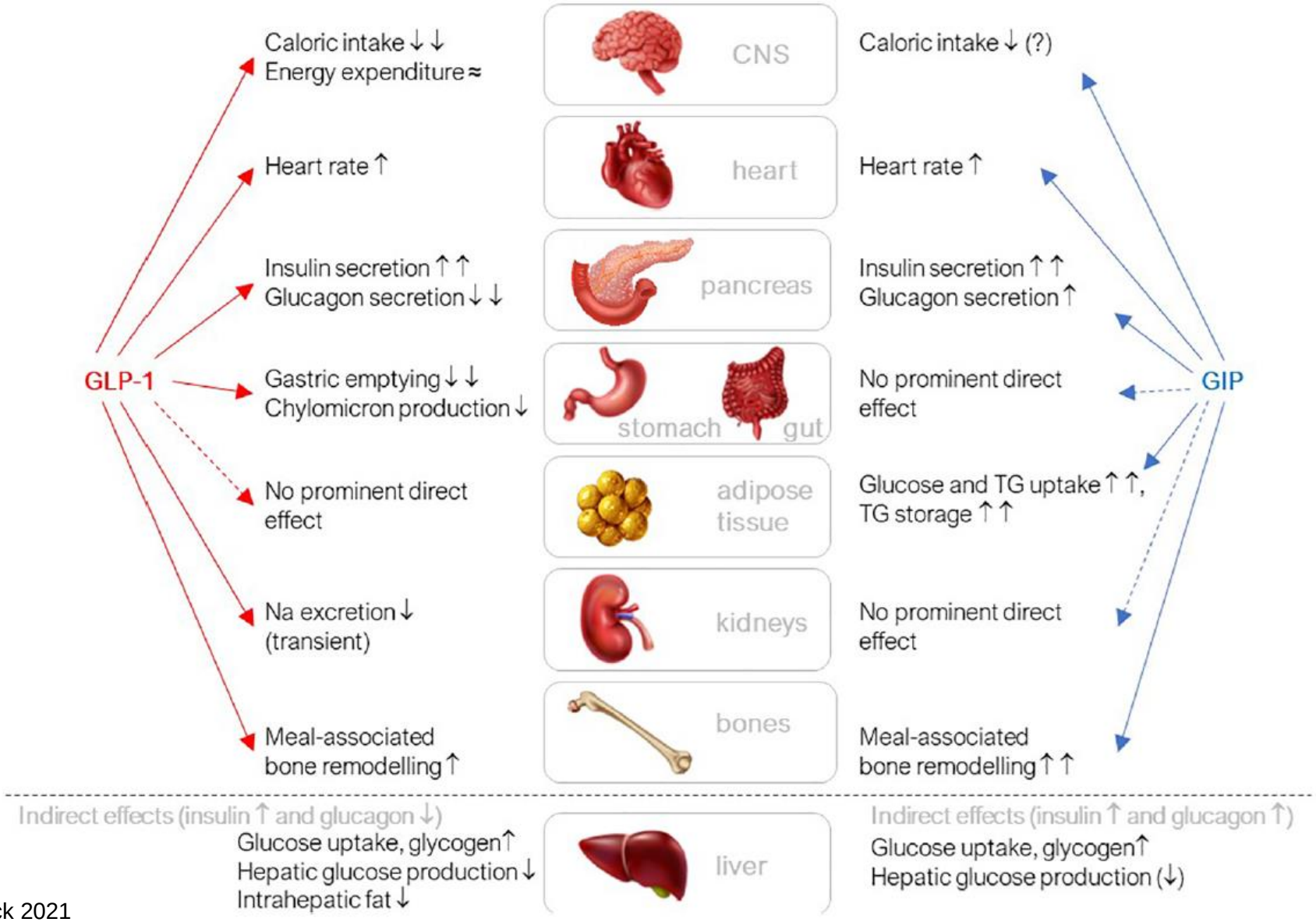
La molécule de tirzépatide est un peptide linéaire de 39 acides aminés conjugué à une fraction d'acide gras C20. Image de Tirzepatide de Lilly.

Tirzepatide

Nouvel agoniste double des récepteurs GIP et GLP-1

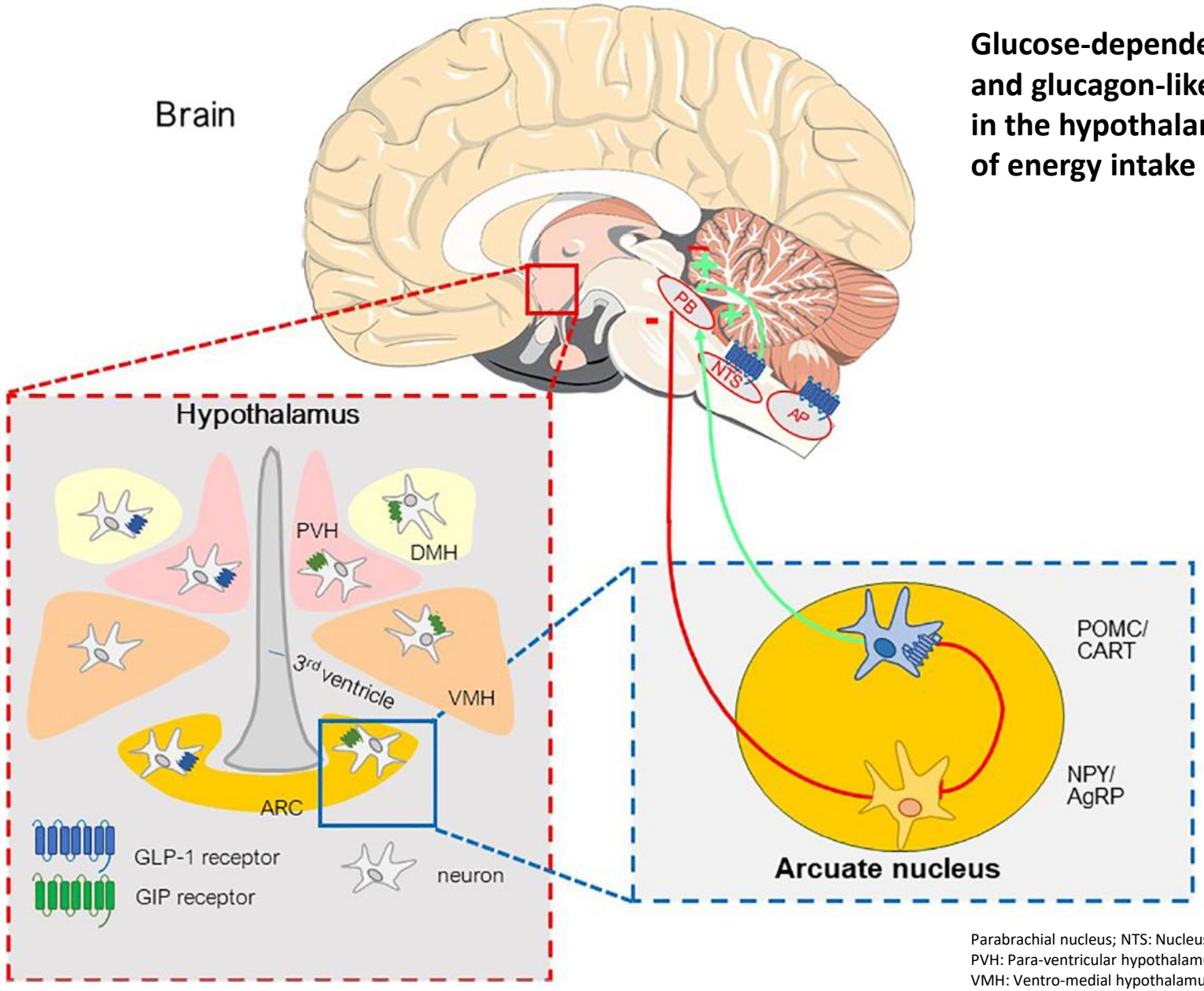
1 inj SC/sem

Overview on biological glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) effects at the organ/tissue level



DOI: 10.1111/dom.14496 Nauck 2021

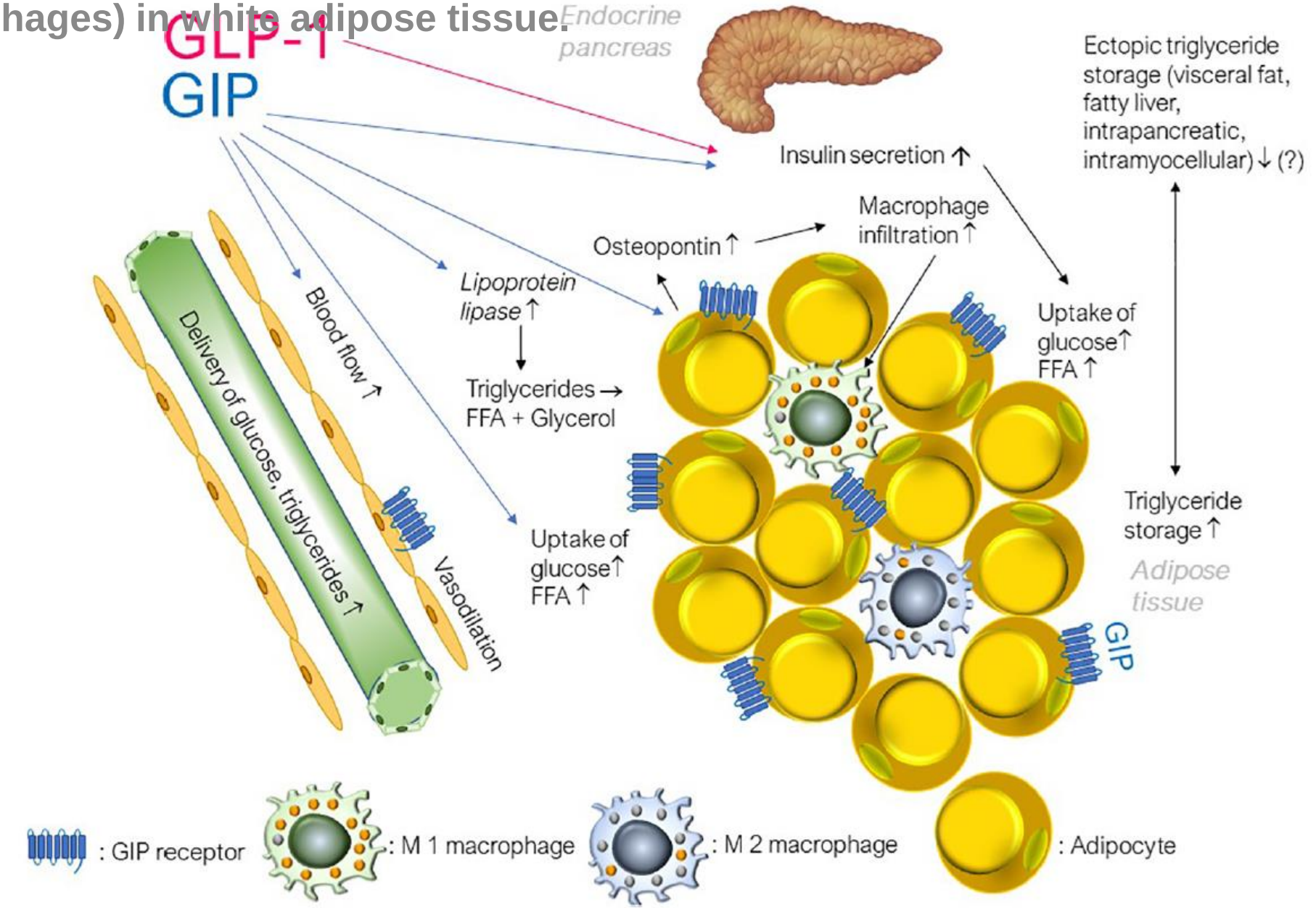
Glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) receptors in the hypothalamus and brainstem involved in the regulation of energy intake (meal initiation and termination) and body weight.



Parabrachial nucleus; NTS: Nucleus tractus solitarii; AP: Area postrema; PVH: Para-ventricular hypothalamus; DMH: Dorso-medial hypothalamus; VMH: Ventro-medial hypothalamus; ARC: Arcuate nucleus; POMC/CART: Proopiomelanocortin/cocaineamphetamine-regulated transcript; NPY: Neuropeptide Y; AgRP: Agoutirelated peptide

DOI: 10.1111/dom.14496 Nauck 2021

Effects of glucosedependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) on blood supply to, substrate uptake into, triglyceride storage in, and infiltration with inflammatory cells (macrophages) in white adipose tissue.



FFA: Free fatty acids

DOI: 10.1111/dom.14496 Nauck 2021

Tirzepatide - SURPASS Clinical Trial Programme

Monotherapy	Combination With OAMs			Combination With Insulin
SURPASS-1 **vs placebo[1]** (mean T2D duration: 4.7 y)	**SURPASS-2** **vs semaglutide[2]** **Add-on to metformin** (mean T2D duration: 8.6 y)	**SURPASS-3** **vs insulin degludec[3]** **Add-on to metformin with or without SGLT2i** (mean T2D duration: 8.4 y)	**SURPASS-4** **vs insulin glargine[4]** **Add-on to ≥1 and ≤3 OAMs (metformin, SGLT2i, or SU)** (mean T2D duration: 11.8 y)	**SURPASS-5** **vs placebo[5]** **Add-on to insulin glargine with or without metformin** (mean T2D duration: 13.3 y) **SURPASS-6[7]** **vs insulin lispro (TID)** **Add-on to insulin glargine with or without metformin (ongoing)**

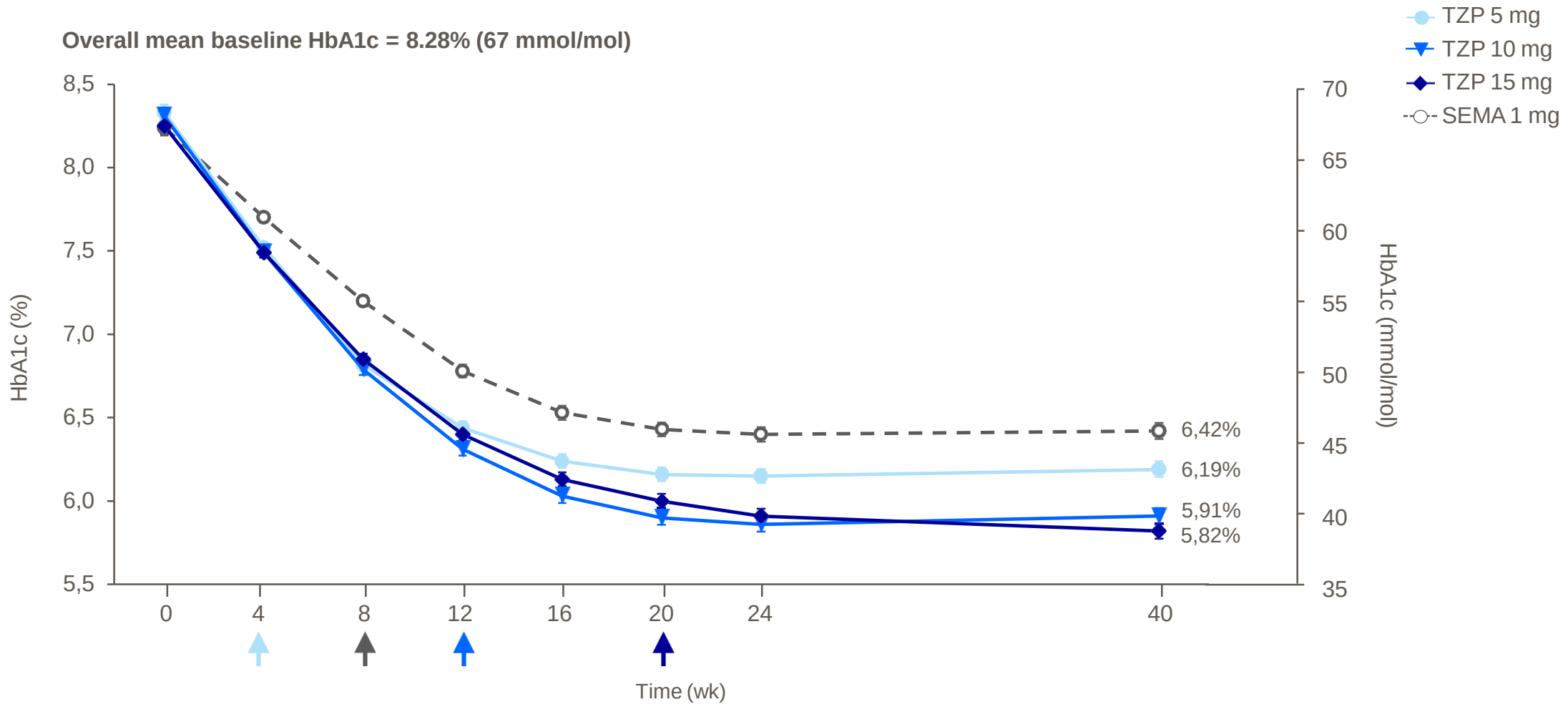
SURPASS-CVOT vs dulaglutide (ongoing)[6]

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

HbA1c Over Time (SURPASS-2)

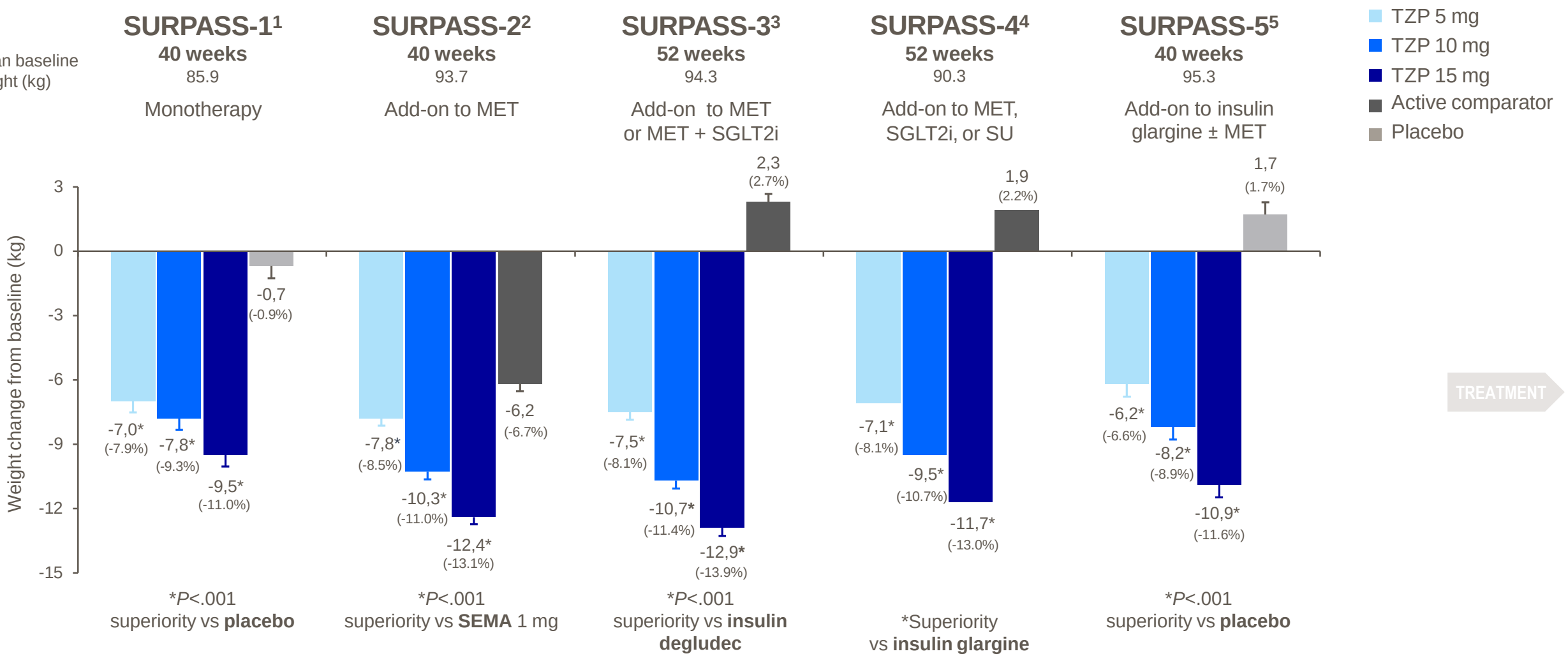
Efficacy Estimand



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, 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.

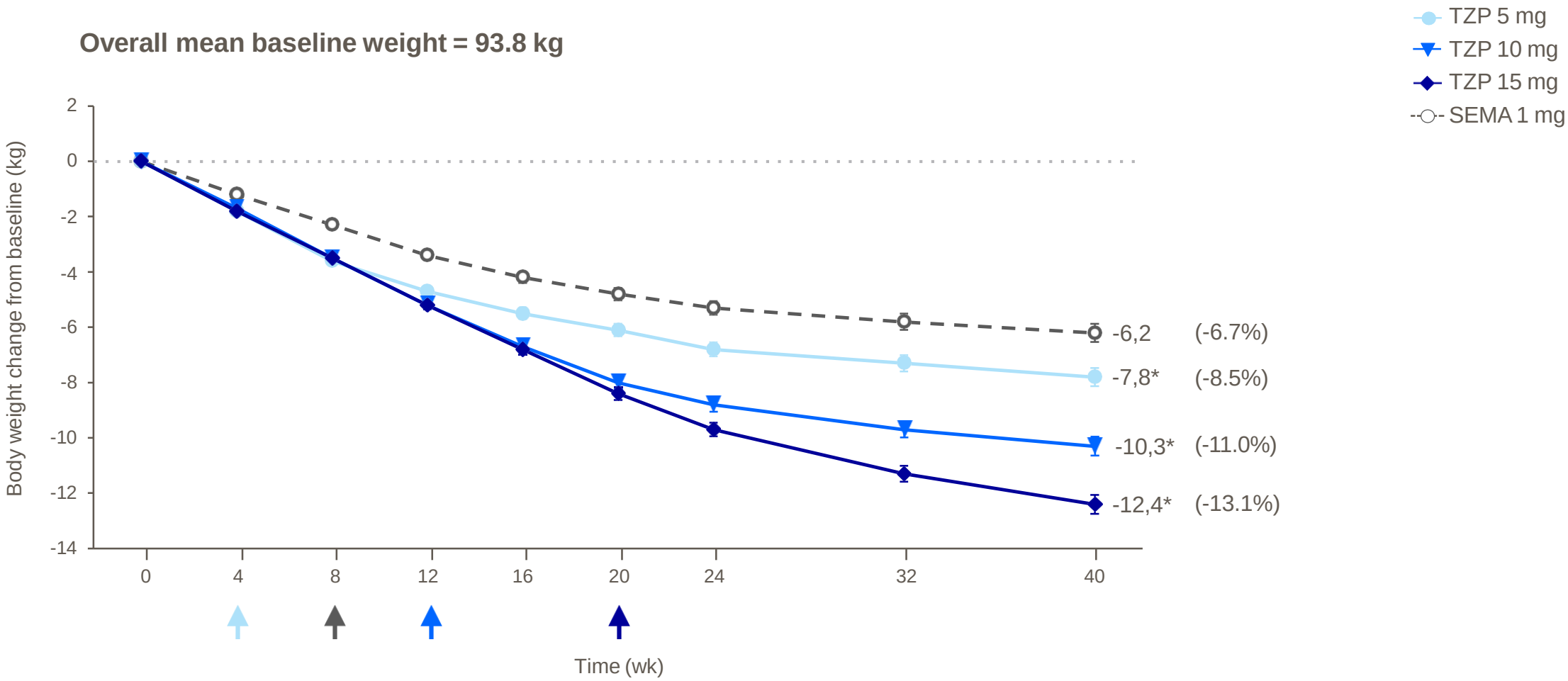
Frias JP, et al. *N Engl J Med*. Published online June 25, 2021.

Tirzepatide - Body Weight Change From Baseline to Primary Endpoint



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; 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.

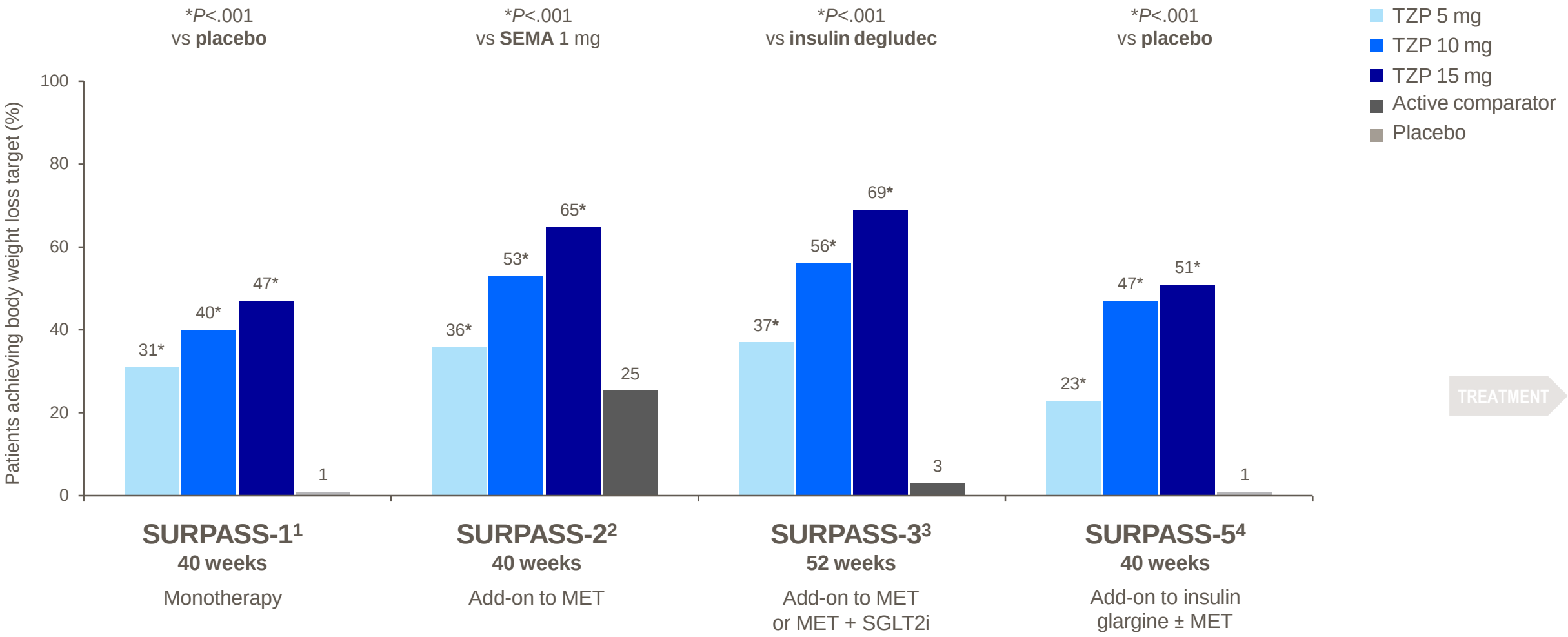
Tirzepatide - Body Weight Change Over Time (SURPASS-2)



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.

Tirzepatide - Proportion of Patients Achieving ≥10% Weight Loss

Efficacy Estimand

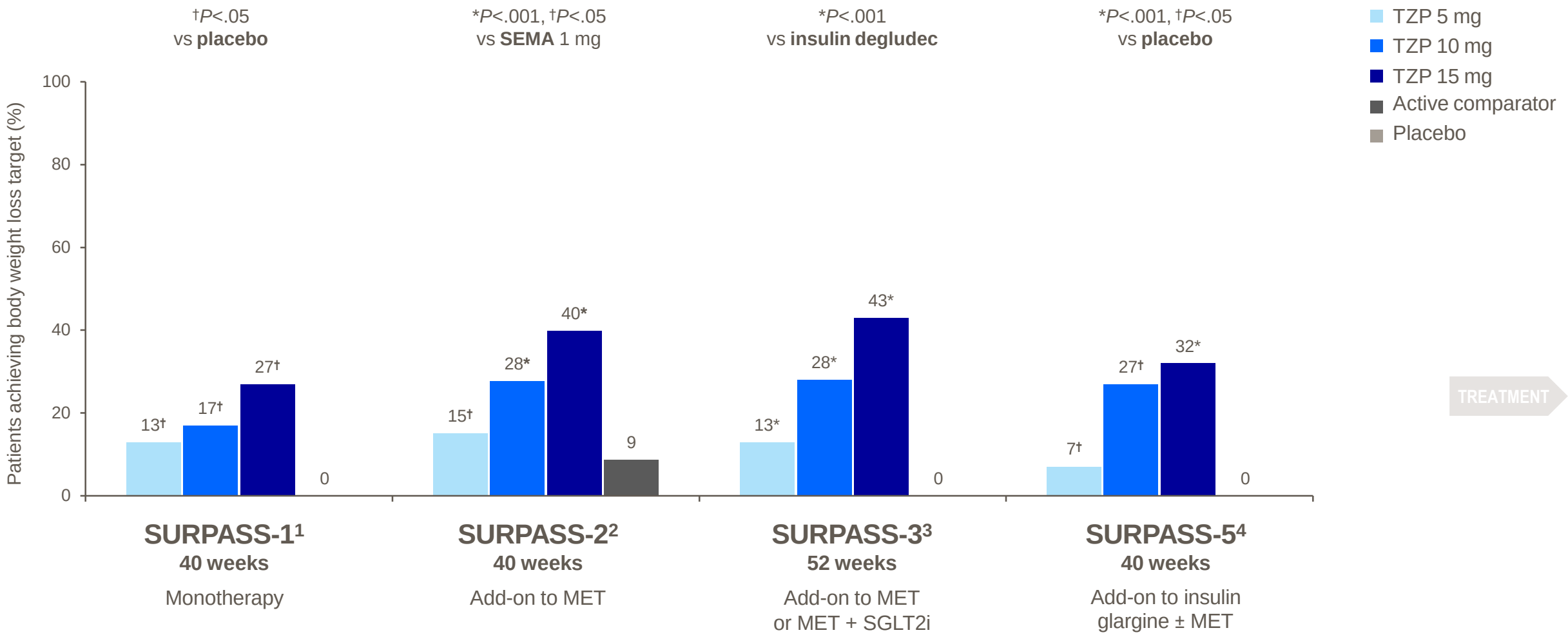


Data are estimated mean; mITT population (efficacy analysis set). Logistic regression.
MET = metformin; mITT = modified intent-to-treat; SGLT2i = sodium-glucose co-transporter-2 inhibitor; SEMA = semaglutide; TZP = tirzepatide.

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.

Tirzepatide - Proportion of Patients Achieving ≥15% Weight Loss

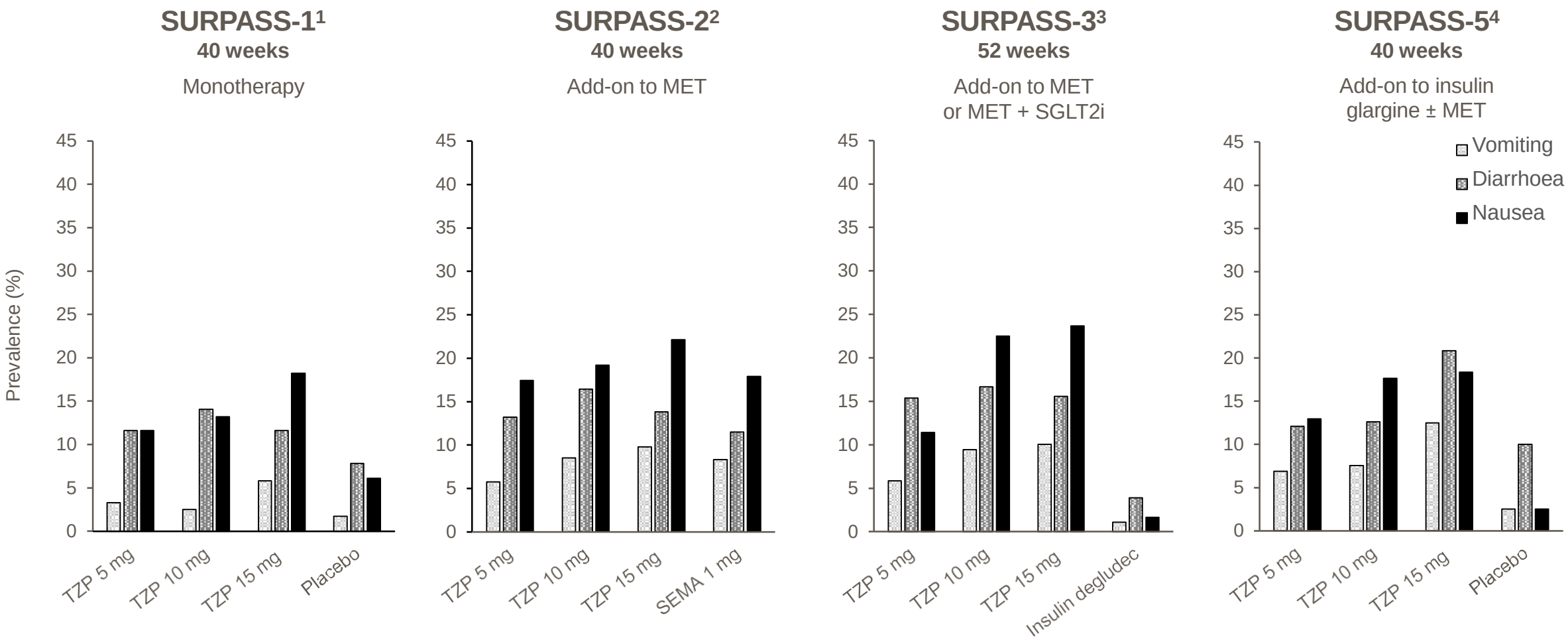
Efficacy Estimand



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.

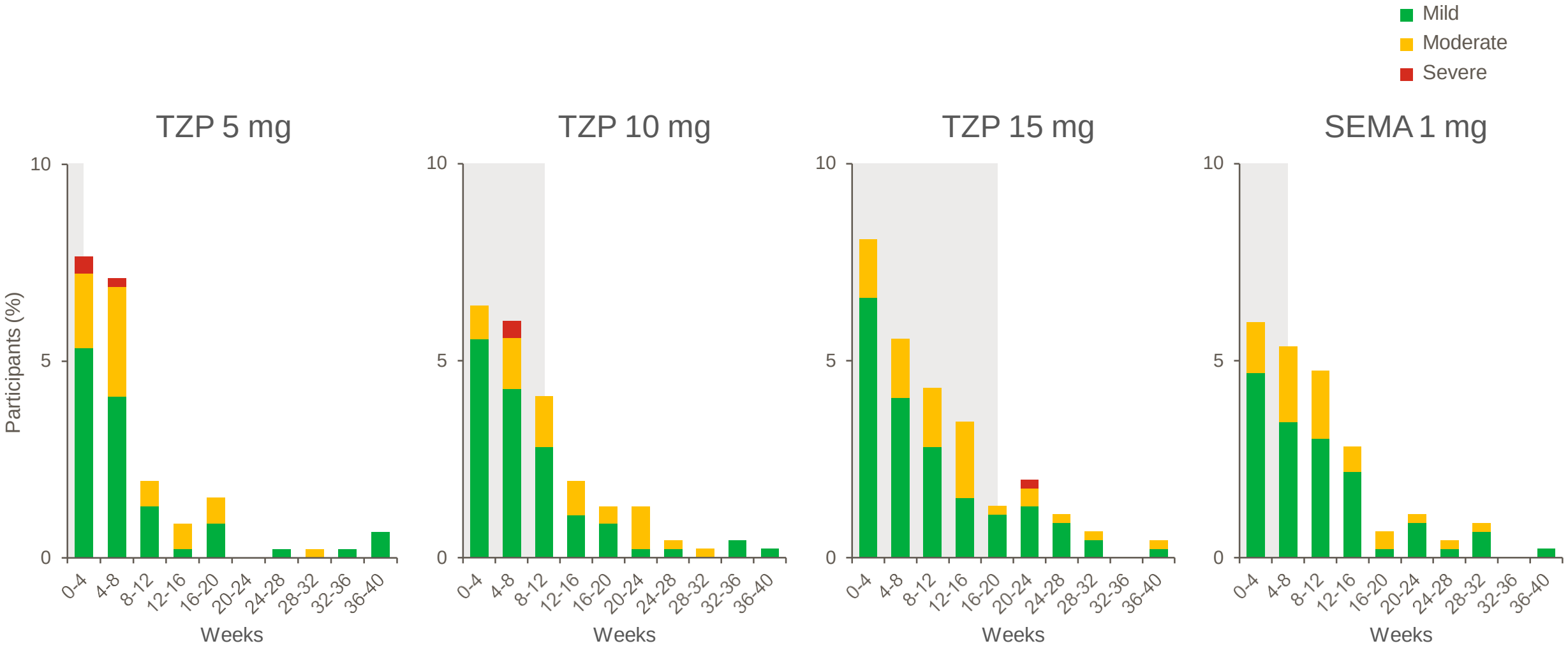
Prevalence of Vomiting, Diarrhoea, and Nausea



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

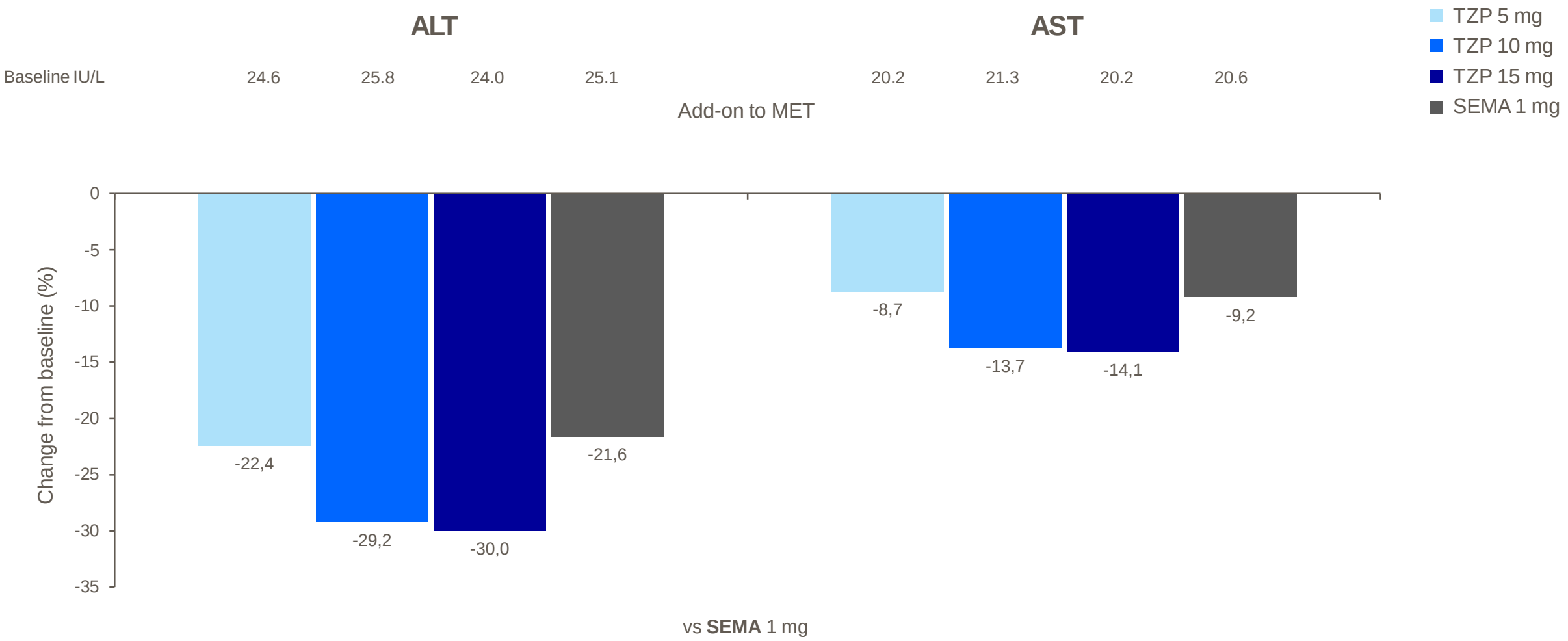
1. Rosenstock J, et al. Presented at the 81st Scientific Sessions of the ADA. 2021. 2. Frias JP, et al. Presented at the 81st Scientific Sessions of the ADA. 2021. 3. Ludvik B, et al. *Lancet*. 2021; In press. 4. Dahl D, et al. Presented at the 81st Scientific Sessions of the ADA. 2021.

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



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.

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

CONCLUSION

- Trois traitements très prometteurs
- ATU très prochainement
- Des stratégies thérapeutiques qui restent à définir dans le parcours de soin
- Prise en charge personnalisée de l’obésité
- Futur plus lointain des triples agonistes (GLP1, Glucagon, GIP)

Merci de votre attention