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Anti Obesity Medication

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Co-Chair Obesity Management Task Force, EASO

Conflict of Interest

- **Consulting**
- MSD,BI,SANOFI,NOVONORDISK,ASTRAZENCA,PFIZER,TEVA,NOVARTIS
- **Lecture**
- MSD,BI,SANOFI,NOVONORDISK,ASTRAZENCA,PFIZER,TEVA,NOVARTIS,DEXON

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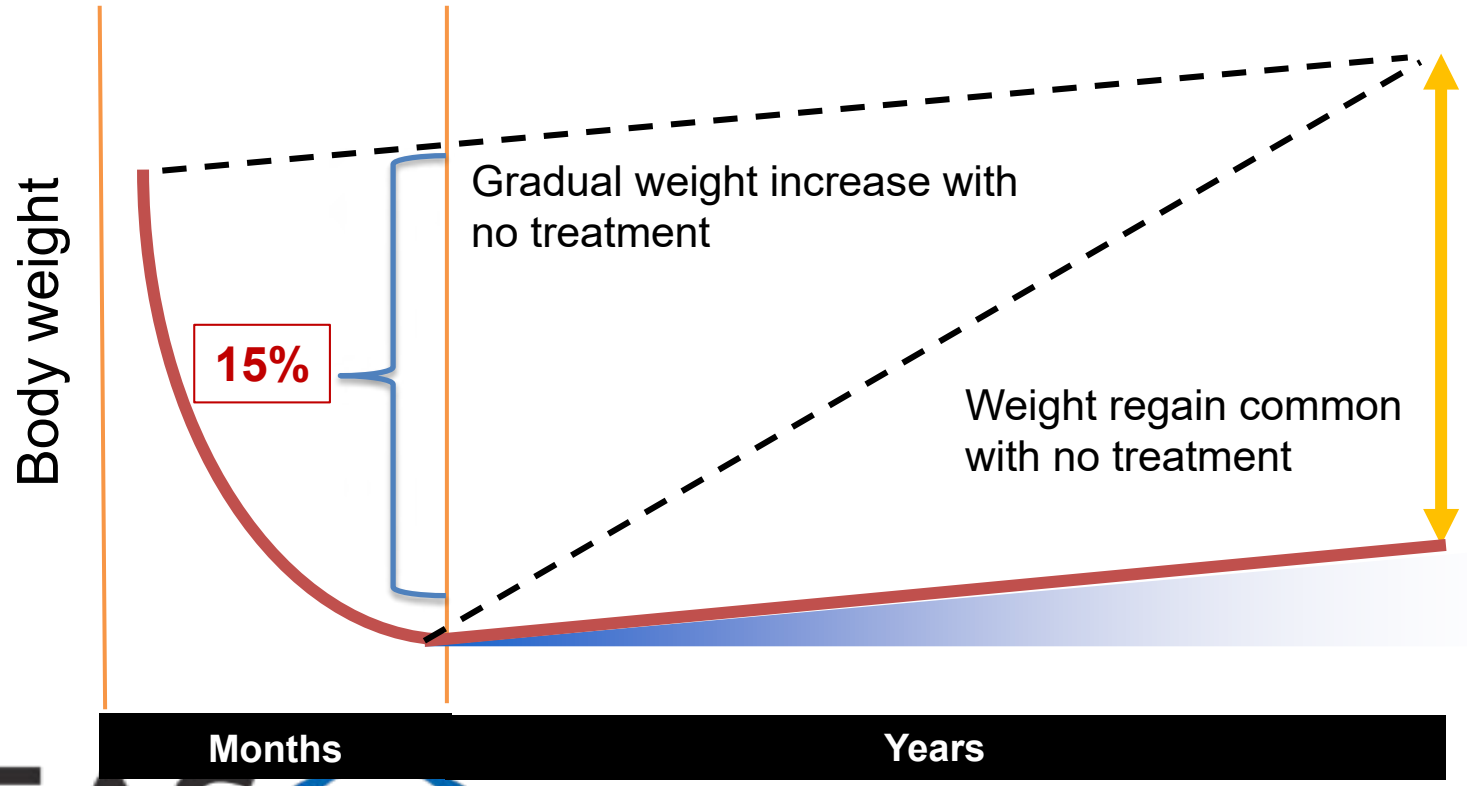
Goals and benefits of effective obesity management

1. Achieve weight loss	2. Maintain weight loss and prevent weight regain	3. Provide clinically meaningful benefits



- Reduce diabetes risk & help manage diabetes
- Reduce cardiovascular risk
- Reduce functional impairment
- Improve quality of life

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1. *Wadden et al. Circulation 2012;125:1157–70; 2. Jensen et al. J Am Coll Cardiol 2014;63(25 Pt B):2985–3023; Purcell et al. Lancet Diabetes Endocrinol 2014;2:954–62; 4. Villareal et al. Am J Clin Nutr 2005;82:923–34.*

Treating chronic diseases to target

	T2D	Hypertension	CVD	ABCD/obesity
Biomarker target	HbA_{1c}	Blood pressure	LDL cholesterol	% weight loss
Reason for target	Prevent complications			
Complications	CKD, retinopathy, neuropathy, CVD	CHF, stroke, CKD	MI, stroke, amputation	T2D, HTN, NAFLD/NASH, CVD risk, CKD, sleep apnea, osteoarthritis

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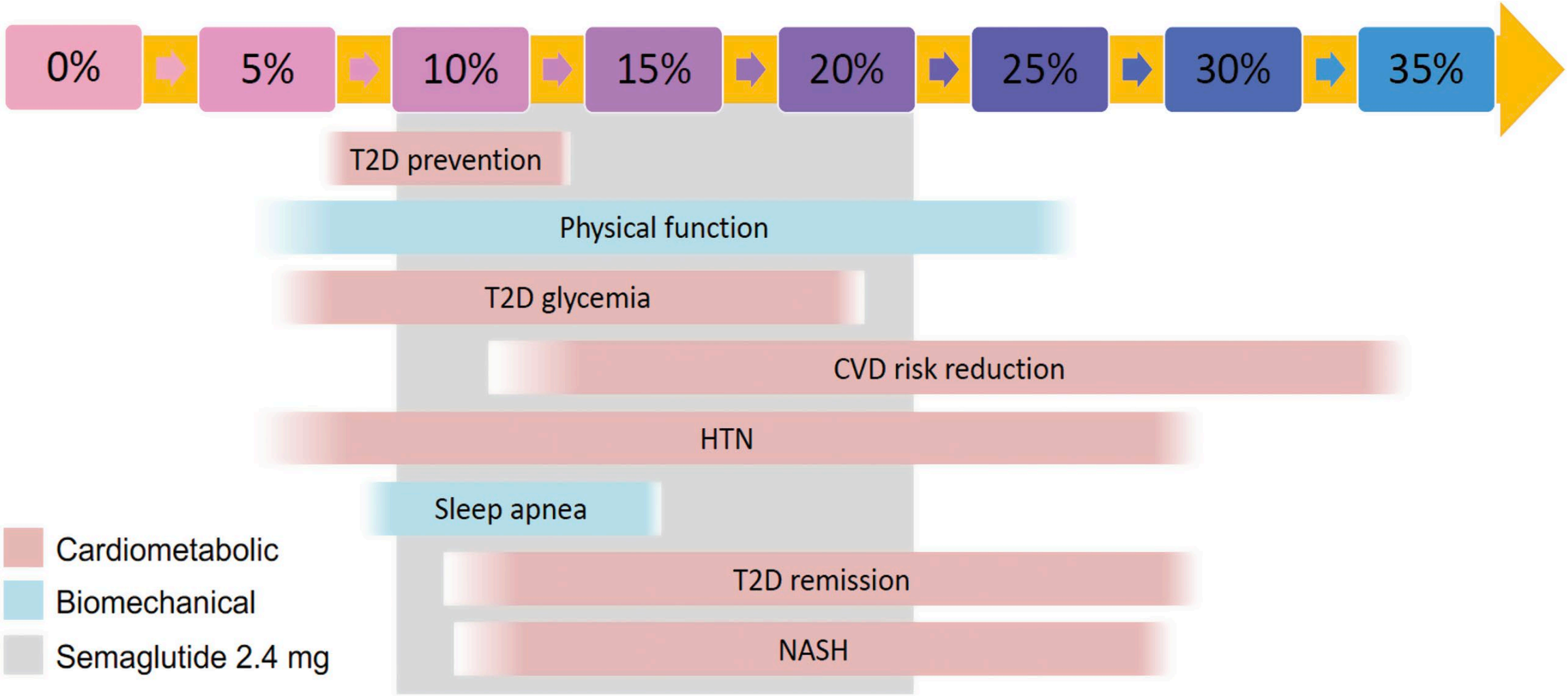
Garvey WT. The Journal of Clinical Endocrinology & Metabolism, 2022

Treating ABCD/obesity to target for prevention and treatment of complications



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Garvey WT. The Journal of Clinical Endocrinology & Metabolism, 2022

Physician and patient expectations on weight loss

Weight-loss goal

Set by a person with obesity for themselves

16%

Received from healthcare professional

17%

Caterson et al. Diabetes Obes Metab 2019;21:1914–24.

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ACTION IO AWARENESS, CARE & TREATMENT IN OBESITY MANAGEMENT - AN INTERNATIONAL OBSERVATION

The role of the brain in regulating appetite

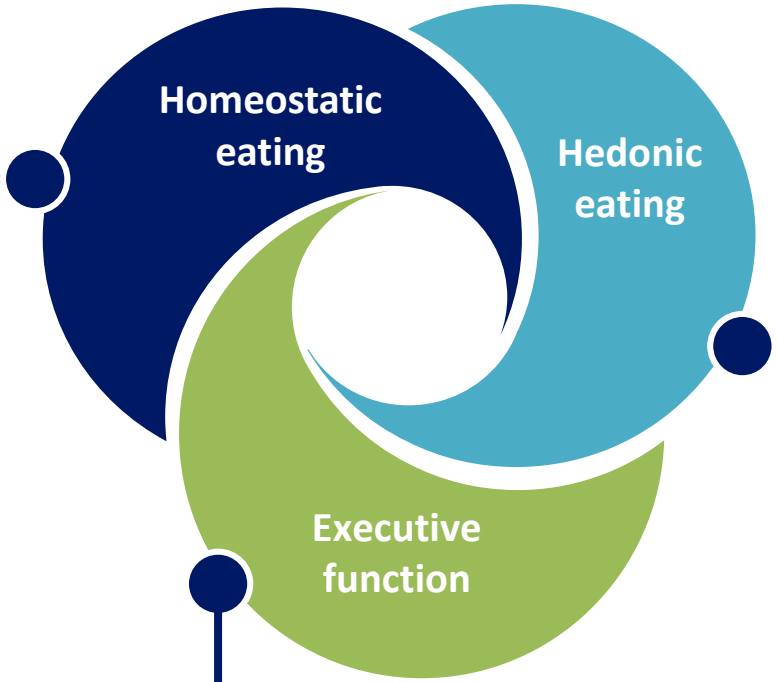
Eating in response to hunger

Satiety

- GLP-1
- Peptide YY
- Oxyntomodulin
- Pancreatic polypeptide
- Amylin

Hunger

- Ghrelin



Eating for pleasure

Dopamine controls WANTING the motivation to eat

Opioid and **cannabinoid** receptors control LIKING the pleasure associated with food

Deciding to eat

Behavioural interventions empower sustainable behaviours in controlling eating

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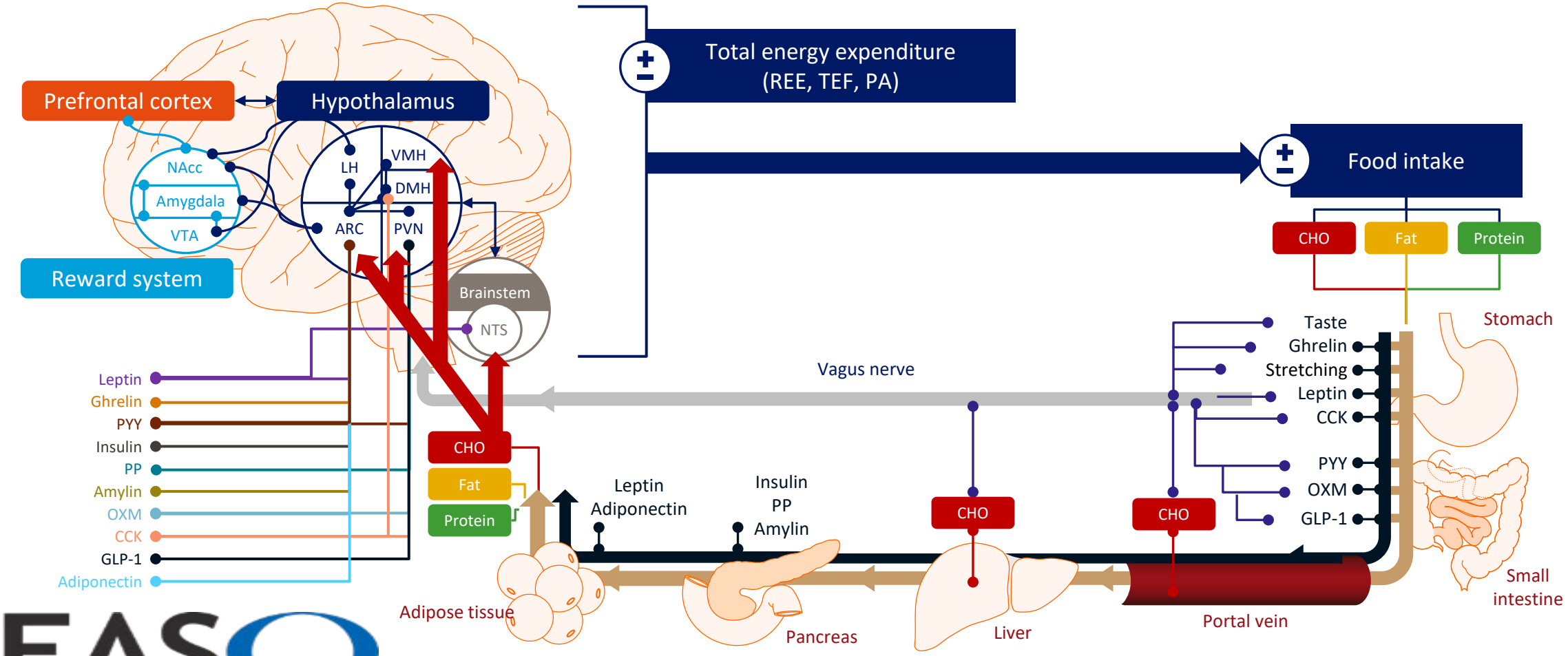
Vallis M. Clin Obes 2019;9:e12299.

The neuro-hormonal actors involved in energy homeostasis



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Theilade S et al. Diabetes Obes Metab 2021;Suppl 1:17–35.

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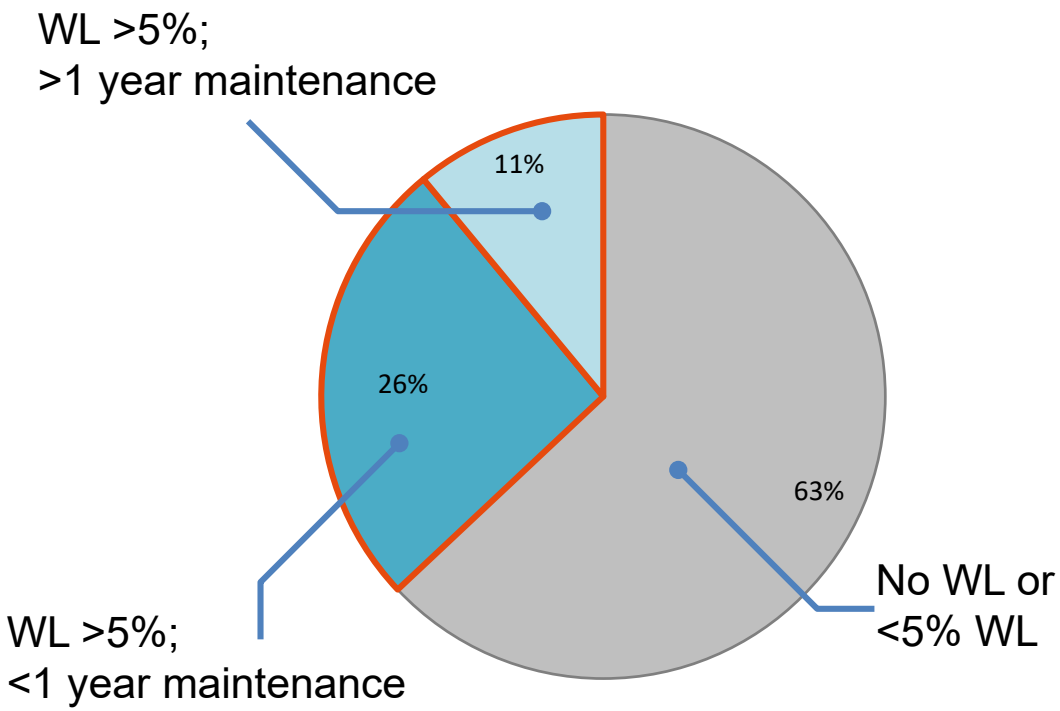
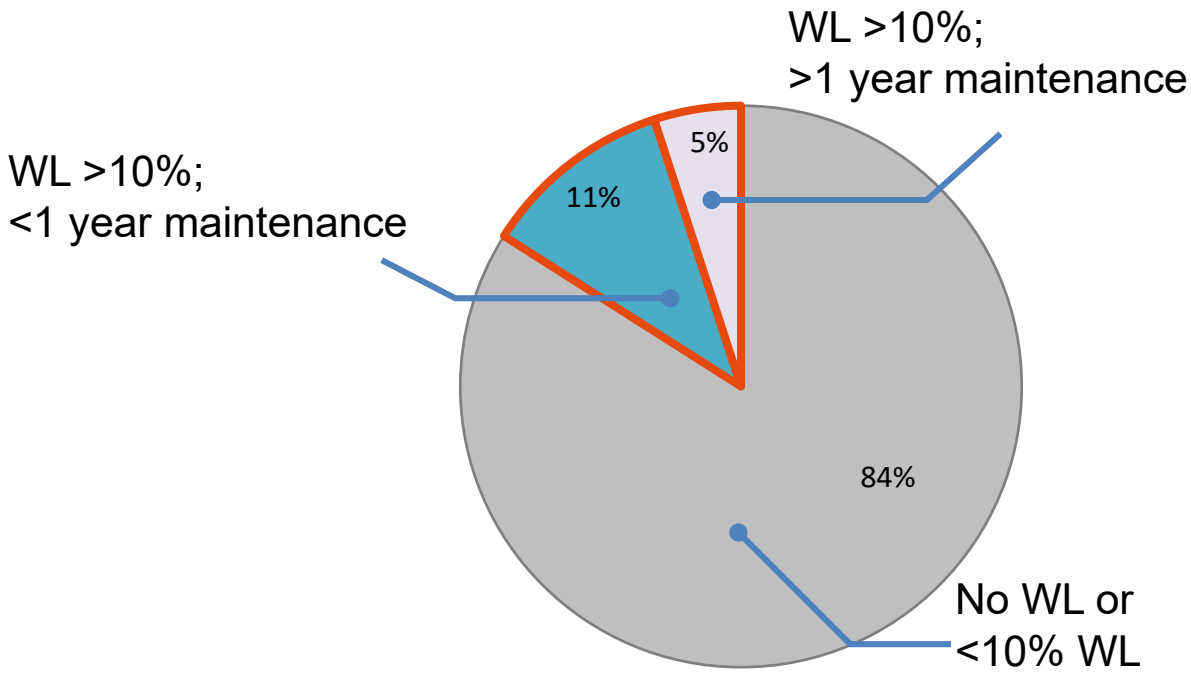
Why Pharmacotherapy ?

Weight loss outcomes

Extent and maintenance of weight loss in last 3 years at threshold of 5%



Extent and maintenance of weight loss in last 3 years at threshold of 10%



n=14,502.
PwO, people with obesity; WL, weight loss.
Caterson ID et al. *Diabetes Obes Metab*. 2019.

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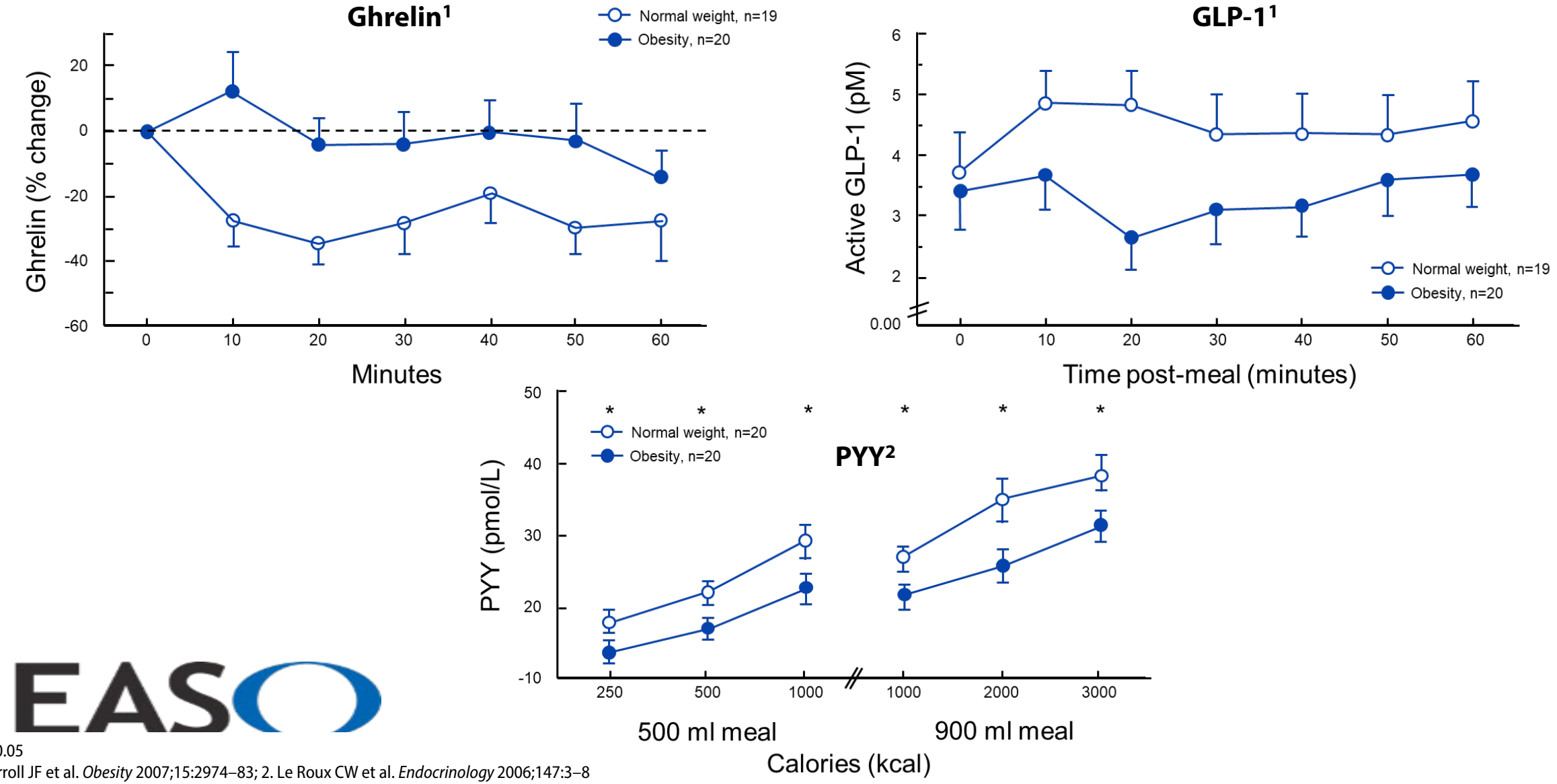
Ghrelin, GLP-1 and PYY in Patients with Obesity Following a Meal

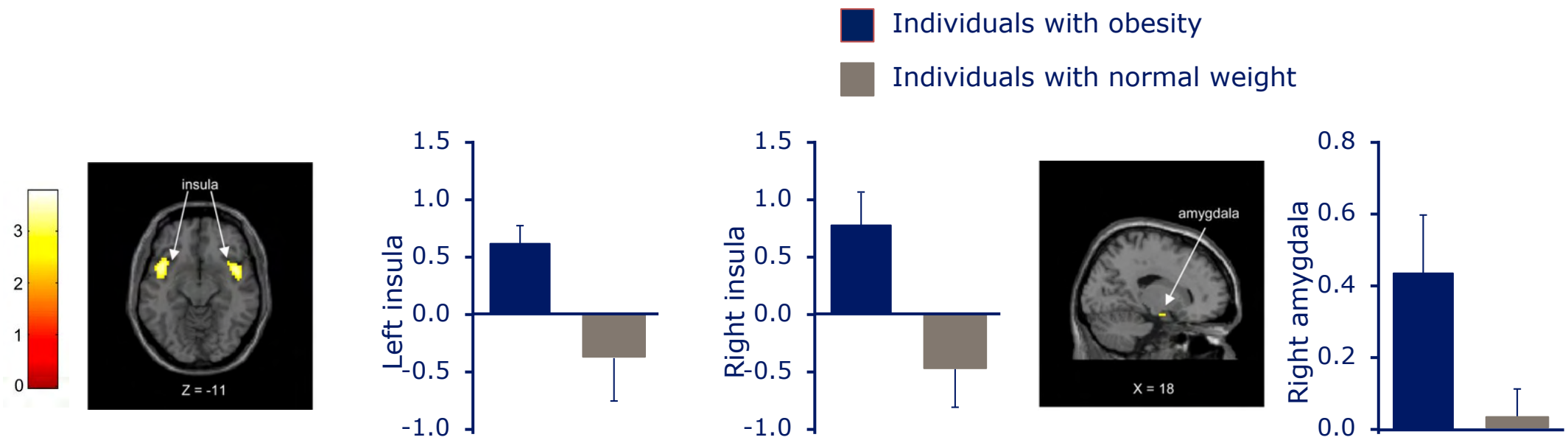


*p <0.05

1. Carroll JF et al. *Obesity* 2007;15:2974–83; 2. Le Roux CW et al. *Endocrinology* 2006;147:3–8

Appetite centre activation is increased in obesity

- Individuals with obesity showed increased brain responses to food pictures in appetite- and reward-related brain regions (insula and amygdala) versus controls



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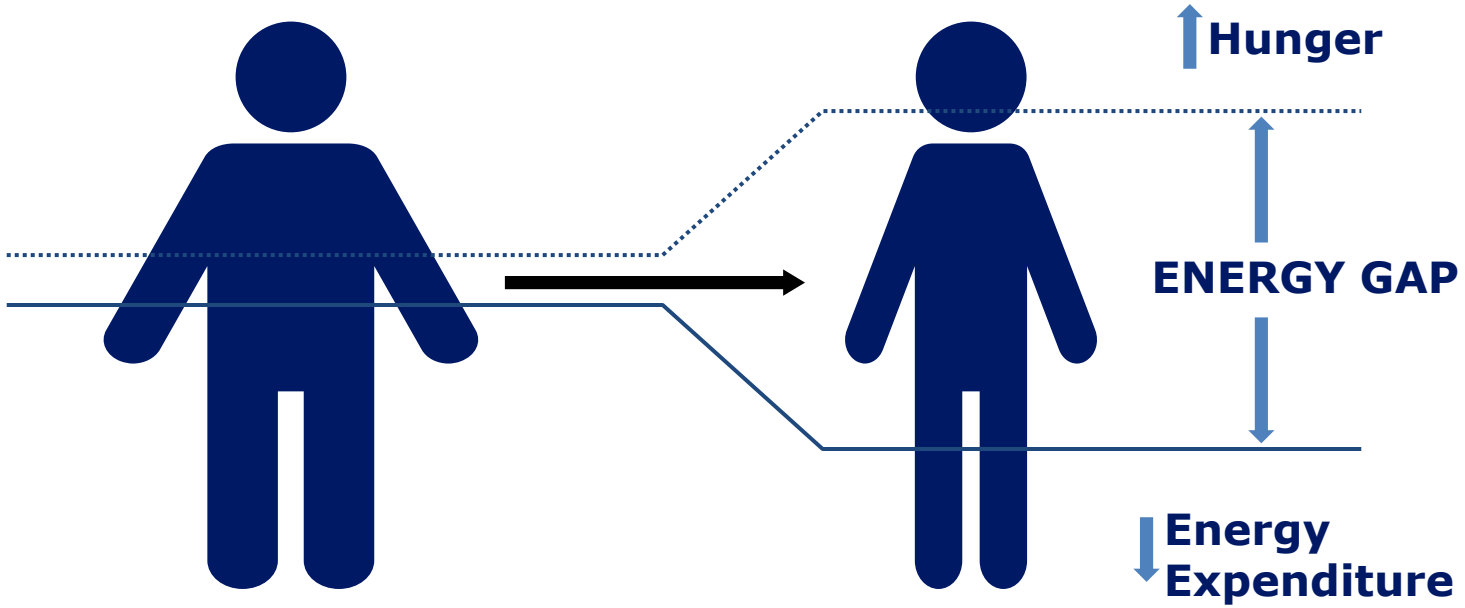
Z is the MNI space Z coordinate of the axial slice and X is the Montreal Neurological Institute space X coordinate of the sagittal slice. The color scale reflects the T value of the functional activity. Results are presented at a threshold of $p<0.05$, family-wise error corrected on the basis of cluster extent. In the graphs on the right, the BOLD signal intensity (effect size) for each group is plotted (arbitrary units), mean and SEM

van Bloemendaal *et al. Diabetes.* 2014;63:4186-96

Metabolic adaptation to a reduced body weight in obesity



↑ Ghrelin
↓ PYY
↓ CCK
↓GLP-1
↓Insulin
↓Leptin
→ ↑Hunger, ↓Satiety, ↓Satiation

↓ SNS Activity
↓ Body Mass
↓ Leptin
↑ Energy Efficiency
→ ↓TDEE, ↓TEF, ↓RMR, ↓PAEE

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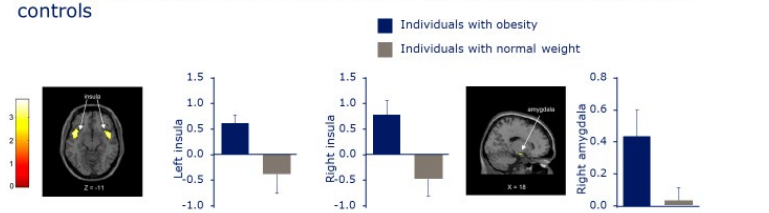
Melby *et al. Nutrients* 2017; 9(5)

The neuro-hormonal actors involved in energy homeostasis

Appetite centre activation is increased in obesity

- Individuals with obesity showed increased brain responses to food pictures in appetite- and reward-related brain regions (insula and amygdala) versus controls



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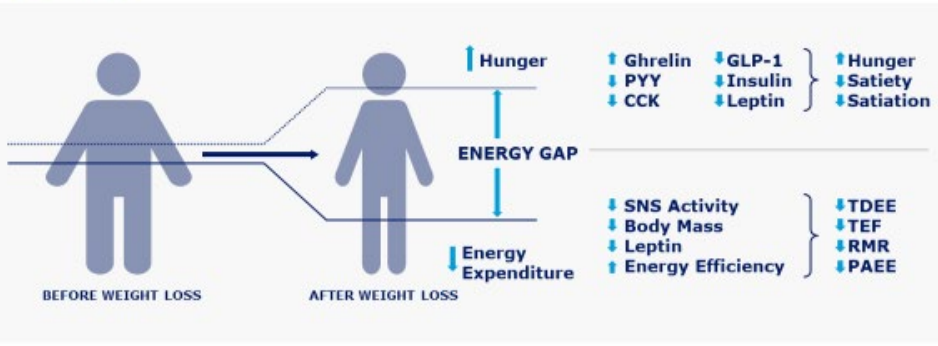
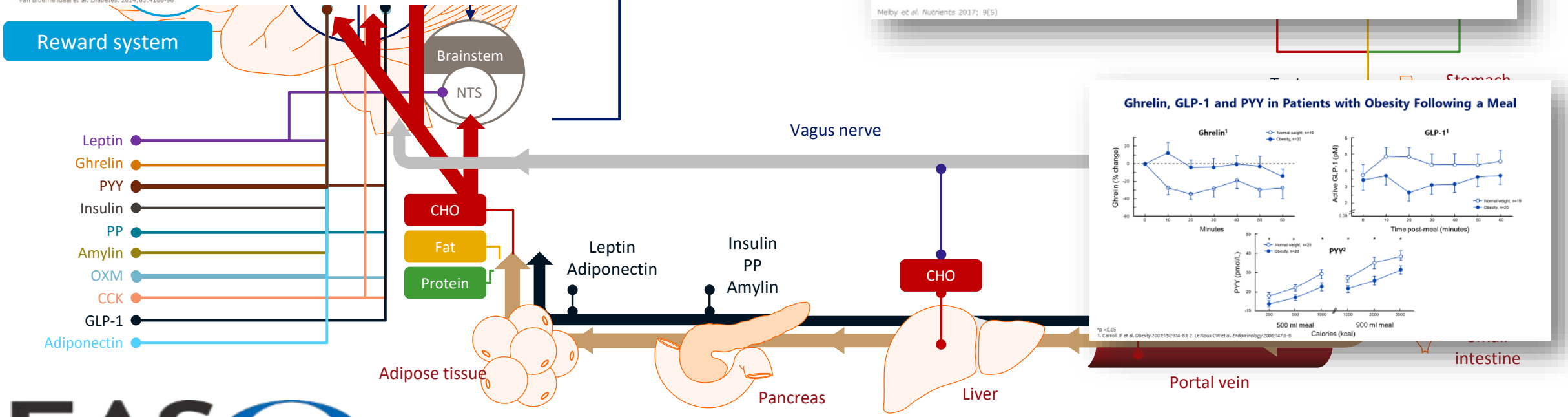


CCK, cholecystokinin; GLP-1, glucagon-like peptide -1; PYY, YY peptide; PAEE, physical activity energy expenditure; RMR, resting metabolic rate; SNS, systemic nervous system; TDEE, total daily energy expenditure; TEF, thermic effect of food

Melby *et al. Nutrients* 2017; 9(5)

Total energy expend
(REE, TEF, PA)



Ghrelin, GLP-1 and PYY in Patients with Obesity Following a Meal

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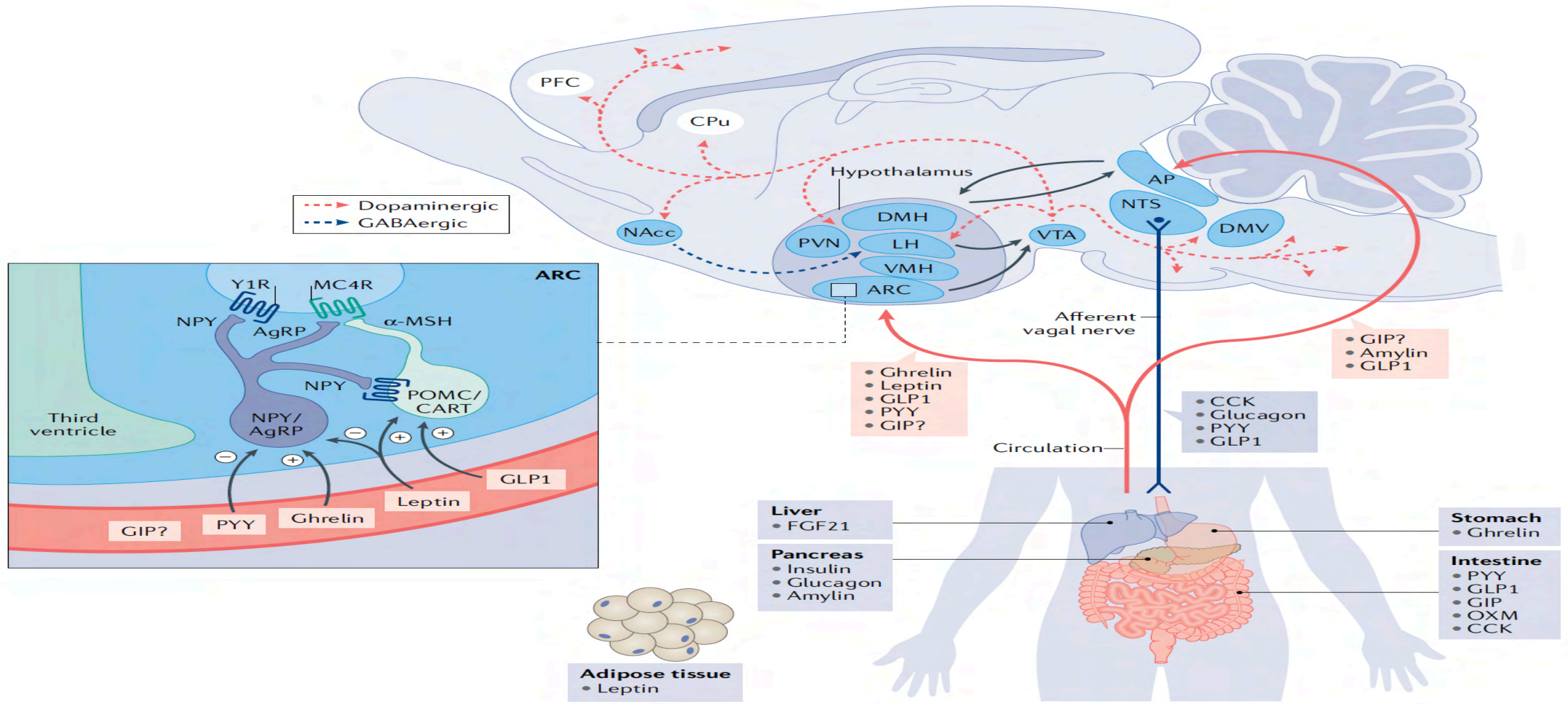
Gut–brain regulation of food intake



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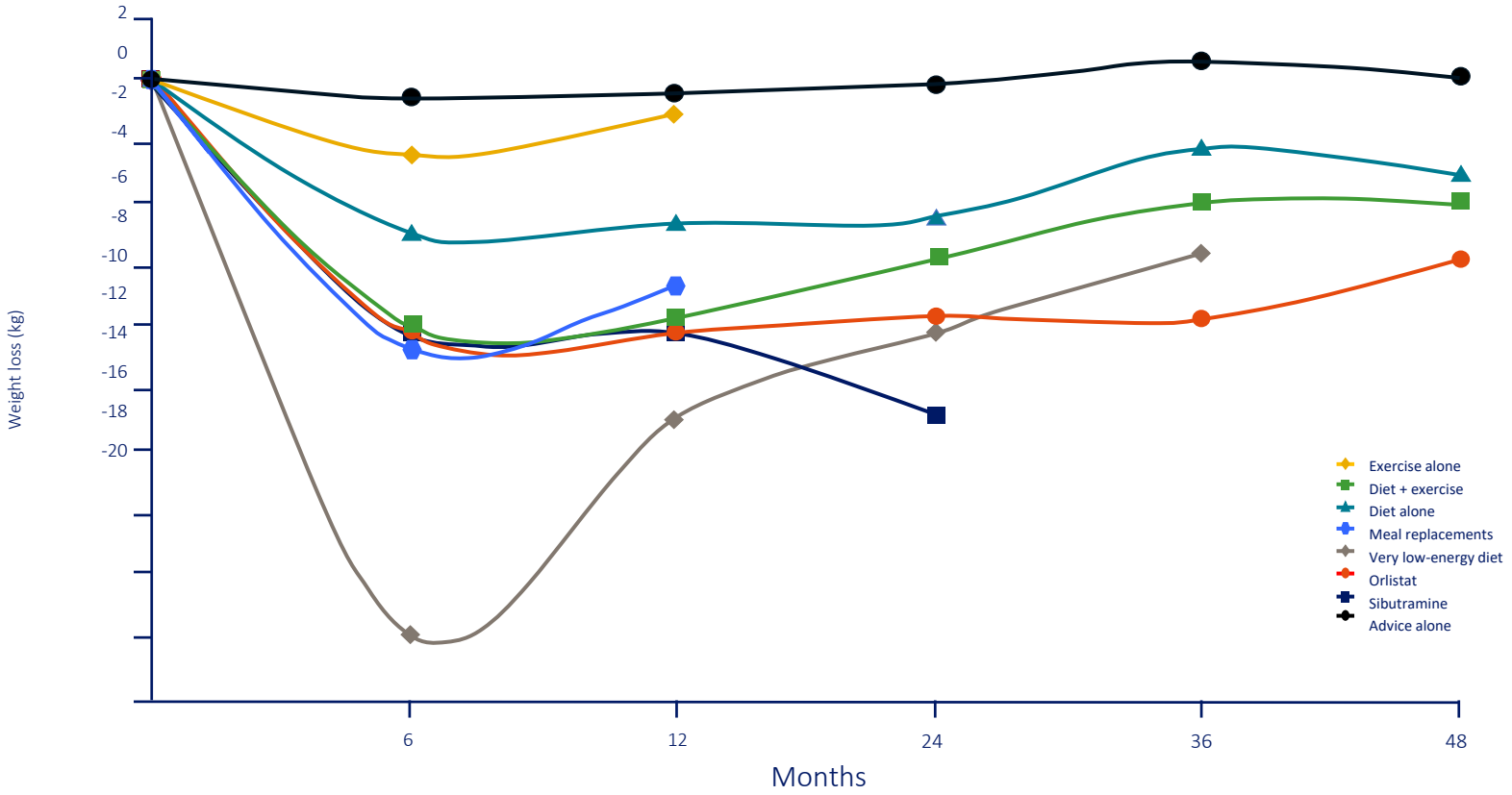
Müller TD, Nature Reviews 2022

Meta-analysis of non-surgical trials with1-year follow-up



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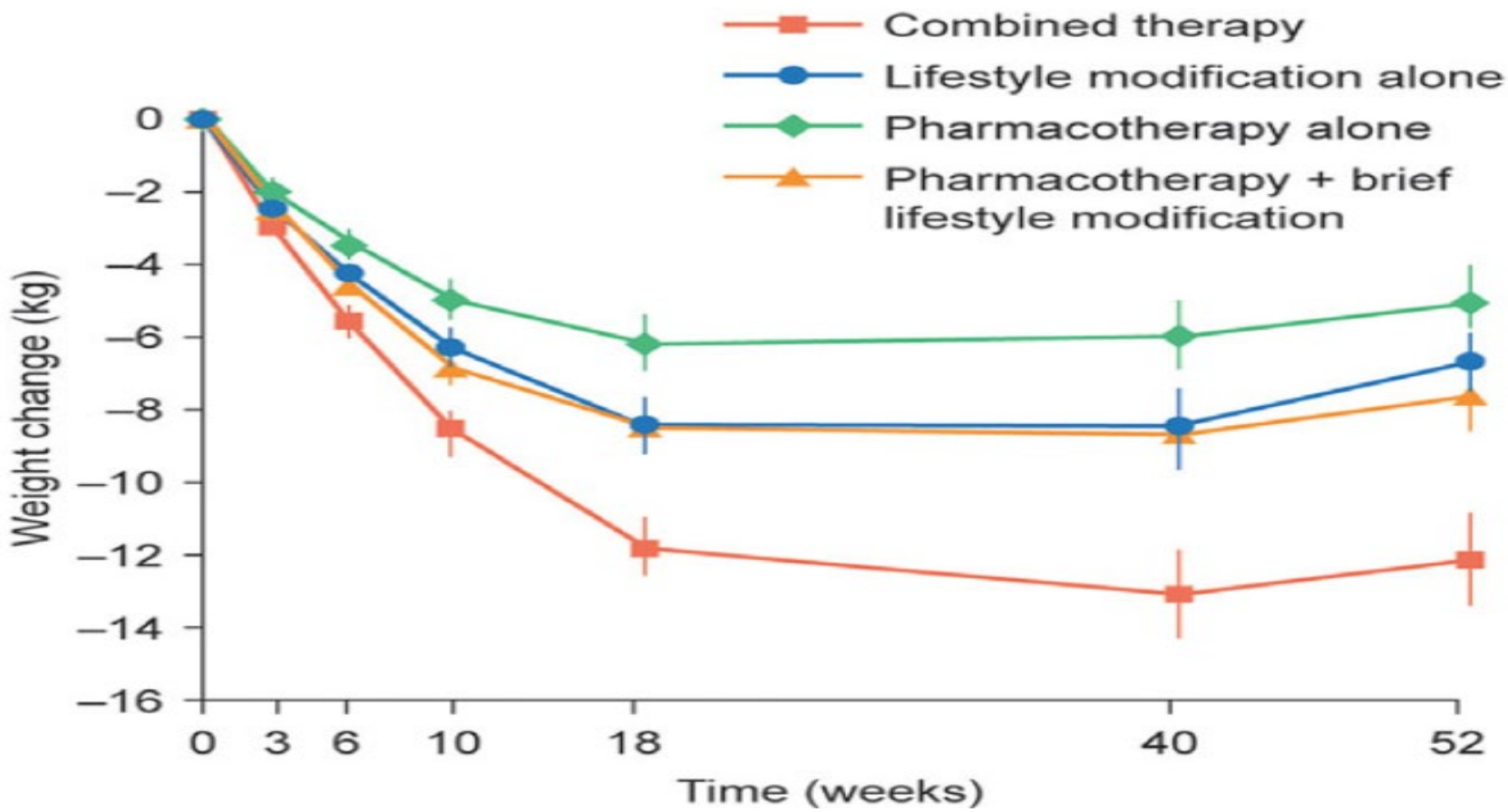
Weight change in response to lifestyle and pharmacotherapy modifications



Wadden et al, NEJM 2005

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Pharmacotherapy in Europe ?

Pharmacological options for weight management

	Orlistat[1]	Naltrexone/ bupropion[2,3]	Liraglutide 3.0 mg[4]	Phentermine/ topiramate[5] 3.75 mg/23 mg & 15 mg/92 mg	Semaglutide 2.4 mg[6]
MoA	Energy wastage	Appetite suppressant	Appetite suppressant	Appetite suppressant	Appetite regulation
Weight loss	Baseline to 1 year: Intervention 10.6 kg Placebo: 6.2 kg	Baseline to week 56: Intervention 5.4%/8.1%* Placebo: 1.3%/4.9%*	Baseline to week 56: Intervention 8.0% Placebo 2.6%	Baseline to week 56: Intervention 5.1%/10.9%† Placebo 1.6%	Baseline to week 68: Intervention 14.9% Placebo 2.4%
Effect on CV morbidity/mortality	Improvements in CV risk factors: blood pressure and serum lipid levels	Not established	Safety data from Victoza® CVOT LEADER has been added to label	Not established	Not established
Dosing	Thrice daily	Twice daily, oral	Daily injection	Once daily, oral	Once weekly injection
Most common AEs (>5%)	Oily spotting, flatus with discharge, fecal urgency fatty/oily stool, oily evacuation, increased defecation and fecal incontinence	Nausea, constipation, headache, vomiting, dizziness, insomnia, dry mouth, diarrhoea	Nausea, hypoglycaemia, diarrhoea, constipation, vomiting, headache, dyspepsia, fatigue, dizziness, abdominal pain	Paraesthesia, dizziness, dysgeusia, insomnia, constipation, dry mouth	Nausea, diarrhoea, constipation, vomiting, abdominal pain, headache, fatigue, dyspepsia, dizziness, abdominal distension, eructation, hypoglycaemia, flatulence, gastroenteritis

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*Data from the phase 3 Contrave obesity research I and II studies, respectively; †Data are for 3.75 mg/23 mg and 15 mg/92 mg doses of phentermine/topiramate respectively.
AE, adverse event; CV, cardiovascular; CVOT, cardiovascular outcome trial; GLP-1, glucagon-like peptide-1; 5-HT, 5-hydroxytryptamine; MoA, mechanism of action.

1. Torgerson J. S., et al. Diabetes care 2004;27:155-61; 2. Greenway F. L., et al. Lancet 2010;376:595-605; 3. Apovian C., et al. Obesity 2013;21:935-43; 4. Pi-Sunyer, X., et al. N Engl J Med 2015;373:11-22; 5. Allison D. B., et al. Obesity 2012;20:330-42; 6. Wilding J. H., et al. N Engl J Med 2021; 384:989-1002.

Regulatory requirements

FDA (weight management)[1] Draft 2007	**EMA-CHMP (weight control)[2]** 2016
Population: • Significant risk for weight-related morbidity and mortality • BMI ≥30 kg/m^2, or • BMI ≥27 kg/m^2 + comorbidities • T2D, HTN, DL, OSA, CVD	**Population:** • Significant health risk/risk of increased mortality • BMI ≥30 kg/m^2, or • BMI ≥27 kg/m^2 + weight-related risk factors • Ensure relevant proportions of Class II/III obesity and coexisting cardiovascular risk factors
Size/duration (safety): • n≥3000 (active), n≥1500 (placebo) • 1 year	**Size/duration:** • Not defined • 1 year
Efficacy benchmarks: • Placebo-adjusted mean WL ≥5%, or • ≥35% achieving ≥5% WL + twice that of placebo	**Efficacy benchmarks:** • Mean WL 5–10%, and ≥5% higher than placebo • Percentage of subjects with >10% WL

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1. FDA. Guidance for Industry Developing Products for Weight Management. Available here;
2. EMA. Guideline on clinical evaluation of medicinal products used in weight management. Available here

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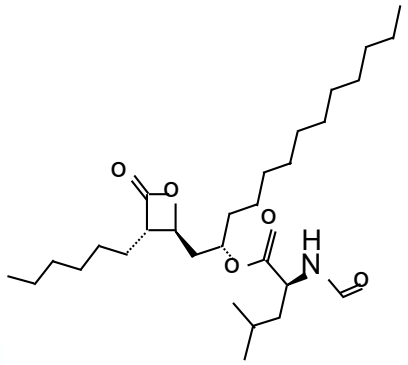
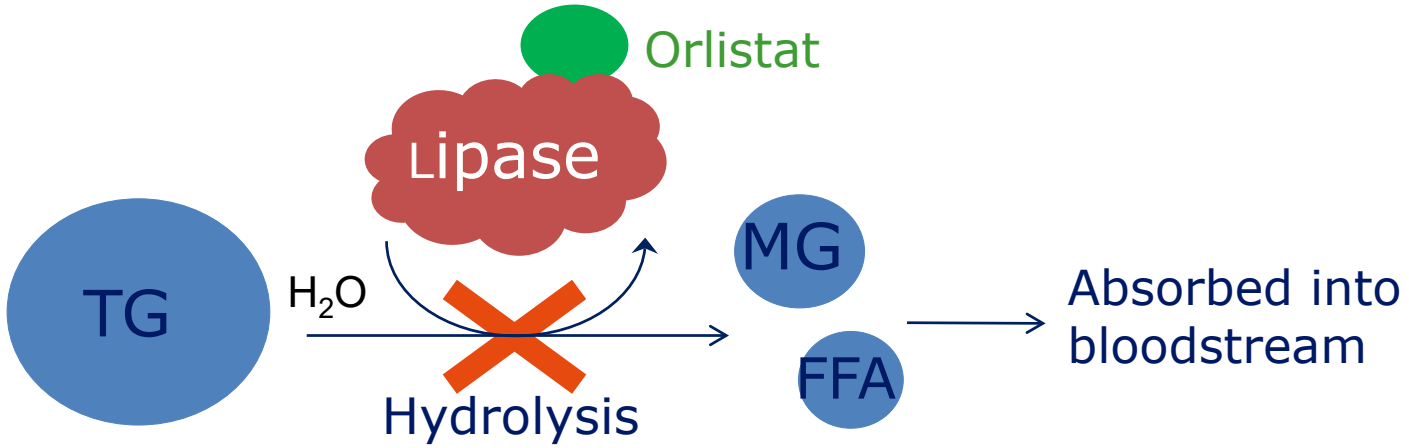


Orlistat

Xenical®/Alli™

Orlistat: mechanism of action

- Lipase enzyme inhibition
  - Covalently binds the serine residue of the active site of gastric and pancreatic lipases, irreversibly inactivating up to 91.4% of these enzymes
  - Partially inhibits hydrolysis of triglycerides, reducing subsequent absorption of monoglycerides and FFAs



FFA, free fatty acid; MG, monoglycerides; TG, triglycerides

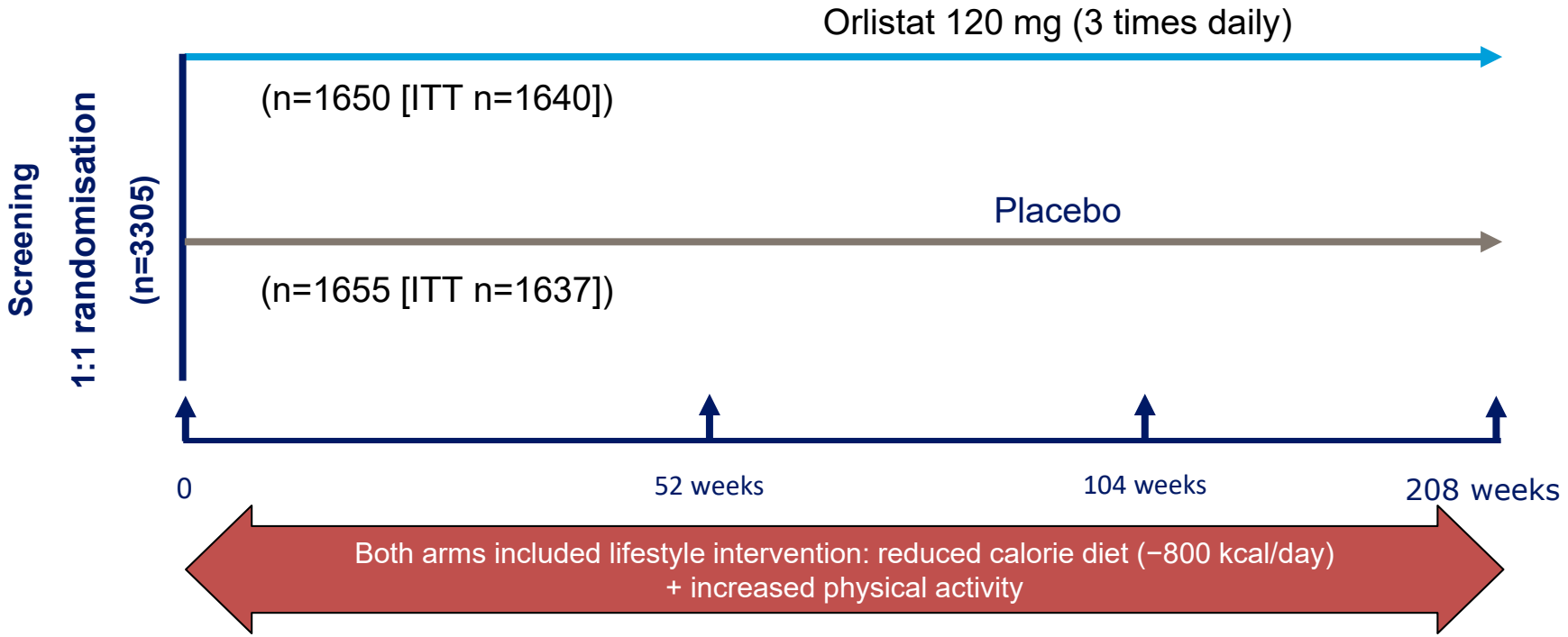
FDA. Xenical® (Orlistat) prescribing information. Click here.

XENDOS: trial design

- **Study objective**:
  - To assess the effects of orlistat on time to onset of type 2 diabetes and change in body weight after 4 years of treatment

Key inclusion criteria

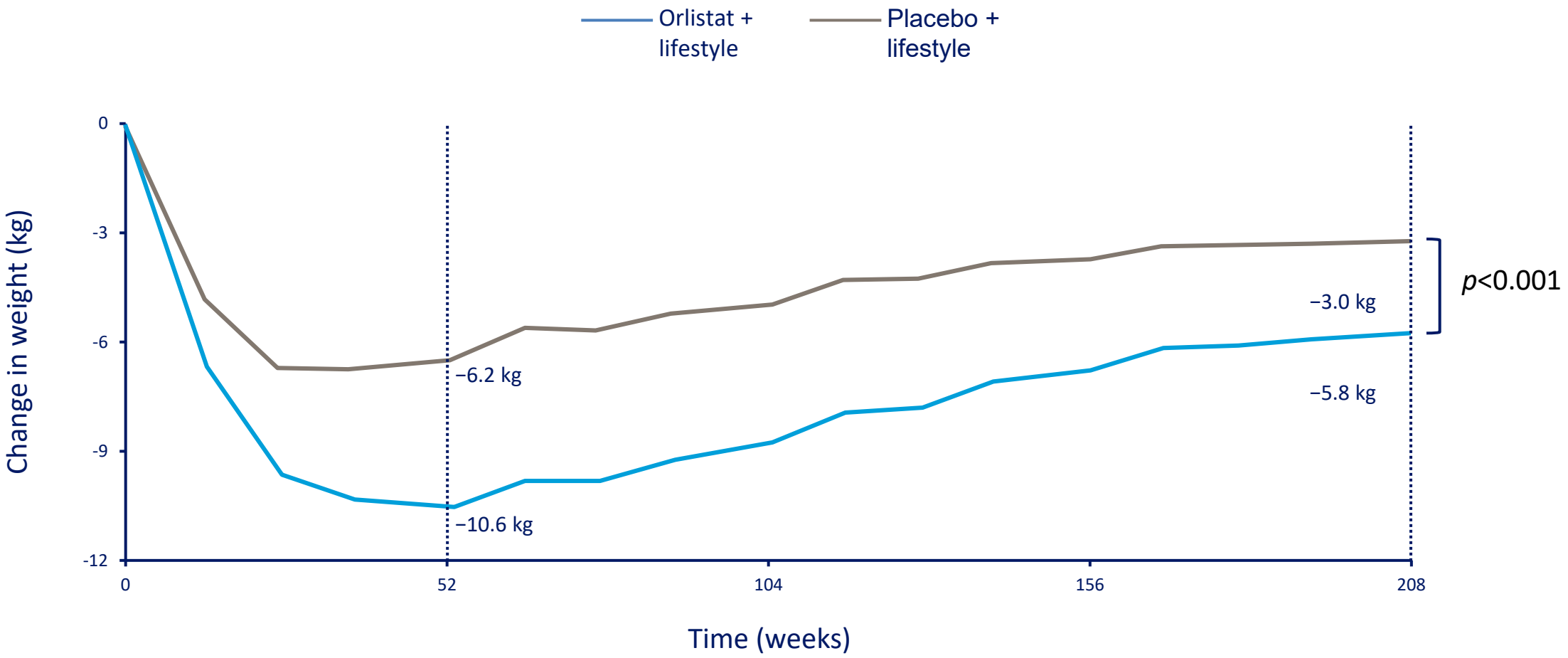
- 30–60 years old
- BMI ≥30.0 kg/m^2
- Patients without diabetes (based on 75-g OGTT at baseline)



ITT, intention to treat; OGTT, oral glucose tolerance test; XENDOS, XENical in the Prevention of Diabetes in Obese Subjects

Torgerson *et al*. *Diabetes Care* 2004;27:155–61

XENDOS: change in weight over time



Baseline: weight, 110.5 kg; BMI, 37 kg/m2. XENDOS, XENical in the Prevention of Diabetes in Obese Subjects

Torgerson *et al*. *Diabetes Care* 2004;27:155–61

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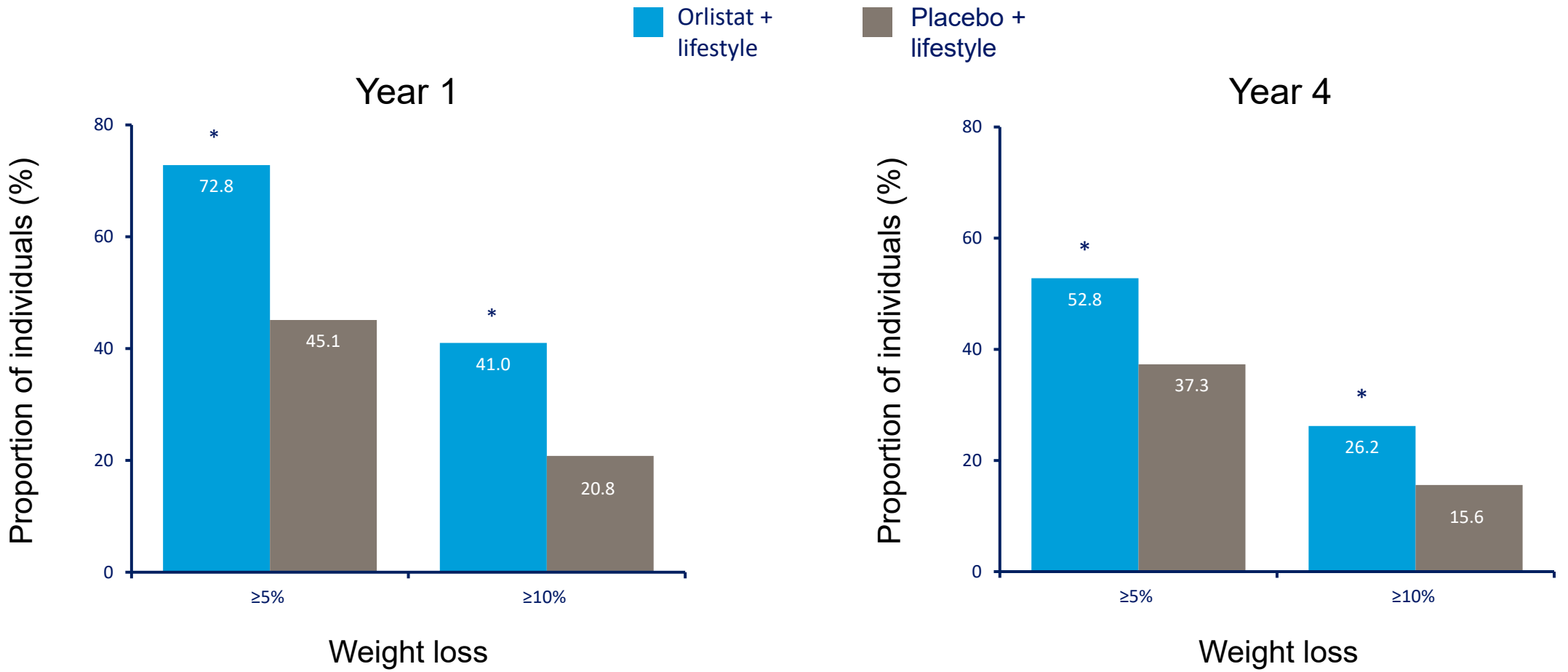
XENDOS: categorical weight loss

Year 1 and Year 4



*p<0.001 vs. placebo
XENDOS, XENical in the Prevention of Diabetes in Obese Subjects

Torgerson *et al*. *Diabetes Care* 2004;27:155–61

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Orlistat: contraindications and warnings

- Contraindications to use:
  - Pregnancy/Breast-feeding
  - Cholestasis
  - Chronic malabsorption syndrome
  - Known hypersensitivity
  - Safety/efficacy in children under 12 years and geriatric populations not established

Stopping rule

Not specified in the US prescribing information and EU summary of product information

- Warnings and precautions:
  - Patients should be encouraged to take a multi-vitamin supplement of fat-soluble vitamins
  - Orlistat and cyclosporine should not be simultaneously co-administered

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FDA. Xenical® (Orlistat) prescribing information. Click here. EMA. Xenical® (Orlistat) Summary of product information. Click here.

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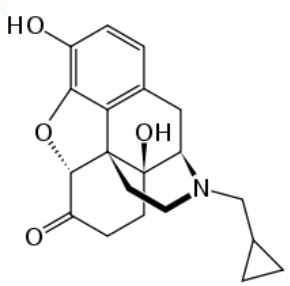
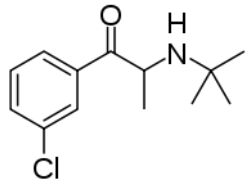


Naltrexone



Bupropion

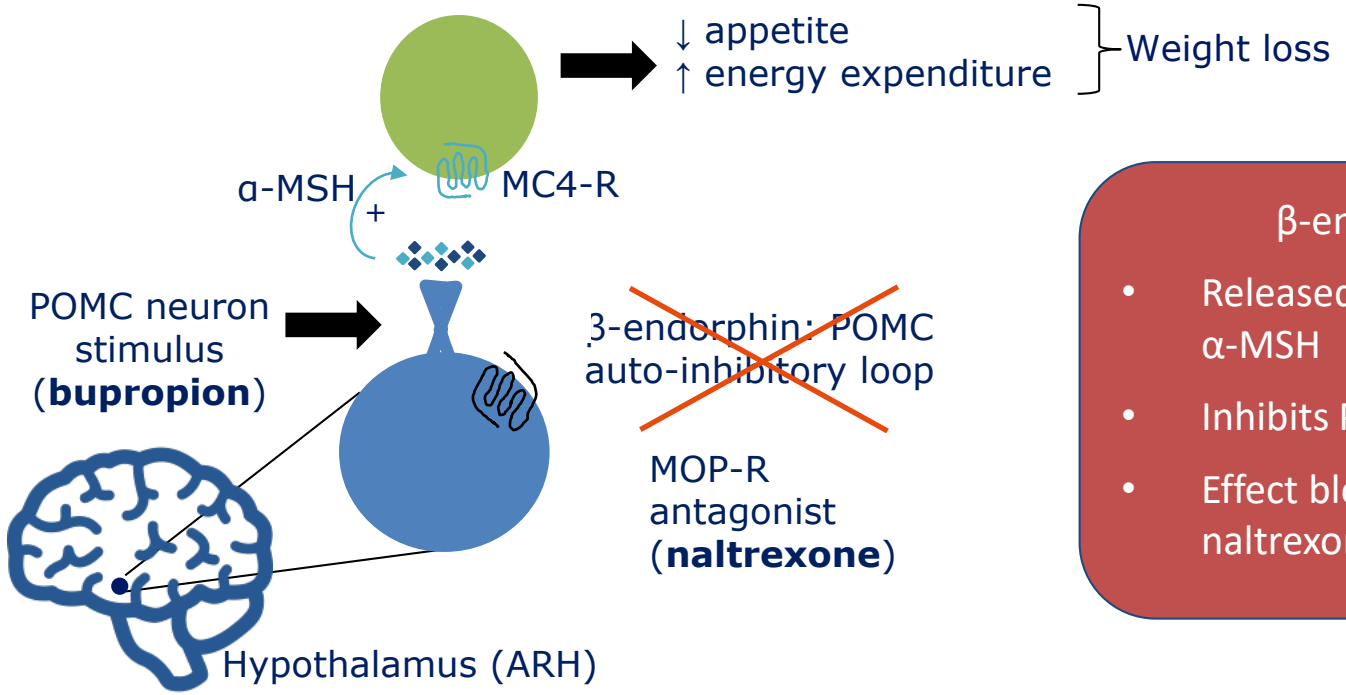
Naltrexone–bupropion

Contrave®

Mysimba®

Naltrexone–bupropion: mechanism of action

- The NB combination synergistically impacts on two different pathways associated with increased energy expenditure and reduced energy intake:



POMC:

- Satiety signal
- Increased firing leads to weight loss
- Activated by bupropion

β-endorphin:

- Released with α-MSH
- Inhibits POMC firing
- Effect blocked by naltrexone

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ARH, arcuate nucleus of the hypothalamus; α-MSH, alpha-melanocyte stimulating hormone; MC4-R, melanocortin-4 receptor; MOP-R, μ-opioid peptide receptor; MSH, melanocyte-stimulating hormone; NB, naltrexone–bupropion; POMC, pro-opiomelanocortin

Ornellas, Chavez. *P.T.* 2011;36:255–62; Padwal. *Curr Opin Investig Drugs* 2009;10:1117–25

Orlistat: in clinical use

- Dosage and administration
  - 1 x 120 mg oral capsule taken three times daily with each main meal containing fat

Prescription drug (120 mg)

OTC drug (60 mg)

- Therapeutic indication
  - Indicated for adults and adolescents in conjunction with a reduced-calorie diet for the treatment of individuals with BMI ≥30 kg/m² or ≥27 (US) or ≥28 kg/m² (EU) with one or more comorbidities (e.g. hypertension, diabetes, dyslipidaemia)
- Regulatory status
  - Approved in the US (for individuals >12 years old only) and the EU

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OTC, over the counter

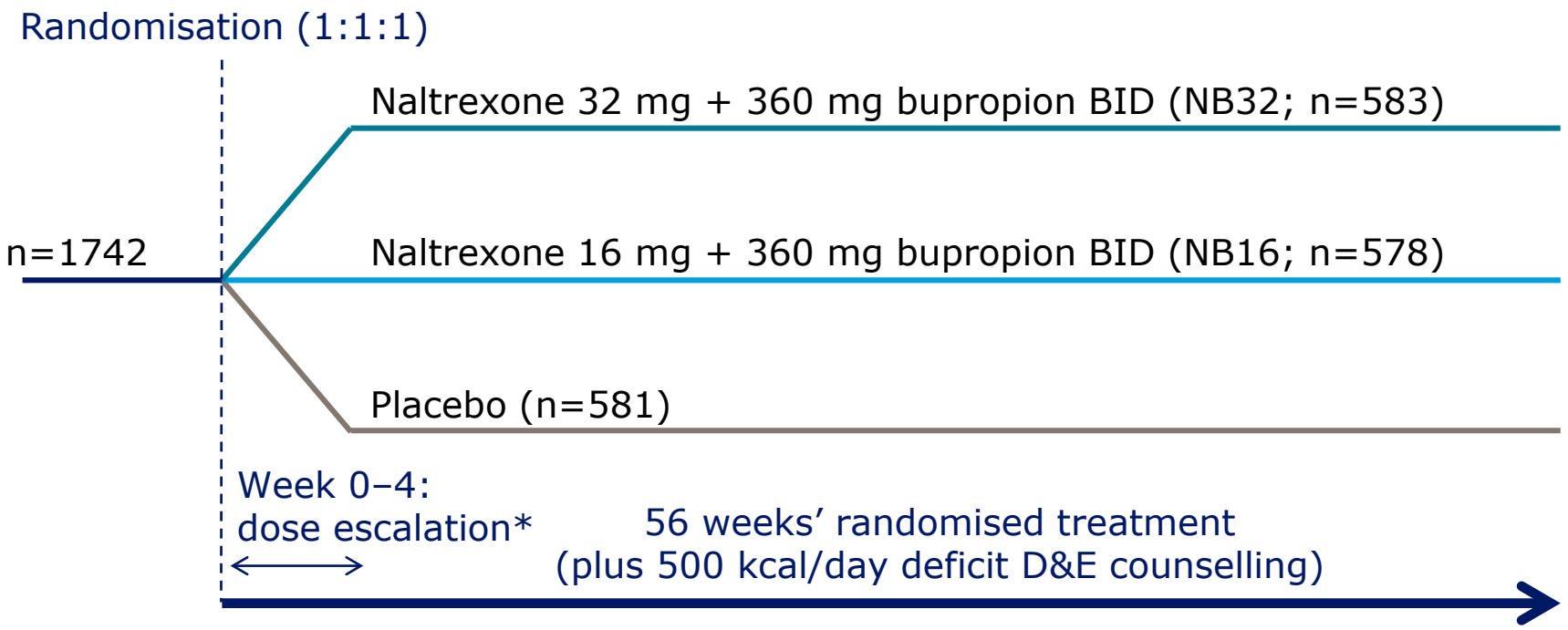
FDA. Xenical® (Orlistat) prescribing information. Click here. EMA. Xenical® (Orlistat) Summary of product information. Click here.

COR-I: study aims and design

Aim: to evaluate the efficacy and safety of sustained-release naltrexone plus bupropion (NB) on weight loss in individuals with overweight or obesity

Inclusion criteria
- Aged 18–65 years
- BMI 30–45 kg/m^2 or 27–45 kg/m^2 with hypertension and/or dyslipidaemia

Exclusion criteria
- Diabetes
- Obesity of endocrine origin
- CV/hepatic/renal disease
- Previous bariatric surgery
- Seizures/psychiatric illness
- Recent weight change ±4 kg
- Previous use of bupropion or naltrexone
- Recent drug/alcohol misuse



*3-week dose escalation, starting with a quarter of full dose, increasing weekly until full dose reached at week 4
BID, twice daily; COR, Contrave® Obesity Research; CV, cardiovascular; D&E, diet and exercise

Greenway *et al. Lancet* 2010;376:595–605

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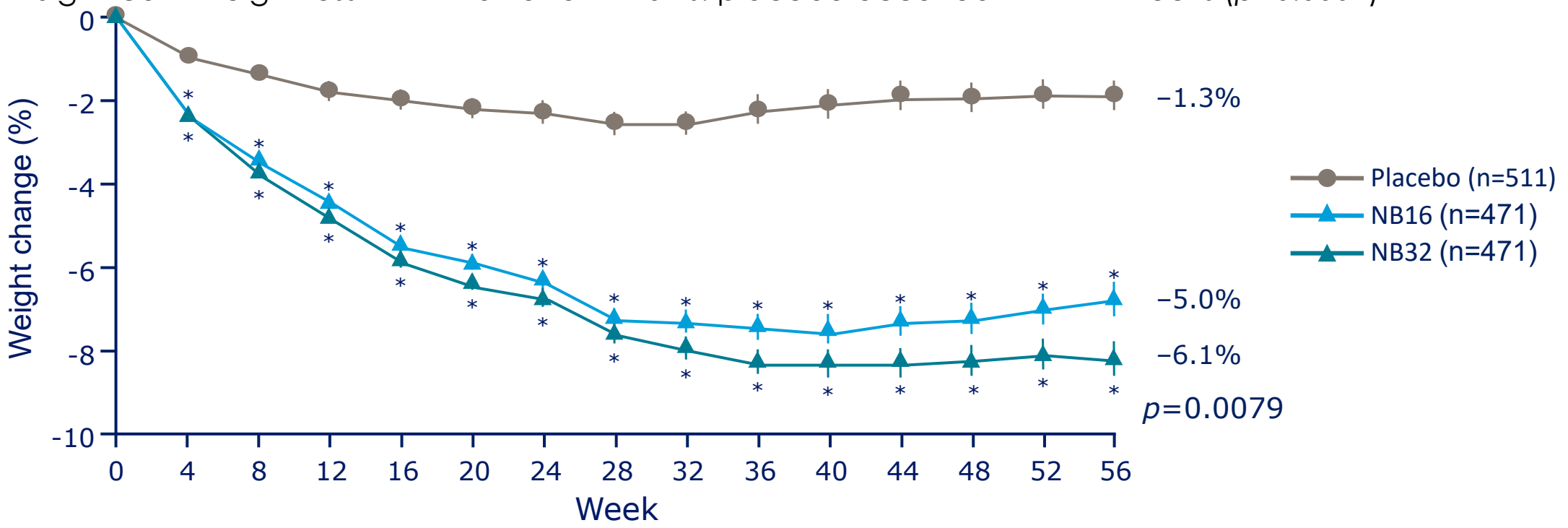
COR-I: weight loss from baseline over 56 weeks

- Significant weight loss with NB32 and NB16 vs. placebo occurred within 4 weeks ($p<0.0001$)



*$p<0.0001$ vs. placebo. Data are least square means (±SE) percentage change from baseline, ITT-LOCF. COR, Contrave® Obesity Research; ITT, intention to treat; LOCF, last observation carried forward; NB16, naltrexone 16 mg/360 mg bupropion; NB32, naltrexone 32 mg/bupropion 360 mg; SE, standard error

Greenway *et al. Lancet* 2010;376:595–605

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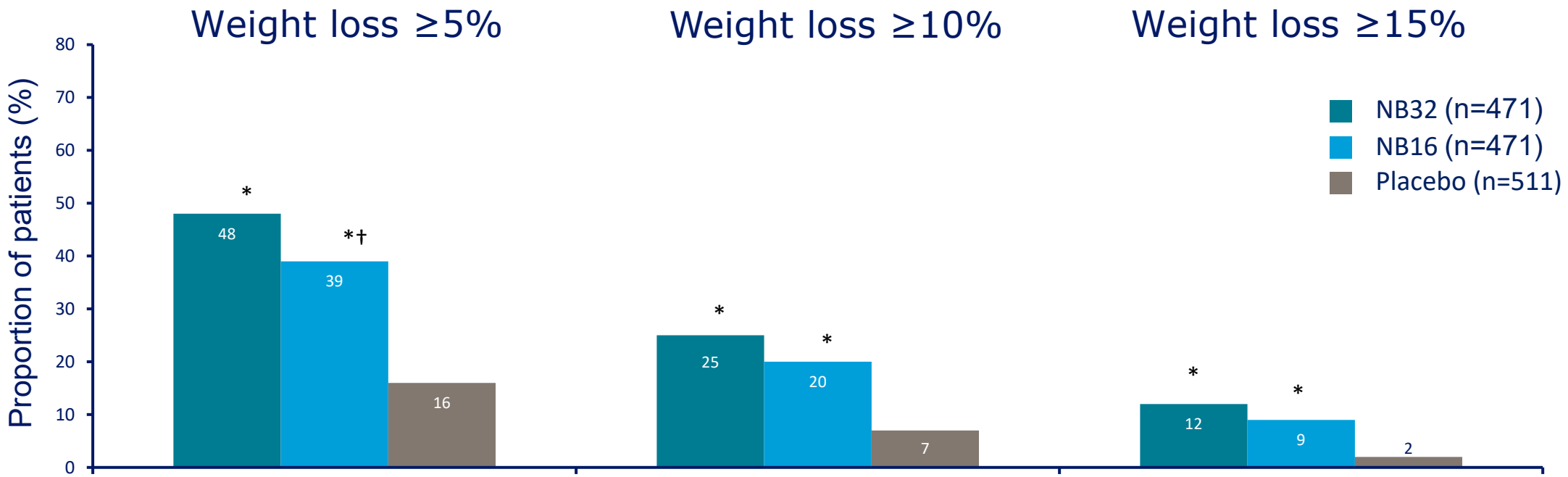
COR-I: categorical weight loss achievers

At 56 weeks (ITT)

- A significantly greater proportion of subjects lost ≥5% body weight with NB32 compared with NB16 (48% vs. 39%; *p*=0.0099)



*p<0.0001 vs. placebo, †p=0.0099 for NB32 vs. NB16. Data are ITT-LOCF. COR, Contrave® Obesity Research; ITT, intent to treat; LOCF, last observation carried forward; NB16, naltrexone 16 mg/360 mg bupropion; NB32, naltrexone 32 mg/bupropion 360 mg

Greenway *et al. Lancet* 2010;376:595–605

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Naltrexone–bupropion: safety summary

- Common (≥5%) and severe (≥0.4%) AEs, such as nausea, constipation and vomiting, were more frequent with NB32 than with placebo
  - Small placebo-adjusted increases in SBP (+1.5 mmHg), DBP (+1.2 mmHg) and heart rate (+1–3 bpm) were observed
    - NB32 appears to attenuate blood pressure and heart-rate reductions normally seen with weight loss
- Increased overall psychiatric (18% vs. 13%) and nervous system (34% vs. 19%) AEs were observed with NB32 when compared with placebo, respectively
  - Anxiety (6.6% vs. 4.4%), sleep disorders (11.4% vs. 7.1%), insomnia (9.2% vs. 5.9%), dizziness (9.9% vs. 3.4%) and headache (17.6% vs. 10.4%) were all more common with NB32 than with placebo, respectively
- Small mean increases in serum creatinine were reported with NB32 treatment

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AE, adverse event; bpm, beats per minute; DBP, diastolic blood pressure; NB32, naltrexone 32 mg/bupropion 360 mg; SBP, systolic blood pressure

Contrave® Advisory Committee Briefing Document http://www.fda.gov/

Naltrexone–bupropion: contraindications and warnings

- Contraindications to use:
  - Uncontrolled hypertension
  - Current seizure disorder or a history of seizures
  - Pregnancy
  - During abrupt cessation of alcohol, benzodiazepines, barbiturates, or antiepileptic drugs
  - Chronic opioid use
  - Monoamine oxidase inhibitors use

Stopping rule

Contrave®: evaluate response after 12 weeks at maintenance dosage and discontinue if patient has not lost ≥5% of their initial body weight

Mysimba®: discontinue after 16 weeks if patient has not lost ≥5% of their initial body weight

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FDA. Contrave® (naltrexone–bupropion) prescribing information. Click here; EMA. Mysimba® (naltrexone-bupropion) SmPC. Click here.

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Liraglutide 3.0 mg

Saxenda®

Liraglutide is a once-daily, human GLP-1 analogue

Human endogenous GLP-1

$T_{½}$= ~2 mins

C-16 fatty acid (palmitoyl)

Liraglutide

97% amino acid homology to human GLP-1; improved PK: albumin binding through acylation; heptamer formation

↓

Slow absorption from subcutis
Resistant to DPP-4
Long plasma half-life
($T_{½}$=13 h)

Knudsen *et al. J Med Chem* 2000;43:1664–9; Degn *et al. Diabetes* 2004;53:1187–94

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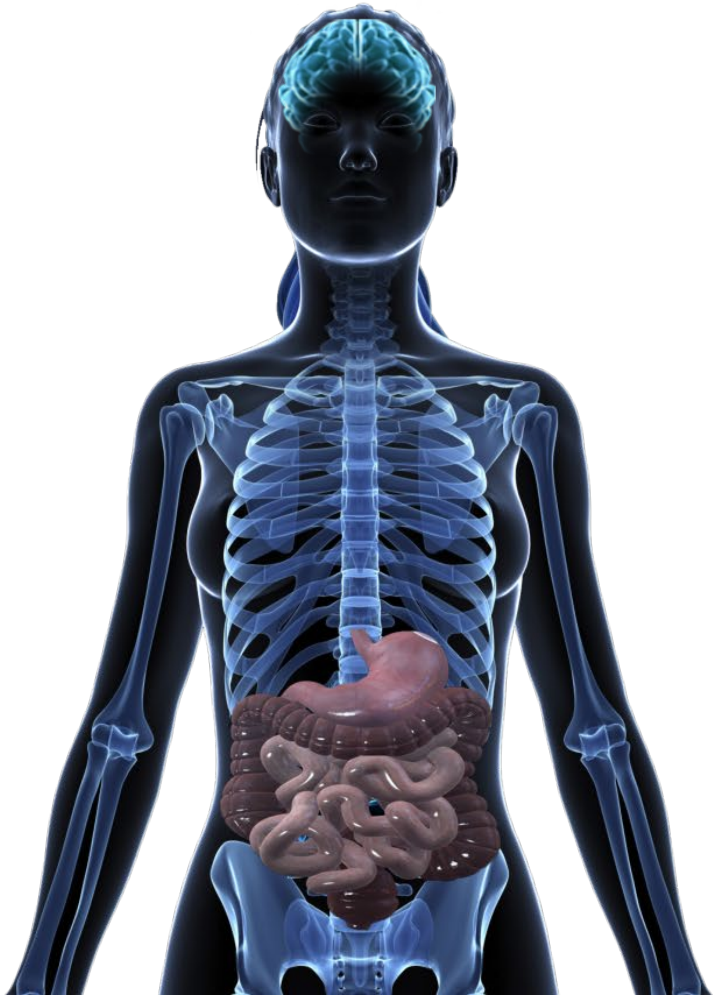
Metabolic and gastric effects of GLP-1

Appetite[1]

- ↑ Satiety
- ↑ Fullness
- ↓ Hunger
- ↓ Prospective food consumption
- ↓ Energy intake



Glucose regulation[2]

(Glucose-dependent)

- ↑ Insulin secretion
- ↓ Glucagon secretion

Gastric effects[3,4]

- ↓ Gastric acid
- ↓ Gastric emptying

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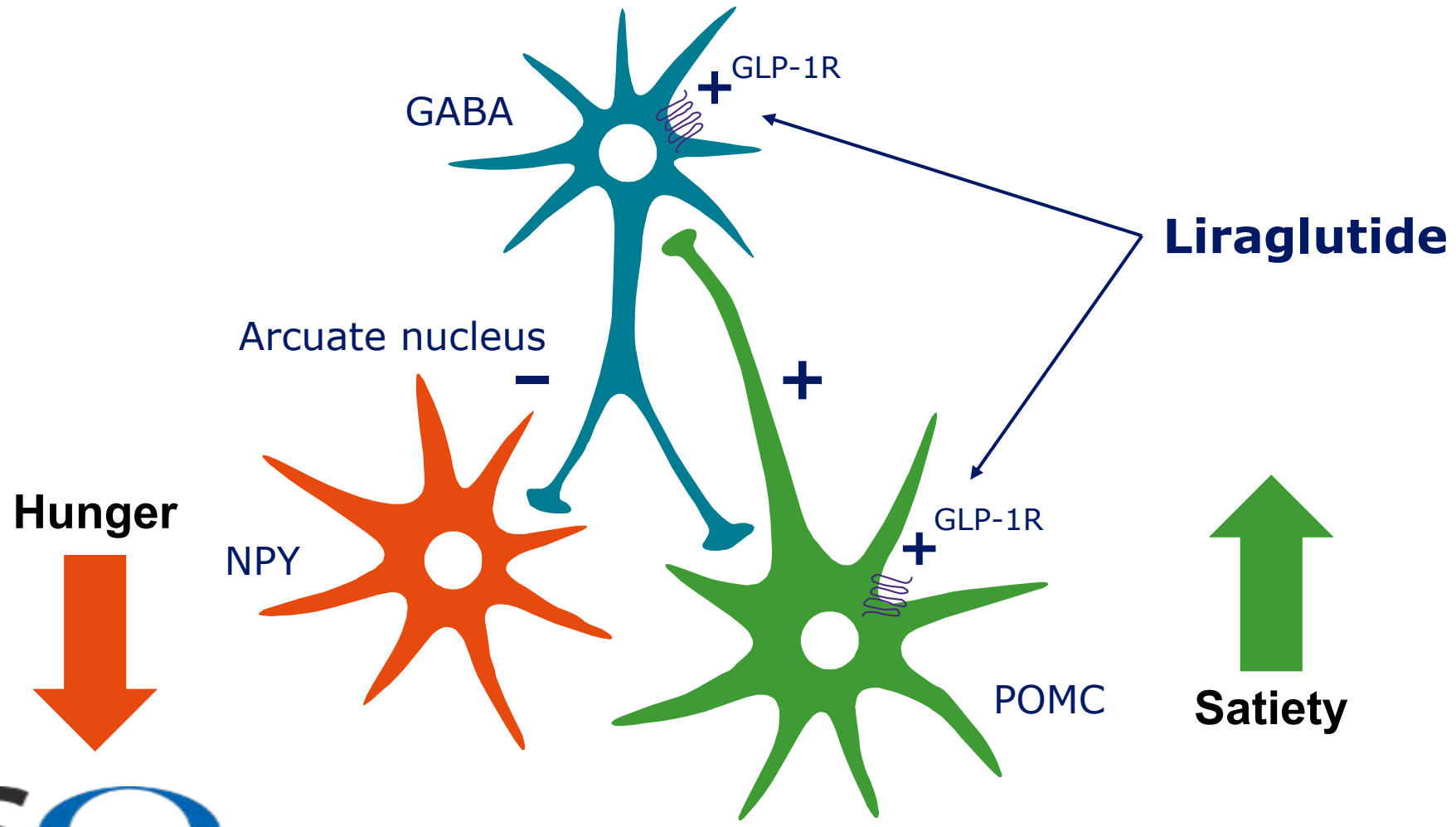
1. Flint *et al. J Clin Invest* 1998;101:515–20; 2. Nauck *et al. Diabetologia* 1993;36:741–4; 3. O'Halloran *et al. J Endocrinol* 1990;126:169–73; 4. Nauck *et al. Am J Physiol* 1997;273:E981–8

POMC/CART and NYP/AgRP neurons may mediate liraglutide-induced weight loss

Proposed mechanism



Secher *et al. J Clin Invest* 2014;124:4473–88

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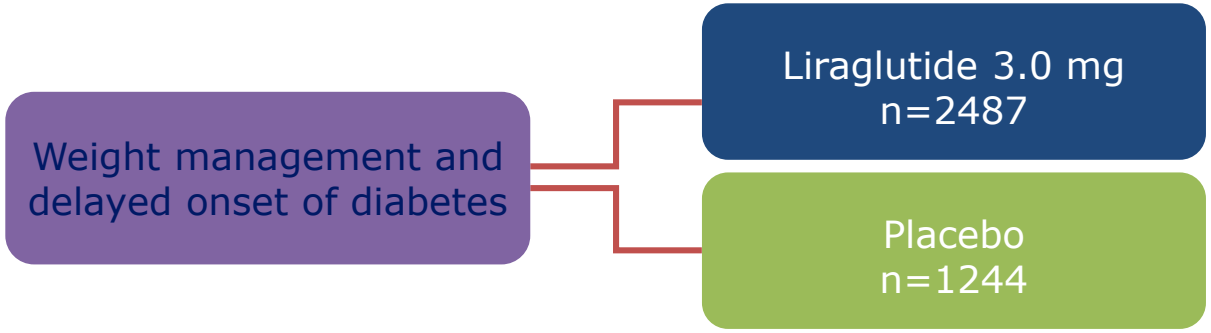
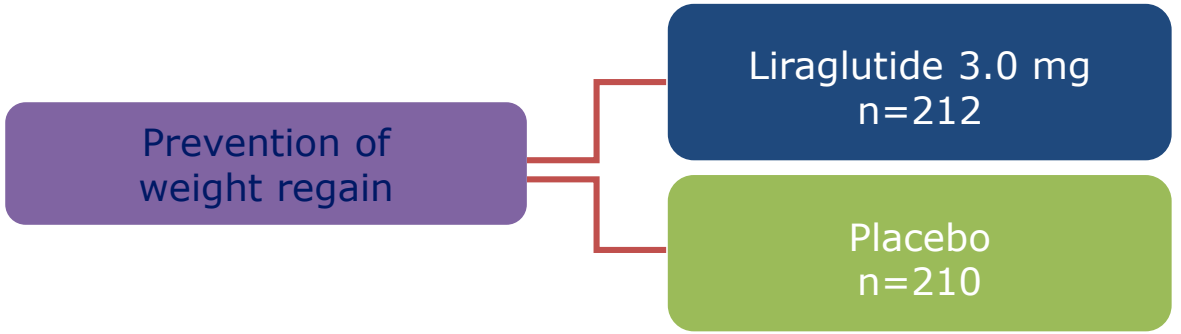
SCALE Phase 3a clinical trial programme

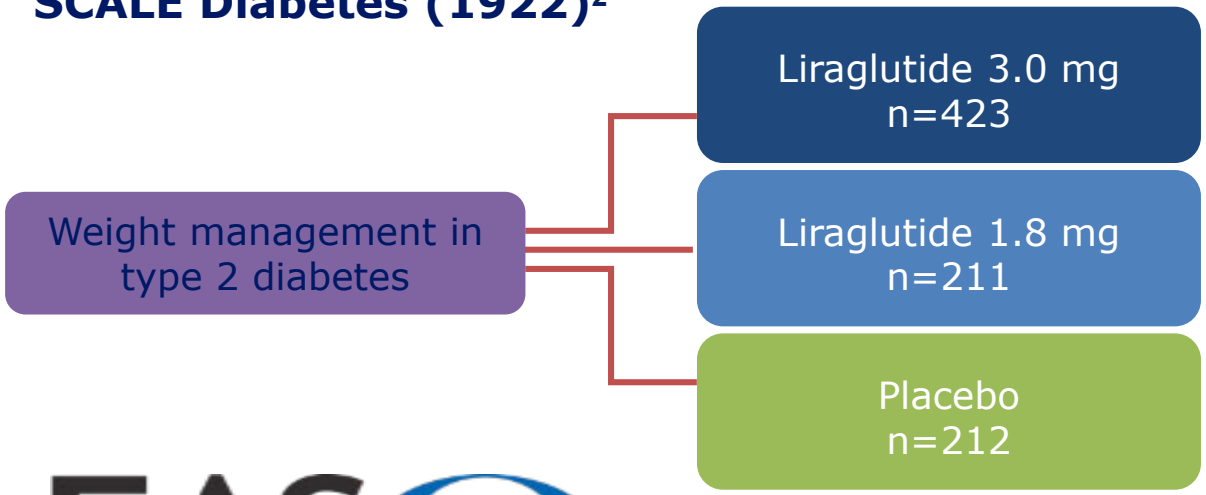
SCALE Obesity and Prediabetes (1839)[1]



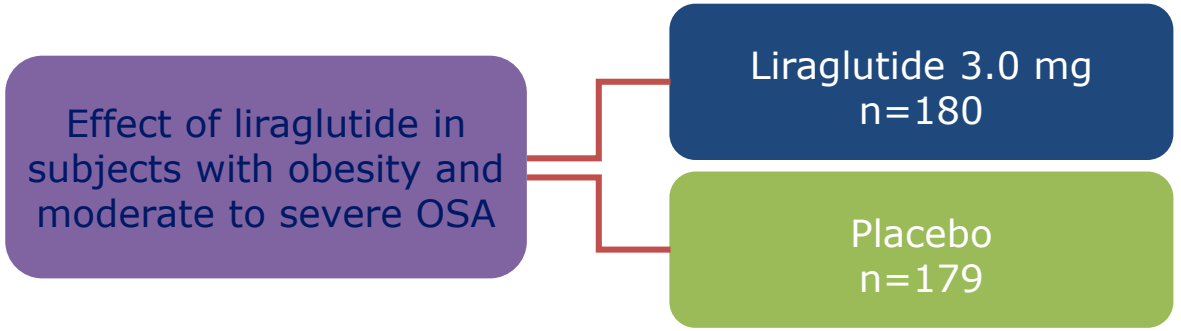
SCALE Maintenance (1923)[3]



SCALE Diabetes (1922)[2]



SCALE Sleep Apnoea (3970)[4]



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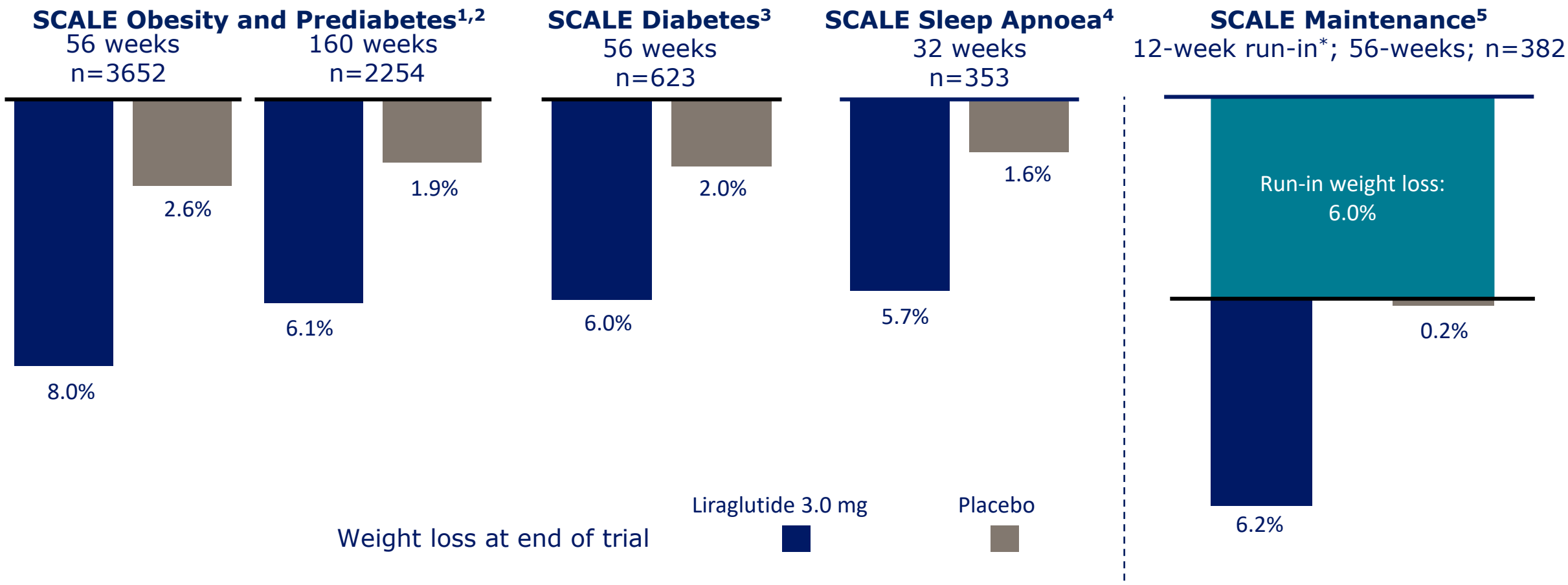
*SCALE, Sleep apnoea 3970 trial BMI ≥30 kg/m^2 plus co-morbidities;
BMI, body mass index; OSA, obstructive sleep apnoea; SCALE, Satiety and Clinical Adiposity – Liraglutide Evidence in individuals with and without diabetes

1. Pi-Sunyer *et al. N Engl J Med* 2015;373:11–22; 2. Davies *et al. JAMA* 2015;314:687–99; 3. Wadden *et al. Int J Obes (Lond)* 2013;37:1443–51;
4. Blackman *et al. Int J Obes (Lond).* 2016;40:1310-9

Weight loss across SCALE 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

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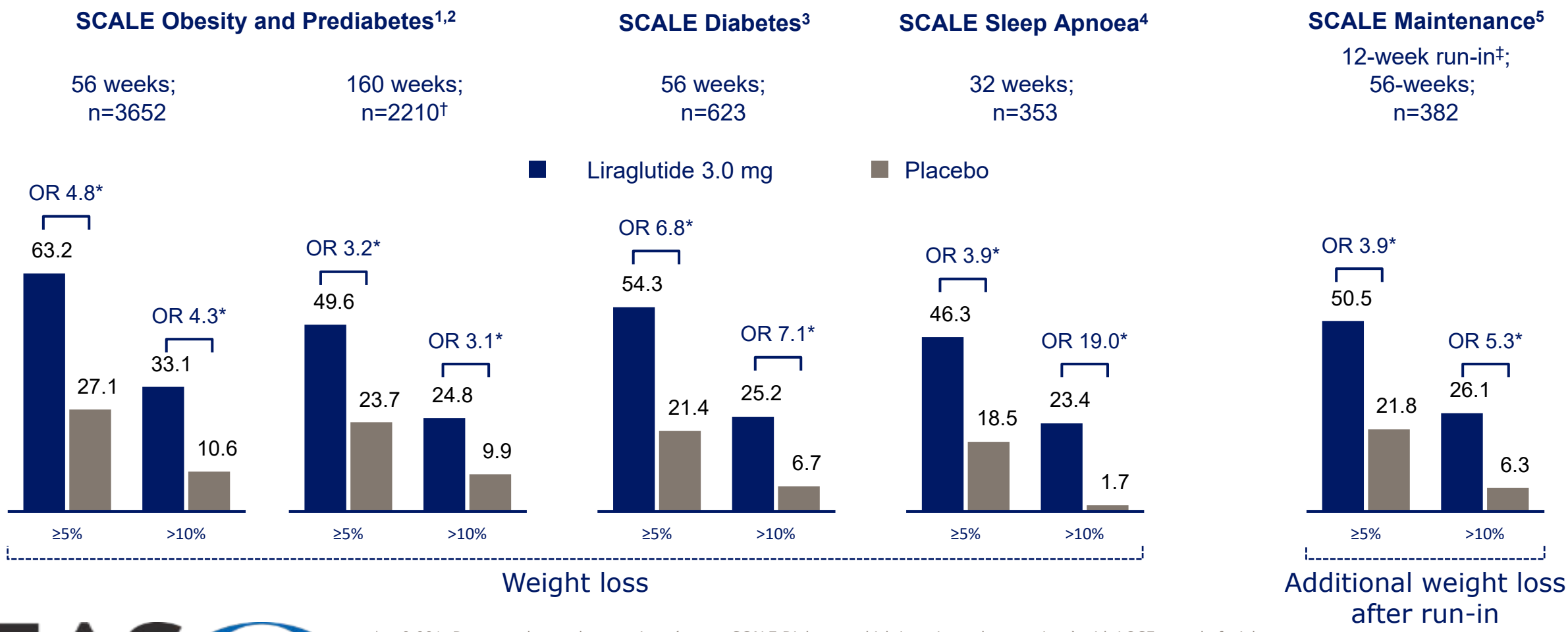
Categorical weight loss across SCALE trials



*p<0.001. Data are observed proportions (except SCALE Diabetes, which is estimated proportions) with LOCF at end of trial;
†, individuals with prediabetes at trial entry; ‡, low calorie diet (total energy intake 1200–1400 kcal/day);
LOCF, last observation carried forward; N, number contributing to the analysis

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

SCALE Efficacy Summary

Key efficacy outcomes with liraglutide 3.0 mg

SCALE Obesity and Prediabetes[1,2]

-9.2%

change in body weight after 1 year

80%

reduction in the risk of T2D over 3 years

SCALE Diabetes[3]

-6.0%

change in body weight after 56 weeks

-1.3%

change in HbA_{1c} from baseline

SCALE Maintenance[4]

81%

maintained ≥5% weight loss after 1 year

6.2%

additional weight loss with liraglutide 3.0 mg*

SCALE Sleep Apnoea[5]

-12.2

events p/h vs. 6.1 with placebo

-5.7%

change in body weight after 32 weeks

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*Following lifestyle intervention induced weight loss of ≥5% over a 12 week run in period

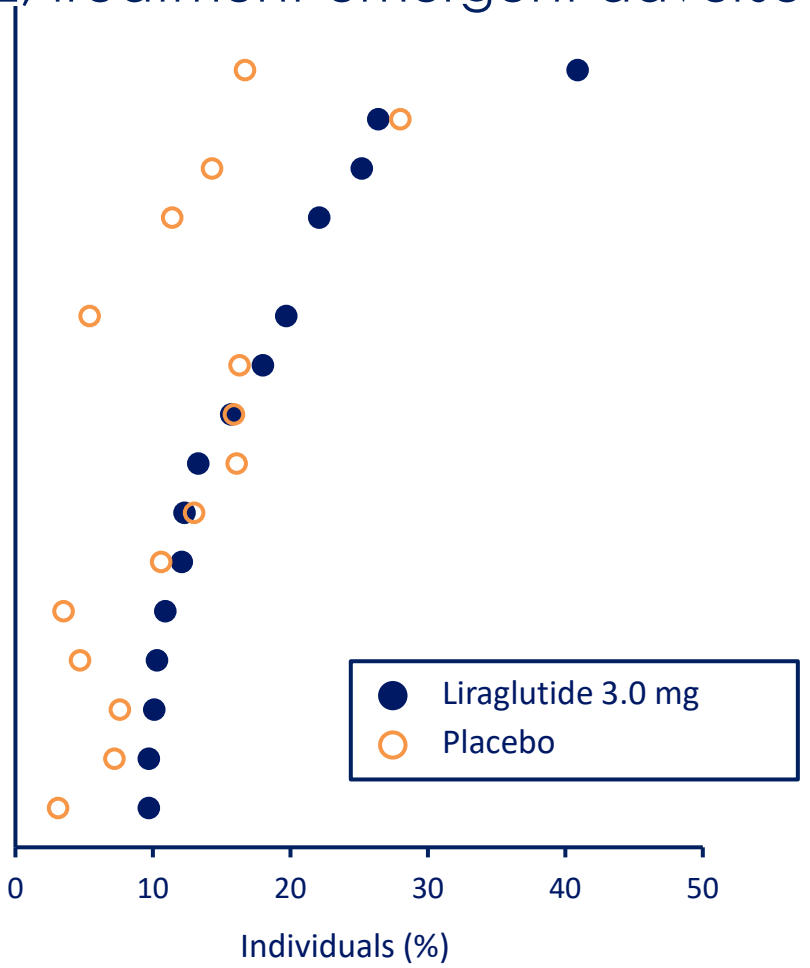
1. Pi-Sunyer *et al*. *N Engl J Med* 2015;373:11–22; 2. le Roux *et al*. *Lancet* 2017;389:1399–409; 3. Davies *et al*. *JAMA* 2015;314:687–99; 4. Wadden *et al*. *Int J Obes (Lond)* 2013;37:1443–51; 5. Blackman *et al*. *Int J Obes (Lond)* 2016;40:1310–19

Adverse events in ≥5% of participants (1/2)

SCALE Obesity and Prediabetes: 0-162 weeks

R, event rate per 100 years of observation time; TEAE, treatment-emergent adverse event le Roux et al. Lancet 2017;389:1399–409

	Liraglutide 3.0 mg		Placebo	
	%	R	%	R
Nausea	40.9	29.9	16.7	11.3
Nasopharyngitis	26.4	23.5	28.0	27.5
Diarrhoea	25.2	19.0	14.3	9.9
Constipation	22.1	13.0	11.4	6.8
Vomiting	19.7	14.7	5.4	3.6
Headache	18.0	13.3	16.3	14.9
Upper respiratory tract infection	15.7	12.1	15.9	14.4
Back pain	13.3	8.9	16.1	11.0
Arthralgia	12.3	7.1	13.0	9.2
Influenza	12.1	7.8	10.6	8.3
Decreased appetite	10.9	5.5	3.5	1.8
Dyspepsia	10.3	6.0	4.7	2.7
Fatigue	10.1	5.8	7.6	4.5
Dizziness	9.7	6.1	7.2	4.9
Lipase increased	9.7	6.5	3.1	1.7



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SCALE Safety Summary

Key safety outcomes with liraglutide 3.0 mg

GI adverse events

93%

of events were mild or moderate[1]

Pancreatitis

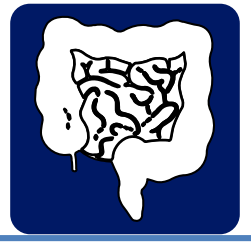
<.01 events

were recorded per individual over 172 weeks[1]

Breast cancer

10 cases

were recorded over 172 weeks[1]



Colon cancer

<.01 events

were reported per individual over 120 weeks[2]

MTC

0 cases

of MTC or confirmed C-cell hyperplasia with liraglutide[1]

MACE

No signal

for increased MACE was observed[2]

Neuro-psychiatric

Similar rates vs. placebo

observed in the SCALE programme[3]

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GI, gastrointestinal; MTC, medullary thyroid carcinoma; ULN, upper limits of normal

1. le Roux *et al*. *Lancet* 2017;389:1399–409; 2. Novo Nordisk Briefing Document: Liraglutide 3.0 mg for weight management NDA 206-321. FDA Endocrinologic and Metabolic Drugs Advisory Committee Meeting. September 11, 2014; 3. O'Neil *et al*. *Diabetes Obes Metab* 2017;19:1529–36

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Future Anti-Obesity Medications

Definition of a Second-generation Obesity Medication

- Ability to safely produce an average of >10% placebo-subtracted weight loss in randomized clinical trials (ie, over that attributable to lifestyle interventions) in the majority of patients

or

- Ability to safely produce a ≥15% weight loss in over half the patients as an adjunct to lifestyle.

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Garvey WT. The Journal of Clinical Endocrinology & Metabolism, 2022

Efficacy of obesity medications in randomized clinical trials

Drug	% Weight loss		% with ≥ 10%		% with ≥ 15%		% with ≥ 20%	
	Drug	Placebo	Drug	Placebo	Drug	Placebo	Drug	Placebo
Orlistat (ref 25)								
XENDOS 1 year	10.6	6.2	41	20.8				
XENDOS 4 year	5.8	3.0	26.2	15.6				
Phentermine/topiramate ER[a] (26-28)								
EQUIP	10.9	1.6	47.2	7.4	32.3	3.4		
CONQUER	9.8	1.2	37.0	7.0				
SEQUEL 2 yr	9.3	1.8	50.3	11.5	24.2	6.6	9.2	2.2
Naltrexone ER/bupropion ER (29-31)								
COR-I	6.1	1.3	25.0	7.0	12	2		
COR-II	6.4	1.2	28.3	5.7	13.5	2.4		
COR-BMOD	9.3	5.1	41.5	20.2	29.1	10.9		
Liraglutide 3 mg (32-34)								
SCALE Maintenance	6.7	0.1	26.1	6.3	11.0	3.1		
SCALE Ob & PreDM 1 year	9.2	3.5	33.1	10.6	14.4	3.5		
SCALE Ob & PreDM 3 year	7.1	2.7	24.8	9.9	11.0	3.1		
Semaglutide 2.4 mg (22-24,35,36)								
STEP 1	14.8	2.4	69.1	12.0	50.5	4.9	32.0	1.7
STEP 3	16.0	5.7	75.3	27.0	55.8	13.2	35.7	3.7
STEP 4	17.4	5.0	79.0	20.4	63.7	9.2	39.6	4.8
STEP 5 2 year	15.2	2.6	61.6	13.3	52.1	7.0	36.1	2.8
STEP 8	15.8	1.9	70.9	15.4	55.6	6.4	38.5	2.6

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Garvey WT. The Journal of Clinical Endocrinology & Metabolism, 2022

Summary of relative effects of weight-lowering drugs on benefit and harm outcomes

	Benefit outcomes		Harm outcomes	
	High or moderate certainty evidence	Low or very low certainty evidence	High or moderate certainty evidence	Low or very low certainty evidence
Among the best	Definitely better than lifestyle modification alone	May be better than lifestyle modification alone	No more harmful than lifestyle modification alone	No more harmful than lifestyle modification alone
Intermediate—possibly better	Possibly better than lifestyle modification alone	Might be better than lifestyle modification alone	More harmful than lifestyle modification alone, but no worse than other interventions	More harmful than lifestyle modification alone, but no worse than other interventions
Intermediate—possibly worse	Possibly no better than lifestyle modification alone	Might be no better than lifestyle modification alone		
Among the worst	Definitely no better than lifestyle modification alone	May be no better than lifestyle modification alone	More harmful than lifestyle modification alone and some other interventions	More harmful than lifestyle modification alone and some other interventions

	Benefit outcomes					Harm outcomes	
	Percentage bodyweight change from baseline, MD (95%)	Participants with bodyweight reduction ≥5%, OR (95% CI)	Participants with bodyweight reduction ≥10%, OR (95% CI)	Quality-of-life score, SMD (95% CI)	Depression symptom score, SMD (95% CI)	Discontinuation due to any adverse event, OR (95% CI)	Total gastrointestinal adverse events, IRR (95% CI)
Phentermine–topiramate	−7·97 (−9·28 to −6·66)	8·02 (5·24 to 12·27)	9·74 (5·95 to 15·94)	0·42 (0·19 to 0·65)	−0·17 (−0·59 to 0·26)	2·40 (1·69 to 3·42)	1·62 (1·13 to 2·31)
GLP-1 receptor agonists	−5·76 (−6·30 to −5·21)	6·33 (5·00 to 8·00)	7·83 (5·89 to 10·40)	0·29 (0·15 to 0·43)	−0·08 (−0·36 to 0·20)	2·17 (1·71 to 2·77)	2·79 (2·42 to 3·23)
Naltrexone–bupropion	−4·11 (−5·19 to −3·02)	5·04 (3·50 to 7·27)	5·19 (3·33 to 8·08)	0·36 (0·18 to 0·54)	0·19 (−0·06 to 0·45)	2·69 (2·11 to 3·43)	3·86 (2·93 to 5·08)
Orlistat	−3·16 (−3·53 to −2·78)	2·73 (2·32 to 3·22)	2·43 (1·94 to 3·04)	0·15 (−0·24 to 0·53)	−0·04 (−0·75 to 0·66)	1·72 (1·44 to 2·05)	2·03 (1·80 to 2·29)
Metformin	−2·50 (−3·25 to −1·74)	2·10 (1·13 to 3·91)	2·11 (0·85 to 5·24)	..	..	1·19 (0·62 to 2·28)	2·05 (1·53 to 2·74)
SGLT2 inhibitors	−2·07 (−3·01 to −1·13)	2·88 (1·69 to 4·90)	0·96 (0·26 to 3·58)	..	..	1·42 (0·82 to 2·46)	0·95 (0·58 to 1·54)
Pramlintide	−2·19 (−4·36 to −0·03)	2·24 (0·97 to 5·14)	3·21 (0·99 to 10·45)	..	..	2·43 (0·46 to 12·79)	1·92 (0·51 to 7·14)
Levocarnitine	−1·88 (−3·80 to 0·04)	..	..	..	..	1·11 (0·60 to 2·08)	1·45 (0·66 to 3·19)
Drug effect for GLP-1 receptor agonists							
Semaglutide	−11·41 (−12·54 to −10·27)	9·82 (7·09 to 13·61)	13·32 (9·94 to 17·83)	0·27 (0·08 to 0·46)	..	1·99 (1·35 to 2·92)	2·79 (2·14 to 3·64)
Liraglutide	−4·68 (−5·30 to −4·06)	4·91 (3·78 to 6·38)	4·80 (3·60 to 6·41)	0·32 (0·08 to 0·56)	−0·08 (−0·36 to 0·20)	2·45 (1·80 to 3·33)	3·10 (2·59 to 3·71)
Exenatide	−3·72 (−4·82 to −2·62)	2·86 (1·27 to 6·47)	3·12 (1·17 to 8·32)	..	..	1·50 (0·66 to 3·44)	1·72 (1·19 to 2·50)

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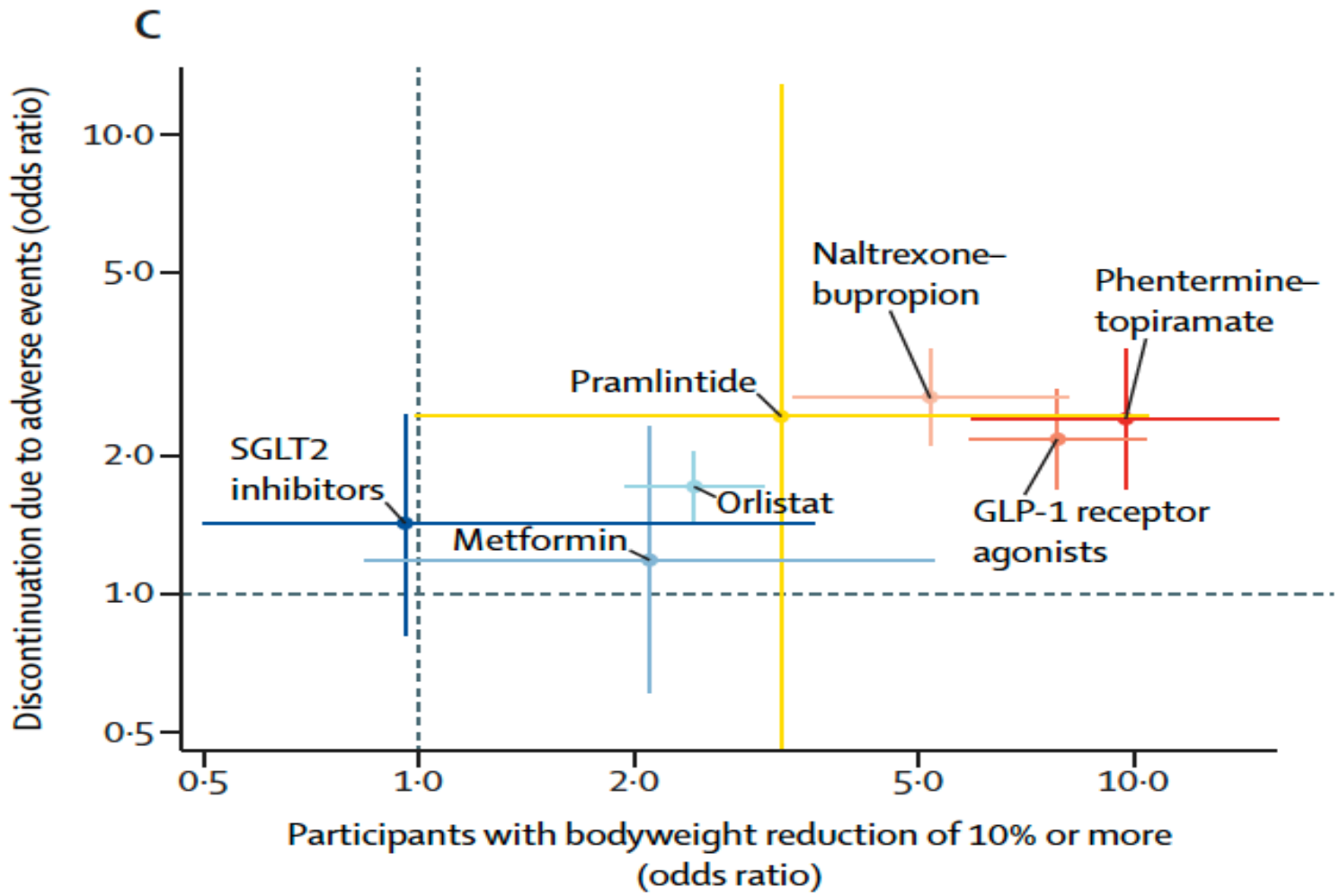
Shi Q, Lancet 2022

Body weight reduction of 10% or more versus discontinuation due to adverse events



Shi Q, Lancet 2022

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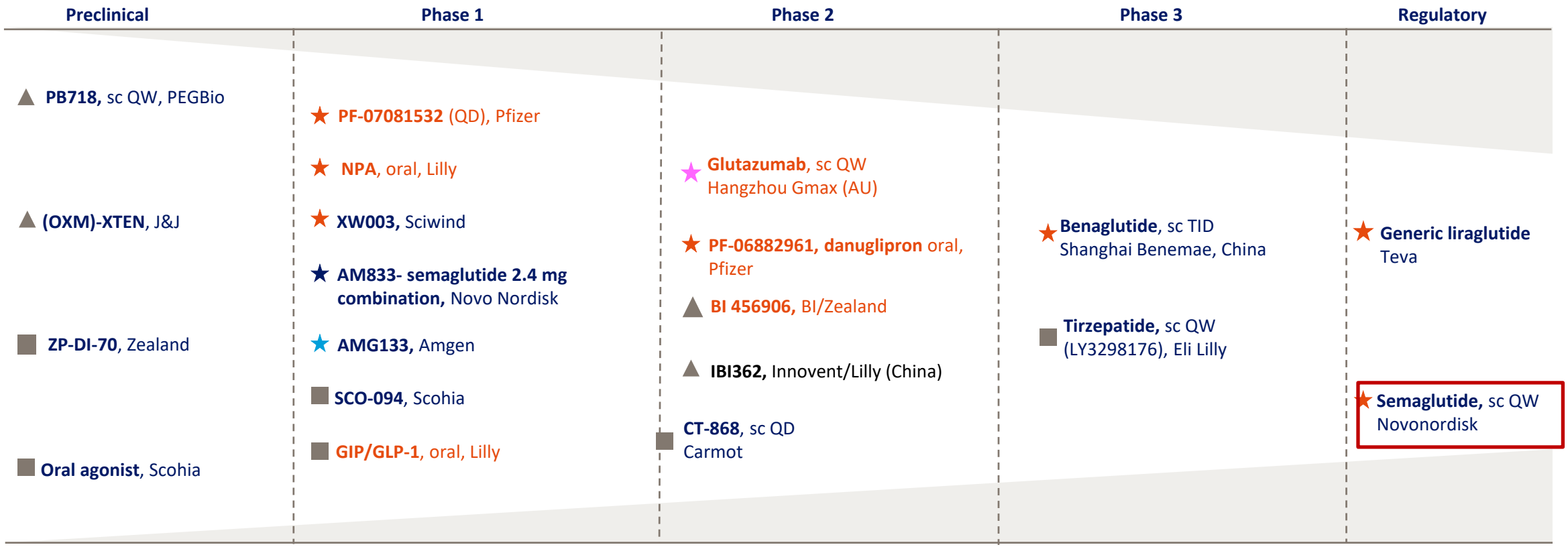
GLP-1-based compounds in development for weight management



GIP antag. mabt&GLP-1 agonist

GIP/GLP-1 dual agonist

GLP-1/glucagon dual agon.

Anti-GLP1 R mab fused to GLP-1

GLP-1R agonist

GLP-1 – amyling analogue combination

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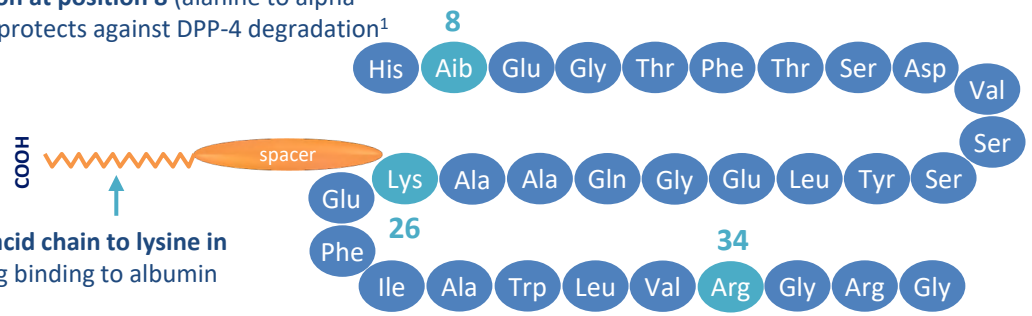
Red text: Compounds in development for people living with T2D and overweight/obesity. Updated: *February 2021*

Mechanism of action of semaglutide

Semaglutide is a human GLP-1 analogue

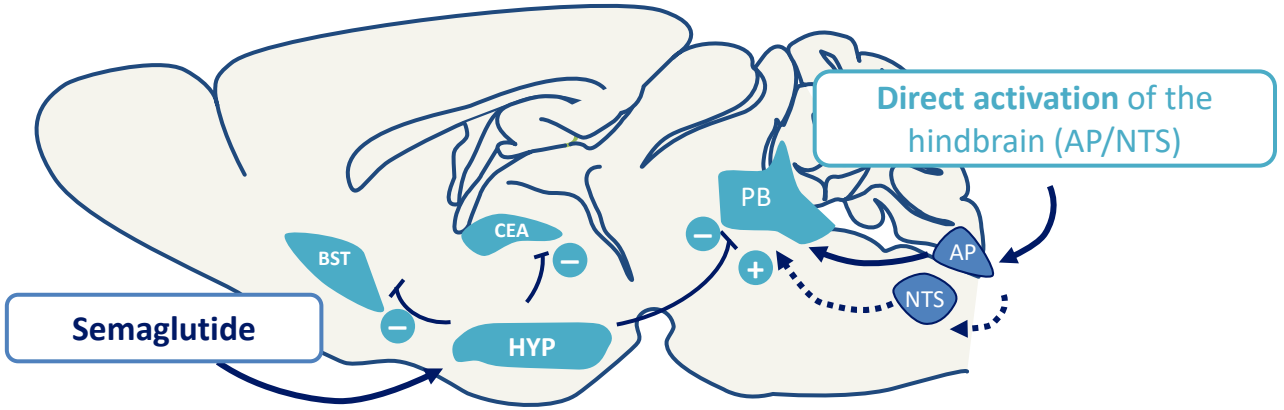
- 94% homology to human GLP-1
- $t_{½}$ of approximately 1 week

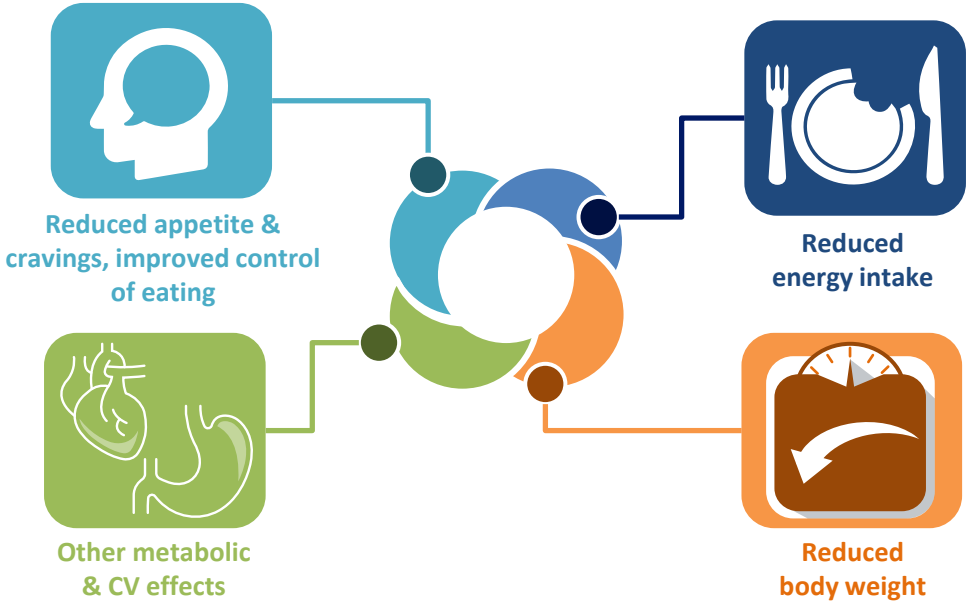
Amino acid substitution at position 8 (alanine to alpha-aminoisobutyric acid) protects against DPP-4 degradation[1]



Spacer and C-18 fatty di-acid chain to lysine in position 26 provide strong binding to albumin

Amino acid substitution at position 34 (lysine to arginine) prevents C-18 fatty di-acid binding at the wrong site





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Phase 3 programme

Effects of semaglutide 2.4 mg once-weekly in patients with obesity

Semaglutide is not approved in the Europe for weight management

The primary endpoint for all STEP trials is **weight loss**

STEP is the phase 3a/3b clinical development programme for subcutaneous semaglutide 2.4 mg weekly for weight management

STEP 1–4
Phase 3a

Semaglutide 2.4 mg

68 weeks + 7 week follow-up

STEP 5
Phase 3b

Semaglutide 2.4 mg

104 weeks + 7 week follow-up

STEP 6
East Asian
Phase 3a

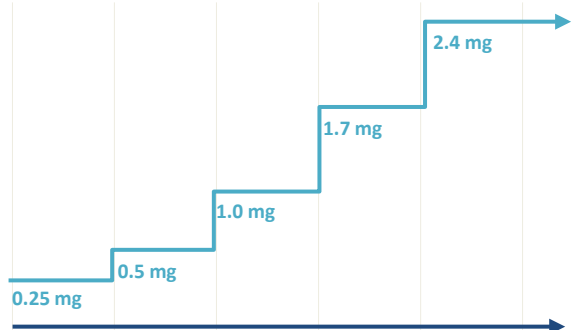
Semaglutide 2.4 mg

68 weeks + 7 week follow-up

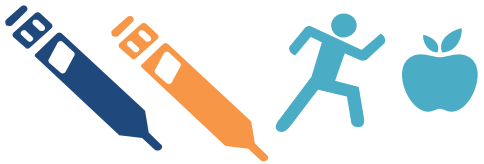
The treatment period in all STEP trials is followed by a 7-week period off treatment to account for the long half-life of semaglutide

Dose escalation

Semaglutide 2.4 mg OW treatment is initiated at 0.25 mg, followed by increments every 4 weeks to 0.5, 1.0, 1.7, and 2.4 mg OW

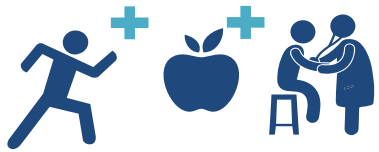


Across the STEP programme



Treatment with semaglutide 2.4 mg OW will be compared to placebo, as an adjunct to lifestyle intervention

STEP 3



In STEP 3 only, lifestyle intervention comprises IBT, an initial 8-week low-energy diet and higher target for physical activity

STEP 7 (China MRCT) Weight management in a mostly Chinese population (44 weeks)

STEP 8 Head-to-head vs liraglutide

SELECT CV outcomes trial

HFpEF in patients with obesity and heart failure with preserved ejection fraction

Knee OA in patients with obesity and knee osteoarthritis

European Association for the Study of Obesity

STEP programme at a glance

Global phase 3a

STEP 1
Weight management
(N=1,961)

STEP 2
WM in T2D
(N=1,210)

STEP 3
WM with IBT
(N=611)

STEP 4
Sustained WM
(N=803)

STEP TEENS
WM in adolescents
(N=200)

STEP Young
WM in children and adolescents
(N=210)

STEP HFpEF
Semaglutide in obesity
(N=516)

STEP HFpEF
Semaglutide in T2D
(N=610)

Regional phase 3a

STEP 6
East Asian trial
(N=400)

STEP 7
China, Brazil, Korea, Hong Kong MRCT
(N=375)

Phase 3b

STEP 5
Long-term WM
(N=300)

STEP 8
H2H vs liraglutide
(N=336)

STEP 9
Semaglutide in knee OA
(N=375)

STEP 10
Reversal of pre-diabetes
(N=375)

SELECT
CVOT
(N=17,500)

STEP 11
Korea/ Thailand trial
(N=195)

Phase 4

US employer
US employer trial

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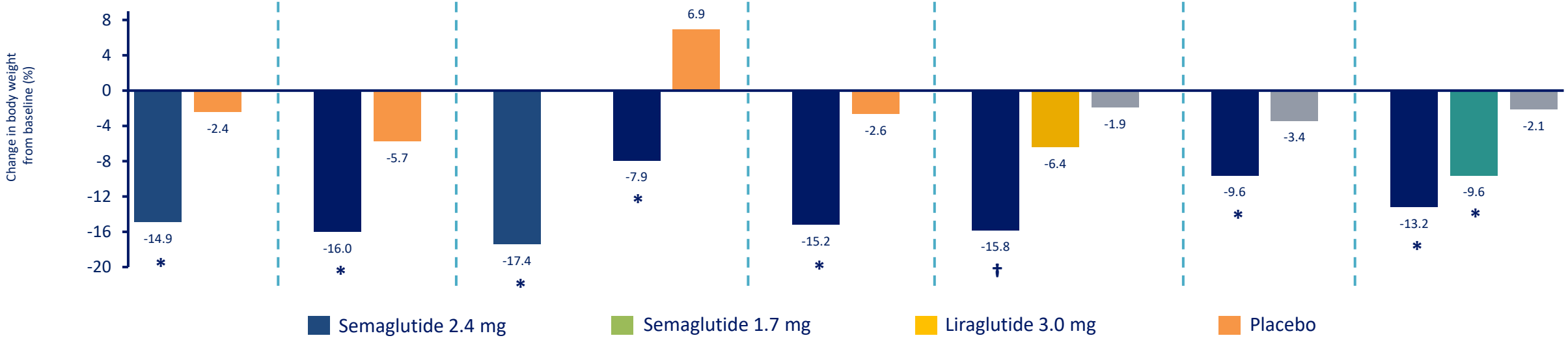
STEP 7: China, Brazil, Korea, Hong Kong (left to right) multi-regional clinical trial; Novo Nordisk. Data on file.
CVOT, cardiovascular outcomes trial; HFpEF, heart failure with preserved ejection fraction; H2H, head-to-head; IBT, intensive behavioural therapy; MRCT, multi-regional clinical trial (including China and ≥1 additional East Asian country); OA, osteoarthritis; WM, weight management.

Weight loss across STEP trials

Semaglutide 2.4 mg once-weekly in participants with overweight or obesity

	STEP 1[1]	STEP 3[3]	STEP 4[4]		STEP 5[5]	STEP 8[7]	STEP 2[2]	STEP 6[6]
	Weight management	Weight management with IBT	Sustained weight management		Long term weight management	Head to head vs. liraglutide 3.0 mg	Weight management in T2D	Weight management in East Asian population
Baseline BW	105.3 kg	105.8 kg	107.2 kg	96.1 kg	106.0 kg	104.5 kg	99.8 kg	87.5 kg
	After 68 weeks	After 68 weeks	After 68 weeks	20–68 weeks	104 weeks	After 68 weeks	After 68 weeks	After 68 weeks



*Statistically significant vs placebo.† Statistically significant vs. liraglutide 3.0 mg
BW, body weight; IBT, intensive behavioural therapy.

1. Wilding et al. N Engl J Med 2021; doi:10.1056/NEJMoa2032183; 2. Davies et al. Lancet, 2021; doi.org/10.1016/S0140-6736(21)00213-0: 3. Wadden et al. JAMA. doi:10.1001/jama.2021.1831; 4. Rubino et al. JAMA. 2021 Apr 13;325(14):1414-1425. doi: 10.1001/jama.2021.3224. 5. Garvey et al. Presented at the 39th Annual Meeting of The Obesity Society (TOS) held at ObesityWeek®, virtual meeting, November 1–5, 2021; 6. Kadowaki et al. Presented at the International Congress on Metabolic Syndrome hybrid meeting .September 2-4, 2021; 7. Rubino et al. Presented at the 39th Annual Meeting of The Obesity Society (TOS) held at ObesityWeek®, virtual meeting, November 1–5, 2021.

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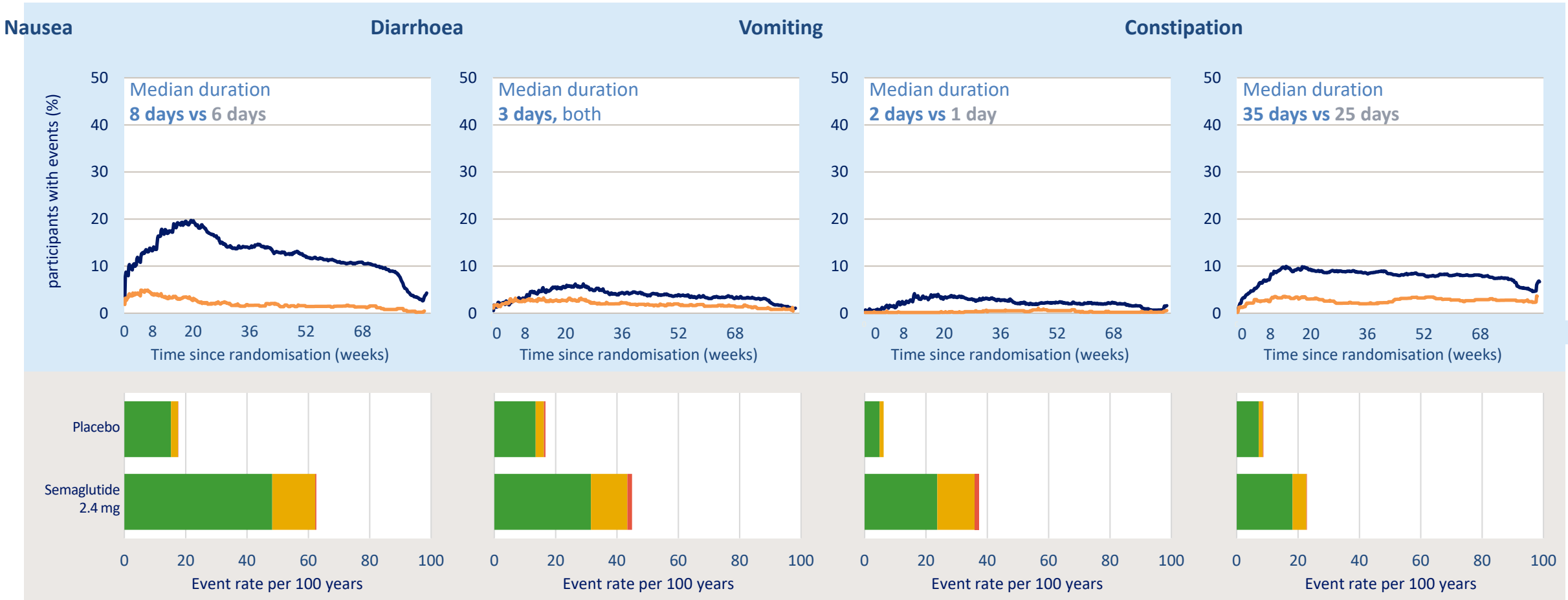
Prevalence and severity of selected GI events

STEP 1



- Data are for the on-treatment observation period.
GI, gastrointestinal.
Wilding et al. N Engl J Med 2021;384:989-1002.

Severity: Severe, Moderate, Mild

Semaglutide 2.4 mg

Placebo

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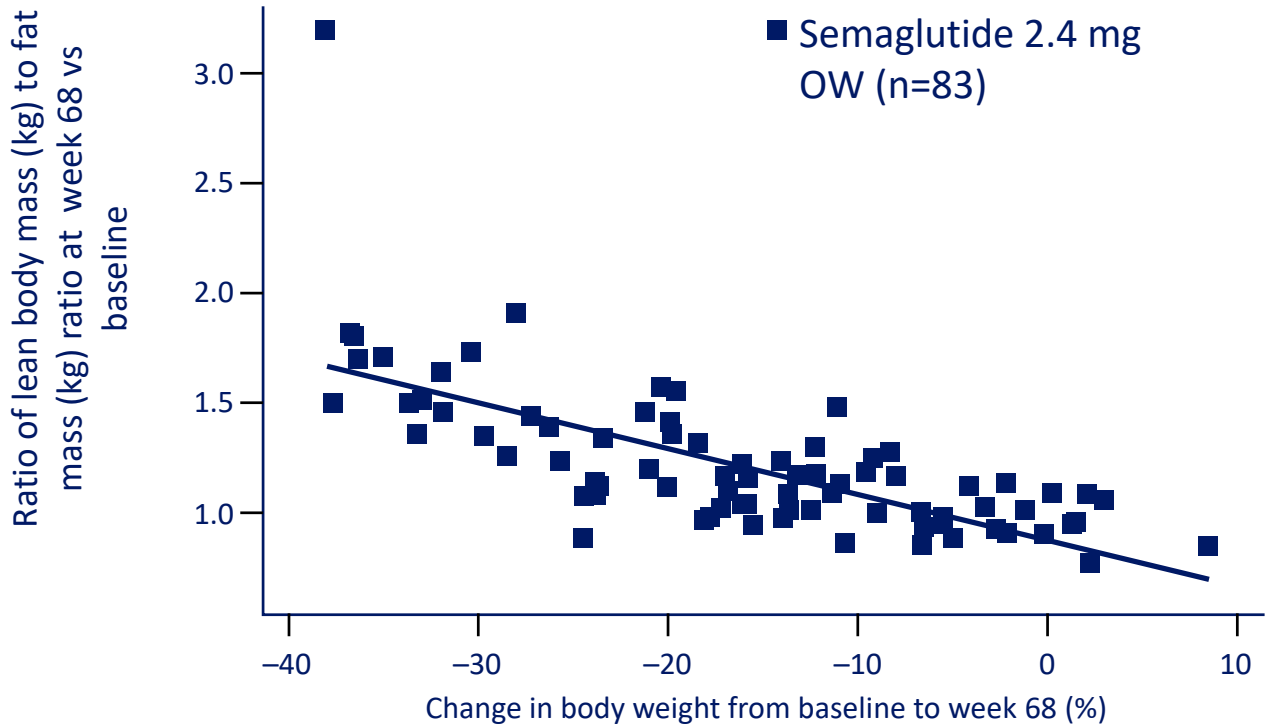
Change from baseline to week 68 in ratio of lean body mass to total body mass: Overall and by weight change

Ratio of week 68 vs baseline lean body mass (kg) to fat mass (kg) ratio plotted by change from baseline to week 68 in body weight



Lean body mass (kg) to total body fat mass (kg) ratio in the semaglutide group

	Mean [95% CI]
Baseline (n=83)	1.34 [1.22, 1.47]
Week 68 (n=83)	1.57 [1.44, 1.71]
Change from baseline to week 68	
Overall treatment group (n=83)	0.23 [0.14, 0.32]
Pts with weight loss ≥15% (n=44)	0.41 [0.28, 0.53]
Pts with weight loss <15% or not known (n=39)	0.03 [-0.05, 0.12]

Observed data; no imputation for missing data.
CI, confidence interval; OW, once-weekly; Pt, participants.
Wilding et al. Presented at the Endocrine Society (ENDO) virtual meeting, March 20-23, 2021.

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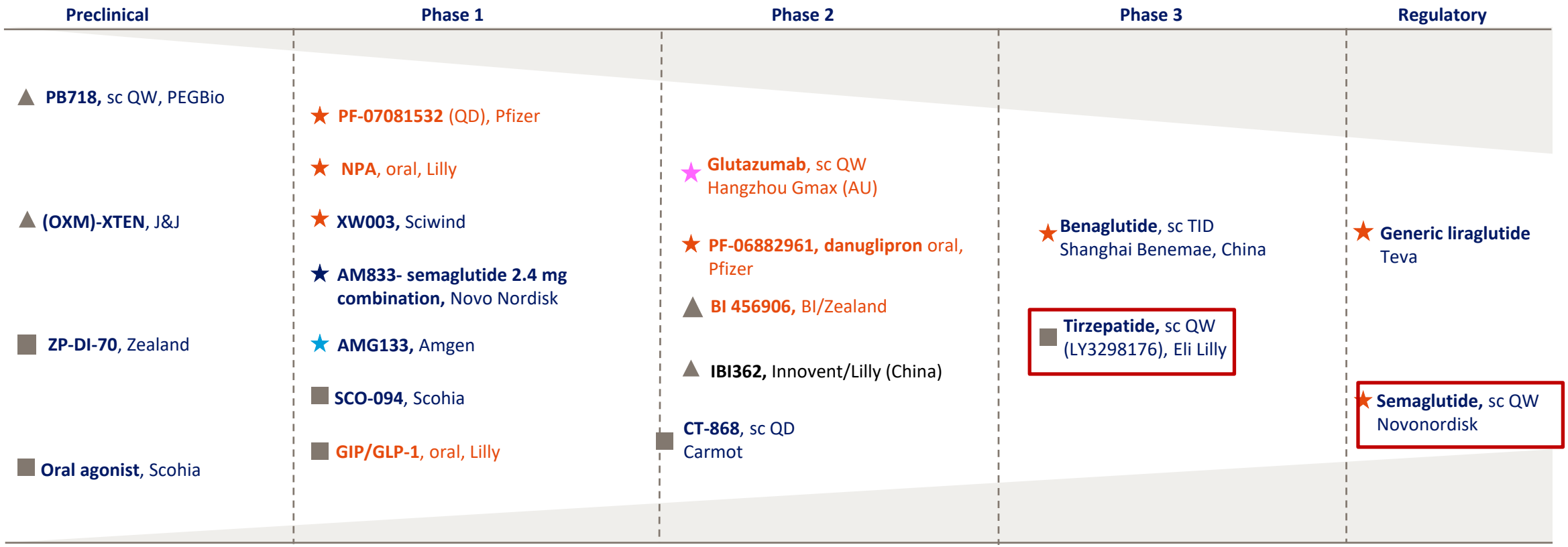
GLP-1-based compounds in development for weight management



GIP antag. mabt&GLP-1 agonist

GIP/GLP-1 dual agonist

GLP-1/glucagon dual agon.

Anti-GLP1 R mab fused to GLP-1

GLP-1R agonist

GLP-1 – amyling analogue combination

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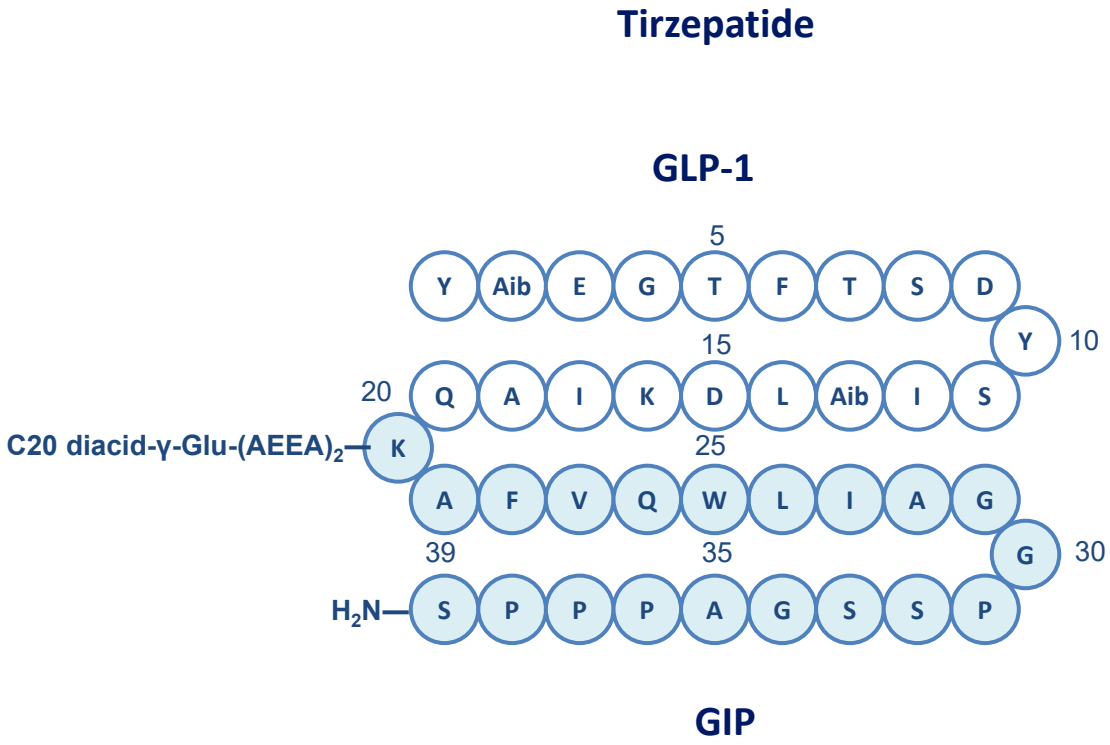
Red text: Compounds in development for people living with T2D and overweight/obesity. Updated: *February 2021*

Tirzepatide

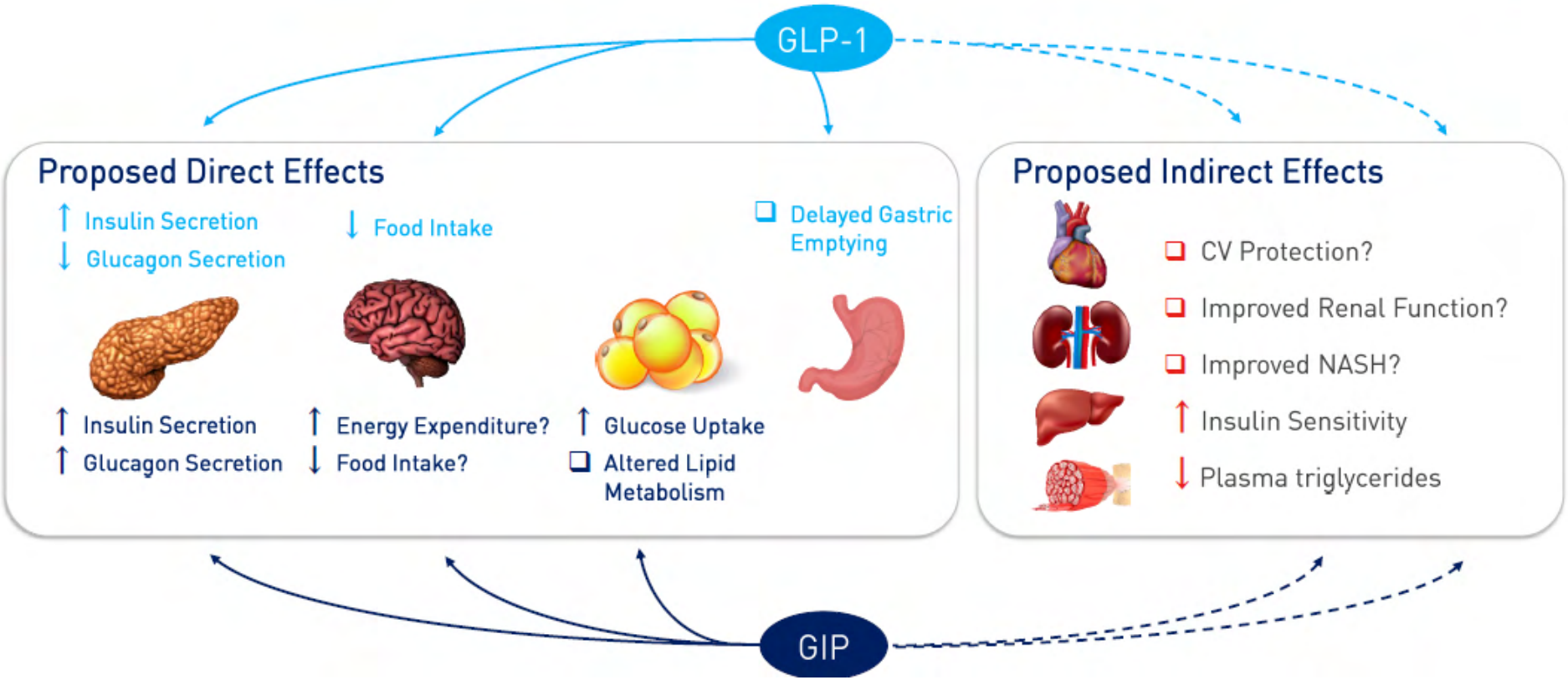
- Tirzepatide once-weekly (LY3298176) is a novel dual GIP and GLP-1 receptor agonist[1,2]
  - It has greater affinity for the GIP receptor than for the GLP-1 receptor[2]
- Tirzepatide is currently in phase 3 development for the treatment of:[3]
  - T2D (SURPASS)
  - Obesity (SURMOUNT)
  - HFpEF (SUMMIT HFpEF)
- It is also in phase 2 development for the treatment of NASH (SYNERGY-NASH)[4]



GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide-1; HFpEF, heart failure with preserved ejection fraction; NASH, non-alcoholic steatohepatitis.

1. Willard FS et al. JCI Insight 2020;5:e140532; 2. Coskun T et al. Mol Metab 2018;18:3–14; 3. Eli Lilly. 2021 Guidance Call. Available at: https://investor.lilly.com/static-files/635ce8ea-cd6b-4e3f-aca6-d53eb52c20cf. Accessed September 2021;
4. Eli Lilly. A Study of Tirzepatide (LY3298176) in Participants With Nonalcoholic Steatohepatitis (NASH) (SYNERGY-NASH). Available at: https://clinicaltrials.gov/ct2/show/NCT04166773. Accessed September 2021.

Proposed mode of action of GLP-1/GIP dual agonists



CV, cardiovascular; GIP, gastric inhibitory polypeptide; GLP-1, glucagon-like peptide-1; NASH, non-alcoholic steatohepatitis.

Eli Lilly. Diabetes Update Call. Presented at the 54th Annual Meeting of the European Association for the Study of Diabetes, 1–5 October, 2018, Berlin, Germany.

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Phase 3

SURMOUNT-1

Efficacy and safety of tirzepatide once weekly in participants without type 2 diabetes who have obesity or are overweight with weight-related comorbidities: a randomized, double-blind, placebo-controlled trial (SURMOUNT-1)

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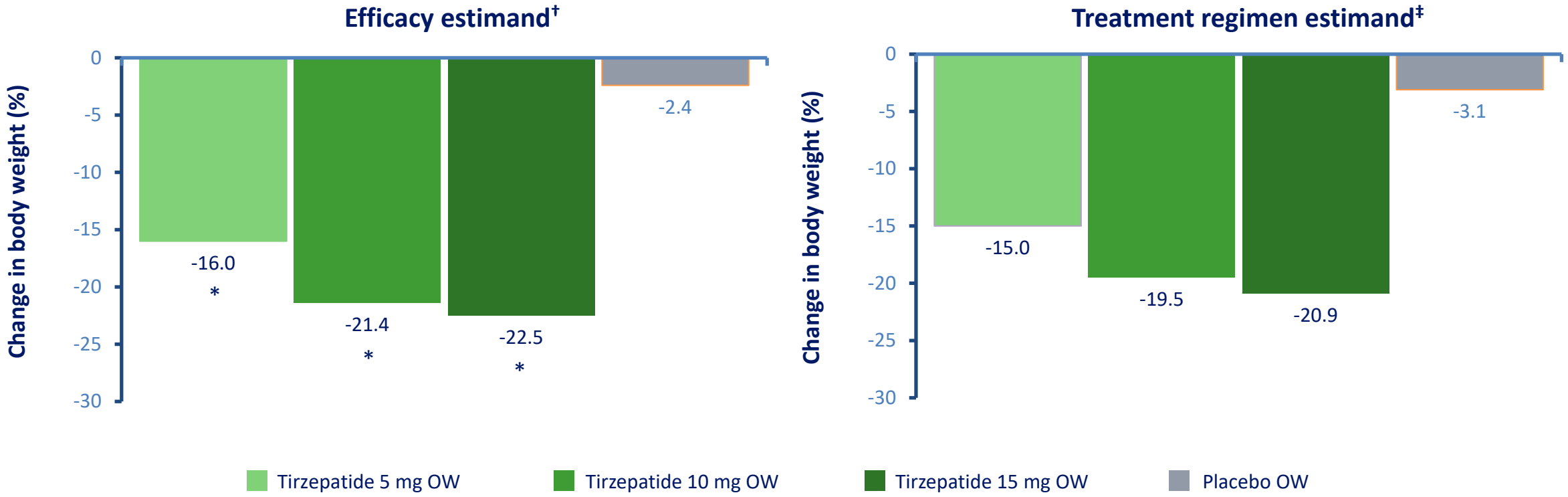
Eli Lilly and Company. Lilly's tirzepatide delivered up to 22.5% weight loss in adults with obesity or overweight in SURMOUNT-1. 2022 28 April 2022; Available from: https://investor.lilly.com/news-releases/news-release-details/lillys-tirzepatide-delivered-225-weight-loss-adults-obesity-or. Accessed April 2022.

Percent change in body weight from baseline to week 72 (co-primary endpoint)

SURMOUNT 1 (vs placebo)

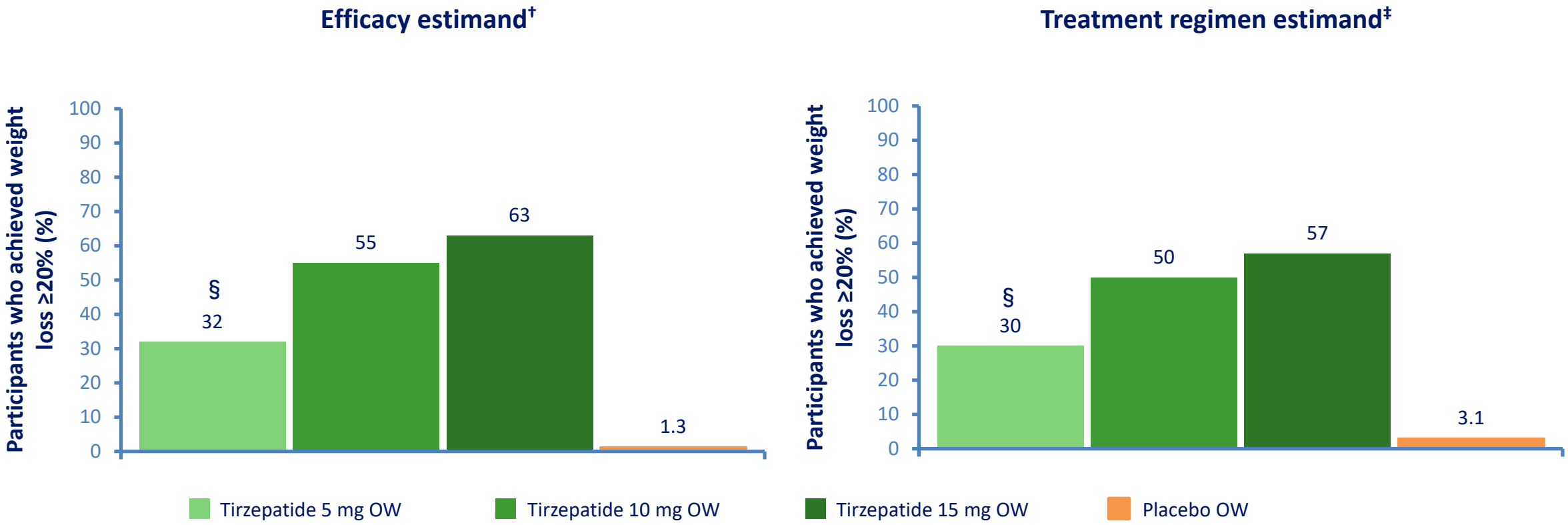
Baseline body weight: 105 kg



†Trial product estimand. ‡Treatment policy estimand. *Statistically significant values versus placebo (details not reported).
OW, once weekly.

Jastreboff AM, Aronne LJ, Ahmad NN, et al. Tirzepatide once weekly for the treatment of obesity. N Engl J Med. DOI: 10.1056/NEJMoa2206038.

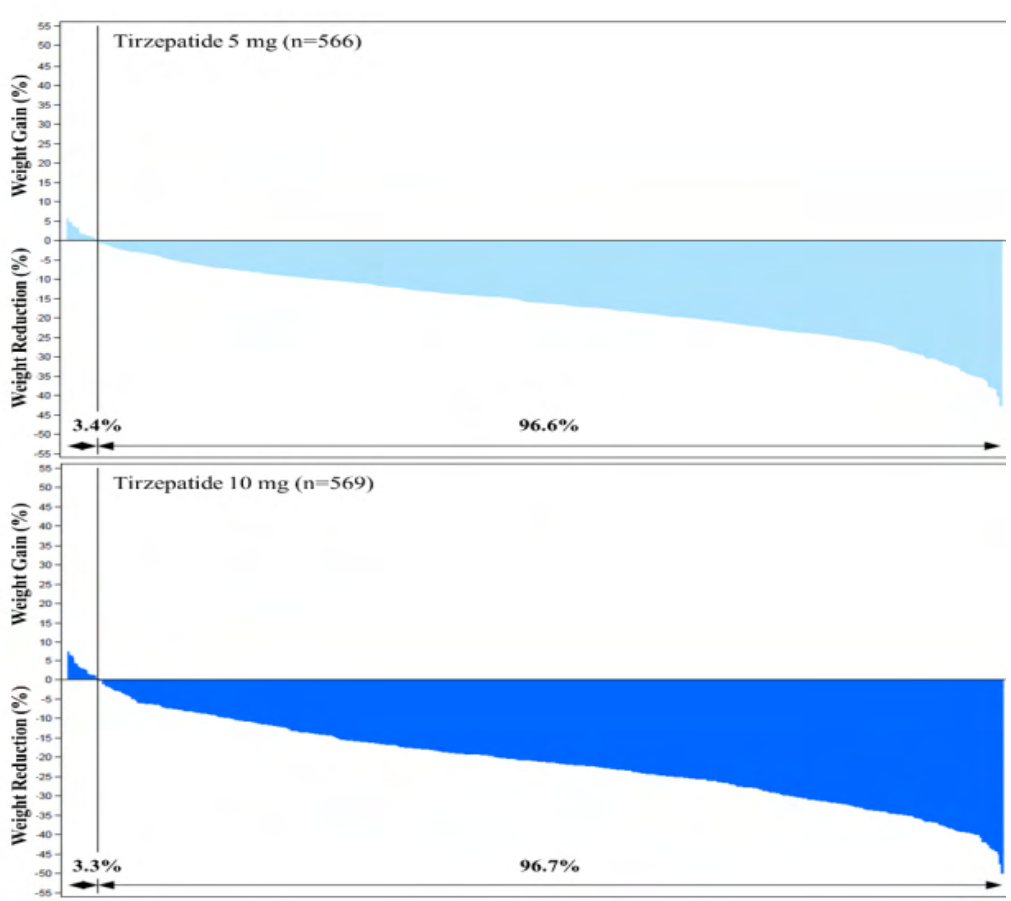
Percentage of participants who achieved weight loss ≥20% at week 72

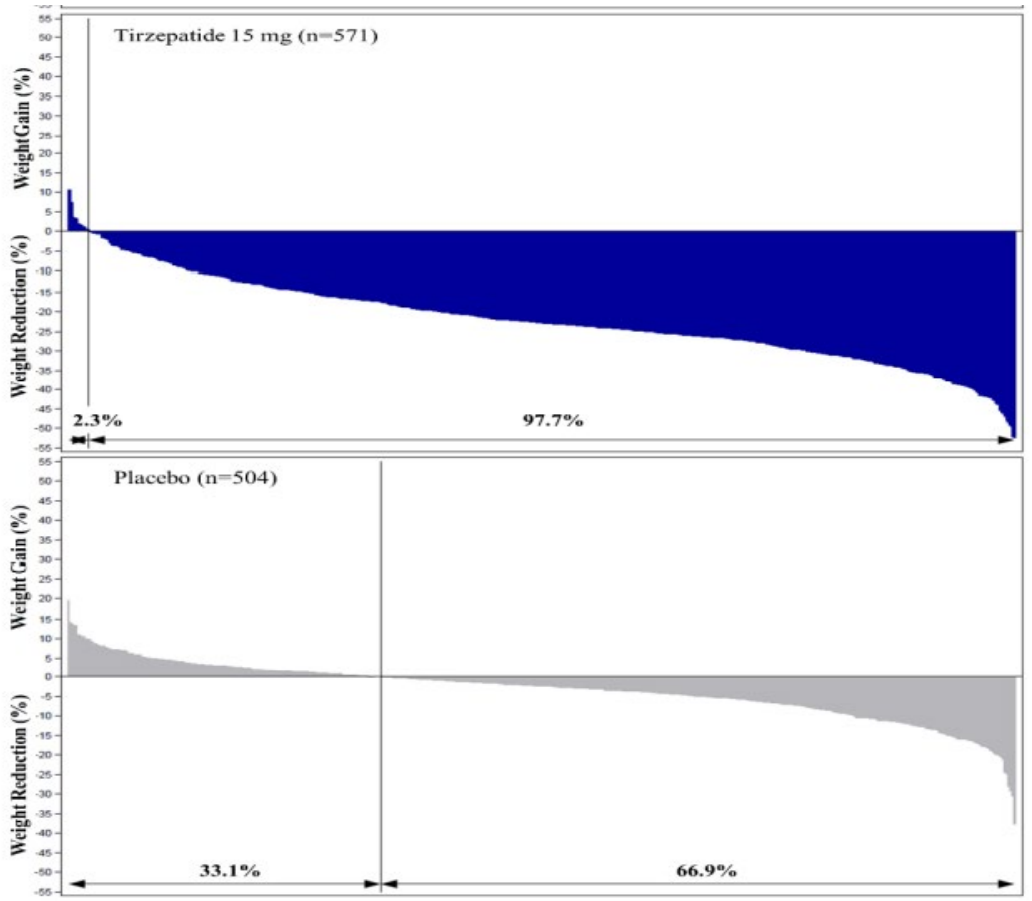


†Trial product estimand. ‡Treatment policy estimand. § Not controlled for type 1 error.
OW, once weekly.

: Jastreboff AM, Aronne LJ, Ahmad NN, et al. Tirzepatide once weekly for the treatment of obesity. N Engl J Med. DOI: 10.1056/NEJMoa2206038.

Waterfall plots of individual responses to tirzepatide





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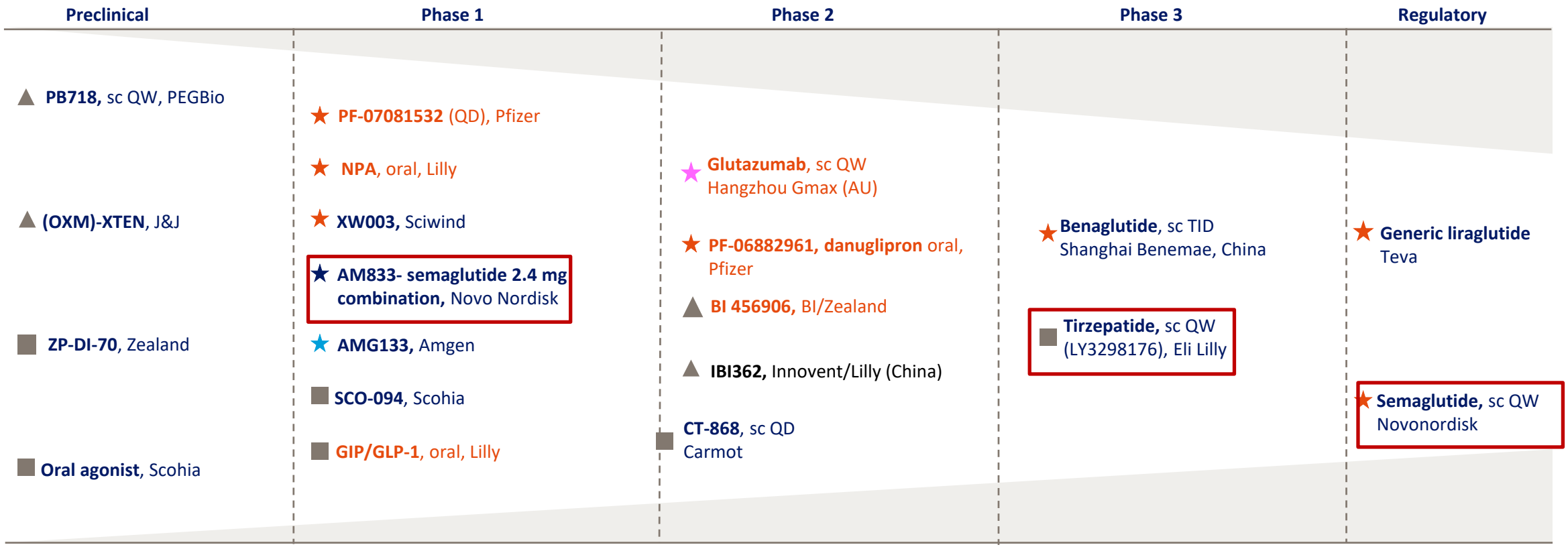
Supplement to: Jastreboff AM, Aronne LJ, Ahmad NN, et al. Tirzepatide once weekly for the treatment of obesity. N Engl J Med. DOI: 10.1056/NEJMoa2206038

GLP-1-based compounds in development for weight management



GIP antag. mabt&GLP-1 agonist

GIP/GLP-1 dual agonist

GLP-1/glucagon dual agon.

Anti-GLP1 R mab fused to GLP-1

GLP-1R agonist

GLP-1 – amyling analogue combination

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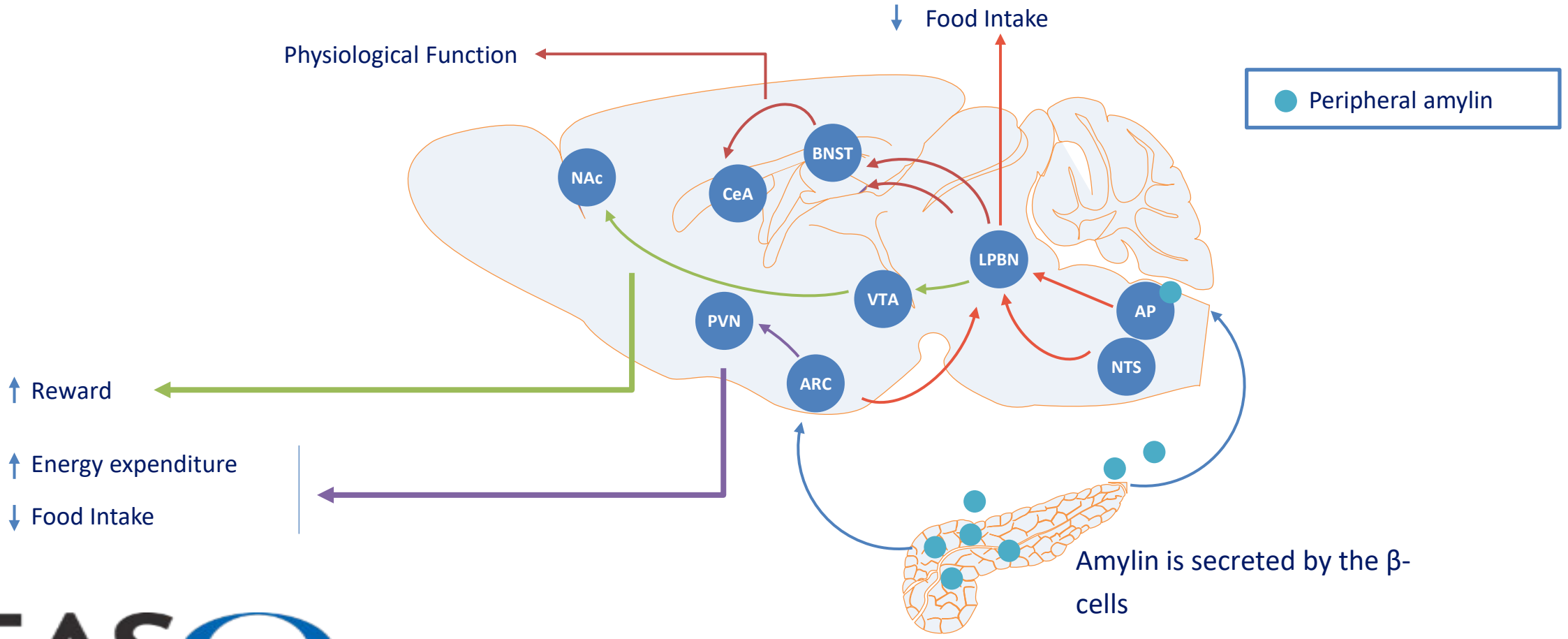
Red text: Compounds in development for people living with T2D and overweight/obesity. Updated: *February 2021*

Proposed primary and secondary brain activation pathways by amylin



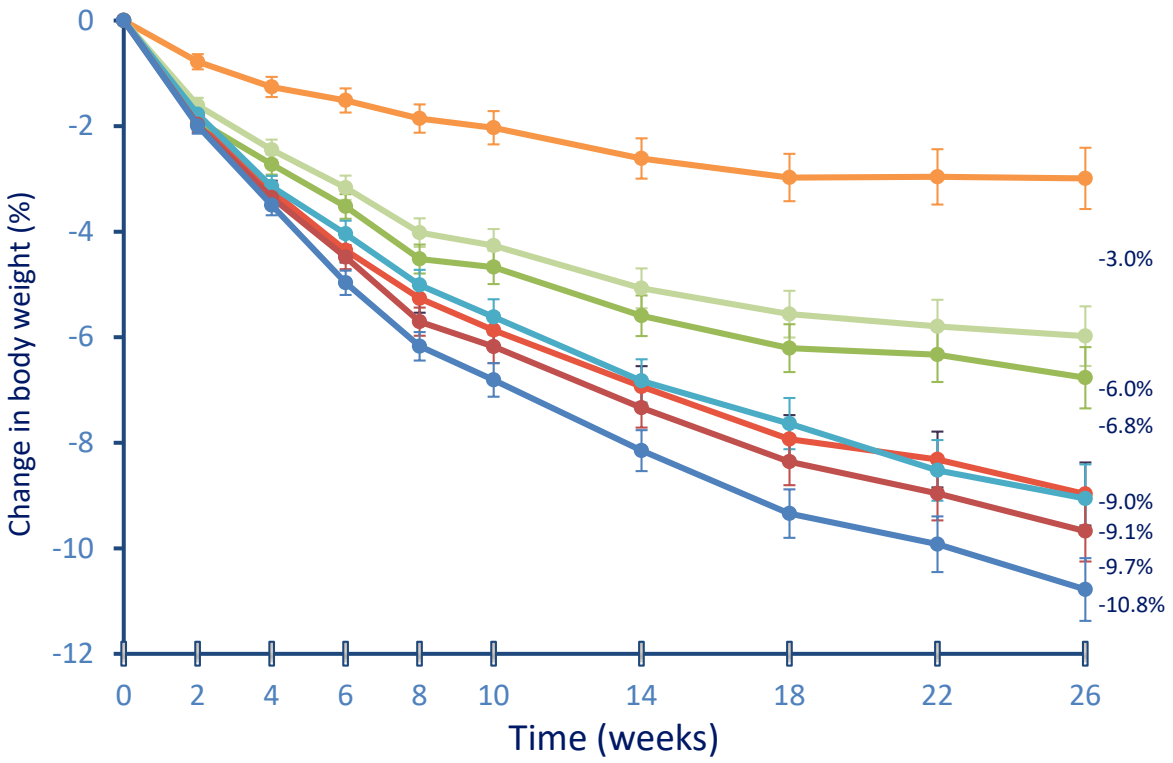
ARC, arcuate nucleus; AP, area pstrema; NTS, nucleus tractus solitarius; LPBN, lateral parabranchial nucleus; VTA, ventral tegmental area; PVN, paraventricular nucleus; BNST, bed nucleus of stria terminalis; CeA, central nucleus of amygdala; NAc, nucleus accumbens

Boccia et al. Peptides 2020; 132: 170366;

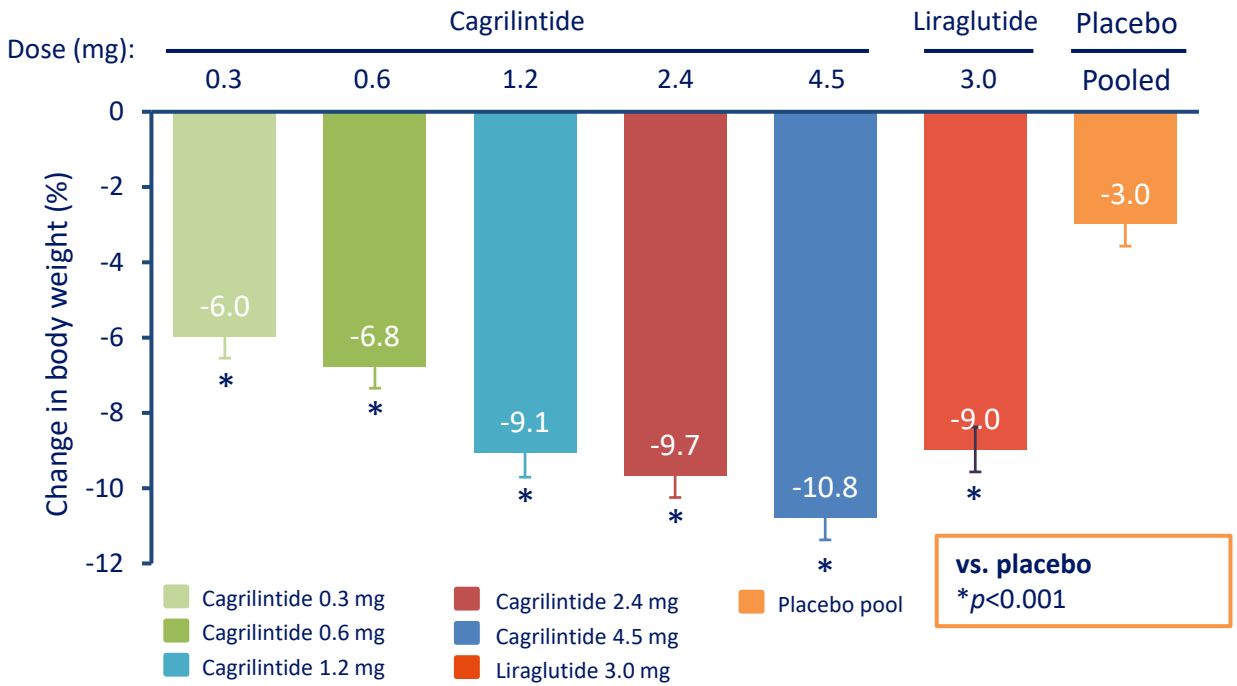
Cagrilintide – Phase 2 trial

Change in body weight (%) Primary estimand

Observed change in body weight by treatment week



Estimated mean change in body weight from baseline to week 26



Bodyweight decreased progressively in all active treatment groups and did not appear to plateau by week 26

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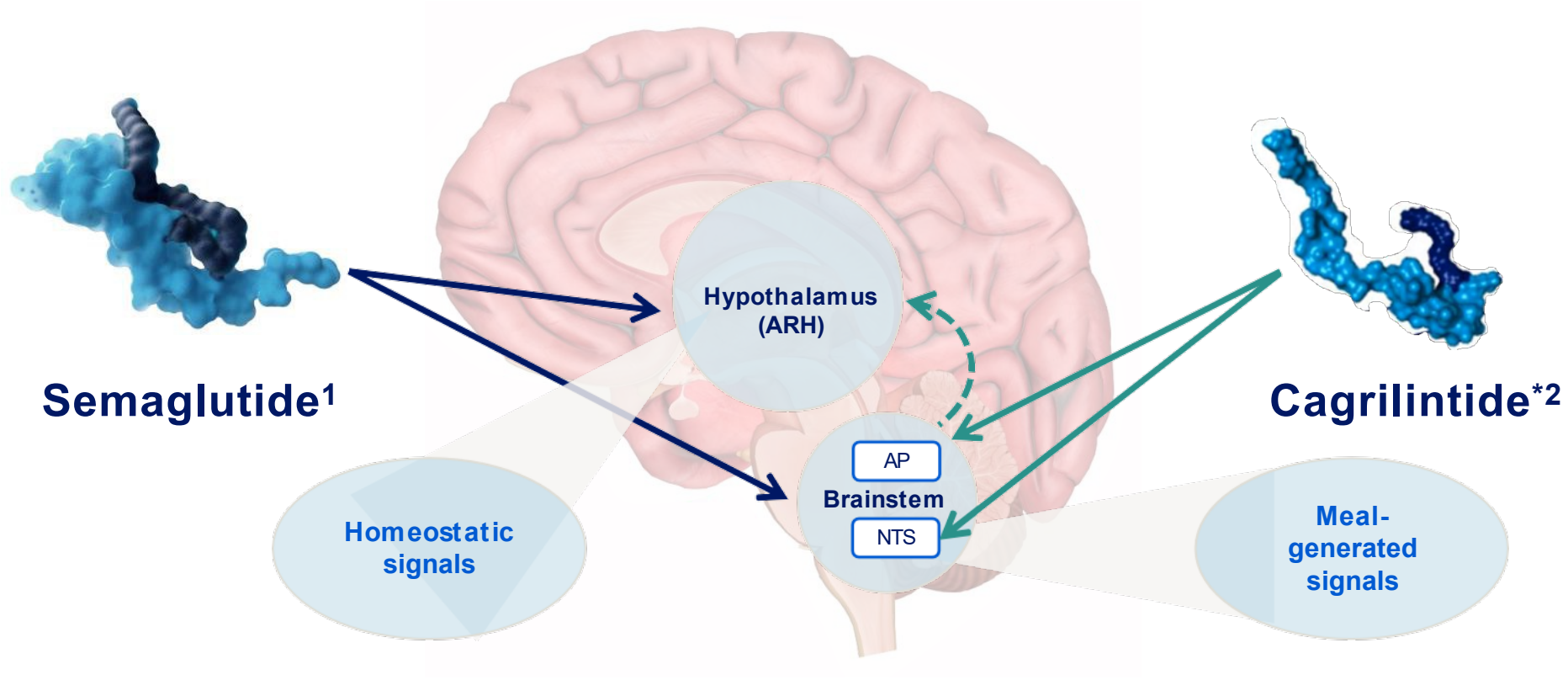
*Estimated change in bodyweight using ANCOVA with imputation of missing data and data during treatment non-adherence ; Mean (SE) observed change from baseline in bodyweight (%); Error bars indicate SEs. ETD=estimated treatment difference

Lau, et al. Lancet. 2021 Nov 16 ; doi.org/10.1016/S0140-6736(21)01751-7

The potential of cagrilintide and semaglutide combination therapy for weight management



AP, area postrema; ARH, arcuate hypothalamic nucleus; NTS, nucleus of solitary tract.

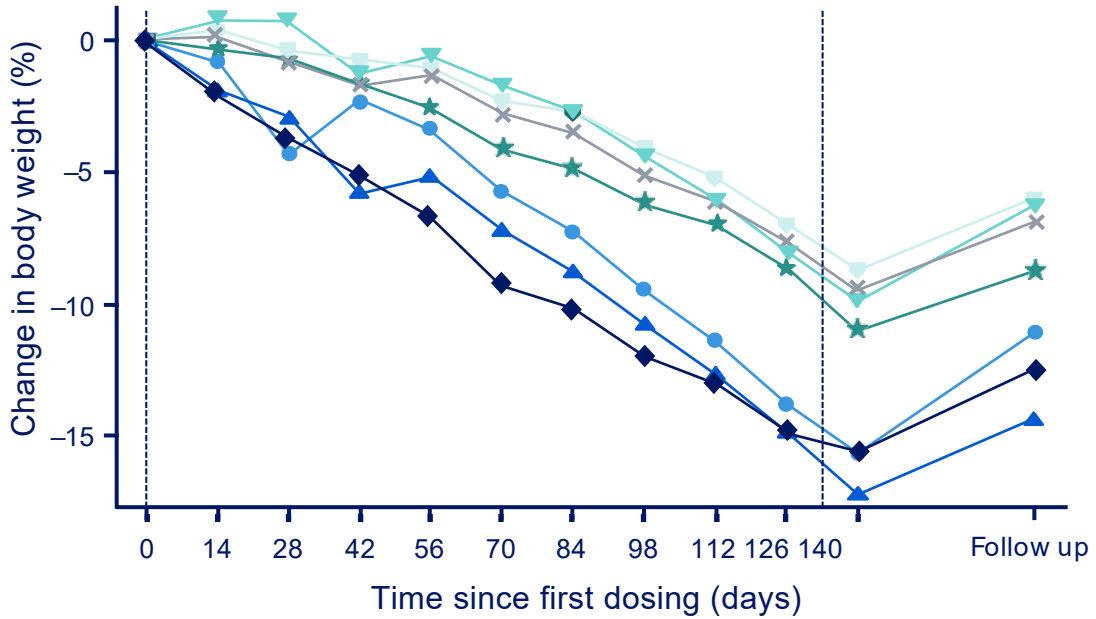
**Cagrilintide may not have a direct binding in the hypothalamic regions, including ARH and ventral tegmental areas.*

1. Jensen CB et al. Diabetes 2017;66:A305; 2. Adapted from: Boccia L et al. Peptides 2020;132:170366.

ECO 2021 Poster 0047

Change in body weight (%)

EXPLORATORY ENDPOINT – COHORTS 1–6, BASELINE TO WEEK 20



	Mean estimate	ETD vs pooled placebo, semaglutide 2.4 mg	95% CI
Cagrilintide 0.16 mg, Semaglutide 2.4 mg	–8.5	**0.9**	[–2.9; 4.7]
Cagrilintide 0.3 mg, Semaglutide 2.4 mg	–9.9	**–0.4**	[–4.0; 3.1]
Cagrilintide 0.6 mg, Semaglutide 2.4 mg	–10.5	**–1.0**	[–4.9; 2.9]
Cagrilintide 1.2 mg, Semaglutide 2.4 mg	–15.6	**–6.2**	[–9.9; –2.5]
Cagrilintide 2.4 mg, Semaglutide 2.4 mg	–17.0	**–7.6**	[–11.2; –4.0]
Cagrilintide 4.5 mg, Semaglutide 2.4 mg	–15.6	**–6.2**	[–9.8; –2.6]
Placebo, Semaglutide 2.4 mg	–9.5	—	—

Change in body weight is analysed using a mixed model for repeated measurements, where all changes from baseline in body weight measurements enter as the dependent variables and treatment, visit and baseline body weight enter as fixed effects. Treatment and baseline body weight are nested within visit. Vertical reference lines represent first and last dosing of cagrilintide and semaglutide.

CI, confidence interval; ETD, estimated treatment difference.

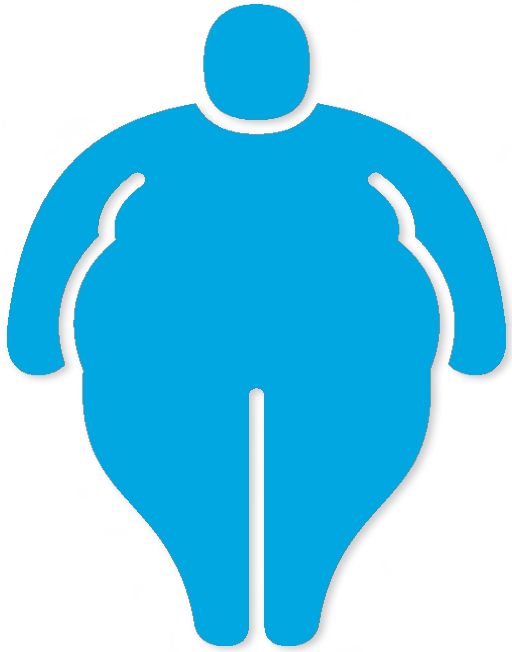
Enebo L, et al. Poster/oral 047, ECO2021, May 10–13, 2021

ECO 2021 Poster 0047

ECO 2021 Poster 0047

Severe Obesity due to MC4R Pathway Deficiencies

This ultra-rare disease is a genetic disorder, linked to the presence of variants in the POMC, LEPR or PCSK1 genes, leading to an alteration in the function of the MC4R pathway



BMI > 40 Kg/ M^2

- Early-onset, severe obesity
- Hyperphagia: a pathological hunger associated with persistent and potentially extreme food- seeking behavior
- Resistant or refractory to therapies and interventions for general obese
- Multiple complications and co-morbidities associated with obesity

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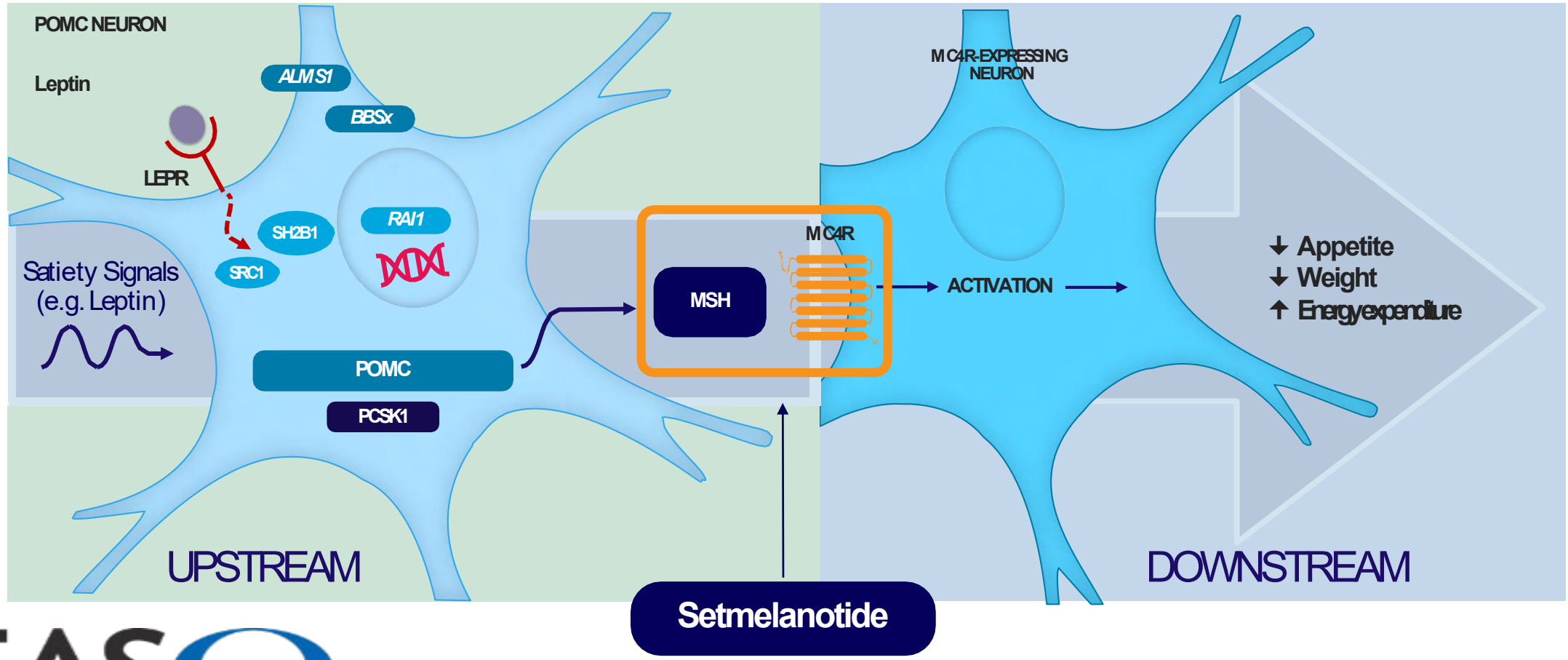
Shah BM et al. Keystone Symposia on Molecular and Cellular Biology: Functional Neurocircuitry of Feeding and Feeding Disorders; 2019; Alberta, Canada. MC4R-Melanocortin -4 Receptor; POMC-proopiomelanocortin; LEPR-leptin receptor; PCSK1-proprotein convertase subtilisin /kexin type 1

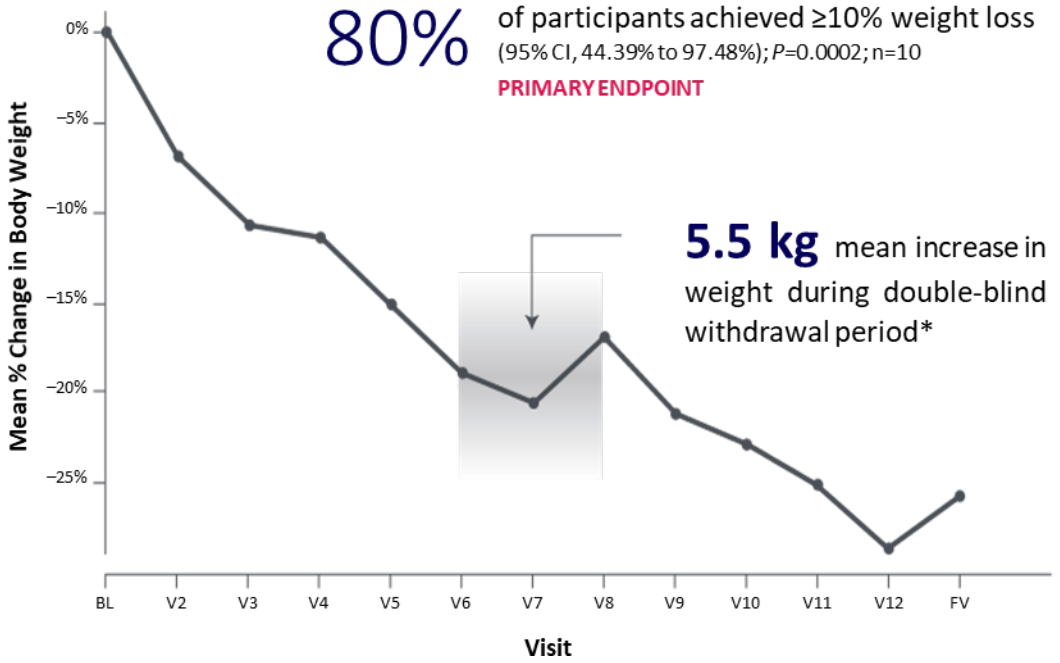
melanocortin 4 (MC4) receptor agonist



MC4R-Melanocortin -4 Receptor; POMC-proopiomelanocortin; LEPR-leptin receptor; PCSK1-proprotein convertase subtilisin /kexin type 1; α-MSH- α-melanocyte stimulating hormone

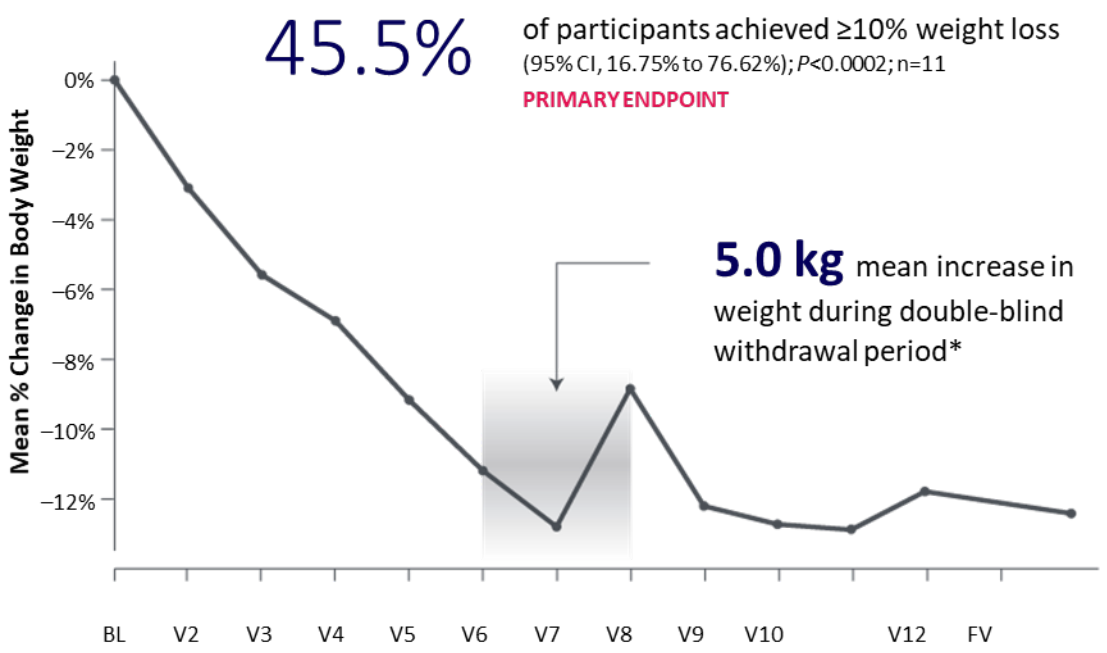
Largest Studies Conducted in Obesity due to POMC, PCSK1 or LEPR Deficiency Showed Statically Significant Weight Loss of At Least 10%

POMC/PCSK1



BL, baseline; PCSK1, proprotein convertase subtilisin/kexin type 1; POMC, proopiomelanocortin; FV, final visit; V, visit. The withdrawal period lasted 8 weeks, which included 4 weeks of setmelanotide followed by 4 weeks of placebo.
†N=9 participants who achieved weight loss threshold (5 kg or 5% if <100 kg) after the first open-label active treatment phase.
Reference: IMCIVREE Prescribing Information

LEPR



BL, baseline; FV, final visit; LEPR, leptin receptor; V, visit.
The withdrawal period lasted 8 weeks, which included 4 weeks of setmelanotide followed by 4 weeks of placebo;
†N=7 participants who achieved weight loss threshold (5 kg or 5% if <100 kg) after the first open-label active treatment phase. **Reference:** IMCIVREE Prescribing Information.

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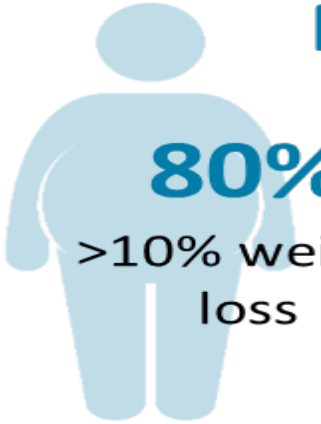
Setmelanotide Demonstrated Statistically Significant, Clinically Meaningful Reductions in Weight and Hunger



POMC Phase 3 Topline Data* (n=10)

80%
>10% weight loss

-25.4%
mean weight reduction

-27.8%
mean hunger score reduction

31.9kg / 70.2lbs
mean weight loss in 1 year

LEPR Phase 3 Topline Data* (n=11)

45.5%
>10% weight loss

-12.5%
mean weight reduction

-41.9%
mean hunger score reduction

16.7kg / 36.8lbs
mean weight loss in 1 year

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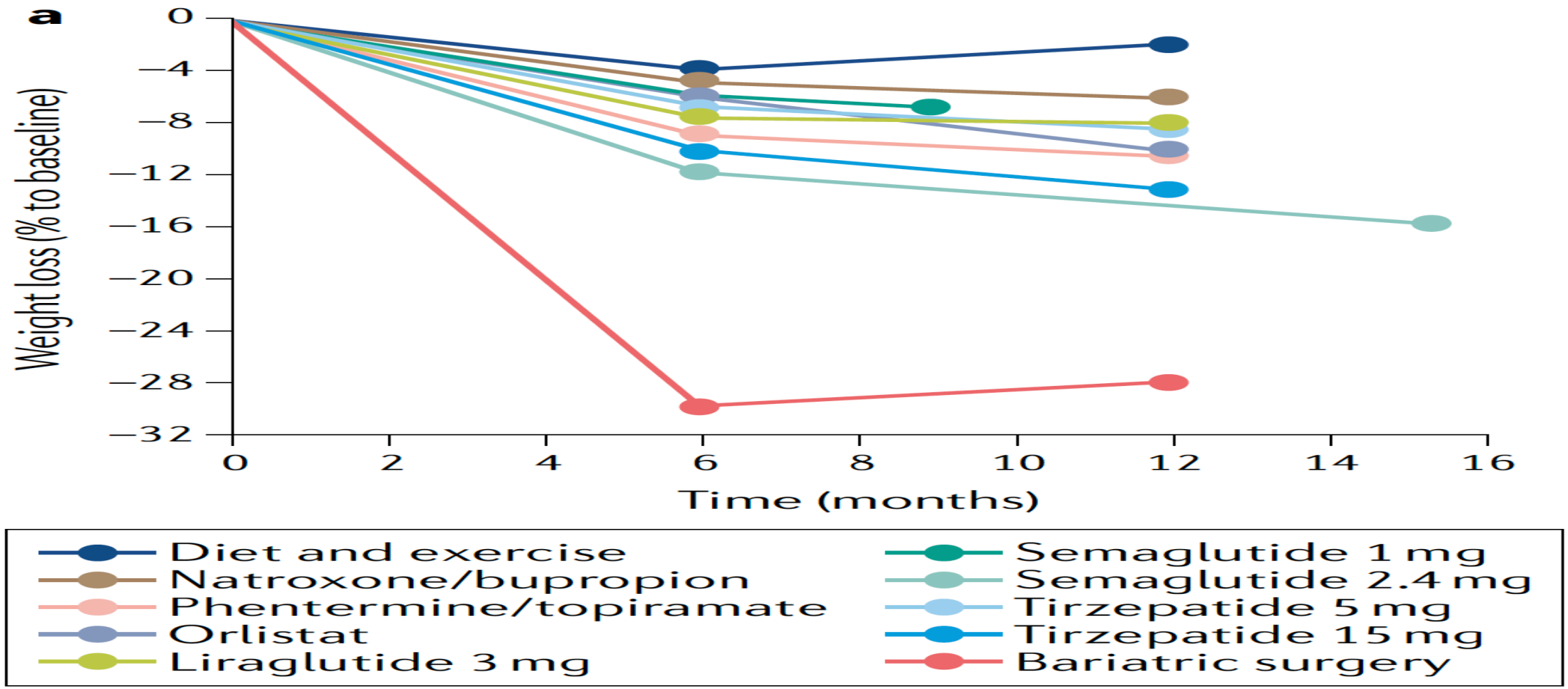
*Data announced by Rhythm in August 2019 and presented at The Obesity Society annual meeting during ObesityWeek in November 2019. ** Data as of April 16, 2020; LTE study is ongoing; two additional LEPR patients expected to enroll pending local regulatory approval. One POMC patient did not continue in LTE study.

*** All patients in the supplemental cohorts, as well as most patients in the pivotal cohorts, were enrolled by European investigators.

Body weight loss by AOMs in humans and rodents



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Müller TD, Nature Reviews 2022

EASO

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Thank You

Case study: Sara

- 27 years old, 87 kg, BMI is 35 kg/m^2
- Abdominal gunshot wound 5 years ago
- Highly selective vagotomy
- Since then, no satiety and gaining weight
- Her obesity risk factors are:
  - Craving for carbohydrate
  - Severe sleep depravation
  - Stressful life: anxiety
  - Medication: metoprolol 1.25 mg

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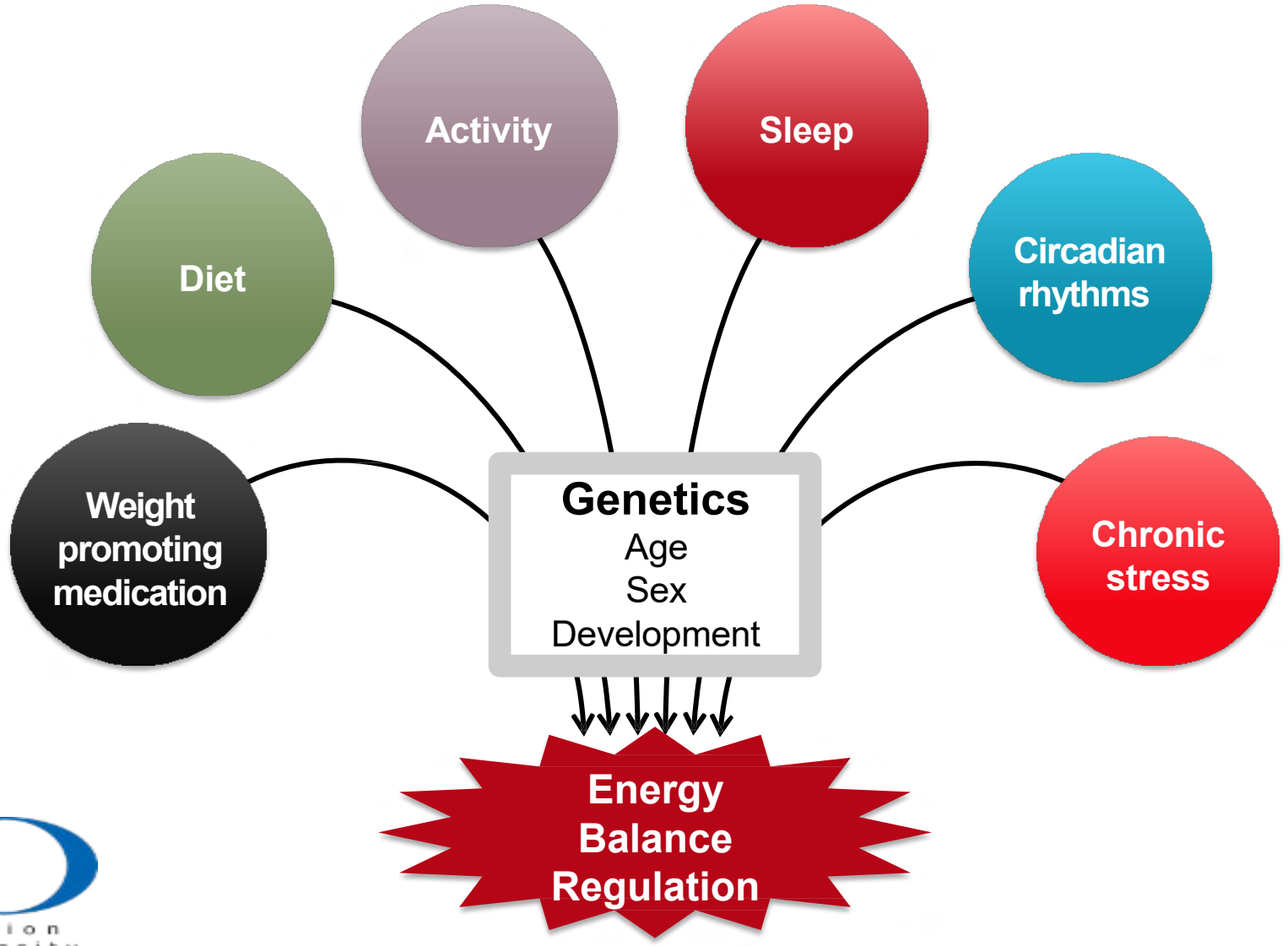
BMI, body mass index

The multidisciplinary/multilevel approach



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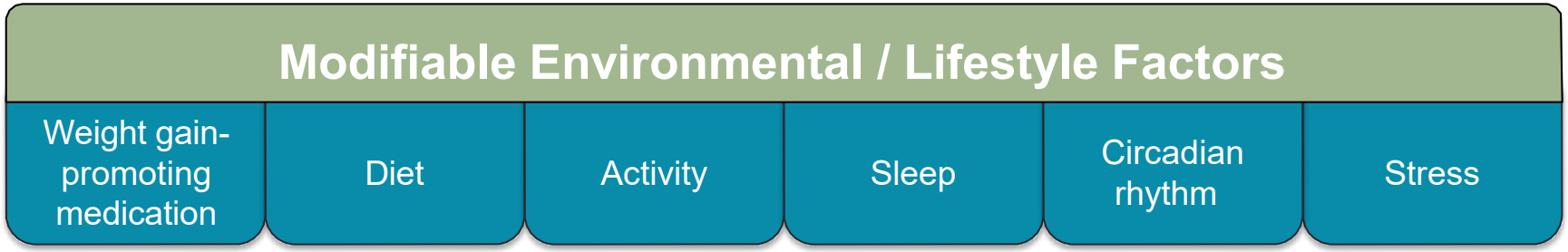
The multidisciplinary/multilevel approach



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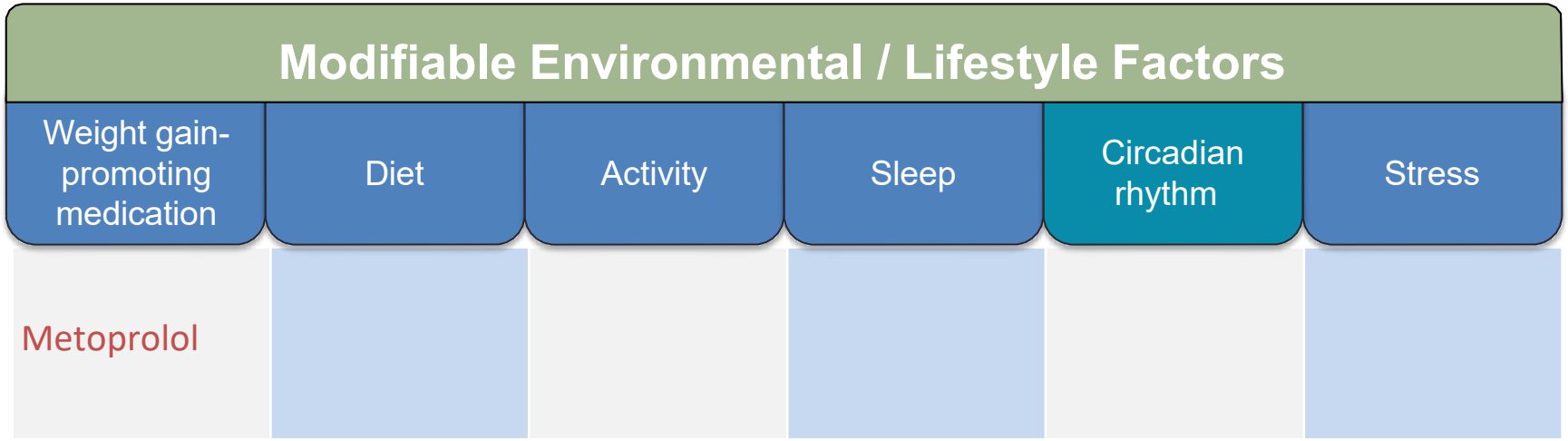
The multidisciplinary/multilevel approach



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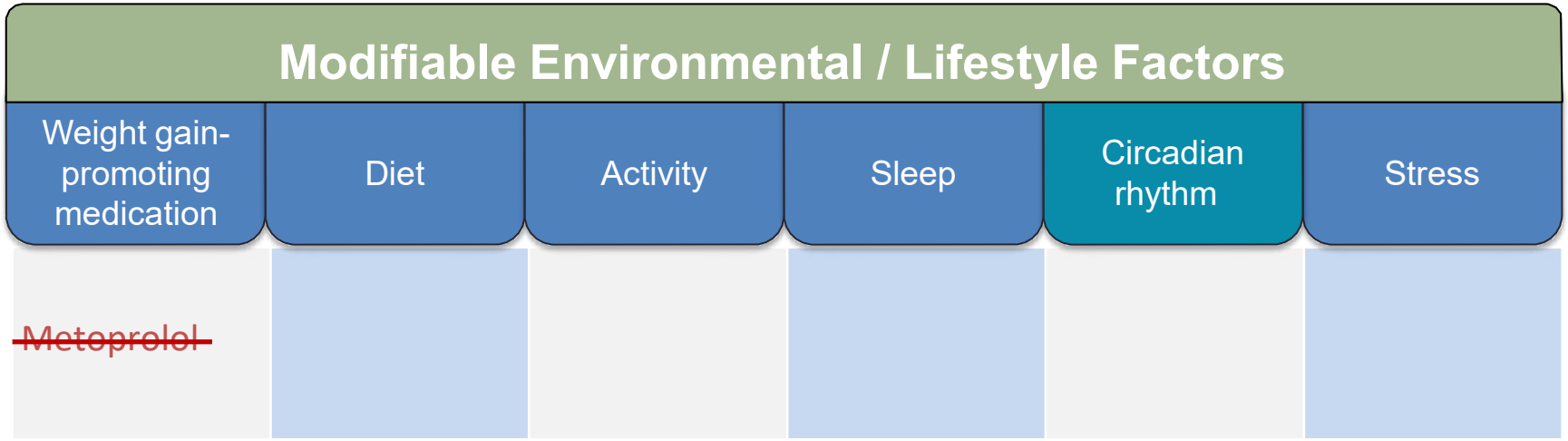
The multidisciplinary/multilevel approach



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The multidisciplinary/multilevel approach

Modifiable Environmental / Lifestyle Factors					
Weight gain-promoting medication	Diet	Activity	Sleep	Circadian rhythm	Stress
~~Metoprolol~~	Med/low carb	3 hours/week 10000steps	Biofeedback		Psychological treatment

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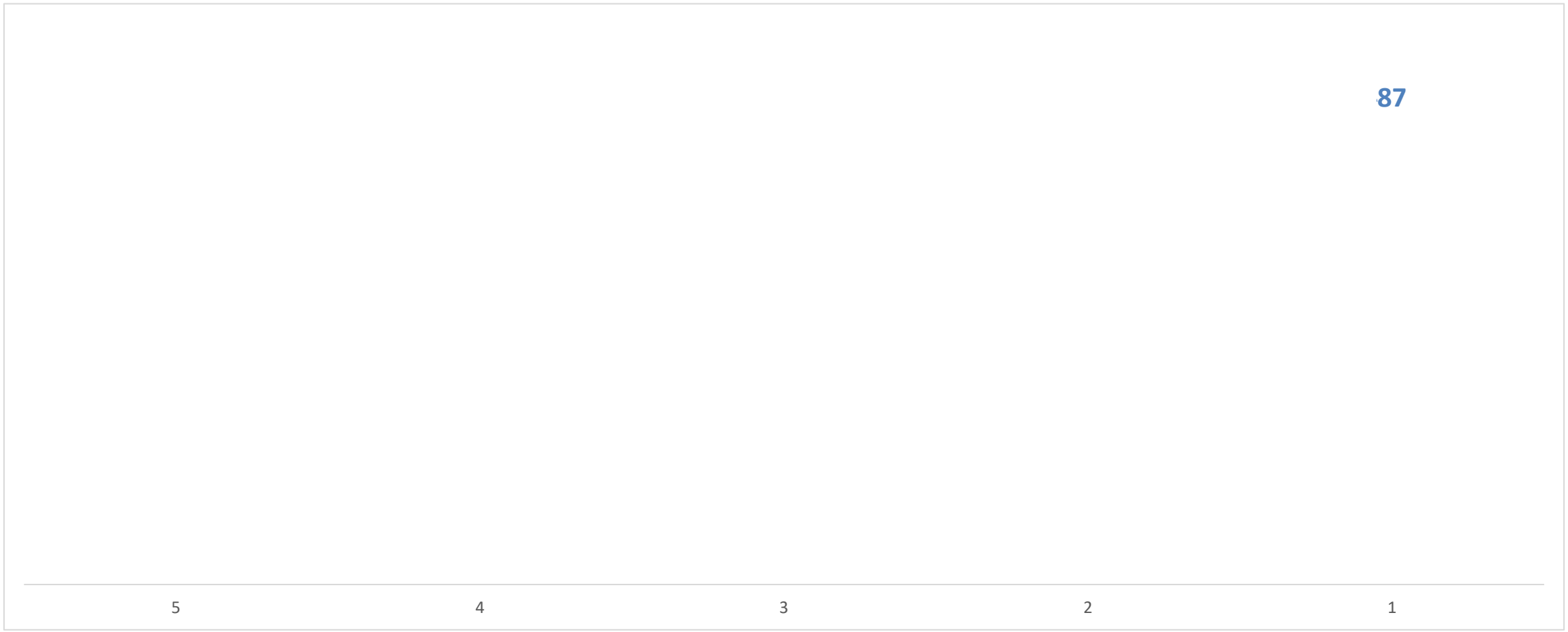

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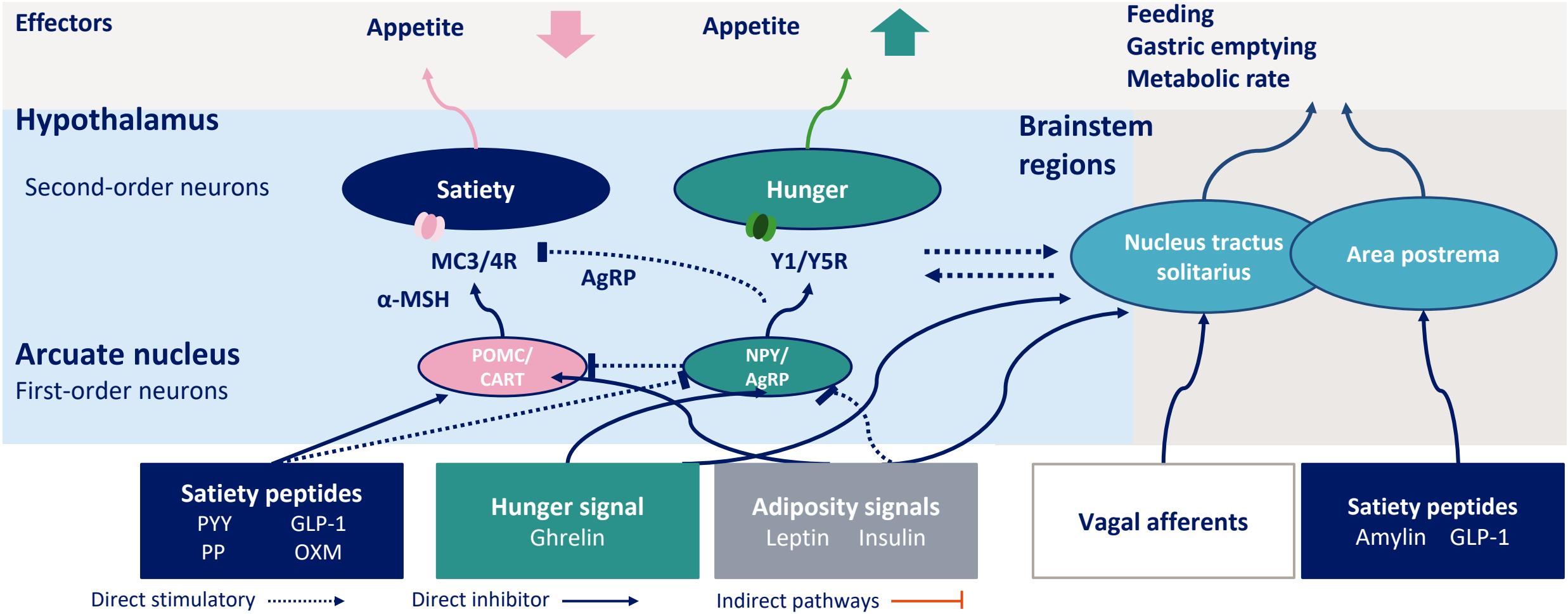
Homeostatic regulation of appetite



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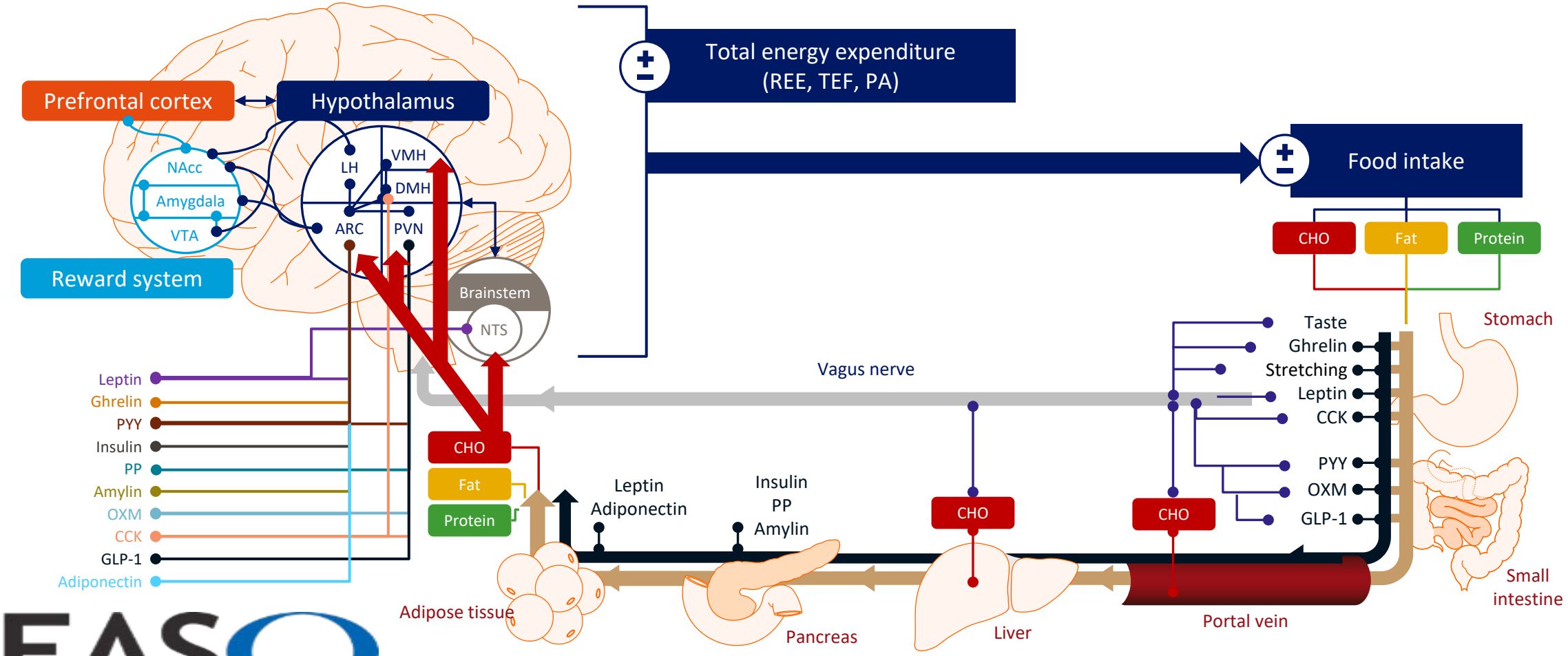
a-MSH, a-melanocyte stimulating hormone; AgRP, Agouti-related peptide; CART, cocaine- and amphetamine-regulated transcript; GLP-1, glucagon-like peptide-1; MC3/4R, melanocortin 3/4 receptor; NPY, neuropeptide Y; OXM, oxyntomodulin; POMC, pro-opiomelanocortin; PP, pancreatic polypeptide; PYY, peptide YY; Y1/Y5R, Y1/Y5 receptor.
Adapted from: Badman et al. Science 2005;307:1909–14; Seo et al. Endocr J 2008;55:867–74; Secher et al. J Clin Invest 2014;124:4473–88.

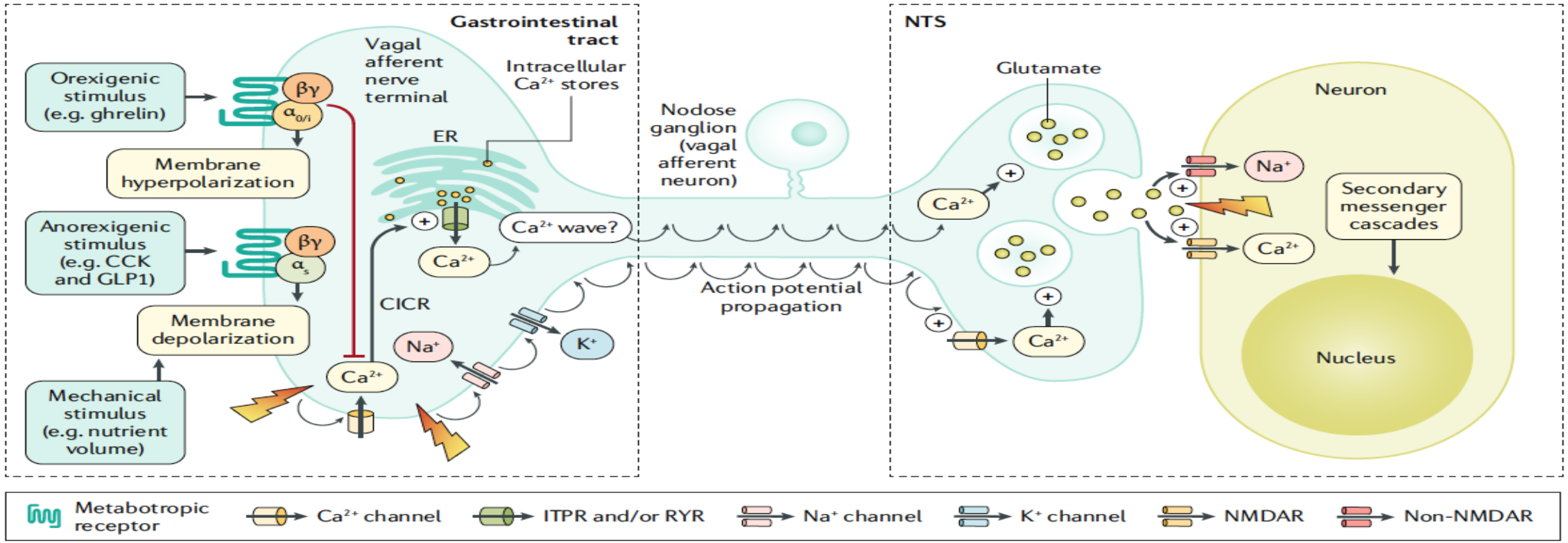
The neuro-hormonal actors involved in energy homeostasis



European Association for the Study of Obesity

Theilade S et al. Diabetes Obes Metab 2021;Suppl 1:17–35.

Schematic diagram for the proposed signal transmission pathways for the vagal afferent system



Waise TMZ, Natute Reviews | Gastroenterology & Hepatology 2018

WORKING HYPOTHESIS: Phenotype-guided Interventions

** Validated in randomized clinical trials	Hungry brain	Hungry gut	Emotional hunger	Slow Burn
LIFESTYLE INTERVENTION	• Hungry brain diet	• Hungry gut diet	• Behavioral therapy • Hungry feelings diet	• Intense exercise plan • Slow burn diet
MEDICATION**	• Phentermine-Topiramate ER • Lorcaserin	• Liraglutide	• Bupropion-Naltrexone SR	• Phentermine
DEVICE**	• Vagal nerve block • Endoscopy sleeve gastroplasty	• Intragastric balloons • Intragastric gels		
SURGERY	• Laparoscopic sleeve gastrectomy	• Roux-en-Y gastric bypass		

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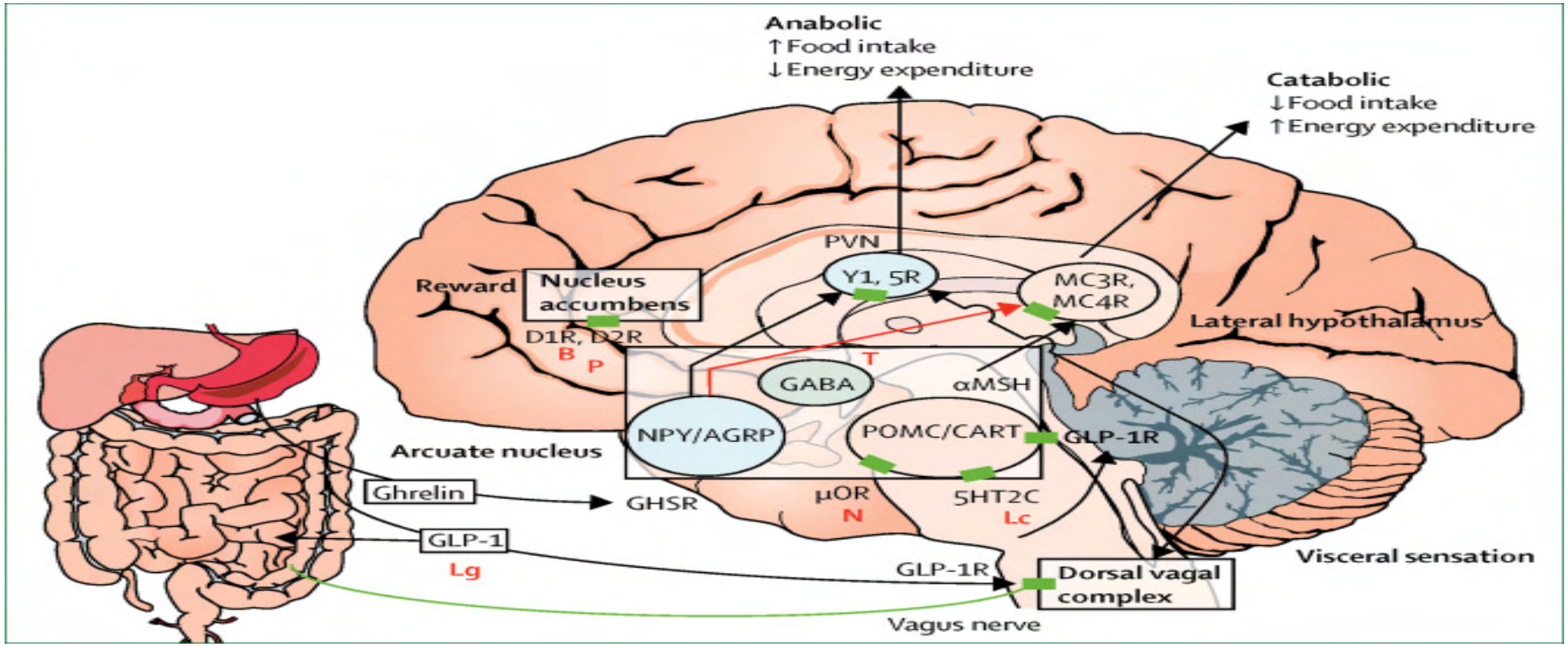
Schematic depiction of the regions of the brain involved in regulation of appetite and energy expenditure



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Daniel H Bessesen, Luc F Van Gaal, ***Lancet Diabetes Endocrinol*** **2018**

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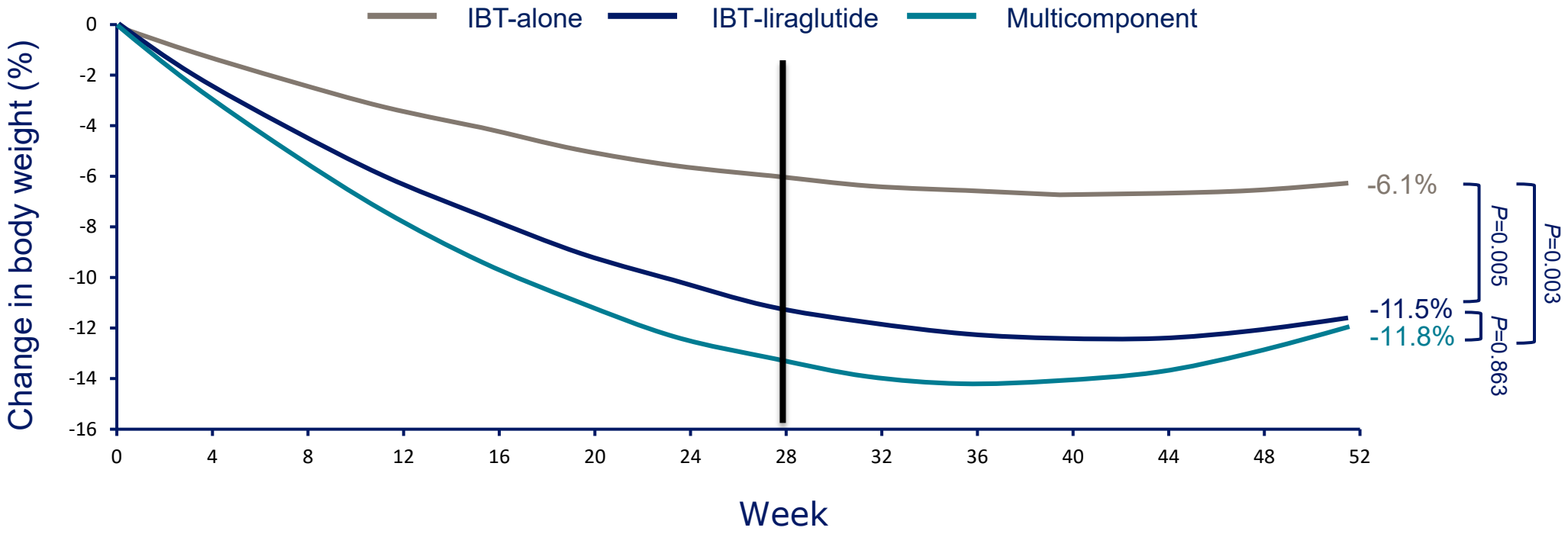
Estimated mean percentage reduction in baseline weight over 52 weeks in the intention to-treat-population



IBT (IBT-alone), providing 21 counselling visits; IBT combined with liraglutide (IBT-liraglutide); or IBT-liraglutide combined for 12 weeks with a 1,000- to 1,200-kcal/d meal-replacement diet (Multicomponent).

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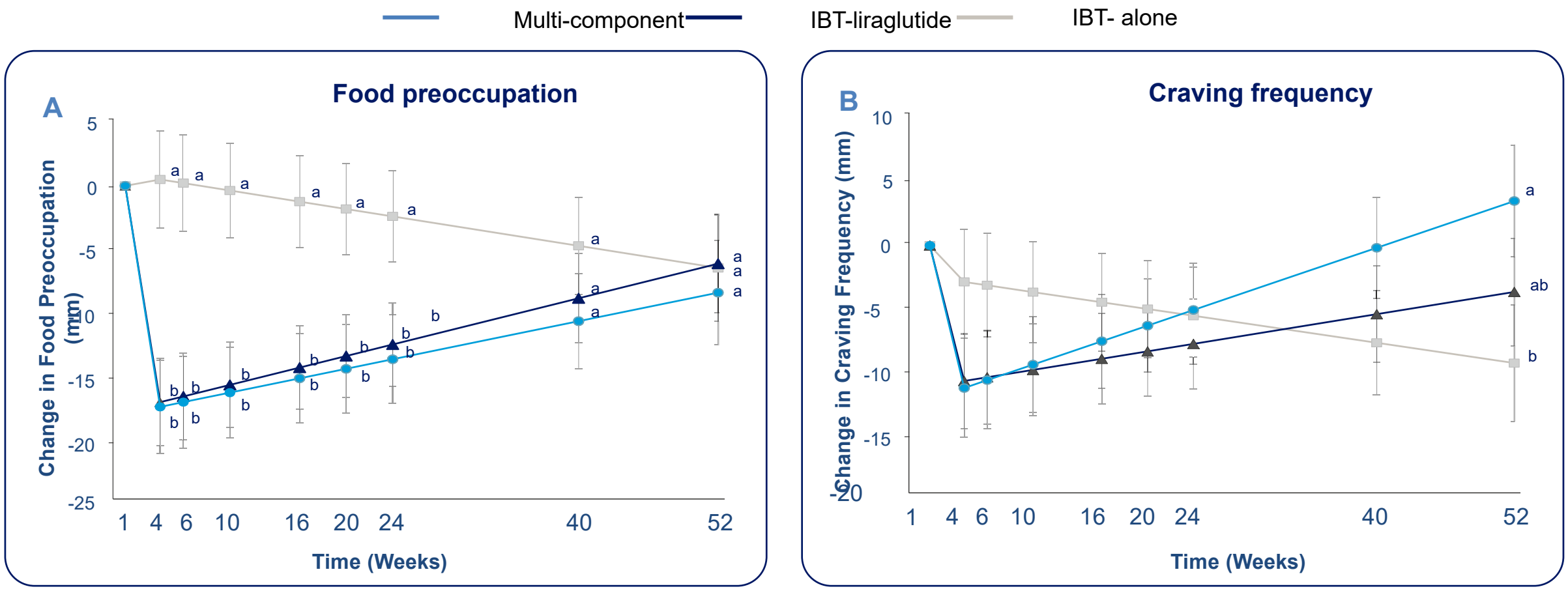
Wadden, T.A., et al., Obesity (Silver Spring), 2019; 27(1): 75-86.

Effects of liraglutide on appetite, food preoccupation, and food liking: results of a randomized controlled trial



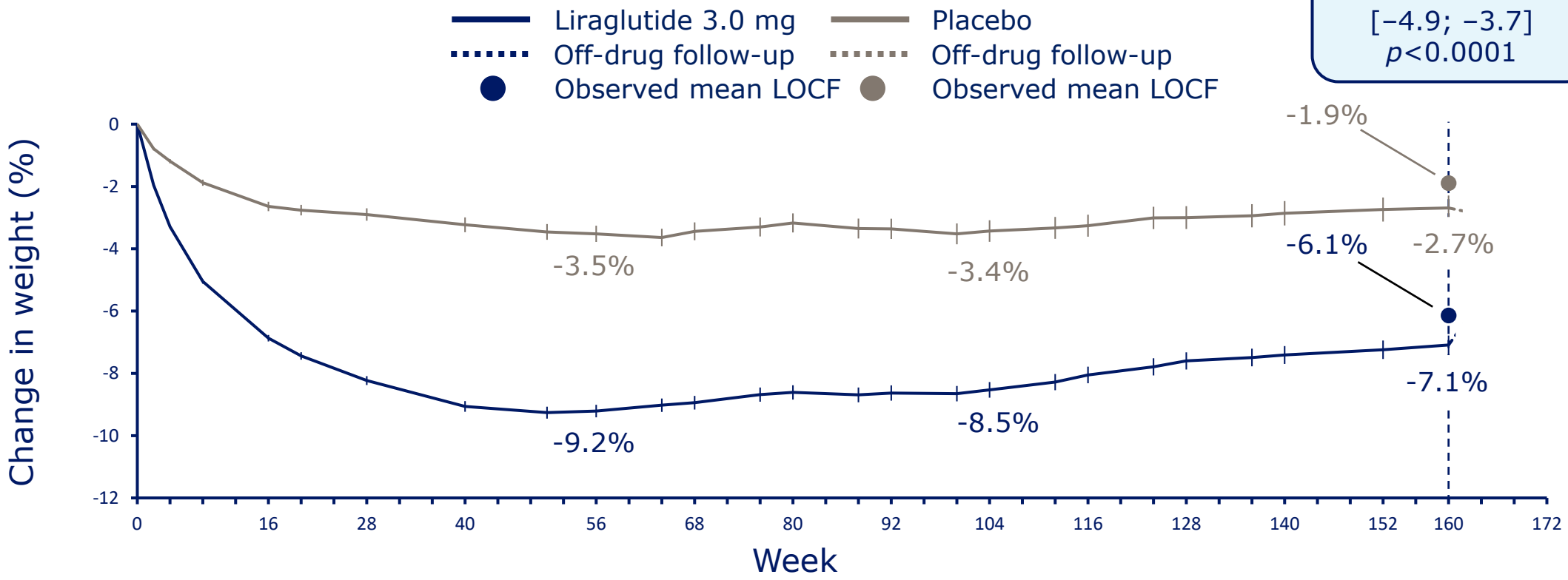
All Values are estimated modelled mean changes relative to baseline (±SE) in the intention to treat population (n=113).
Values with different superscripts (a vs. b) differ significantly from each other at p <0.05. Values that share a superscript do not differ significantly

Tronieri, J.S., et al., *Int J Obes (Lond)*, 2019; doi: 10.1038/s41366-019-0348-6

Change in body weight (%)

0–172 weeks

ETD at week 160:
−4.3%
[−4.9; −3.7]
$p<0.0001$



n=	1467	1295	1223	1161	1100	1030	971	911	885	849	830	805	780	747	778
n=	734	635	576	544	508	465	436	399	375	365	354	336	327	322	320

Full analysis set, fasting visit data only. Line graphs are observed means (±SE)
LOCF, last observation carried forward; SE, standard error

le Roux *et al*. *Lancet* 2017;389:1399–409

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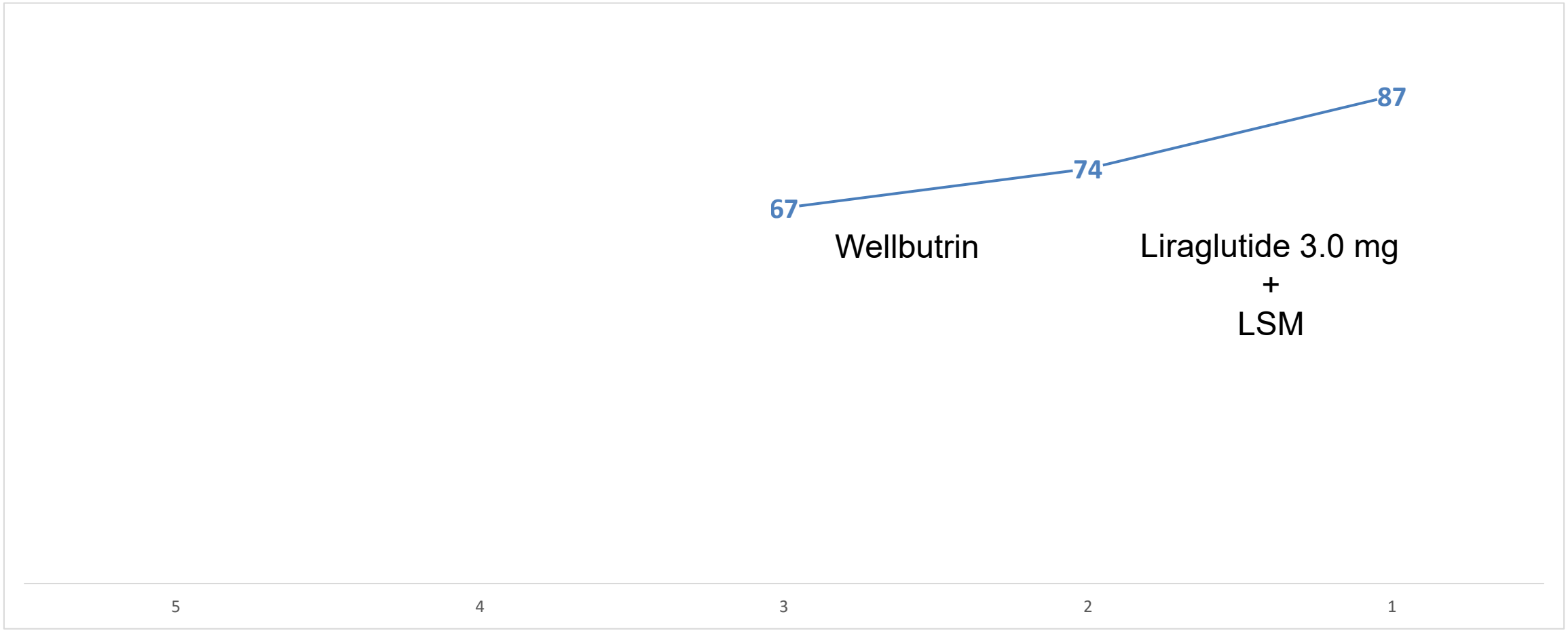

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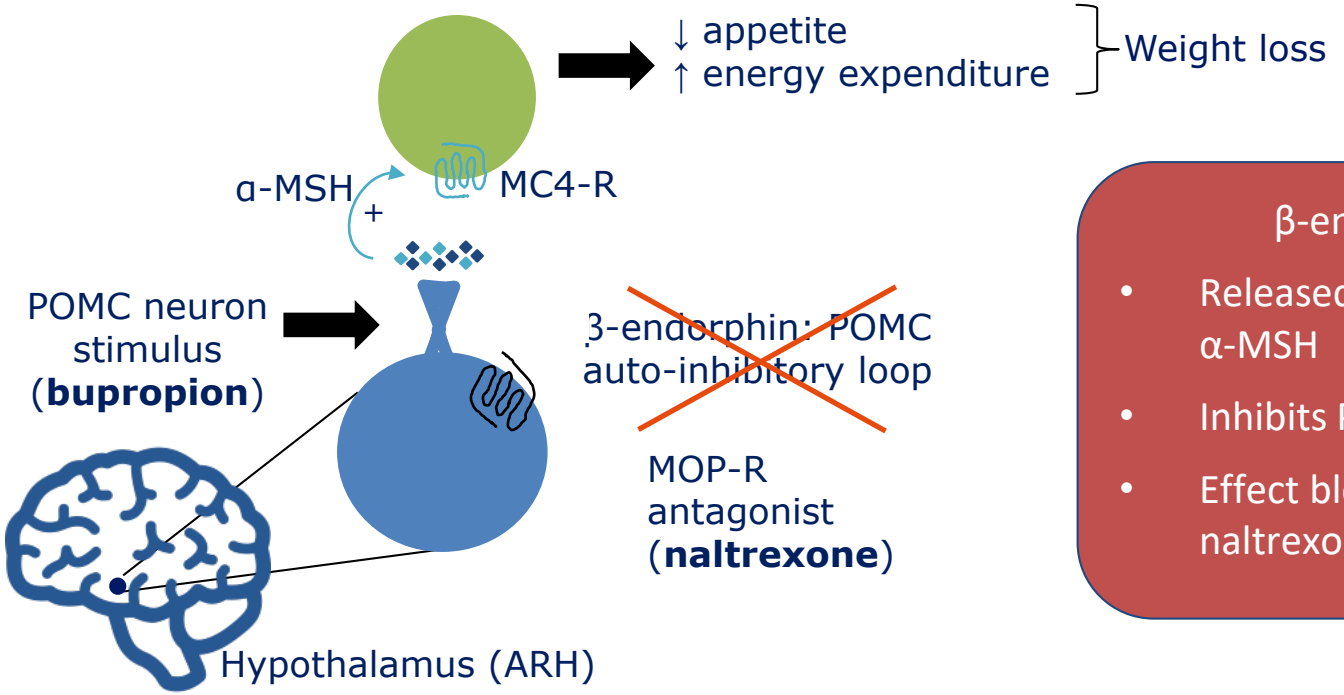
Naltrexone–bupropion: mechanism of action

- The NB combination synergistically impacts on two different pathways associated with increased energy expenditure and reduced energy intake:



POMC:

- Satiety signal
- Increased firing leads to weight loss
- Activated by bupropion

β-endorphin:

- Released with α-MSH
- Inhibits POMC firing
- Effect blocked by naltrexone

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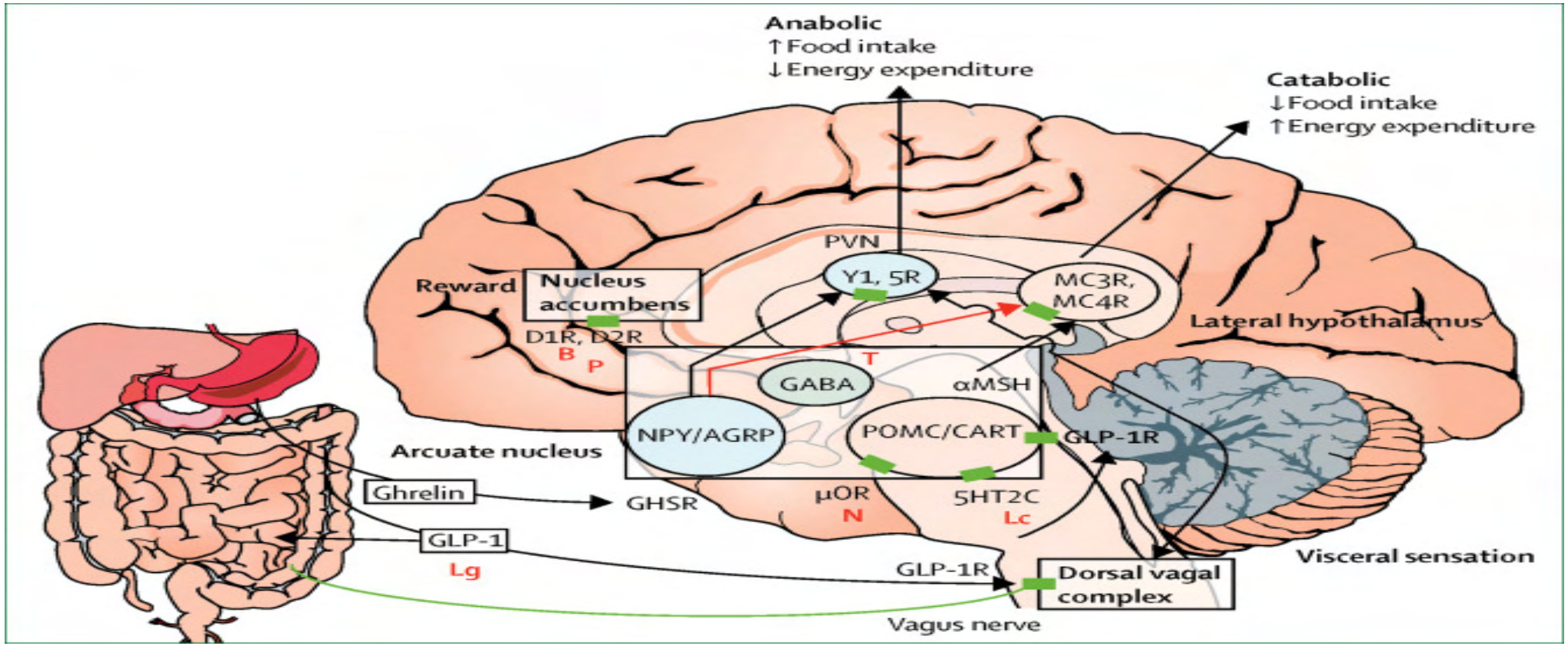
ARH, arcuate nucleus of the hypothalamus; α-MSH, alpha-melanocyte stimulating hormone; MC4-R, melanocortin-4 receptor; MOP-R, μ-opioid peptide receptor; MSH, melanocyte-stimulating hormone; NB, naltrexone–bupropion; POMC, pro-opiomelanocortin

Ornellas, Chavez. *P.T.* 2011;36:255–62; Padwal. *Curr Opin Investig Drugs* 2009;10:1117–25

Schematic depiction of the regions of the brain involved in regulation of appetite and energy expenditure



EASO
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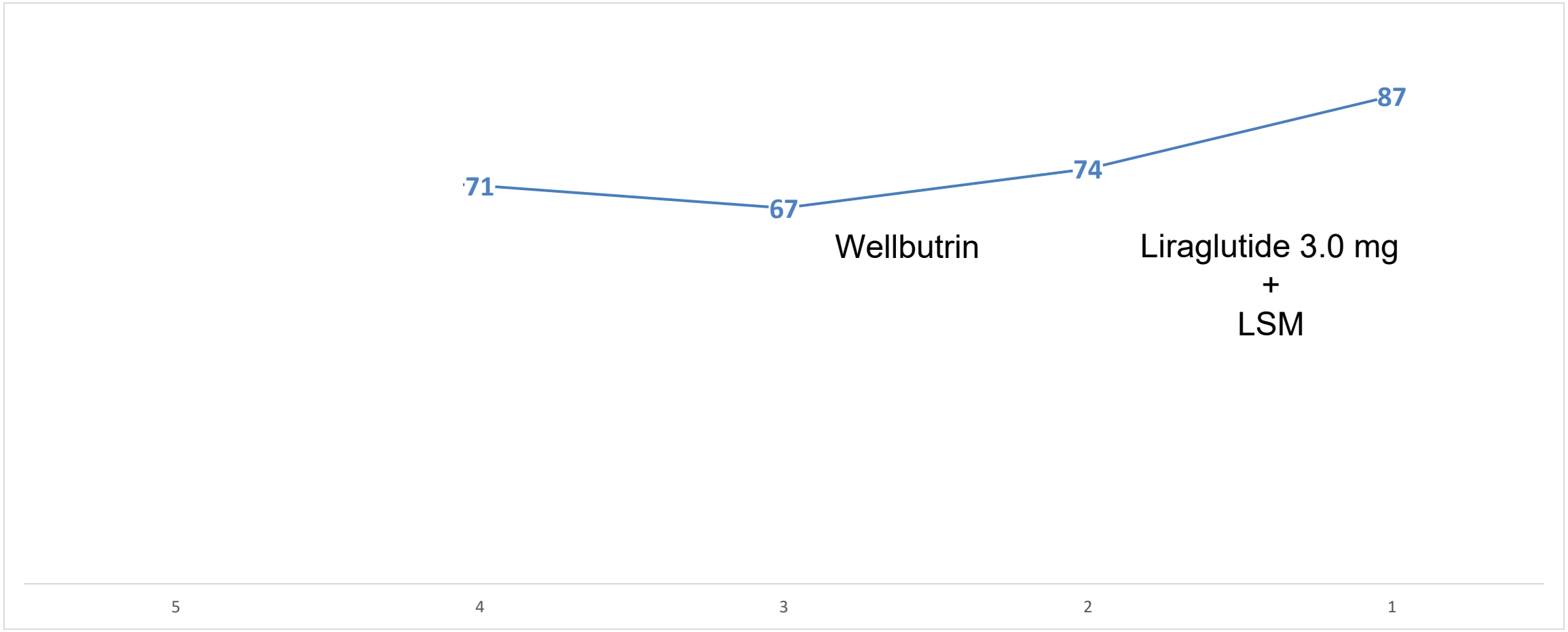
Daniel H Bessesen, Luc F Van Gaal, ***Lancet Diabetes Endocrinol*** **2018**



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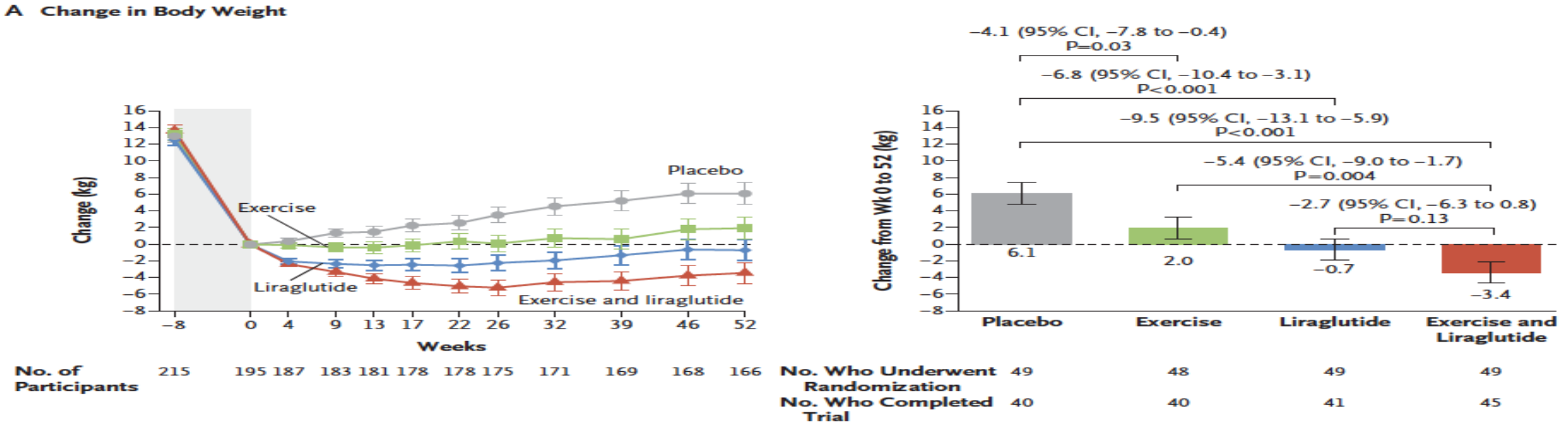
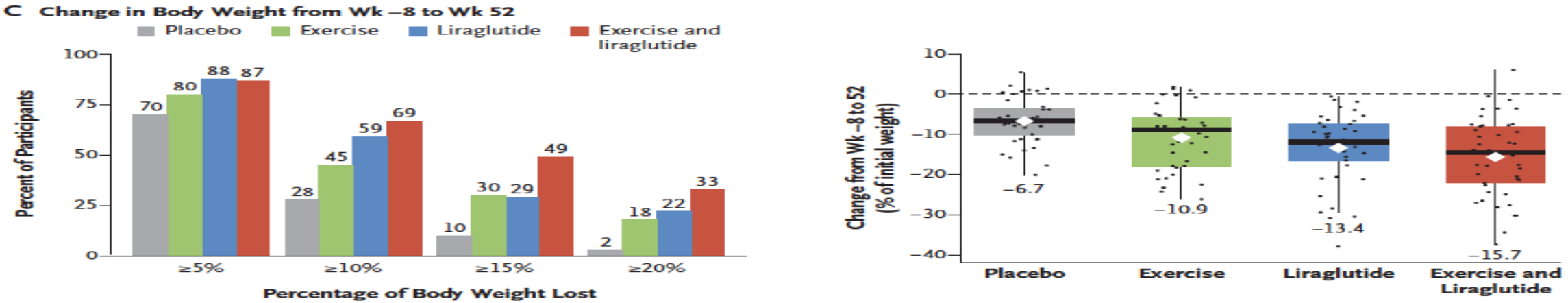
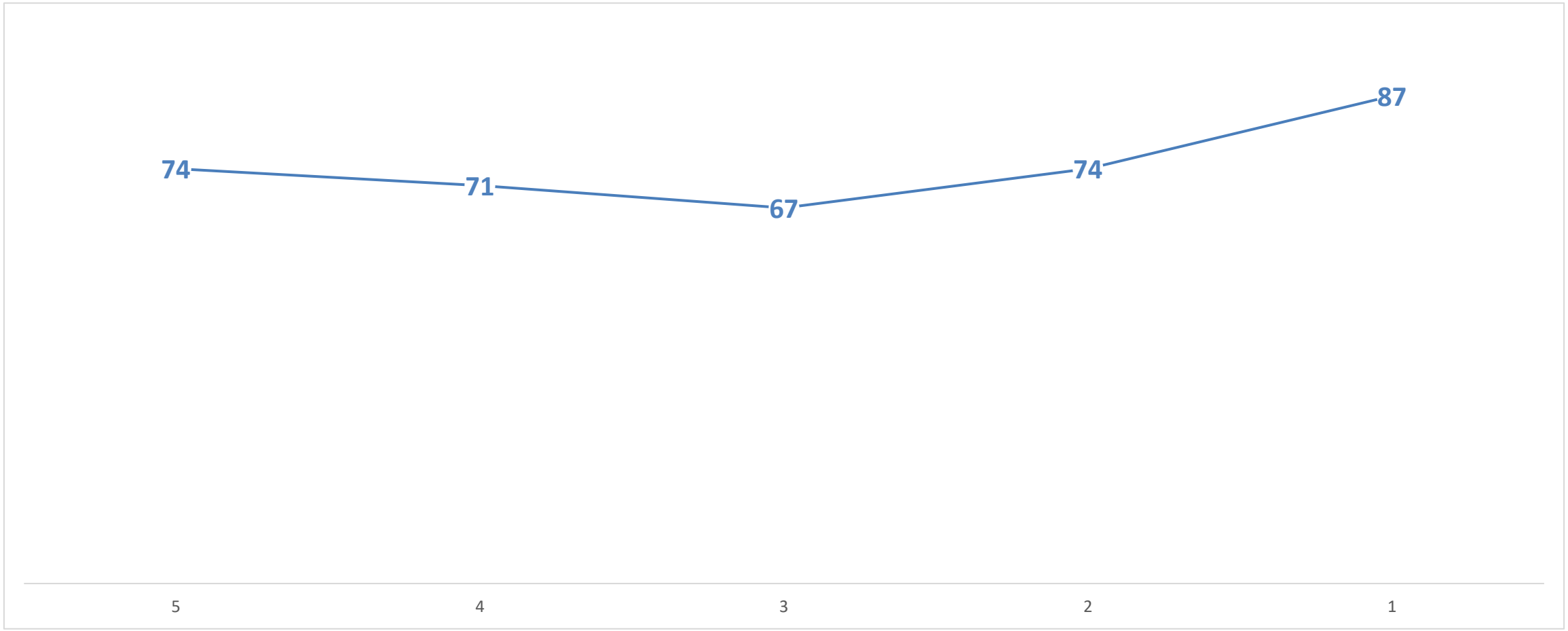
Multimodality Weight loss Maintenance





EASOCOM
EASO Collaborating Centre for Obesity Management

Lundgren JR, NEJM 2021



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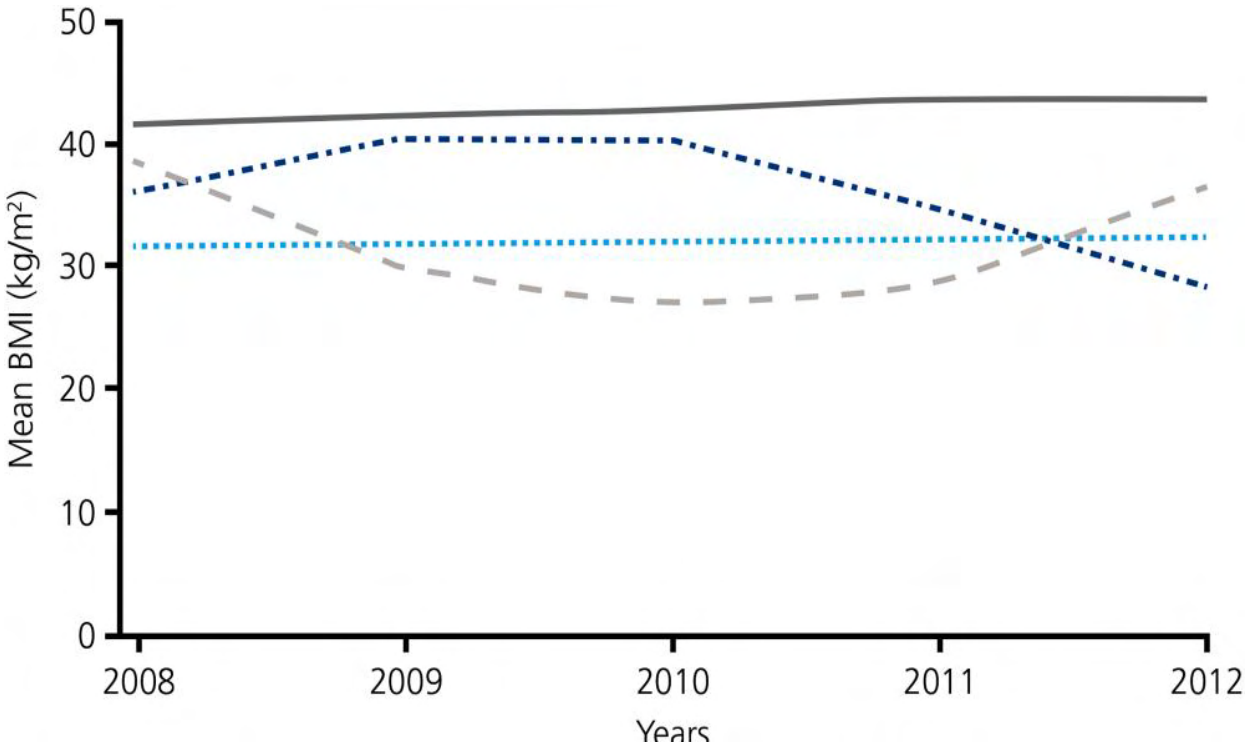
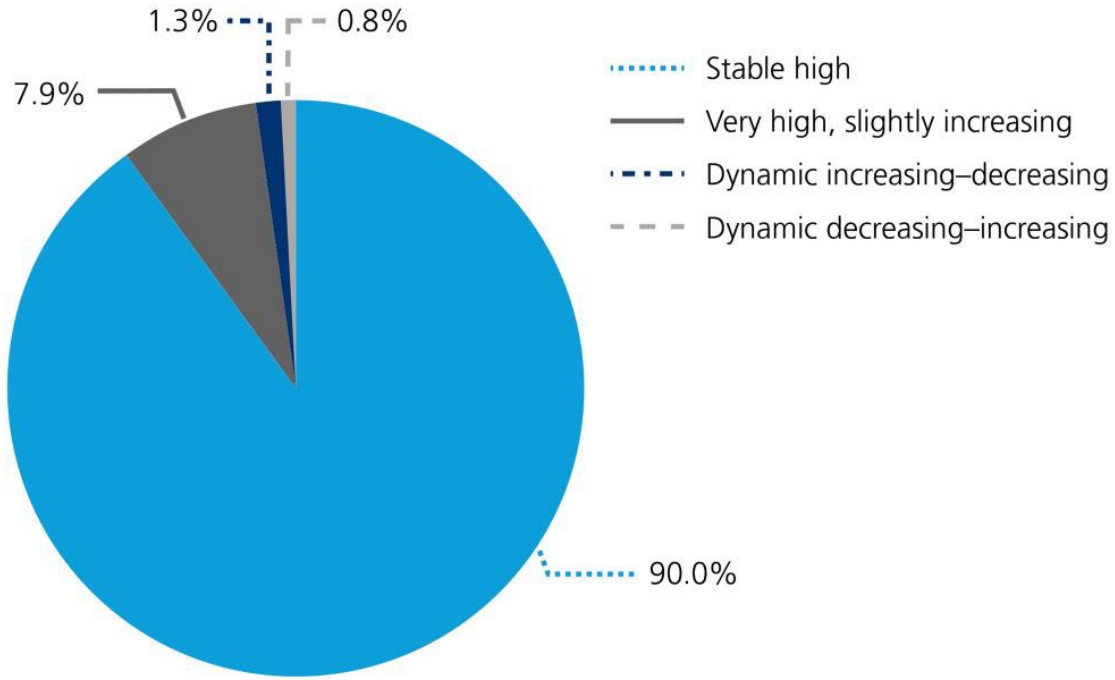
Longitudinal BMI trajectory clusters over the 5-years study period and proportions of individuals in each cluster. (360,000 PwO)





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Reges O, Dicker D et.al. Obes Sci Pract. 2020c

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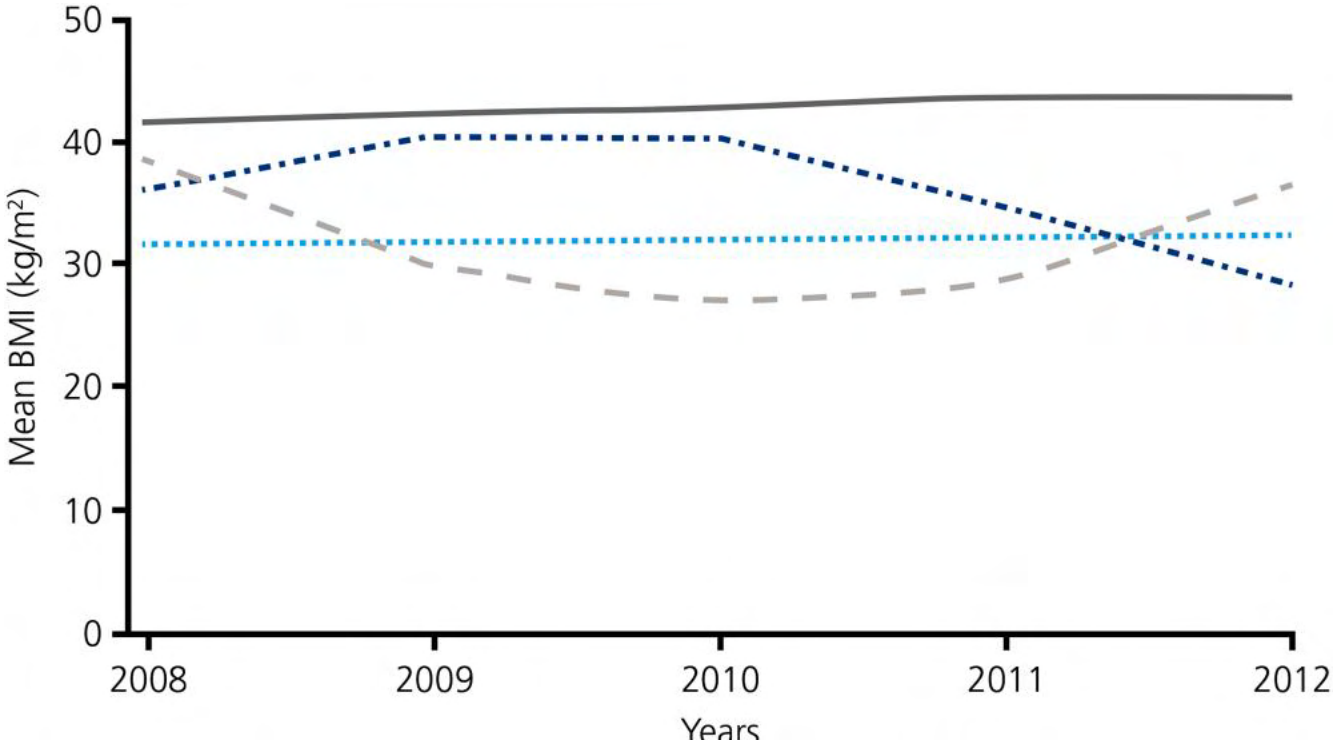
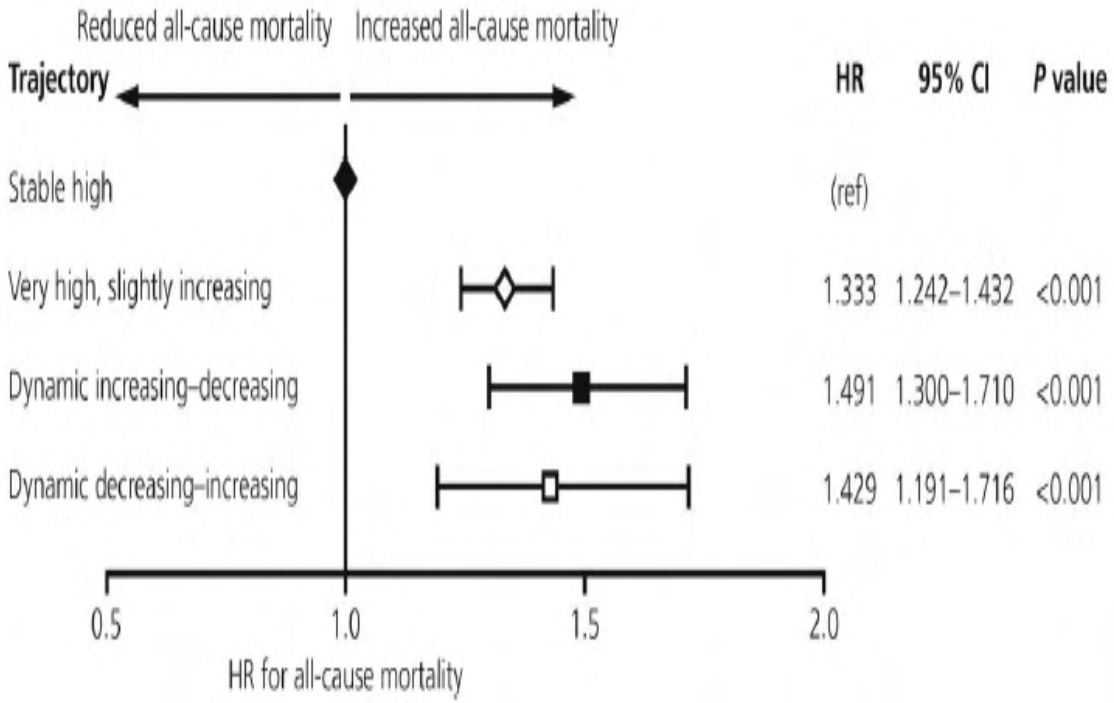




EASO
European Association for the Study of Obesity

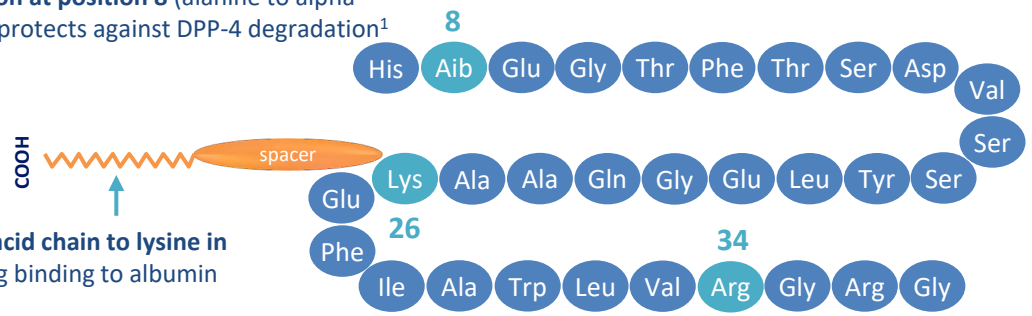
Reges O, Dicker D et.al. Obes Sci Pract. 2020

Mechanism of action of semaglutide

Semaglutide is a human GLP-1 analogue

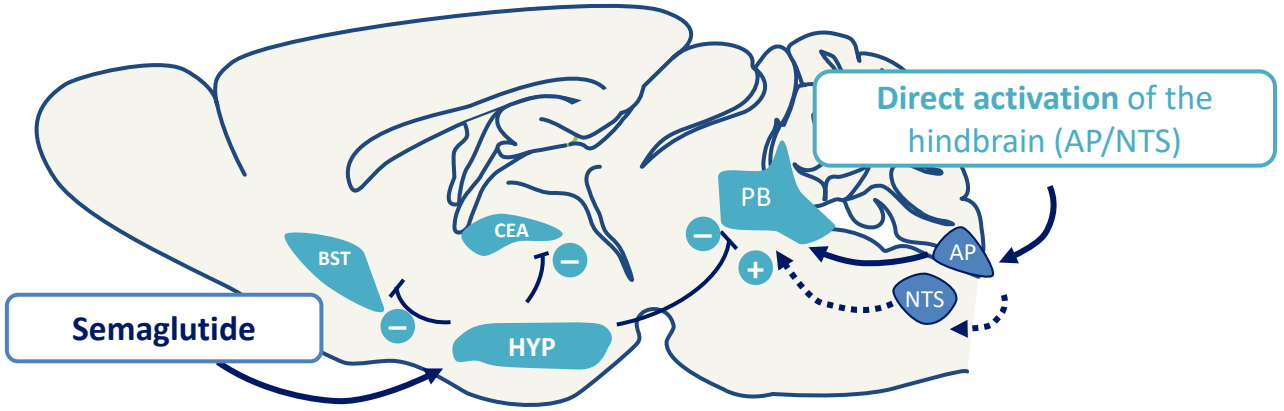
- 94% homology to human GLP-1
- $t_{½}$ of approximately 1 week

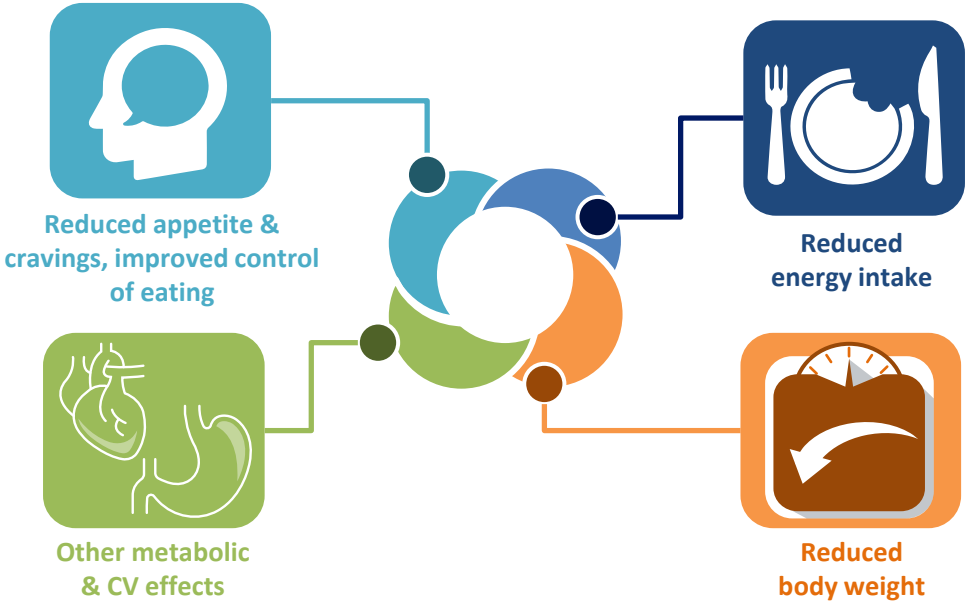
Amino acid substitution at position 8 (alanine to alpha-aminoisobutyric acid) protects against DPP-4 degradation[1]



Spacer and C-18 fatty di-acid chain to lysine in position 26 provide strong binding to albumin

Amino acid substitution at position 34 (lysine to arginine) prevents C-18 fatty di-acid binding at the wrong site





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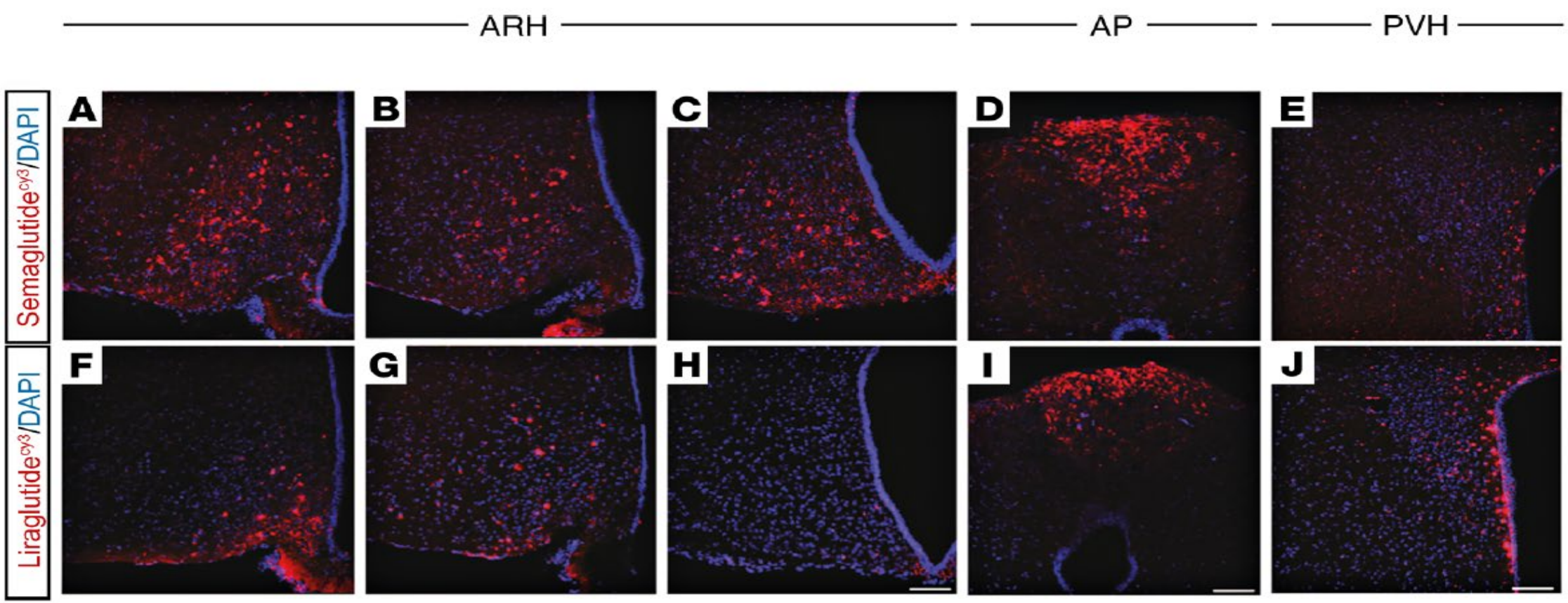
Differential distribution of semaglutide^{Cy3} and liraglutide^{Cy3} in the hypothalamus and AP.

Semaglutide is not approved in the Europe for weight management



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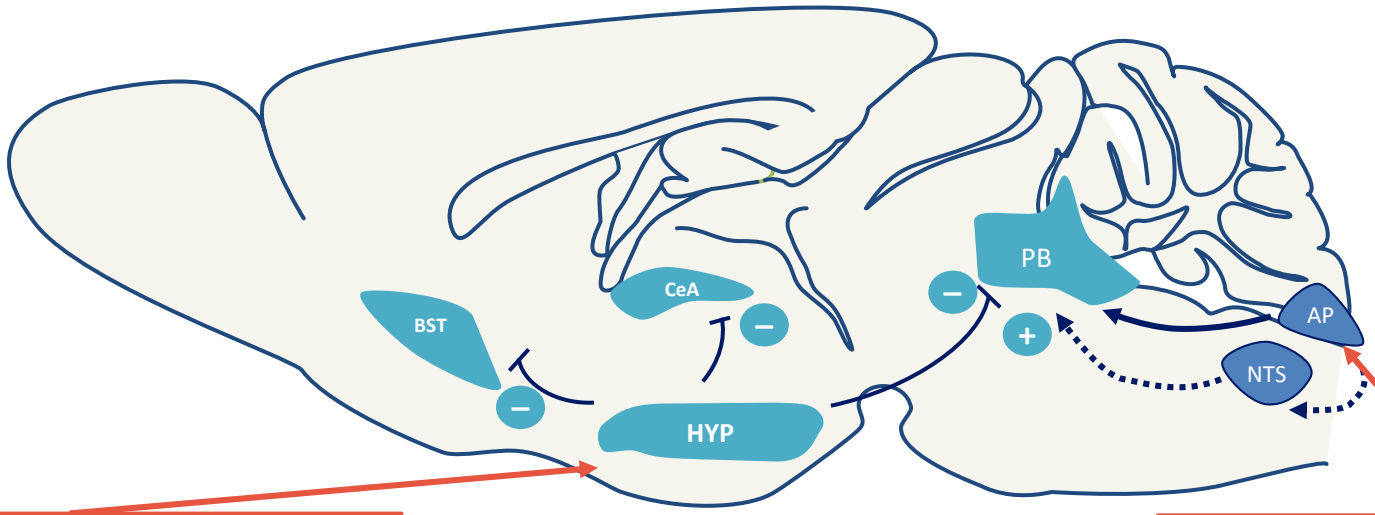
Gabery S et al. JCI Insight 2020;5

Semaglutide mechanism of action

Appetite regulation in rodents



Semaglutide

Direct activation of the hypothalamus (HYP)

Homestatic appetite regulation

Semaglutide

Direct activation of the hindbrain (AP/NTS)

Hedonic appetite regulation

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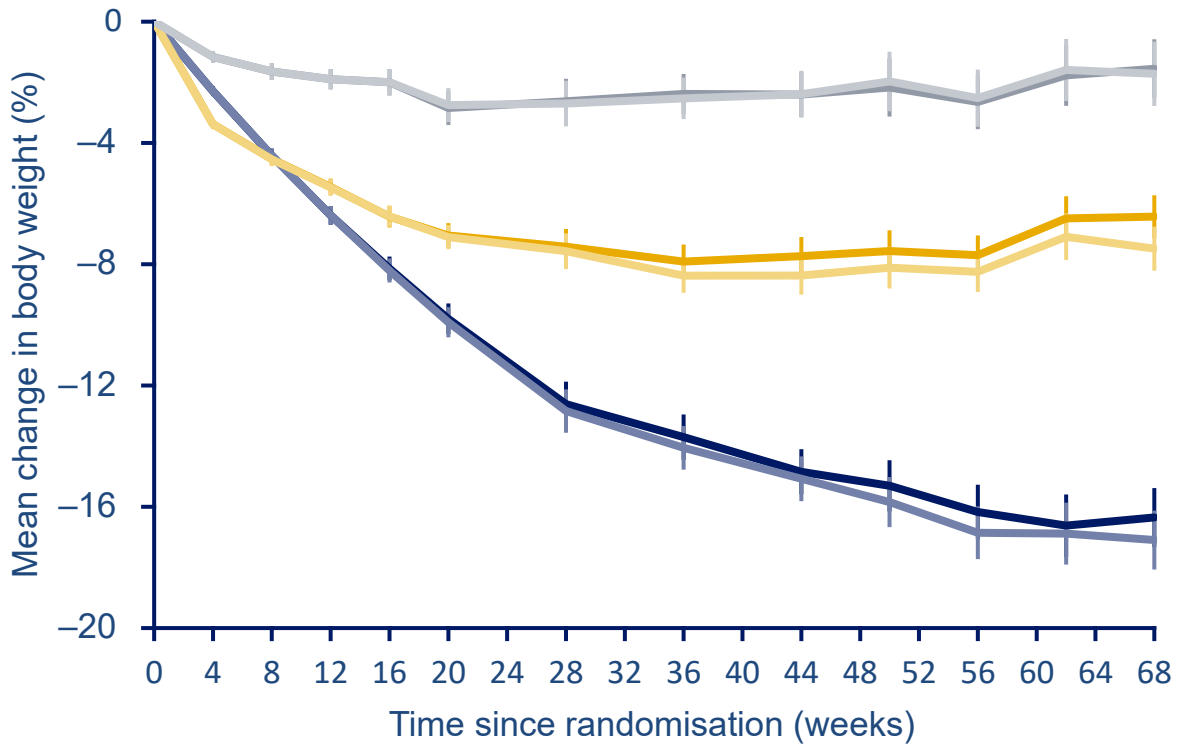
AP, area prostrema; ARH, arcuate nucleus; BST, bed nuclei of the stria terminalis; CeA; central amygdala nucleus; HYP, hypothalamus; NTS, nucleus tractus solitarius; PB, parabrachial nucleus.
Adapted from Gabery et al. JCI Insight 2020;5:e133429.

Body weight change

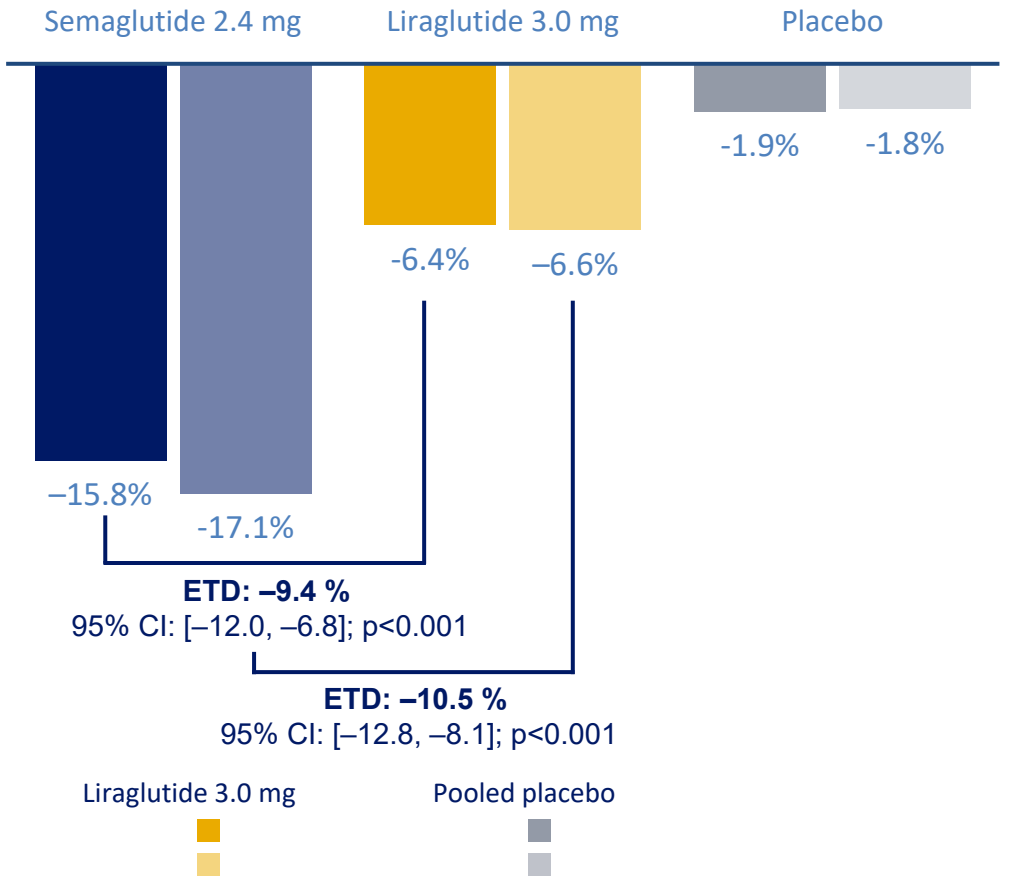
STEP 8

Observed mean change over time*

(Mean at baseline: 104.5 kg)



Estimated mean change from baseline to week 68†



Semaglutide 2.4 mg | Liraglutide 3.0 mg | Pooled placebo

In-trial period/treatment policy estimand:

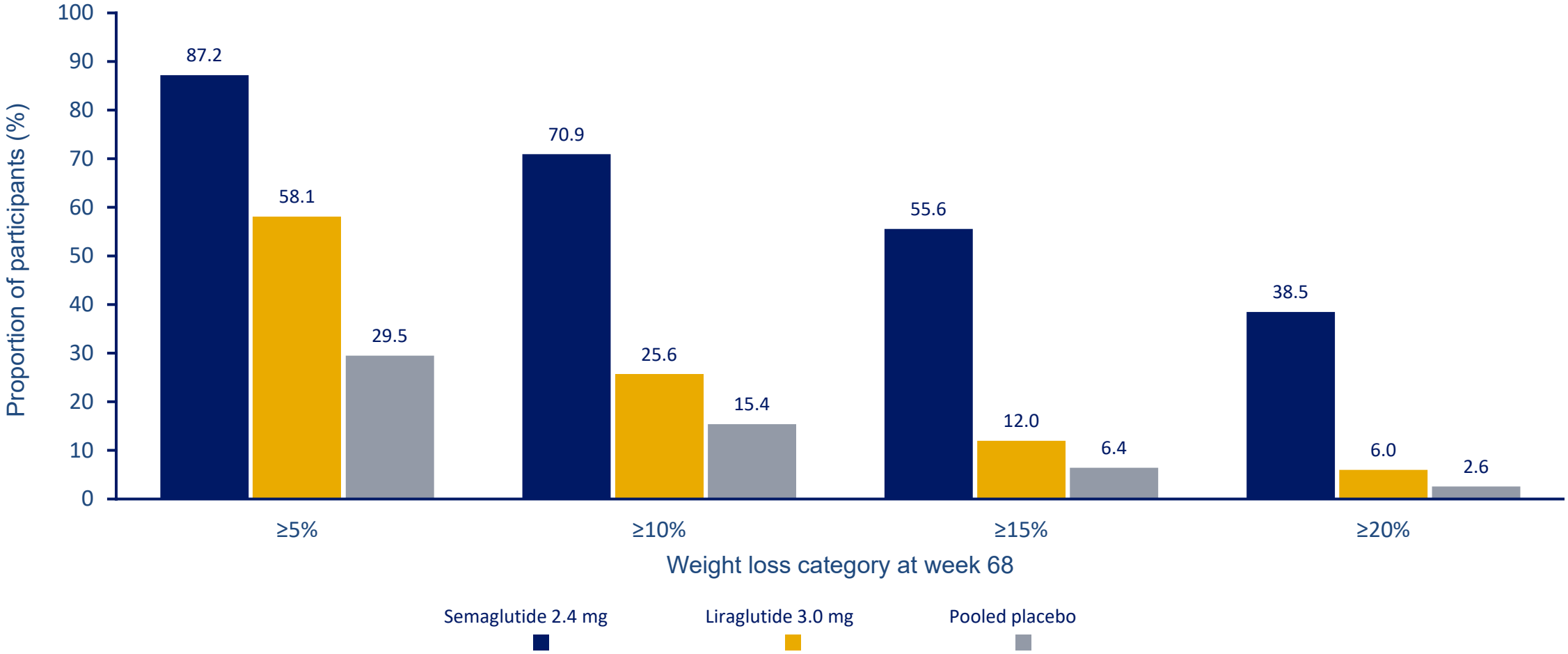
On-treatment period/trial product estimand:

**Observed data for the in-trial and on-treatment periods.† Estimated data for the treatment policy estimand (regardless of treatment adherence or rescue intervention use) and the trial product estimand (until first discontinuation or initiation of rescue intervention). CI, confidence interval; ETD, estimated treatment difference.*

Rubino et al. Presented at the 39th Annual Meeting of The Obesity Society (TOS) held at ObesityWeek®, virtual meeting, November 1–5, 2021.

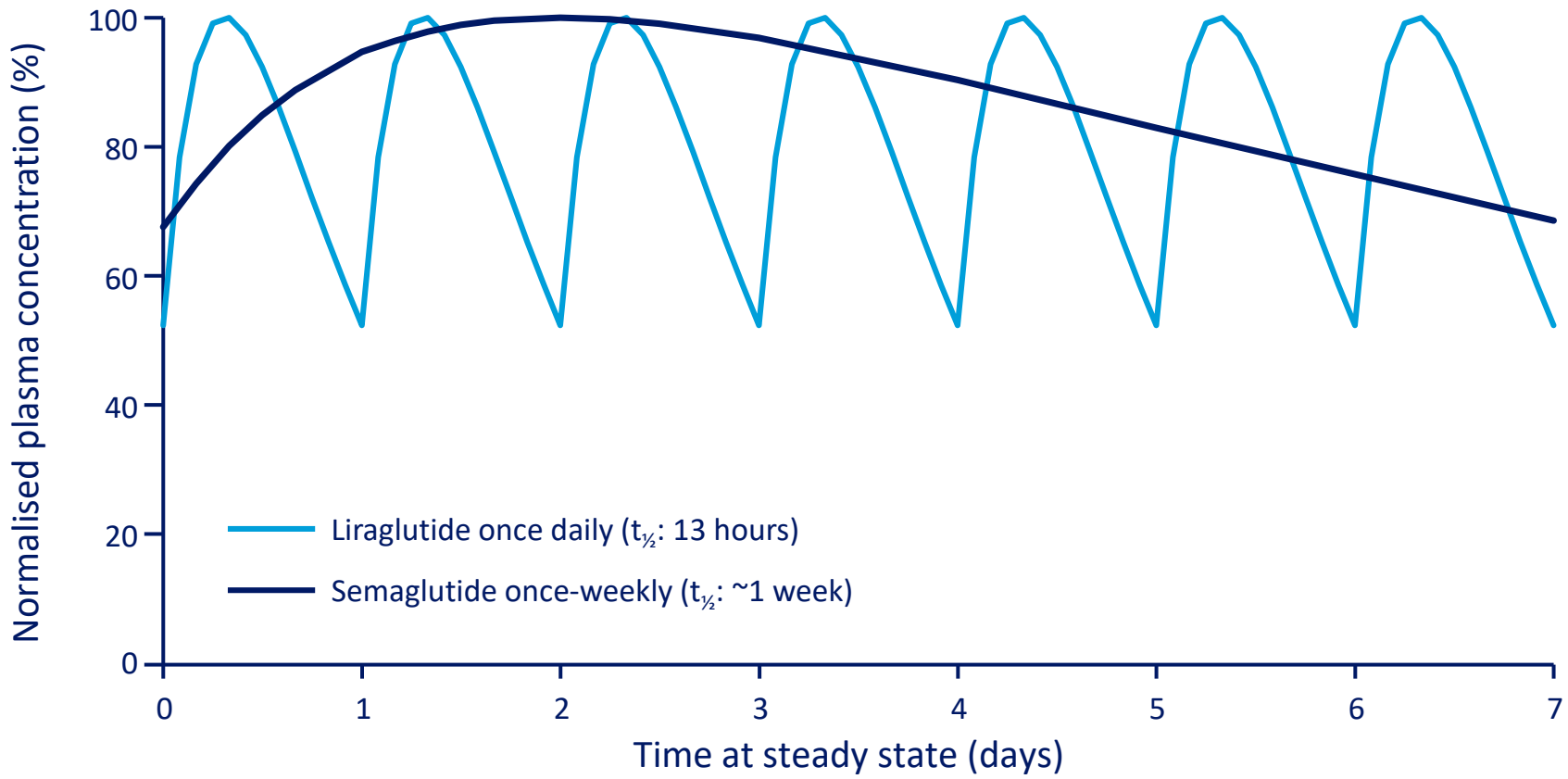
Categorical body weight loss

STEP 8



Observed proportions for the in-trial period. P values are for estimated odds ratios, assessed for the treatment policy estimand (regardless of treatment adherence or rescue intervention use).
Rubino et al. Presented at the 39th Annual Meeting of The Obesity Society (TOS) held at ObesityWeek®, virtual meeting, November 1–5, 2021.

Semaglutide provides more constant plasma levels compared with liraglutide



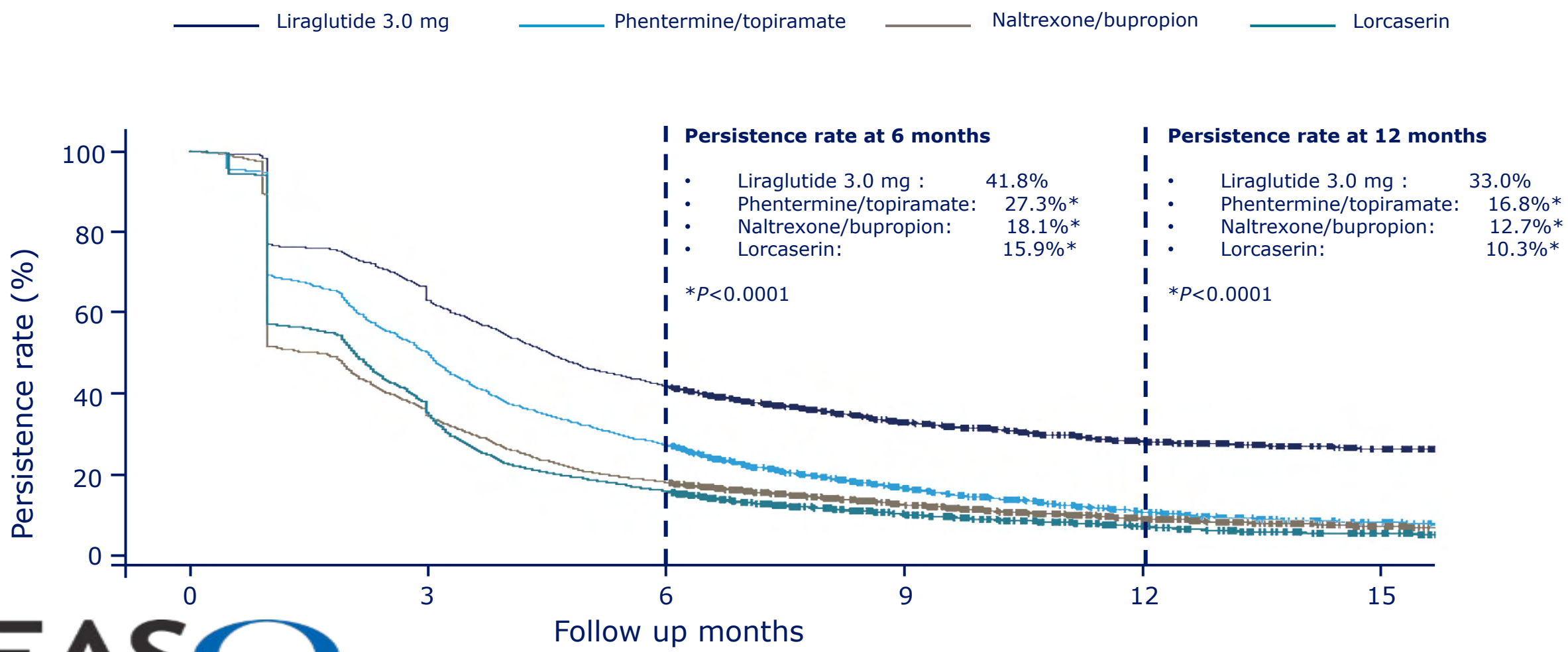
Profiles were based on simulated modelling. Liraglutide is the only GLP-1RA that is approved by the US FDA and EMA for use in overweight/obese p
dosed once daily.

EMA, European Medicines Agency; FDA, US Food and Drug Administration; GLP-1RA, glucagon-like peptide-1 receptor agonist; t½, half life.

Elbrønd et al. Diabetes Care 2002;25:1398–404; Marbury et al. Clin Pharmacokinet 2017;56:1381–90; Novo Nordisk. Data on file.

Perseistence with obesity pharmacothery is low

Kaplan–Meier plot



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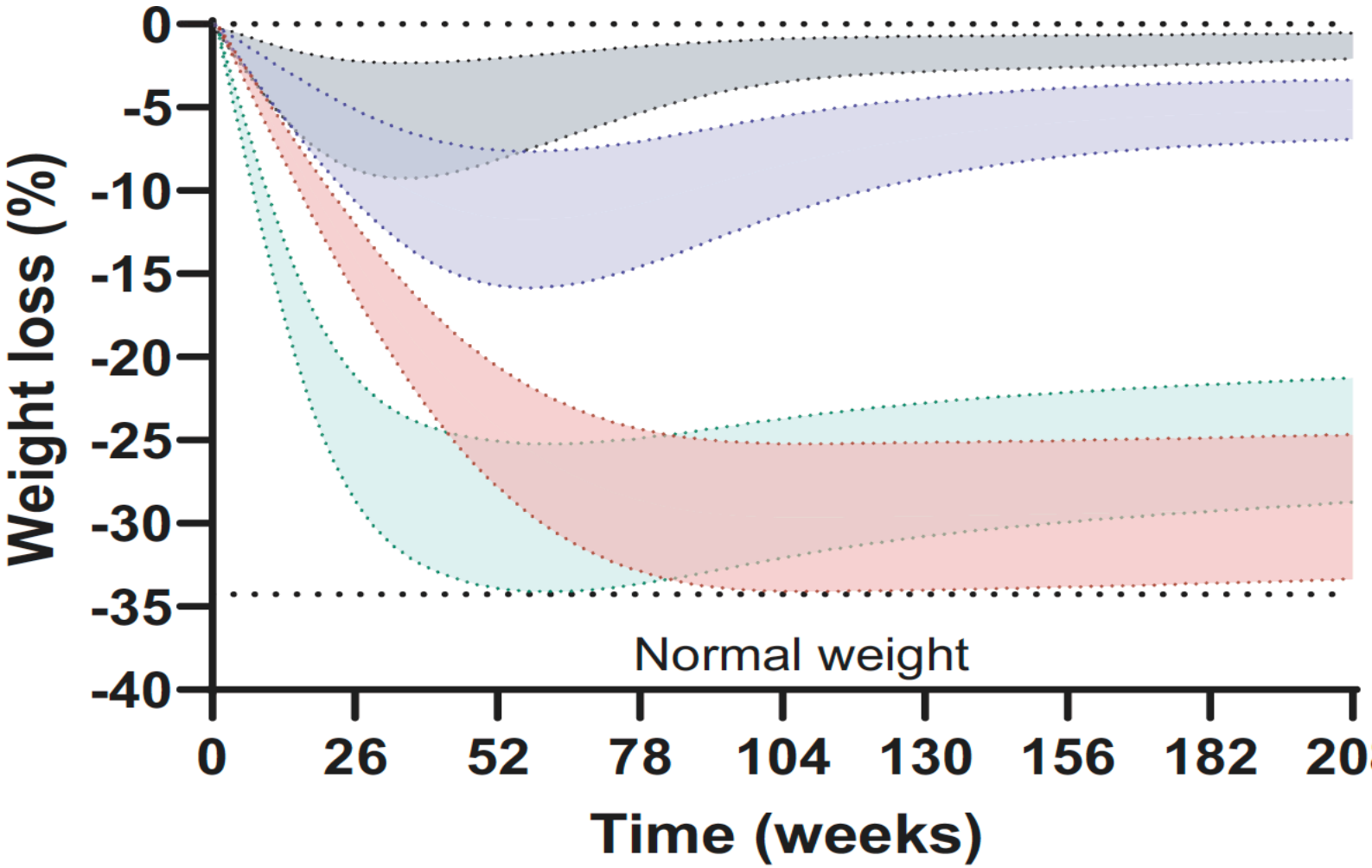
Ganguly *et al. Diabetes Res Clin Pract* 2018;143:348–356

Weight loss and maintenance Trajectories



Life style intervention

Pharmacotherapy

RYGB

Aspiration for future pharmacotherapies: Improved weight loss and maintenance; improved body composition

EASO Collaborating Centre for Obesity Management

Christoffersen B, Obesity 2021

EASO

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Thank You