Adipositas-assoziierten Erkrankungen rechtzeitig und effektiv vorbeugen

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1. Medizinische Abteilung

Wiener Gesundheitsverbund
Klinik Landstraße

Für die Stadt Wien

KARL LANDSTEINER GESELLSCHAFT

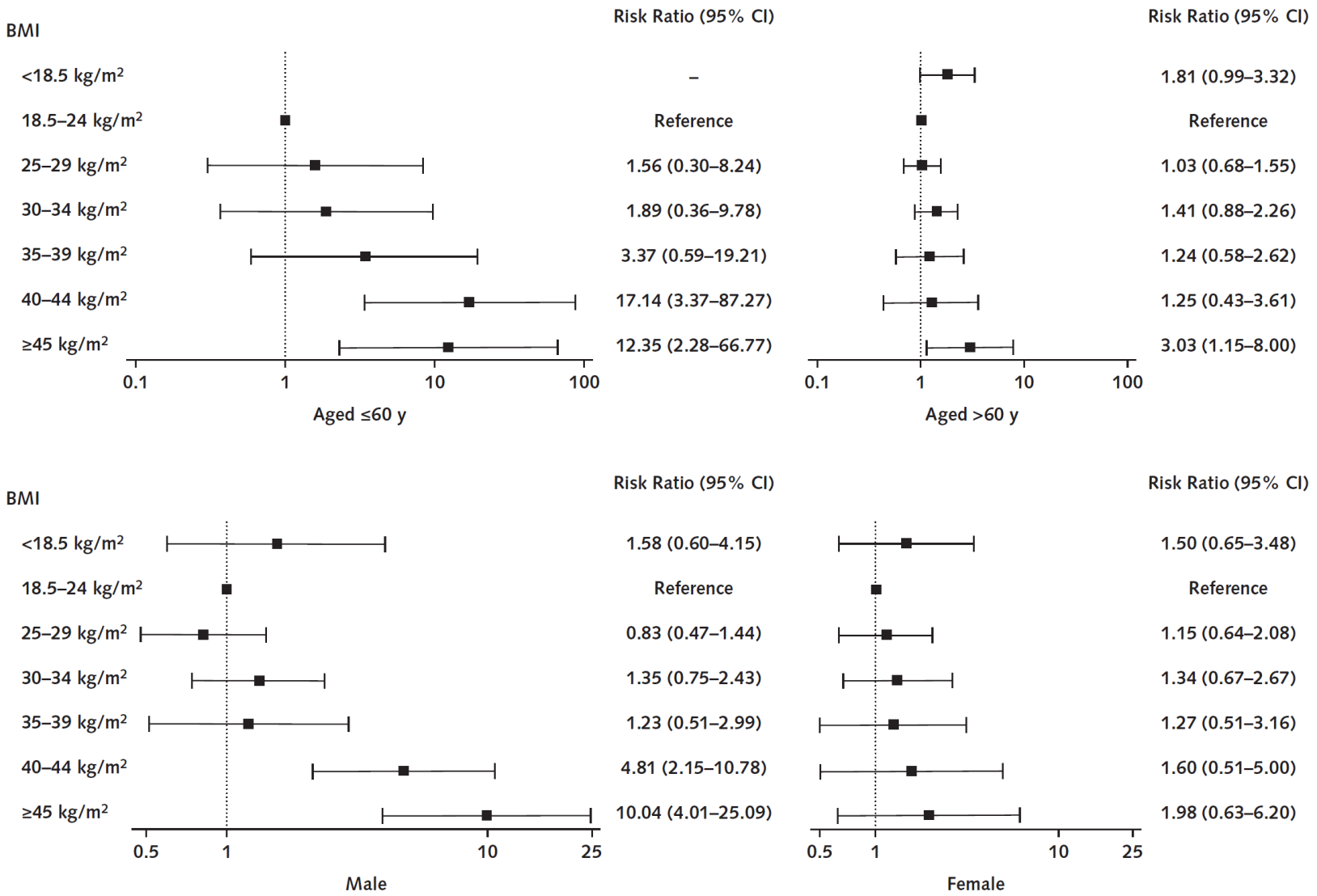
Interessenskonflikte

Mit freundlicher Unterstützung von

Disclosure

- Abbott
- AstraZeneca
- Boehringer Ingelheim
- Eli Lilly
- Novo Nordisk
- Sanofi-aventis

Spätestens jetzt kann man Adipositas nicht länger ignorieren …



Tartof S et al.: Ann Intern Med 2020 Nov 17; 173(10): 773-81

In der Europäischen Region der WHO

1 von 3

11-Jährigen

übergewichtig

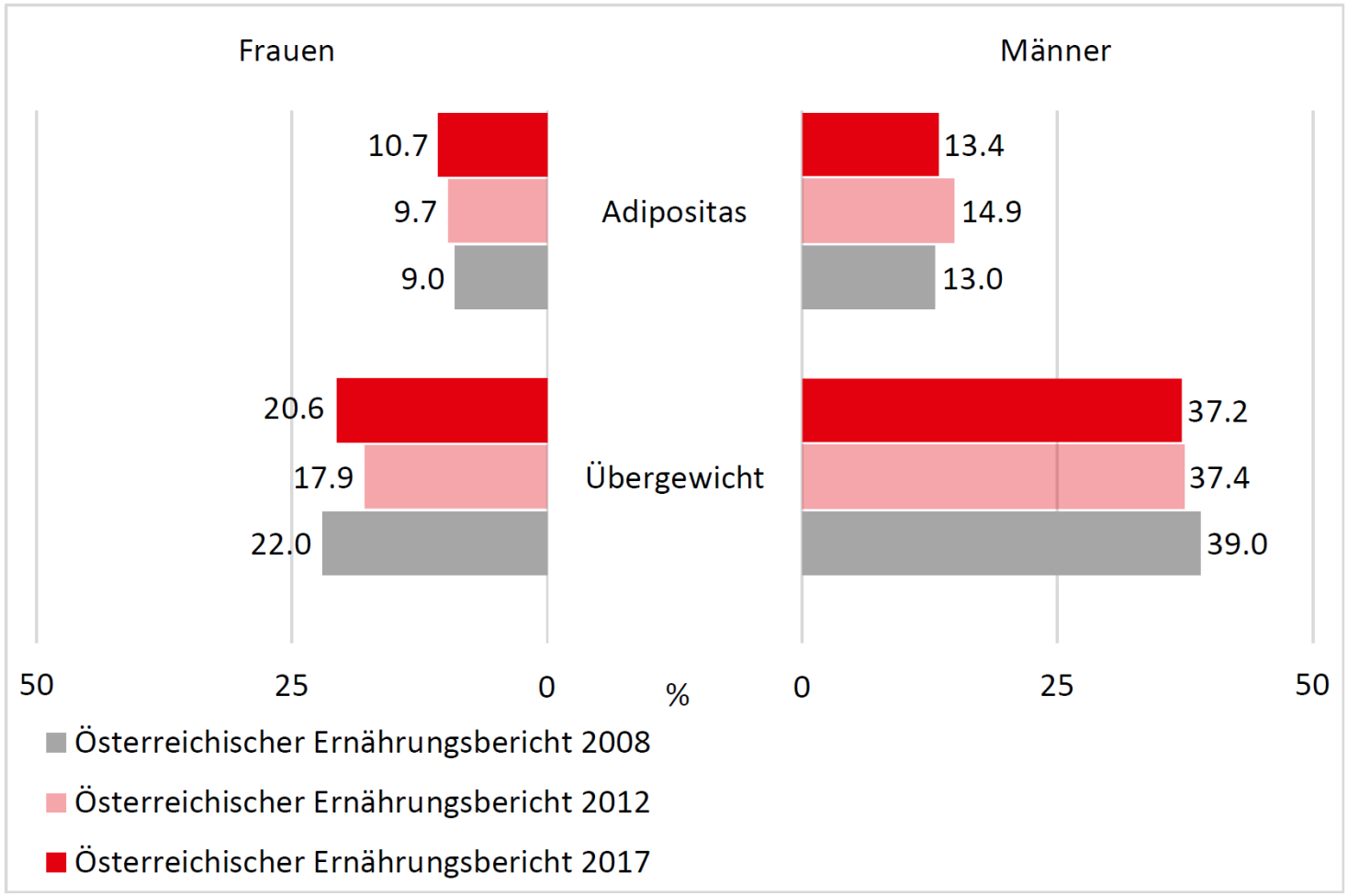
oder

adipös

www.euro.who.int/obesity

Weltgesundheitsorganisation
REGIONALBÜRO FÜR Europa

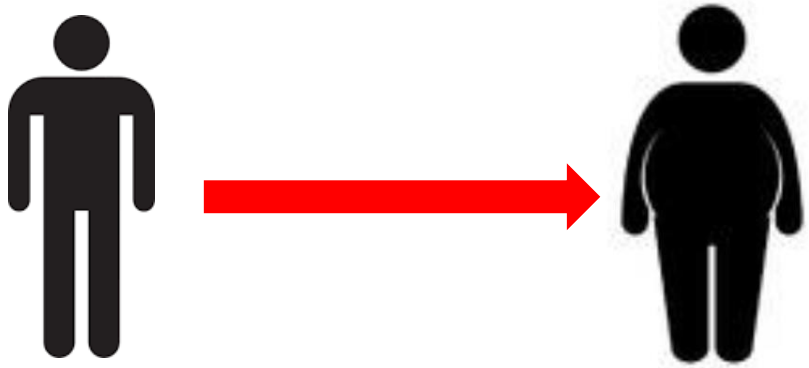
Wie ist es in Österreich?



Österreichischer Ernährungsbericht 2017

Was verschärft das Problem?

Circulus vitiosus



- Altered brain response to food images and taste
- Reduced satiety hormones (PYY and GLP-1)
- Leptin and Insulin Resistance

Very low calory diet
Weight reduction

- Increase in ghrelin, increased hunger
- Further decrease in PYY and GLP-1
- Reduced insulin and ghrelin
- Increased reward of the value of food
- Reduced energy expenditure

R. Batterham. ECO 2016

Was kann man also tun?

1. Ansprechen

Sprechen Sie mit Ihren Patienten über das Thema Adipositas und auch die damit assoziierten Folgeerkrankungen?

- Regelmäßig
- 1x/Jahr
- Selten
- Ich spreche das Thema nur bei morbider Adipositas (BMI > 40 kg/m²) an.

2. Bewegung

Bewegung im harten Lockdown – Spanien

Subgroup Analysis	Before Confinement	During Confinement	*p* Value	Effect Size	Before Confinement	During Confinement	*p* Value	Effect Size	Before Confinement	During Confinement	*p* Value	Effect Size	Before Confinement	During Confinement	*p* Value	Effect Size
	Time in Vigorous Activities				Time in Moderate Activities				Walking Time				Sitting Time *			
Total (n = 3800)	219 ± 196	182 ± 184	<0.001	0.195 [a]	149 ± 174	145 ± 170	0.102	0.023 [a]	282 ± 253	116 ± 189.3	<0.001	0.743 [c]	(n = 3687) 6.1 ± 3.6	8 ± 5.1	<0.001	0.430 [b]
Women (n = 1746)	175 ± 176	159 ± 174	<0.001	0.091 [a]	133 ± 160	144 ± 159	<0.05	0.069 [a]	302 ± 260	122 ± 199.3	<0.001	0.777 [c]	(n = 1694) 6.3 ± 3.9	7.9 ± 3.9	<0.001	0.410 [b]
Men (n = 2054)	256 ± 204	202 ± 190	<0.001	0.274 [b]	163 ± 185	145 ± 179	<0.001	0.099 [a]	265 ± 247	110 ± 180.1	<0.001	0.717 [c]	(n = 1993) 6 ± 3.1	8.1 ± 5.9	<0.001	0.446 [b]
Workers (n = 2956)	212.1 ± 189.9	177.3 ± 179.4	<0.001	0.188 [a]	143 ± 169.2	142.2 ± 170.6	0.811	0.005 [a]	269.3 ± 246.2	113.7 ± 182.7	<0.001	0.718 [c]	(n = 2865) 6.2 ± 3.5	8.0 ± 5.4	<0.001	0.396 [b]
Students (n = 267)	295.5 ± 221.0	223.7 ± 199.1	<0.001	0.341 [b]	171.1 ± 191.8	143.5 ± 157.1	<0.05	0.157 [a]	298.8 ± 246.1	98.8 ± 189.7	<0.001	0.910 [c]	(n = 262) 6.4 ± 2.4	8.8 ± 3.2	<0.001	0.849 [c]
Study–work (n = 374)	223.6 ± 196.8	193.2 ± 195.2	<0.001	0.155 [a]	157.4 ± 177.1	144 ± 160.6	0.141	0.079 [a]	301.3 ± 249.5	106.1 ± 179.6	<0.001	0.898 [c]	(n = 361) 6.3 ± 4.1	8.3 ± 3.4	<0.001	0.531 [c]
Nothing (n = 203)	213.9 ± 228.4	179.6 ± 201.1	0.013	0.159 [a]	198 ± 208.8	184.6 ± 190.4	0.316	0.067 [a]	403.3 ± 326.3	186.6 ± 267.2	<0.001	0.727 [c]	(n = 199) 4.4 ± 2.4	6.5 ± 3.5	<0.001	0.700 [c]

Castanado-Babarro A: Int J Environt Res and Public Health 2020

Bewegung im harten Lockdown – Italien

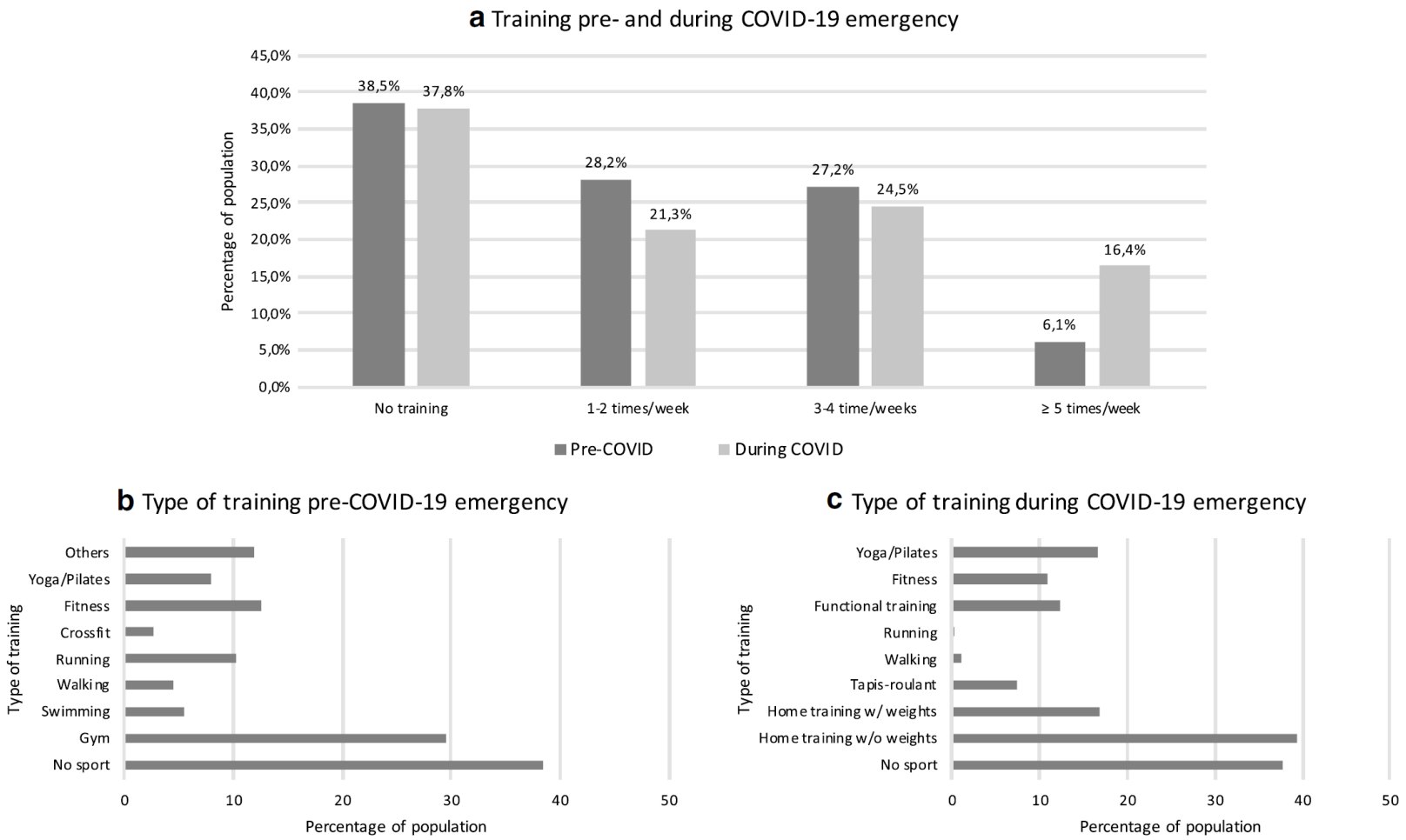


Fig. 1 Frequency (**a**) and type of training (**b**, **c**) before and during the COVID-19 emergency

DiRenzo L et al.: J Transl Med 2020

3. Ernährung

pubmed.ncbi.nlm.nih.gov/?term=diet+weight+loss&filter=pubt.review&sort=date

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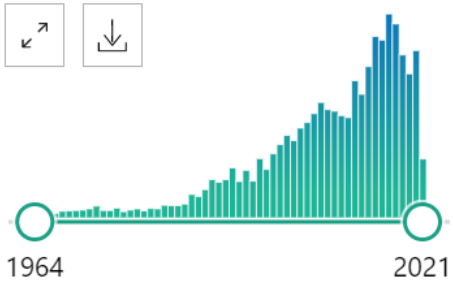

Filters applied: Review. Clear all

1 Cite Share

Exercise and Adipose Tissue Immunity: Outrunning Inflammation.

Winn NC, Cottam MA, Wasserman DH, Hasty AH.

Obesity (Silver Spring). 2021 May;29(5):790-801. doi: 10.1002/oby.23147.

PMID: 33899336 Review.

., immune cells, endothelial cells, fibroblasts, adipocyte progenitors), and (3) perturbed AT immune cell function. Exercise, along with **diet** management, is a cornerstone in promoting **weight loss** and preventing **weight** regain. ...

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TEXT AVAILABILITY

4. Pharmakotherapie

Wer sind die Kandidaten für die Pharmakotherapie?

- BMI > 30 kg/m² oder
- BMI > 27 kg/m² und Adipositas-assoziierte Komorbiditäten

➡ zusätzlich zu Lebensstiländerung

Management

Nutrition
Reduce energy intake by 500–1,000 kcal/day

Physical activity
Initially at least 150 min/week moderate aerobic exercise combined with 1–3 sessions/week resistance exercise

Cognitive behaviour therapy

Pharmacotherapy
BMI ≥ 30 kg/m^2 or BMI ≥ 27 kg/m^2 with co-morbidities
Adjunct to lifestyle modification

Bariatric/metabolic surgery
BMI≥40 kg/m^2 or BMI between 35.0–39.9 kg/m^2 + co-morbidities or BMI between 30.0-34.9 kg/m^2 with type 2 diabetes on individual basis. Consider if other weight loss attempts fail; requires lifelong medical monitoring

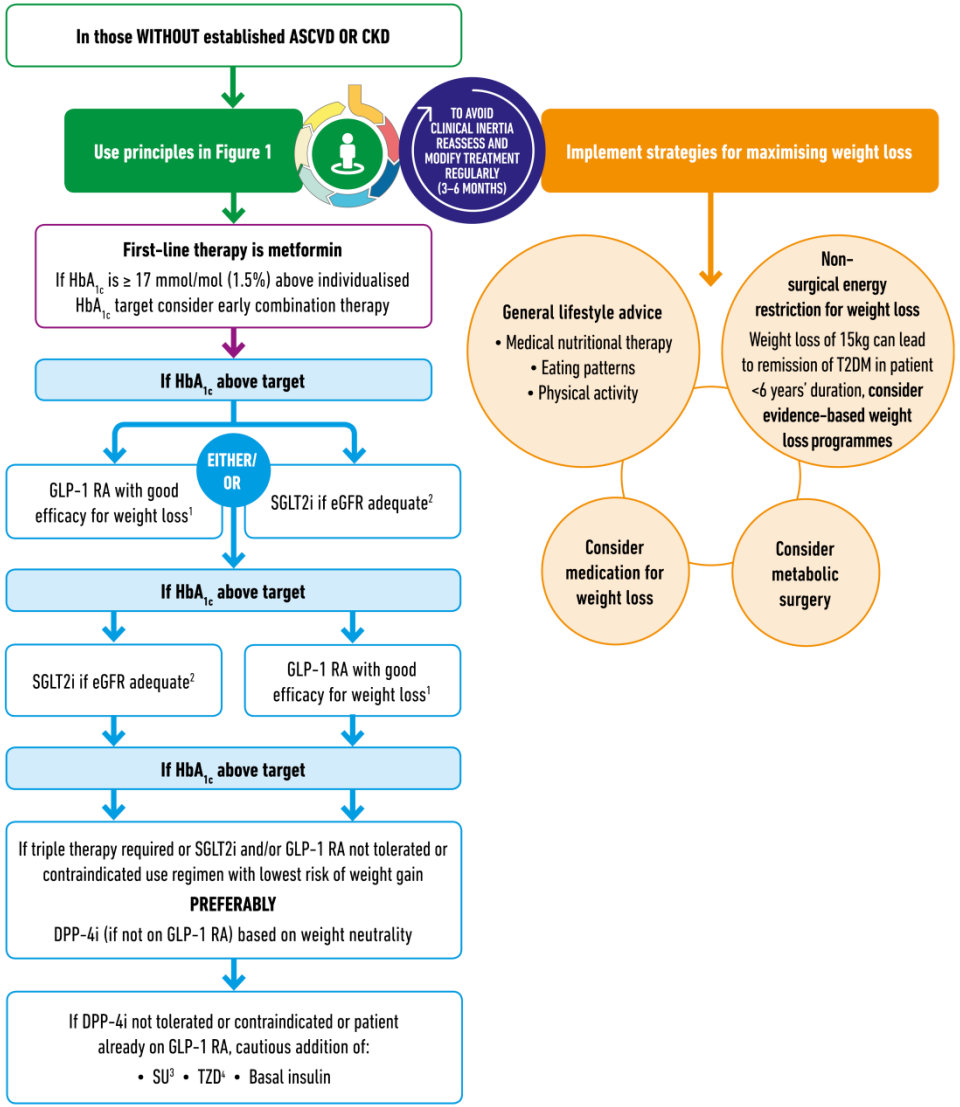
Prevention and treatment of co-morbidities

Yumuk V et al.: Europ Guidelines for Obesity Management. Obes Facts 2015

Dazu zählen:

- Typ-2-Diabetes
- Arterielle Hypertonie
- Hyperlipidämie
- Obstruktives Schlafapnoe-Syndrom
- Adipositas-assoziiertes Hypoventilationssyndrom
- NAFLD („non-alcoholic fatty liver disease“)
- NASH
- Gastroösophagealer Reflux (GERD)
- Asthma
- Venöse Insuffizienz
- Arthritis
- Schwere Harninkontinenz
- Venöse Insuffizienz
- „Considerably impaired quality of life“

ADA/EASD-Konsensus

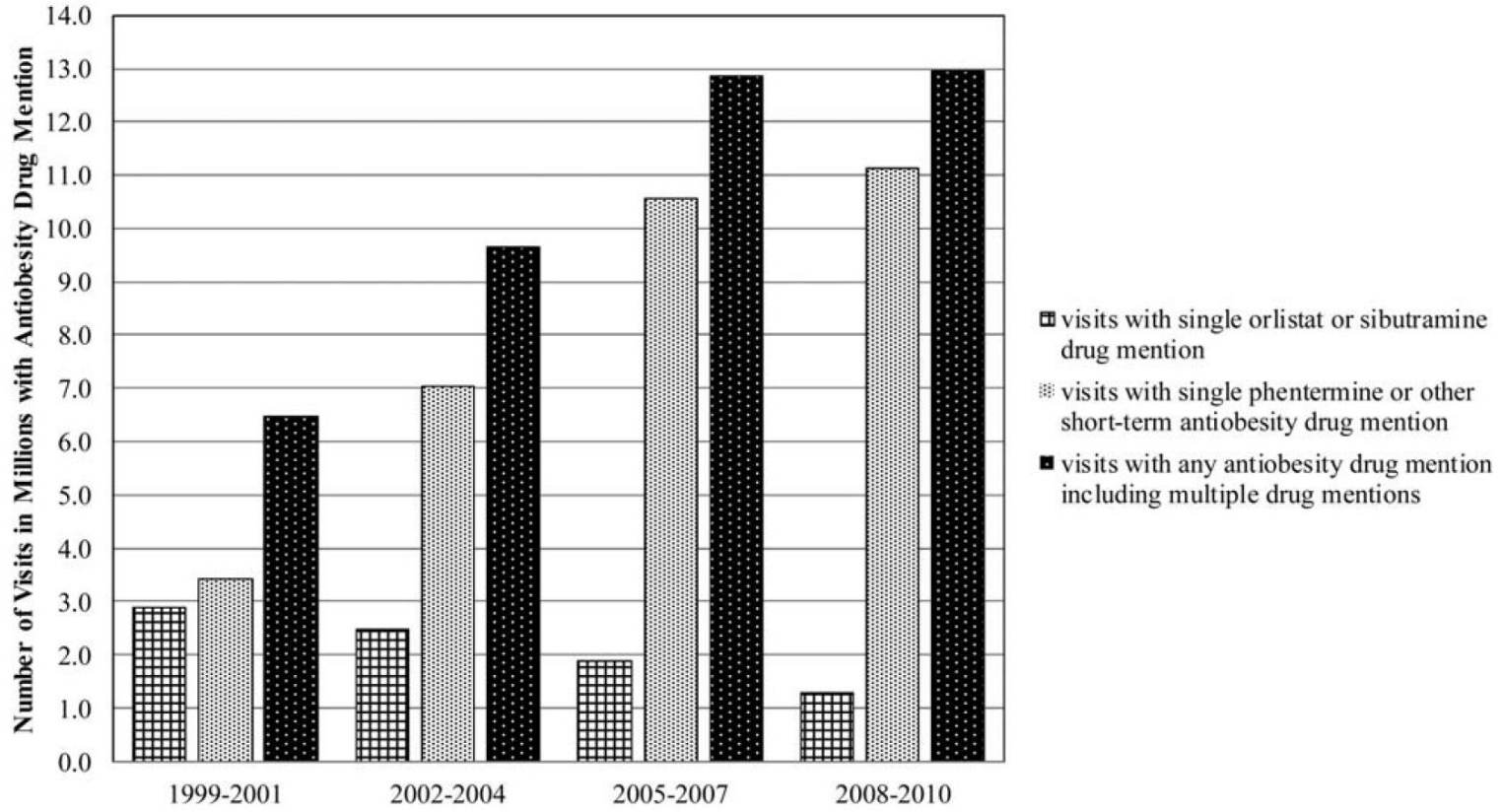


1. Semaglutide > liraglutide > dulaglutide > exenatide > lixisenatide
2. Be aware that SGLT2i vary by region and individual agent with regard to indicated level of eGFR for initiation and continued use
3. Choose later generation SU with lower risk of hypoglycaemia
4. Low dose may be better tolerated though less well studied for CVD effects

. 4 Choosing glucose-lowering medication if compelling need to minimise weight gain or promote weight loss

Davies MD et al.: Diabetologia 2018; 61: 2461-98

Wie viele Menschen erhalten Pharmakotherapie?



987 Millionen Arztkontakte von Menschen mit Adipositas

Xia Y et al.: Obesity 2015; 23: 1721-8

Wie viele Menschen erhalten Pharmakotherapie?

- Obwohl circa die Hälfte aller US-Amerikaner mit Adipositas diese Kriterien erfüllt, erhalten ≤ 3,5 % Verschreibungen (= 1 von 50 adipösen Patienten).
- Dies sind vor allem kaukasische (86 %) Frauen (85 %) < 44 Jahren, Selbstzahler.
- Nicht alle waren überhaupt übergewichtig …
- Verschrieben vor allem von praktischen Ärzten

Xia Y et al.: Obesity 2015; 23: 1721-8

Patient A. W., geb. 1966

- Gewicht 98 kg, BMI 33,3 kg/m²
- Internist in einem KH, viele Nachtdienste
- Fährt mit dem Rad in die Arbeit, gegessen wird abends mit seiner Partnerin oder im Nachtdienst relativ spät.
- Da oft große Portionen
- Danach Snacking als Stressbewältigung

Patientin M. W., geb. 1985

- Gewicht 86 kg, BMI 31,6 kg/m²
- Kinderwunsch seit mehreren Jahren
- Erste IVF steht bevor.
- Hat bereits privat eine Diätologin besucht

Patientin S. D., geb. 1980

- Gewicht 91 kg, BMI 31,5 kg/m²
- 2-fache Mutter (Kinder 5a und 7a)
- Hatte vor Kurzem schwierige Scheidung
- Arbeitet 20 h
- Möchte Gewichtsreduktion, um „neue Episode“ zu beginnen

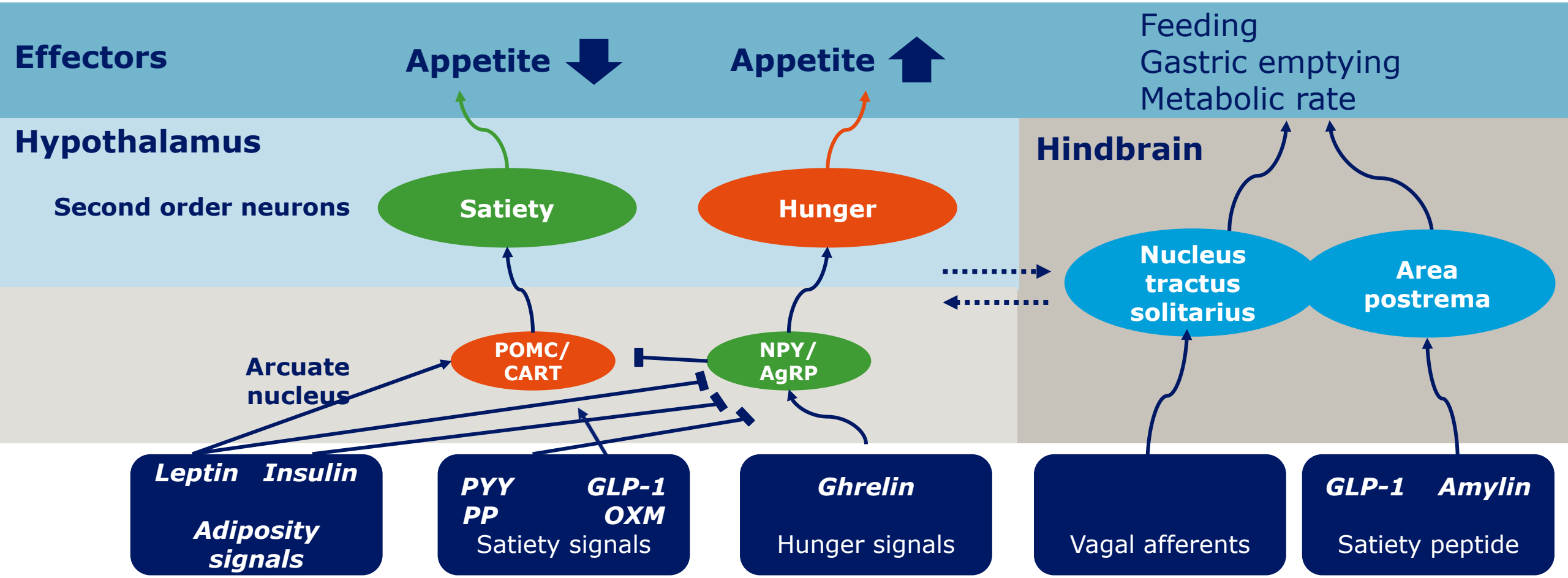
Wie kann Pharmakotherapie überhaupt helfen?

- Patienten mit Übergewicht können nur durch eine negative Energiebilanz auf Dauer abnehmen. Diese wird durch mehr Bewegung und weniger Kalorienzufuhr erreicht.
- Anti-Adipositas-Medikamente können durch eine Reduktion von Hunger oder des „Cravings“ sowie eine Verbesserung des Sättigungsgefühls diese Bemühungen unterstützen.

Xia Y et al.: Obesity 2015; 23: 1721-8

Hypothalamic regulation of appetite

Peripheral signals modulate appetite and energy expenditure via hypothalamic neurons



α-MSH, α-melanocyte stimulating hormone; AgRP, Agouti-related protein; CART, cocaine and amphetamine regulated transcript; GLP-1, glucagon-like peptide-1; NPY, neuropeptide Y; OXM, oxyntomodulin; POMC, pro-opiomelanocortin; PP, pancreatic polypeptide; PYY, peptide YY

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; Boyle *et al. Mol Metab* 2018;8:203–10

Homeostatic vs. hedonic regulation of appetite

Homeostatic regulation

Biological systems that acts to **maintain** body weight by:

- Regulation via peptide hormones that can induce hunger/satiety
- Changes in energy expenditure

Hedonic regulation

Reward of **survival behaviours** (e.g. sex or eating) through **pleasure**

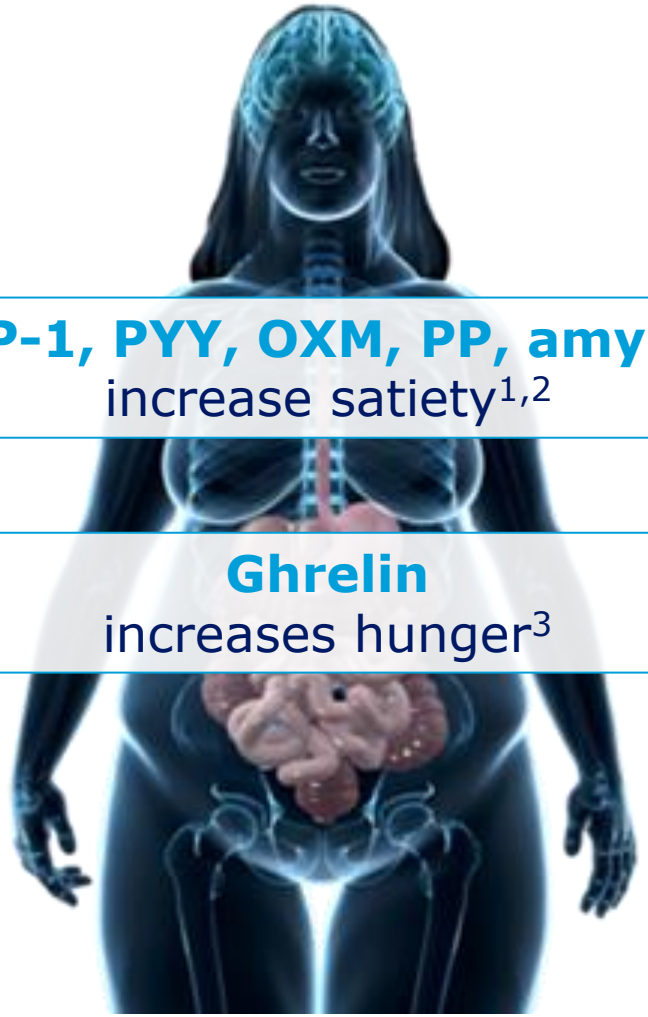
- Operates even in the presence of satiety signals
- Can lead to food consumption beyond homeostatic need
- Link between hedonic attraction to high calorie foods and obesity

Hall et al.: *Am J Public Health* 2014; 104(7): 1169-75

The role of the brain in controlling eating

Homeostatic eating

'eating for hunger'



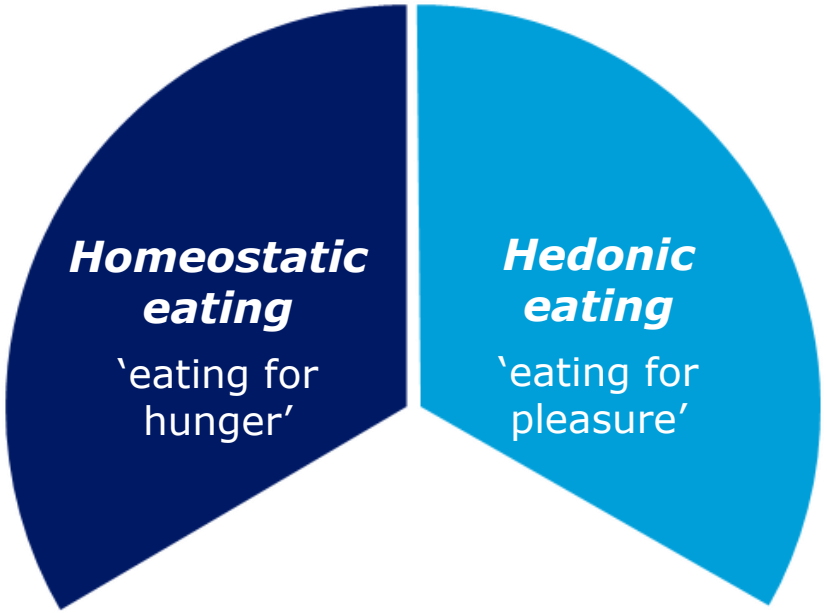
GLP-1, PYY, OXM, PP, amylin
increase satiety[1,2]

Ghrelin
increases hunger[3]

GLP-1, glucagon-like peptide-1; POMC, pro-opiomelanocortin; PP, pancreatic polypeptide; PYY, peptide YY; OXM, oxyntomodulin

1. Badman *et al.: Science* 2005; 307: 1909-14; 2. van Bloemendaal *et al.: Diabetes* 2014; 63: 4186-96; 3. Klok *et al.: Obes Rev* 2007; 8: 21-34

The role of the brain in controlling eating

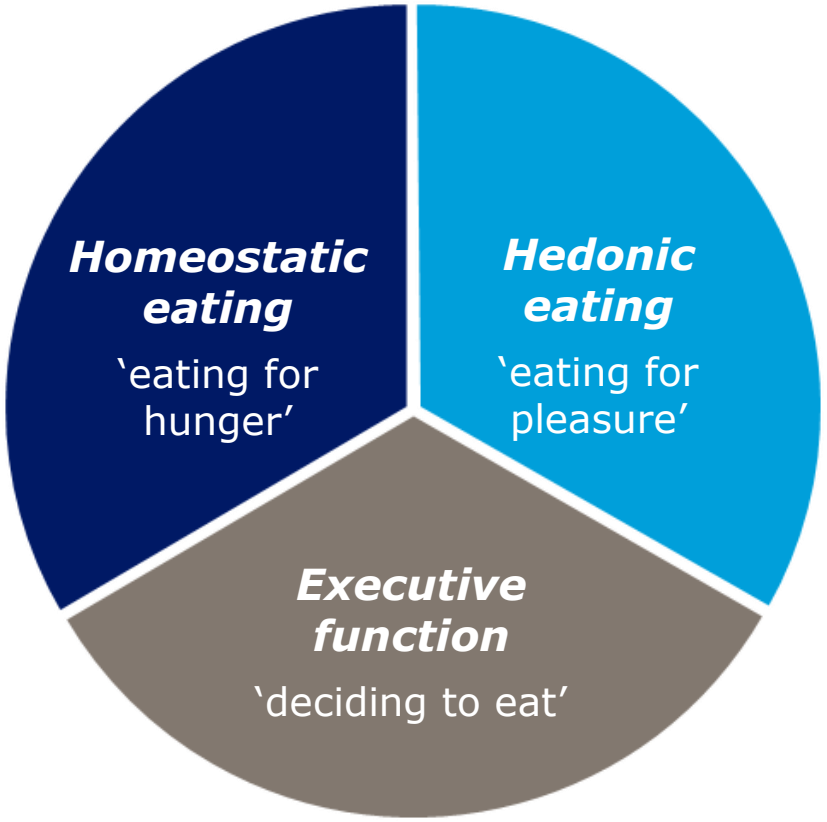


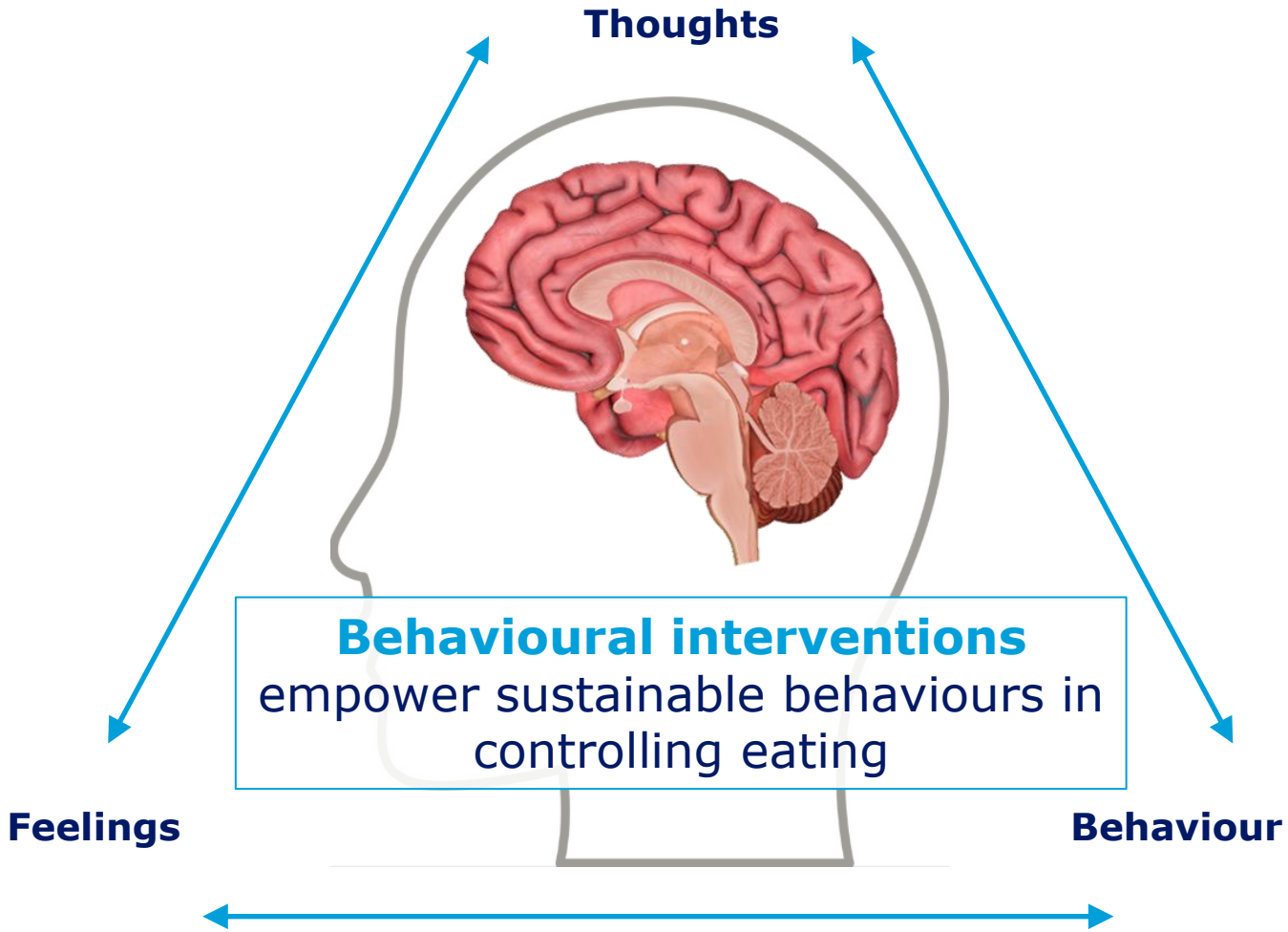
Dopamine controls WANTING, the motivation/drive to eat

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

Berridge *et al.: Brain Res* 2010; 1350: 43-64

The role of the brain in controlling eating





Vallis *et al.: Clin Obes* 2019; 9: e12299

Wie viel Prozent Gewichtsreduktion erwarten Sie sich von einem Medikament zur Behandlung der Adipositas, damit ein Einsatz gerechtfertigt ist?

a. > 5 %

b. > 10 %

c. > 15 %

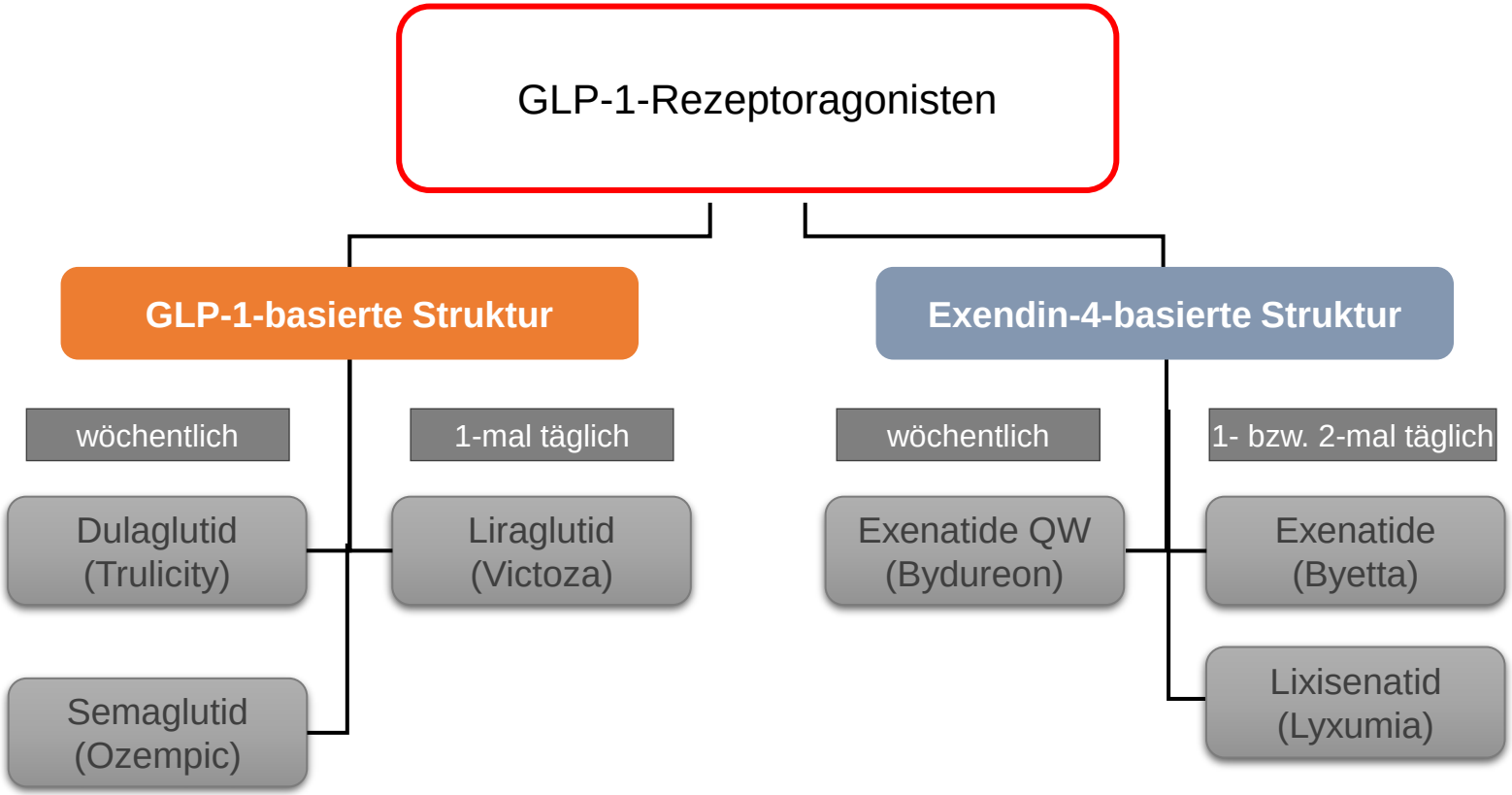
d. Gewichtsabnahme ist immer individuell.

Zugelassene Pharmakotherapie

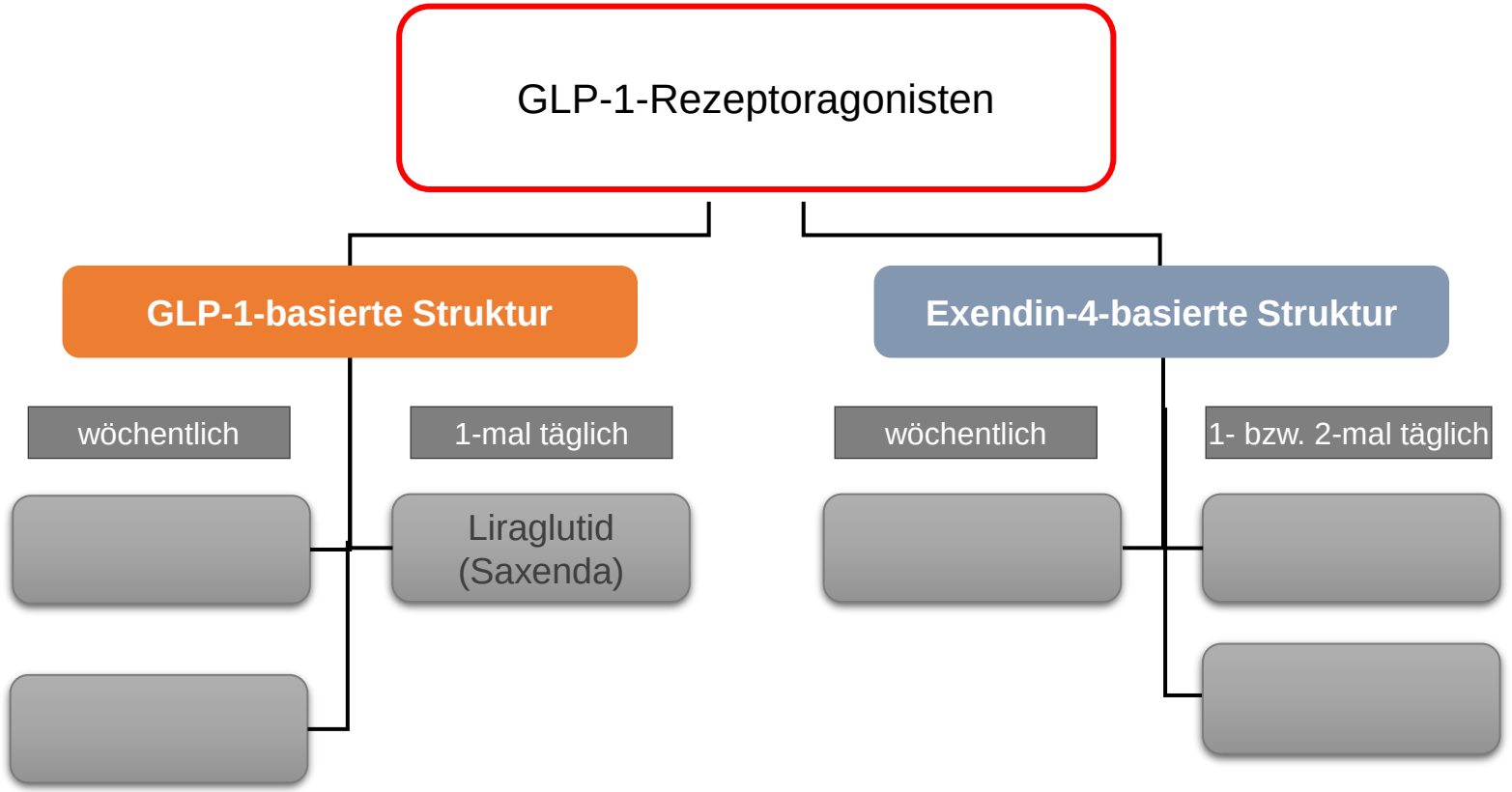
			**Mode of action**	**Indications**
Orlistat (Xenical®, Alli®)	✓	✓	Energy wastage	Zusätzlich zu Diät und Bewegung für das chronische Gewichtsmanagement bei a) Adipositas BMI ≥30 kg/m² b) Übergewicht BMI ≥ 27 kg/m² mit einer Komorbidität
Phentermine* (Adipex-P®, Suprenza®)	✗	✓	Appetite suppression	
Phentermine/topiramate (Qsymia®)	✗	✓	Appetite suppression	
Lorcaserin (Belviq®, Belviq XR®)	✗	✓	Appetite suppression	
Naltrexone/Bupropion (Mysimba®, Contrave®)	✓	✓	Appetite suppression	
Liraglutide 3.0 mg (Saxenda®)	✓	✓	Appetite suppression	
Sibutramine (Merida®)	✗	✗	Appetite suppression	n/a

*Approved for short-term use. FDA Drugs: http://www.fda.gov/Drugs/default.htm; EMA Medicines: http://www.ema.europa.eu/

Überblick über zugelassene GLP-1-Rezeptoragonisten in Österreich zur Behandlung von Diabetes mellitus Typ 2



Überblick über zugelassene GLP-1-Rezeptoragonisten in Österreich zur Behandlung von Adipositas

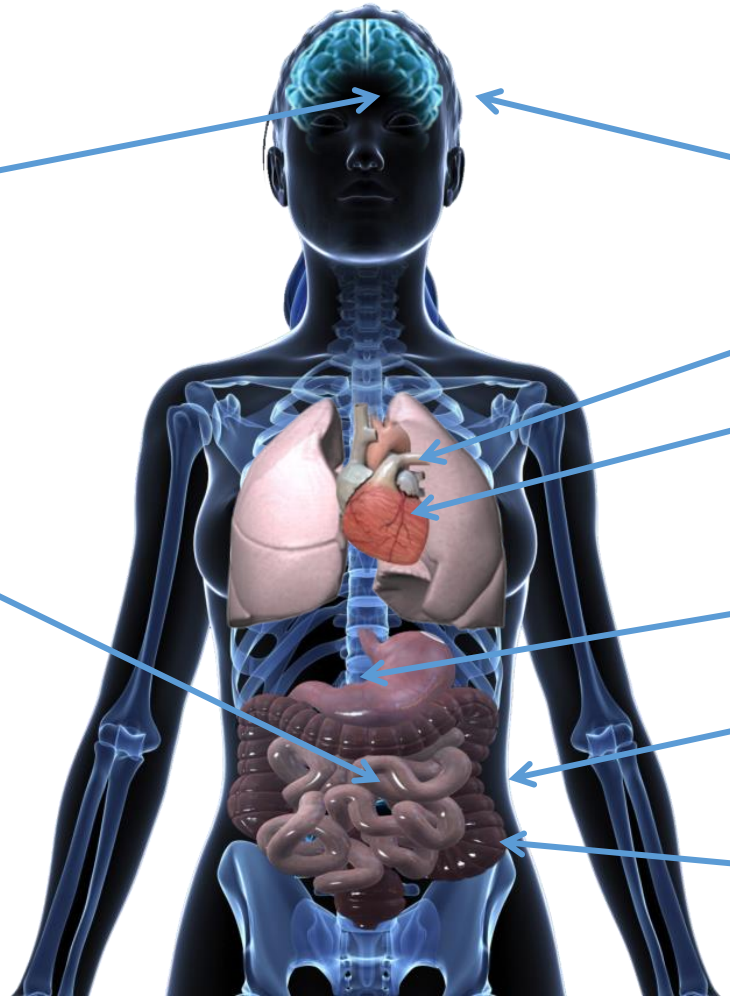


Natürliche GLP-1-Sekretion und -Rezeptor-Expression

GLP-1 wird sezerniert von:

Nucleus tractus solitarii

L-Zellen des Darms



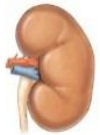
GLP-1-Rezeptoren:

im Gehirn

im Endothelium

im Myokardium

in der Bauchspeicheldrüse



in den Nieren

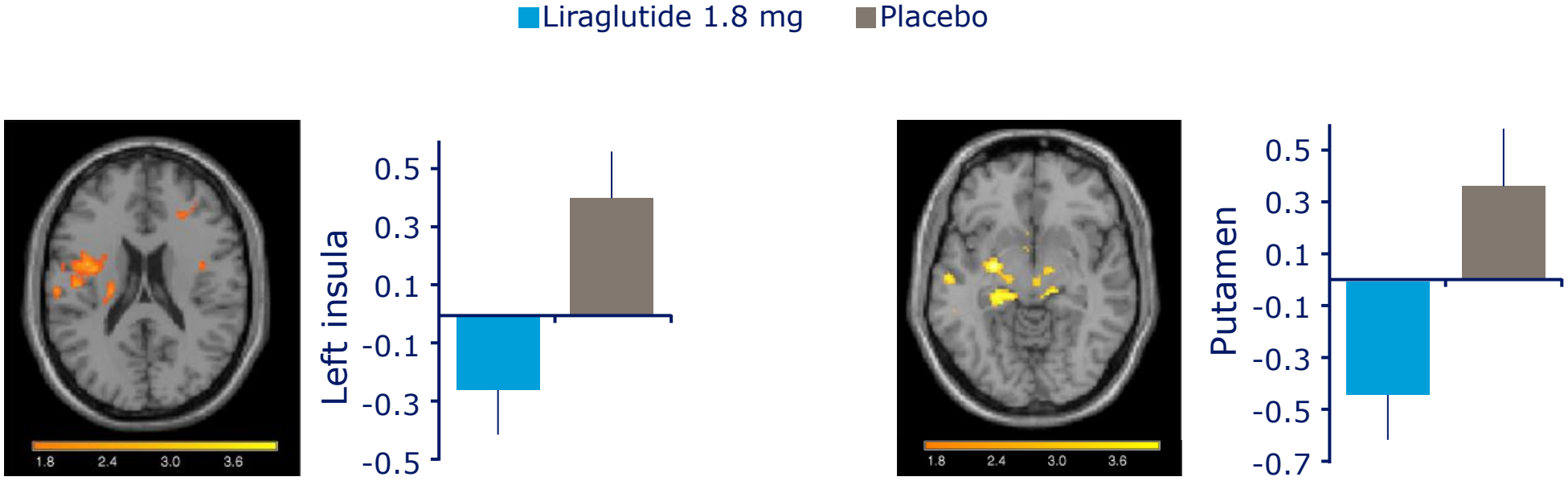
im Magen-Darm-Trakt

GLP-1, Glucagon-ähnliches Peptid 1; GLP-1R, GLP-1-Rezeptor

Literaturangaben: 1. Vrang N et al.: *Prog Neurobiol* 2010; 92: 442-62. **2.** Baggio LL et al.: *Gastroenterology* 2007; 132: 2131-57.
3. Merchenthaler I et al.: *J Comp Neurol* 1999; 403: 261-80. **4.** Pyke C et al.: *Endocrinology* 2014; 155: 1280-90. **5.** Ban K et al.: *Circulation* 2008; 117: 2340-50.

Liraglutide reduces brain activity related to highly desirable food cues

- Liraglutide 1.8 mg decreased activation of the:
  - parietal cortex in response to highly desirable food images
  - insula and putamen, areas involved in the reward system

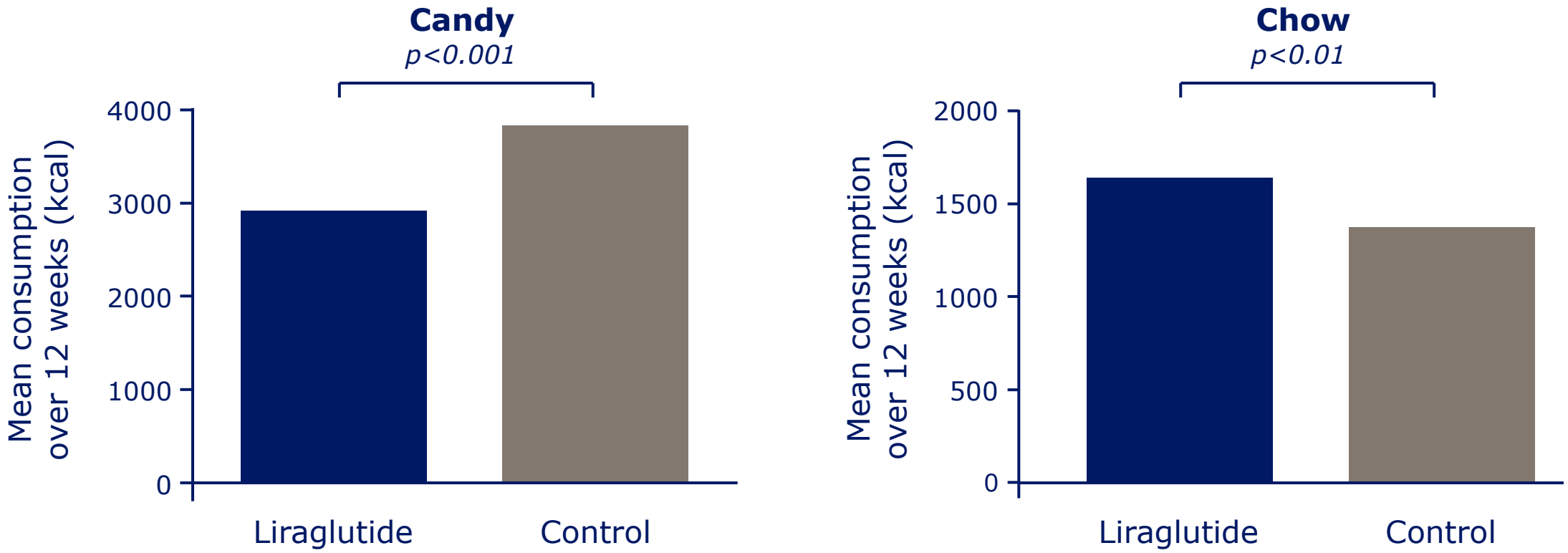


The y-axis represents effect size of the activation (z scores). Blood oxygen level-dependent contrasts are superimposed on a T1 structural image in neurological orientation. The colour bar represents voxel T value

Farr *et al.: Diabetologia* 2016; 59: 954-65

Liraglutide affects food preference in rats

Food choices switch away from candy



Female Sprague-Dawley rats made obese through supplementary candy feeding could select candy (five different kinds) or chow.

Adapted from Raun *et al.: Diabetes* 2007; 56: 8-15

SCALE trial programme

The SCALE programme

6600

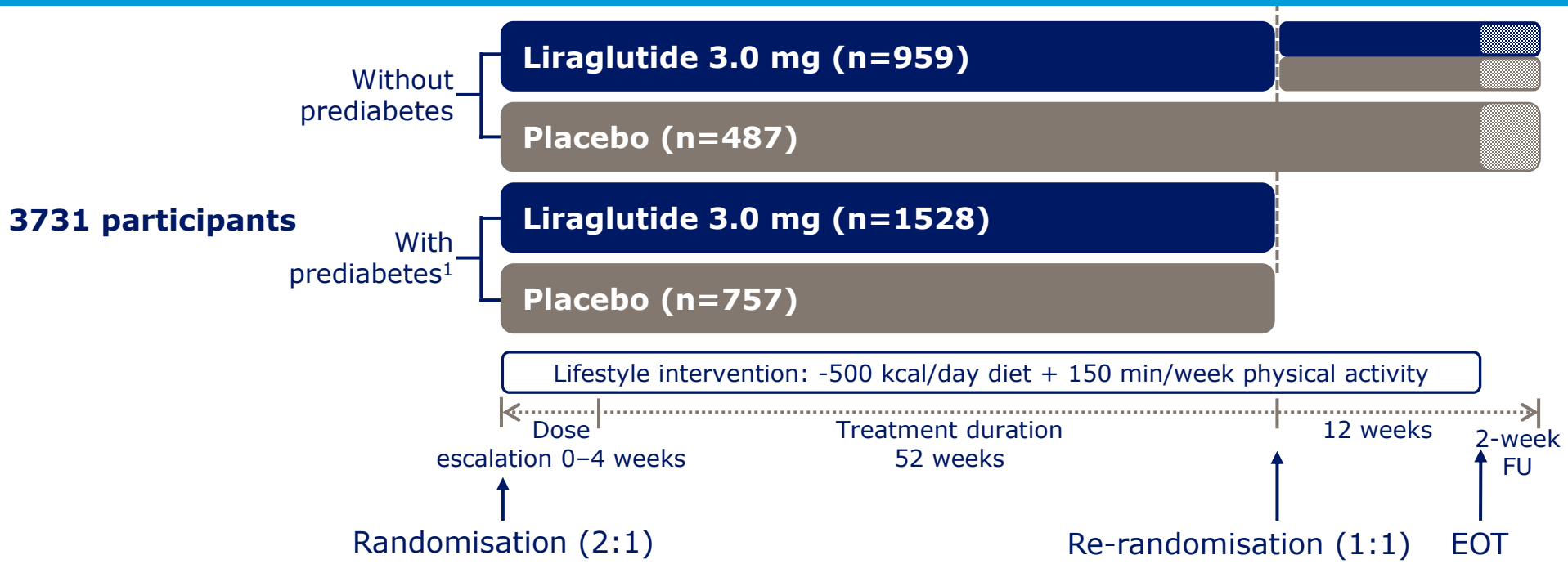
Subjects enrolled

Trial design: SCALE Obesity and Prediabetes

Liraglutide 3.0 mg in weight management (56 weeks)

Trial objective

Efficacy and safety of liraglutide 3.0 mg, as adjunct to D&E, in participants with obesity or overweight plus comorbidities, without diabetes



Trial information

- June 2011 to March 2013
- Randomised controlled double-blind study
- 191 sites in 27 countries
- Duration: 56 weeks (with prediabetes), 68 weeks (without prediabetes)

1. ADA. *Diabetes Care* 2010; 33(Suppl. 1): S11-61

BW, body weight; D&E, diet and exercise; EOT, end of treatment; FU, follow-up; HRQoL, health-related quality of life; WC, waist circumference

Pi-Sunyer *et al.*: *N Engl J Med* 2015; 373: 11-22

Trial design: SCALE Obesity and Prediabetes

Liraglutide 3.0 mg in weight management (56 weeks)

Inclusion criteria

- ≥18 years
- Stable BW
- BMI ≥30 kg/m^2
  or
  ≥27 kg/m^2 + comorbidities

Key endpoints

- Three co-primary: BW change, 5% or 10% BW loss
- Secondary: Changes from baseline in BMI, WC, glycaemic control variables, cardiometabolic risk factors, and HRQoL

1. ADA. *Diabetes Care* 2010; 33(Suppl. 1): S11-61

BW, body weight; D&E, diet and exercise; EOT, end of treatment; FU, follow-up; HRQoL, health-related quality of life; WC, waist circumference

Pi-Sunyer *et al.*: *N Engl J Med* 2015; 373: 11-22

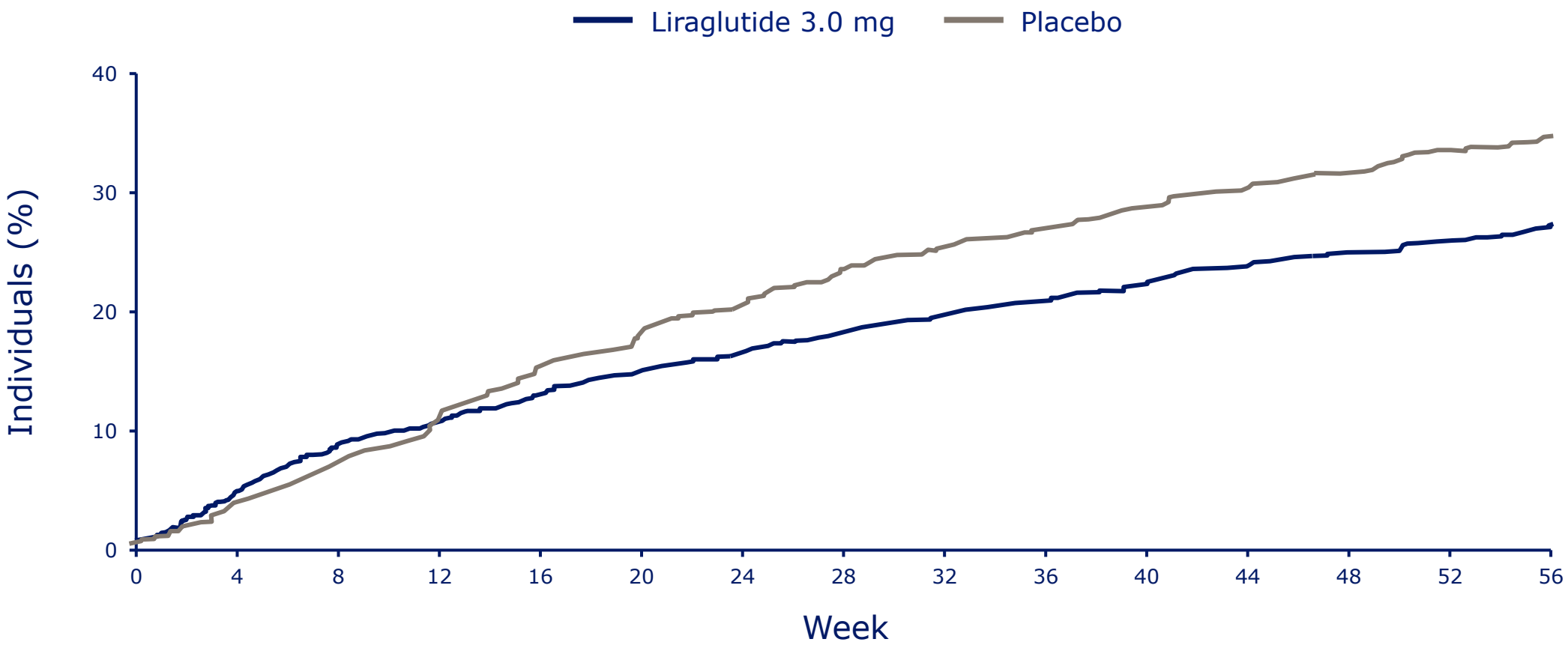
Baseline characteristics

	Without prediabetes§				With prediabetes			
	Liraglutide 3.0 mg		Placebo		Liraglutide 3.0 mg		Placebo	
	n	(%)	n	(%)	n	(%)	n	(%)
Number of subjects	959	(100.0)	487	(100.0)	1528	(100.0)	757	(100.0)
Female	801	(83.5)	390	(80.1)	1156	(75.7)	581	(76.8)
Race – White - no. (%)†	831	(86.7)	426	(87.5)	1276	(83.5)	635	(83.9)
Mean age (years)	41.6		41.5		47.4		47.2	
Mean body weight (kg)	104.0		103.6		107.6		107.9	
Mean BMI‡ (kg/m^2)	37.5		37.4		38.8		39.0	
≤29.9	27	(2.8)	21	(4.3)	39	(2.6)	23	(3.0)
30.0–34.9 – Obese class I	372	(38.8)	190	(39.0)	434	(28.4)	198	(26.2)
35.0–39.9 – Obese class II	288	(30.0)	147	(30.2)	499	(32.7)	251	(33.2)
≥40.0 – Obese class III	272	(28.4)	129	(26.5)	556	(36.4)	285	(37.6)
Hypertension¶	211	(22.0)	130	(26.7)	639	(41.8)	316	(41.7)
Dyslipidaemia¶	233	(24.3)	113	(23.2)	504	(33.0)	246	(32.5)

All subjects randomised. BMI, body mass index. §Prediabetes was defined according to ADA 2010 criteria. †Race and ethnic group were self-reported. ‡The body-mass index is the weight in kilograms divided by the square of the height in meters. ¶Dyslipidemia and hypertension were based on reported medical history

Pi-Sunyer *et al.: N Engl J Med* 2015; 373: 11-22

Geringe Abbruchrate

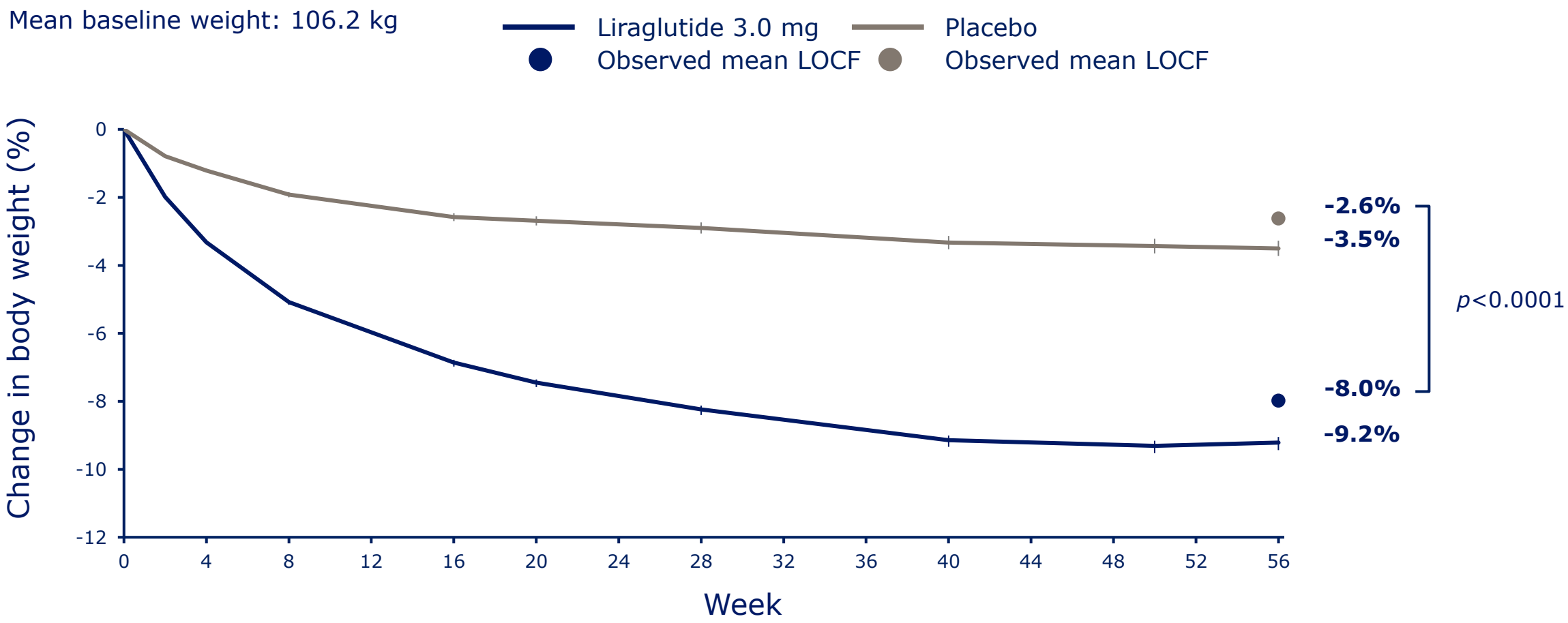


Safety analysis set

Fujioka *et al.*: Presentation at Obesity Week 4th November 2014. Presentation #: T-3031-OR

Veränderung des Körpergewichtes (%)

0–56 Wochen

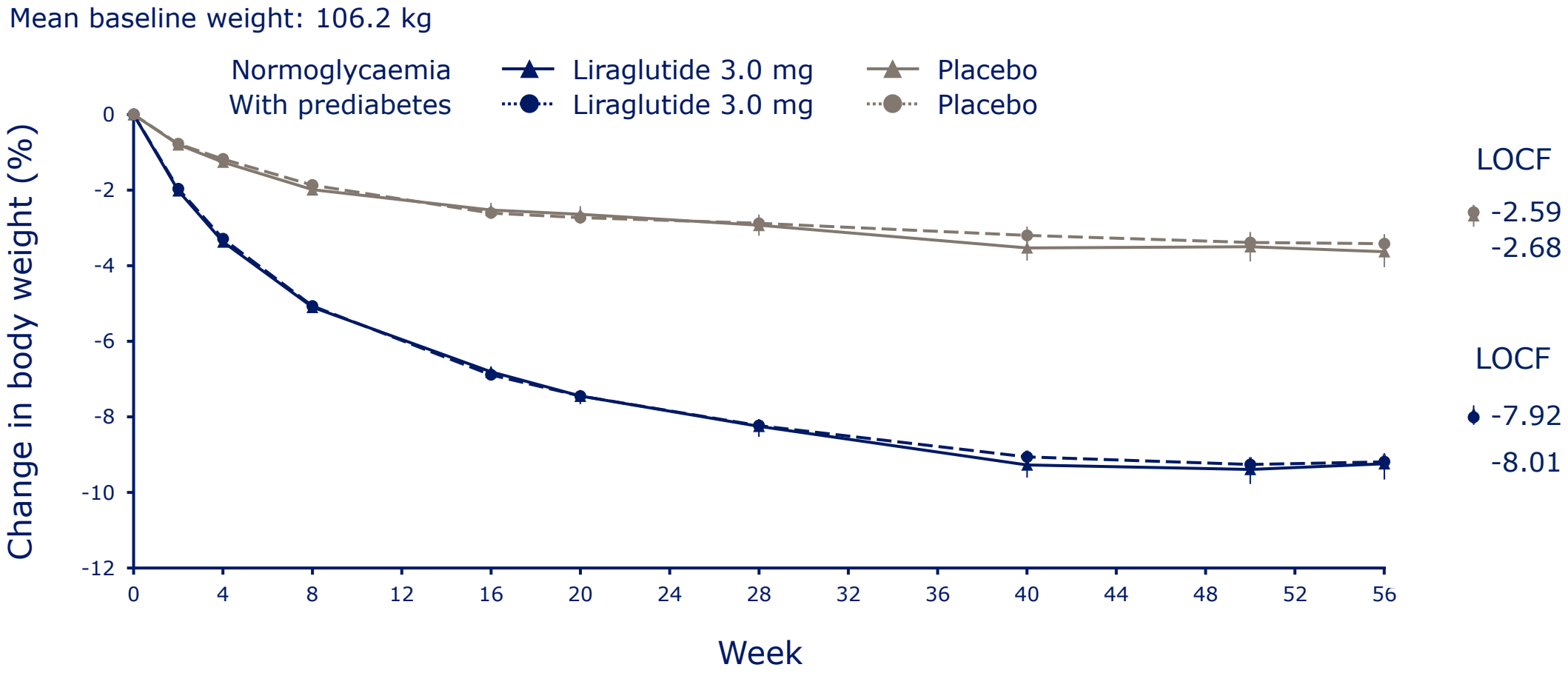


FAS, fasting visit data only. Line graphs are observed means (±SE). Statistical analysis is ANCOVA.
FAS, full analysis set; LOCF, last observation carried forward; SE, standard error

Pi-Sunyer *et al.: Diabetologia* 2014; 57(Suppl. 1): Abstract 73-OR

Veränderung des Körpergewichtes (%)

Nach Prädiabetes-Status: 0–56 Wochen



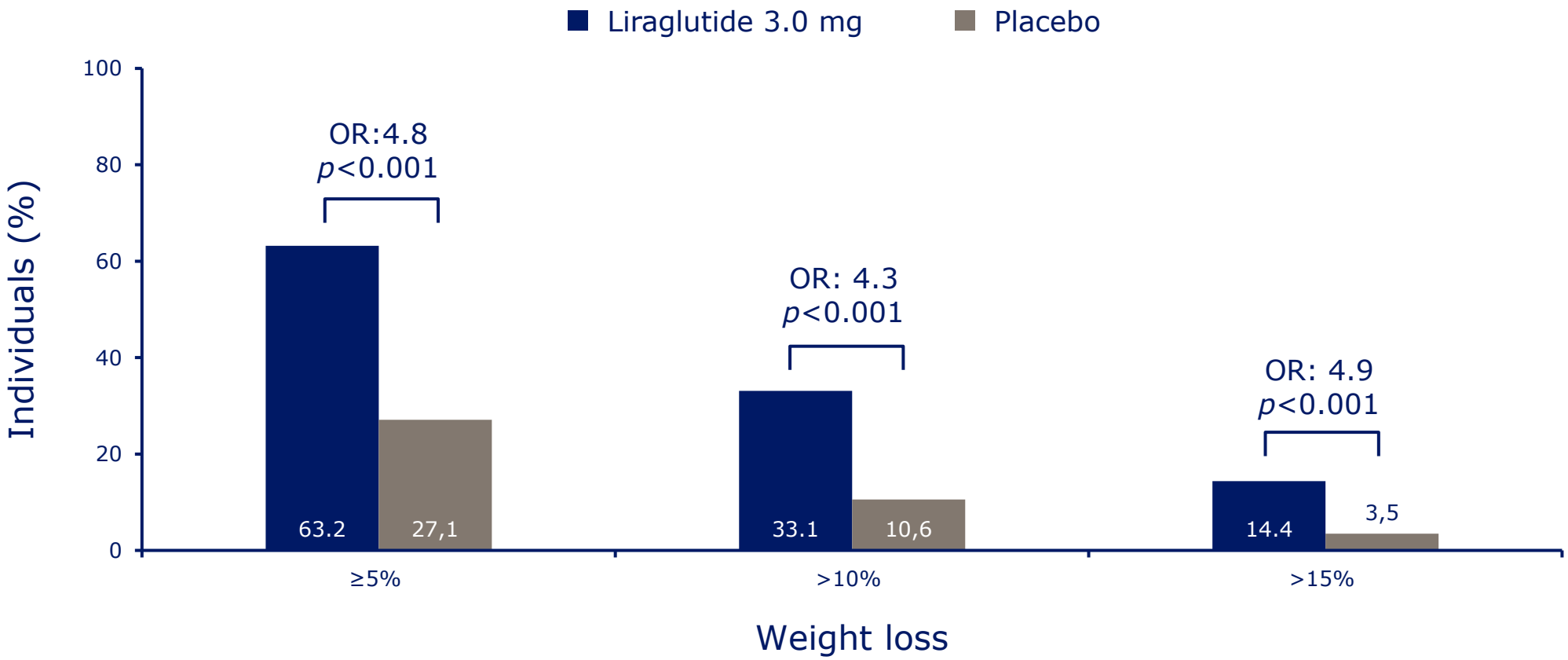
Data are observed means with standard error bars, and the symbols at the right represent the 56-week weight change using last observation carried forward (LOCF) imputation. LOCF, last observation carried forward

Pi-Sunyer *et al.: N Engl J Med* 2015; 373: 11-22

Wie viel Prozent erreichen > 5 %/> 10 % Gewichtsreduktion?

Woche 56

Mean baseline weight: 106.2 kg

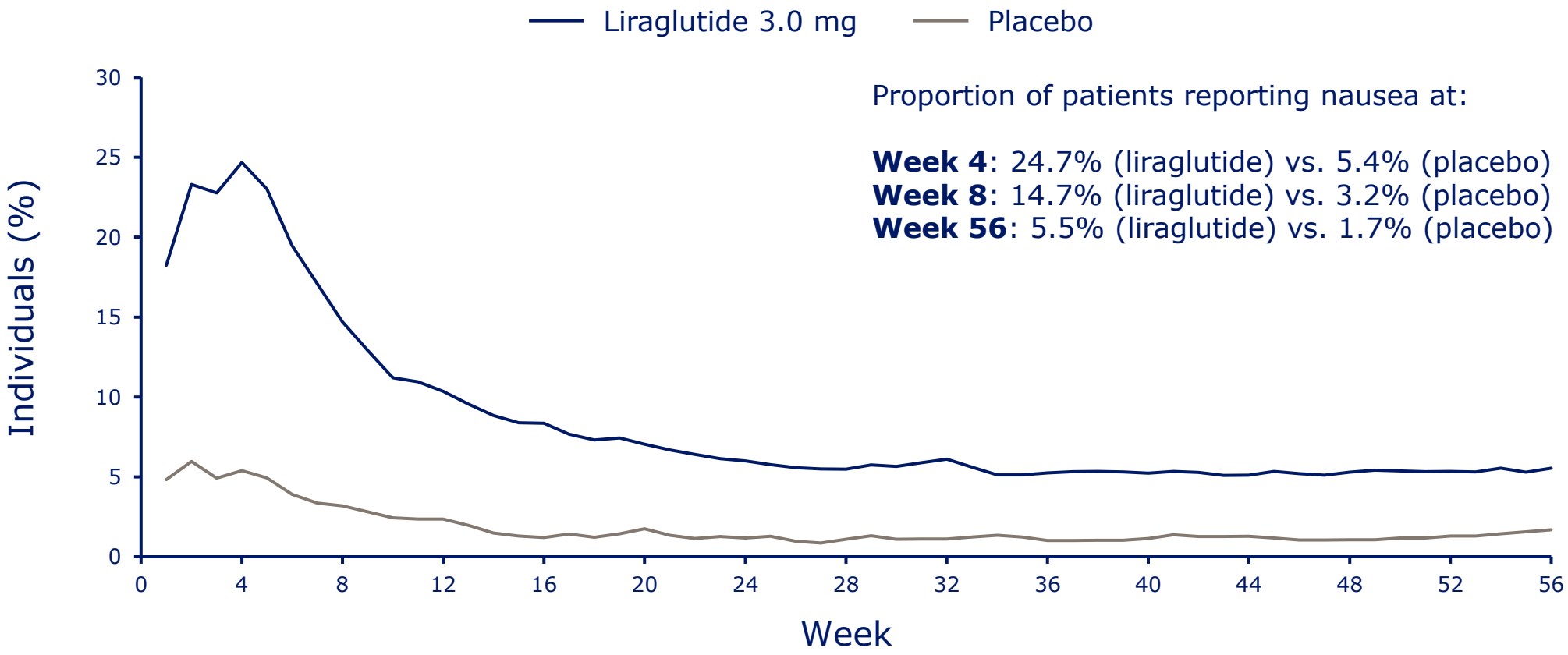


Data are observed means for the full analysis set (with LOCF) and the odds ratios (OR) shown are from a logistic regression analysis (the analysis for achieving 15% weight loss was performed post hoc). LOCF, last observation carried forward; OR, odds ratio

Pi-Sunyer *et al.: N Engl J Med* 2015; 373: 11-22

Anzahl der Teilnehmer mit Übelkeit

0–56 Wochen



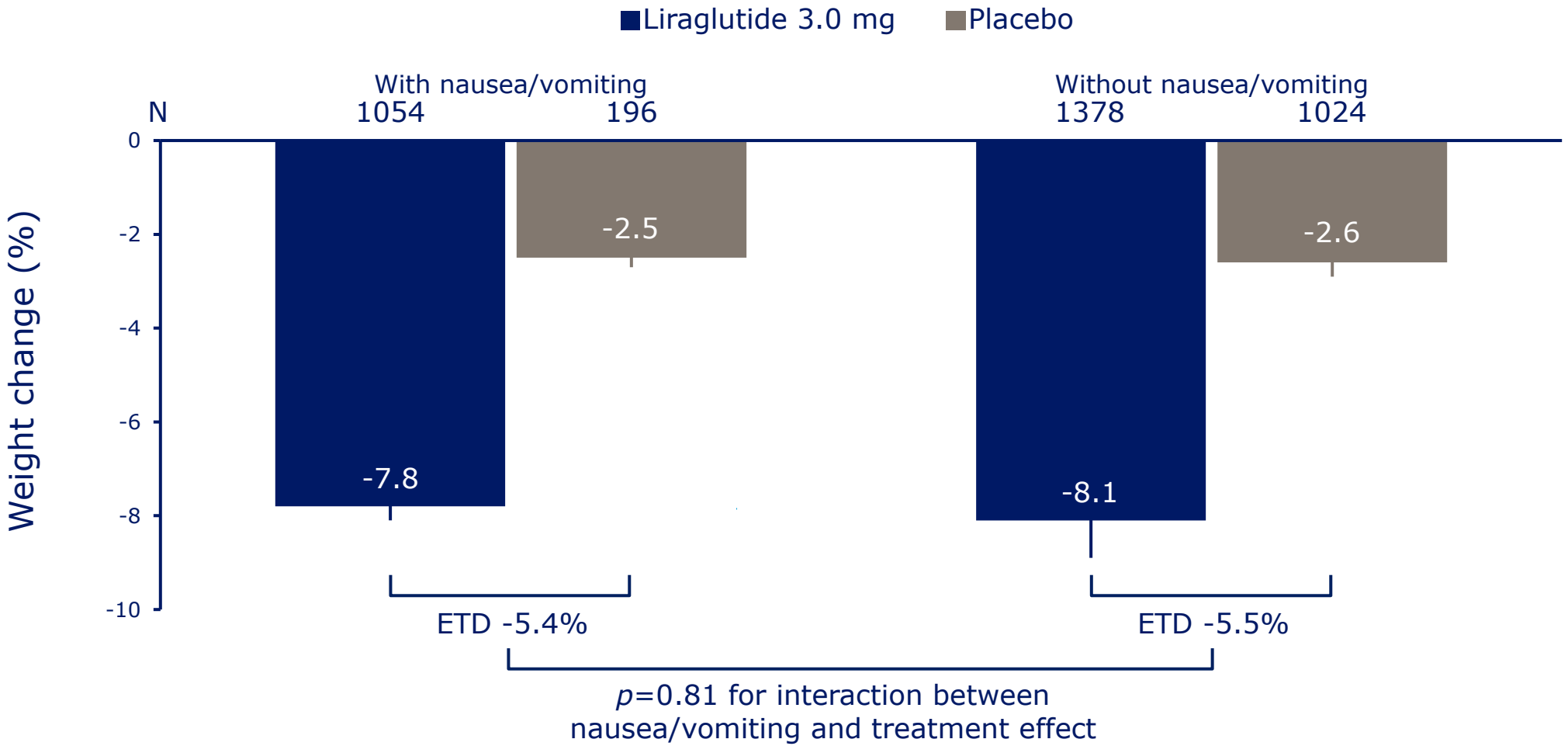
Proportion of patients reporting nausea at:

Week 4: 24.7% (liraglutide) vs. 5.4% (placebo)
Week 8: 14.7% (liraglutide) vs. 3.2% (placebo)
Week 56: 5.5% (liraglutide) vs. 1.7% (placebo)

Safety analysis set

Pi-Sunyer *et al.: N Engl J Med* 2015; 373: 11-22

Gewichtsreduktion mit Liraglutide 3,0 mg ist nicht assoziiert mit Übelkeit/Erbrechen



SCALE Obesity and Prediabetes. Least square means (± standard error); LOCF at end-of-treatment (56 weeks); ETD, estimated treatment difference; LOCF, last observation carried forward; N, number of subjects contributing to analysis

Pi-Sunyer et al. *N Engl J Med* 2015; 373(1): 11-22

Patientin S. K., geb. 1982

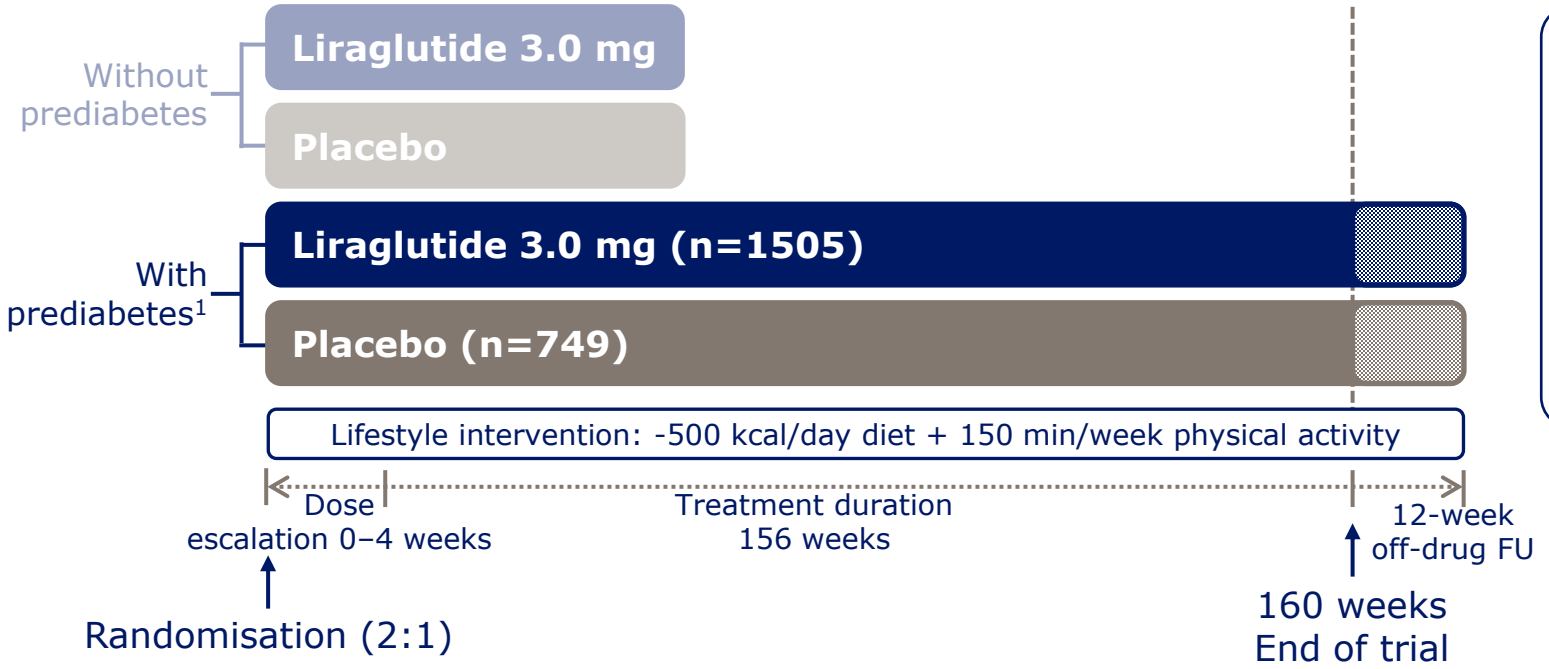
- Gewicht 91 kg, BMI 31,9 kg/m²
- Z. n. GDM
- Positive Familienanamnese für Diabetes

Trial design: SCALE Obesity and Prediabetes

Liraglutide 3.0 mg in weight management (160 weeks)

Trial objective

Efficacy of liraglutide 3.0 mg (after 160 weeks of treatment) in delaying the onset of T2D in participants with obesity or overweight with comorbidities, and diagnosed with prediabetes at screening



Trial information

- June 2011 to March 2015
- Randomised controlled double-blind study
- 191 sites in 27 countries

1. ADA. *Diabetes Care* 2010; 33(Suppl. 1): S62-9

BW, body weight; D&E, diet and exercise; FU, follow-up; HRQoL, health-related quality of life; T2D, type 2 diabetes

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

Trial design: SCALE Obesity and Prediabetes

Liraglutide 3.0 mg in weight management (160 weeks)

Inclusion criteria

- ≥18 years
- Stable BW
- BMI ≥30 kg/m^2
  or
  ≥27 kg/m^2 + comorbidities

Key endpoints

- Primary: time to onset of T2D at 160 weeks
- Secondary: weight measures, glycaemic control variables, cardiometabolic risk factors, HRQoL, safety and tolerability

1. ADA. *Diabetes Care* 2010; 33(Suppl. 1): S62-9

BW, body weight; D&E, diet and exercise; FU, follow-up; HRQoL, health-related quality of life; T2D, type 2 diabetes

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

Diagnosis of prediabetes at screening[1]

Based on ADA criteria

Impaired fasting glucose (IFG)

5.6 to 6.9 mmol/L
(100 to 125 mg/dL)

and/
or

Impaired glucose tolerance (IGT)

7.8 to 11.0 mmol/L
(140 to 199 mg/dL)

and/
or

HbA_{1c}

5.7 to 6.4%

All listed values are inclusive

American Diabetes Association. *Diabetes Care* 2010; 33: S62-9

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

Summary of baseline characteristics

All randomised participants entering the 3-year treatment arms

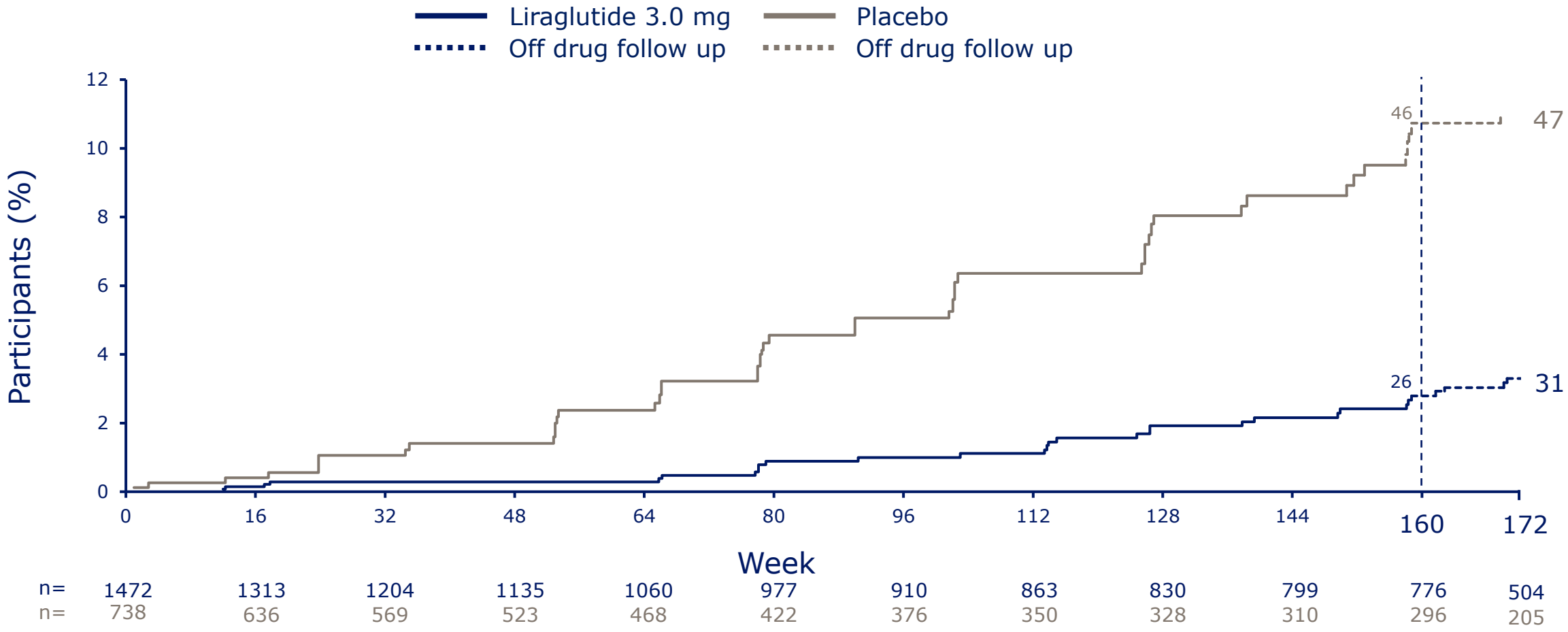
	Liraglutide 3.0 mg (n=1505)	Placebo (n=749)
Sex, female	1141 (76)	573 (77)
Sex, male	364 (24)	176 (23)
Mean age, years	47.5 ± 11.7	47.3 ± 11.8
White	1256 (83)	628 (84)
Mean fasting body weight, kg	107.5 ± 21.6	107.9 ± 21.8
Mean BMI, kg/m^2	38.8 ± 6.4	39.0 ± 6.3
Mean HbA_{1c}, %	5.8 ± 0.3	5.7 ± 0.3
Mean FPG, mmol/L	5.5 ± 0.6	5.5 ± 0.5
Mean 2-hour PG during OGTT, mmol/L	7.4 ± 1.8	7.4 ± 1.7
History of dyslipidaemia	499 (33)	249 (33)
History of hypertension	635 (42)	312 (42)

Data are observed means ± SD or number (%)
FPG, fasting plasma glucose; OGTT, oral glucose-tolerance test; PG, plasma glucose; SD, standard deviation
*The diagnoses of dyslipidaemia and hypertension were based on reported medical history

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

Participants diagnosed with T2D over time

Kaplan-Meier plot: 0–172 weeks

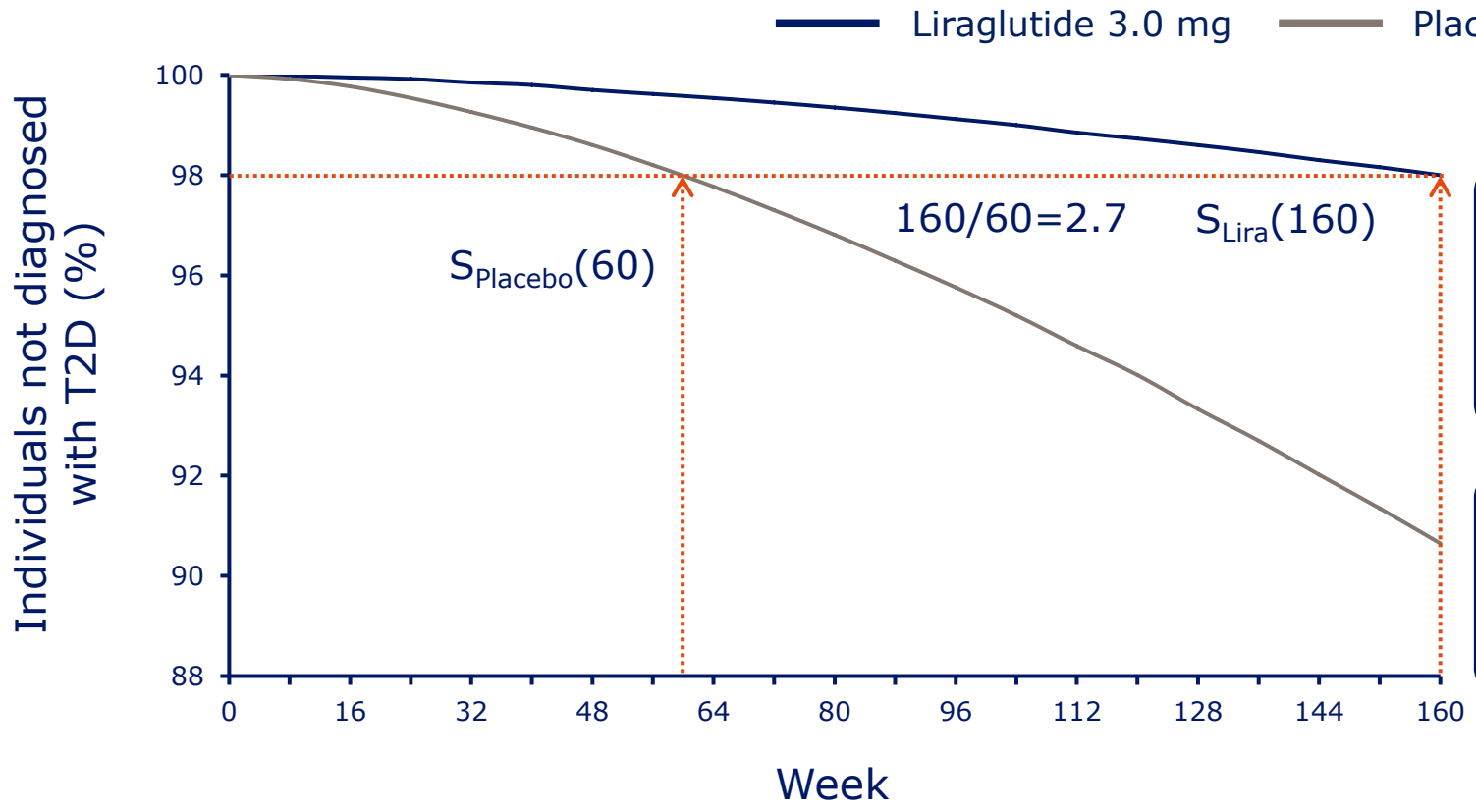


Full analysis set. Numbers in the figure correspond to the accumulated number of diagnosed participants
T2D, type 2 diabetes

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

Time to onset of T2D

How is the prolongation of time to T2D with liraglutide 3.0 mg interpreted?



If 2% of the **placebo** population gets diabetes within **1 year**, we would expect it to take **2.7 years** until 2% of the **liraglutide 3.0 mg** population gets diabetes

2.7 must be interpreted as a **risk reduction of around 80%,** as seen when the prolongation factor is converted to a **hazard ratio of 0.21**

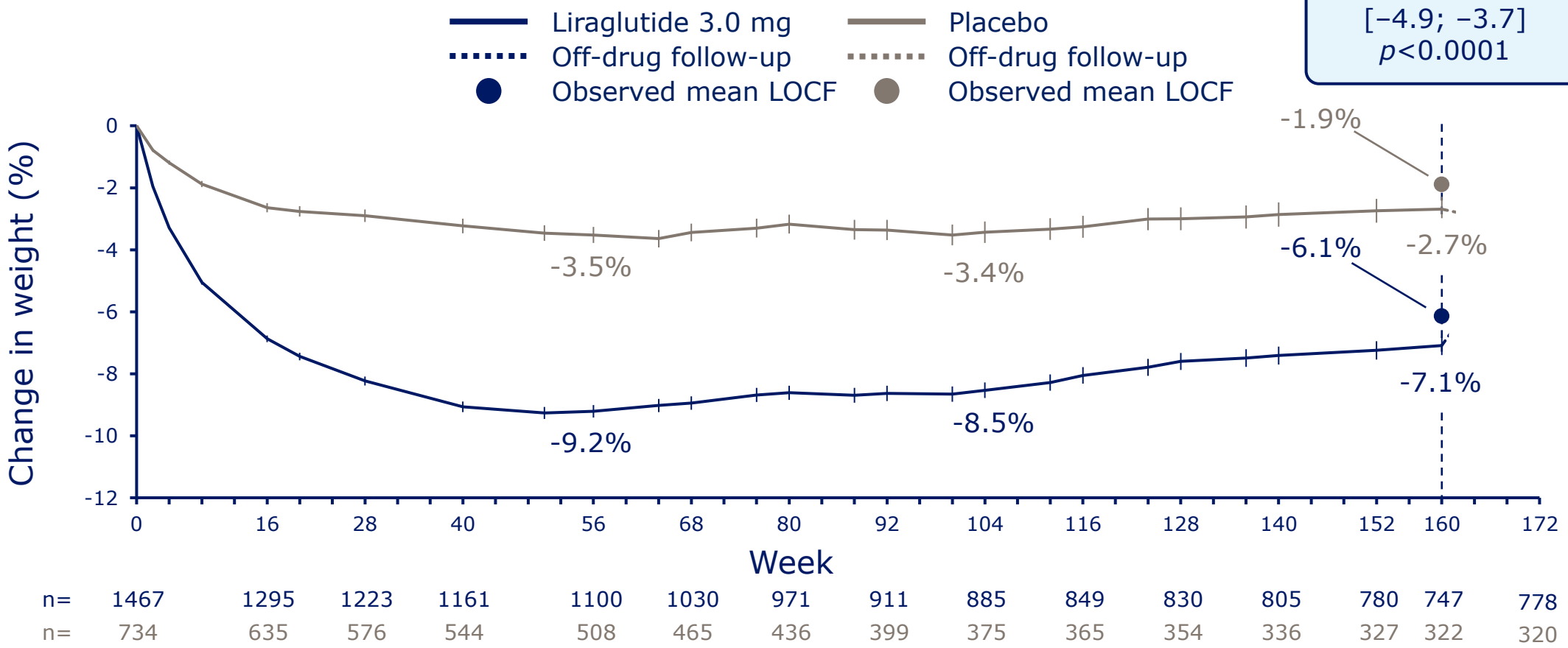
Full analysis set. The time of onset of T2D occurs in between the first of the two required registrations of elevated HbA_{1c}, FPG or 2-hour OGTT plasma glucose, and the diabetes assessment visit prior to the first registration. T2D, type 2 diabetes

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

Change in body weight (%)

0–172 weeks

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



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

Patientin S. H., geb. 1978

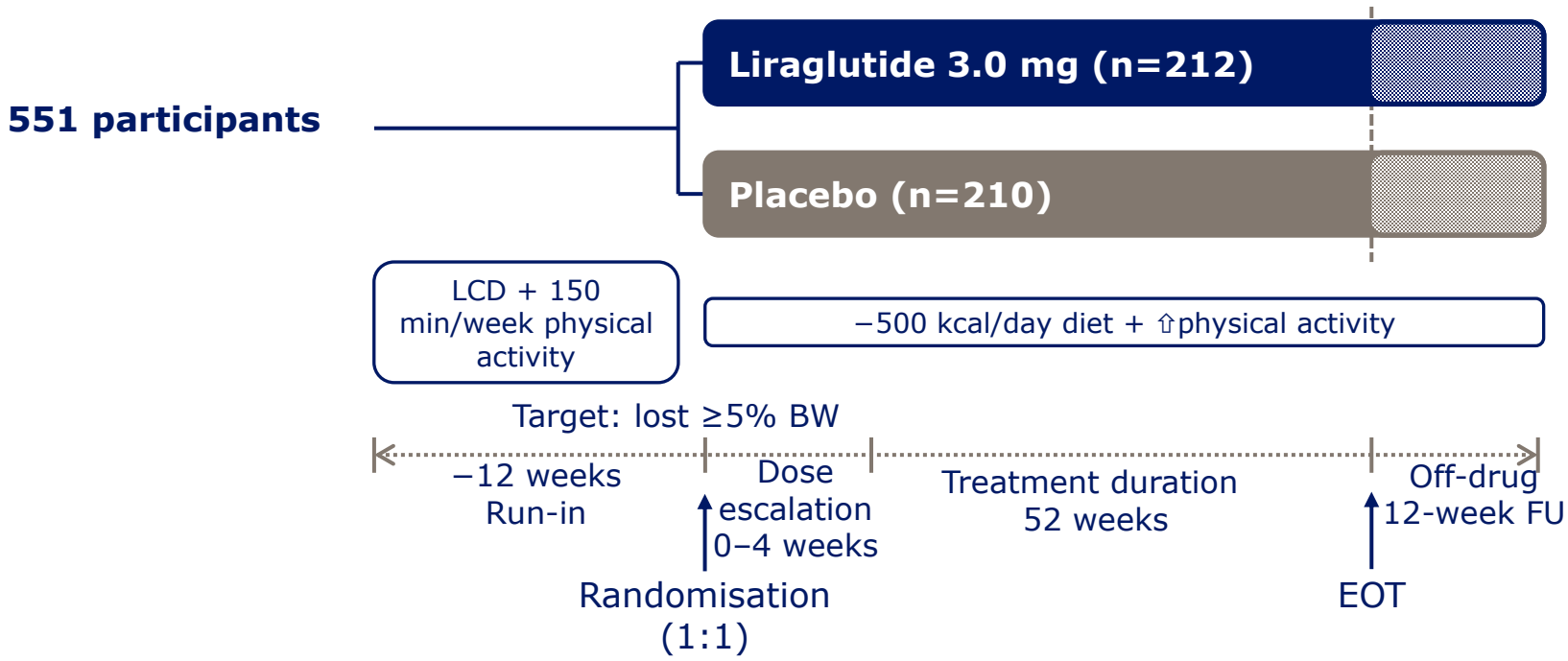
- Gewicht 105 kg, BMI 38,6 kg/m²
- 2-fache Mutter
- Schichtarbeit als DGKS
- Hat vor dem ersten Lockdown durch „intermittent fasting“ 15 kg abgenommen
- Hat während des ersten Lockdowns 18 kg zugenommen
- Hat nun wieder mit „intermittent fasting“ begonnen, ist aber nicht so erfolgreich – Gewicht steht.

Trial design: SCALE Maintenance

Weight maintenance with liraglutide 3.0 mg after LCD-induced weight loss

Trial objective

Efficacy of liraglutide 3.0 mg in maintaining weight loss achieved with a LCD (1200–1400 kcal/day) and increased physical activity (150 min/week) during run-in



Trial information

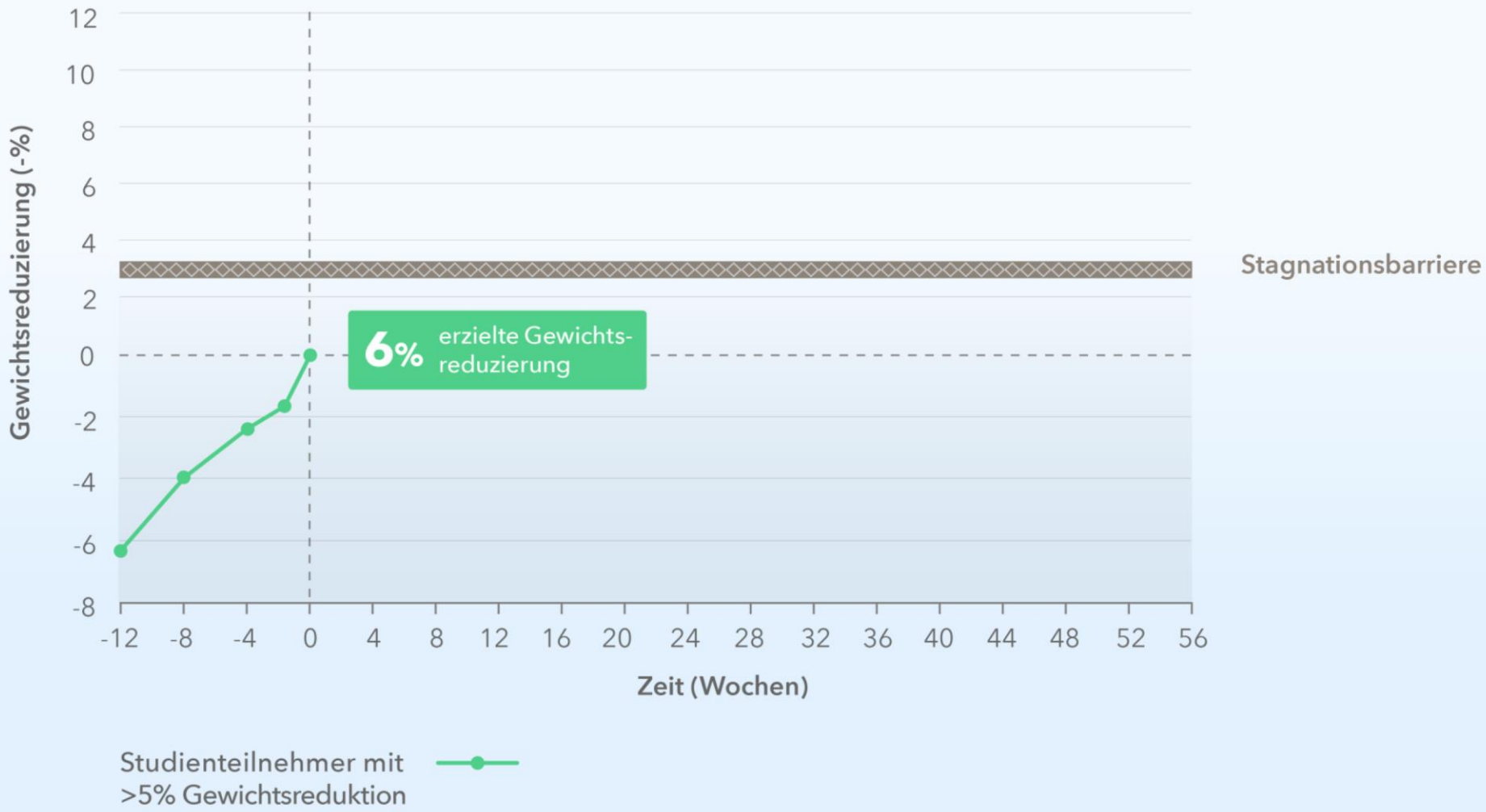
- October 2008 to January 2009
- Randomised controlled double-blind study
- 36 sites (US and Canada)

BW, body weight; EOT, end of treatment; FPG, fasting plasma glucose; FU, follow-up; LCD, low-calorie diet; WL, weight loss

Wadden *et al.*: *Int J Obes (Lond)* 2013; 37: 1443-51

Stagnation durchbrechen[5,6]

Saxenda®
liraglutide injection

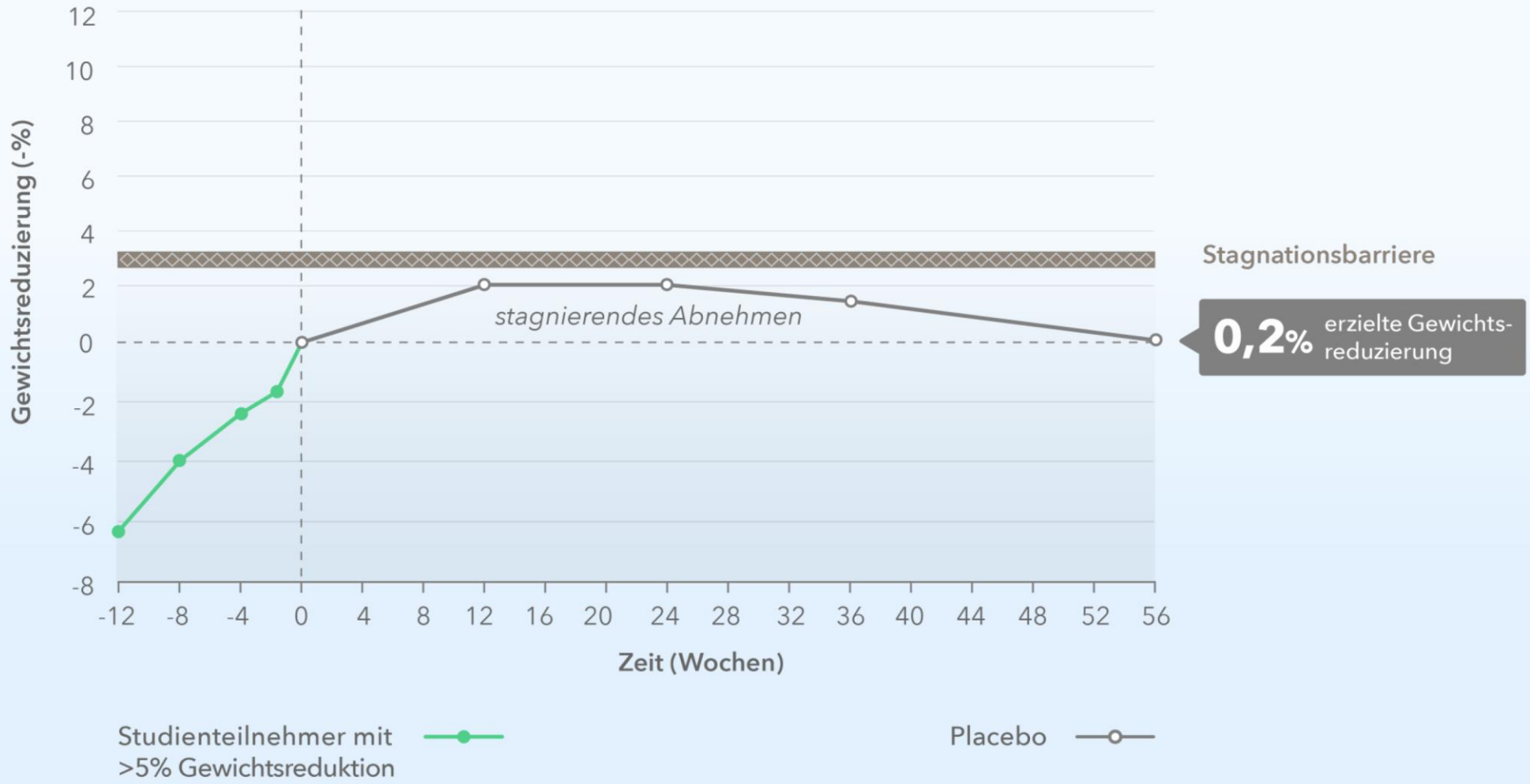


AT21SX00002

modifiziert nach: Wadden et al.[5] und Wharton et al.[6]

Stagnation durchbrechen[5,6]

Saxenda®
liraglutide injection

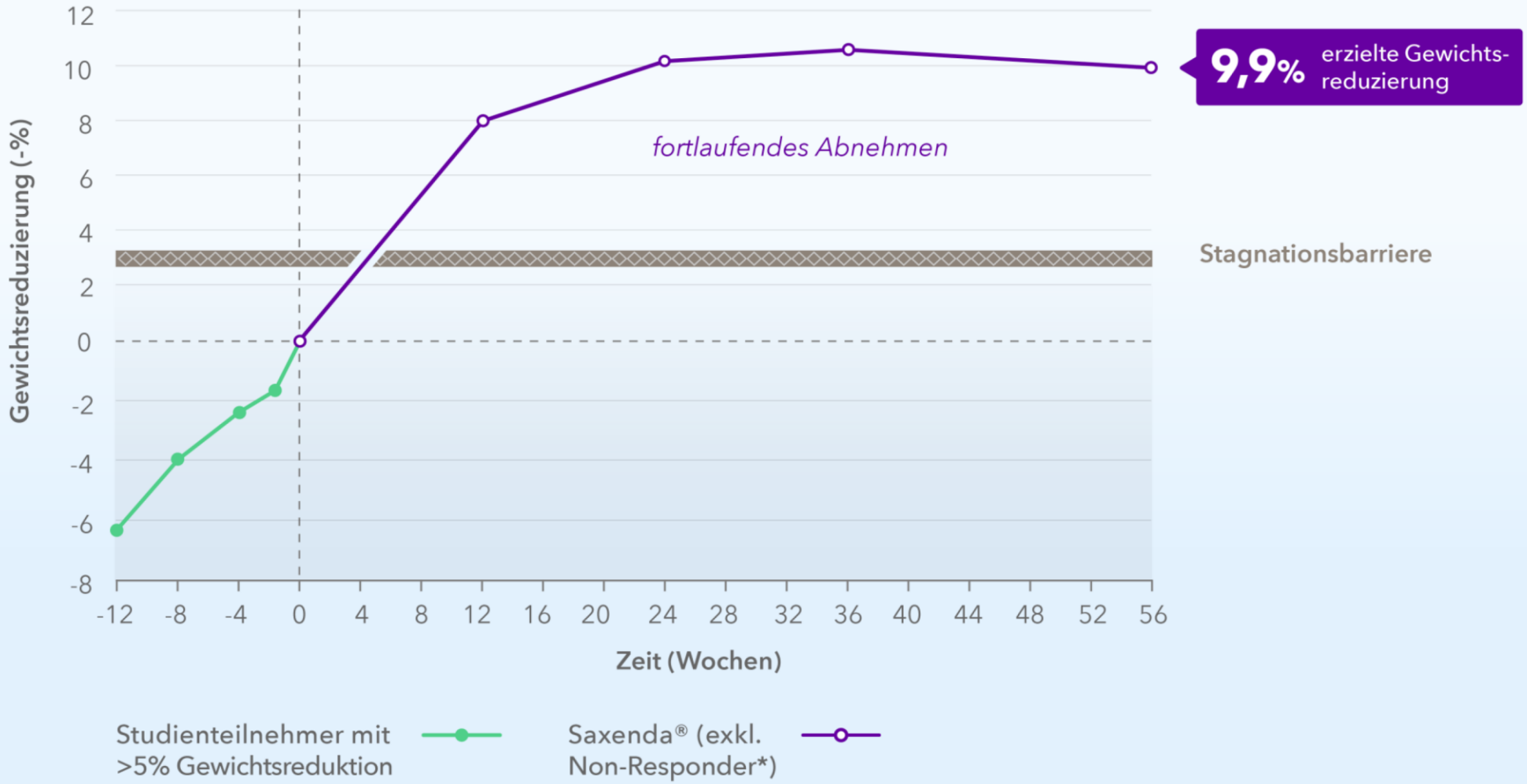


modifiziert nach: Wadden et al.[5] und Wharton et al.[6]

AT21SX00002

Stagnation durchbrechen[5,6]

Saxenda®
liraglutide injection

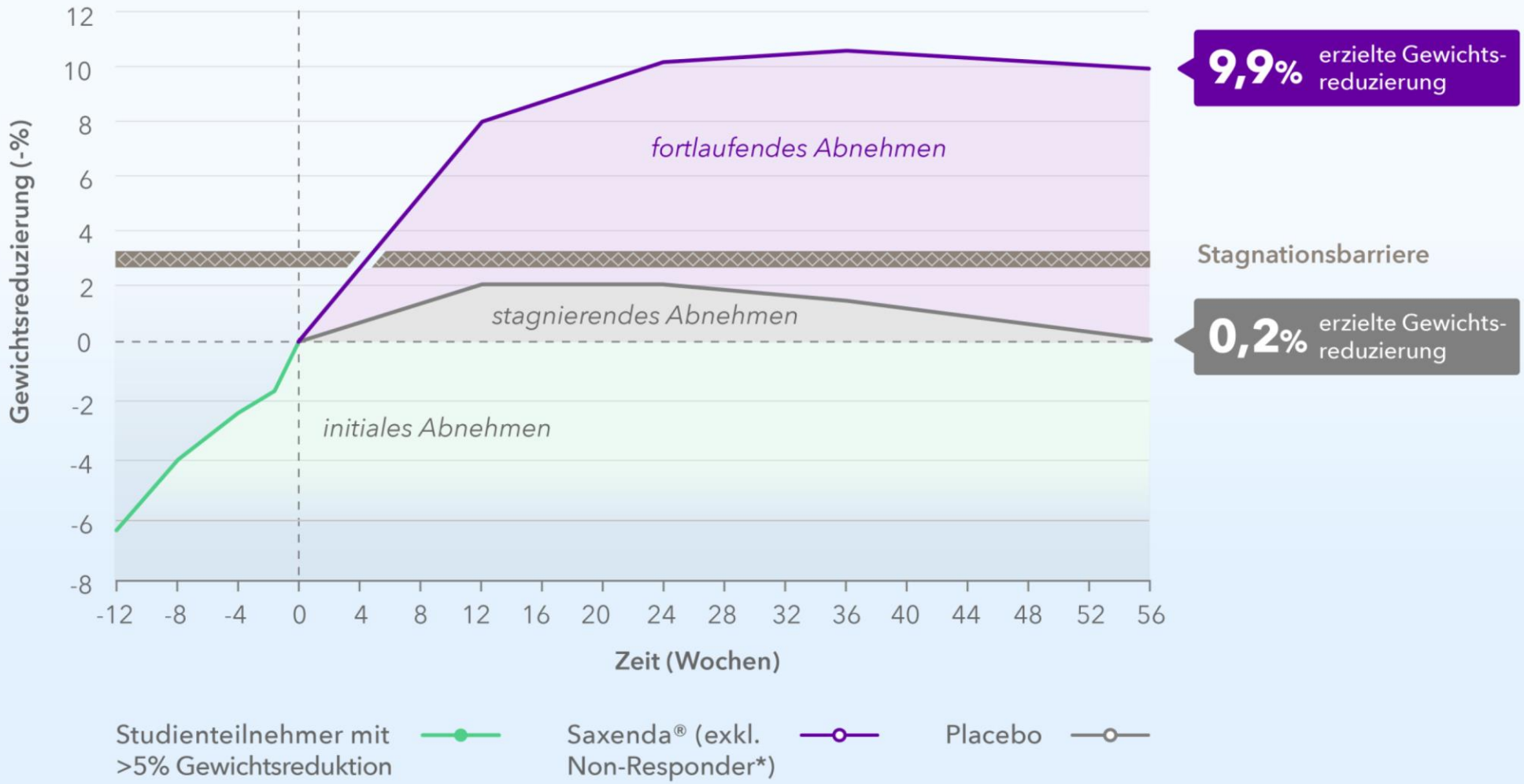


modifiziert nach: Wadden et al.[5] und Wharton et al.[6]
*Gewichtsreduzierung <5% nach 16 Wochen

AT21SX00002

Stagnation durchbrechen[5,6]

Saxenda®
liraglutide injection



modifiziert nach: Wadden et al.[5] und Wharton et al.[6]
*Gewichtsreduzierung <5% nach 16 Wochen

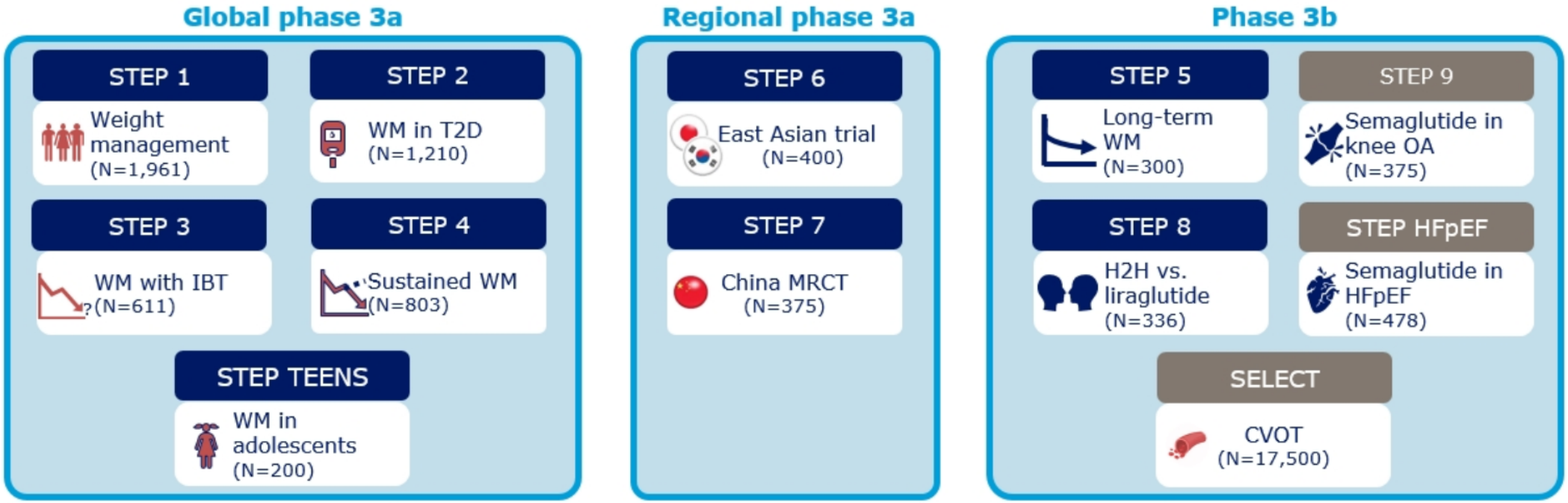
AT21SX00002

Pat. Ch. E.

- 45a
- 2003 Magenband
- 2012 Konversion in Magenbypass
- Seither Probleme mit „weight regain“
- Februar 2020: Gewicht 121 kg, BMI 34,9 kg/m² – Beginn Liraglutide
- August 2020: Gewicht 103 kg, BMI 29,8 kg/m²
- November 2020: Gewicht 109 kg, BMI 31,5 kg/m²
- Februar 2021: BMI 30,5 kg/m²

- Falls Corona (hoffentlich nicht) noch länger weitergeht?

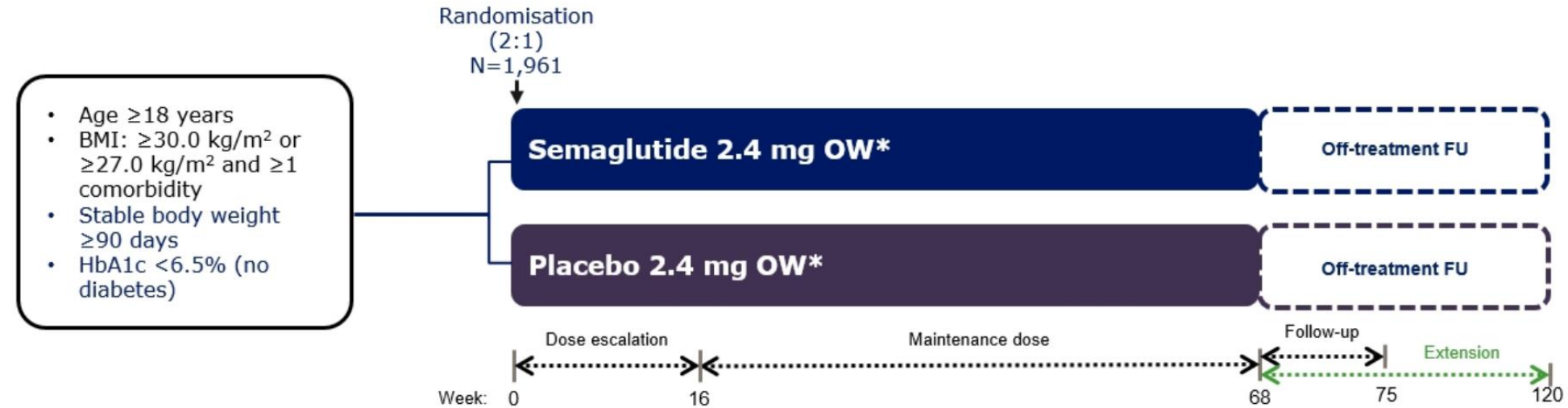
STEP programme at a glance



CVOT, cardiovascular outcomes trial; HFpEF, heart failure with preserved ejection fraction; H2H, head-to-head; IBT, intensive behavioral therapy; MRCT, multi-regional clinical trial (including China and ≥1 additional East Asian country); OA, osteoarthritis; WM, weight management

Weight Management :STEP 1 trial design

Randomised, double-blind, placebo-controlled trial



Trial objective

- To compare the effect of semaglutide vs. placebo on body weight
- To compare the effect of semaglutide versus placebo on cardiovascular risk factors, Clinical Outcome Assessments (COAs), glucose metabolism, other factors related to body weight and safety and tolerability

Primary endpoint

- Change from baseline at week 0 to week 68 in body weight (%)
- Proportion of subjects achieving ≥5% weight loss

Confirmatory secondary endpoints

- Proportion of subjects achieving ≥10% and ≥15% weight loss
- Change in waist circumference, systolic blood pressure, SF-36, IWQoL-Lite for CT

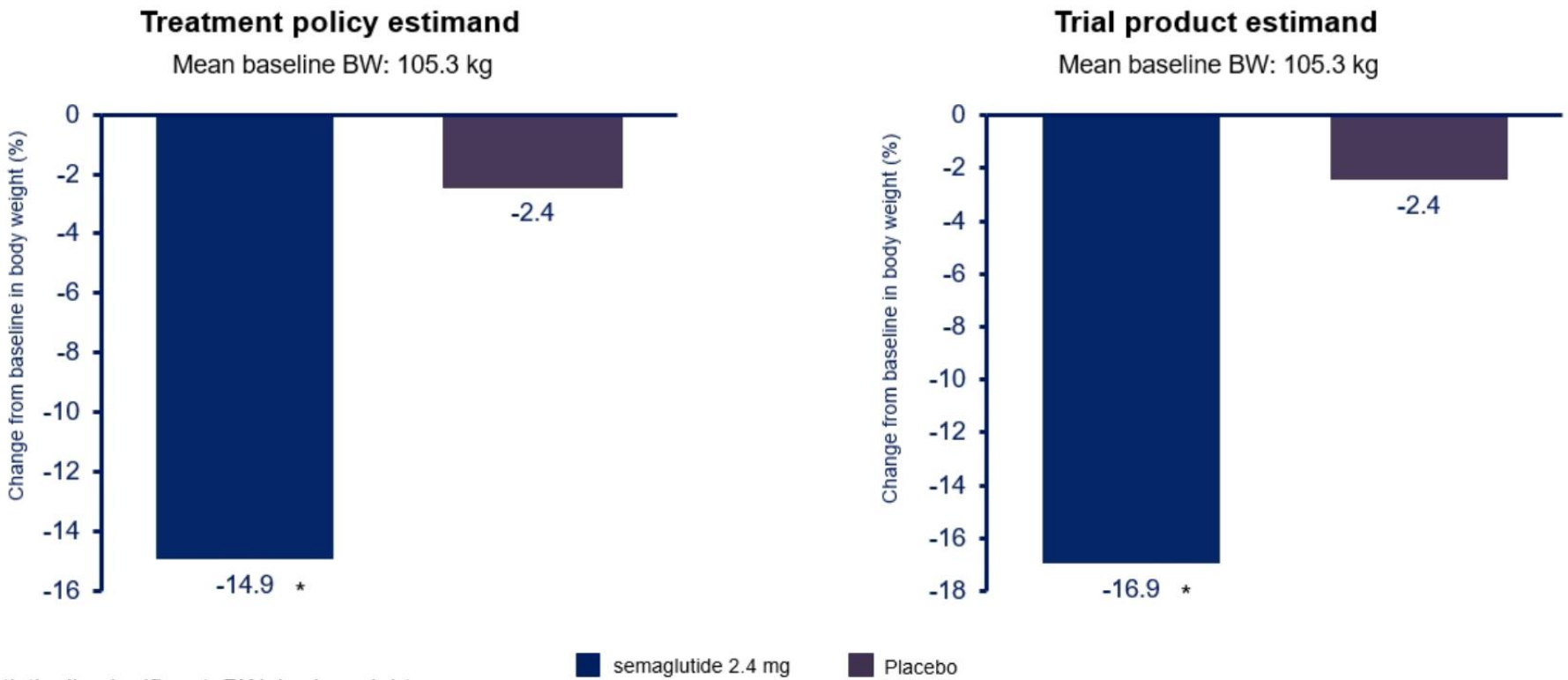
an adjunct to lifestyle intervention (-500 NCT03548935. Available at: https://clinicaltrials.gov/ct2/show/NCT03548935?term=step+1&draw=2&rank=1

23 / 38 07:38

Adapted from: Kushner et al.: Obesity 2020; 28(6): 1050-61

Change in body weight from baseline to end of treatment

Treatment policy and trial product estimands at week 68



* Statistically significant. BW, body weight.

Novo Nordisk. https://www.novonordisk.com/media/news-details.2314024.html. (Accessed: 4.Jun.2020)

4. Bariatrische Chirurgie

Patient M. R., geb. 1996

- Gewicht 140 kg, BMI 44,4 kg/m²
- Art Hypertone
- Steatosis hepatis
- Findet nach einer Kochlehre keinen Job

Patient R. A., geb. 1974

- Gewicht 132 kg, BMI 42,8 kg/m²
- Diabetes mellitus Typ 2 seit 6 Jahren
- Nikotinabusus
- Zunehmende Wirbelsäulenschmerzen
- Arbeitet bei einer Versicherung
- Pos. Familienanamnese für Insulte

Patientin A. M., geb. 1986

- Gewicht 128 kg, BMI 47,0 kg/m²
- Z. n. 2 x GDM
- Starkes Craving nach Süßem

Leitlinien bariatrische Chirurgie – welcher Patient kommt in Frage?

- Alter 18–65
- BMI > 40 kg/m²
- BMI > 35 kg/m² und eine Komorbidität, für die Gewichtsverlust eine Verbesserung darstellt (metabolische Erkrankungen, Herz-Kreislauf-Erkrankungen, schwere Gelenkerkrankungen, Adipositas-assoziierte psychologische Erkrankungen)
- In bestimmten Fällen kann die bariatrische Chirurgie auch bei einem BMI von 30–35 kg/m² durchgeführt werden.

Dazu zählen:

- Typ-2-Diabetes
- Arterielle Hypertonie
- Hyperlipidämie
- Obstruktives Schlafapnoe-Syndrom
- Adipositas-assoziiertes Hypoventilationssyndrom
- NAFLD („non-alcoholic fatty liver disease“)
- NASH
- Gastroösophagealer Reflux (GERD)
- Asthma
- Venöse Insuffizienz
- Arthritis
- Schwere Harninkontinenz
- „Considerably impaired quality of life“

Leitlinien bariatrische Chirurgie – welcher Patient kommt in Frage?

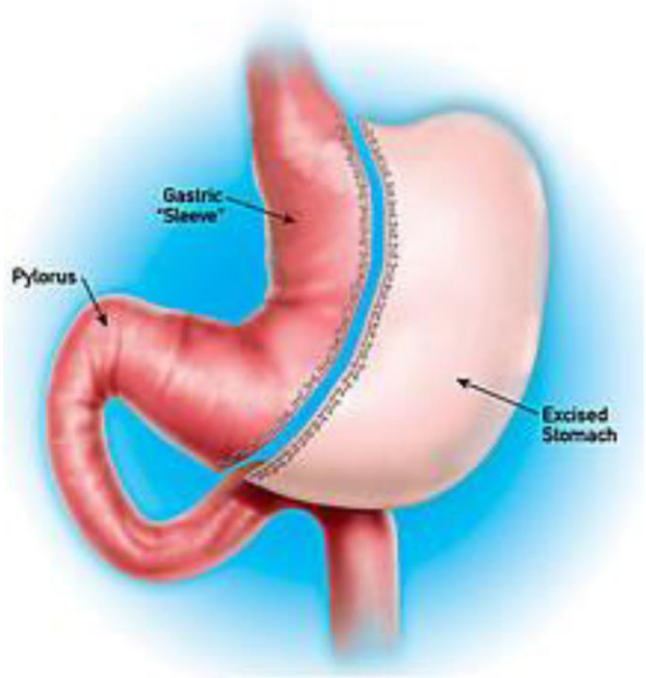
- Der BMI kann ein aktueller oder ein vorangegangener BMI sein:

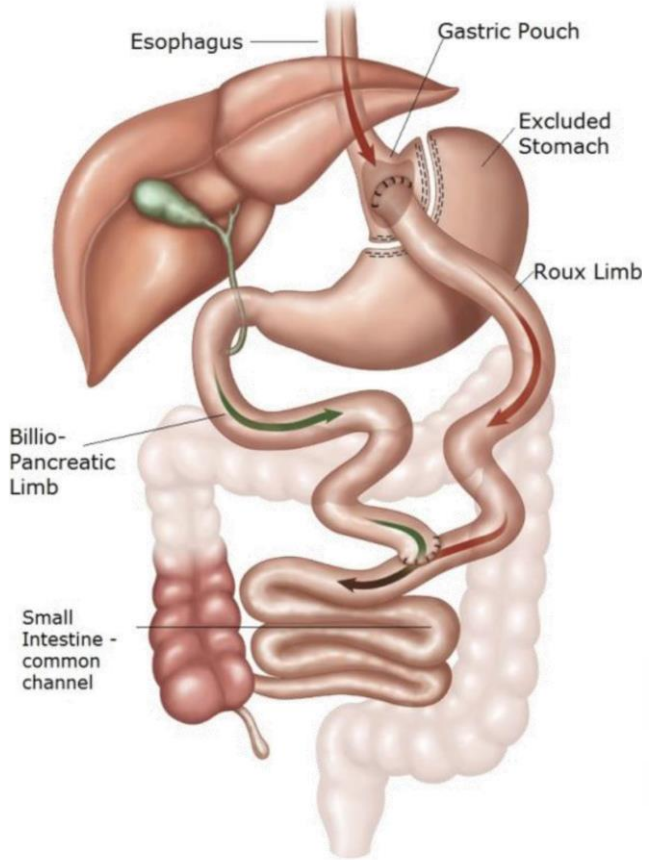
  a. Wenn der BMI bei Patienten mit Gewichtsreduktion nach intensivierter Behandlung niedriger als 40 kg/m² bzw. 35 kg/m² ist , stellt dies keine Kontraindikation für die Operation dar.

  b. Die bariatrische Chirurgie ist indiziert für Patienten, die nach einer deutlichen Gewichtsreduktion mit konservativen Methoden wieder Gewicht zugenommen haben.

- Jeder Patient muss auf konservative, kontrollierte Weise Gewicht abnehmen, um für eine Operation in Frage zu kommen.

Die hauptsächlich durchgeführten Operationen





Number needed to treat to prevent one patient …

- To prevent patients with type 2 diabetes over 10 years

  NNT for IFG patients: 1.3

  NNT for NGT patients: 7.0

- To prevent cardiovascular events over 15 years

  NNT for patients fasting insulin ≥ 17 µU/L: 21

  NNT for patients fasting insulin ≤ 17 U/L: 173

Sjöström L et al.: JAMA 2012; Sjöström L et al.: Journ of Internal Med 2013

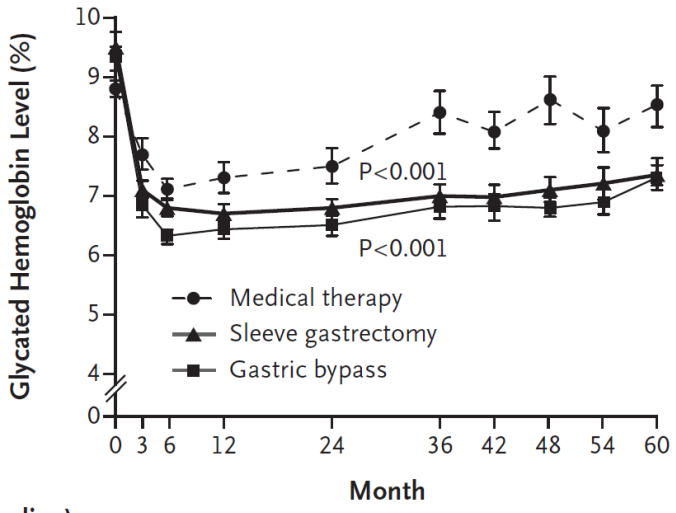
Bariatric Surgery versus Intensive Medical Therapy for Diabetes – 5 years outcome

Characteristic	Medical Therapy (N = 50)	Gastric Bypass (N = 50)	Sleeve Gastrectomy (N = 50)	P Value
Duration of diabetes — yr	8.9±5.8	8.2±5.5	8.5±4.8	0.72
Use of insulin — no. (%)	22 (44)	22 (44)	22 (44)	1.00
Age — yr	49.7±7.4	48.3±8.4	47.9±8.0	0.46
Female sex — no. (%)	31 (62)	29 (58)	39 (78)	0.08
Body-mass index†				
Value	36.8±3.0	37.0±3.3	36.2±3.9	0.42
<35 — no. (%)	19 (38)	14 (28)	18 (36)	0.54
Body weight — kg	106.5±14.7	106.7±14.8	100.8±16.4	0.10
Waist circumference — cm	114.5±9.4	116.4±9.2	114.0±10.4	0.43
Waist-to-hip ratio	0.95±0.09	0.96±0.07	0.96±0.09	0.88
White race — no. (%)‡	37 (74)	37 (74)	36 (72)	0.97
Smoker — no./total no. (%)	15/42 (36)	20/50 (40)	11/50 (22)	0.14
Metabolic syndrome — no. (%)	46 (92)	45 (90)	47 (94)	1.00
History of dyslipidemia — no./total no. (%)	36/43 (84)	44/50 (88)	40/50 (80)	0.55
History of hypertension — no./total no. (%)	26/43 (60)	35/50 (70)	30/50 (60)	0.51

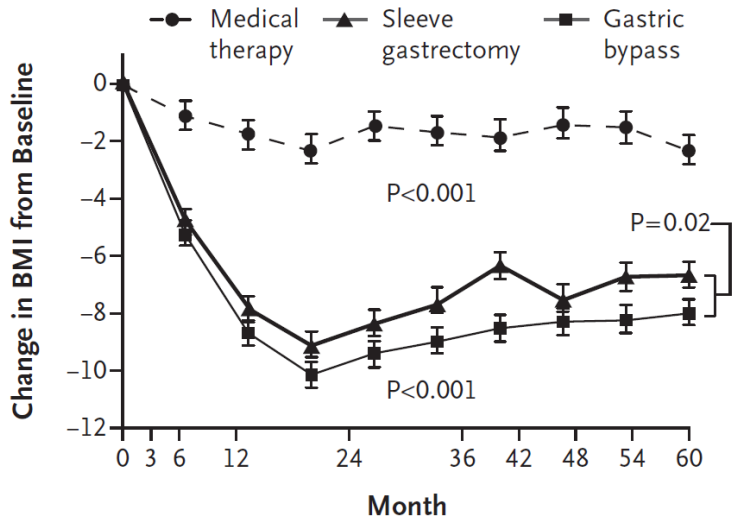
Schauer P et al.: NEJM 2014

Bariatric Surgery versus Intensive Medical Therapy for Diabetes – 5 years outcome

A Glycated Hemoglobin



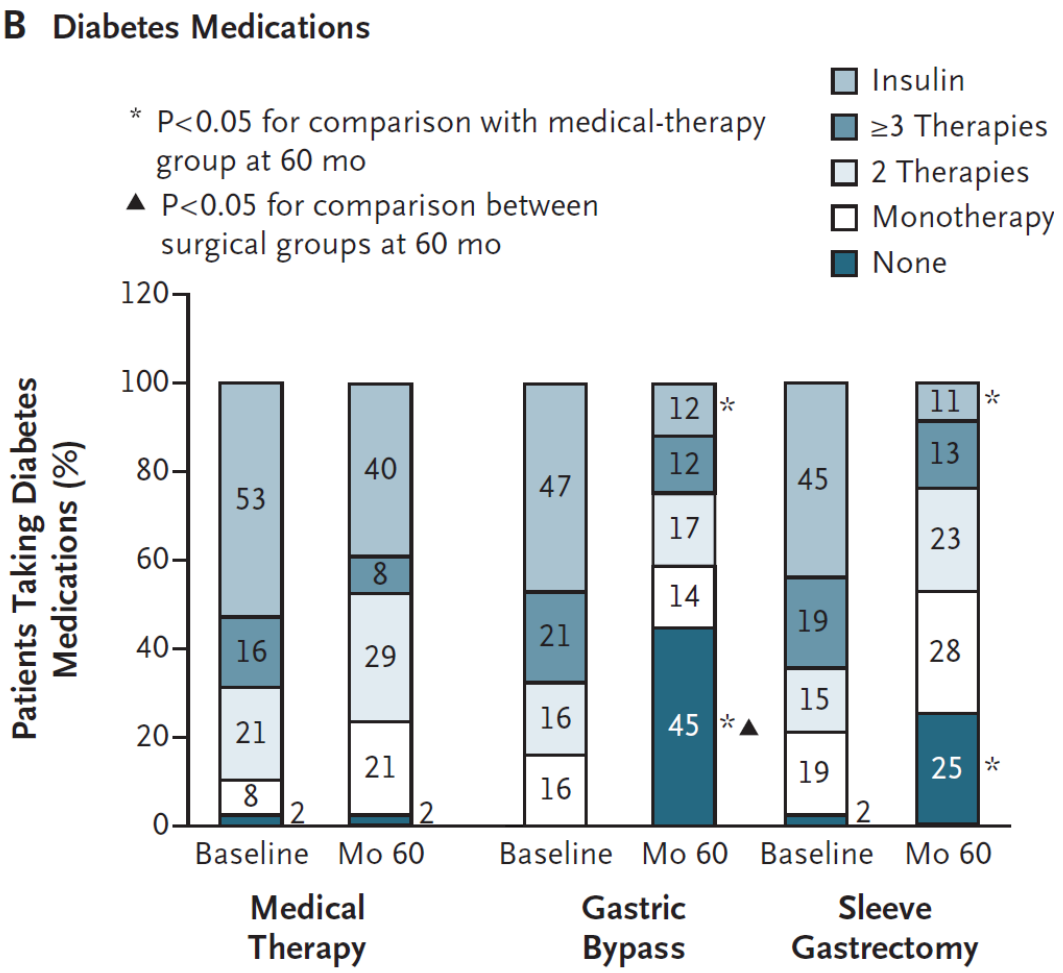
Mean (median) Value at Visit						
Medical therapy	8.8 (8.6)	7.3 (6.8)	7.5 (7.2)	8.4 (7.7)	8.6 (8.2)	8.5 (8.0)
Gastric bypass	9.3 (9.4)	6.4 (6.2)	6.5 (6.4)	6.8 (6.6)	6.8 (6.8)	7.3 (6.9)
Sleeve gastrectomy	9.5 (8.9)	6.7 (6.4)	6.8 (6.8)	7.0 (6.7)	7.1 (6.6)	7.4 (7.2)



Mean Value at Visit						
Medical therapy	36.4	34.1	35.0	34.8	35.1	34.0
Gastric bypass	37.0	26.9	27.4	28.2	28.6	28.9
Sleeve gastrectomy	36.0	26.9	27.7	28.1	28.2	29.3

Schauer P et al.: NEJM 2017

Bariatric Surgery versus Intensive Medical Therapy for Diabetes – 5 years outcome



Schauer P et al.: NEJM 2017

Vielen Dank für Ihre Aufmerksamkeit!

Backup Slides

Behandlungsoptionen für Menschen mit Diabetes und Adipositas

	BMI Kategorien				
	25.0-26.9	27.0-29.9	30.0-34.9	35.0-39.9	≥40.0
Diät, Bewegung, Verhaltenstherapie	+	+	+	+	+
Pharmakotherapie		+	+	+	+
Metabolische Chirurgie			+	+	+

+ Behandlung kann indiziert sein für ausgewählte motivierte Patienten

- Metabolic surgery should be recommended as an option to treat type 2 diabetes in appropriate surgical candidates with BMI ≥40 kg/m2 (BMI ≥ 37.5 kg/m2 in Asian Americans), regardless of the level of glycemic control or complexity of glucose-lowering regimens, and in adults with BMI 35.0–39.9 kg/m2 (32.5–37.4 kg/m2 in Asian Americans) when hyperglycemia is inadequately controlled despite lifestyle and optimal medical therapy. **A**
- Metabolic surgery should be considered as an option for adults with type 2 diabetes and BMI 30.0–34.9 kg/m2 (27.5–32.4 kg/m2 in Asian Americans) if hyperglycemia is inadequately controlled despite optimal medical control by either oral or injectable medications (including insulin). **B**

American Diabetes Association Diab Care 2018; 41: S73-S85

Antiobesity Drugs That Have Been Withdrawn From the Market

Drug	Mechanism of Action	Regulatory Status	References
Dinitrophenol	Thermogenesis (uncouples oxidative phosphorylation)	Withdrawn in 1938 due to the risk of neuropathy and cataracts	74, 75, 11
Aminorex	5-HT releaser and reuptake inhibitor; also potent monoamine oxidase inhibitor	Withdrawn in 1968 due to the concern of pulmonary arterial hypertension	76
Fenfluramine and dexfenfluramine	5-HT_{2B} receptor agonist	Withdrawn after reports of valvular heart damage and primary pulmonary hypertension in 1997	77-78
Mazindol	Norepinephrine reuptake inhibitor	Withdrawn in 2000 due to an unfavorable risk to benefits ratio	80
Methamphetamine	Appetite suppression	Withdrawn in 2000 due to dependency and abuse potential, cardiovascular adverse effects	76
Phenylpropanolamine	Norepinephrine/dopamine releasing stimulator	Withdrawn for increased risk of hemorrhagic stroke in 2000	81
Phendimetrazine	Appetite suppressant	Currently indicated for the management of exogenous obesity as short-term adjunct, but their use is restricted because of their adverse effects such as pulmonary arterial hypertension, valvulopathy, and the potential for abuse and dependency so it had been withdrawn by European union at the year 2000. Still available in United States	11
Diethylpropion	Appetite suppression	Currently approved drug by US FDA for short-term weight management. But it had been withdrawn by European union at the year 2000 itself due to an unfavorable risk to benefits ratio	80,82
Rimonabant	Selective CB1 receptor blocker	Withdrawn in 2009 due to potential of serious psychiatric disorders including depressed mood disorders, anxiety, and suicidal ideation	89,90
Sibutramine	Selective combined serotonin and noradrenaline reuptake inhibitor (appetite suppression)	Withdrawn in 2010 due to increased risk of heart attack and stroke in high-risk patients with cardiac disease	91

Abbreviation: FDA, Food and Drug Administration.

Journal of Cardiovascular Pharmacology and Therapeutics 2014; Vol 19(1): 65-76

Emerging drugs for the treatment of obesity

Compound	Company	Structure	Phase	Mechanism of action
Centrally acting				
Setmelanotide (RM-493)	Rhythm Pharmaceuticals	$C_{49}H_{72}N_{18}O_9S_2$	2	Melanocortin 4 receptor agonist
S-237648	Shionogi	$C_{20}H_{17}N_3O_3S$	2	Neuropeptide Y5 receptor antagonist
Tesofensine	Saniona	$C_{17}H_{23}Cl_2NO$	3	Noradrenalin/serotonin/dopamine reuptake inhibitor
Bupropion + zonisamide SR (empatic)	Orexigen	$C_{21}H_{26}ClN_3O_4S$	2	Dopamine/noradrenalin reuptake inhibitor GABA receptor agonist
Peripherally acting				
Cetilistat	Takeda/Norgine	$C_{25}H_{39}NO_3$	4	Pancreas lipase inhibitor
PAZ-320 (BTI-320)	Boston Therapeutics	–	3	Carbohydrate hydrolyzing inhibitor
Canagliflozin	Mitsubishi Tanabe Pharma/Johnson & Johnson/Daiichi Sankyo	$C_{24}H_{25}F0_5S$	2	Sodium/glucose cotransporter 2 inhibitor
LIK-066	Novartis	–	2	Sodium/glucose cotransporter 2 inhibitor
Beloranib	Zafgen	$C_{29}H_{41}NO_6$	2[a]	Methionine aminopeptidase-2 and angiogenesis inhibitor
ALS-L1023	AngioLab	–	3	Angiogenesis and matrix metalloproteinase inhibitor
IONIS-FGFR4Rx	Ionis Pharmaceuticals	–	2	Fibroblast growth factor receptor 4 inhibitor
MB-11055	KT&G Life Sciences	–	2	AMPK activator
Salmeterol xinofoate	Neothetics	$C_{61}H_{76}F_3NO_{12}S$	2	Long-acting β2-adrenergic receptor agonist
Peripherally + centrally acting				
Langlenatide (efpeglenatide)	Hanmi	$C_{19}H_{37}N_3O_6$	2	Long-acting glucagon-like peptide 1 agonist
Semaglutide	Novo Nordisk	$C_{187}H_{291}N_{45}O_{59}$	2	Long-acting glucagon-like peptide 1 agonist
Exenatide ER (bydureon)	Astra Zeneca	$C_{184}H_{282}N_{50}O_{60}S$	2	Long-acting glucagon-like peptide 1 agonist
TT-401	Transition Therapeutics	–	2	Glucagon-like peptide 1/glucagon dual agonist

[a]Development terminated in 2016.
SR: Sustained release; ER: extended release.

EXPERT OPINION ON EMERGING DRUGS 2017; VOL. 22, NO. 1: 87-99