UNIVERSITÄT LEIPZIG

HelmholtzZentrum münchen
German Research Center for Environmental Health

Helmholtz Diabetes Center

Adipositas – neue Therapien: Eine Chance für Patienten

Matthias Blüher

HELMHOLTZ RESEARCH FOR GRAND CHALLENGES

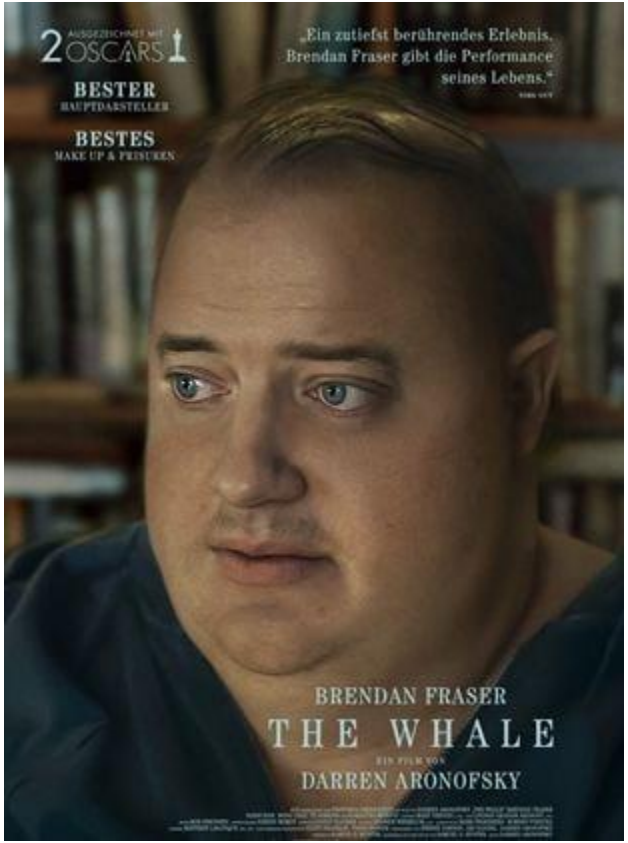
9. D-Day in Wetzlar „Diabetes unterm Dom“ am 07.10.2023

Transparenzerklärung

Hiermit lege ich offen, dass ich von folgenden Firmen finanzielle Unterstützung erhalten habe, die sich auf Vorträge oder Beratertätigkeiten bezieht:

- Amgen
- Astra Zeneca
- Bayer
- Boehringer Ingelheim
- Lilly
- Novo Nordisk
- Novartis
- Pfizer
- Sanofi

Gewichtsmanagement erfreut sich großer Aufmerksamkeit…



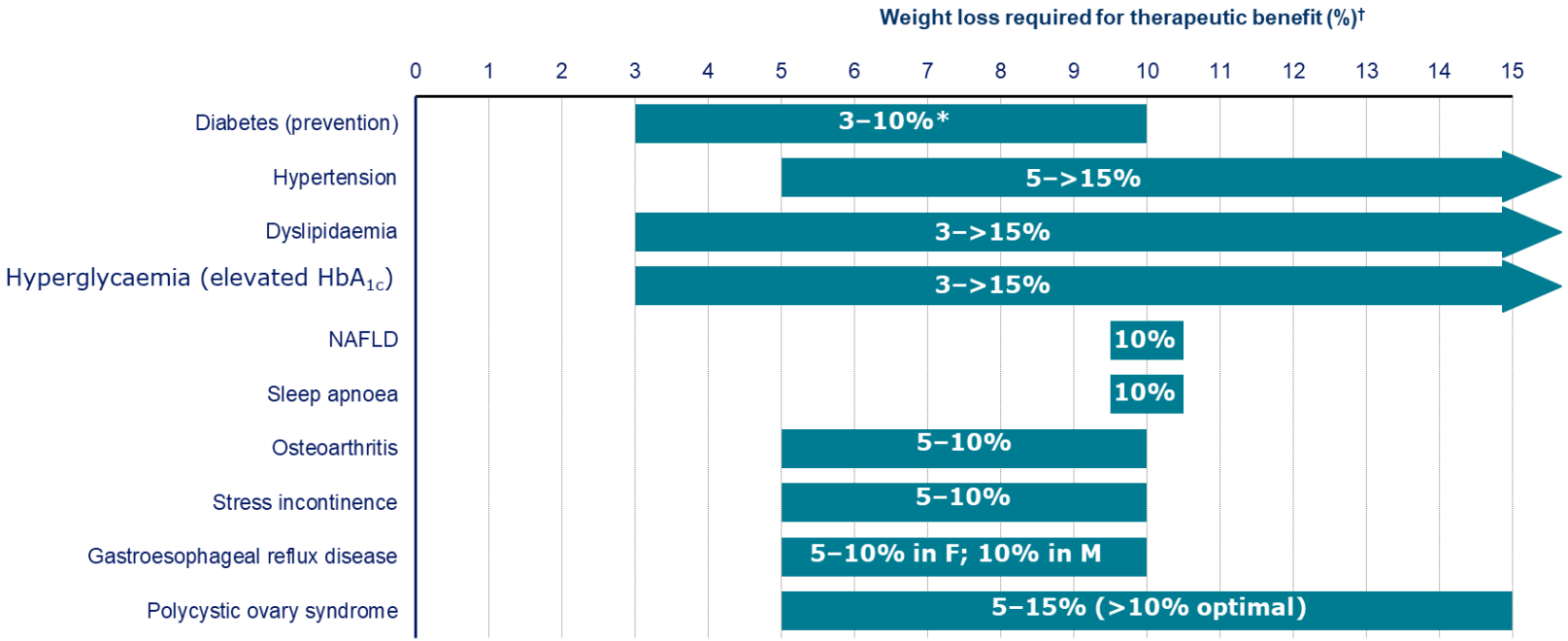
Adipositas ist kein kosmetisches Problem…

23% Adipositas Prävalenz in Deutschland

Kann man durch

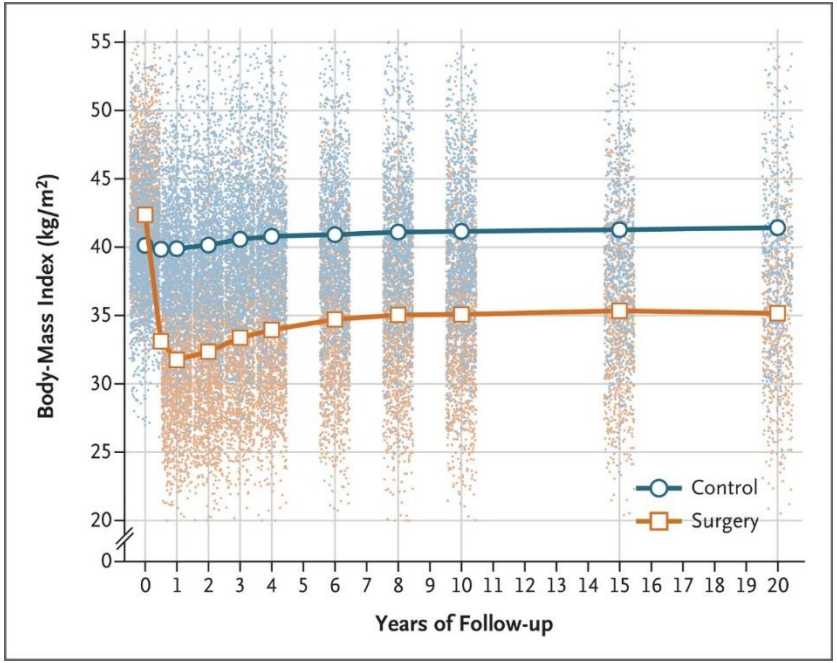
Adipositastherapie Leben retten?

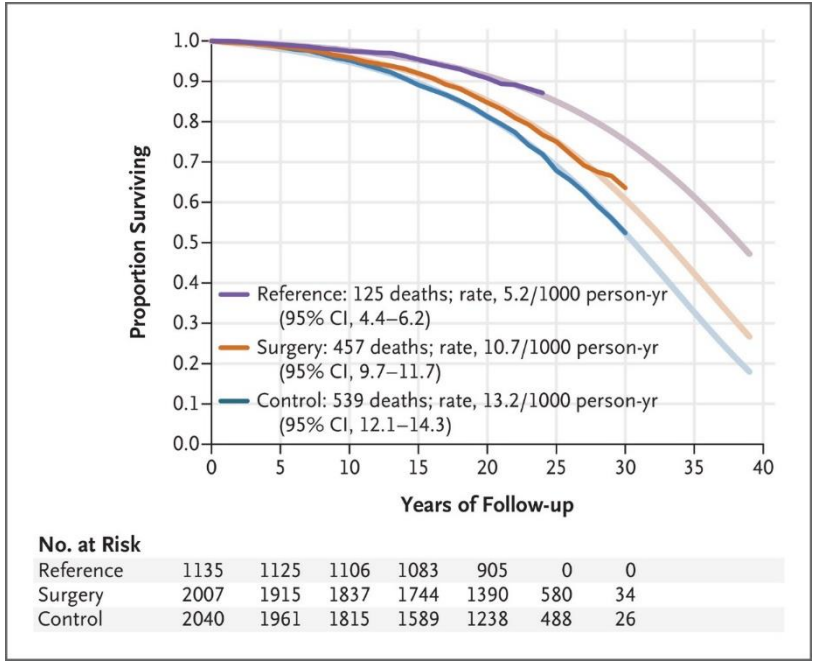
Gewichtsverlust verbessert Komorbiditäten, aber auch kardiovaskuläre Endpunkte?



Cefalu et al. *Diabetes Care* 2015;38:1567–82

Gewichtsverlust verbessert Lebenserwartung





No. at Risk

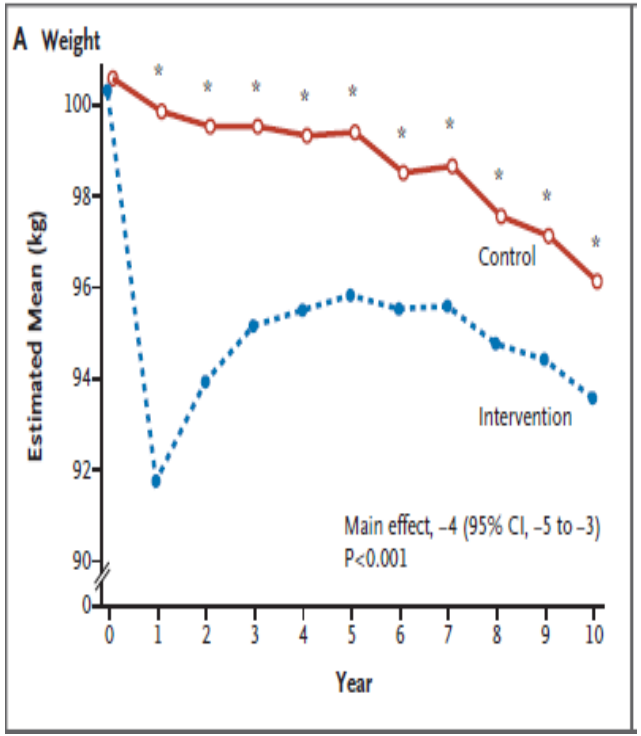
Reference	1135	1125	1106	1083	905	0	0
Surgery	2007	1915	1837	1744	1390	580	34
Control	2040	1961	1815	1589	1238	488	26

Carlsson et al., N Engl J Med. 2020;383:1535-1543.

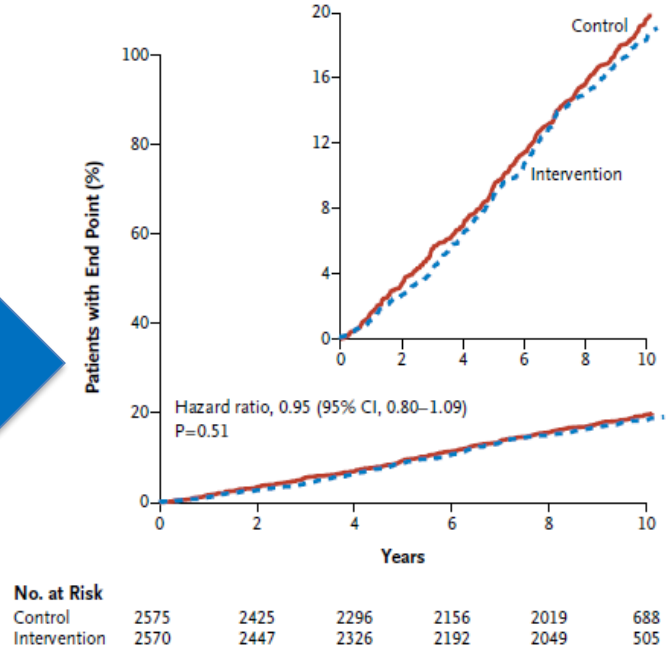
Bis August 2023 gab es keinen Beleg, dass durch Gewichtsverlust bei Menschen mit Adipositas kardiovaskuläre Endpukte positiv beeinflusst werden können…

LOOK AHEAD:

Kein Effekt auf kardiovaskulären Schutz



7% Gewicht ↓



Look Ahead: N Engl J Med 2013; 369:145-154 (n=5.145)

LOOK AHEAD: Best responders hatten CV-Nutzen

Post-hoc Analyse der **Look AHEAD** Studie

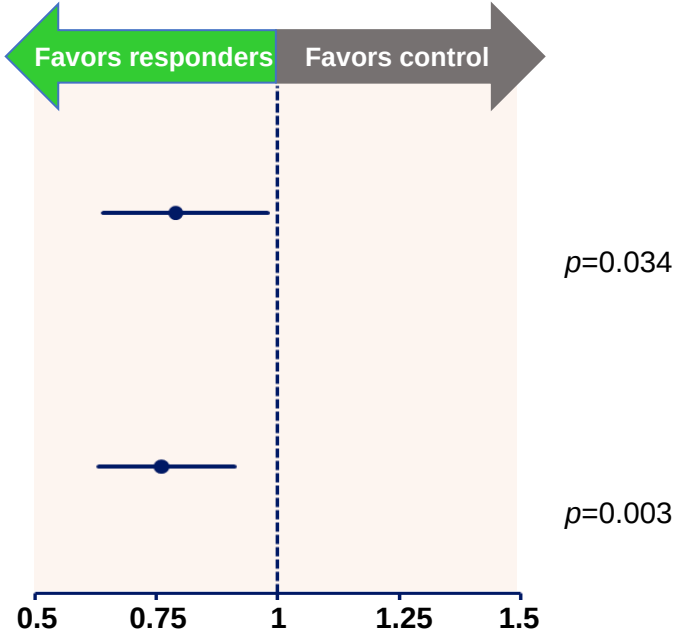
Responder: > 10% Gewichtsverlust im ersten Jahr der Studie

Primärer Endpunkt – 21% besser

CV death, non-fatal acute MI, non-fatal stroke, or admission to hospital for angina

Sekundärer Endpunkt – 24% besser

As above plus CABG, carotid endartectomy, PCI, hospitalisation for CHF, peripheral vascular disease, or total mortality

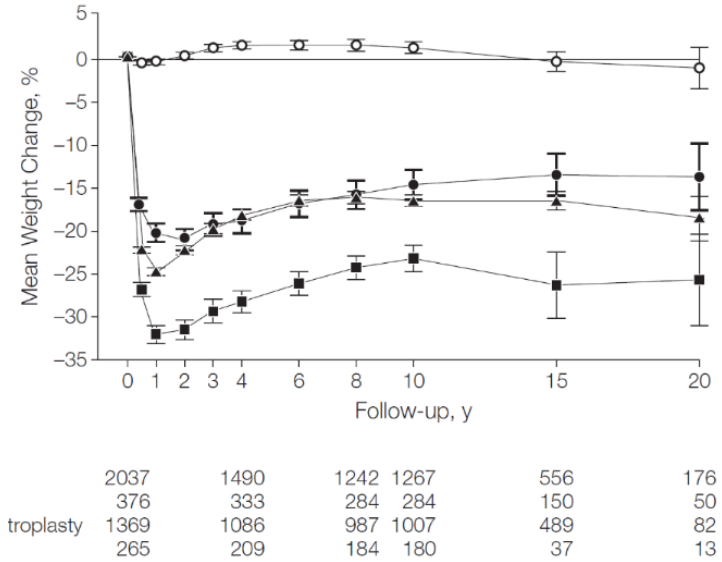


CABG, coronary artery bypass grafting; CHF, congestive heart failure; CV, cardiovascular; MI, myocardial infarction; PCI, percutaneous coronary intervention
N=4406 participants with T2D to an intensive lifestyle intervention

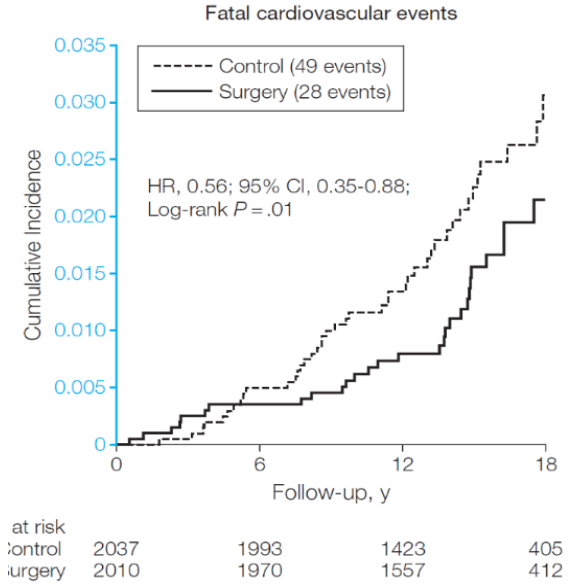
Look AHEAD Research Group. *Lancet Diabetes Endocrinol*. 2016;4:913–921.

Gewichtsverlust nach bariatrischer OP reduziert kardiovaskuläre Ereignisse

...aber bisher keine prospektive Studie



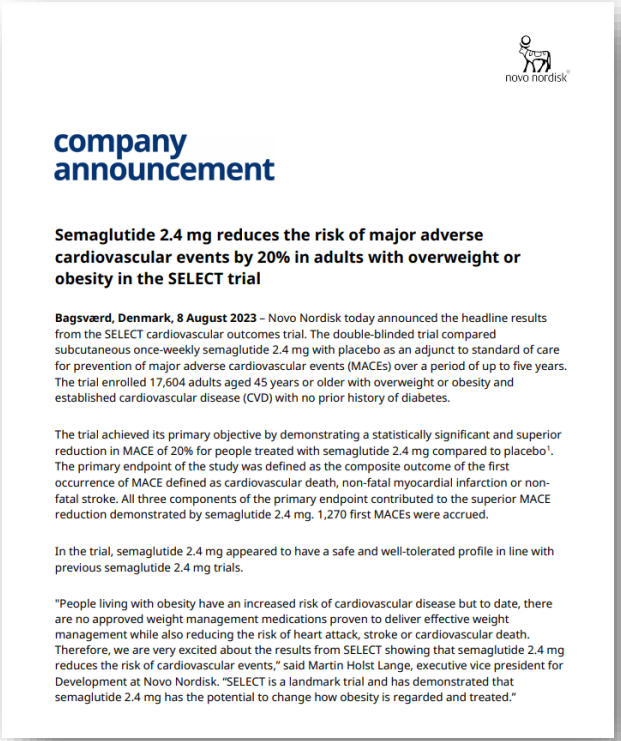
~20% Gewicht ↓



SOS Studie: Sjöström et al., JAMA. 2012;307: 56-65 (n=4.047)

SELECT Topline Ergebnisse

Semaglutid bei Patienten mít Adipositas



novo nordisk

company announcement

Semaglutide 2.4 mg reduces the risk of major adverse cardiovascular events by 20% in adults with overweight or obesity in the SELECT trial

Bagsværd, Denmark, 8 August 2023 – Novo Nordisk today announced the headline results from the SELECT cardiovascular outcomes trial. The double-blinded trial compared subcutaneous once-weekly semaglutide 2.4 mg with placebo as an adjunct to standard of care for prevention of major adverse cardiovascular events (MACEs) over a period of up to five years. The trial enrolled 17,604 adults aged 45 years or older with overweight or obesity and established cardiovascular disease (CVD) with no prior history of diabetes.

The trial achieved its primary objective by demonstrating a statistically significant and superior reduction in MACE of 20% for people treated with semaglutide 2.4 mg compared to placebo[1]. The primary endpoint of the study was defined as the composite outcome of the first occurrence of MACE defined as cardiovascular death, non-fatal myocardial infarction or non-fatal stroke. All three components of the primary endpoint contributed to the superior MACE reduction demonstrated by semaglutide 2.4 mg. 1,270 first MACEs were accrued.

In the trial, semaglutide 2.4 mg appeared to have a safe and well-tolerated profile in line with previous semaglutide 2.4 mg trials.

"People living with obesity have an increased risk of cardiovascular disease but to date, there are no approved weight management medications proven to deliver effective weight management while also reducing the risk of heart attack, stroke or cardiovascular death. Therefore, we are very excited about the results from SELECT showing that semaglutide 2.4 mg reduces the risk of cardiovascular events," said Martin Holst Lange, executive vice president for Development at Novo Nordisk. "SELECT is a landmark trial and has demonstrated that semaglutide 2.4 mg has the potential to change how obesity is regarded and treated."

20% Reduktion bei MACE

August 8, 2023

Was sind für Sie die größten Herausforderungen in der Adipositastherapie?

Herausforderungen der Adipositastherapie

Verhaltensprävention versagt häufig

Verhältnisprävention scheint nicht gewollt

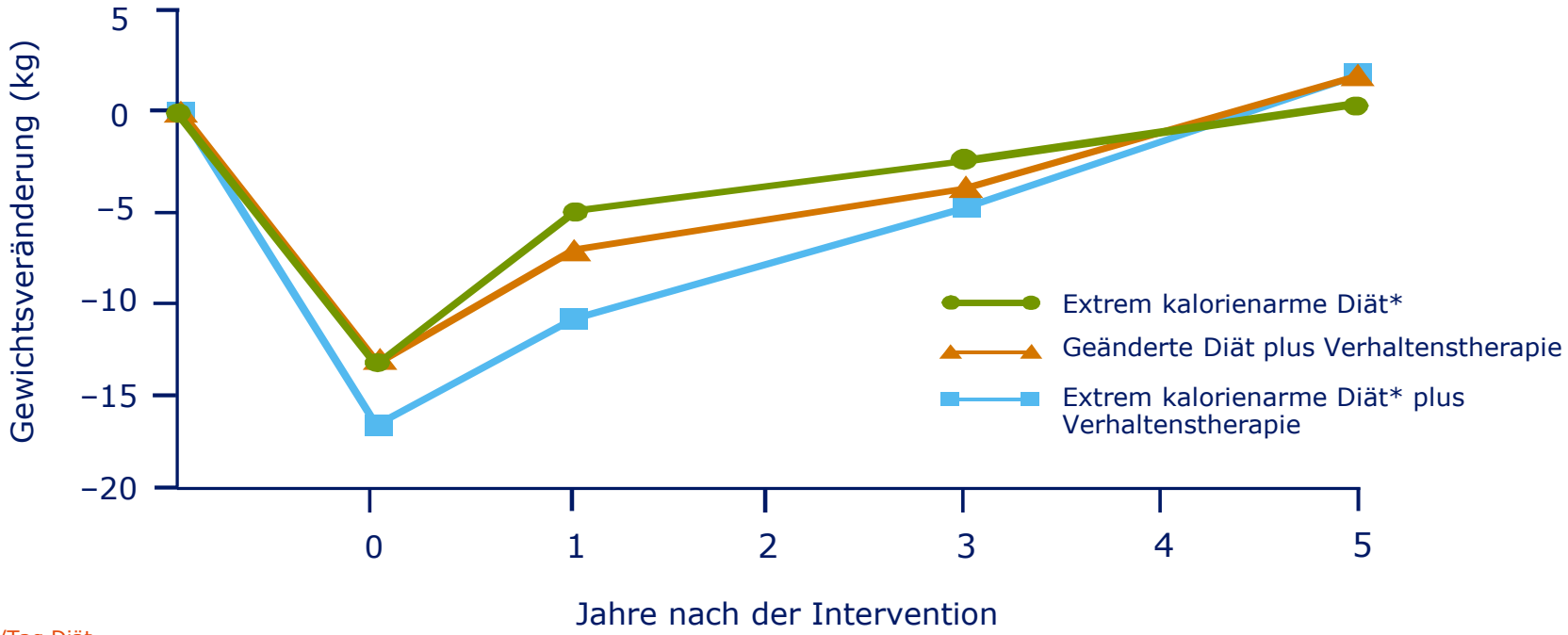
Chirurgische Therapie ist zwar sehr effektiv, aber „riskant“

Adipositas ist nicht heilbar – aber behandelbar

Herausforderung

Warum funktioniert das Konzept „Weniger Essen und mehr Bewegen“ so schlecht?

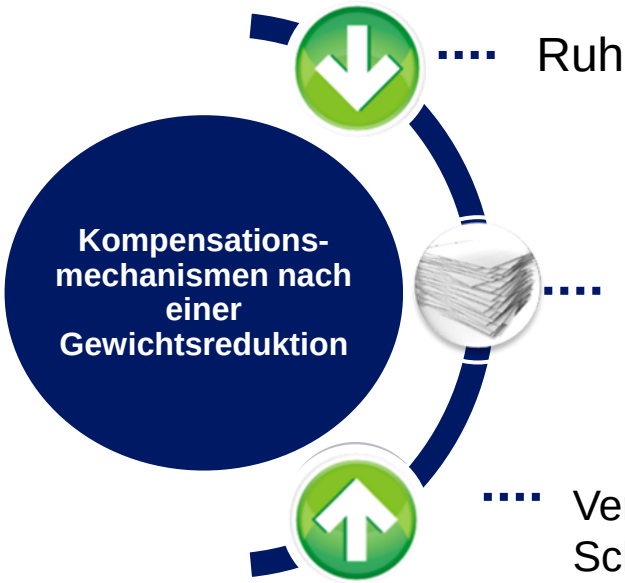
Unser Körper „verteidigt“ sehr effektiv das Gewicht



*1200 Kcal/Tag Diät

Wadden TA et al. *Ann Intern Med* 1993; 119:688–93.

Unser Körper „verteidigt“ sehr effektiv das Gewicht



Ruheumsatz sinkt nach Gewichtsabnahme[1]

Kompensationsmechanismen:

- Verringerung des täglichen Ruheumsatzes: 15,4 ± 8,7 kcal/kg* Körpergewichtsreduktion[2]
- zunehmendes Verlangen nach Essen, Hunger, ständiges Denken an Essen[3]

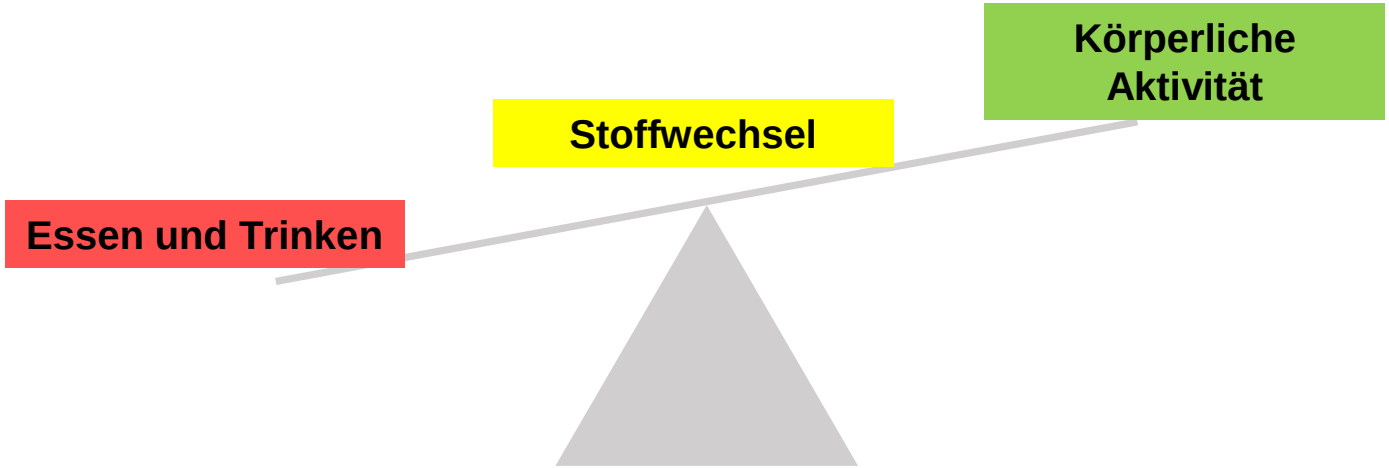
Veränderungen der Verdauungshormone, Unterdrückung der Schilddrüsen-Achse und Erhöhung der Cortisolkonzentrationen[4]

1. Pasman WJ et al. *Obes Res* 1999; 7:43–50. 2. Schwartz A, Doucet E. *Obes Rev* 2010; 11:531–47.
3. Doucet E et al. *Int J Obes Relat Metab Disord* 2000; 24:906–14. 4. Blomain ES et al. *ISRN Obes* 2013; 2013:210524.

Diese Mechanismen müssen

„überlistet“ werden

Wo setzen Pharmakotherapien an?



Früher: Appetitzügler

Modern: GLP-1RA

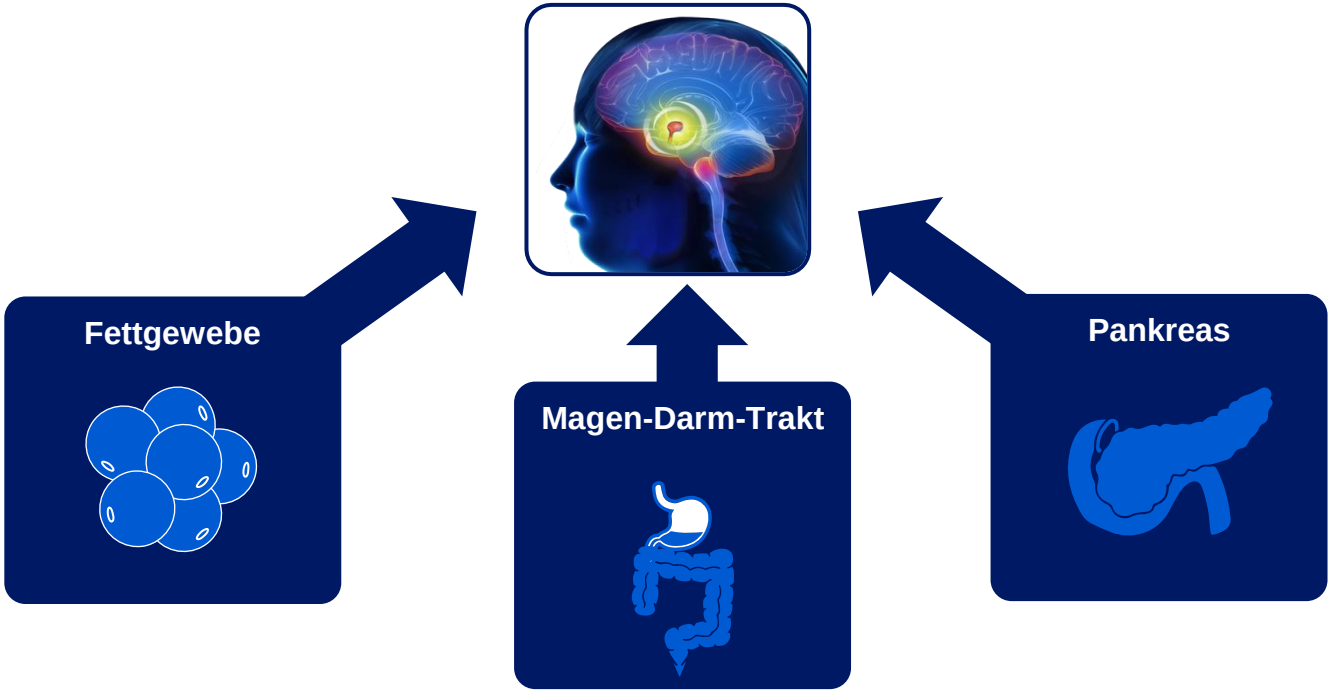
Früher: Schilddrüsenhormone

Modern: GLP-1RA

Früher: Amfetamine

„Exercise mimetics“?

Regulation des Energiestoffwechsels



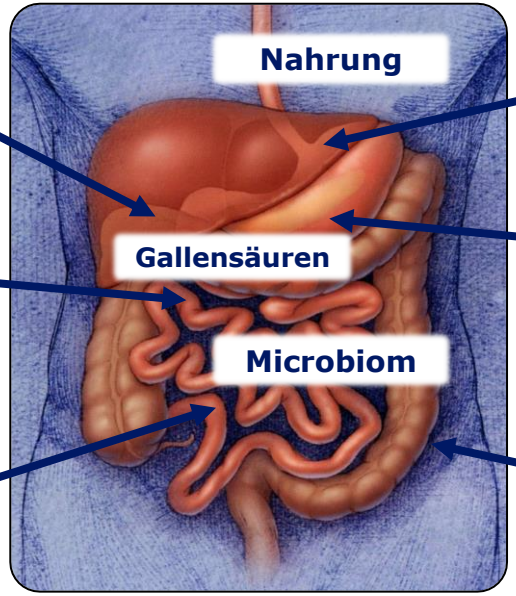
Woods et al. Int J Obes Relat Metab Disord 2002;26:S8–S10; Badman, Flier. Science 2005;307:1909–14

Signale aus Magen und Darm modulieren die zentrale Regulation des Energiestoffwechsels

DUODENUM
- Cholecystokinin
- Gastric inhibitory peptide (GIP)
- Ghrelin

JEJUNUM
- Glucagon-like peptide-1
- Peptide YY
- Gastric inhibitory peptide

ILEUM
- Glucagon-like peptide-1
- Oxyntomodulin
- Peptide YY
- Fibroblast growth factor-19



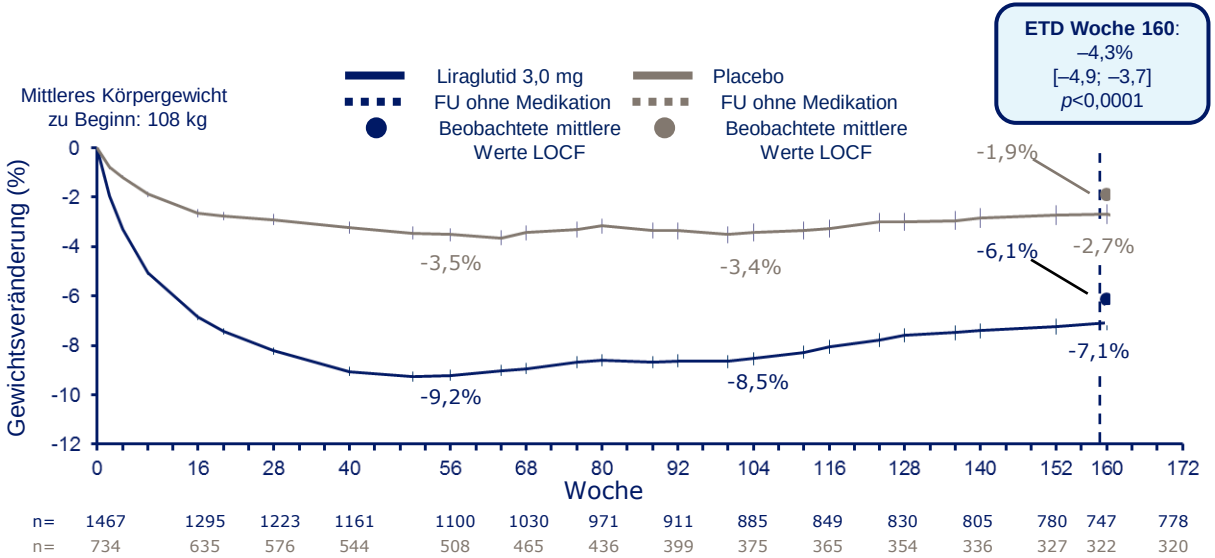
MAGEN
- Ghrelin

PANCREAS
- Insulin
- Glucagon
- Amylin
- Pancreatic polypeptide

COLON
- Glucagon-like peptide-1
- Oxyntomodulin
- Peptide YY

Cote *et al. J Biol Chem*. 2014;25:11642–11649; Stanley *et al. Am J Physiol Gastrointest Liver Physiol.* 2004;286:G693–G697

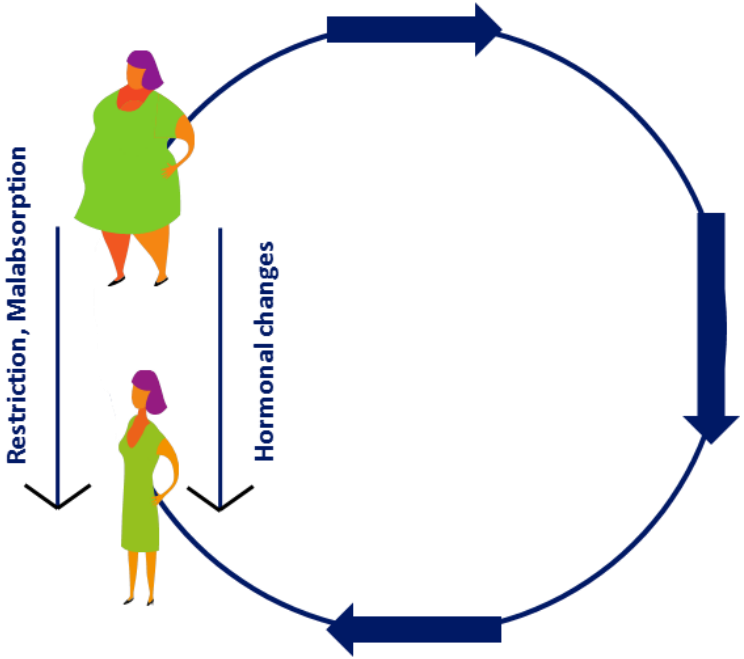
Liraglutid 3mg: Plateaueffekt nach Gewichtsverlust



Full analysis set (Gesamtpopulation). Nur Daten aus der Nüchtern-Visite. Die Linien zeigen beobachtete Mittelwerte (± Standardfehler). ETD, estimated treatment difference, geschätzter Therapieunterschied; FU, Follow-up, Nachbeobachtung; LOCF, last observation carried forward.

le Roux CW et al. Lancet 2017;389:1399-1409.

Zukunft der Pharmakotherapie



- **Stärker wirksame GLP-1RA**

z.B. Semaglutid

- Nicht-Peptid GLP-1RA

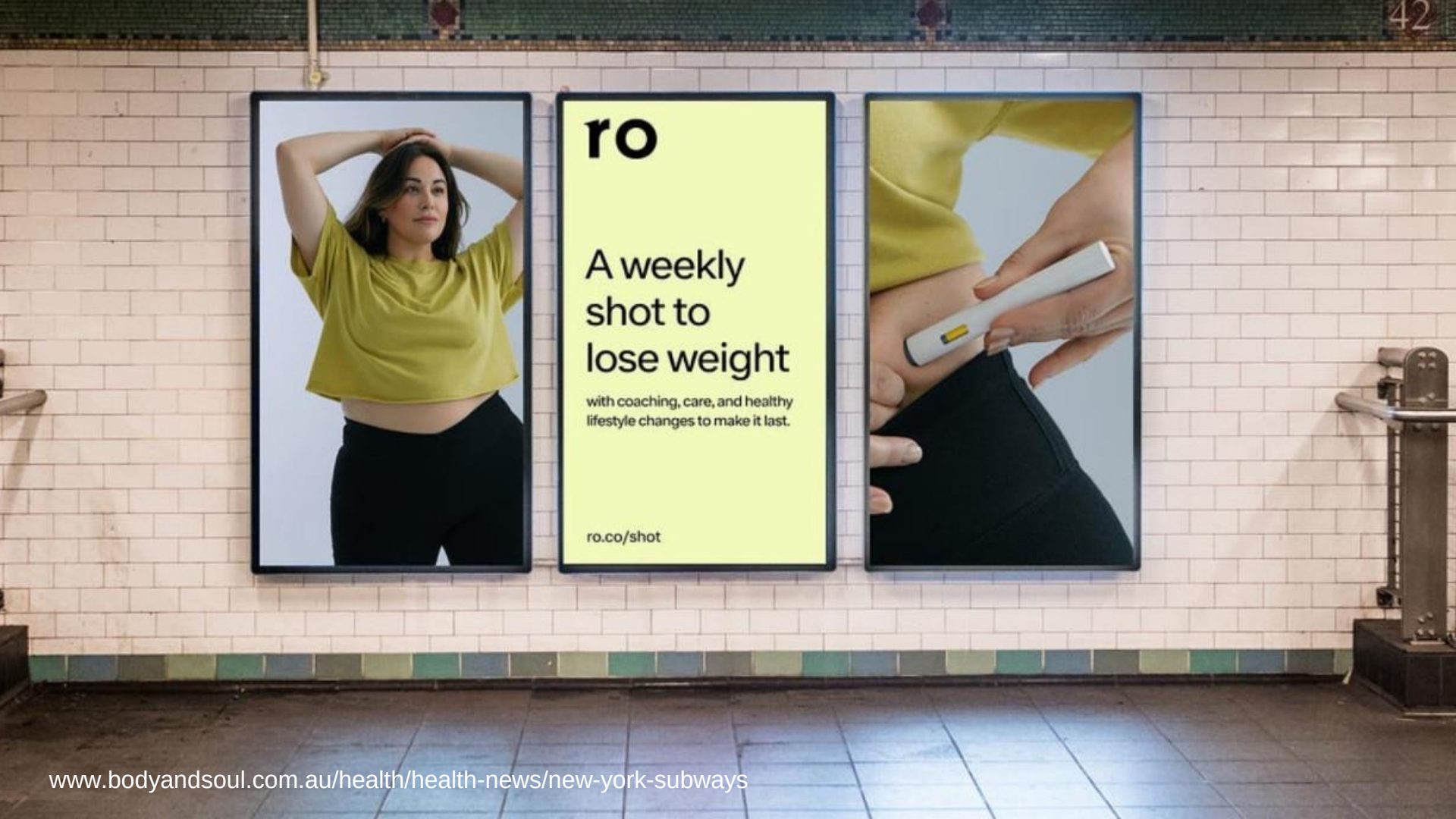
z.B. Orforglipron

- Duale Inkretinagonisten

z. B. Tirzepatid; Finan et al., Sci Transl Med. 2013

- Triagonisten

z. B. Rattrutid; Finan et al., Nat Med. 2015; 21



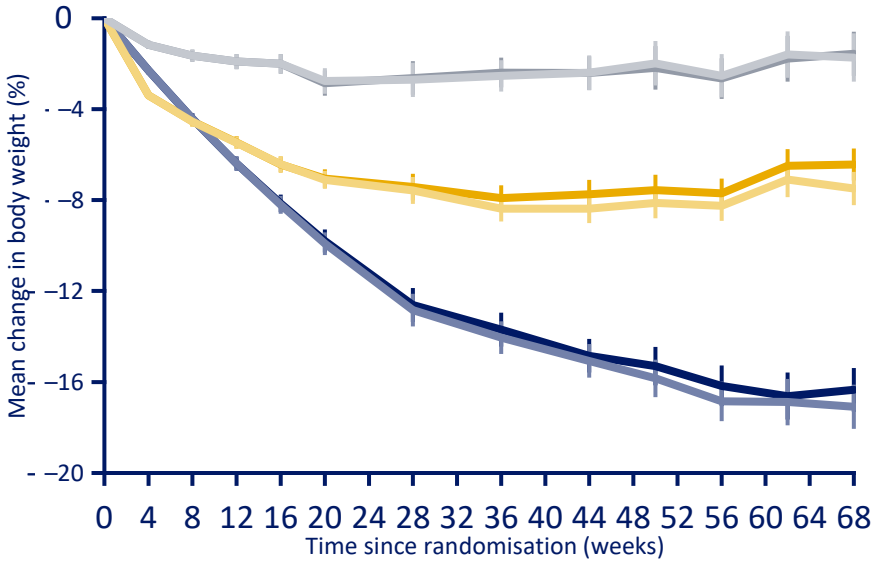
www.bodyandsoul.com.au/health/health-news/new-york-subways

Vergleich Liraglutid - Semaglutid

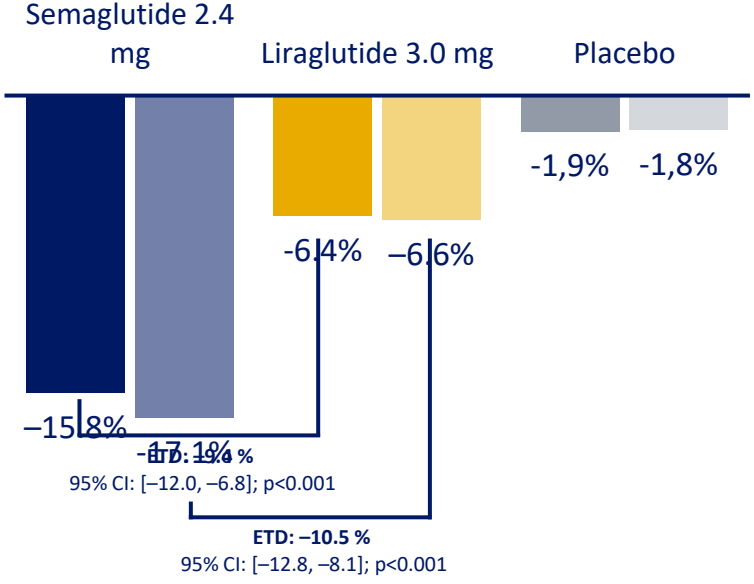
STEP 8

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

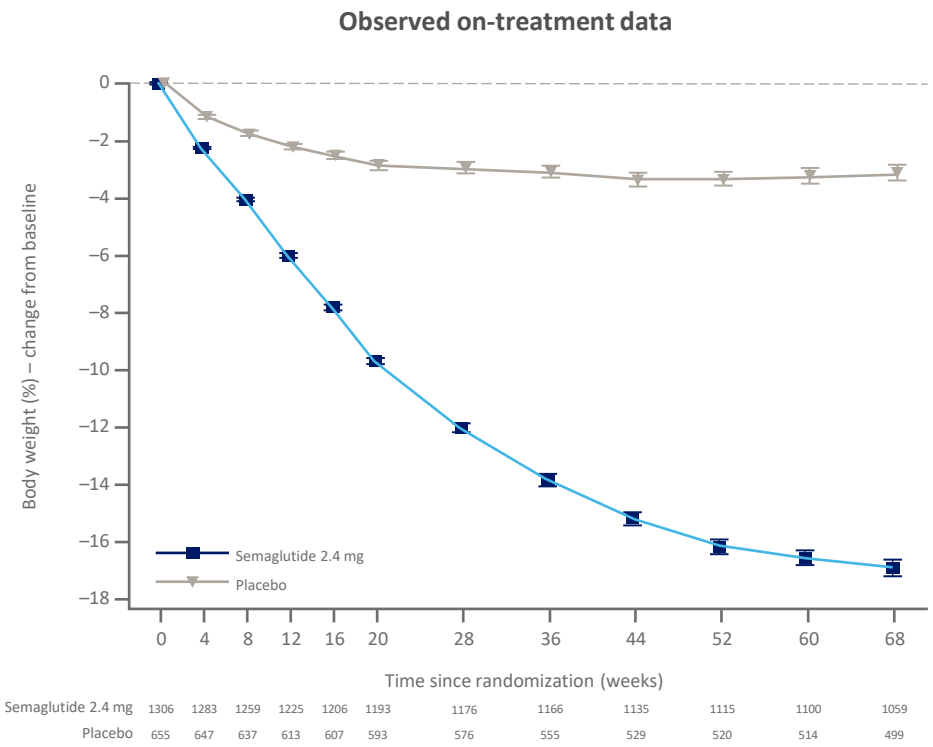
In-trial period/treatment policy estimand:

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.

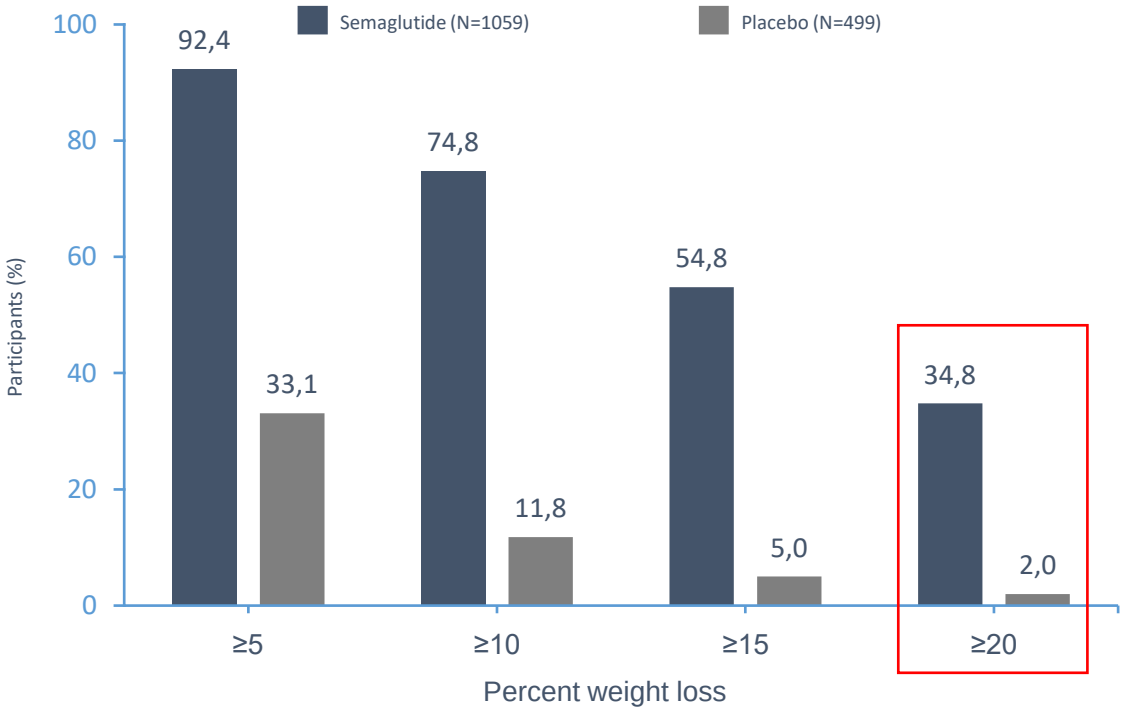
Rubino et al. Presented at the 39th Annual Meeting of The Obesity Society (TOS) held at ObesityWeek®, virtual meeting, November 1–5, 2021.

Semaglutid in der Adipositastherapie (STEP-1)



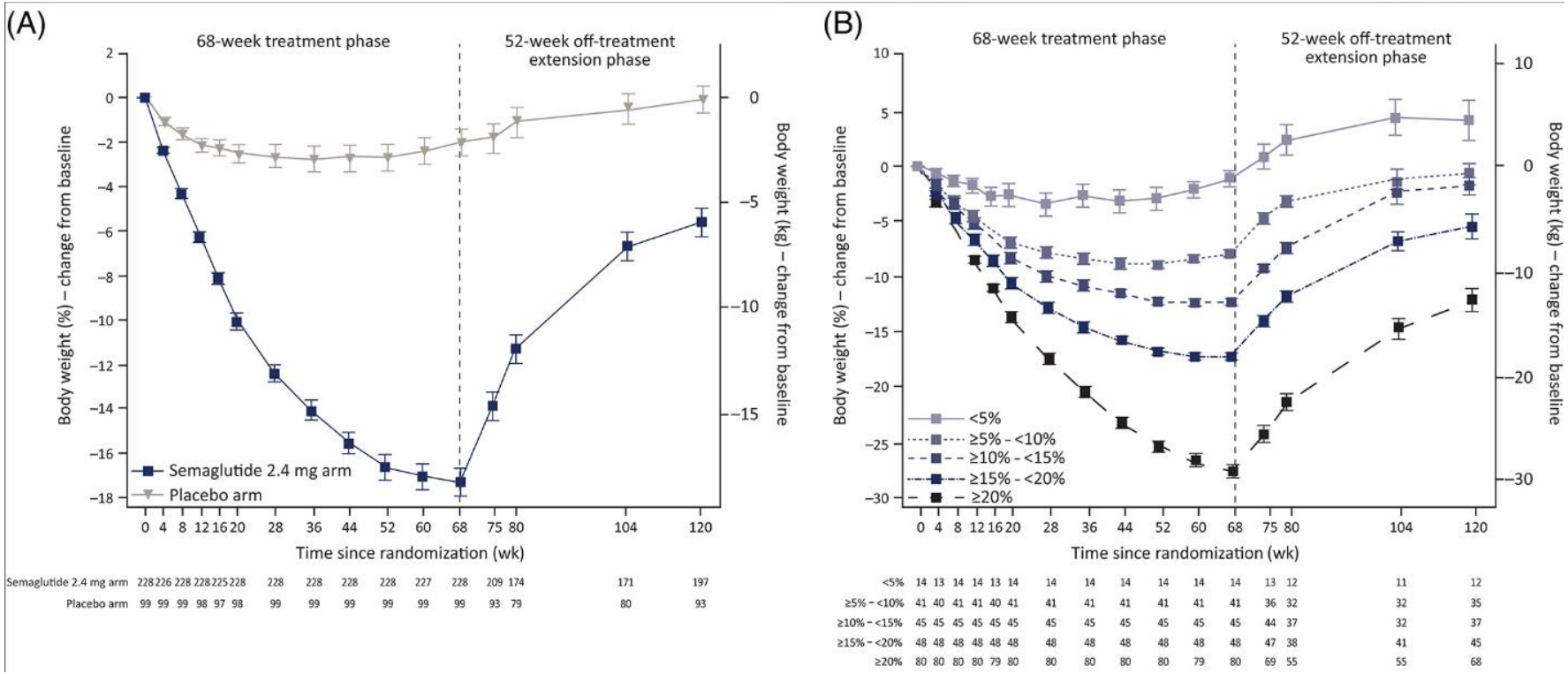
Wilding et al., N Engl J Med. 2021;384: 989.

Semaglutid in der Adipositastherapie (STEP-1)



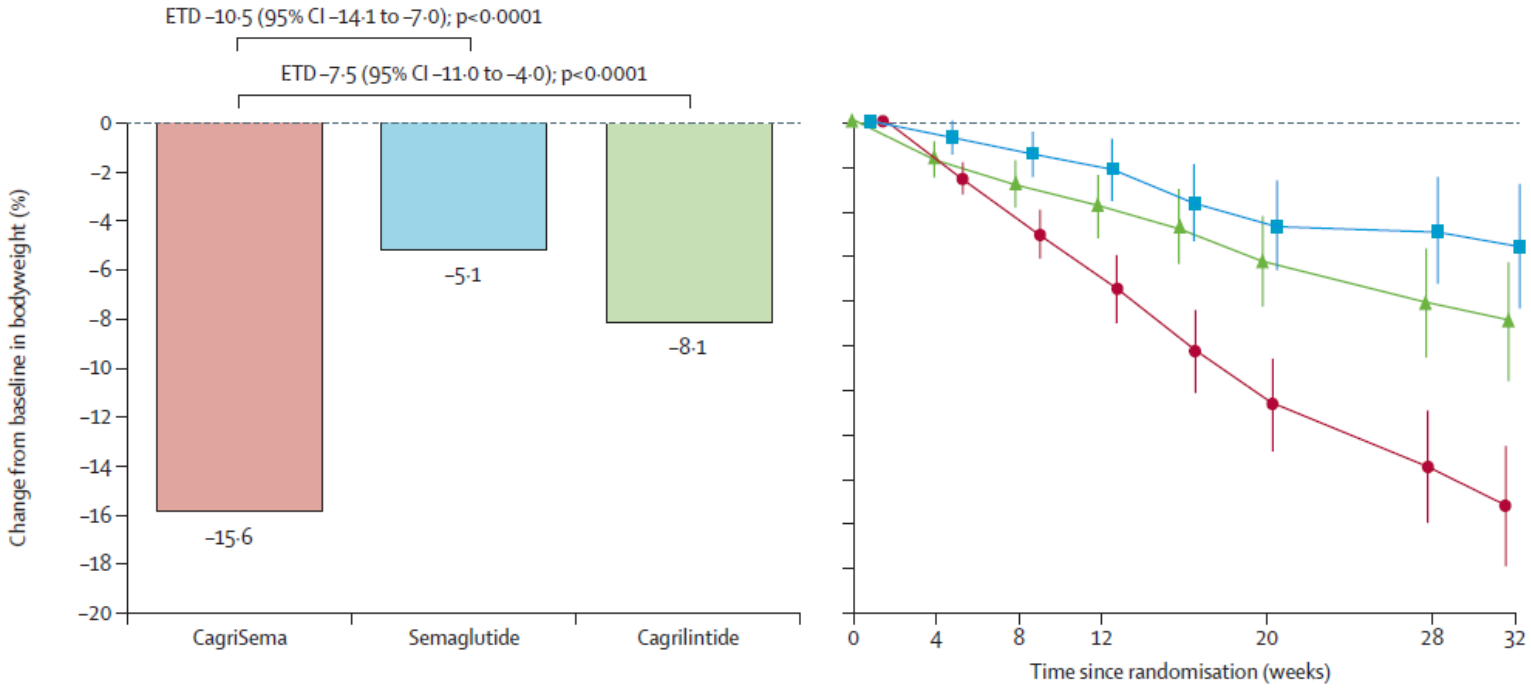
Wilding et al., N Engl J Med. 2021;384: 989.

STEP 1- Extension:
Medikamente wirken, so lange sie eingenommen werden…



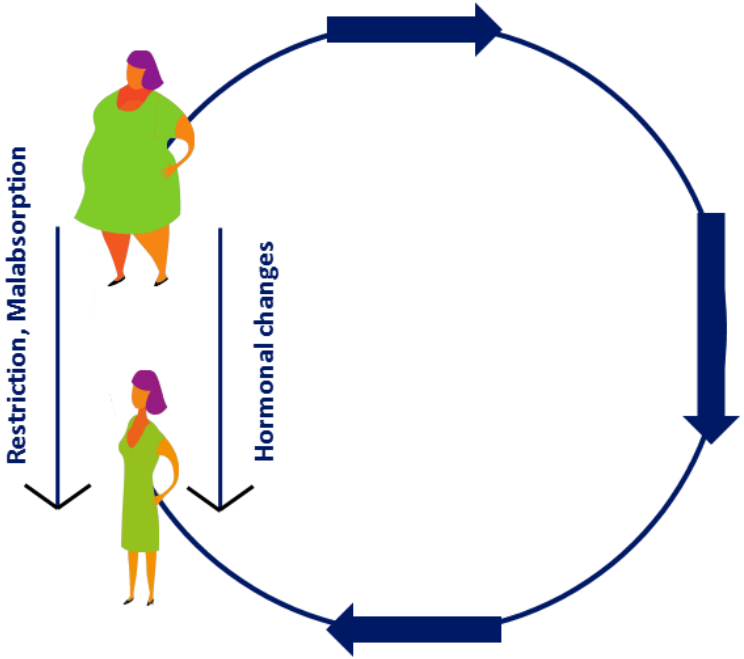
Wilding et al., DOM, 2022

CagriSema: Cagrilintid + Semaglutid



Frias et al., Lancet 2023, published online, June 2023

Zukunft der Pharmakotherapie



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The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Daily Oral GLP-1 Receptor Agonist Orforglipron for Adults with Obesity

Sean Wharton, M.D., Thomas Blevins, M.D., Lisa Connery, M.D., Julio Rosenstock, M.D., Sohini Raha, Ph.D., Rong Liu, Ph.D., Xiaosu Ma, Ph.D., Kieren J. Mather, M.D., Axel Haupt, M.D., Deborah Robins, M.S., Edward Pratt, M.D., Christof Kazda, M.D., and Manige Konig, M.D., Ph.D., for the GZGI Investigators*

ABSTRACT

BACKGROUND

Obesity is a major risk factor for many leading causes of illness and death worldwide. Data are needed regarding the efficacy and safety of the nonpeptide glucagon-like peptide-1 (GLP-1) receptor agonist orforglipron as a once-daily oral therapy for weight reduction in adults with obesity.

METHODS

In this phase 2, randomized, double-blind trial, we enrolled adults with obesity, or with overweight plus at least one weight-related coexisting condition, and without diabetes. Participants were randomly assigned to receive orforglipron at one of four doses (12, 24, 36, or 45 mg) or placebo once daily for 36 weeks. The percentage change from baseline in body weight was assessed at week 26 (primary end point) and at week 36 (secondary end point).

RESULTS

A total of 272 participants underwent randomization. At baseline, the mean body weight was 108.7 kg, and the mean body-mass index (the weight in kilograms divided by the square of the height in meters) was 37.9. At week 26, the mean change from baseline in body weight ranged from −8.6% to −12.6% across the orforglipron dose cohorts and was −2.0% in the placebo group. At week 36, the mean change ranged from −9.4% to −14.7% with orforglipron and was −2.3% with placebo. A weight reduction of at least 10% by week 36 occurred in 46 to 75% of the participants who received orforglipron, as compared with 9% who received placebo. The use of orforglipron led to improvement in all prespecified weight-related and cardiometabolic measures. The most common adverse events reported with orforglipron were gastrointestinal events, which were mild to moderate, occurred primarily during dose escalation, and led to discontinuation of orforglipron in 10 to 17% of participants across dose cohorts. The safety profile of orforglipron was consistent with that of the GLP-1 receptor agonist class.

CONCLUSIONS

Daily oral orforglipron, a nonpeptide GLP-1 receptor agonist, was associated with weight reduction. Adverse events reported with orforglipron were similar to those with injectable GLP-1 receptor agonists. (Funded by Eli Lilly; GZGI ClinicalTrials.gov number, NCT05051579.)

From McMaster University, York University, and Wharton Weight Management Clinic — all in Toronto (S.W.); Texas Diabetes and Endocrinology, Austin (T.B.), and Velocity Clinical Research at Medical City, Dallas (J.R.) — both in Texas; Alliance for Multispecialty Research, Norman, OK (L.C.); and Eli Lilly, Indianapolis (S.R., R.L., X.M., K.J.M., A.H., D.R., E.P., C.K., M.K.). Dr. Konig can be contacted at konig_manige@lilly.com or at Eli Lilly, 893 Delaware St., Indianapolis, IN 46225.

*A complete list of GZGI Investigators is provided in the Supplementary Appendix, available at NEJM.org.

This article was published on June 23, 2023, at NEJM.org.

DOI: 10.1056/NEJMoa2302392

Orforglipron Oraler GLP-1-Rezeptoragonist

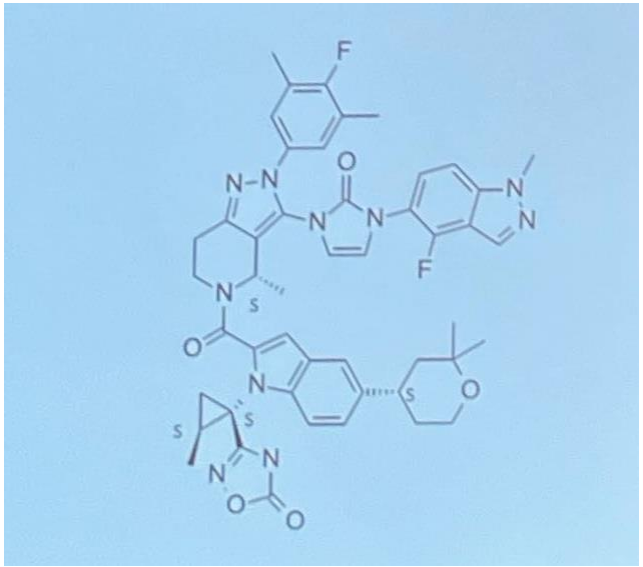
Phase 2 Studien bei Adipositas

Wharton S. Diabetes 2023;72(Suppl.1):52-OR- Oral presentation at the American Diabetes Association 83rd Scientific Sessions, June 23-26 2023, San Diego, USA.

Wirkung des oralen Nicht-Peptid-GLP-1-Rezeptor-Agonisten Orforglipron (LY3502970) bei Teilnehmern mit Adipositas oder Übergewicht - eine Phase-2-Studie

- In der Entwicklung zur oralen Applikation in der Behandlung von Adipositas und T2D bei Erwachsenen.
- Halbwertszeit von 29-49 Stunden ermöglicht einmal tägliche Einnahme.
- orale Bioverfügbarkeit ca. 30-40 %
- Kann ohne Einschränkung von Nahrung, Wasser oder anderen Medikamenten eingenommen werden.

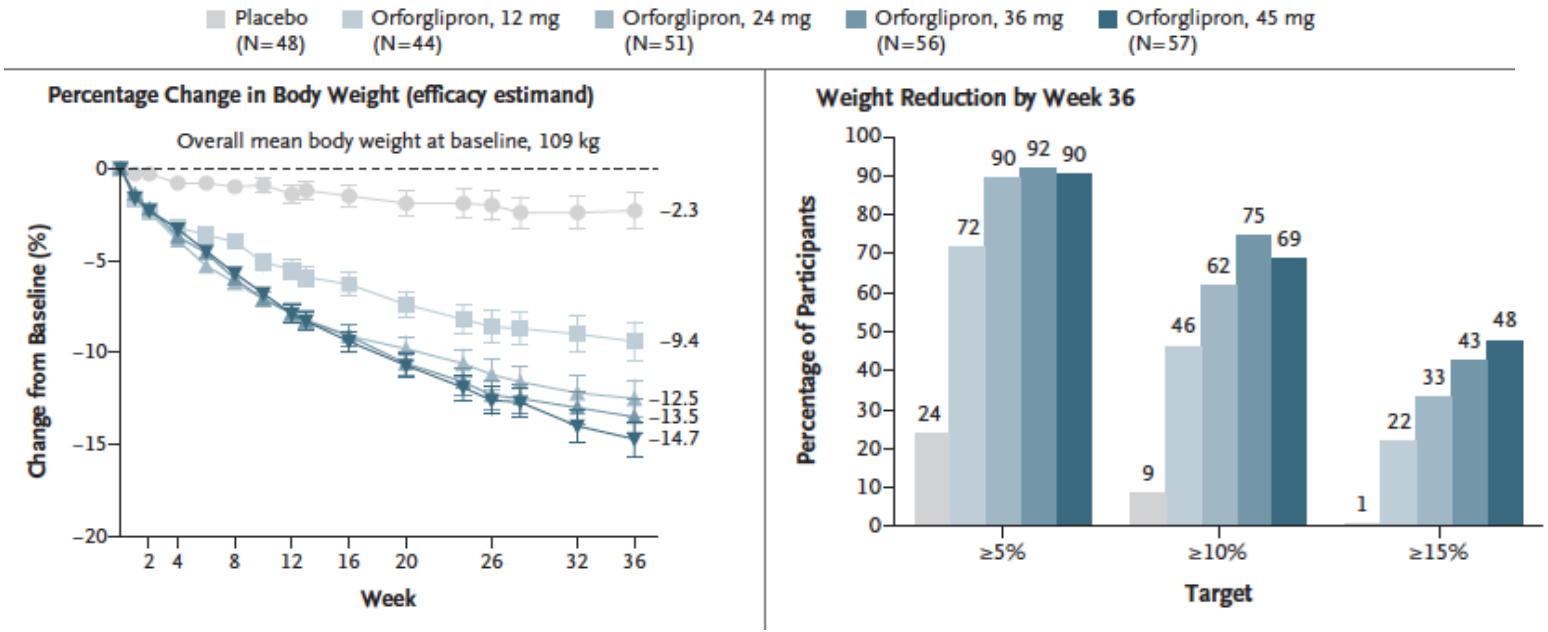
- ***Studienziel:***
  - Bewertung der Wirksamkeit und Sicherheit von Orforglipron vs. Placebo bzgl. Gewichtskontrolle



Orforglipron ist nicht zugelassen

Wharton S, N Engl J Med . 2023 Jun 23. doi: 10.1056/NEJMoa2302392. Online ahead of print.
Wharton S. Diabetes 2023;72(Suppl.1):52-OR- Oral presentation at the American Diabetes Association 83rd Scientific Sessions, June 23-26 2023, San Diego, USA.

Orforglipron (LY3502970) bei Übergewicht/Adipositas
Endpunkte zur Gewichtsreduktion nach 36 Wochen



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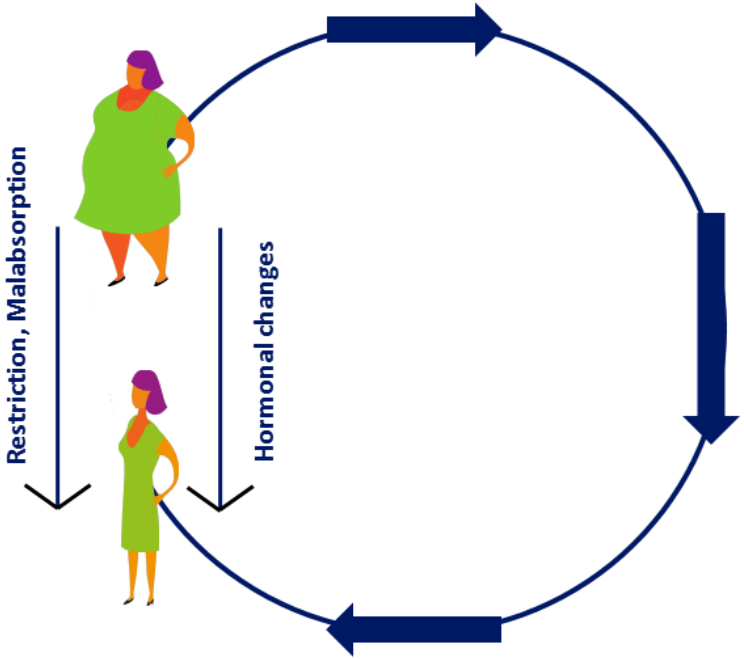
Orforglipron (LY3502970) bei Übergewicht/Adipositas
Sicherheitsprofil

Event	Orforglipron								Placebo (N=50)
	12 mg (N=50)	24 mg (N=53)	36 mg, Subcohort 1 (N=29)	36 mg, Subcohort 2 (N=29)	36 mg, Pooled (N=58)	45 mg, Subcohort 1 (N=31)	45 mg, Subcohort 2 (N=30)	45 mg, Pooled (N=61)	
	number of participants (percent)								
Any adverse event	43 (86)	46 (87)	24 (83)	28 (97)	—	28 (90)	27 (90)	—	38 (76)
Any serious adverse event	0	2 (4)	0	3 (10)	—	2 (6)	0	—	0
Adverse event that led to discontinuation of orforglipron or placebo	7 (14)	10 (19)	3 (10)	6 (21)	—	5 (16)	4 (13)	—	1 (2)
Adverse event that occurred in ≥5% of participants in any trial group									
Nausea	25 (50)	31 (58)	12 (41)	14 (48)	—	13 (42)	11 (37)	—	5 (10)
Vomiting	13 (26)	17 (32)	8 (28)	4 (14)	—	9 (29)	8 (27)	—	3 (6)
Constipation	12 (24)	17 (32)	8 (28)	7 (24)	—	6 (19)	4 (13)	—	3 (6)
Diarrhea	12 (24)	19 (36)	1 (3)	4 (14)	—	5 (16)	10 (33)	—	5 (10)
Coronavirus disease 2019	9 (18)	9 (17)	4 (14)	7 (24)	—	5 (16)	5 (17)	—	9 (18)
Eructation	9 (18)	11 (21)	5 (17)	2 (7)	—	2 (6)	6 (20)	—	0
Headache	4 (8)	8 (15)	3 (10)	2 (7)	—	4 (13)	2 (7)	—	5 (10)
Fatigue	2 (4)	7 (13)	4 (14)	2 (7)	—	4 (13)	4 (13)	—	1 (2)
Gastroesophageal reflux disease	4 (8)	5 (9)	3 (10)	4 (14)	—	4 (13)	2 (7)	—	1 (2)
Dyspepsia	8 (16)	4 (8)	1 (3)	1 (3)	—	3 (10)	2 (7)	—	3 (6)
Dizziness	5 (10)	2 (4)	1 (3)	1 (3)	—	2 (6)	4 (13)	—	1 (2)
Abdominal pain	4 (8)	4 (8)	0	2 (7)	—	2 (6)	1 (3)	—	2 (4)
Decreased appetite	4 (8)	4 (8)	0	1 (3)	—	3 (10)	2 (7)	—	1 (2)
Urinary tract infection	2 (4)	3 (6)	0	3 (10)	—	1 (3)	2 (7)	—	3 (6)

Wharton S, N Engl J Med . 2023 Jun 23. doi: 10.1056/NEJMoa2302392. Online ahead of print.
Wharton S. Diabetes 2023;72(Suppl.1):52-OR- Oral presentation at the American Diabetes Association 83rd Scientific Sessions, June 23-26 2023, San Diego, USA.

Zukunft der Pharmakotherapie



- Stärker wirksame GLP-1RA

z.B. Semaglutid

- Nicht-Peptid GLP-1RA

z.B. Orforglipron

- **Duale Inkretinagonisten**

z. B. Tirzepatid; Finan et al., Sci Transl Med. 2013

- Triagonisten

z. B. Rattrutid; Finan et al., Nat Med. 2015; 21

ADA 2023 Banting Lecture adressierte alle relevanten Entwicklungen zur Therapie des T2D und Adipositas von 1994 - 2030

Entdeckung des ersten unimolekularen dualen GLP-1/GIP Ko-Agonisten

RESEARCH ARTICLE

OBESITY

Unimolecular Dual Incretins Maximize Metabolic Benefits in Rodents, Monkeys, and Humans

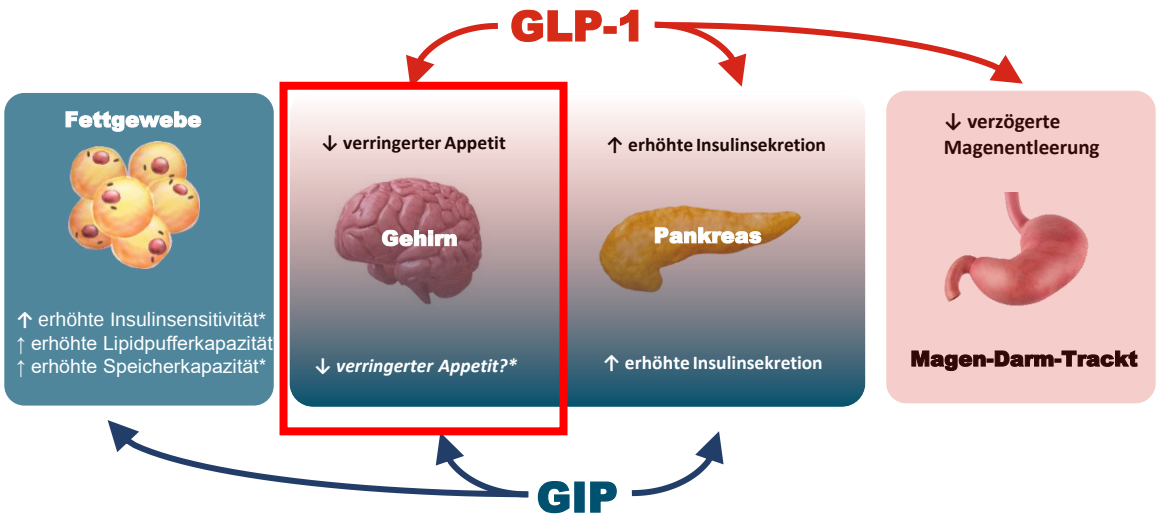
Brian Finan,[1,2,3*] Tao Ma,[3,4*] Nickki Ottaway,[5] Timo D. Müller,[1,2] Kirk M. Habegger,[5] Kristy M. Heppner,[5] Henriette Kirchner,[6] Jenna Holland,[5] Jazzminn Hembree,[5] Christine Raver,[5] Sarah H. Lockie,[7] David L. Smiley,[3] Vasily Gelfanov,[3] Bin Yang,[3,8] Susanna Hofmann,[2] Dennis Bruemmer,[9] Daniel J. Drucker,[10] Paul T. Pfluger,[1,2,5] Diego Perez-Tilve,[5] Jaswant Gidda,[8] Louis Vignati,[8] Lianshan Zhang,[8] Jonathan B. Hauptman,[11] Emmanuelle Lainaut,[11] Michele Lau,[11] Elena Sebokova,[11] Sabine Uhles,[11] William Riboulet,[11] Mathieu Brecheisen,[11] Karin Conde-Knape,[11] Anish Konkar,[11] Richard D. DiMarchi,[3†] Matthias H. Tschöp[1,2,5†]

We report the discovery and translational therapeutic efficacy of a peptide with potent, balanced co-agonism at both of the receptors for the incretin hormones glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). This unimolecular dual incretin is derived from an intermixed sequence of GLP-1 and GIP, and demonstrated enhanced antihyperglycemic and insulinotropic efficacy relative to selective GLP-1 agonists. Notably, this superior efficacy translated across rodent models of obesity and diabetes, including *db/db* mice and ZDF rats, to primates (cynomolgus monkeys and humans). Furthermore, this co-agonist demonstrated negligible weight-lowering efficacy. The fat mass in obese rodents, whereas a selective GIP agonist exhibited synergism in reducing adiposity-induced insulin resistance and unimolecular dual incretins corrected two causal mechanisms of diabetes, including the duration of action of the unimolecular dual incretins was refined through site-specific lipidation or PEGylation to support less frequent administration. These peptides provide comparable pharmacology to the native peptides and enhanced efficacy relative to similarly modified selective GLP-1 agonists. The pharmacokinetic enhancement lessened peak drug exposure and, in combination with less dependence on GLP-1–mediated pharmacology, avoided the adverse gastrointestinal effects that typify selective GLP-1–based agonists. This discovery and validation of a balanced and high-potency dual incretin agonist enables a more physiological approach to management of diseases associated with impaired glucose tolerance.

INTRODUCTION

Finan B, et al. Sci Transl Med. 2013; 5:209ra151. Forschungsarbeiten von 2005-2013

Kombinierte Wirkungen von GIP und GLP-1



GIP = Glukose-abhängiges insulinotropes Polypeptid; GLP-1 = Glukagon-ähnliches Peptid 1

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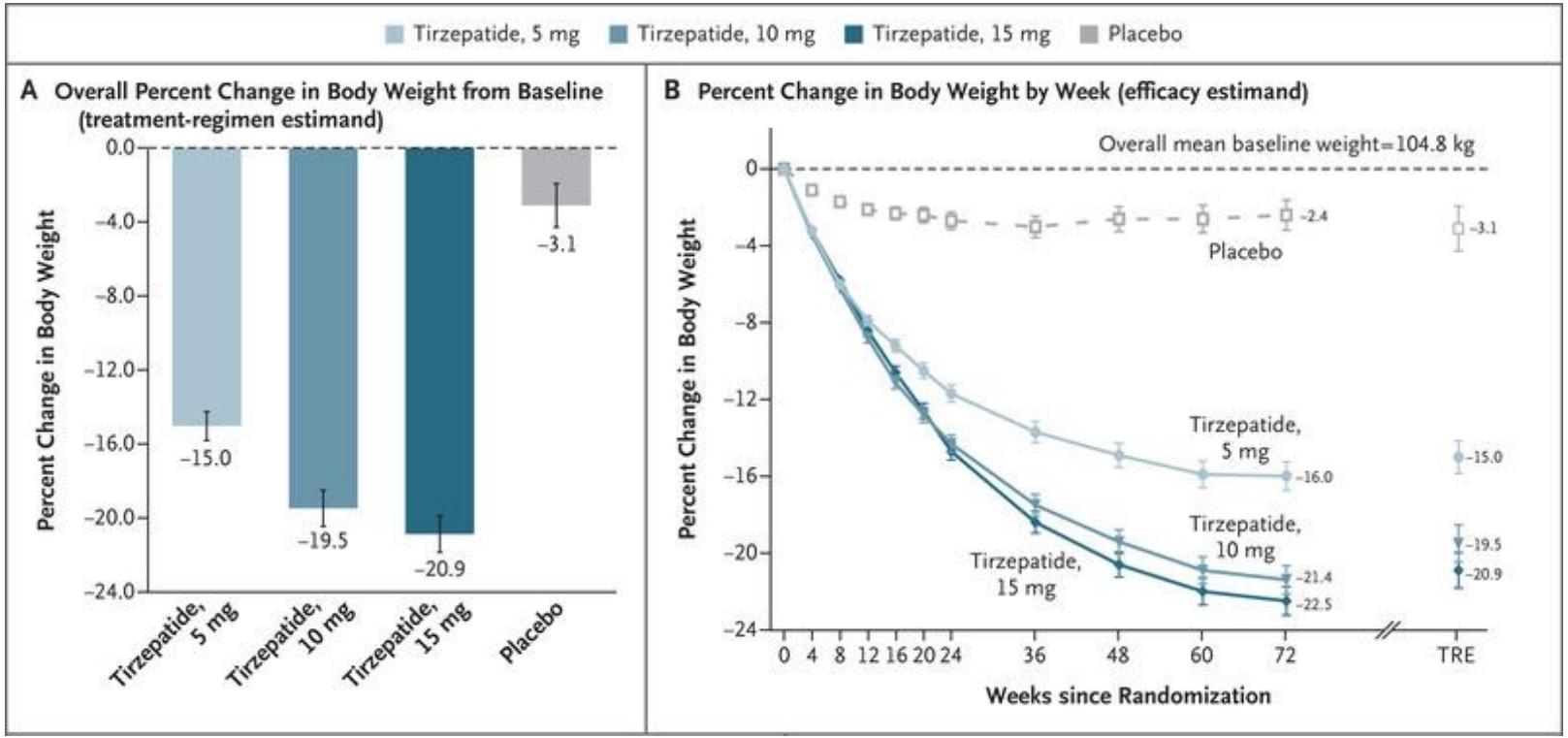
SURMOUNT-1

Tirzepatide Once Weekly for the Treatment of Obesity



Jastreboff et al., N Engl J Med 2022; doi: 10.1056/NEJMoa2206038

Tirzepatid ist nicht zur Behandlung der Adipositas zugelassen

SURMOUNT-2

Articles

Tirzepatide once weekly for the treatment of obesity in people with type 2 diabetes (SURMOUNT-2): a double-blind, randomised, multicentre, placebo-controlled, phase 3 trial

W Timothy Garvey, Juan P Frias, Ania M Jastreboff, Carel W le Roux, Naveed Sattar, Diego Aizenberg, Huzhang Mao, Shuyu Zhang, Nadia N Ahmad, Mathijs C Bunck, Irmare Rosenstock, Xiaolan M Zhang, for the SURMOUNT-2 investigators

Summary

Background Weight reduction is essential for improving health outcomes in people with obesity and type 2 diabetes. We assessed the efficacy and safety of tirzepatide, a glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1 receptor agonist, versus placebo, for weight management in people living with obesity and type 2 diabetes.

Methods This phase 3, double-blind, randomised, placebo-controlled trial was conducted in seven countries. Adults (aged ≥18 years) with a body-mass index (BMI) of 27 kg/m² or higher and glycated haemoglobin (HbA_{1c}) of 7–10% (53–86 mmol/mol) were randomly assigned (1:1:1), using a computer-generated random sequence via a validated interactive web-response system, to receive either once-weekly, subcutaneous tirzepatide (10 mg or 15 mg) or placebo for 72 weeks. All participants, investigators, and the sponsor were masked to treatment assignment. Coprimary endpoints were the percent change in bodyweight from baseline and bodyweight reduction of 5% or higher. The treatment-regimen estimand assessed effects regardless of treatment discontinuation or initiation of antihyperglycaemic rescue therapy. Efficacy and safety endpoints were analysed with data from all randomly assigned participants (intention-to-treat population). This trial is registered with ClinicalTrials.gov, NCT04657003.

Findings Between March 29, 2021, and April 10, 2023, of 1514 adults assessed for eligibility, 938 (mean age 54·2 years [SD 10·6], 476 [51%] were female, 730 [76%] were White, and 561 [60%] were Hispanic or Latino) were randomly assigned and received at least one dose of tirzepatide 10 mg (n=312), tirzepatide 15 mg (n=311), or placebo (n=315). Baseline mean bodyweight was 100·7 kg (SD 21·1), BMI 36·1 kg/m² (SD 6·6), and HbA_{1c} 8·02% (SD 0·89; 64·1 mmol/mol [SD 9·7]). Least-squares mean change in bodyweight at week 72 with tirzepatide 10 mg and 15 mg was −12·8% (SE 0·6) and −14·7% (0·5), respectively, and −3·2% (0·5) with placebo, resulting in estimated treatment differences versus placebo of −9·6% percentage points (95% CI −11·1 to −8·1) with tirzepatide 10 mg and −11·6% percentage points (−13·0 to −10·1) with tirzepatide 15 mg (all p<0·0001). More participants treated with tirzepatide versus placebo met bodyweight reduction thresholds of 5% or higher (79–83% vs 32%). The most frequent adverse events with tirzepatide were gastrointestinal-related, including nausea, diarrhoea, and vomiting and were mostly mild to moderate in severity, with few events leading to treatment discontinuation (<5%). Serious adverse events were reported by 68 (7%) participants overall and two deaths occurred in the tirzepatide 10 mg group, but deaths were not considered to be related to the study treatment by the investigator.

Interpretation In this 72-week trial in adults living with obesity and type 2 diabetes, once-weekly tirzepatide 10 mg and 15 mg provided substantial and clinically meaningful reduction in bodyweight, with a safety profile that was similar to other incretin-based therapies for weight management.

Funding Eli Lilly and Company.

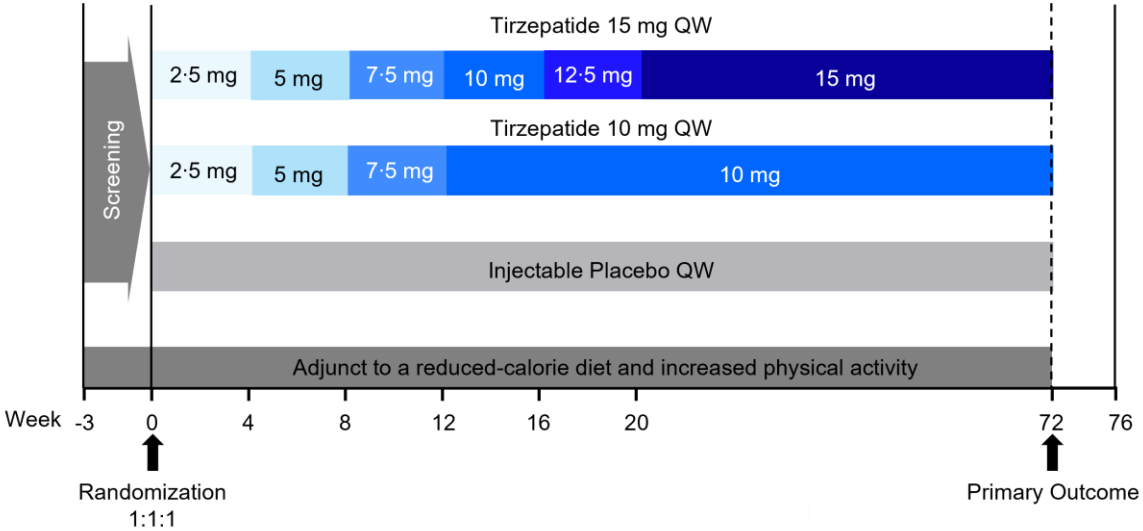
Introduction

The prevalence of obesity is anticipated to rise to 24% globally by 2035, impacting the lives of nearly 2 billion people.[1] Obesity is a chronic disease that is associated with an increased risk of over 200 weight-related complications that impair health and reduce survival, including several cardiovascular diseases, type 2 diabetes, non-alcoholic steatohepatitis, and chronic kidney disease.[2-4]

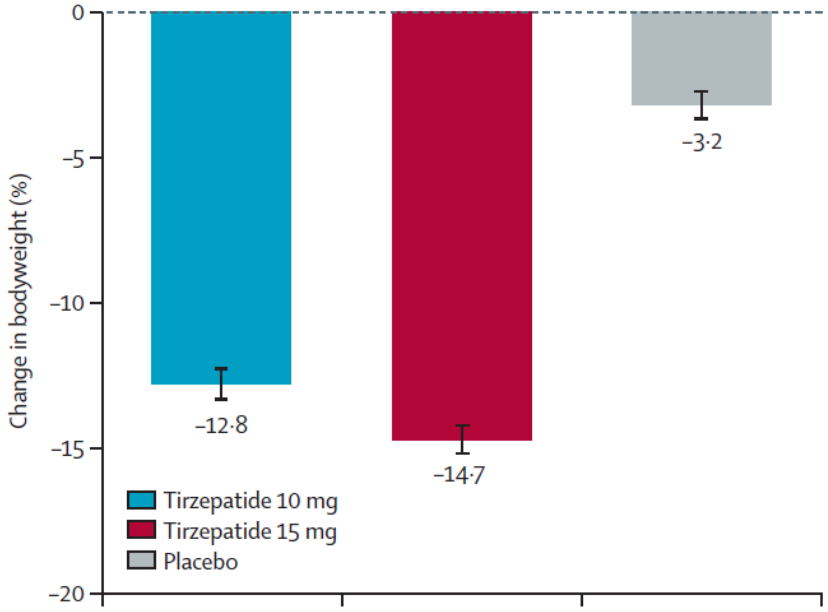
The most recent consensus report by the American Diabetes Association and the European Association for the Study of Diabetes emphasises the importance of weight management as a key component of type 2 diabetes treatment, with the understanding that reaching weight reduction thresholds of more than 5% to more than 15% translates to health benefits that go beyond glycaemic control.[1]

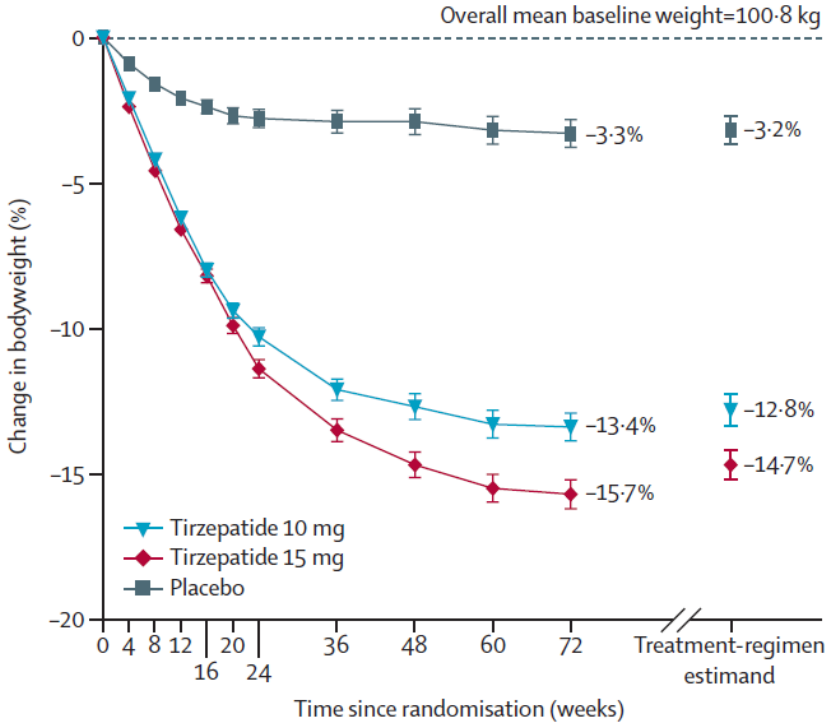
Tirzepatide is a once-weekly injectable, subcutaneous glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) receptor agonist.[5] It is currently approved by the US Food and Drug Administration (FDA) and European Medicines Agency

www.thelancet.com Published online June 24, 2023 https://doi.org/10.1016/S0140-6736(23)01200-X



Percent Change from Baseline in Body Weight (%) at Week 72

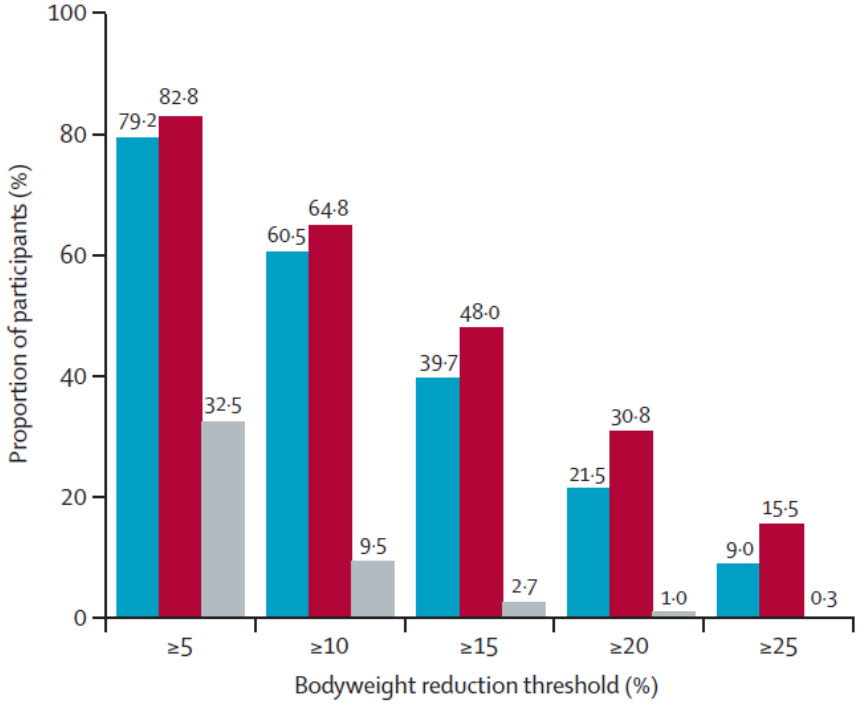




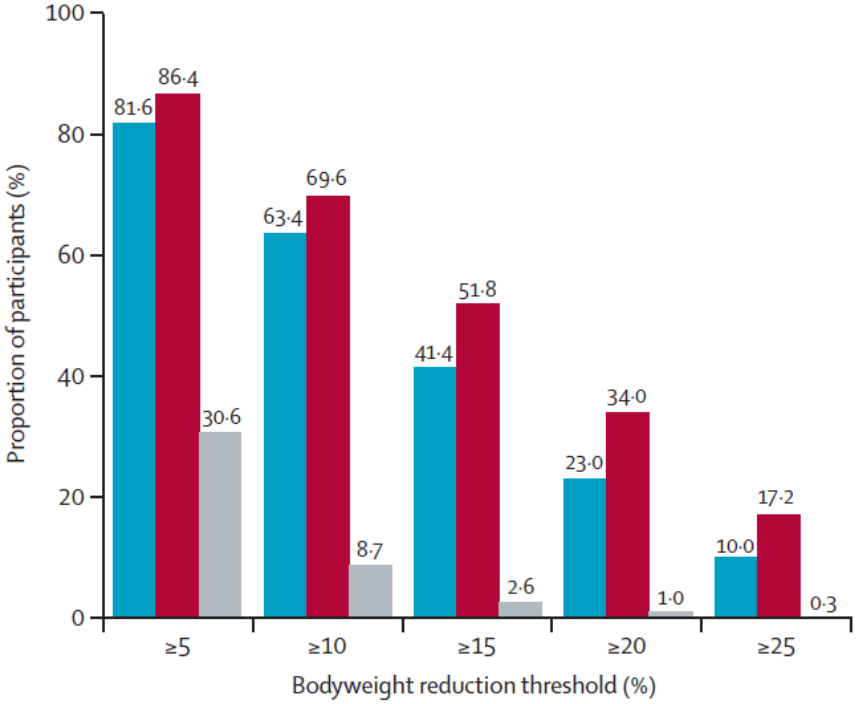
Garvey et al., Lancet, June 24th, 2023

Proportion of Participants Achieving Body Weight (%) Reduction Targets at 72 Weeks

Efficacy Estimand



Treatment-Regimen Estimand



Garvey et al., Lancet, June 24th, 2023

Tirzepatid Dosierung

Schritt 1

STARTDOSIS[a]

1× wöchentlich

2,5 mg

4 Wochen

ERSTE 4 WOCHEN

Schritt 2

ERHALTUNGSDOSIS

1× wöchentlich

5 mg

mind. 4 Wochen

NACH 4 WOCHEN

Bei Bedarf ist eine Individualisierung möglich

ÜBERGANGS-DOSIS

1× wöchentlich

7,5 mg

4 Wochen

ERHALTUNGS-DOSIS

1× wöchentlich

10 mg

mind. 4 Wochen

ÜBERGANGS-DOSIS

1× wöchentlich

12,5 mg

4 Wochen

ERHALTUNGS-DOSIS

1× wöchentlich

15 mg

Höchstdosis

FRÜHESTENS AB WOCHE 9

Bei Bedarf kann die Dosis in 2,5-mg-Schritten bis zur Höchstdosis von 15 mg erhöht werden, nachdem eine Behandlung für mindestens vier Wochen mit der jeweils aktuellen Dosis erfolgt ist. Die empfohlenen Erhaltungsdosen betragen 5 mg, 10 mg oder 15 mg.

1. Gebrauchsinformation Tirzepatid, aktueller Stand.

a) Die Anfangsdosis von Tirzepatid beträgt 2,5 mg 1x wöchentlich. Nach vier Wochen sollte die Dosis auf 5 mg 1x wöchentlich erhöht werden. Bei Bedarf kann die Dosis in 2,5-mg-Schritten bis zur Höchstdosis von 15 mg erhöht werden, nachdem eine Behandlung für mindestens vier Wochen mit der jeweils aktuellen Dosis erfolgt ist. Die empfohlenen Erhaltungsdosen betragen 5 mg, 10 mg oder 15 mg.

1. Fachinformation Tirzepatid, aktueller Stand.

GLP-1/Glucagon Coagonists

Boehringer Ingelheim | About Us | Human Health | Animal Health | Science & Innovation | Partnering

Boehringer Ingelheim to advance survodutide into three global Phase III studies in obesity

Ingelheim, Germany, Thursday, 17/08/2023 - 06:00

- Phase II data showed up to 19 percent weight loss in people living with overweight or obesity[1]
- Phase III studies will investigate the efficacy and safety of survodutide
- Details of the studies will be disclosed prior to their initiation and enrollment of patients is planned before the end of 2023

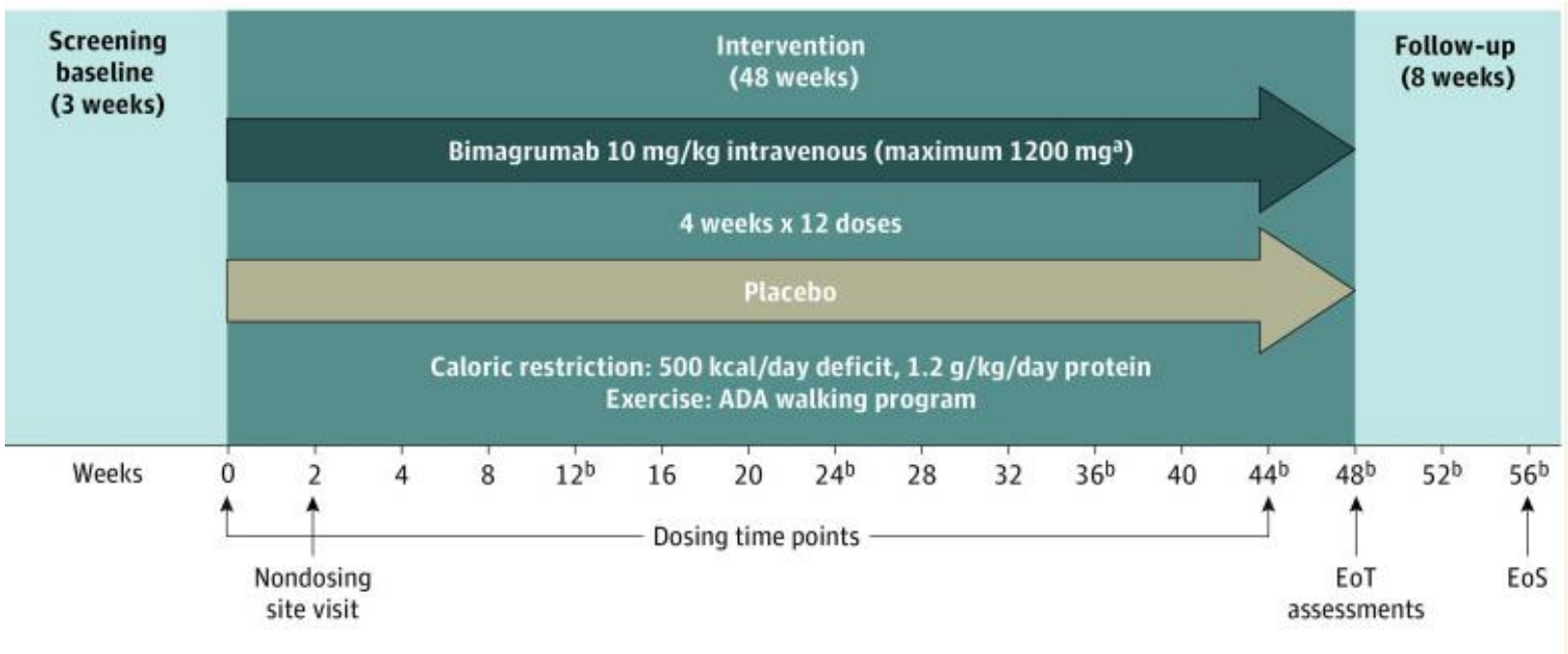
Boehringer Ingelheim today announced it will advance survodutide, its glucagon/GLP-1 receptor dual agonist, into three registrational Phase III studies for people living with overweight or obesity. This decision was based on recently presented data from a Phase II dose finding study in people living with overweight or obesity. The study demonstrated up to 19 percent weight loss after 46 weeks of treatment with survodutide.[1]

"With a strong heritage in cardio-renal-metabolic disease, we are continuing to expand and accelerate our portfolio in this area with the aim of bringing survodutide to patients in need as quickly as possible," said Carinne Brouillon, Head of Human Pharma, Boehringer Ingelheim. "There is a significant unmet medical need for effective treatments for obesity. With its dual mode of action, survodutide has the potential to further improve outcomes for people living with the disease and its associated complications."

Insights from previous studies will now be applied to the design of three global Phase III studies, which will investigate the efficacy and safety of survodutide. Details of the studies will be disclosed prior to their initiation and enrollment of patients is planned before the end of 2023.

https://www.boehringer-ingelheim.com/human-health/metabolic-diseases/obesity/survodutide-phase-iii-study-weight-loss

Bimagrumab, ein Antikörper, der Activin Typ II-Rezeptoren blockiert und Muskelwachstum fördert



Heymsfield et al., JAMA Netw Open. 2021; 4: e2033457.

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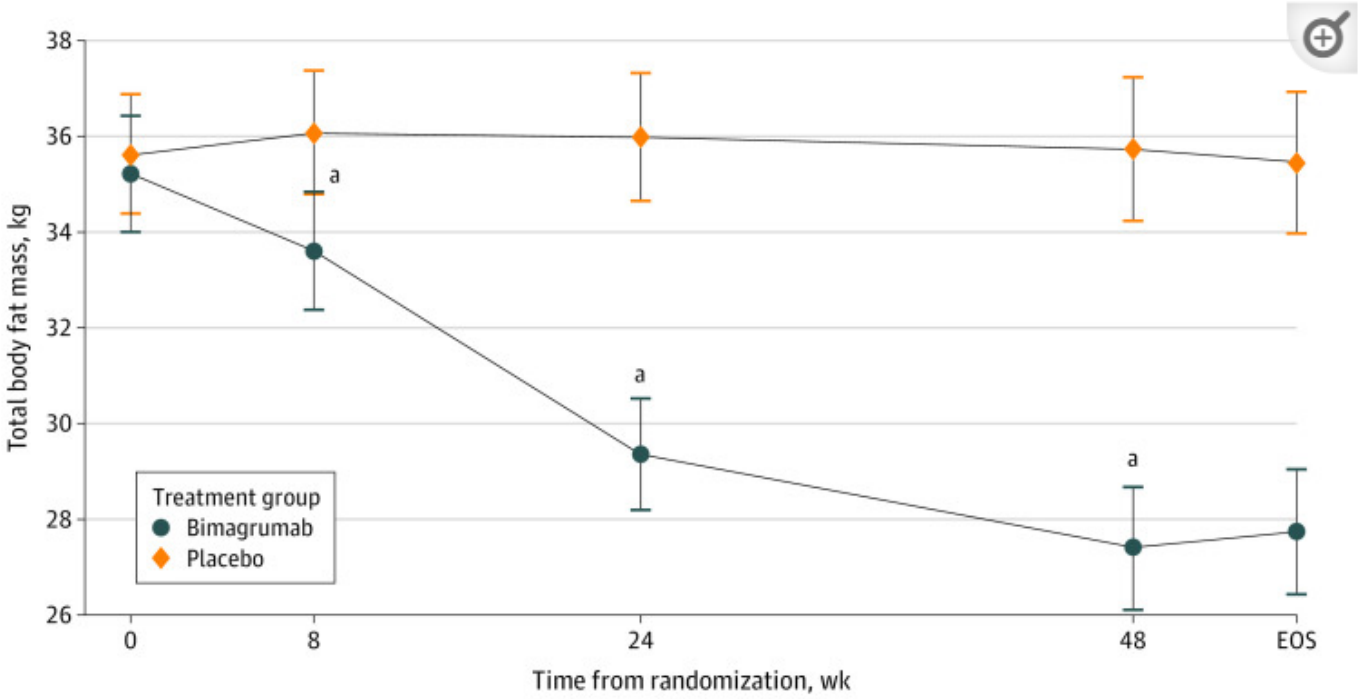

Heymsfield et al., JAMA Netw Open. 2021; 4: e2033457.

Bimagrumab, ein Antikörper, der Activin Typ II-Rezeptoren blockiert und Muskelwachstum fördert

Adverse event	Patients, No. (%)	
	Bimagrumab group	Placebo group
Death	0	0
Serious adverse events	3 (8)	3 (8)
Any adverse event	31 (84)	31 (82)
Adverse event leading to study discontinuation	5 (14)	0
Most frequent adverse events[b]		
Diarrhea	15 (41)	4 (11)
Muscle spasms	15 (41)	1 (3)
Upper respiratory tract infection	6 (16)	5 (13)
Lipase level increased	4 (11)	2 (5)
Headache	0	5 (13)
Hypertension	3 (8)	1 (3)
Nausea	4 (11)	0
Rash	2 (5)	2 (5)

[a] Adverse events were any untoward medical occurrence in a patient who provided written informed consent for participation in the study until the end of study visit.

[b] Incidence greater than 5%.

Heymsfield et al., JAMA Netw Open. 2021; 4: e2033457.

AMG-133: Aktivierung von GLP1R & GIPR Inhibition

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Press Releases

AMGEN PRESENTS NEW AMG 133 PHASE 1 CLINICAL DATA AT WCIRDC 2022

AMG 133 is a First-in-Class Investigational Bispecific Molecule That Activates GLP-1R and Inhibits GIPR

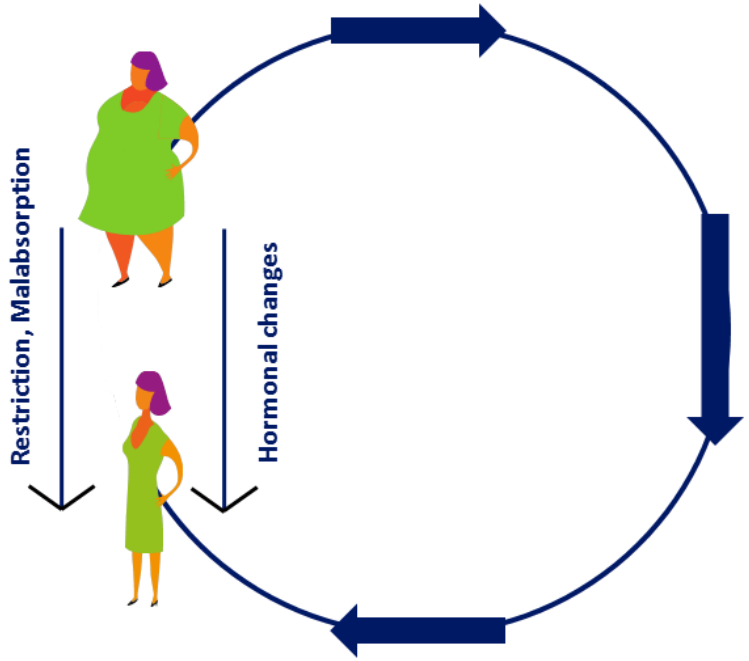
Phase 1 Results Showed up to 14.5% Reduction in Body Weight at the Highest Dose After 12 Weeks

Initiating Phase 2 Study in Early 2023

THOUSAND OAKS, Calif., Dec. 1, 2022 /PRNewswire/ -- Amgen (NASDAQ:AMGN) today announced new Phase 1 data from AMG 133, a novel bispecific glucose-dependent insulinotropic polypeptide receptor (GIPR) antagonist and glucagon-like peptide-1 (GLP-1) receptor agonist molecule. This first-in-human study was designed to evaluate the safety, tolerability, pharmacokinetic and pharmacodynamic effects of AMG 133 in people with obesity and without diabetes (NCT04478708).

These data will be presented as part of an oral presentation on Saturday, Dec. 3 at the 20th World Congress of Insulin Resistance, Diabetes and Cardiovascular Disease (WCIRDC) Hybrid Conference.

Zukunft der Pharmakotherapie



- Stärker wirksame GLP-1RA

z.B. Semaglutid

- Nicht-Peptid GLP-1RA

z.B. Orforglipron

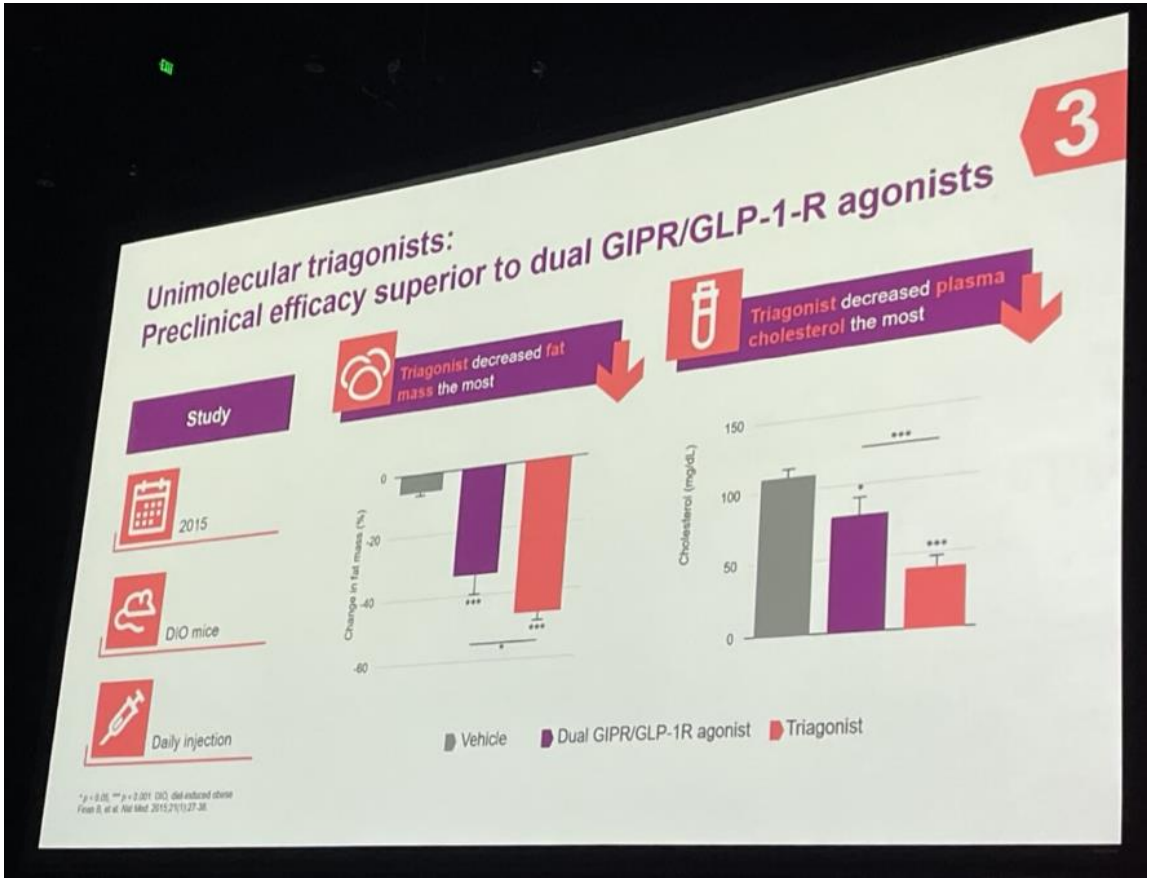
- Duale Inkretinagonisten

z. B. Tirzepatid; Finan et al., Sci Transl Med. 2013

- **Triagonisten**

z. B. Rattrutid; Finan et al., Nat Med. 2015; 21

Nächste Idee: Unimolekulare Triagonisten - GLP-1/GIP/Glukagon Agonisten



Tripleagonist (GIP, GLP-1, Glucagon) Retatrutid

Phase 2 Studien in den Indikationen Typ 2 Diabetes und Adipositas

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Triple–Hormone-Receptor Agonist Retatrutide for Obesity — A Phase 2 Trial

Ania M. Jastreboff, M.D., Ph.D., Lee M. Kaplan, M.D., Ph.D., Juan P. Frías, M.D., Qiwei Wu, Ph.D., Yu Du, Ph.D., Sirel Gurbuz, M.D., Tamer Coskun, M.D., Ph.D., Axel Haupt, M.D., Ph.D., Zvonko Milicevic, M.D., and Mark L. Hartman, M.D., for the Retatrutide Phase 2 Obesity Trial Investigators*

ABSTRACT

BACKGROUND

Retatrutide (LY3437943) is an agonist of the glucose-dependent insulinotropic polypeptide, glucagon-like peptide 1, and glucagon receptors. Its dose–response relationships with respect to side effects, safety, and efficacy for the treatment of obesity are not known.

METHODS

We conducted a phase 2, double-blind, randomized, placebo-controlled trial involving adults who had a body-mass index (BMI, the weight in kilograms divided by the square of the height in meters) of 30 or higher or who had a BMI of 27 to less than 30 plus at least one weight-related condition. Participants were randomly assigned in a 2:1:1:1:1:2:2 ratio to receive subcutaneous retatrutide (1 mg, 4 mg [initial dose, 2 mg], 4 mg [initial dose, 4 mg], 8 mg [initial dose, 2 mg], 8 mg [initial dose, 4 mg], or 12 mg [initial dose, 2 mg]) or placebo once weekly for 48 weeks. The primary end point was the percentage change in body weight from baseline to 24 weeks. Secondary end points included the percentage change in body weight from baseline to 48 weeks and a weight reduction of 5% or more, 10% or more, or 15% or more. Safety was also assessed.

RESULTS

We enrolled 338 adults, 51.8% of whom were men. The least-squares mean percentage change in body weight at 24 weeks in the retatrutide groups was −7.2% in the 1-mg group, −12.9% in the combined 4-mg group, −17.3% in the combined 8-mg group, and −17.5% in the 12-mg group, as compared with −1.6% in the placebo group. At 48 weeks, the least-squares mean percentage change in the retatrutide groups was −8.7% in the 1-mg group, −17.1% in the combined 4-mg group, −22.8% in the combined 8-mg group, and −24.2% in the 12-mg group, as compared with −2.1% in the placebo group. At 48 weeks, a weight reduction of 5% or more, 10% or more, and 15% or more had occurred in 92%, 75%, and 60%, respectively, of the participants who received 4 mg of retatrutide; 100%, 91%, and 75% of those who received 8 mg; 100%, 93%, and 83% of those who received 12 mg; and 27%, 9%, and 2% of those who received placebo. The most common adverse events in the retatrutide groups were gastrointestinal; these events were dose-related, were mostly mild to moderate in severity, and were partially mitigated with a lower starting dose (2 mg vs. 4 mg). Dose-dependent increases in heart rate peaked at 24 weeks and declined thereafter.

CONCLUSIONS

In adults with obesity, retatrutide treatment for 48 weeks resulted in substantial reductions in body weight. (Funded by Eli Lilly; ClinicalTrials.gov number, NCT04881760.)

From the Departments of Medicine (Endocrinology and Metabolism) and Pediatrics (Pediatric Endocrinology), Yale University School of Medicine, New Haven, CT (A.M.J.); the Obesity and Metabolism Institute and Department of Medicine, Harvard Medical School, Boston (L.M.K.); Velocity Clinical Research, Los Angeles (J.P.F.); and Eli Lilly, Indianapolis (Q.W., Y.D., S.G., T.C., A.H., Z.M., M.L.H.). Dr. Jastreboff can be contacted at ania.jastreboff@yale.edu or at the Yale University School of Medicine (Endocrinology and Metabolism), 333 Cedar St., P.O. Box 208020, New Haven, CT 06520.

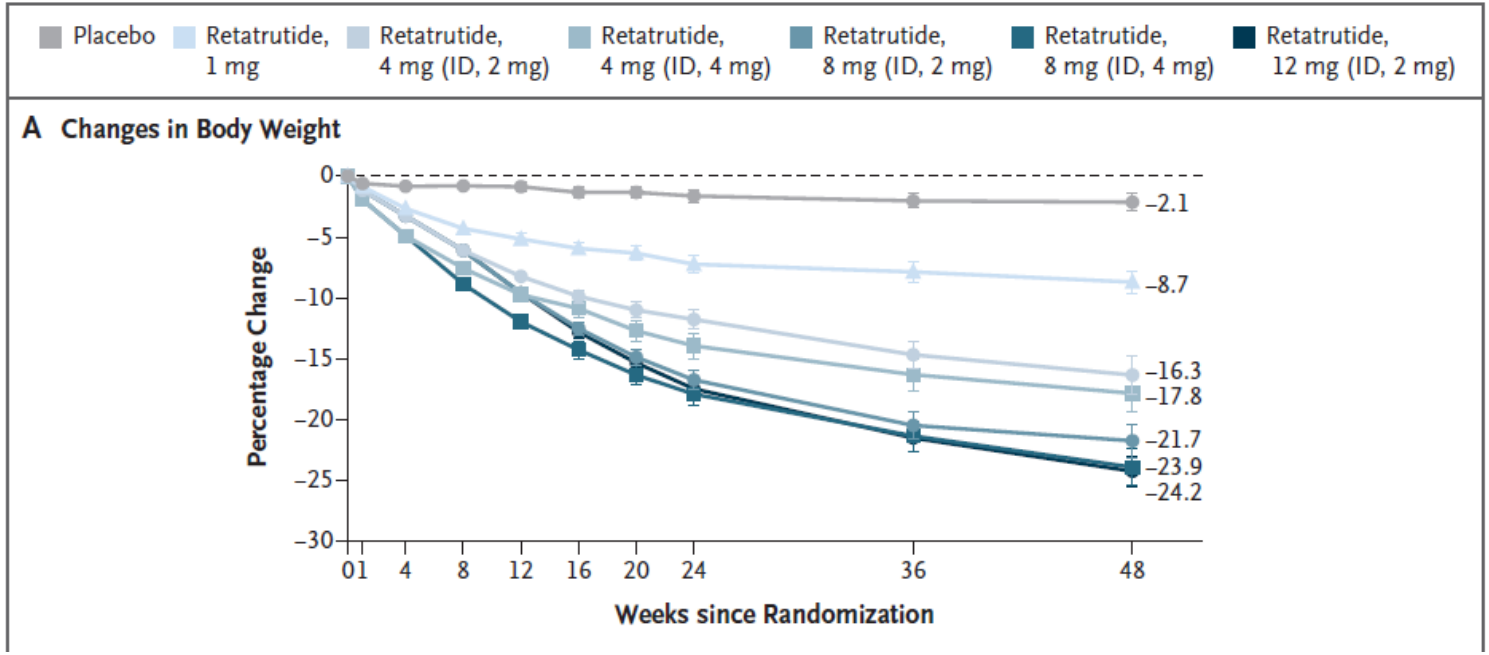
*A full list of the Retatrutide Phase 2 Obesity Trial Investigators is provided in the Supplementary Appendix, available at NEJM.org.

This article was published on June 26, 2023, at NEJM.org.

DOI: 10.1056/NEJMoa2301972

Tripleagonist (GIP, GLP-1, Glucagon) Retatrutid

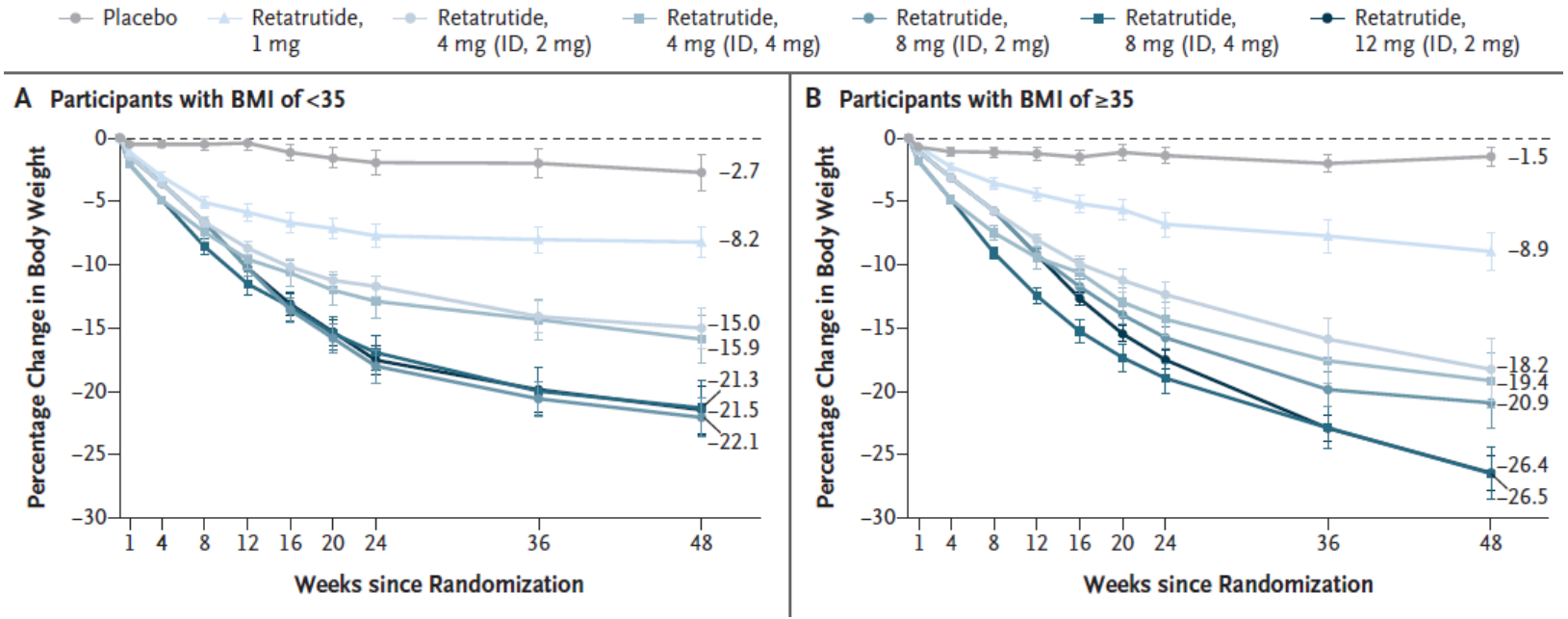
Phase 2 Studie in der Indikation Adipositas



Jastreboff et al., N Engl J Med, June 24th, 2023

Tripleagonist (GIP, GLP-1, Glucagon) Retatrutid

Phase 2 Studie in der Indikation Adipositas



Jastreboff et al., N Engl J Med, June 24th, 2023

Gibt es Prädiktoren für erfolgreichen Gewichtsverlust?

10 Jahresdaten aus dem National Weight Control Registry + LOOK AHEAD

Erfolgreicher Langzeitgewichtsverlust:

Restriktive Nahrungsaufnahme: ~ 1.400 kcal/Tag

Täglich 1 Stunde Sport (~400 kcal pro Tag)

< 10 Stunden Fernsehen pro Woche

Wenigstens 1x pro Woche wiegen

Frühstücken

Tate& Shukla; Obesity Week 2022

Thomas JG, et al. Am J Prev Med. 2014 & www.cdc.gov/obesity/strategies/index.html

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Vielen Dank!