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Obesity and Metabolism

22nd PostADA/PostENDO Symposium
31.08.2023

Charlotte Hintze, Klinik für Endokrinologie, Diabetologie und Klinische Ernährung

No disclosures

Agenda:

GLP1-RA
- **Orale Semaglutide**
- **Orforglipron**

Dual Agonists
- **Survodutide**

Triple Agonist
- **Retatrutide**

Bariatric Surgery
- **SOS Study**
- **Semaglutide in postbariatric patients**

Nutrition
- **SWAP MEAT**

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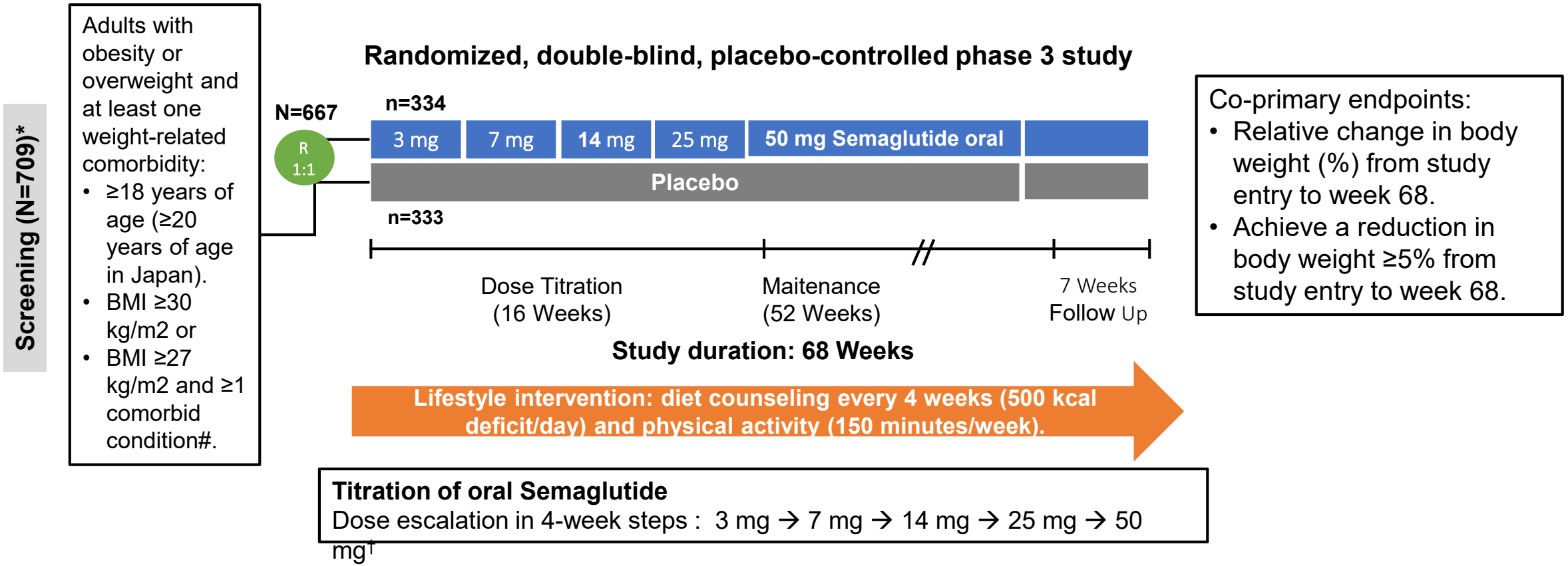
OASIS 1

Study Design

OASIS 1 was designed to evaluate the efficacy and safety of once-daily oral semaglutide 50 mg versus placebo in people with overweight or obesity, concomitant with lifestyle intervention



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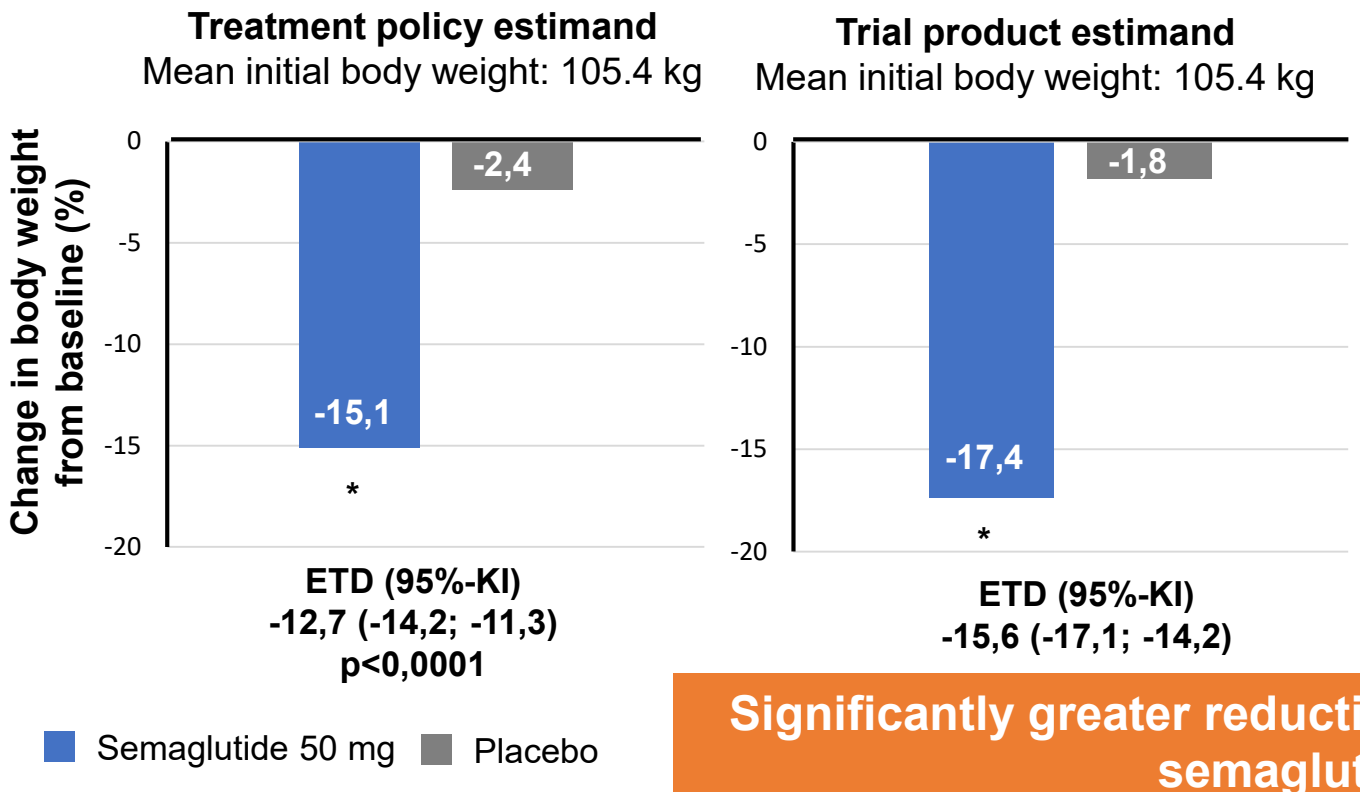
Rosenstock, J et al. presented at the American Diabetes Association 83rd Scientific Sessions – San Diego and Virtual, June 23-26, 2023. Symposium – Oral Semaglutide for Treatment of Obesity and Type 2 Diabetes – Results from OASIS 1 and PIONEER PLUS Trials.

OASIS 1

Co-primary endpoint: Change in body weight (%) at week 68

% change in body weight



Baseline demographic and clinical characteristics

	Semaglutide	Placebo
Female, %	74	71
Mean Age, Years	49	50
Mean body weight, kg	104,5	106,2
Mean BMI, kg/m²	37,3	37,7
Mean HbA_{1c}, %	5,6	5,6
Prediabetes, %	40	39

Significantly greater reduction in body weight with oral therapy with semaglutide 50 mg vs placebo

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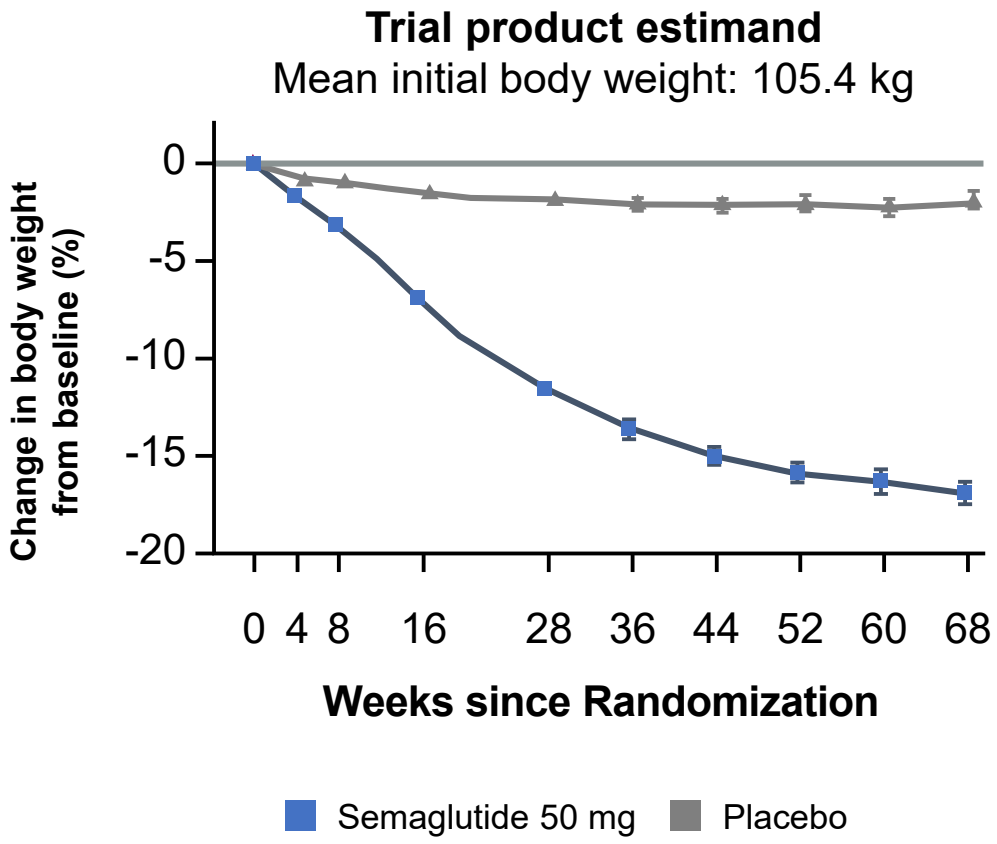
Knop FK, et al. The Lancet; doi 10.1016/S0140-6736(23)01185-6; [Epub ahead of print].
Knop, FK et al. Presented at the American Diabetes Association 83rd Scientific Sessions – San Diego and Virtual, June 23-26, 2023. Symposium – Oral Semaglutide for Treatment of Obesity and Type 2 Diabetes – Results from OASIS 1 and PIONEER PLUS Trials.

OASIS 1

Co-primary endpoint: Change in body weight (%) over time



Data are observed (i.e., measured) mean changes (standard error) in body weight from baseline; numbers below graphs indicate the number of participant:s on which the mean is based (total analysis data set).

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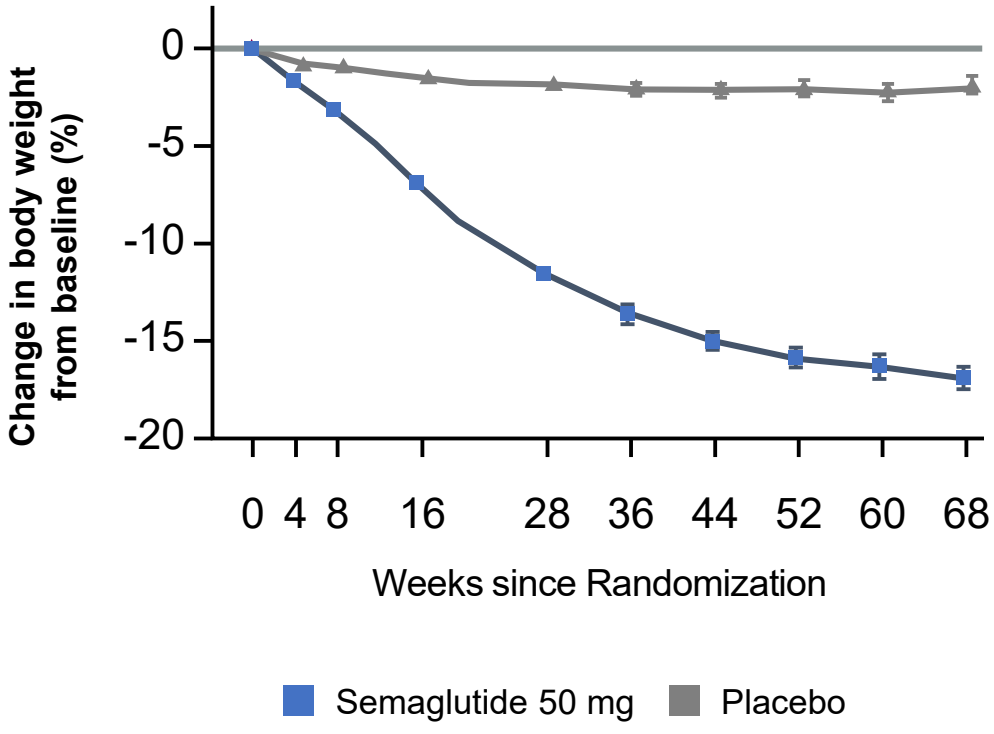
OASIS 1

Co-primary endpoint: Change in body weight (%) over time

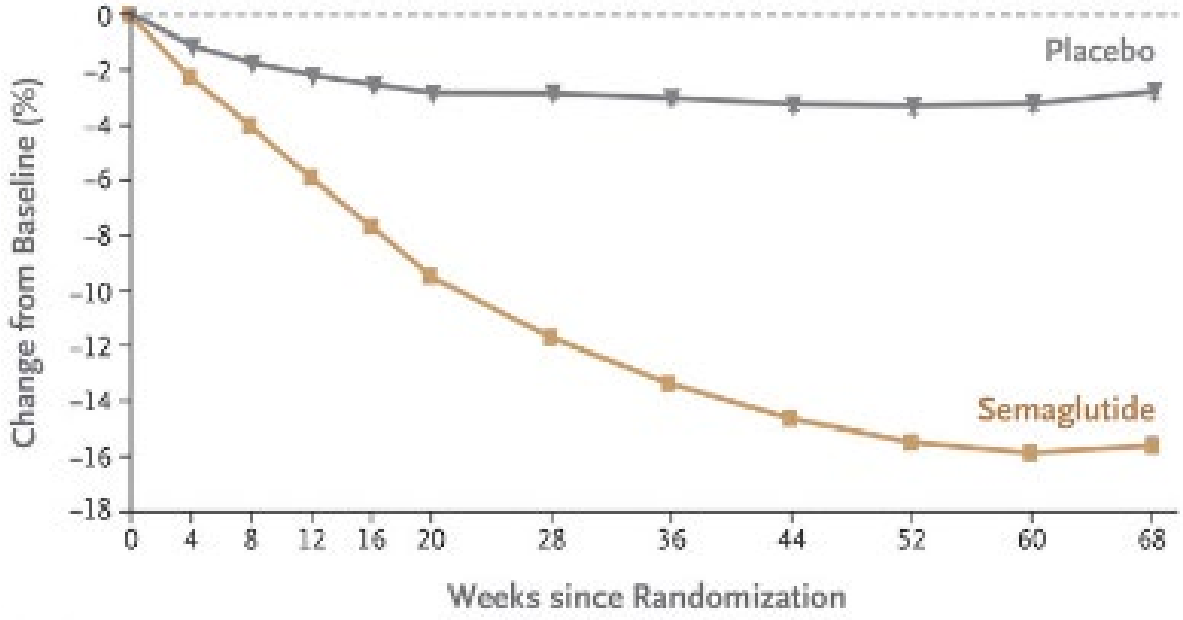
Trial product estimand

Mean initial body weight: 105.4 kg



Trial product estimand

Semaglutid 2.4 mg s.c.



Wilding JPH et al, once-weekly Semaglutid in Adults with Oberweight or Obesity, N Engl J Med 2021; 384:989-1002, DOI: 10.1056/NEJMoa2032183

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OASIS 1

Summary

- The OASIS 1 trial showed that once-daily oral semaglutide 50mg led to a weight loss of 17.4% and was superior to placebo from baseline to week 68 for all co-primary and confirmatory secondary endpoints ($p<0.0001$ for all)
- The overall safety profile of oral semaglutide 50mg was consistent with the safety profile for semaglutide and the GLP-1RA class
- Oral semaglutide 50mg may represent an effective option for the treatment of obesity, particular in patients who prefer oral administration

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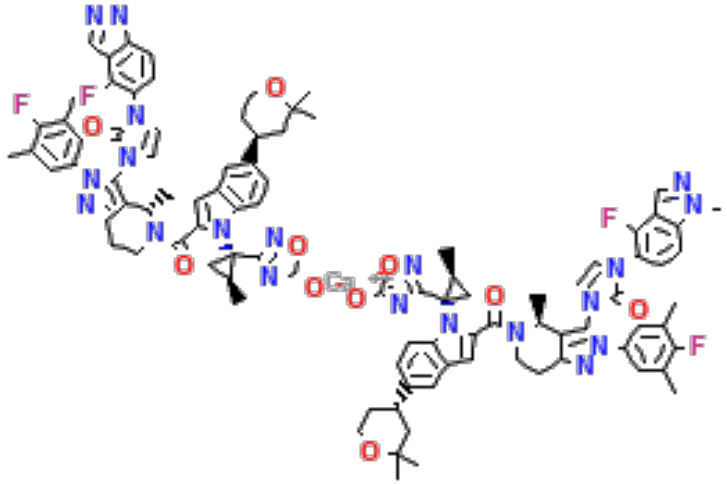
Orforglipron in obesity and overweight, a Phase-II-Study

Backround and Aims

- Orforglipron is an oral, once daily Non-Peptide-GLP-1 Receptor Agonist
- Oral bioavailability is estimated at ~30-40%.
- It can be taken without restriction of food, water or other medications



Primary Objective:

- To demonstrate that at least one maintenance dose of Orforglipron is superior to placebo in percent body weight reduction from Baseline at Week 26

The study objective is to evaluate the efficacy and safety of daily oral Orforglipron compared with placebo for chronic weight management

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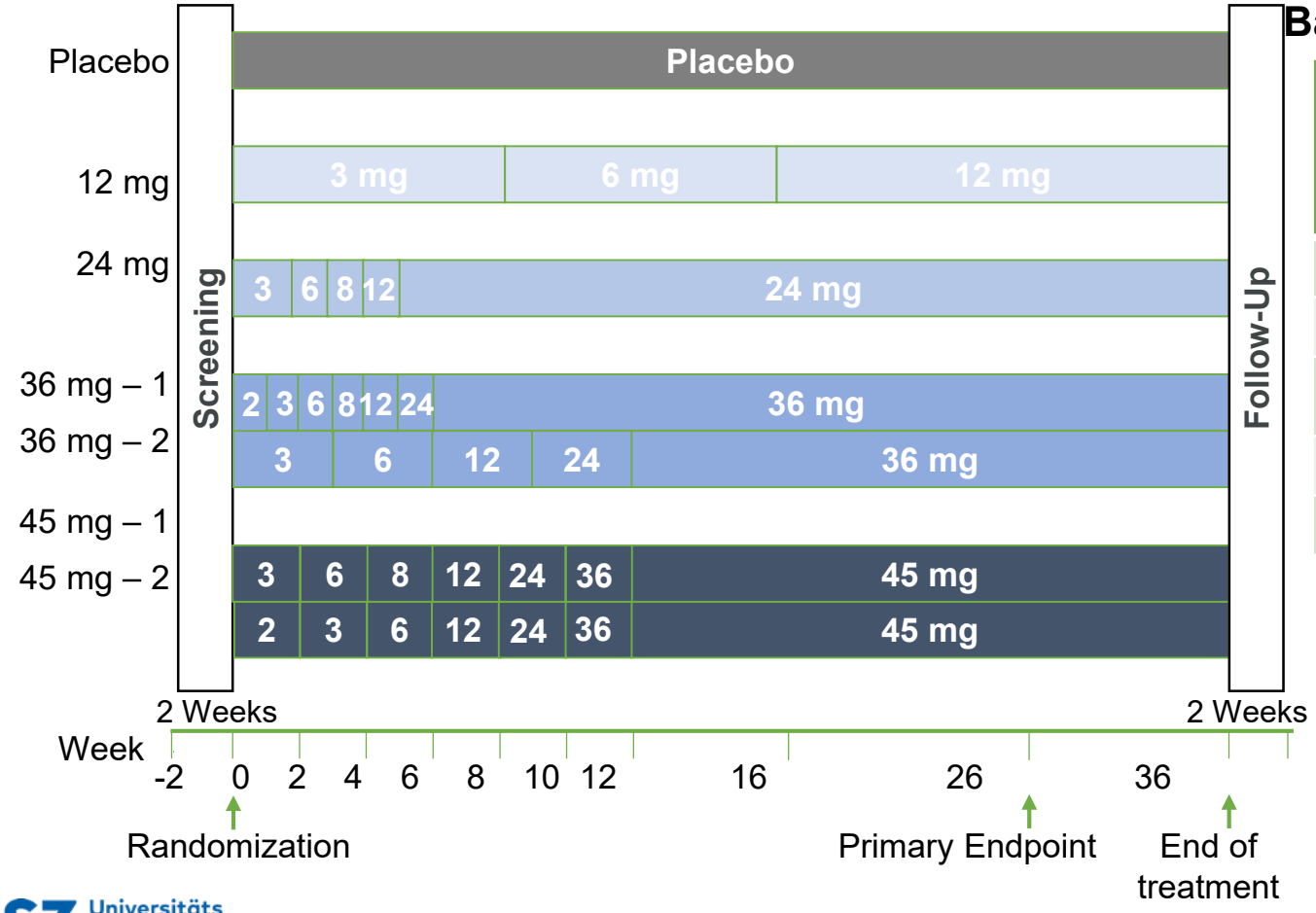
Wharton, S et al. Präsentiert auf dem American Diabetes Association 83rd Scientific Sessions – San Diego and Virtual, June 23-26, 2023.
52-OR. Oral Presentation – Advances in Incretin Therapy.

Orforglipron in obesity and overweight, a Phase-II-Study

Study design and Baseline characteristics

36-weeks, Phase 2, double-blind, randomized
Placebo-controlled trial



Baseline demographic and clinical characteristics

	Total (N=272)
Age, Years	54,2 □ 10,7
Female, %	59,2
Body weight, kg	108,7 □ 26,0
BMI, kg/m^2	37,9 □ 6,9
HbA_{1c}, %	5,6 □ 0,4

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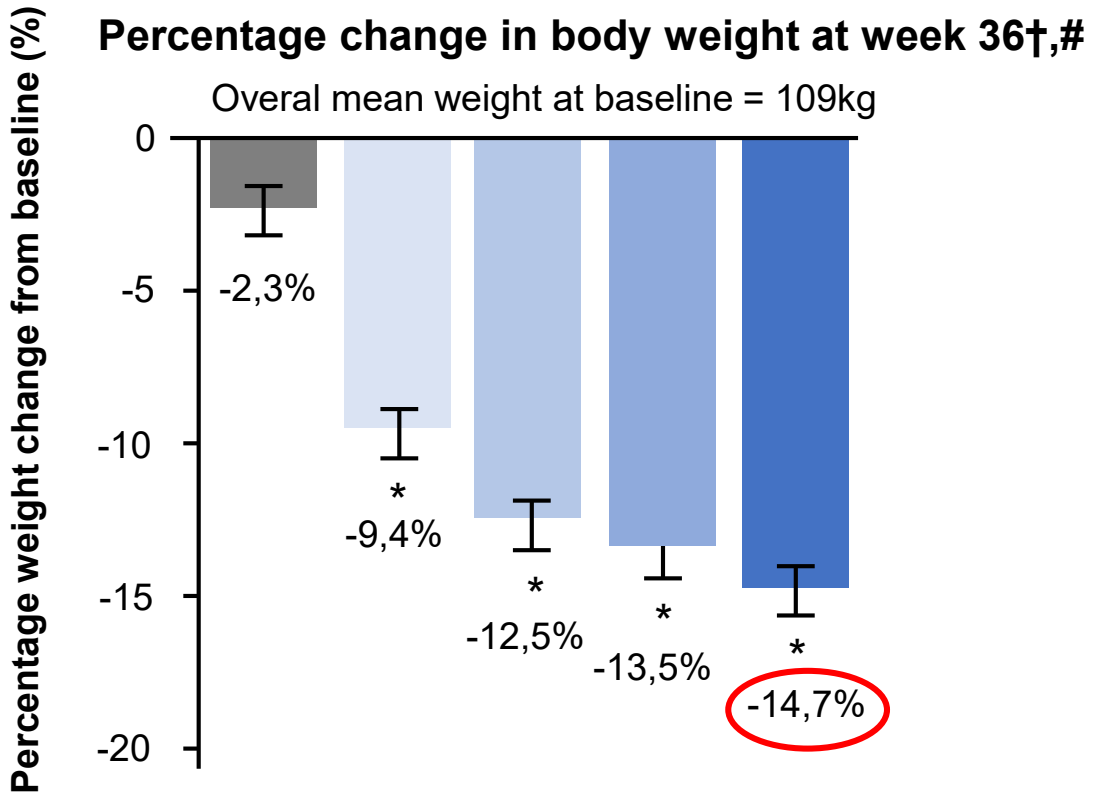
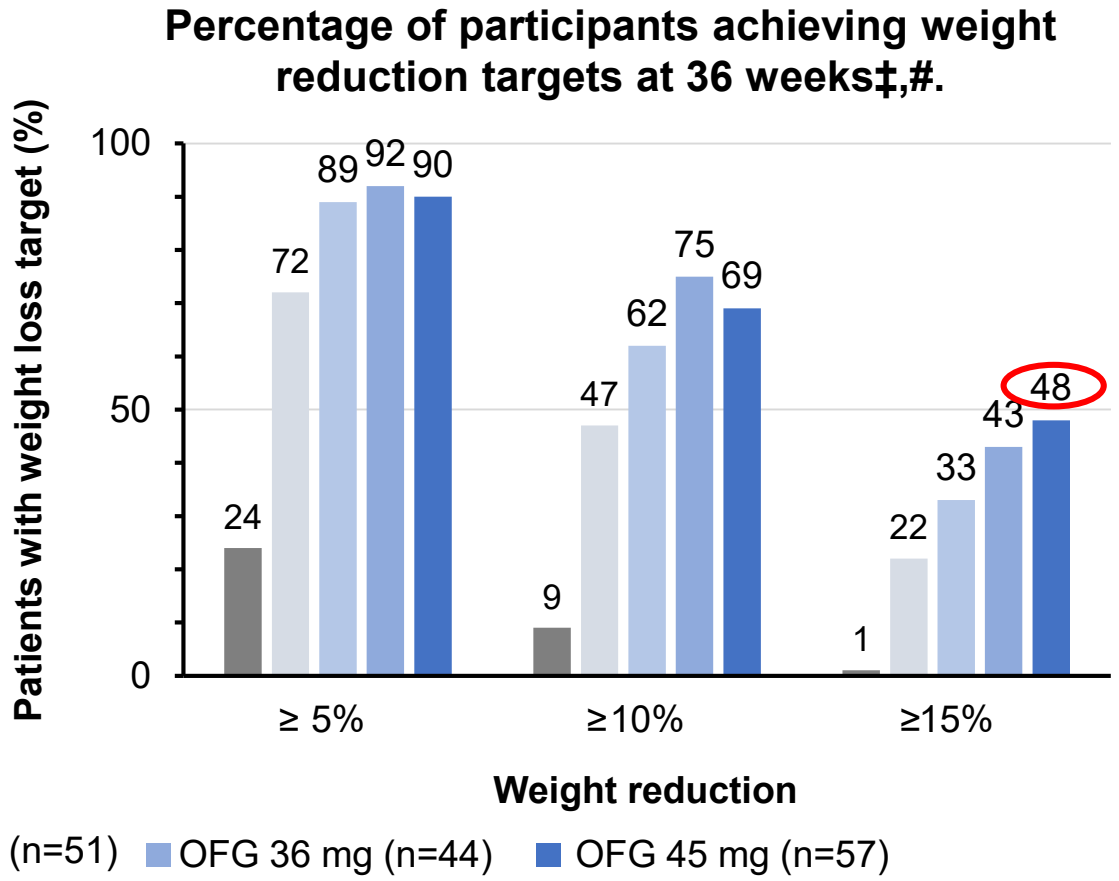
Orforglipron in obesity and overweight, a Phase-II-Study

Change in body weight at Week 36





Placebo (n=48) OFG 12 mg (n=44) OFG 24 mg (n=51) OFG 36 mg (n=44) OFG 45 mg (n=57)

Up to 14,7% body weight reduction at 36 Weeks

After 36 weeks, 50% of participants reached a weight reduction goal of ≥15% with the 45 mg dose.

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*p≤0.001 vs placebo; †Percentage change from baseline in body weight by week 36 (efficacy estimate); ‡Percentage of patients achieving ≥5%, ≥ 10%, and ≥ 15% weight reduction at 36 weeks (efficacy estimate). #36 mg-1 and 36 mg-2 dose group data were pooled for 36 mg; 45 mg-1 and 45 mg-2 dose group data were pooled for 45 mg. OFG, Orforglipron.

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52-OR. Oral Presentation – Advances in Incretin Therapy.

Orforglipron in obesity and overweight, a Phase-II-Study

Summary and Conclusion

- Orforglipron demonstrated a body weight reduction of up to 14.7% at week 36 was observed, with no plateau yet reached
- Efficacy appeared to be comparable to approved injectable GLP-1 RAs
- The most frequent AEs were gastrointestinal-related and mostly mild to moderate in severity
- Orforglipron can be taken without restriction of food, water or other medications and has a half-life which enables once-daily dosing
- These promising data support continued development of orforglipron as an oral treatment for obesity. A Phase 3 program evaluating Orforglipron for chronic weight management has been initiated (ATTAIN)

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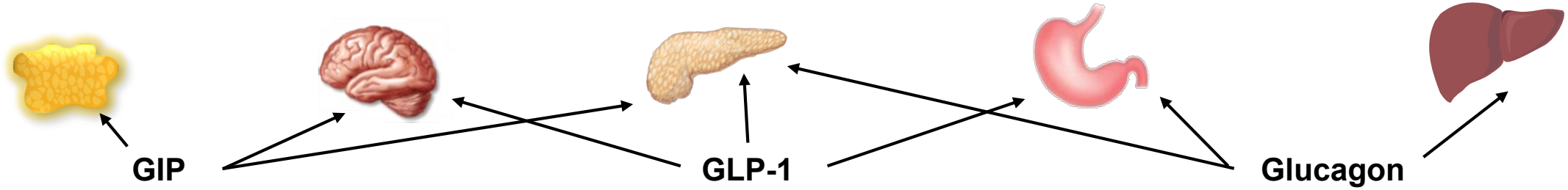
Incretin and glucagon physiology to develop pharmacotherapy for metabolic diseases



GIP

Adipose tissue:
- ↑ Insulin sensitivity
- Regulation of lipid metabolism

CNS:
- ↓ Appetite
- Energy expenditure?

Islet cells:
- ↑ Insulin secretion
- ↑ Glucagon secretion

GLP-1

CNS:
- ↓ Appetite

Islet cells:
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Stomach:
- ↓ gastric emptying

Glucagon

CNS:
- ↑ Energy expenditure
- ↓ Appetite

Islet cellts:
- ↑ Insulin secretion

Stomach:
- ↓ gastric emptying

Liver:
- ↑ Glycogenolysis/Gluconeogenesis
- ↑ Hepatic Glucose-Output
- ↑ Fatty acid oxidation
- ↑ Aminoacid-Catabolism

Survodutide
(GLP-1/GCG-Receptor-Agonist)

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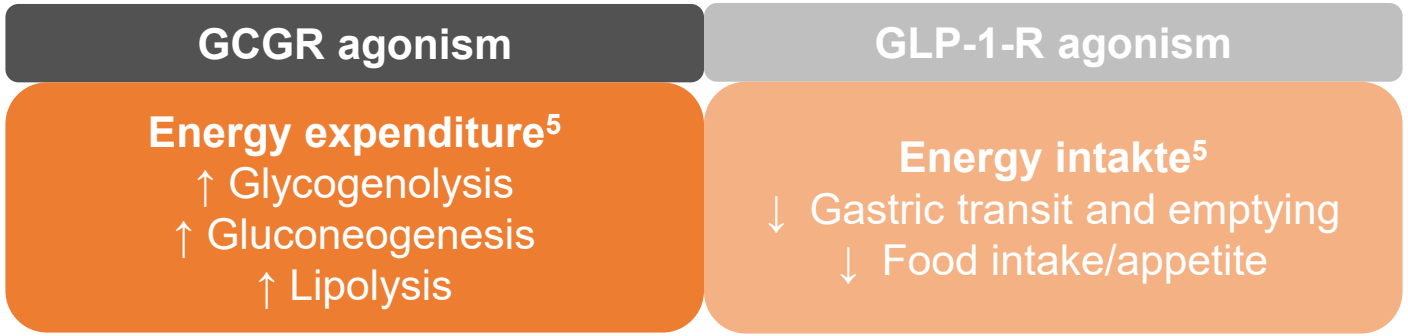
Jastreboff AM, et al. Presented at the American Diabetes Association 83rd Scientific Sessions – San Diego and Virtual, June 23-26, 2023;
Corporate Symposium - Managing NAFLD/NASH in People with T2 Diabetes: Disease Burden · Diagnosis · Current/Emerging Armamentarium.

Survodutide in patients with obesity

Background

The body weight lowering effects of GCGR- und GLP-1-R agonism are additive[3,4]

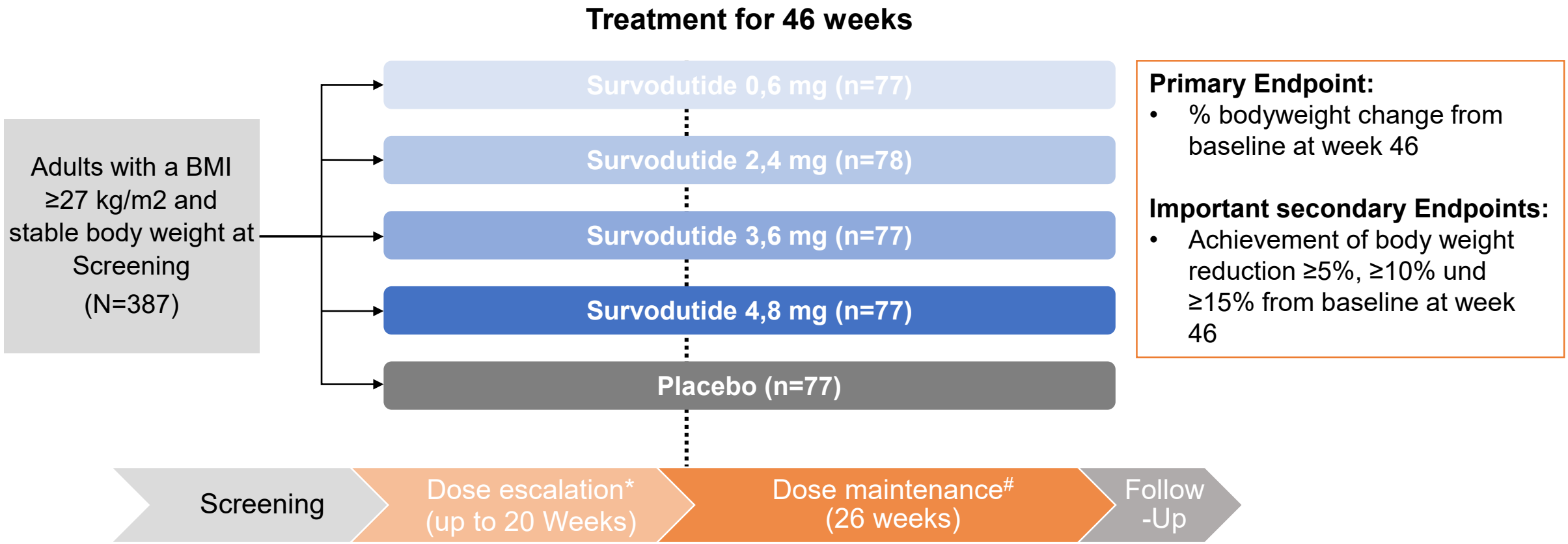


- **Survodutide** is a novel **subcutaneous, once-weekly GCGR/GLP-1-R dual agonist**, currently in the development for the treatment of obesity and NASH[1,2]

1. Jungnik A et al. Diabetes Obes Metab 2023;25:1011-23; 2. Yazawa R et al. Diabetes Obes Metab 2023;25:1973-84; 3. Salem V et al. Diabetes Obes Metab 2016;18:72-81; 4. Hayashi Y et al. J Diabetes Investig 2021;12:32-4; 5. Del Prato S et al. Obesity Rev 2022;23:e13372.
Le Roux CW, et al. Presented at the American Diabetes Association 83rd Scientific Sessions – San Diego and Virtual, June 23-26, 2023;
51-OR. Oral Presentations – Advances in Incretin Therapy.

Survodutide in patients with obesity

Study design



Primary Endpoint:

- % bodyweight change from baseline at week 46

Important secondary Endpoints:

- Achievement of body weight reduction ≥5%, ≥10% und ≥15% from baseline at week 46

*Tolerability was assessed every two weeks; if gastrointestinal UE were intolerable, participants:in remained on the same dose for an additional week before dose escalation. #Participants:in who were intolerant of gastrointestinal UE during dose escalation could receive a lower dose of survodutide (than the dose assigned to them at randomization) for the duration of the maintenance phase. Participants:in who did not tolerate the lowest dose of survodutide tested (0.6 mg) despite all efforts discontinued treatment.

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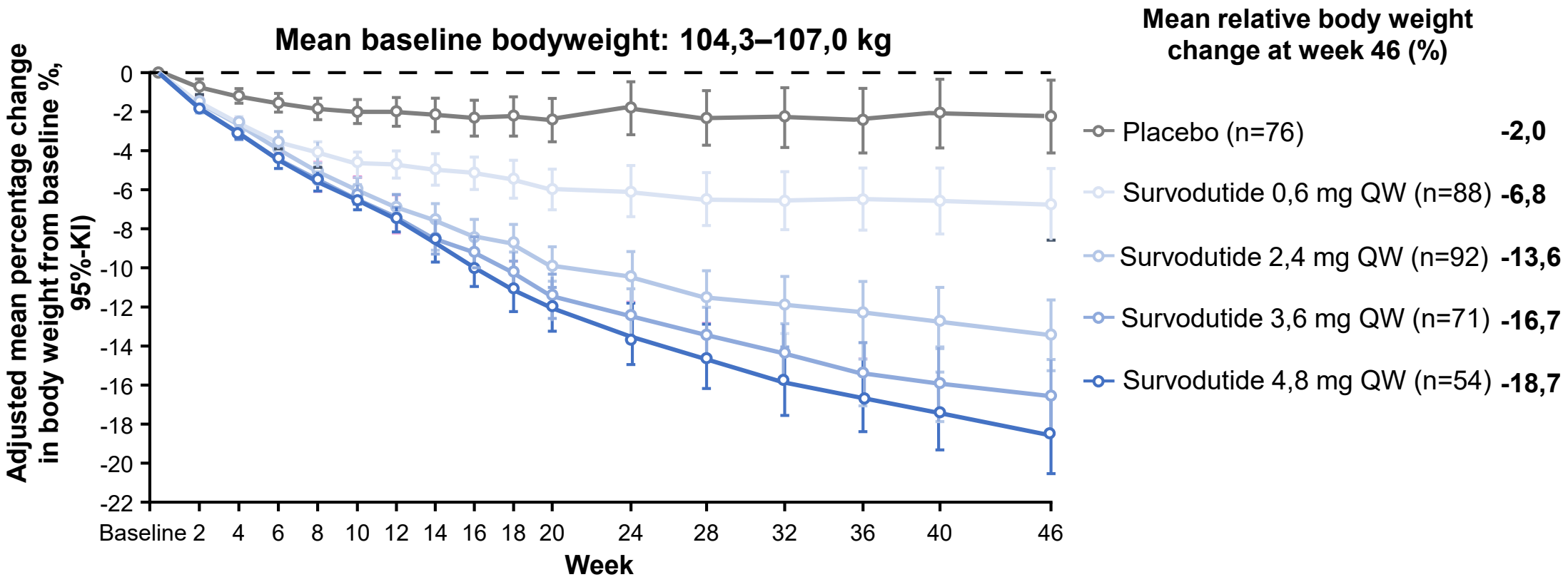
Survodutide in patients with obesity

Body weight reduction (On Treatment)



- **Survodutide treatment dose-dependently reduced bodyweight up to 18,7% over 46 weeks**
- **At week 46, significant weight reductions were seen with all tested survodutide doses vs placebo (p<0,01)**

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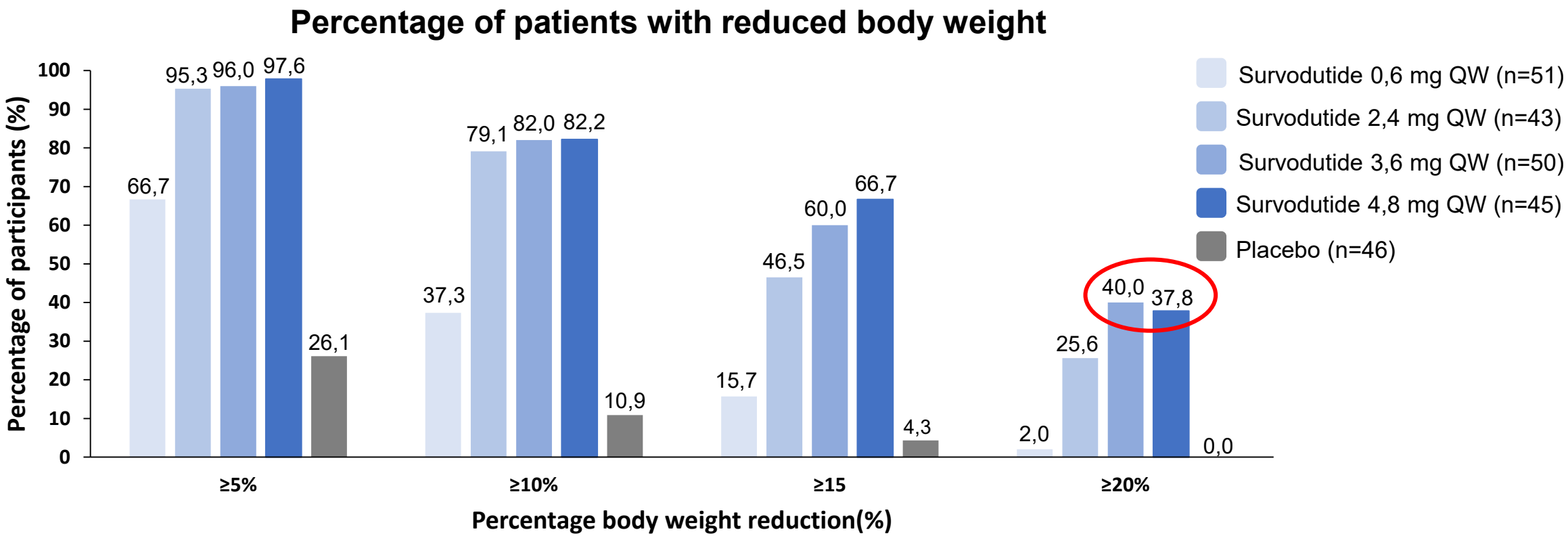
Survodutide in patients with obesity

Body weight reduction (On Treatment)



Up to 40% of participants achieved ≥20% body weight reduction with Survodutide treatment at week 46

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Survodutide in patients with obesity

Summary

- Survodutide treatment resulted in body weight reductions of up to 18.7% body weight reduction with no unexpected safety concerns after 46 weeks

- Up to 40% of participants receiving Survodutide achieved body weight reduction of ≥20% after 46 weeks of treatment

- Body weight reduction had not reached a plateau at week 46; further reductions could be expected with longer treatment duration

Le Roux CW, et al. Presented at the American Diabetes Association 83rd Scientific Sessions – San Diego and Virtual, June 23-26, 2023; 51-OR. Oral Presentations – Advances in Incretin Therapy.

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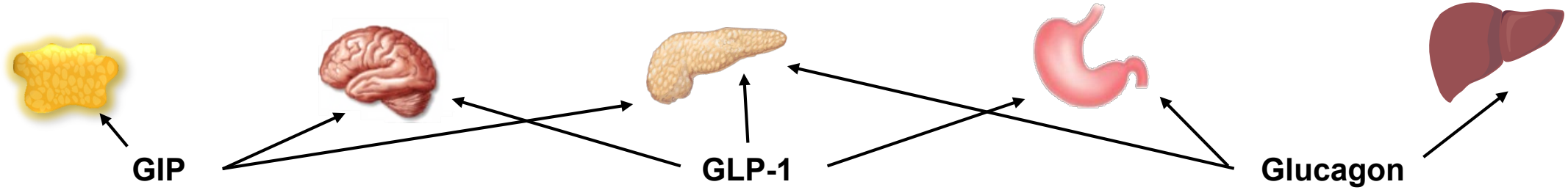

GIP

Adipose tissue:
- ↑ Insulin sensitivity
- Regulation of lipid metabolism

CNS:
- ↓ Appetite
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Islet cells:
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GLP-1

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Stomach:
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Glucagon

CNS:
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Liver:
- ↑ Glycogenolysis/Gluconeogenesis
- ↑ Hepatic Glucose-Output
- ↑ Fatty acid oxidation
- ↑ Aminoacid-Catabolism

Retatrutide
(GIP/GLP-1/GCG-Triple-Receptor-Agonist)

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Jastreboff AM, et al. Presented at the American Diabetes Association 83rd Scientific Sessions – San Diego and Virtual, June 23-26, 2023;
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Retatrutide

Backround

Retatrutide is a once-weekly injectable, triple hormone agonist of the GIP/GLP-1/Glucagon receptors

Efficacy and Safety Results of the 48-Week Obesity Phase 2 Trial

- NAFLD
- T2D

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Retatrutide

Study design

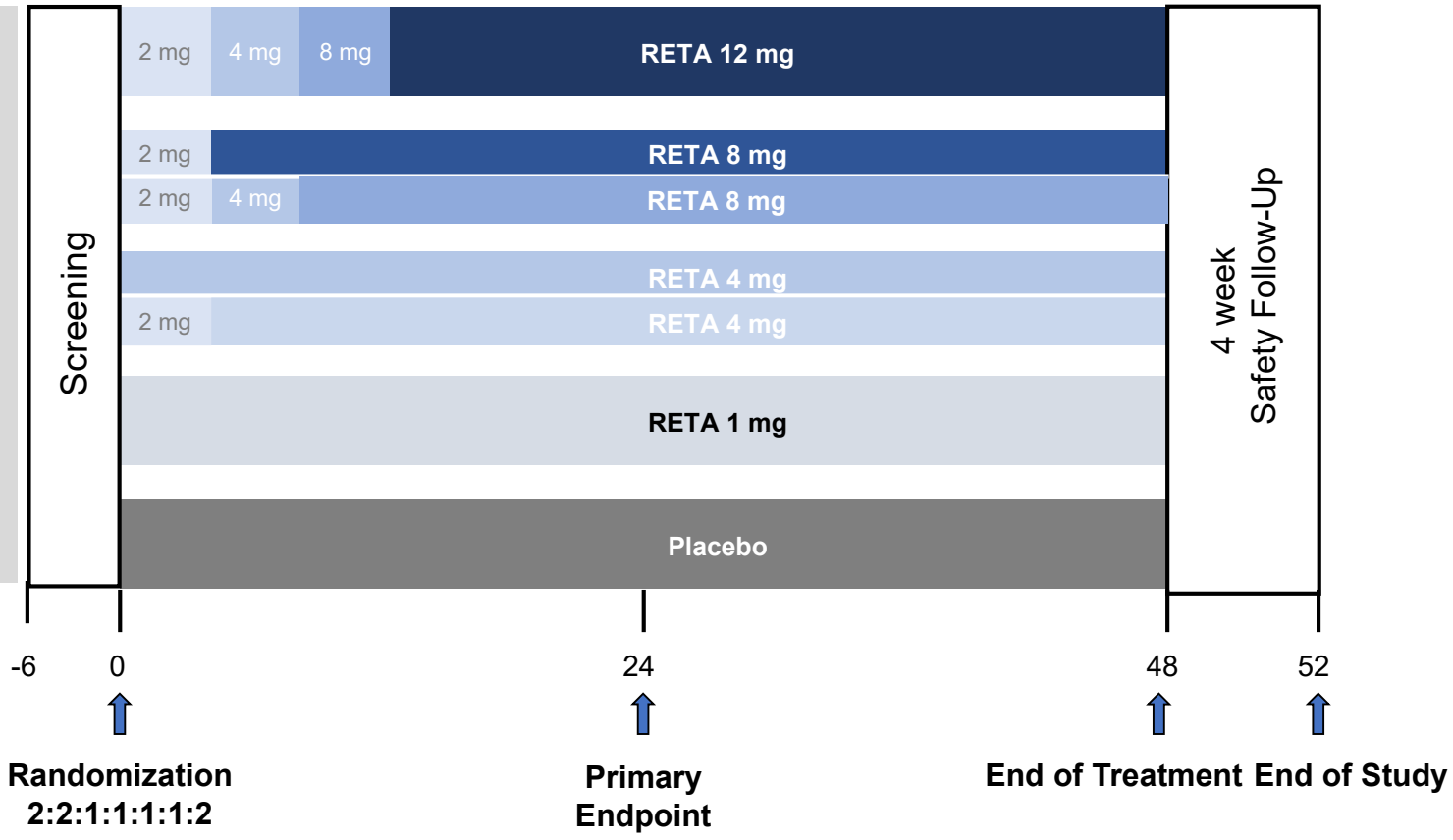
Randomized, double-blind phase 2 trial of weekly Retatrutide vs. placebo

Inclusion criterias

- Age: 18-75
- BMI ≥30 kg/m^2 or ≥ 27 kg/m^2 with at least one weight-related condition:
  - Hypertension
  - Dyslipidemia
  - CV-Disease

Primary Endpoint

- Percent change in weight from baseline at 24 weeks



RETA, Retatrutid

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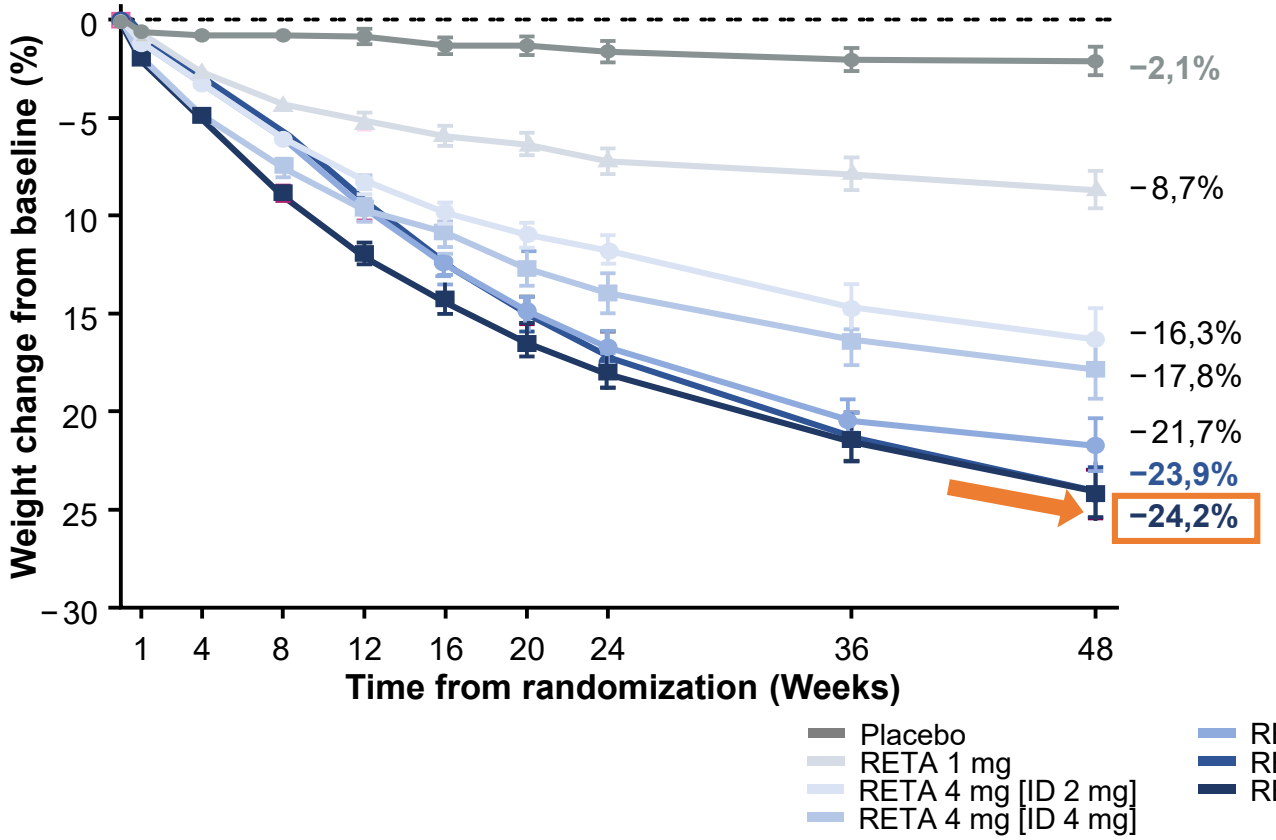
Jastreboff AM, et al. Presented at the American Diabetes Association 83rd Scientific Sessions – San Diego and Virtual, June 23-26, 2023. Symposium - Retatrutid (LY3437943), a Novel GIP/GLP-1/Glucagon Receptor Triagonist—Obesity, NAFLD, and T2D Phase 2 Trial Results.

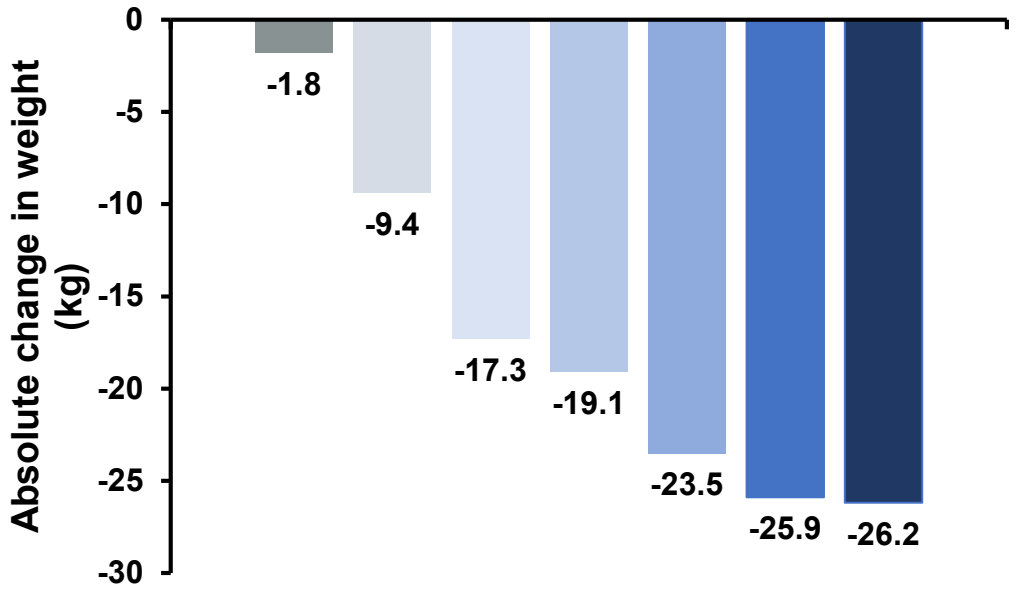
Retatrutide

Weight Reduction over 48 weeks - Key Secondary Outcome

Relative weight change at week 48



Absolute change in weight (kg) at 48 weeks



- Baseline weight: 107 kg

Average weight reduction of 24.2% at 48 weeks of treatment with Retatrutide (12 mg)

Average weight reduction of 26 kg at 48 weeks

RETA, Retatrutid.

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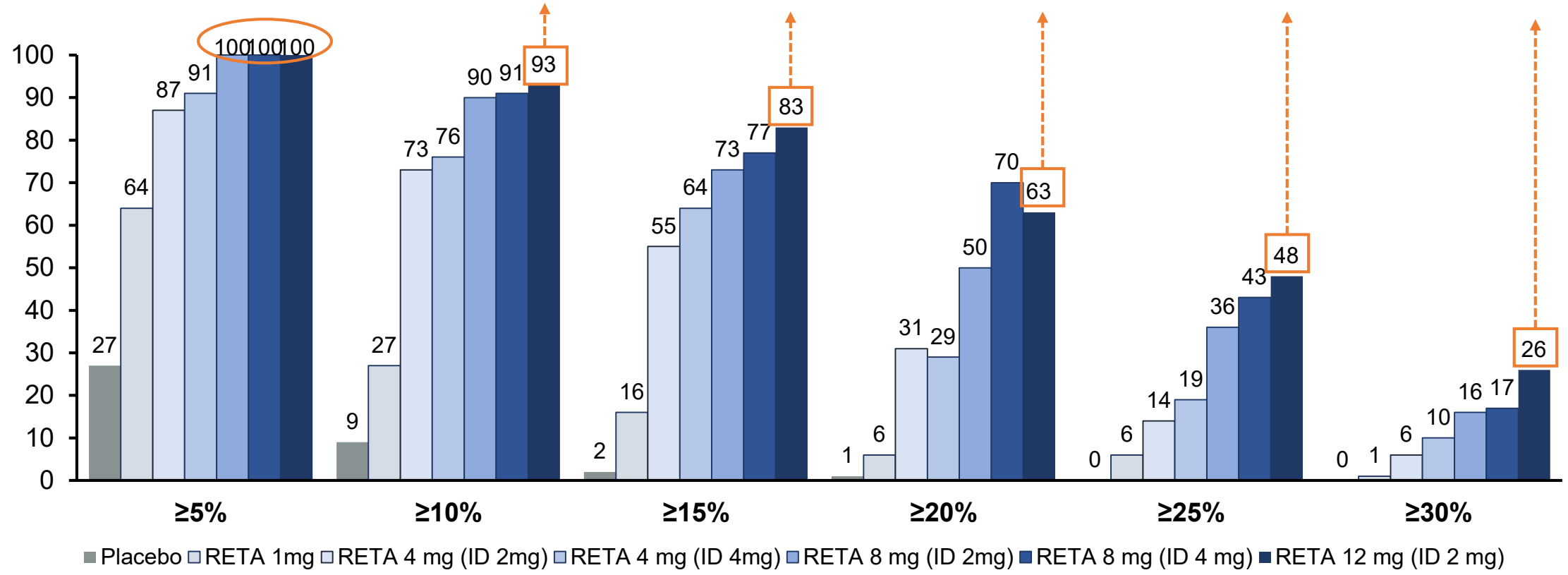
Jastreboff AM, et al. Präsentiert auf dem American Diabetes Association 83rd Scientific Sessions – San Diego and Virtual, June 23-26, 2023. Symposium - Retatrutid (LY3437943), a Novel GIP/GLP-1/Glucagon Receptor Triagonist—Obesity, NAFLD, and T2D Phase 2 Trial Results.

Retatrutide

Percentage of Participants reaching weight reduction thresholds at 48 weeks

12 mg Dose	≥5%	≥10%	≥15%	≥20%	≥25%	≥30%
Percentage of participants	100%	9/10	8/10	Nearly 2/3	Nearly 50%	1/4



RETA, Retatrutid.

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Retatrutide

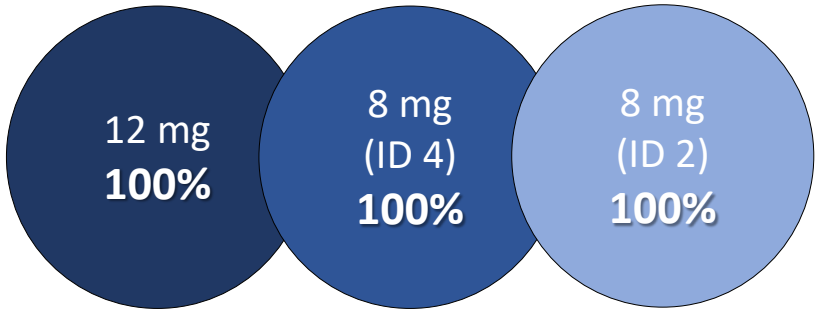
Summary

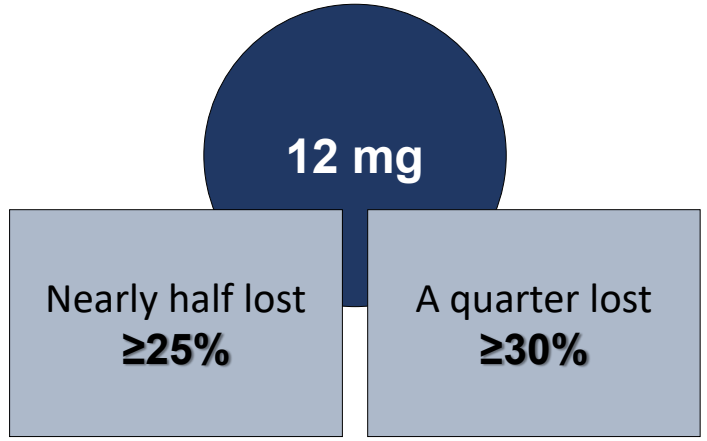
48 Weeks
(11 Months)

12 mg
-24,2%

Average absolute weight reduction
26 kg

Weight-Reduction Threshold
≥5%





- **Discontinuation of Treatment due to adverse events occurred in 6-16% of the participants who received Retatrutide**
- **TRIUMPH Phase 3 Trials: Efficacy and Safety of Retratutide for Obesity and Obesity-related Complications**

ID, Initialdosis.

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The Swedish Obese Subjects (SOS) Study

Background

Prospective intervention trial, which examines the effect of intentional weight loss on mortality and morbidity associated with obesity. Inclusion of > 4000 individuals 1985-2001, follow-up 35 years, matched control group

Bariatric Surgery increases life expectancy

- SOS: 3 years, after follow-up of > 20 years

Aims of the study

- To determine life expectancy, mortality and causes of death after bariatric surgery in relation to baseline T2D status

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Andersson-Assarsson J et al. Presented at the American Diabetes Association 83rd Scientific Sessions – San Diego and Virtual, June 23-26, 2023.
Oral Presentation Bariatric Surgery and Beyond – The Benefits of Battling Obesity

The Swedish Obese Subjects (SOS) Study

Background

Prospective intervention trial, which examines the effect of intentional weight loss on mortality and morbidity associated with obesity. Inclusion of > 4000 indivudials 1985-2001, follow-up 35 years, matched control group

Treatments:

- Surgery group: Banding (19%), Vertical banding gastroplasty (68%), gastric bypass (13%)
- Control group: Exercise, Diet, Weight loss drugs, nothing at all

Included SOS participants (n=4032)

- T2D: surgery n=392, control n=305
- Non-T2D: surgery n= 1609, control n=1726

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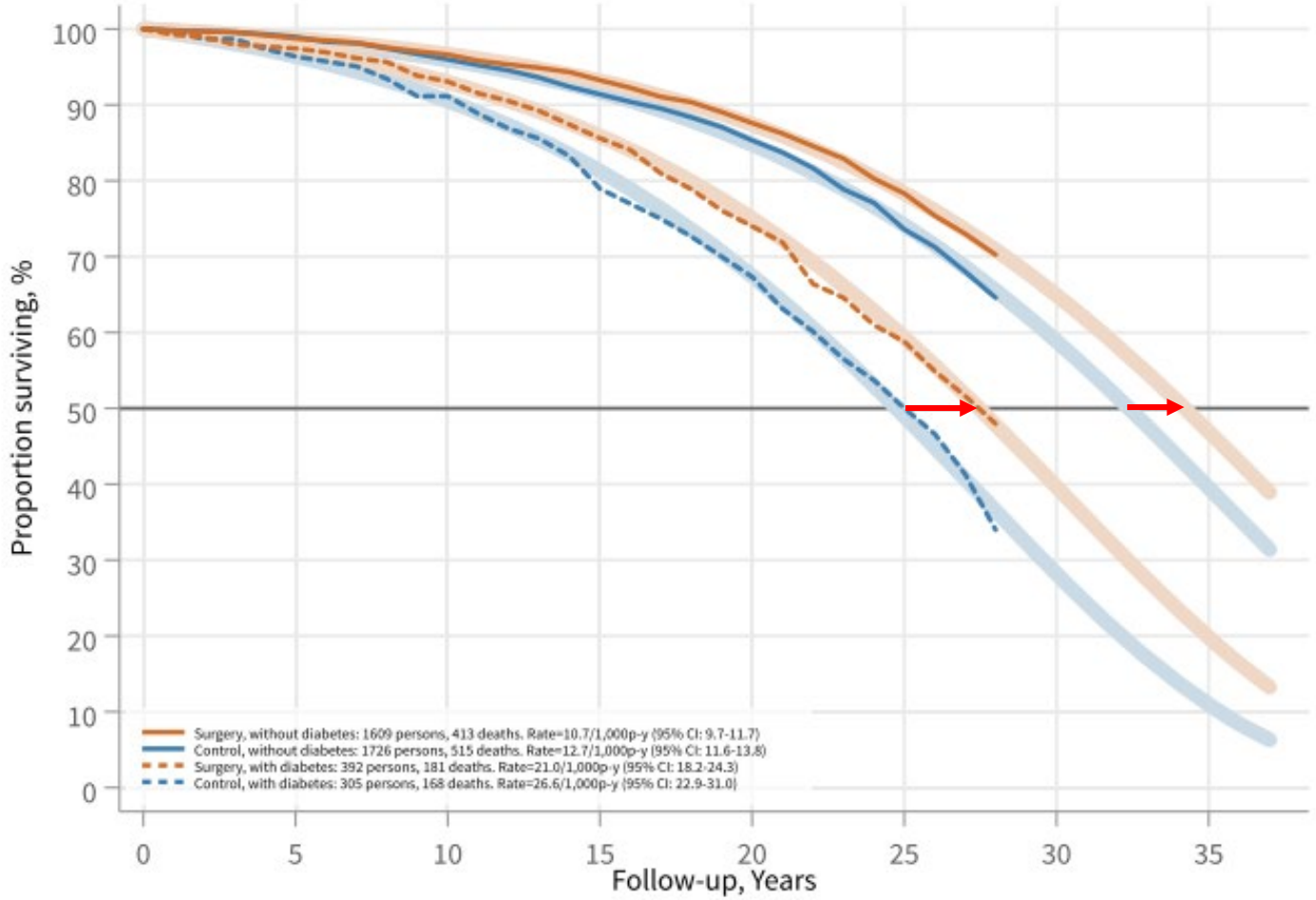
Oral Presentation Bariatric Surgery and Beyond – The Benefits of Battling Obesity

The Swedish Obese Subjects (SOS) Study

Results - Life expectancy



Non-T2DM (solid lines):

- Adj*: 1.6 years (0.5-2.7)

T2D (dashed lines):

- Adj*: 2.1 years (0.2-0.4)

*Adjusted to sex, age, BMI and smoking at baseline, year of inclusion

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The Swedish Obese Subject (SOS) Study

Results and Conclusion

→ Bariatric surgery is associated with similar increased life expectancy and reduction in overall mortality, regardless of baseline diabetes status

T2D and non-T2D, respectively:

- 2.1 and 1.6 years longer life expectancy
- 23% and 18% reduced overall mortality

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Semaglutide in postbariatric patients

Background

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Semaglutide in postbariatric patients

Background

Aim of the Study

- To assess the efficacy of Semaglutide in patients without T2DM but weight regain or insufficient weight loss after bariatric surgery over a 12 months period in a retrospective setting

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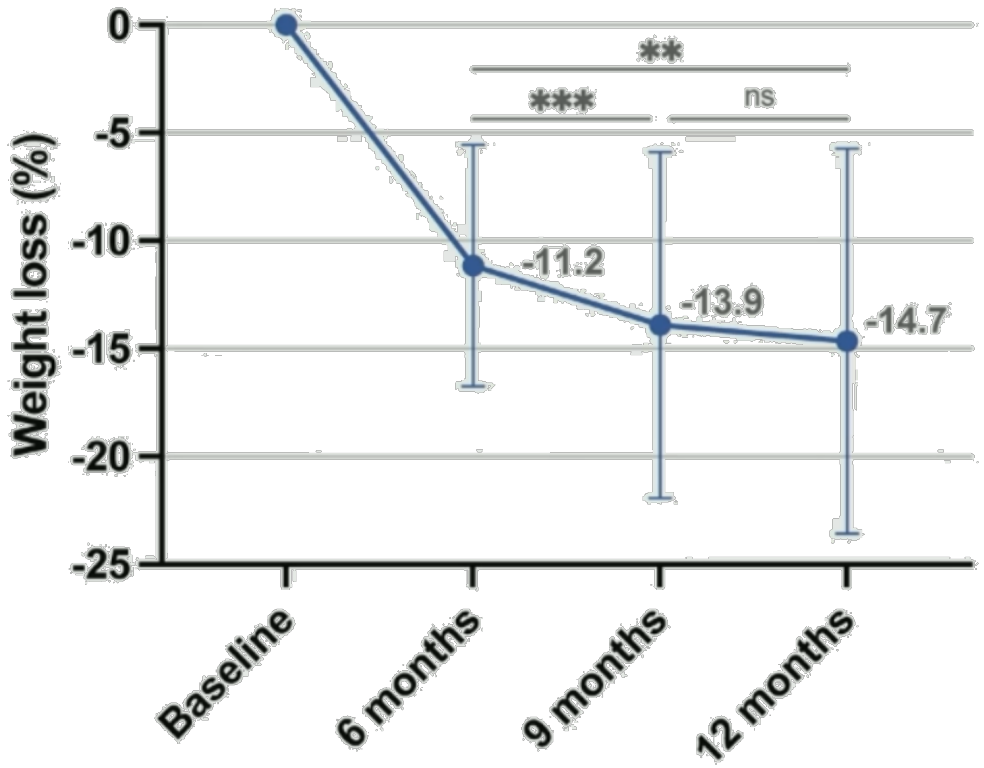
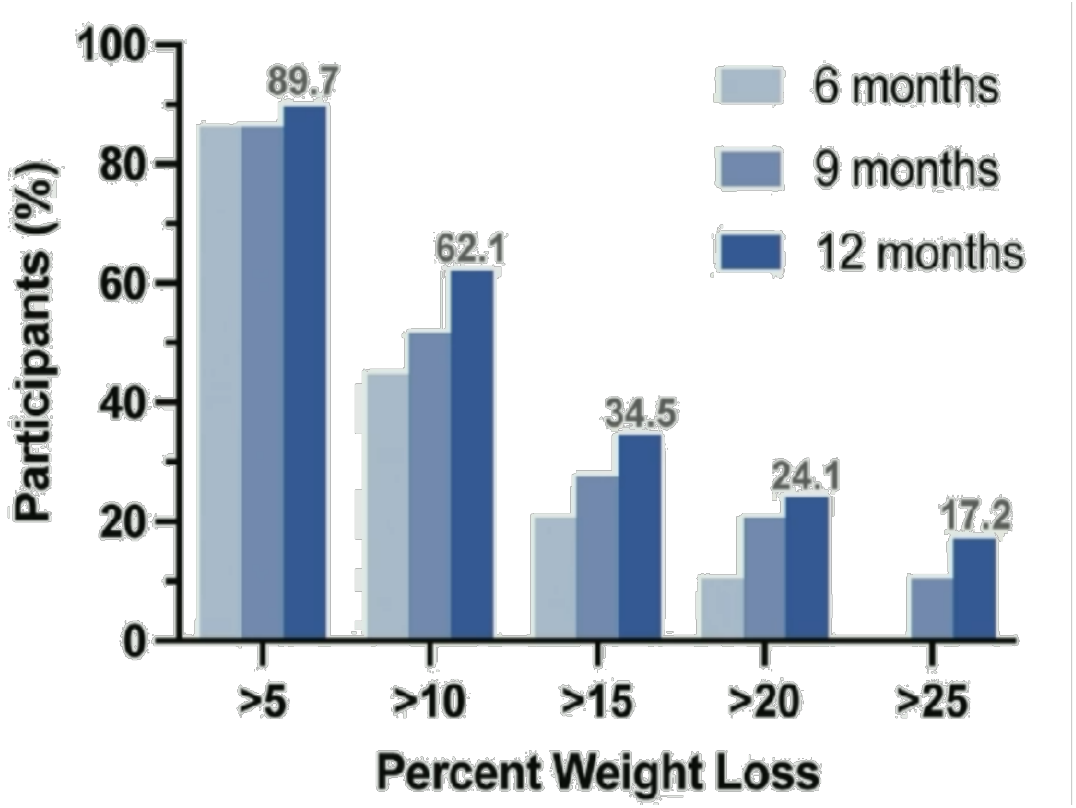
Semaglutide in postbariatric patients

Results





Body weight prior to therapy 110.8 kg

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Semaglutide in postbariatric patients

Summary and Conclusion

- Adjunct pharmacotherapy is an efficacious concept to treat postbariatric treatment failure
- Treatment with Semaglutide QW is of sustained benefit up to 12 months following BS
- Longer RCTs are needed to validate these preliminary data to determine if GLP-1 based pharmacotherapies including GLP-1 RA may close the gap between lifestyle intervention and revision surgery

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Agenda:

GLP1-RA
- **Orale Semaglutide**
- **Orforglipron**

Dual Agonists
- **Survodutide**

Triple Agonist
- **Retatrutide**

Bariatric Surgery
- **SOS Study**
- **Semaglutide in postbariatric patients**

Nutrition
- **SWAP MEAT**

SWAP-MEAT

Study with Appetizing Plantfood-Meat Eating Alternative

Hypothesis

In a crossover study, **if** generally healthy adults consume ≥2 servings/day of animal meat vs plant-based alternative meat (PBAM) for 8 weeks each, **then** selected health outcomes will be better in the PBAM phase

PBAM, plant-based meat alternatives

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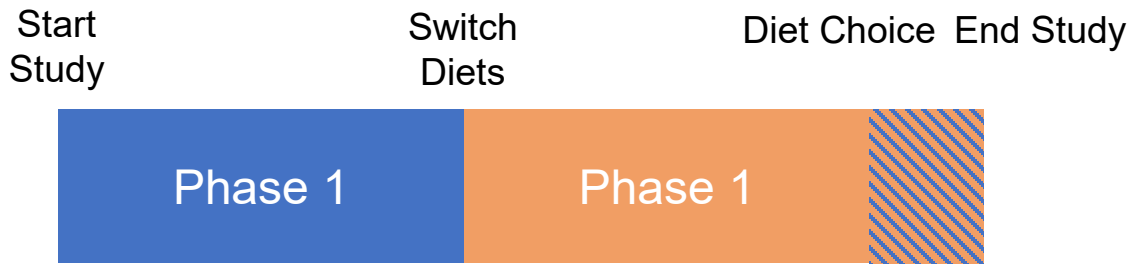
SWAP-MEAT

Studydesgin

- Randomized Crossover-Design
- Healthy adults (>18 years, N=36)
- 8 weeks per phase
- At least 2 servings/day
  - Plant-Based Alternative Meat
  - Animal Meat

Schedule



	Weeks									
	0	2	4	6	8	10	12	14	16	18
Blood Draw (CTRU)	x	x	x		x	x	x		x	
Sample Drop off (SPRC)					x				x	
Food pick up (SPRC)	x	x	x	x						
At-Home Data Collection										
Stoolcollection	x	x	x		x	x	x		x	
Diet Assessment	x	x	x	x	x	x	x	x	x	x
Study Questionnaires	x	x	x	x	x	x	x	x	x	x

CTRU, Klinische Studien-Forschungseinheit; SPRC, Stanford Prevention Research Center.

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SWAP-MEAT

Two Phases and Adherence

Plant Phase

„Plant Protein“

Meat Phase

„Mindful Meat“

- Beyond Meat's mission is to create The Future of Protein - delicious plant-based burgers, sausages, beef crumbles, strips and more - made directly from plants.
- "Good Eggs" was used, a delivery service for "absurdly fresh" food that supports environmental sustainability and the local food economy.

Adherence
Servings/day

Plant Phase	Meat Phase	
2,5 □ 0,6	2,6 □ 0,7	p=0,8

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SWAP-MEAT

Nutrient Profiles of Plant and Animal Meat Products

Plant Products								
Product	**Serving Size (g)**	**Kcal**	**Carbohydrates (g)**	**Protein (g)**	**Total Fat (g)**	**Saturated Fat (g)**	**Fiber (g)**	**Sodium (mg)**
Burger	113	270	3	20	20	5	2	380
Beef Crumbles	55	90	3	12	3	<1	1	240
Breakfast Sausage	65	170	2	13	13	5	1	330
Hot Italien Sausage	76	190	5	16	12	5	3	500
Brat Sausage	76	190	5	16	12	5	3	500
Grilled Chicken Stripes	85	130	6	22	2	0	3	360
Lightly seasoned Chicken Stripes	85	130	5	20	3,5	0	3	340
Animal Products								
Product	**Serving Size (g)**	**Kcal**	**Carbohydrates (g)**	**Protein (g)**	**Total Fat (g)**	**Saturated Fat (g)**	**Fiber (g)**	**Sodium (mg)**
Burger	100	293	0	16	25	9	0	67
Beef Crumbles	100	293	0	16	25	9	0	67
Breakfast Sausage (Pork)	47	110	0	7	9	3	0	320
Hot Italien Sausage	71	170	1	10	14	5	0	480
Brat Sausage (Pork)	57	230	4	8	21	9	0	400
Chickenbreast	113	140	0	26	3	0,5	0	1402

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In the animal phase, some substitutions (no more than 10% of products) were necessary due to limited availability, however neither quantity, quality nor meat were changed.

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SWAP-MEAT

Outcome	Plant Mean(SEM)	Animal Mean(SEM)	Plant Animal Difference Mean (95%-KI)	P-Value
Primary				
TMAO (µM)	2,7 (0,3)	4,7 (0,9)	-2,0 (-3,6; -0,3)	0,012
Secondary				
IGF-1 (ng/mL)	147,6 (7,5)	152,3 (8,3)	-4,7 (-13,9; 4,5)	0,30
Weight (kg)	78,7 (3)	79,6 (3)	-1,0 (-1,5; -0.5)	<0,001
Insulin (µIU/mL)	9,2 (1,1)	8,8 (0,9)	0,4 (-0,7; 1,5)	0,38
Glucose (mg/dL)	94,9 (1,6)	94,5 (1,4)	0,5 (-1,8; 2,8)	0,65
Lipides				
LDL-C	109,9 (4,5)	120,7 (4,5)	-10,8 (-17,3; -4,3)	0,002
HDL-C	62,5 (2,2)	61,8 (2,5)	0,7 (-2,4; 3,8)	0,66
Triglycerides	99,7 (7,3)	100,2 (7,0)	-0,6 (-10,5; 9,2)	0,89
Blood Pressure (mmHg)				
Systolic	114,5 (2,1)	113,1 (1,9)	1,2 (-1,4; 4,1)	0,31
Diastolisch	70,0 (1,4)	68,8 (1,2)	1,1 (-0,8; 3,2)	0,20

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TMAO, Trimethylamin-N-Oxid.

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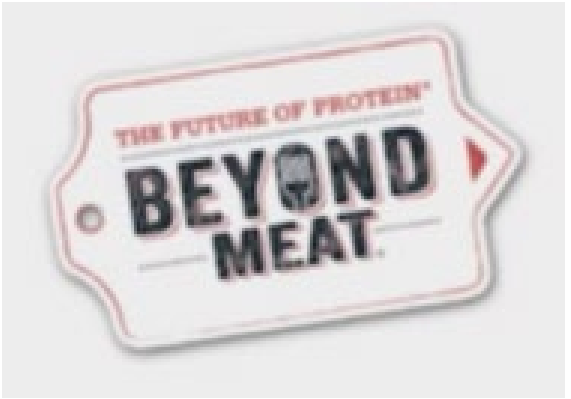
SWAP-MEAT

Conclusion

Animal vs Plant



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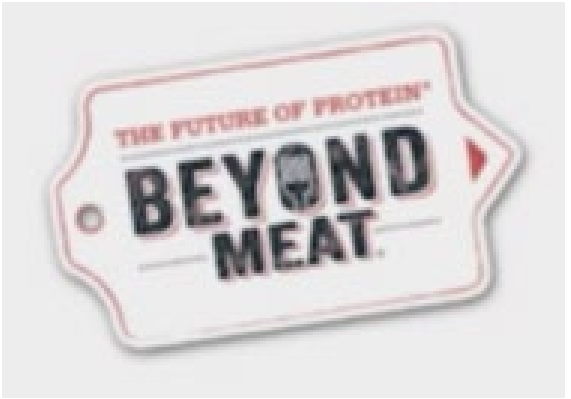
SWAP-MEAT

Conclusion

Plant vs Plant



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Obesity and Metabolism

22nd PostADA/PostENDO Symposium

31.08.2023

Thank you for your attention