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Retatrutide
nuovo GIP/GLP-1/Glucagone recettore triagonista: risultati di efficacia e sicurezza in trial di fase 2

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Dichiarazione Conflitto d'Interessi

La sottoscritta Dott.ssa Cristina Bianchi

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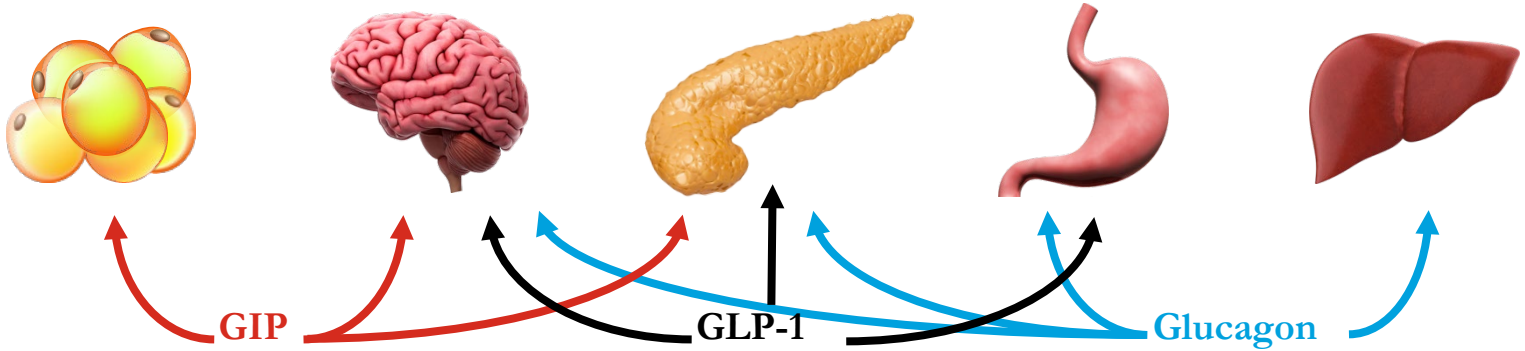
- Novonordisk
- Lilly
- MSD

Cristina Bianchi, MD PhD

Retatrutide: Triple GIP/GLP-1/Glucagon Receptor Agonist



Adipose:
- ↑ Insulin sensitivity
- Improvements in lipid metabolism

CNS:
- Appetite
- Decrease in nausea

Islets:
- ↑ Insulin secretion
- ↑ Glucagon secretion

CNS:
- Appetite

Islets:
- ↑ Insulin secretion
- ↓ Glucagon secretion

Stomach:
- Delayed gastric emptying

CNS:
- ↑ Energy expenditure
- Appetite regulation

Islets:
- ↑ Insulin secretion

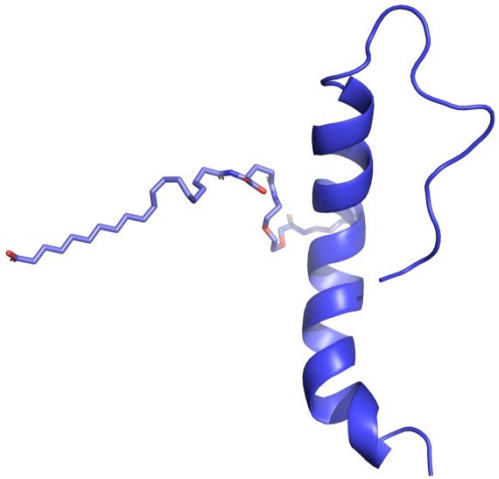
Stomach:
- Delayed gastric emptying

Liver:
- ↑ Glycogenolysis
- ↑ Gluconeogenesis
- Improvements in lipid metabolism

Hædersdal S. Nat Rev Endocrinol 2023;19(6):321-335. - Hammoud R. Nat Rev Endocrinol 2023;19(4):201-216.

Retatrutide:

GIP/GLP-1/Glucagon (GGG) Tri-Agonist



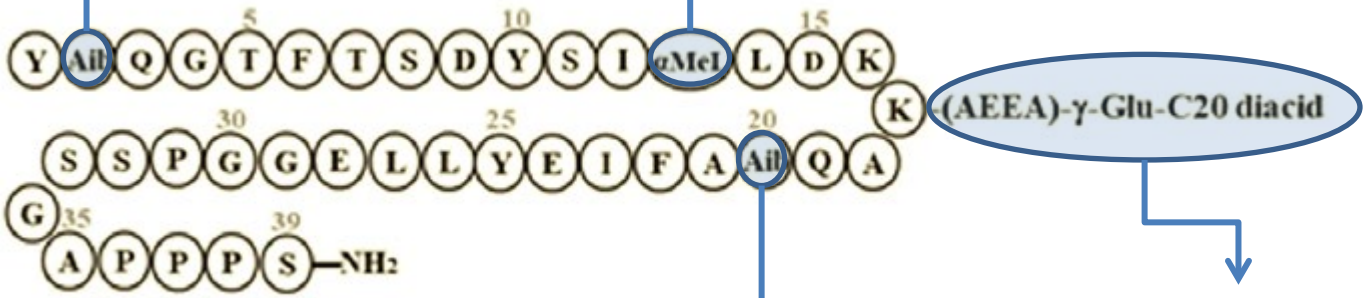
Retatrutide is a novel single molecule engineered from a glucose-dependent insulinotropic polypeptide (GIP) backbone with triple agonist activity on GIP, glucagon-like peptide-1 (GLP-1), and glucagon receptors

Coskun T. Cell Metabolism 2022; 34: 1234-1247

Retatrutide: structure

Aib2 (α-amino isobutyric acid) provides stability against DPP4 cleavage

aMeL13 (α -methyl-L-leucine) contributes to optimal glucagon and GIP activity

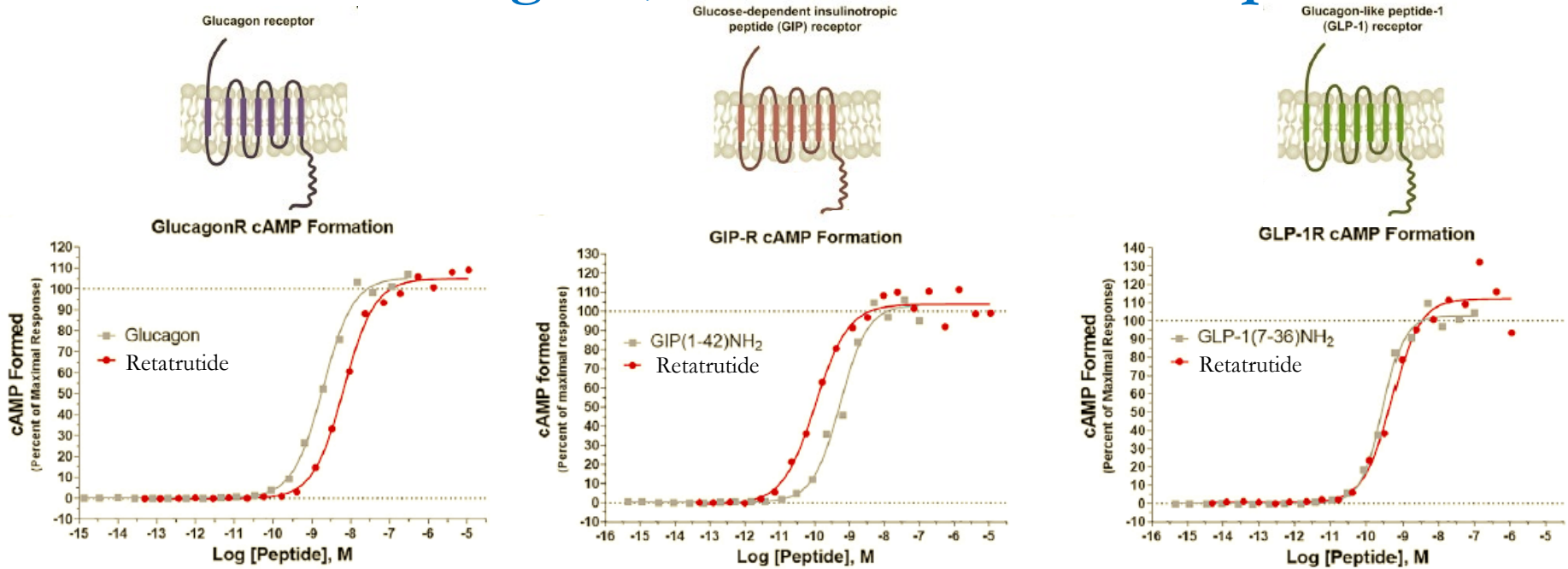


Aib20 contributes to optimal GIP activity, PK profile, and developability.

C20 fatty diacid moiety, linked at the position 17 lysine residue, enable albumin binding as a pharmacokinetic half-life extension strategy

Coskun T. Cell Metabolism 2022; 34: 1234-1247

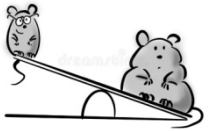
Retatrutide activity
at the Glucagone, GIP and GLP-1 Receptors



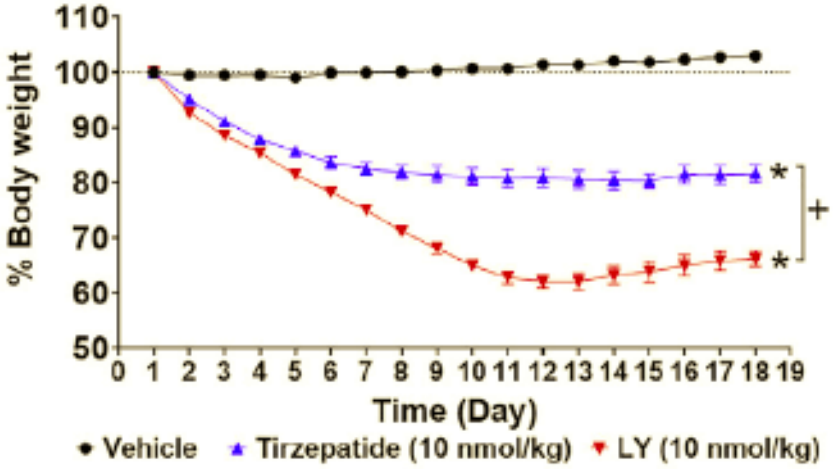
- GIP receptor activity is 9 times more potent compared with the native GIP ligand
- GLP-1 and glucagon receptor activities are balanced and are less potent compared with their native ligands

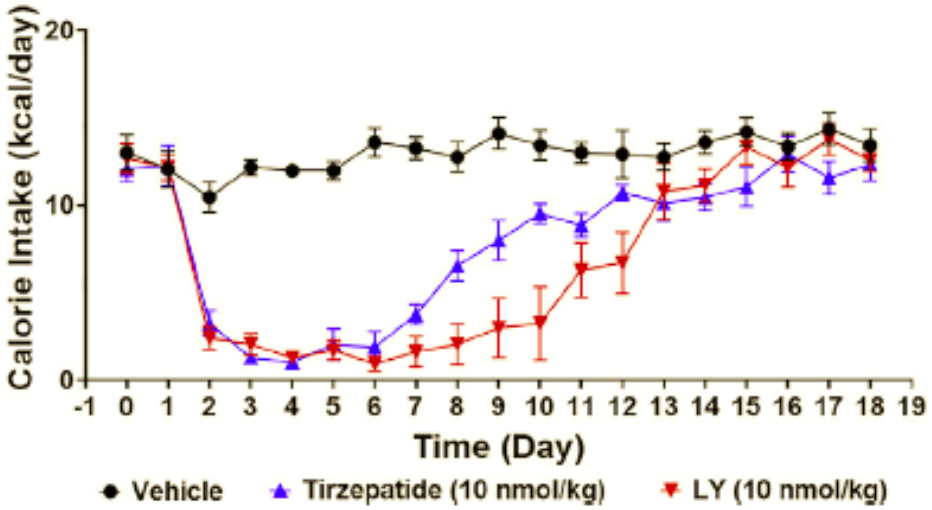
Coskun T. Cell Metabolism 2022; 34: 1234-1247

Retatrutide: caloric intake in animal model



Obese mice (DIO) treated once daily with ascending dose of retatrutide





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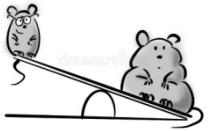
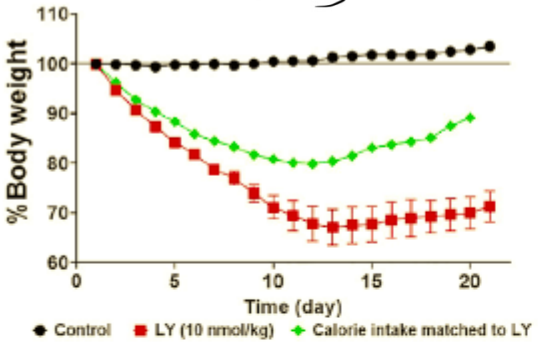
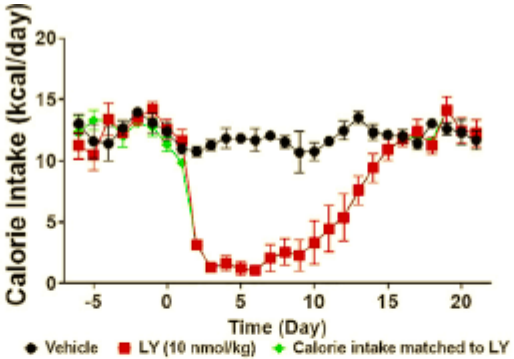
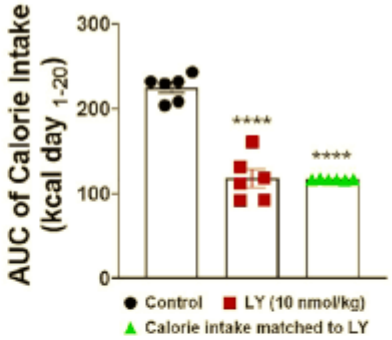
Retatrutide: energy balance in animal model

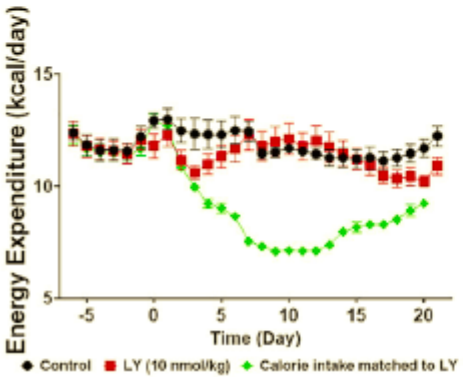


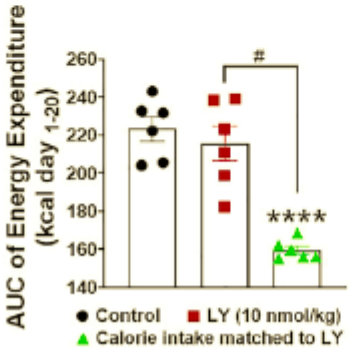
Obese mice (DIO) treated once daily with ascending dose of retatrutide

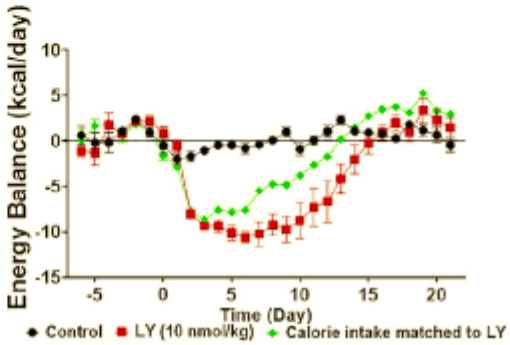


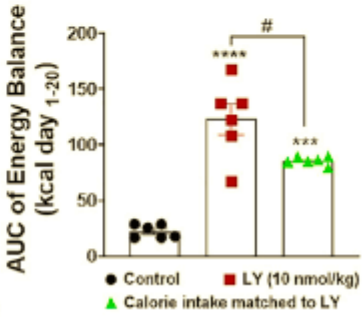










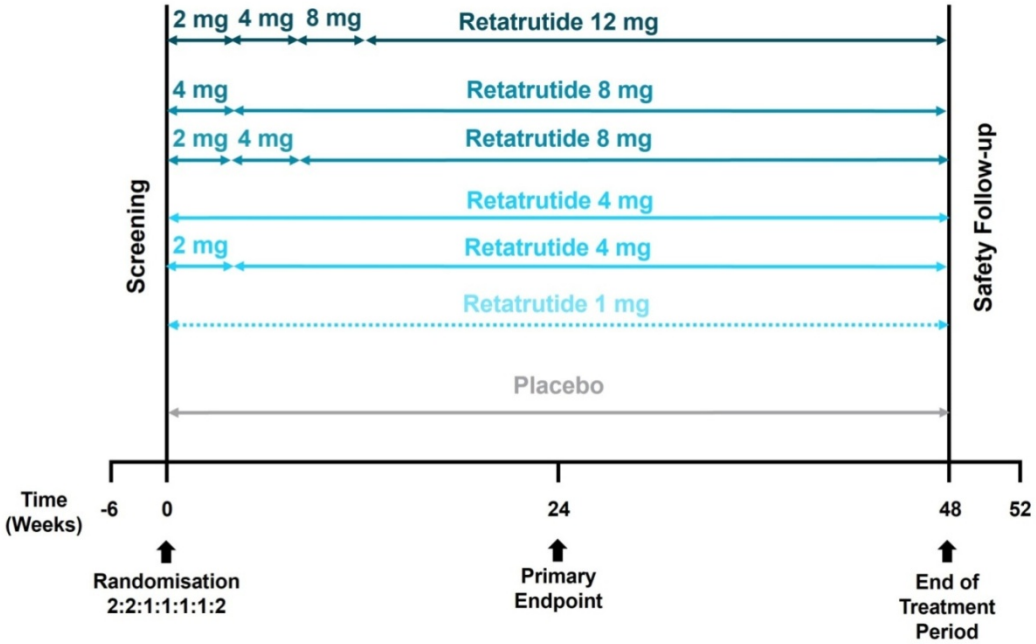


Coskun T. Cell Metabolism 2022; 34: 1234-1247

Retatrutide in obesity: study design

- **Randomised, double-blind, Phase 2 study of weekly retatrutide vs. Placebo**

- **Key Inclusion Criteria**
  - Age 18-75 years
  - BMI ≥30 kg/m^2 or ≥27 kg/m^2 with ≥1 of: hypertension, dyslipidemia or cardiovascular disease
- **Key Exclusion Criteria**
  - Type 1 or type 2 diabetes, or laboratory evidence suggesting diabetes during screening
  - Prior or planned surgical treatment for obesity
  - Use of medications intended to promote weigh loss
- **Primary Endpoint**
  - Percent change in weight from baseline at **24 weeks**



Jastreboff AM. N Engl J Med 2023;389:514-526

Retatrutide in obesity: study population

Parameter	Total (N=338)
Age, years	48.2
Male, n (%)	175 (51.8)
Race, n (%)	
White	298 (88.2)
Body weight, kg	107.7
BMI, kg/m^2	37.3
BMI category, n (%)	
27 to <30	14 (4.1)
≥30 to <35	130 (38.5)
≥35 to <40	92 (27.2)
≥40	102 (30.2)

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Retatrutide in obesity: study population

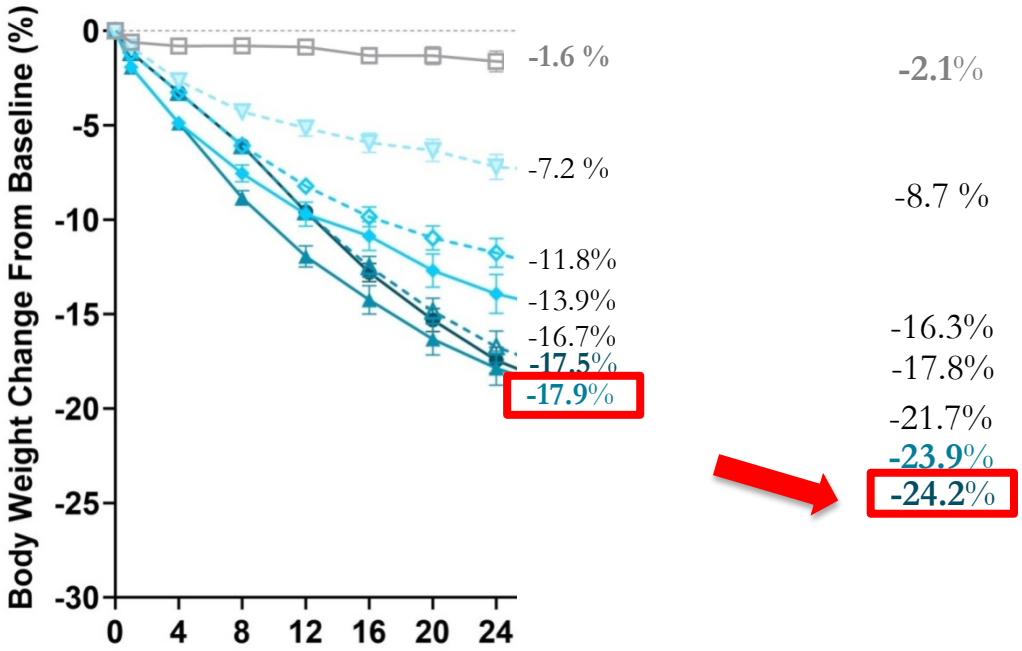
Parameter	Total (N=338)
Prediabetes, n (%)	123 (36.4)
HbA1c, mmol/mol	36.9
Fasting glucose, mg/dL	93.8
Fasting insulin,mU/L	15.3
Hypertension, n (%)	144 (42.6)
Systolic BP, mm Hg	124.6
Diastolic BP, mm Hg	80.8
Pulse, bpm	71.0

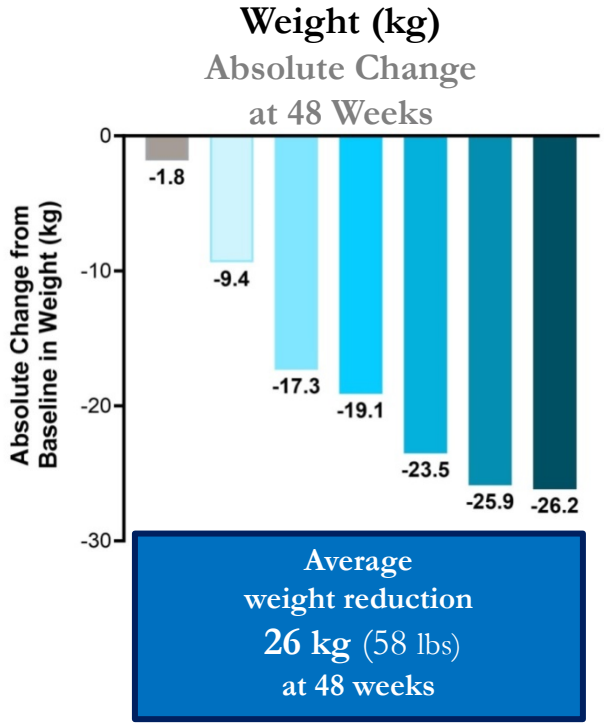
Parameter	Total (N=338)
Dyslipidemia, n (%)	110 (32.5)
Total cholesterol, mg/dL	188.3 (20.3)
HDL-cholesterol, mg/dL	46.2 (25.5)
LDL-cholesterol, mg/dL	111.9 (31.4)
Triglycerides, mg/dL	125.0 (47.0)

No significant differences across treatment groups for all parameters except systolic BP

Jastreboff AM. N Engl J Med 2023;389:514-526

Retatrutide in obesity: body weight changes





Average baseline weight
107.7 kg (237.4 lbs)

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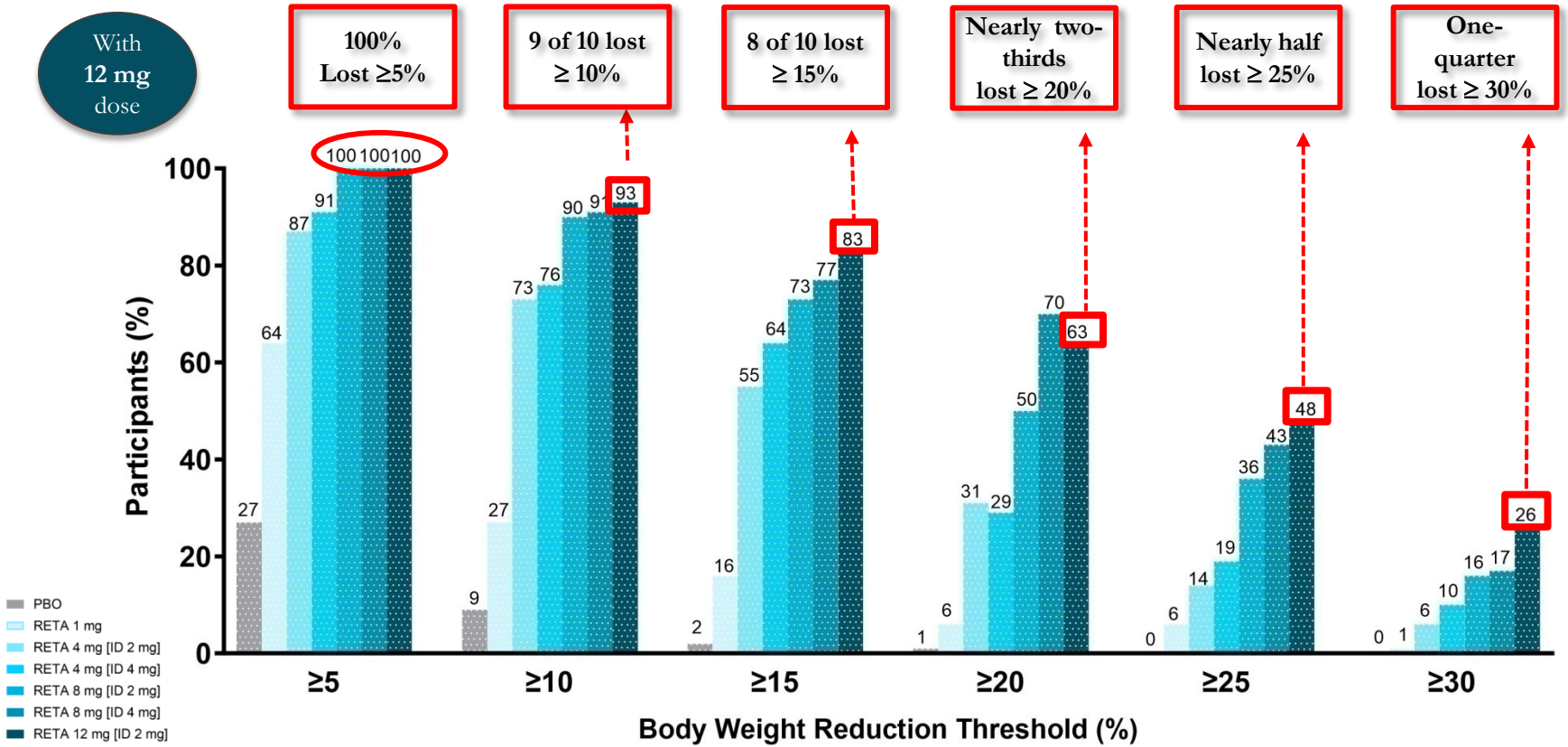
Retatrutide in obesity: target weight loss attainments



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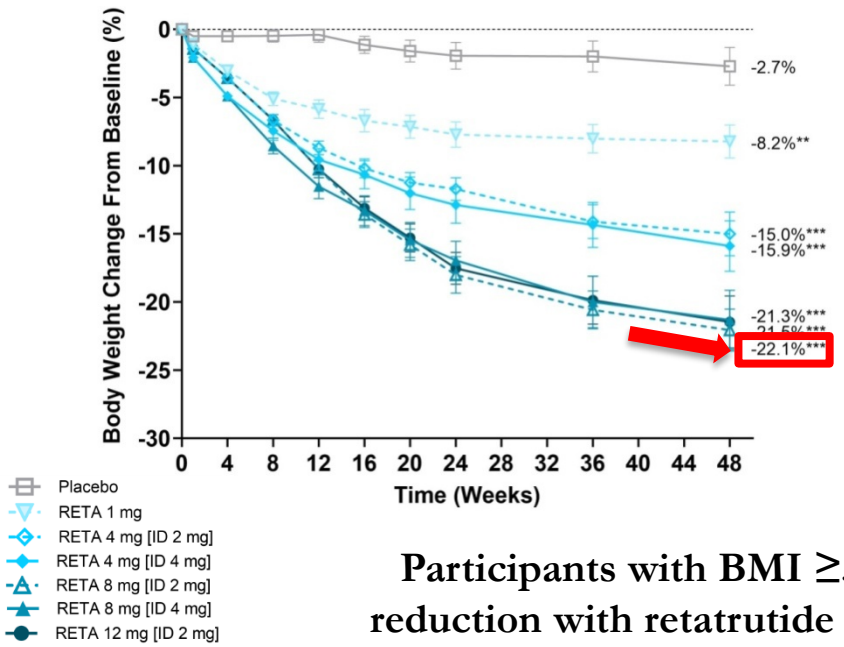
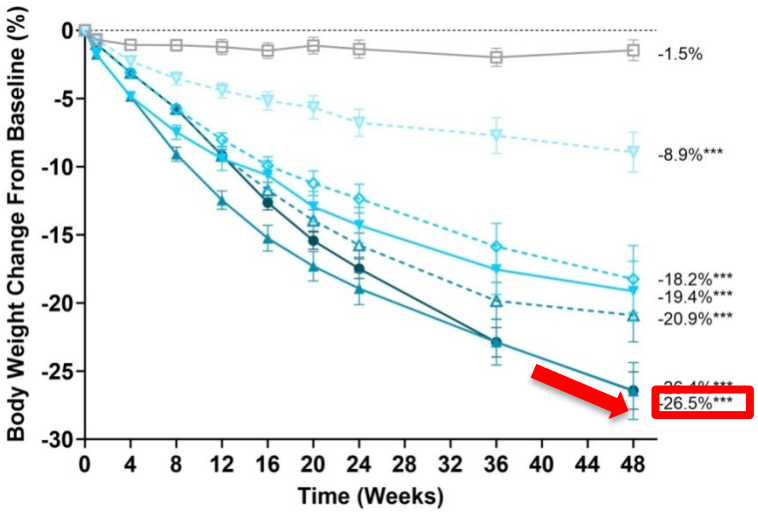
Retatrutide in obesity: weight reduction by baseline BMI

Baseline BMI <35 kg/m^2



Baseline BMI ≥35 kg/m^2



Participants with BMI ≥35 kg/m^2 had numerically greater mean percent reduction with retatrutide compared with participants with BMI <35 kg/m^2

**p<0.01; ***p<0.001 vs. PBO

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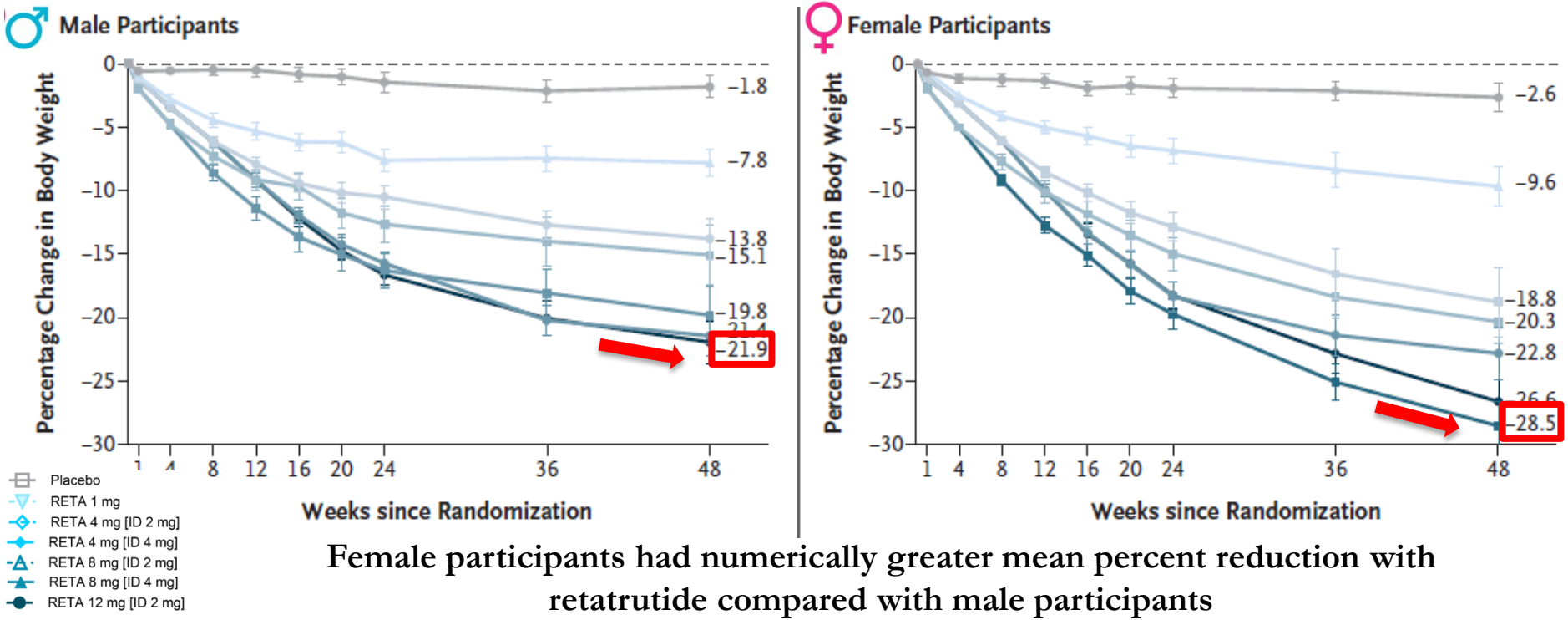
Retatrutide in obesity: weight reduction by gender



Female participants had numerically greater mean percent reduction with retatrutide compared with male participants

**p<0.01; ***p<0.001 vs. PBO

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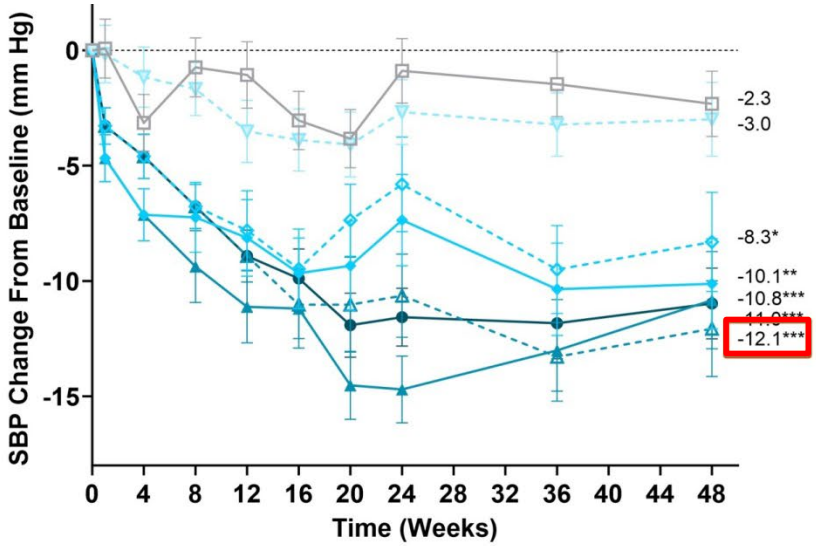
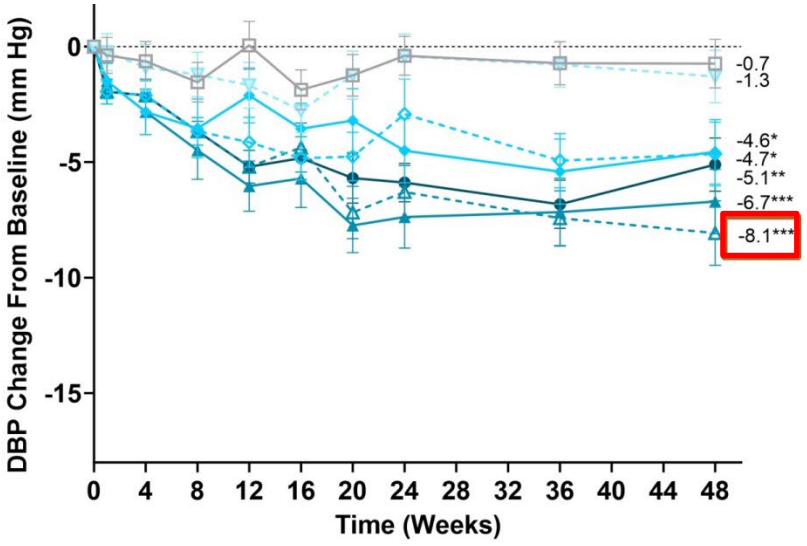
Retatrutide in obesity: blood pressure





Placebo
RETA 1 mg
RETA 4 mg [ID 2 mg]
RETA 4 mg [ID 4 mg]
RETA 8 mg [ID 2 mg]
RETA 8 mg [ID 4 mg]
RETA 12 mg [ID 2 mg]

Improvements in both systolic and diastolic blood pressure at 48 weeks

*p<0.05; **p<0.01; ***p<0.001 vs. PBO

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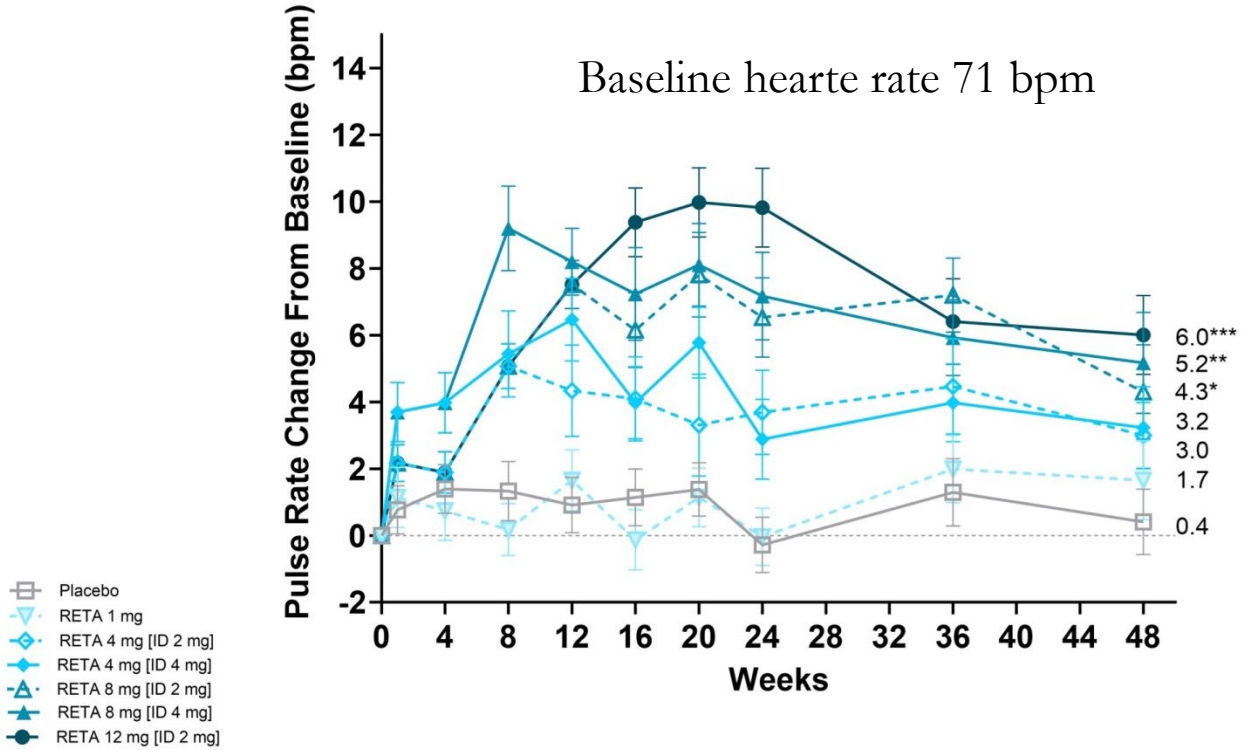
Retatrutide in obesity: heart rate



Dose-dependent increases in pulse rate, leaking at 24 weeks and declining thereafter

*p<0.05; **p<0.01; ***p<0.001 vs. PBO

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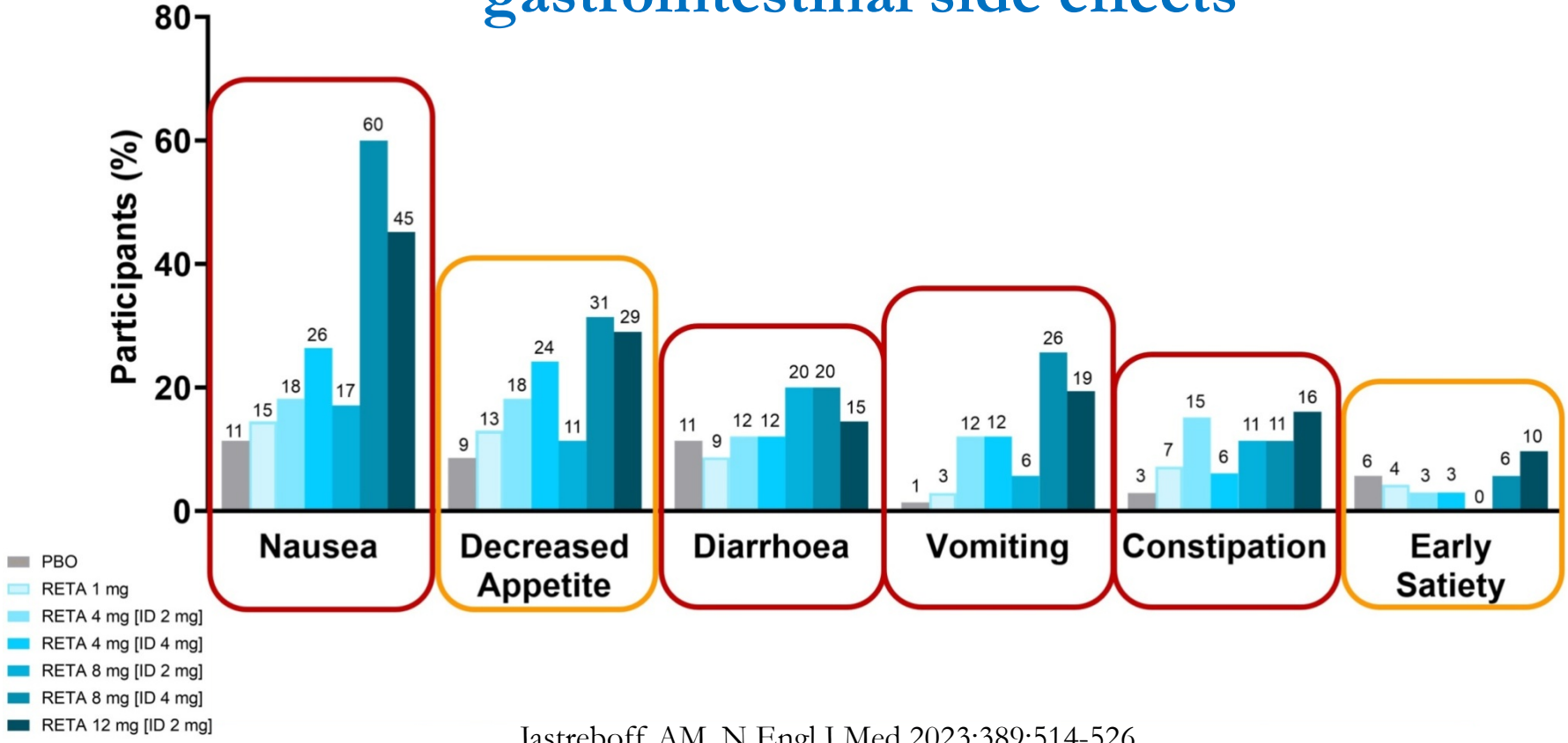
Retatrutide in obesity: gastrointestinal side effects



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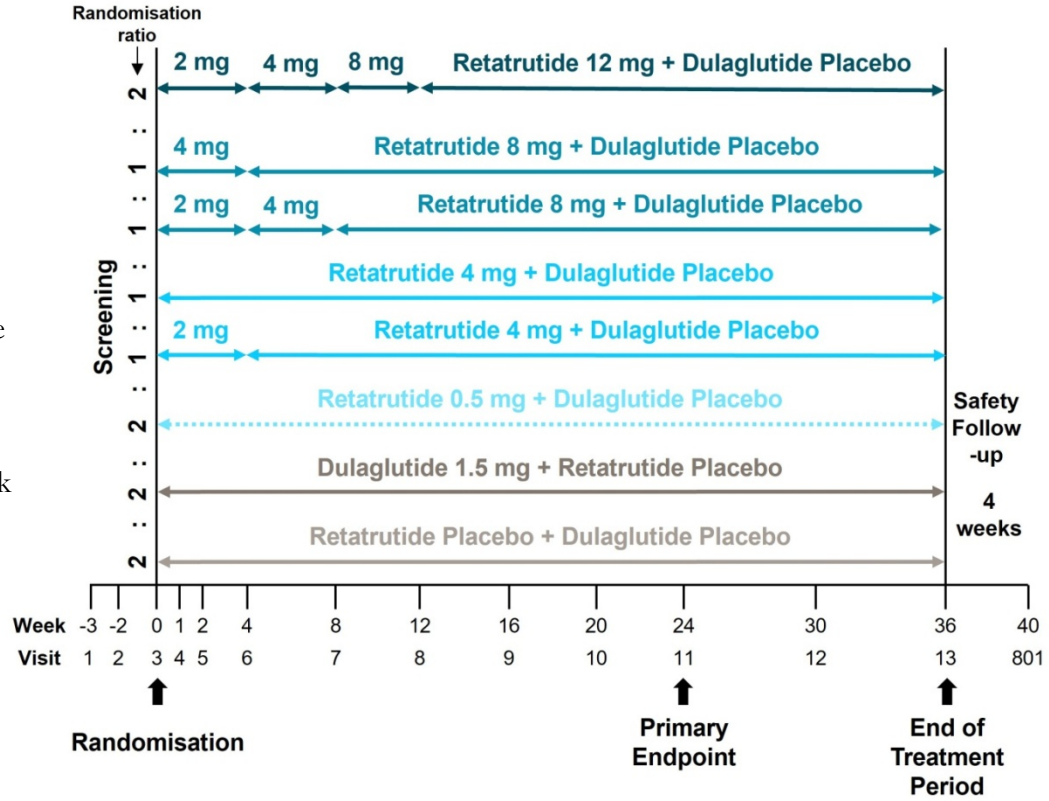
Retatrutide in type 2 diabetes: study design

Phase 2, randomised, double-blind, double-dummy, parallel, placebo- and active comparator–controlled study

- **Key Inclusion Criteria:**
  - Type 2 Diabetes
  - HbA1c ≥53 to ≤91 mmol/mol, treated with diet and exercise alone or with a stable dose of metformin
  - BMI 25-50 kg/m^2
- **Primary Objective:** Demonstrate superiority of retatrutide in change from baseline for HbA1c relative to placebo at Week 24
- **Secondary Objectives:** Compare retatrutide vs. placebo and vs. dulaglutide 1.5 mg for change from baseline to Week 24 and Week 36:
  - Change in HbA1c
  - Participants (%) reaching HbA1c <53 mmol/mol[b]
  - Change in fasting blood glucose
  - Change in body weight
  - Assessment of safety and tolerability
  - Pharmacokinetics



Rosenstock J. Lancet 2023; 402: 529–44

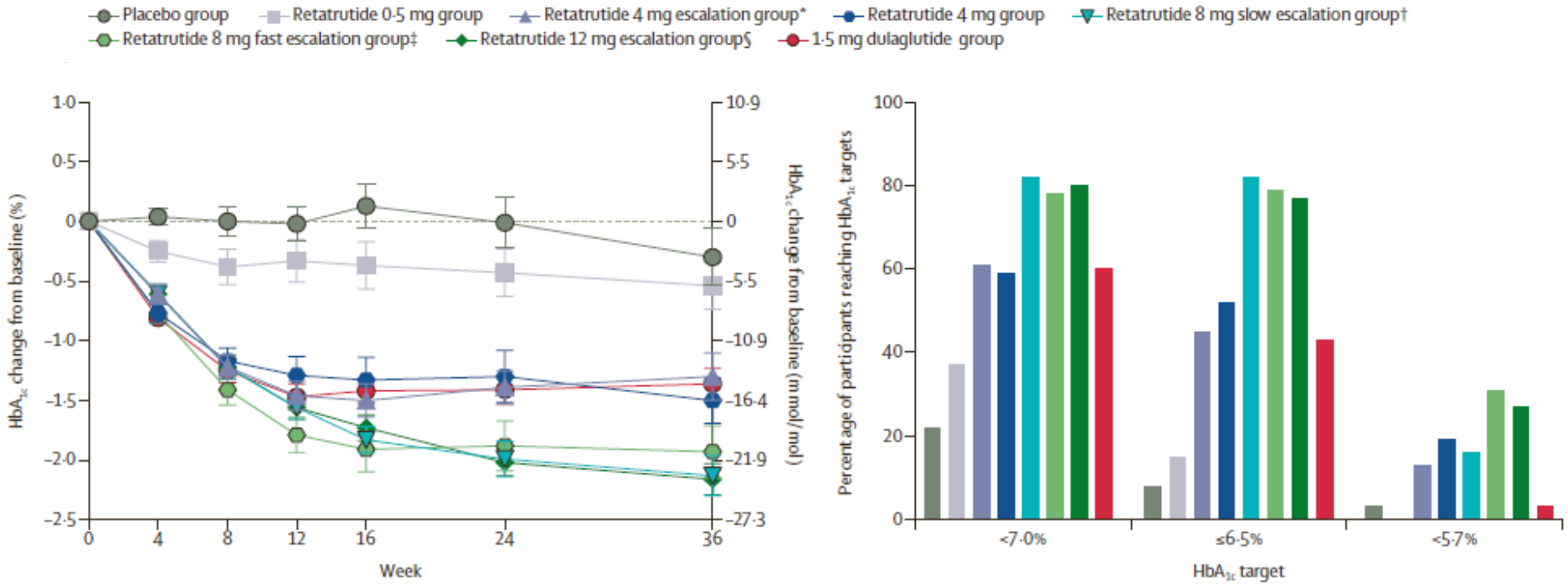
Retatrutide in type 2 diabetes: study population

Parameter (mean ± SD unless stated otherwise)	Total (N=281)
Age, years	56.2 ± 9.7
Female, n (%)	156 (56)
HbA1c	
%	8.3 ± 1.1
mmol/mol	67 ± 12
Fasting serum glucose, mmol/L	9.5 ± 3.0
Duration of diabetes, years	8.1 ± 7.0
Metformin use, n (%)	202 (72)
Body weight, kg	98.2 ± 21.1
BMI, kg/m^2	35.0 ± 6.3
Waist circumference, cm	111.8 ± 15.9
eGFR,[a] mL/min/1.73 m^2	91.2 ± 19.2

No significant differences across treatment groups

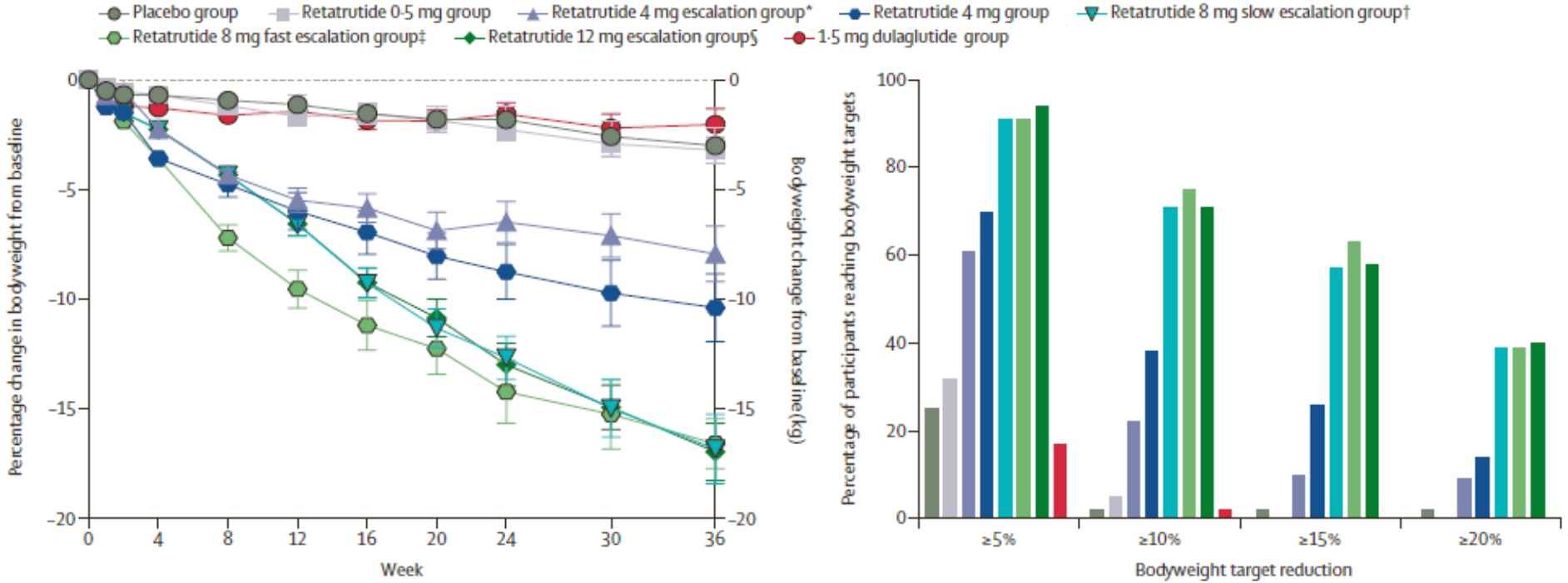
Rosenstock J. Lancet 2023; 402: 529–44

Retatrutide in type 2 diabetes: HbA1c changes



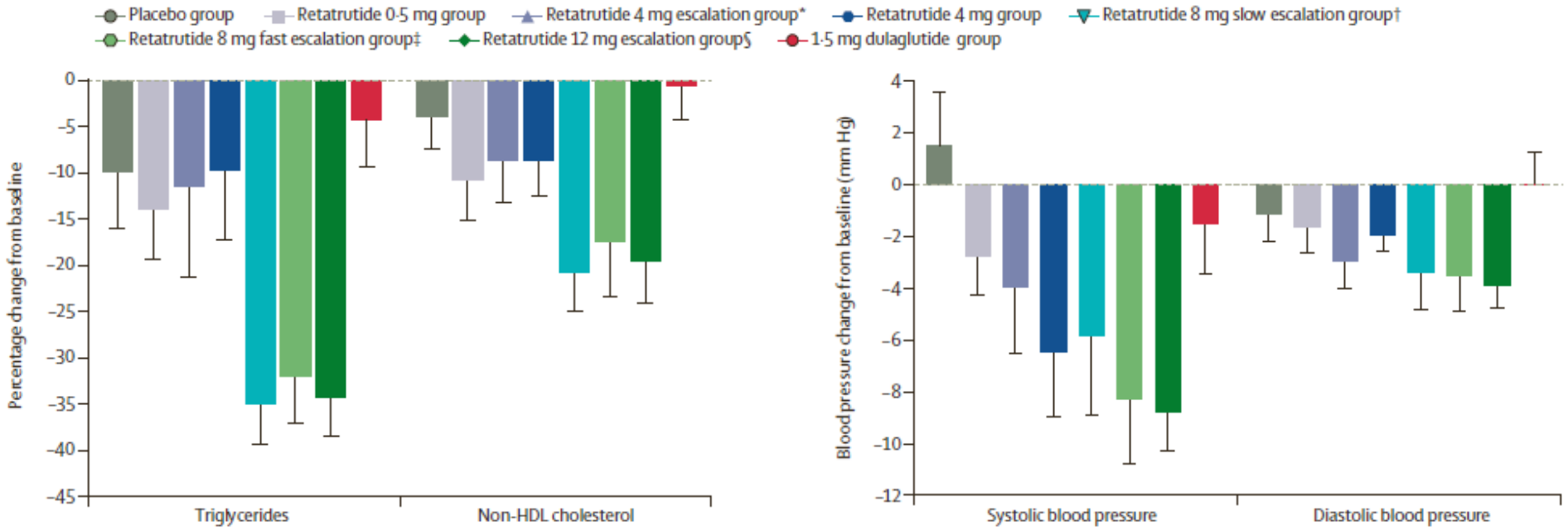
Rosenstock J. Lancet 2023; 402: 529–44

Retatrutide in type 2 diabetes: body weight changes



Rosenstock J. Lancet 2023; 402: 529–44

Retatrutide in type 2 diabetes: Cardiovascular risk factors changes



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Retatrutide in type 2 diabetes: side effects

	Placebo group (n=45)	Retatrutide 0·5 mg group (n=47)	Retatrutide 4 mg escalation group* (n=23)	Retatrutide 4 mg group (n=24)	Retatrutide 8 mg slow escalation group† (n=26)	Retatrutide 8 mg fast escalation group‡ (n=24)	Retatrutide 12 mg escalation group§ (n=46)	1·5 mg dulaglutide group (n=46)	Total (n=281)
Participants with ≥1 treatment-emergent adverse event	28 (62%)	26 (55%)	13 (57%)	19 (79%)	19 (73%)	17 (71%)	35 (76%)	31 (67%)	188 (67%)
Serious adverse events	3 (7%)	3 (6%)	1 (4%)	2 (8%)	2 (8%)	1 (4%)	2 (4%)	1 (2%)	15 (5%)
Death	0	0	0	0	0	0	0	0	0
Adverse events leading to discontinuation of study drug	2 (4%)	1 (2%)	0	1 (4%)	3 (12%)	4 (17%)	7 (15%)	1 (2%)	19 (7%)
Vomiting¶	0	0	0	0	1 (4%)	1 (4%)	1 (2%)	0	3 (1%)
Diarrhoea¶	0	0	0	1 (4%)	0	1 (4%)	0	0	2 (1%)
Acute pancreatitis¶	0	0	0	0	1 (4%)	0	0	0	1 (<1%)
Treatment-emergent adverse events occurring in ≥5% of total participants									
Nausea	2 (4%)	2 (4%)	2 (9%)	6 (25%)	7 (27%)	10 (42%)	9 (20%)	8 (17%)	46 (16%)
Diarrhoea	2 (4%)	1 (2%)	2 (9%)	6 (25%)	5 (19%)	7 (29%)	7 (15%)	4 (9%)	34 (12%)
Decreased appetite	0	2 (4%)	1 (4%)	5 (21%)	5 (19%)	4 (17%)	9 (20%)	6 (13%)	32 (11%)
Constipation	1 (2%)	3 (6%)	2 (9%)	4 (17%)	3 (12%)	2 (8%)	5 (11%)	3 (7%)	23 (8%)
COVID-19	3 (7%)	5 (11%)	3 (13%)	1 (4%)	1 (4%)	1 (4%)	2 (4%)	4 (9%)	20 (7%)
Vomiting	1 (2%)	1 (2%)	1 (4%)	0	2 (8%)	4 (17%)	5 (11%)	4 (9%)	18 (6%)
Headache	2 (4%)	2 (4%)	1 (4%)	1 (4%)	3 (12%)	1 (4%)	1 (2%)	3 (7%)	14 (5%)
Lipase increased	2 (4%)	1 (2%)	1 (4%)	2 (8%)	3 (12%)	1 (4%)	2 (4%)	1 (2%)	13 (5%)
Urinary tract infection	2 (4%)	0	0	1 (4%)	1 (4%)	3 (13%)	5 (11%)	1 (2%)	13 (5%)

Rosenstock J. Lancet 2023; 402: 529–44

Retatrutide: conclusions

- Retatrutide is a novel single molecule engineered from a GIP backbone with triple agonist activity on GIP, GLP-1, and glucagon receptors.
- In Phase 2 studies in people with obesity, once-weekly retatrutide provided substantial weight reduction with tolerability similar to other GLP-1 and GLP-1/GIP treatments.
- The efficacy of retatrutide appears to be greater in individuals with more severe obesity.
- In people with type 2 diabetes, retatrutide demonstrated clinically meaningful improvements in glycaemic control and clinically meaningful body weight loss vs. placebo and dulaglutide 1.5 mg, with a safety profile consistent with GLP-1 RA and GIP/GLP-1 RA classes.

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