Emerging Pharmacological Therapie of Obesity Management

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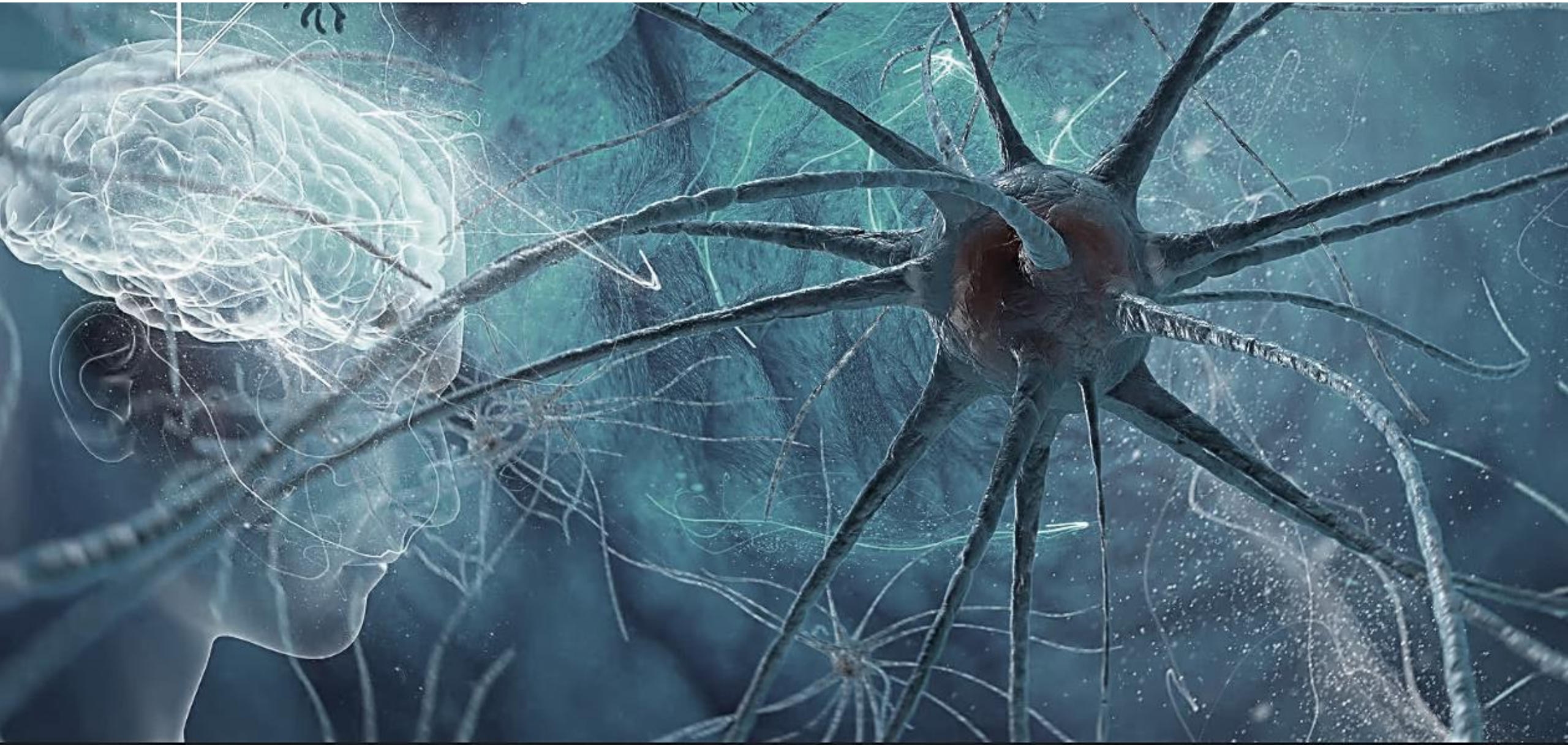
Obesity Problematic

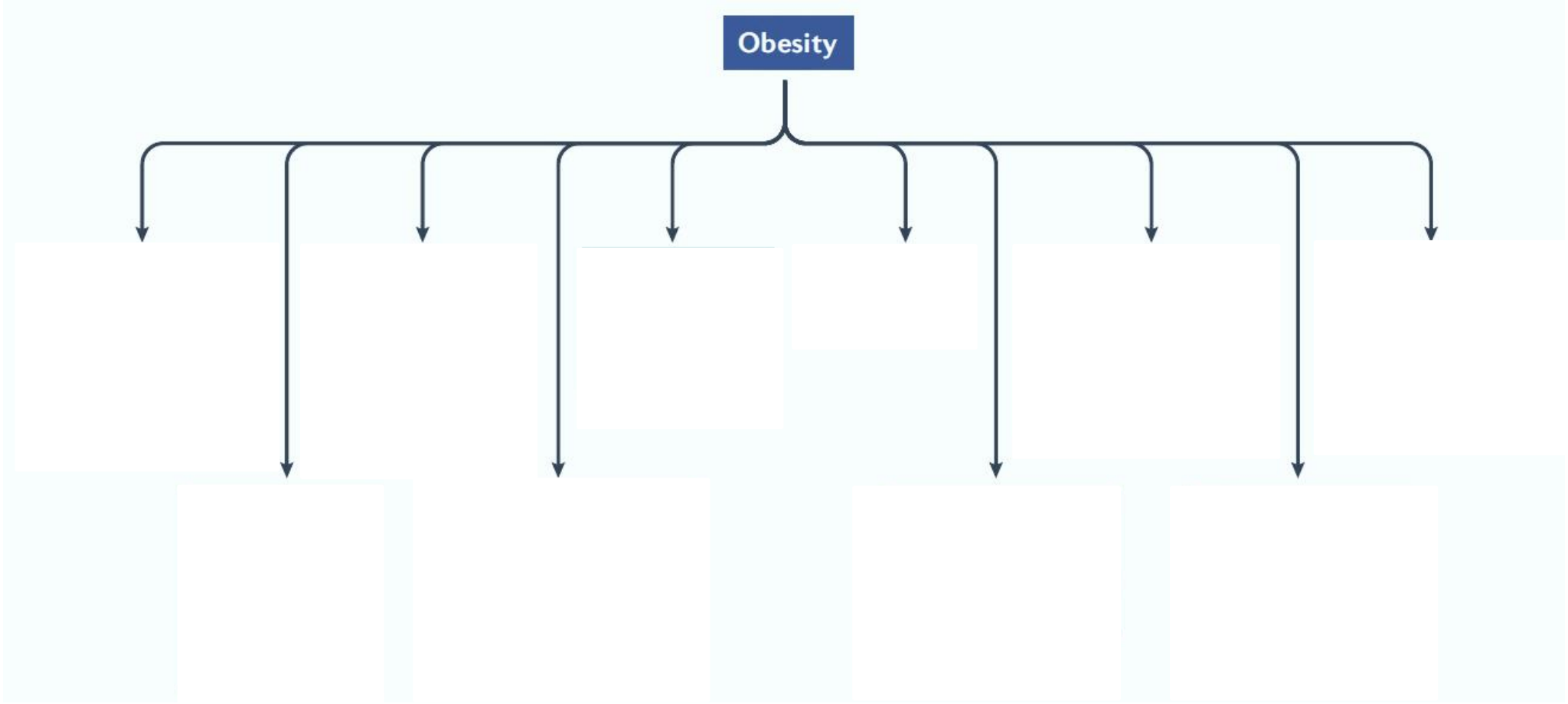


Actual Treatments

Future Medications

Obesity-associated metabolic disturbances

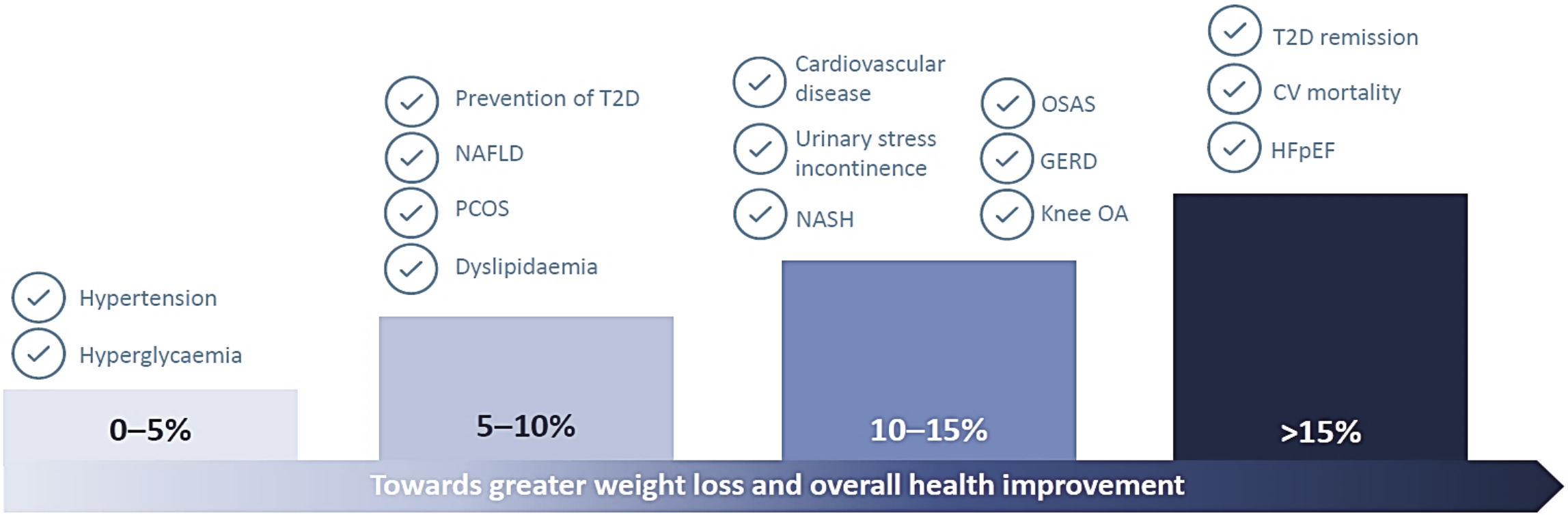
Mental – Cardiovascular – Metabolic – Malignant – Musculoskeletal – Pulmonary



Anti- obesity drug discovery: advances and challenges. NaTure RevIews drug discovery. March 2022 | volume 21

Greater weight loss leads to greater benefits

Overal health improvement



CV, cardiovascular; GERD, gastro-oesophageal reflux disease; HFpEF, heart failure with preserved ejection fraction; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; OA: osteoarthritis; OSAS, obstructive sleep apnoea syndrome; PCOS, polycystic ovary syndrome; T2D, type 2 diabetes; TG, triglycerides.

1. Garvey WT et al. Endocr Pract 2016;22(Suppl. 3):1–203; 2. Look AHEAD Research Group. Lancet Diabetes Endocrinol 2016;4:913–21; 3. Lean ME et al. Lancet 2018;391:541–51; 4. Benraoune F and Litwin SE. Curr Opin Cardiol 2011;26:555–61; 5. Sundström J et al. Circulation 2017;135:1577–85.

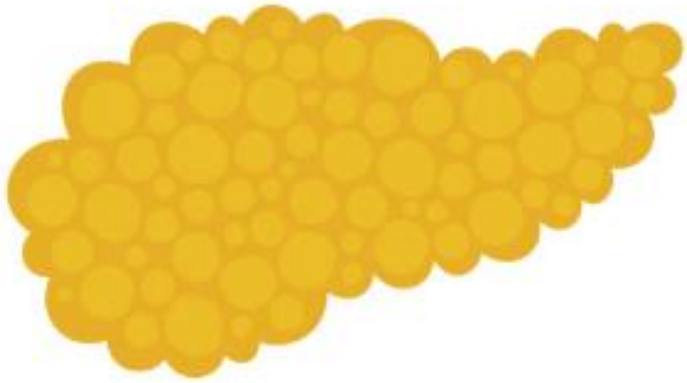
Weight loss issues

Why is it so difficult to lose and maintain weight loss?

We need to store energy to survive

Energy store

Fat mass



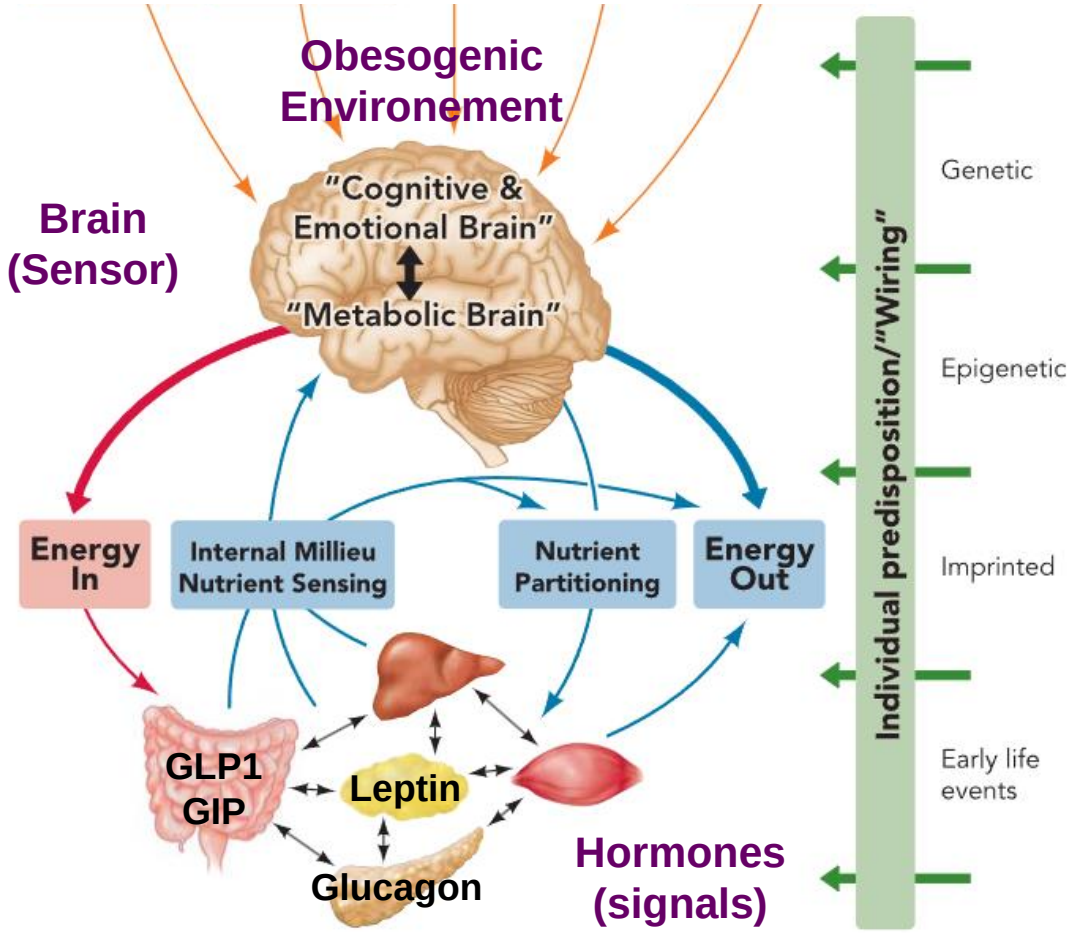
Our body defends energy

Adapted from Diabetes Obes Metab. 2021;23(Suppl. 3):5–29

Dysregulation of the fat mass defenders

We have to reset the system

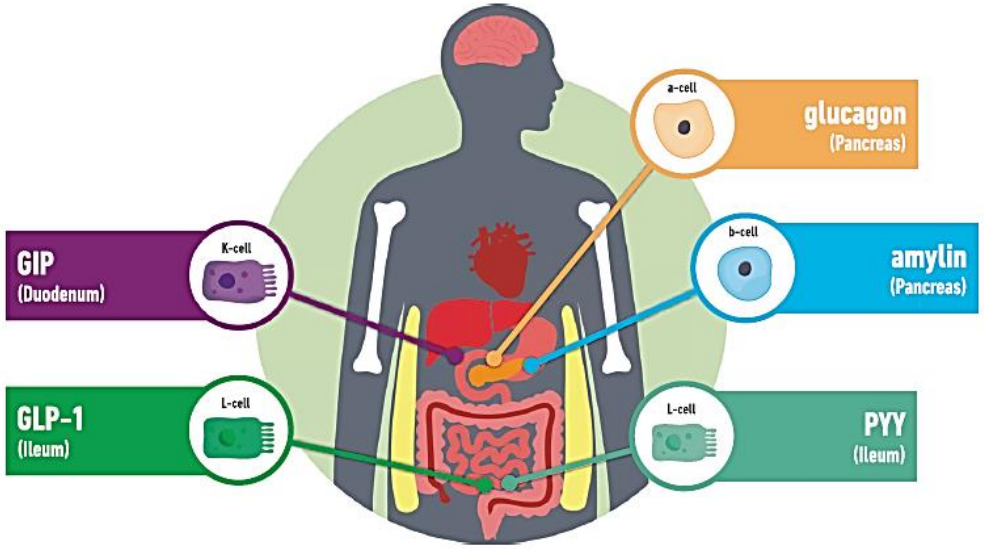
1. **Leptin resistance:**
   - High levels of leptin but a less responsive hypothalamus
   - Persistent hunger and impairs satiety despite energy sufficiency
2. **Insulin resistance:**
   - Impairs insulin role as a satiety signal
3. **Altered gut hormone secretion:**
   - Lower post prandial GLP1 and PYY responses, Ghrelin suppression after meals may be blunted
4. **Reward system hyperactivation:**
   - Stronger drive to eat beyond metabolic needs
5. **Circadian disruption:**
   - Misalignment between circadian rhythms and food intake (late-night eating, irregular meals)
   - Hormonal oscillations (ghrelin, leptin, insulin) lose their normal daily rhythm
   - Feeding outside the biologically optimal windows (eg: late evening) worsen weight gain and metabolic dysfunction



Diabetes Obes Metab. 2021;23(Suppl. 3):5–29

Nutrient Stimulated Hormones

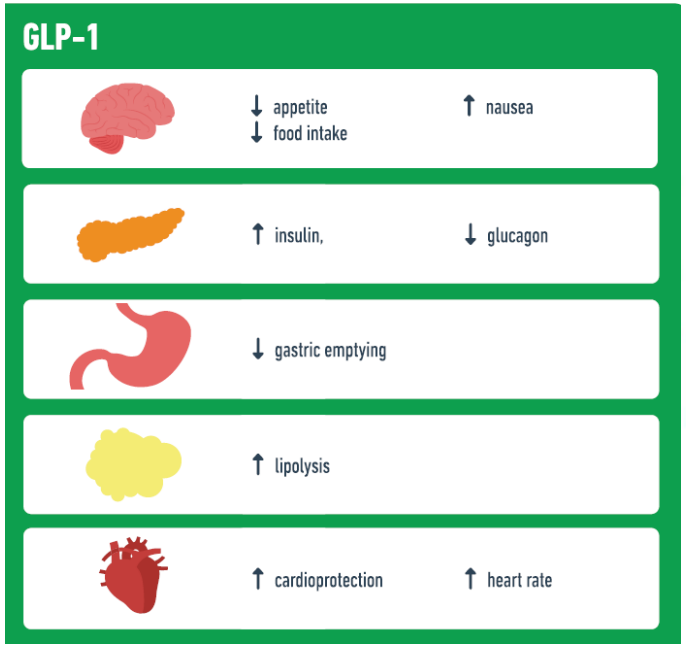
A central and peripheral action: remodeling signaling pathways

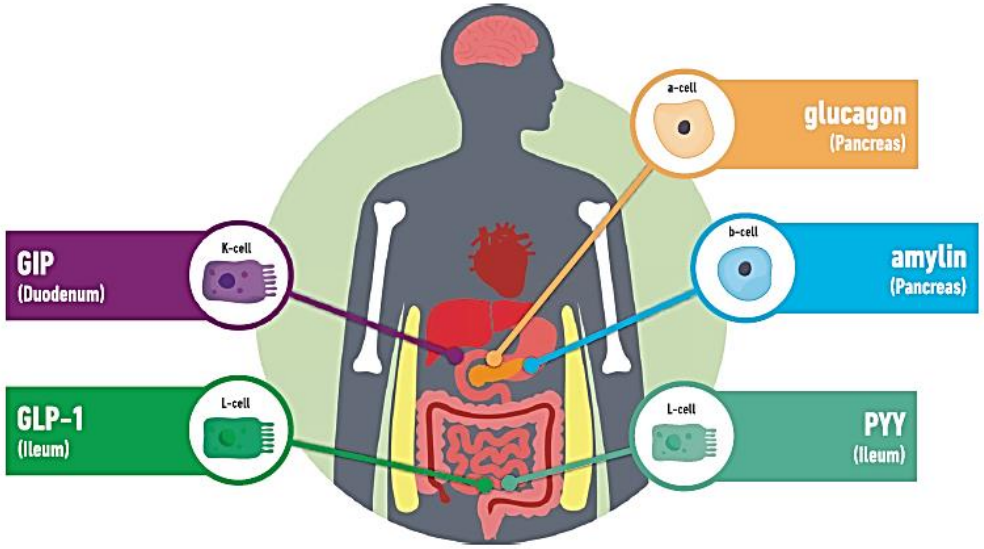


International Journal of Obesity (2025) 49:433–451

Nutrient Stimulated Hormones

A central and peripheral action: remodeling signaling pathways





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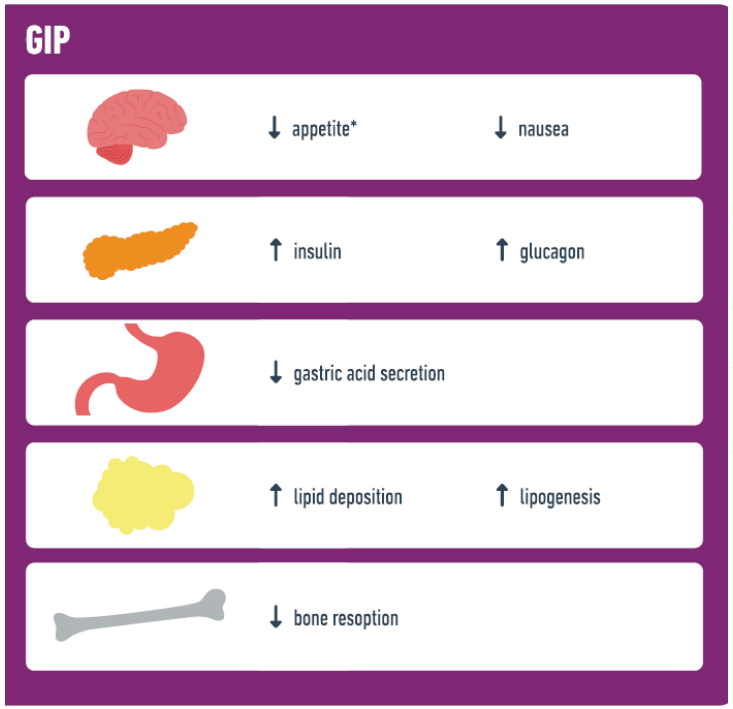

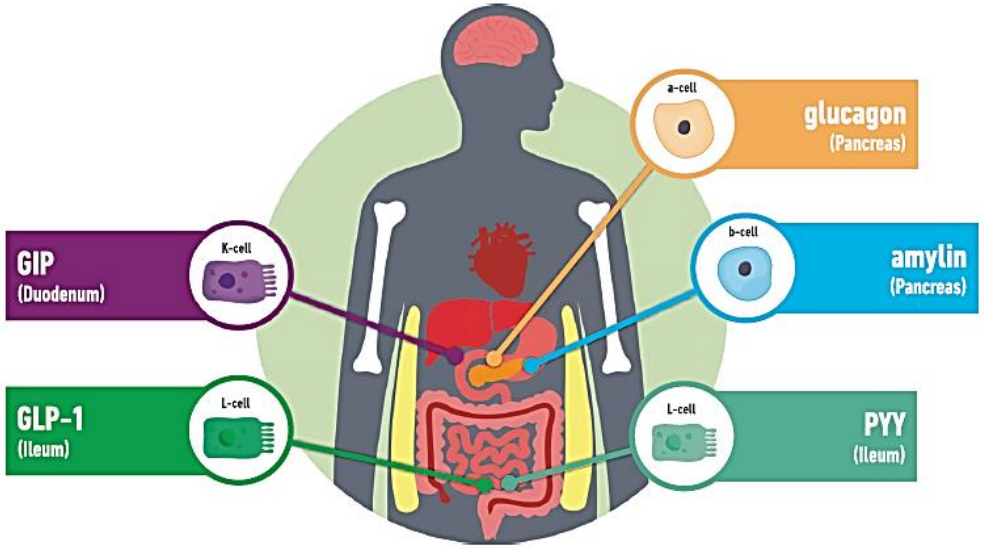

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Weight Loss Medications

A long journey still ongoing

1st Generation | 2nd Generation | 3rd Generation

1959 | 1997 | 1999 | 2008 | 2010 | 2012 | 2014 | 2020 | 2021 | 2023

- 1959: Phentermine
- 1997: Fen/Phen
- 1999: Orlistat
- 2008: Rimonabant
- 2010: Sibutramine
- 2012: Phentermine/Topiramate
- 2014: Naltrexone/Bupropion; Liraglutide 3mg
- 2020: Lorcaserin
- 2021: Semaglutide
- 2023: Tirzepatide

Weight Loss Medications

A long journey still ongoing

Semaglutide: GLP1 Agonist once weekly → **FDA approved 2021**

Tirzepatide: GLP1/GIP Agonist once weekly → **FDA approved 2023**

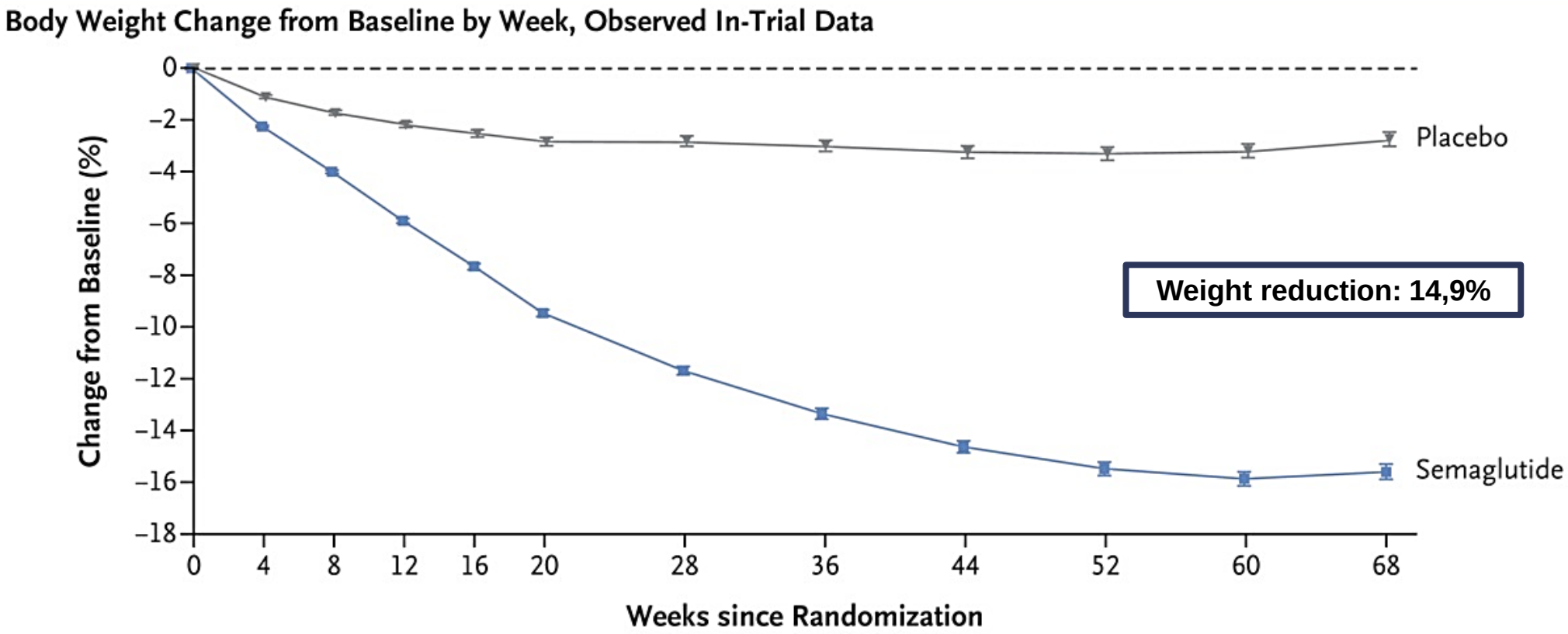
Actual Treatments

SEMAGLUTIDE: STEP 1 Trial

Evaluated in patients with obesity without T2D: Semaglutide 2,4 mg

RCT: N 1961
BMI avg: 38 kg/m2
Age avg: 46-47 yo

Cardiometabolic mesures	
HbA1c	-0,5%
SBP	-7,1
DBP	-3
TChol	- 4%
LDL	- 4%
HDL	+ 5%
TG	- 24%



N Engl J Med 2021;384:989-1002

Other Semaglutide Trials

SELECT CVOT- STEP-HFpEF - FLOW

SELECT CVOT

Individuals with CVD with obesity without diabetes

↓ 20% CV death, non fatal MI, non fatal stroke

Lincoff et.al; NEJM, 2023

STEP-HFpEF

Individuals with HFpEF with obesity without diabetes

Significant reduction in heart failure- related symptoms and physical limitations

Kosiborod et.al; NEJM, 2023

FLOW

Individuals with CKD with type 2 diabetes

↓ 24% in risk of kidney disease progression and kidney and CV death

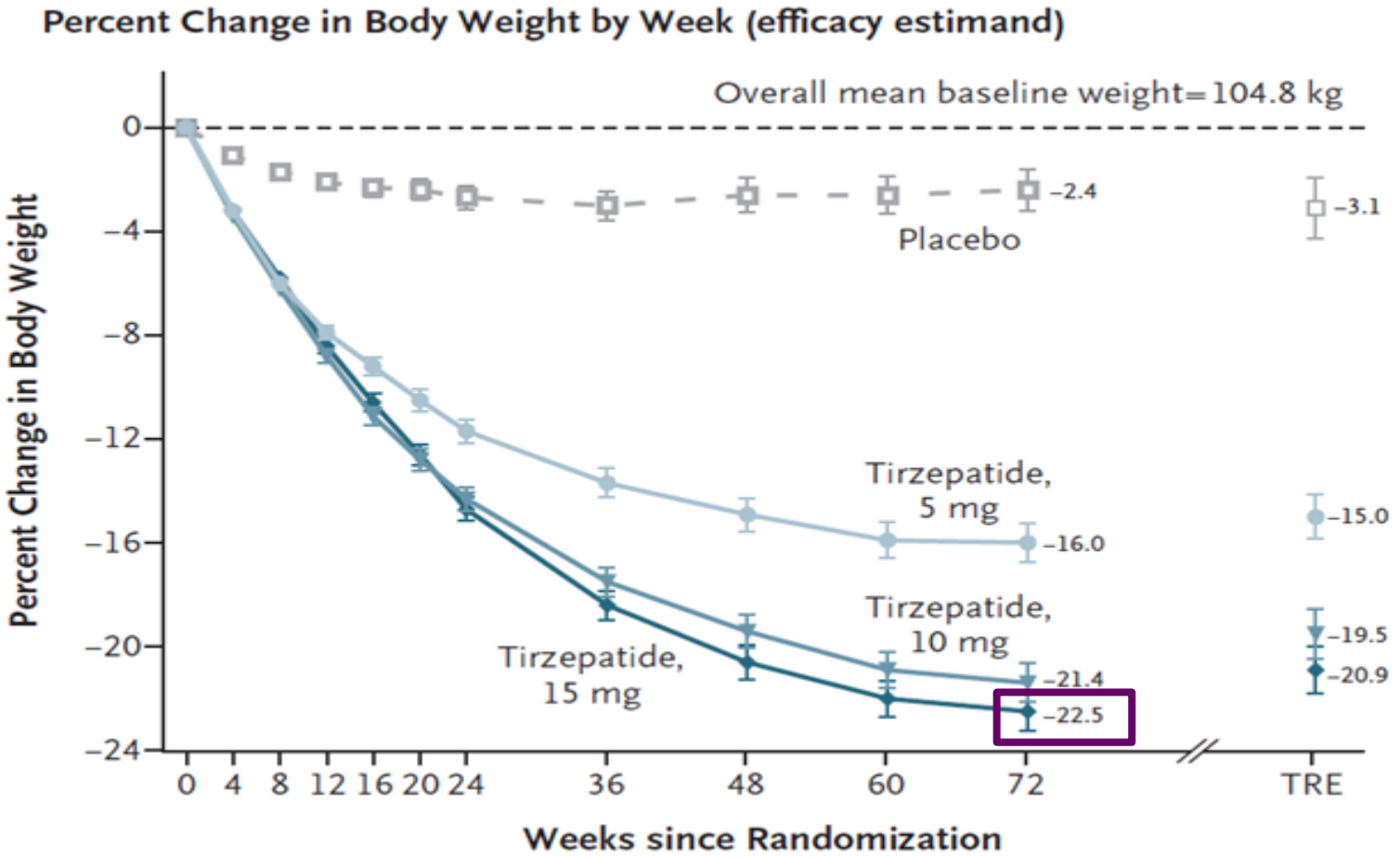
Percovik et.al; NEJM, 2024

TIRZEPATIDE: SURMOUNT 1 Trial

Double Agonist (GLP1/GIP) in patients with obesity without diabetes

RCT: N 2539
BMI avg: 38 kg/m2
Base line weight: 104,8 kg
40% prediabetes

Cardiometabolic mesures	
HbA1c	-0,5%
SBP	-8,2
DBP	-5,5
TChol	-7,4%
LDL	-8,6%
HDL	+8,2%
TG	-31,4%



On treatment with Tirzepatide 15 mg, nearly 40% of participants lost > 25% of total body weight

n engl j med 387;3 nejm.org July 21, 2022

Other Tirzepatide Trials

SURMOUNT MMO – SUMMIT-HFpEF – SURMOUNT OSA

SURMOUNT MMO

Individuals with CVD with obesity without T2D

Primary and secondary CV prevention

NCT05556512

SUMMIT-HFpEF

Individuals with HFpEF with obesity without T2D

Significant reduction in HF outcome and improvement in heart failure- related symptoms and physical limitations

Packer M ; NEJM, 2024

SURMOUNT OSA

Individuals with OSA with obesity without T2D

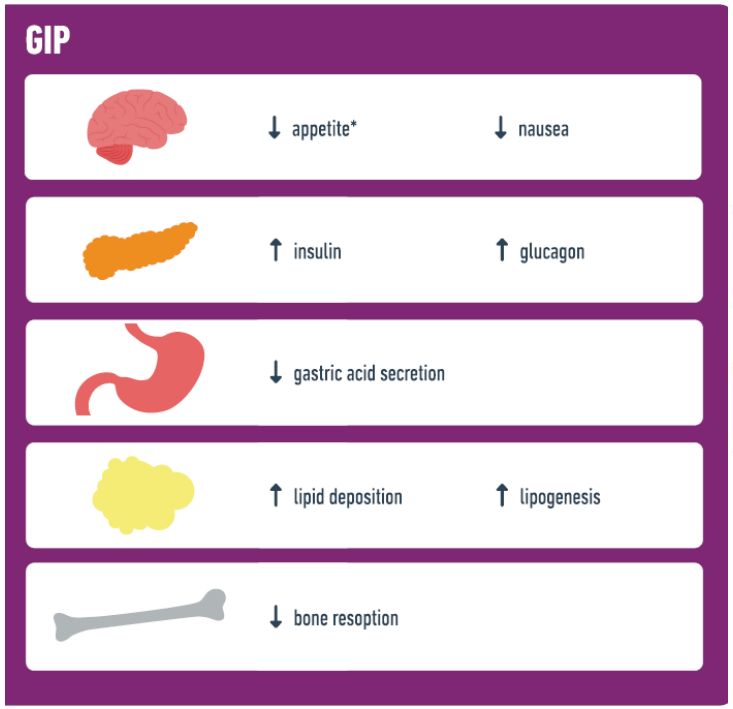
Significant reduction in AHI. First medication approved for OSA

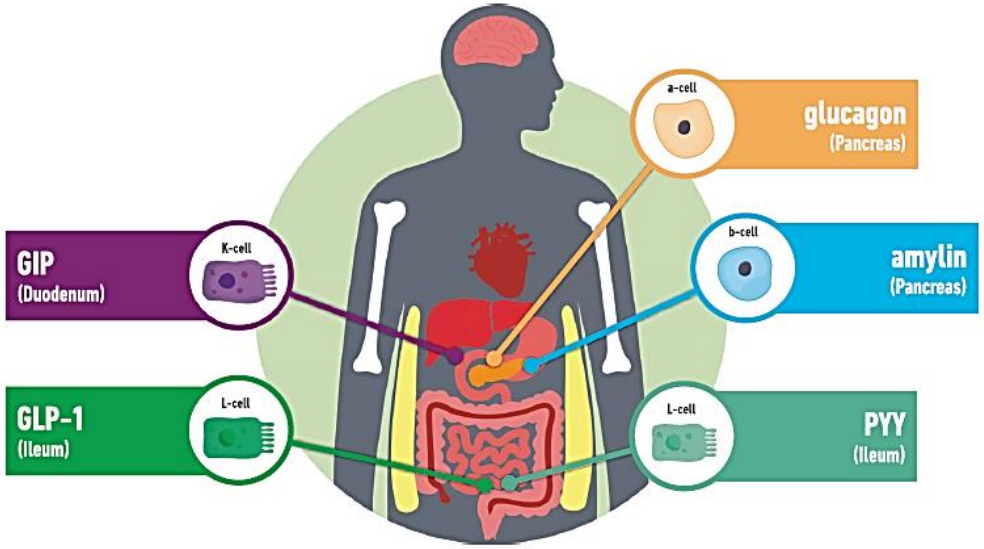
Malhotra et.al; NEJM, 2024

Future Medications

Nutrient Stimulated Hormones

Other promising targets





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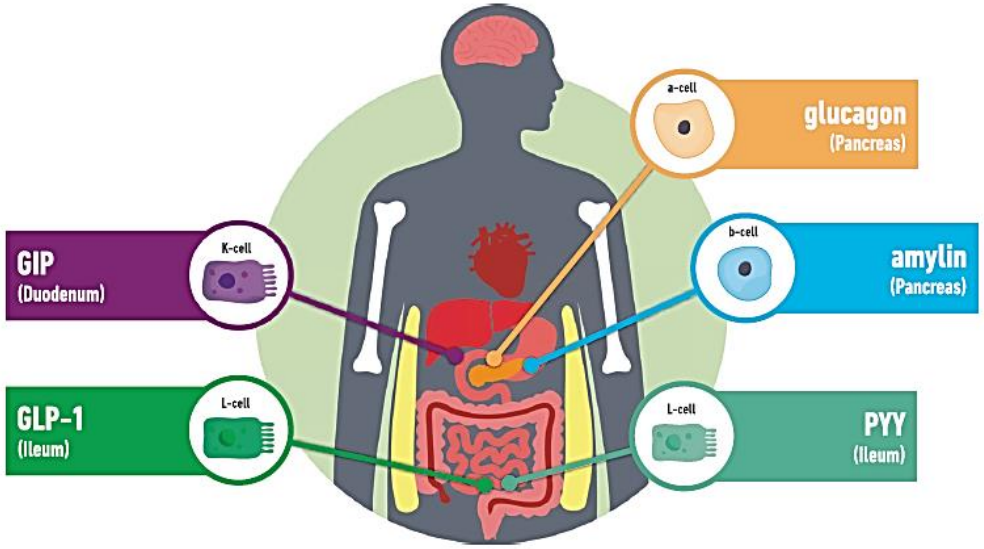
Nutrient Stimulated Hormones

Other promising targets

GIP

- ↓ appetite*
- ↓ nausea
- ↑ insulin
- ↑ glucagon
- ↓ gastric acid secretion
- ↑ lipid deposition
- ↑ lipogenesis
- ↓ bone resoption



Glucagon

- ↓ appetite
- ↓ food intake
- ↑ nausea
- ↑ insulin
- ↑ hepatic glucose production
- ↑ lipid oxidation
- ↓ hepatic lipid synthesis
- ↓ gastric emptying
- ↑ energy expenditure
- ↑ heart rate

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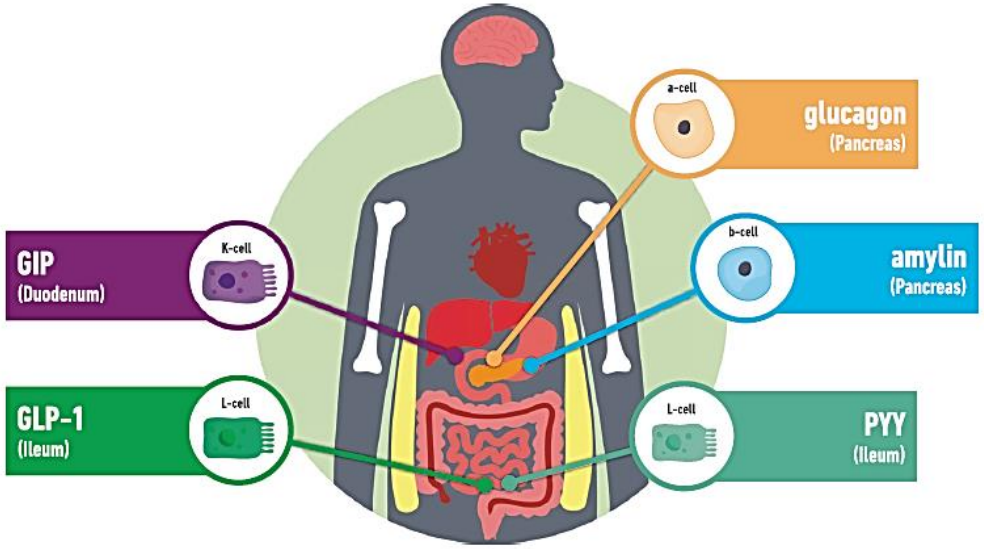

Glucagon

Amylin

- ↓ appetite ↓ food intake
- ↓ glucagon
- ↑ energy expenditure*
- ↓ gastric emptying
- ↓ osteoclast activity ↑ osteoblast activity

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Nutrient Stimulated Hormones

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GIP

- ↓ appetite* ↓ nausea
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- ↓ gastric acid secretion
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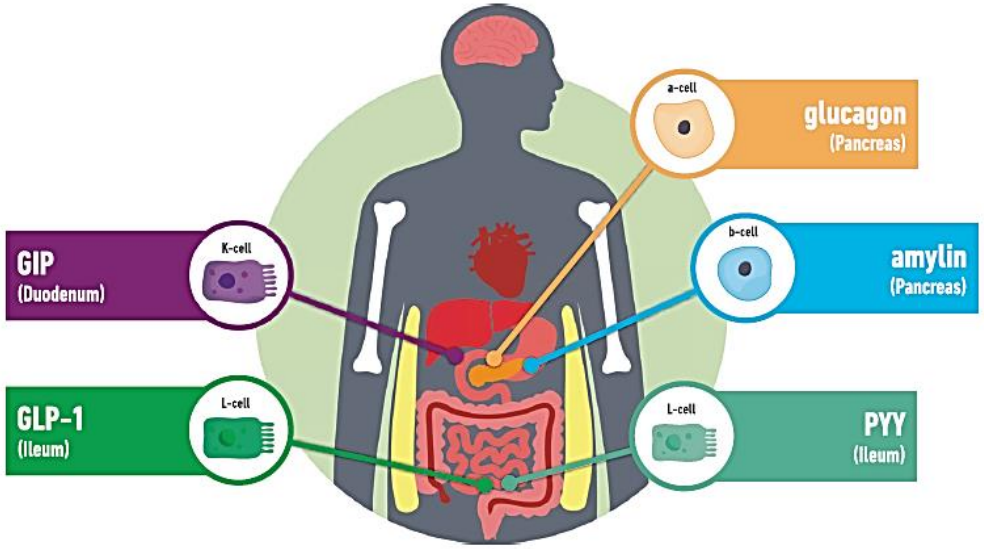
- ↓ bone resoption



Glucagon

Amylin

PYY

- ↓ appetite ↓ food intake ↑ nausea
- ↓ gastric emptying
- ↑ energy expenditure*

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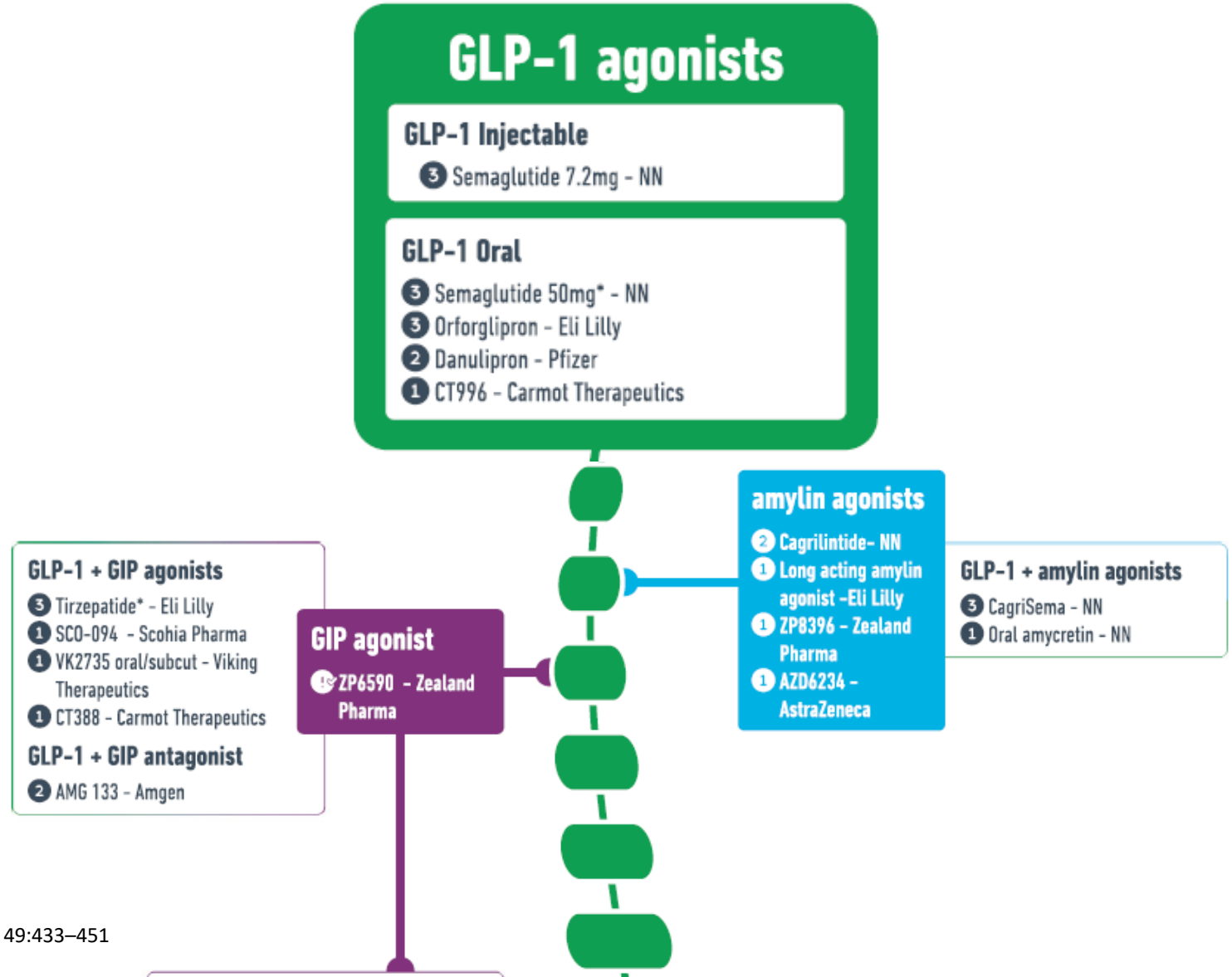
Anti obesity drugs pipeline

A new perspective



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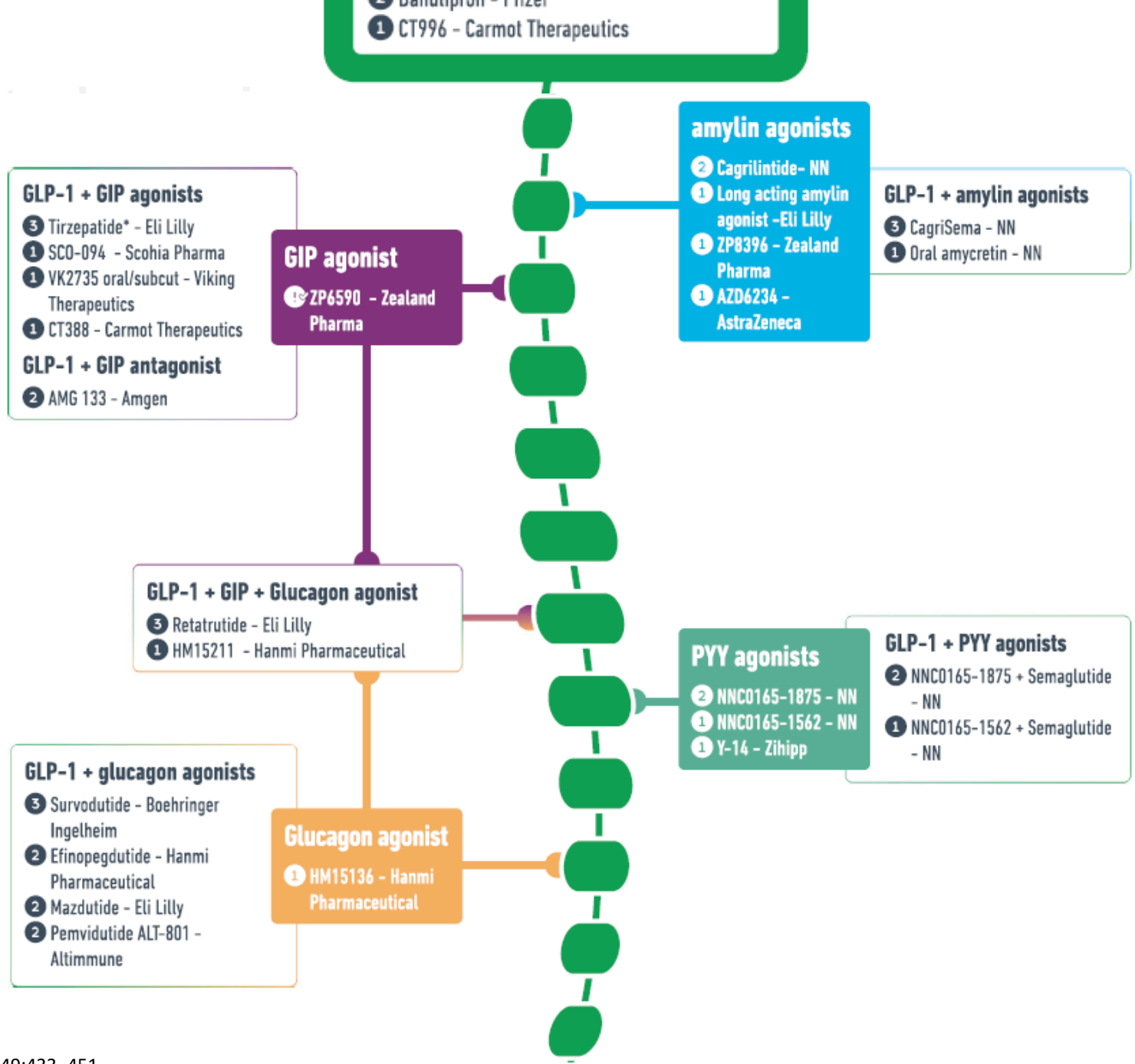

1 CT996 - Carmot Therapeutics
amylin agonists
2 Cagrilintide- NN
1 Long acting amylin agonist -Eli Lilly
1 ZP8396 - Zealand Pharma
1 AZD6234 - AstraZeneca
GLP-1 + amylin agonists
3 CagriSema - NN
1 Oral amycretin - NN
GLP-1 + GIP agonists
3 Tirzepatide* - Eli Lilly
1 SCO-094 - Scohia Pharma
1 VK2735 oral/subcut - Viking Therapeutics
1 CT388 - Carmot Therapeutics
GLP-1 + GIP antagonist
2 AMG 133 - Amgen
GIP agonist
ZP6590 - Zealand Pharma
GLP-1 + GIP + Glucagon agonist
3 Retatrutide - Eli Lilly
1 HM15211 - Hanmi Pharmaceutical
PYY agonists
2 NNC0165-1875 - NN
1 NNC0165-1562 - NN
1 Y-14 - Zihipp
GLP-1 + PYY agonists
2 NNC0165-1875 + Semaglutide - NN
1 NNC0165-1562 + Semaglutide - NN
GLP-1 + glucagon agonists
3 Survodutide - Boehringer Ingelheim
2 Efinopegdutide - Hanmi Pharmaceutical
2 Mazdutide - Eli Lilly
2 Pemvidutide ALT-801 - Altimmune
Glucagon agonist
1 HM15136 - Hanmi Pharmaceutical

CAGRILINTIDE/SEMAGLUTIDE: CAGRISEMA REDEFINE 1

Treatment of overweight or obesity without T2D

Objective[1]

This study assessed the efficacy and safety of **CAGRISEMA** for treatment of overweight or obesity in participants without diabetes

Participants[1]

Adults ≥18 years of age, BMI ≥30 kg/m^2 or ≥27 kg/m^2 with ≥1 weight-related comorbidity, no diabetes mellitus

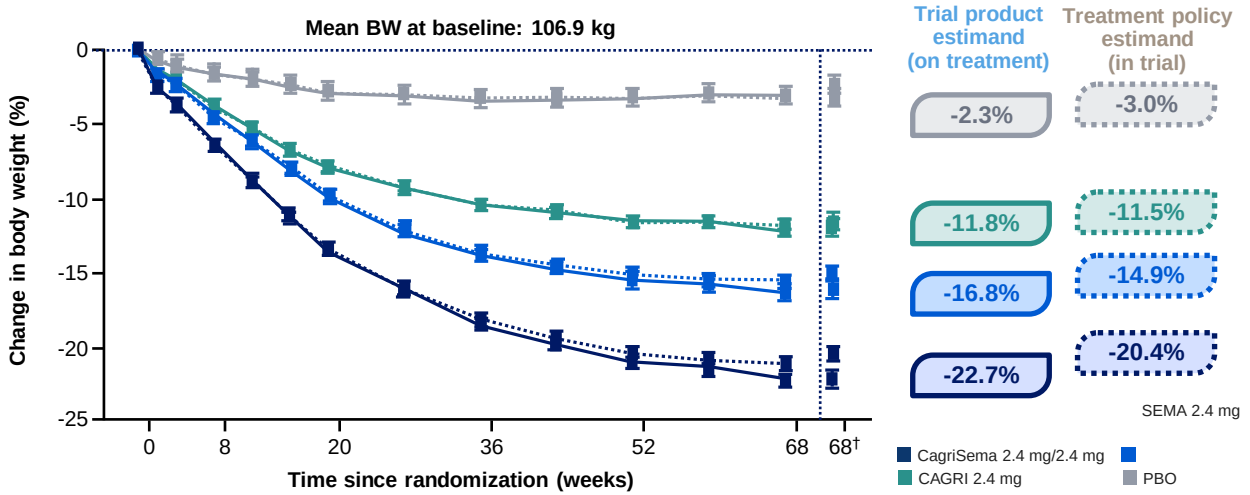
Design[1]

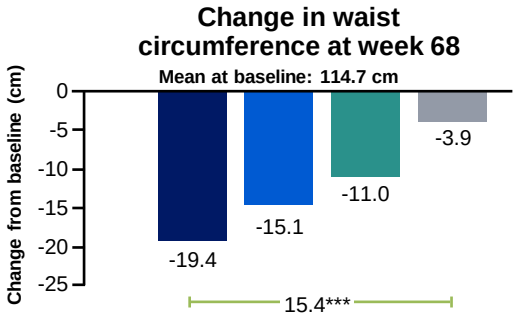
Phase 3a, 68-week study. Participants randomized to 2.4/2.4 mg **CAGRISEMA**, 2.4 mg **SEMA**, 2.4 mg **CAGRI**, or **PBO**

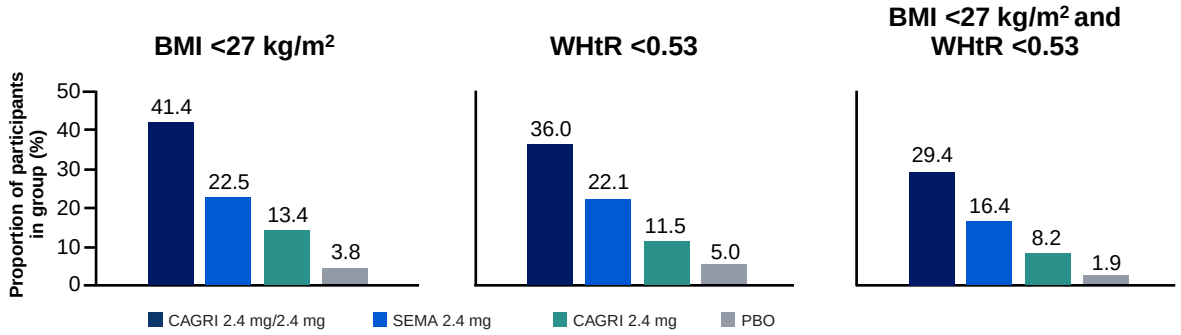
Primary endpoints: relative change in BW, achievement of ≥5% BW reduction

CAGRISEMA produced greater reductions in BW and WC than **CAGRI** or **SEMA** alone[2]

More participants on **CAGRISEMA** achieved a BMI <27 kg/m^2, a WHtR <.53, or both parameters[2]







HbA1c, FSG, glycemic status, SBP, DBP, lipid levels, hsCRP, and IWQOL-Lite-CT physical function scores improved with **CAGRISEMA** but did not differ from that for **SEMA** or **CAGRI** alone[2]

67% of BW reduction on **CAGRISEMA** was due to fat mass loss[2]

CAGRI = cagrilintide; FSG = fasting serum glucose; hsCRP = high-sensitivity C-reactive protein; IWQOL-LITE-CT = Impact of Weight on Quality of Life-Lite Clinical Trials Version.

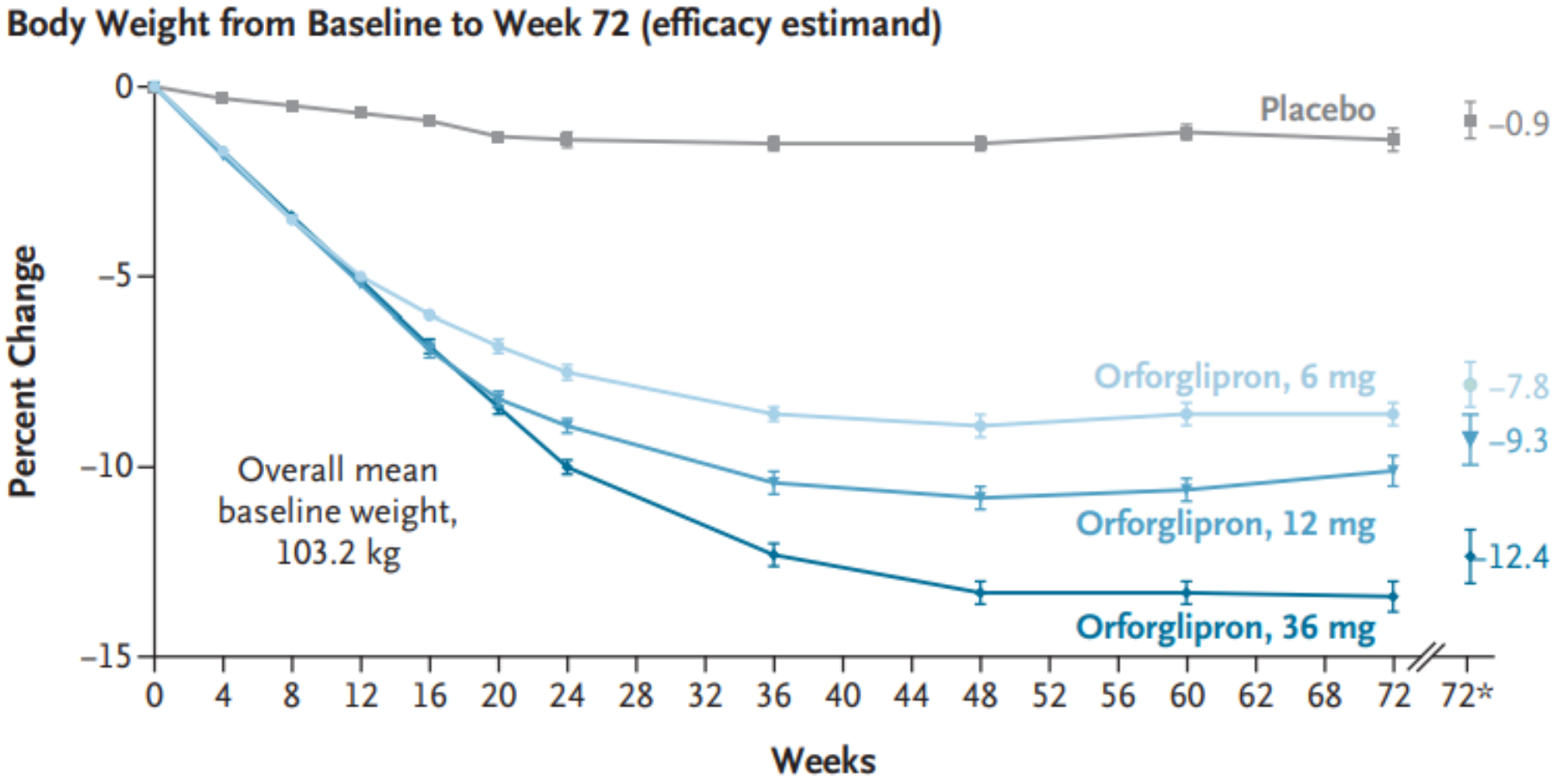
1. Rosenstock J. 85th American Diabetes Association Annual Scientific Sessions; June 20-23, 2025. Oral Presentation. 2. Garvey WT. 85th American Diabetes Association Annual Scientific Sessions; June 20-23, 2025. Oral Presentation.

ORFROGLIPRON ATTAIN 1 Trial

First completed phase 3 trial on Oral Small-Molecule GLP-1 Receptor Agonist for Obesity Treatment

RCT: N 3127
Weight: 103,2 kg
Age avg: 45 yo

Cardiometabolic mesures	
SBP	-5,7
DBP	-2,4
TChol	- 4,1%
LDL	- 4,8%
TG	- 14,8%

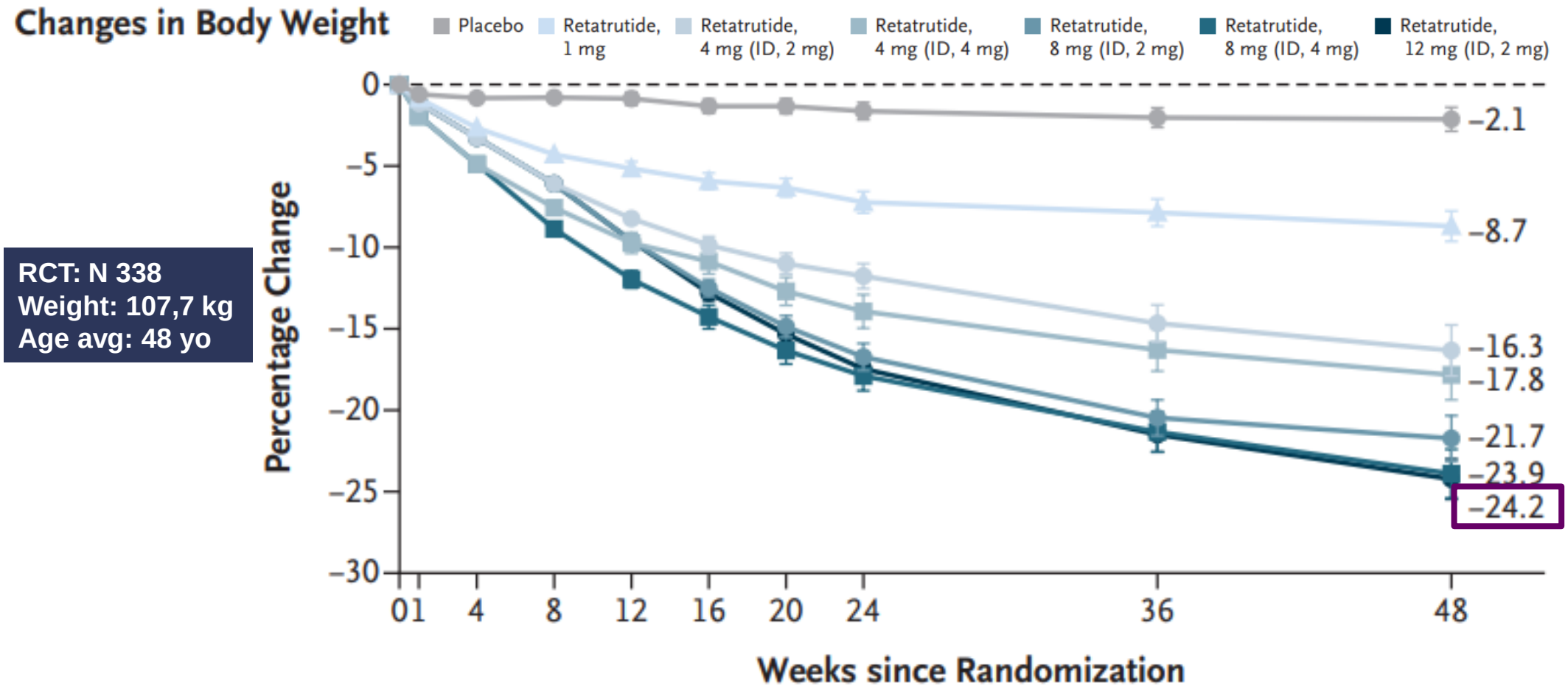


Wharton et.al; NEJM September 16, 2025

RETATRUTIDE phase 2 Clinical Trial (GLP1-GIP-Glucagon)

Triple–Hormone-Receptor Agonist Retatrutide for Obesity

RCT: N 338
Weight: 107,7 kg
Age avg: 48 yo

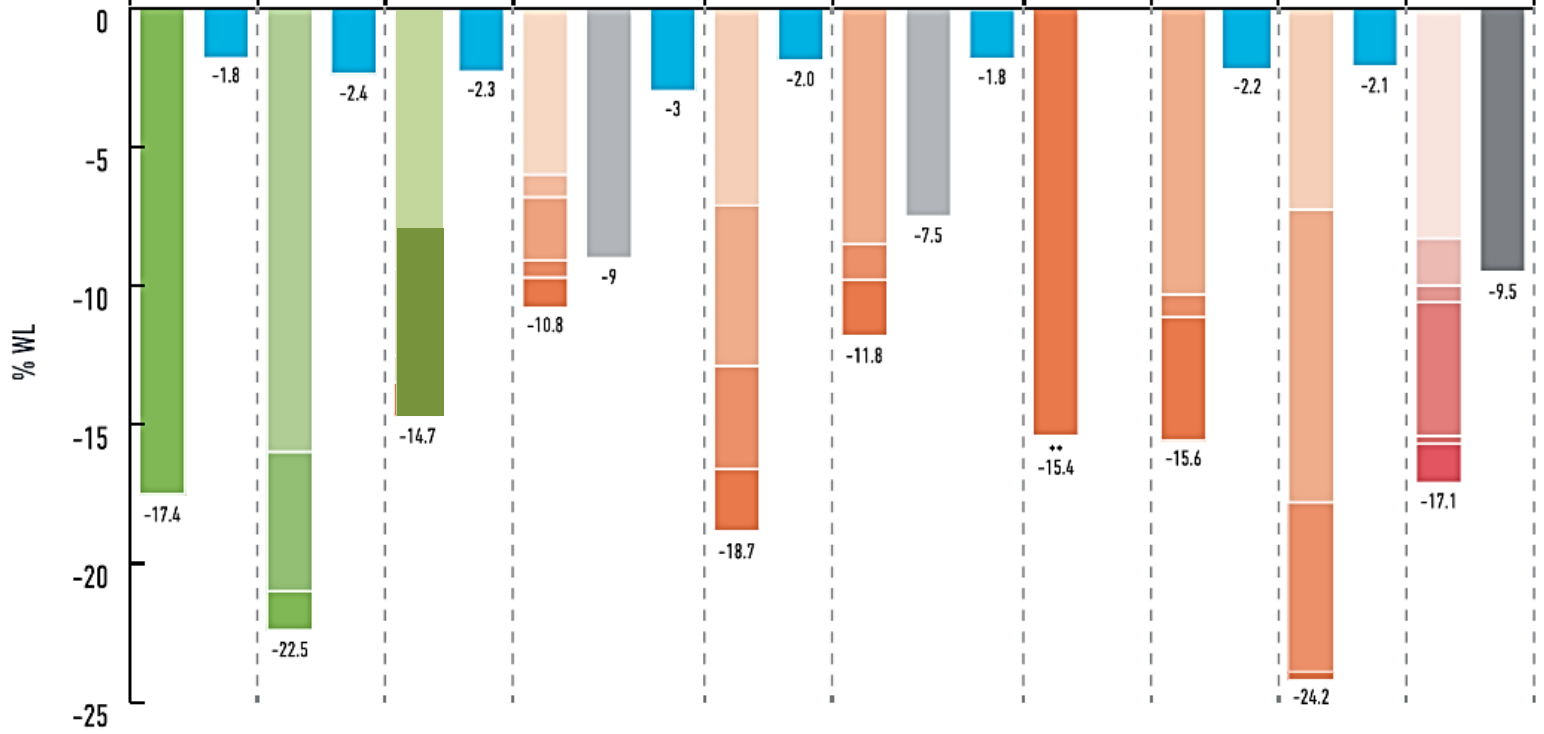


N Engl J Med 2023;389:514-26

Weight loss with the obesity pharmacotherapies pipeline

People without diabetes

	Oral Semaglutide[A]	Tirzepatide[A]	Orfoglipron[A]	Cagrilintide[A]	Survodutide[A*]	Efinopegdutide[B]	Mazdutide[C*]	Pemvidutide[A*]	Retatrutide[A]	CagriSema[B]
Dose and frequency	50mg OD	5/10/15mg OW	12/24/36/45mg OD	0.3/0.6/1.2/2.4/4.5mg OW	0.6/2.4/3.6 4.8mg OW	5/7.4/10mg OW	9mg OW	1.2/1.8/2.4mg OW	1/4/8/12mg OW	0.16/0.3/0.6/ 1.2/2.4/4.5 +SEMA 2.4mg OW
Route	PO	SC	PO	SC	SC	SC	SC	SC	SC	SC
Mechanism of action	GLP-1	GLP-1 + GIP	GLP-1	Amylin	GLP-1 + GCG	GLP-1 + GCG	GLP-1 + GCG	GLP-1 + GCG	GLP-1 + GIP + GCG	GLP-1 + Amylin
Number of participants	667	2539	272	706	387	474	80	391	338	95
Timepoint (weeks)	68	72	36	26	46	26	24	48	48	20
Baseline weight (kg)	105.4	104.8	108.7	107.4	105.7	113.3	96.9	104	107.7	95.7 – 99.6
Comparator	PBO	PBO	PBO	LIRA 3.0mg / PBO	PBO	LIRA 3.0mg / PBO	PBO	PBO	PBO	PBO+SEMA 2.4mg



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Conclusion

A new dawn in obesity management

Actual vision of obesity treatment:

- A complex
- Chronic disease requiring long-term medical management

Multiple metabolic pathways are targeted:

- Significant weight loss
- Improvements in obesity-related complications

Obesity pharmacotherapy has advanced rapidly with:

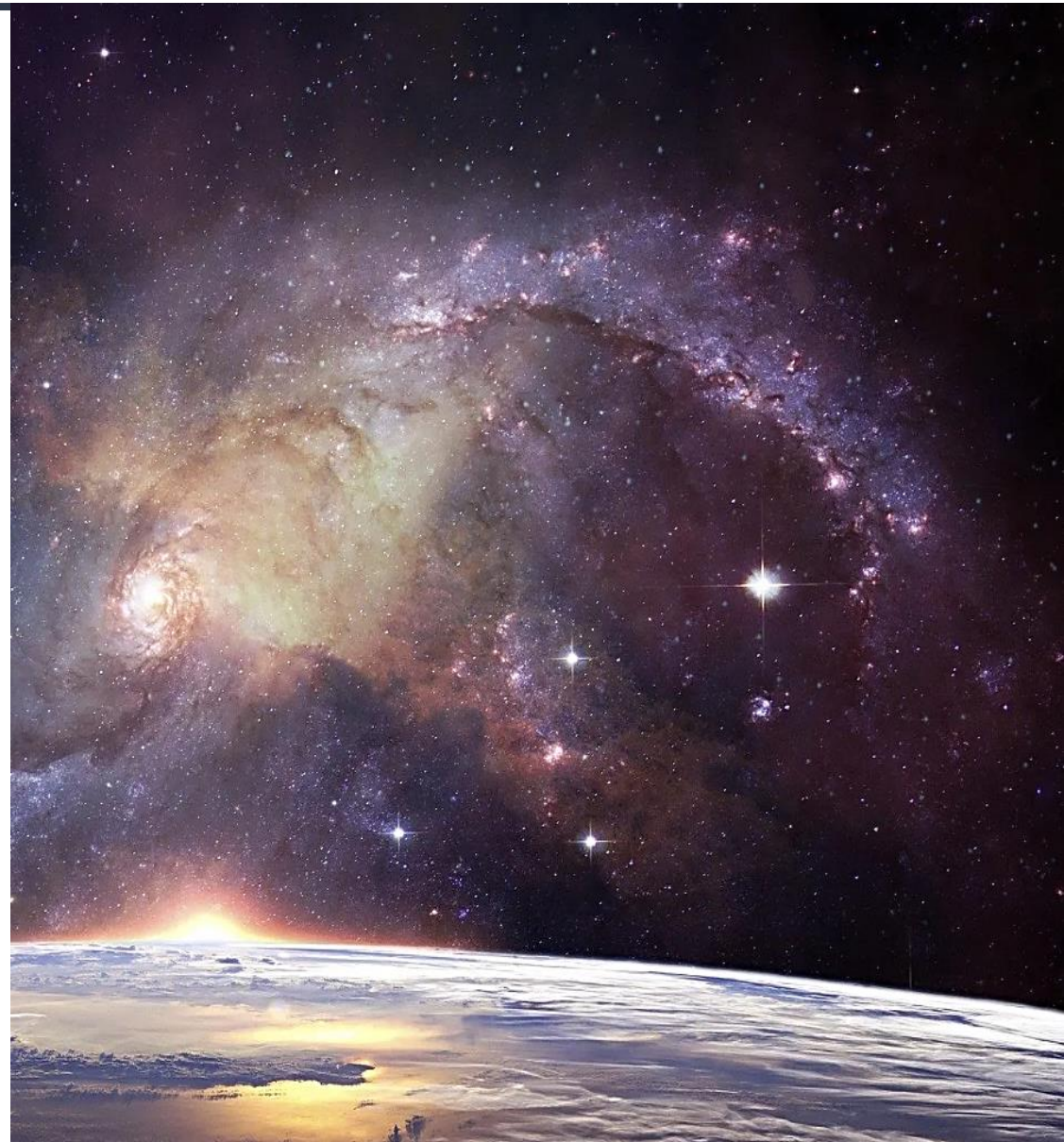
- The success of GLP-1 agonists
- The enhanced efficacy of dual and triple agonists

Multi-agonist therapies may:

- Redefine the standard of care
- Improve outcomes for millions living with obesity

Oral Quadruple Agonist:

- A promising potential
- Another step in this long journey?



GLP1 Phase 3 Clinical Trials: 2013 - 2018

Once weekly and Oral GLP1