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# Emerging Nutrient-stimulated Hormone Receptor Dual and Tri-agonists

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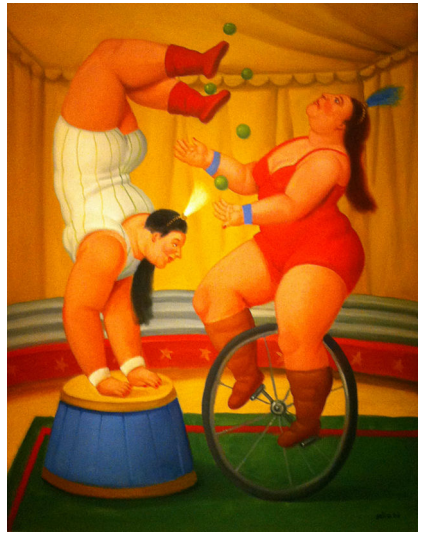
17 May 2023



*Fernando Botero, 1932-*

What Matters to Patients: Metabolic Health Beyond Weight Loss

# Disclosures

I am currently or have recently been a paid consultant to the following companies and organizations:

Altimmune
Amgen
Boehringer Ingelheim
Gelesis
Gilead Sciences
Eli Lilly & Company
Novo Nordisk
Pfizer
Rhythm Pharmaceuticals
Sidekick Health
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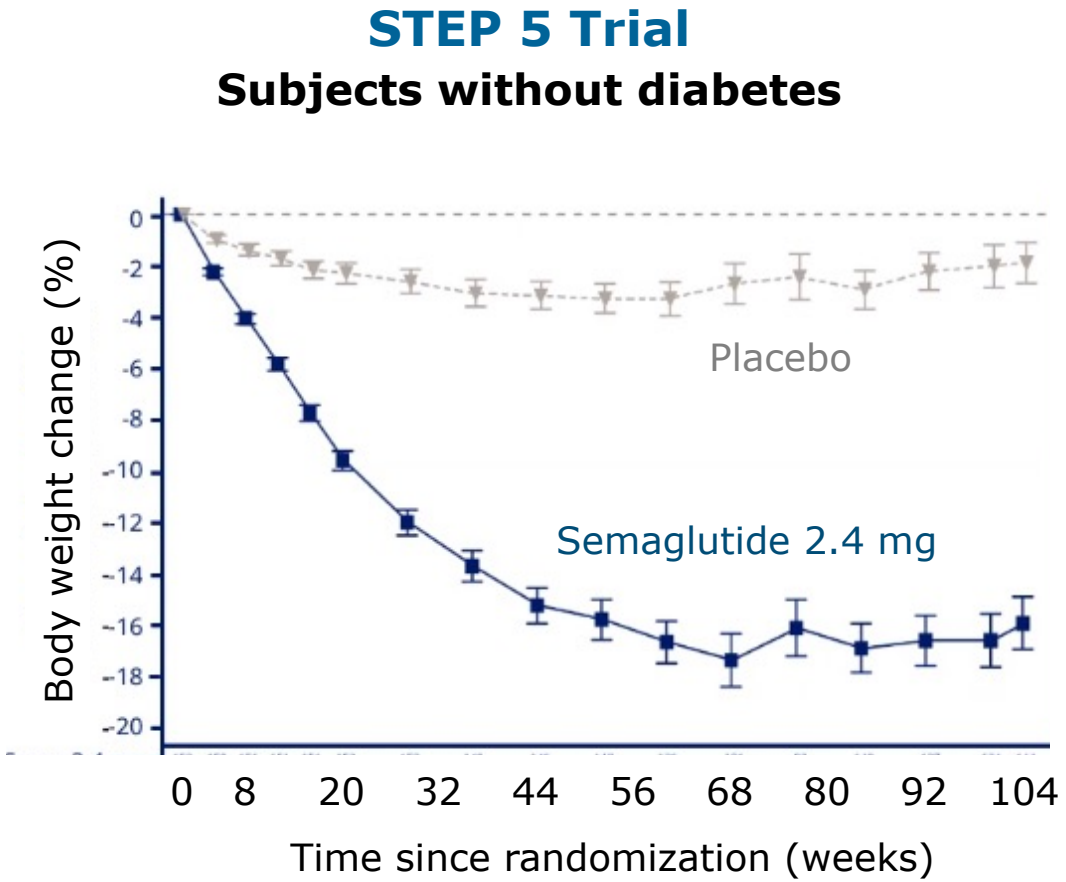
Xeno Biosciences

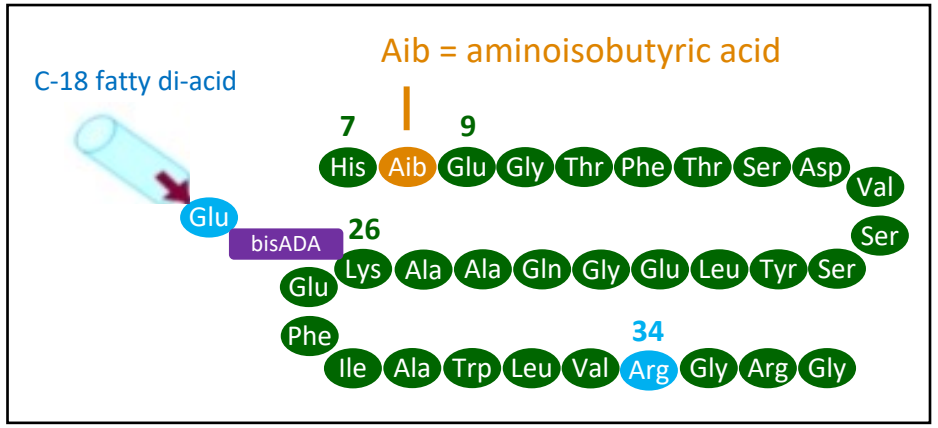
# Semaglutide induces profound, sustained weight loss






Garvey WT *et al.*, 2022

# Lessons of semaglutide




- GLP-1 receptor activity may not be necessary to prevent obesity, but it is **sufficient to overcome** the pathophysiological lesions of many types of obesity
- Despite the complexity of body fat regulation, there is at least one mechanism (GLP-1 signaling) that can substantially **re-regulate the whole system**



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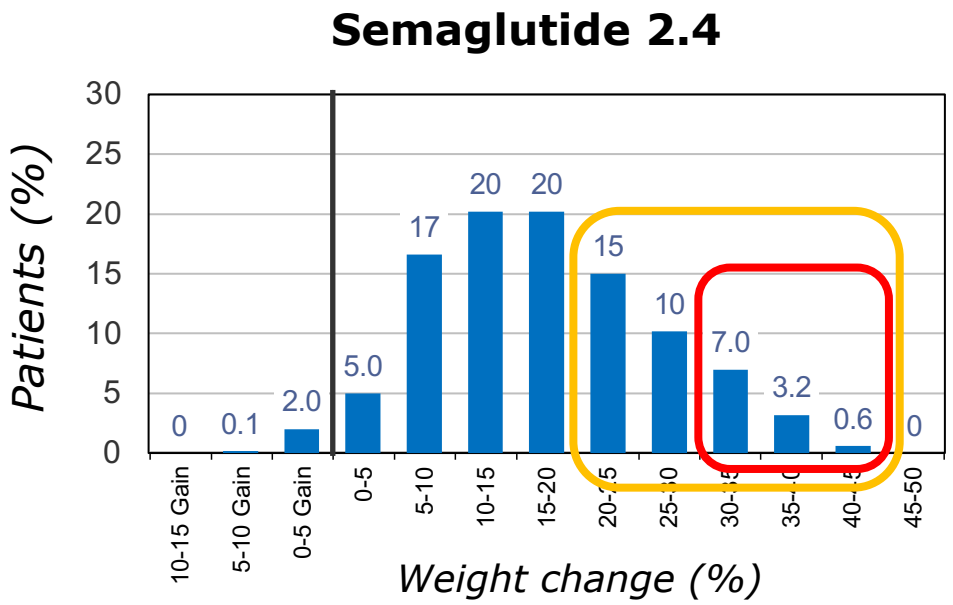
# Implications of profound weight loss with semaglutide 2.4




35% of patients lose more than 20% body weight

11% of patients lose more than 30% body weight

Adapted from Wilding JPH *et al.*, *NEJM* 2021
STEP 1 Obesity Trial



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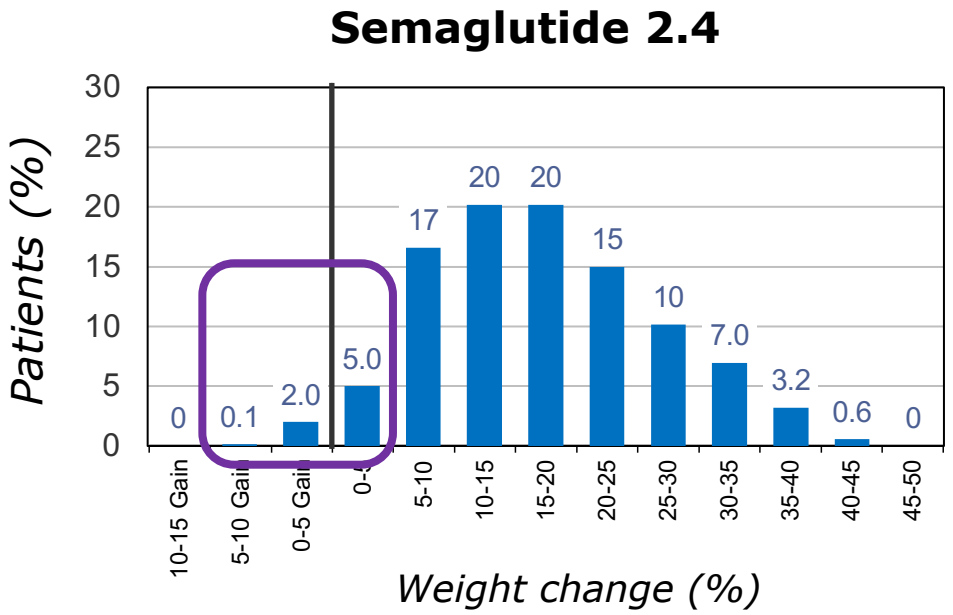
# Implications of variable responses to semaglutide 2.4

7-13% of patients lose less than 5% body weight

(31% if have T2D)




Adapted from Wilding JPH *et al.*, *NEJM* 2021 STEP 1 Obesity Trial

# Is GLP-1 a unicorn?

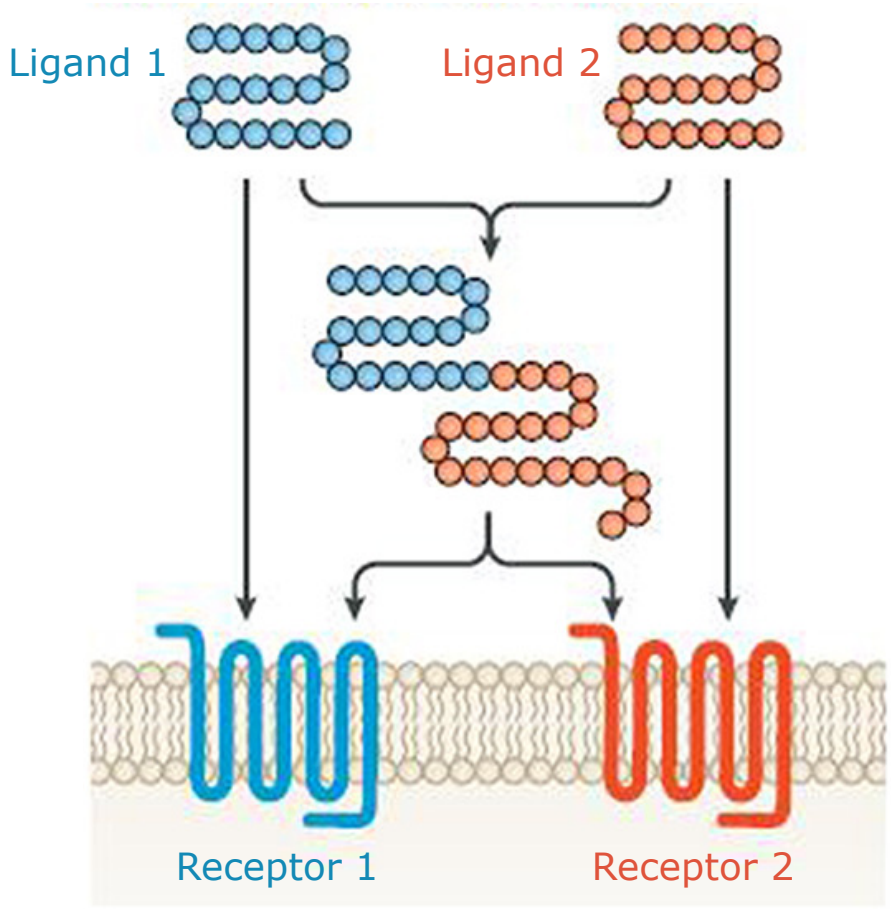
- Are there mechanisms other than GLP-1 that can exert **widespread, beneficial influence** on fat mass regulation?
- Identifying other mechanisms **sufficient to normalize body fat regulation** will determine future opportunities in managing and preventing obesity

# Potential complements to GLP-1 receptor agonists

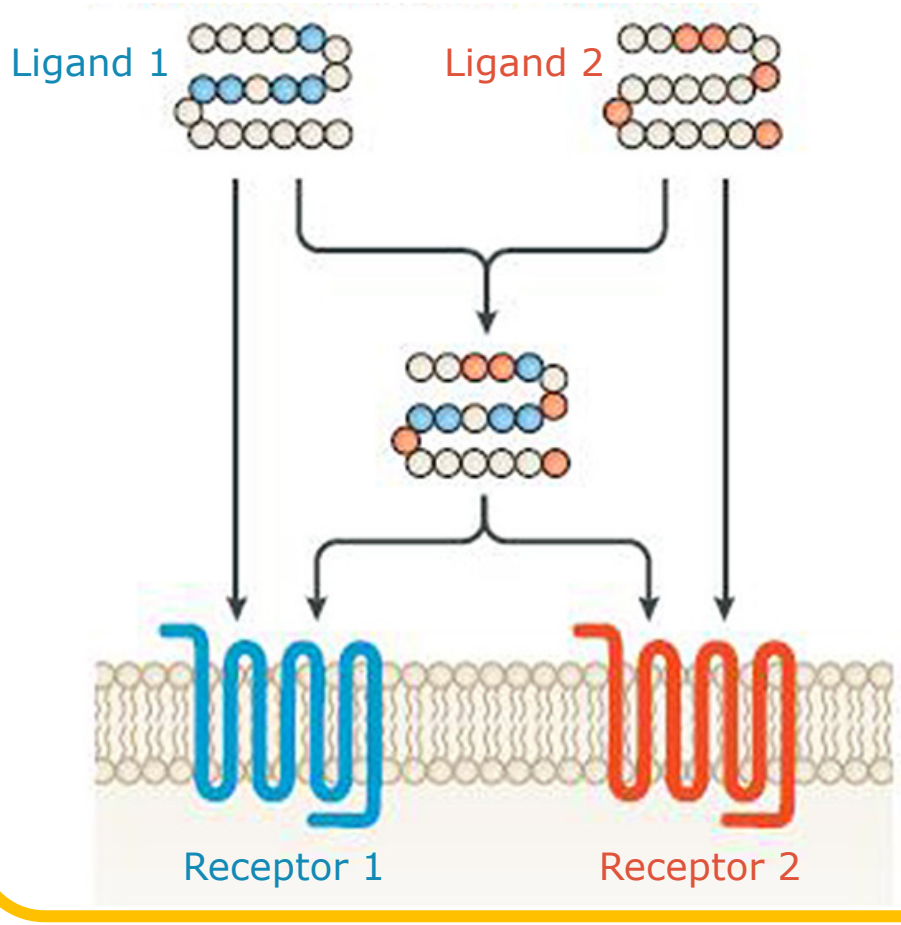
- **GIP** – like GLP-1, an incretin secreted from gut enteroendocrine cells
  - reduces food intake, delays gastric emptying, increases meal-stimulated insulin secretion, and inhibits glucagon secretion
  - decreases body weight in some studies, but effect debated
- **Anti-GIP receptor antibodies** – GIP receptor antagonist
- **Amylin** – co-secreted with insulin by pancreatic β-cells
  - promotes satiety and weight loss; slows gastric emptying; inhibits meal-induced glucagon secretion
- **Glucagon** – part of peptide precursor of GLP-1, GLP-2, oxyntomodulin; secreted by pancreatic α–cells
  - promotes decreased food intake, weight loss, hyperglycemia
- **Oxyntomodulin** – activates both GLP-1 and glucagon receptors
- **PYY** – gut peptide secreted from gut enteroendocrine cells; promotes weight loss

# Design of dual agonists

## Peptide fusion




## Peptide chimera

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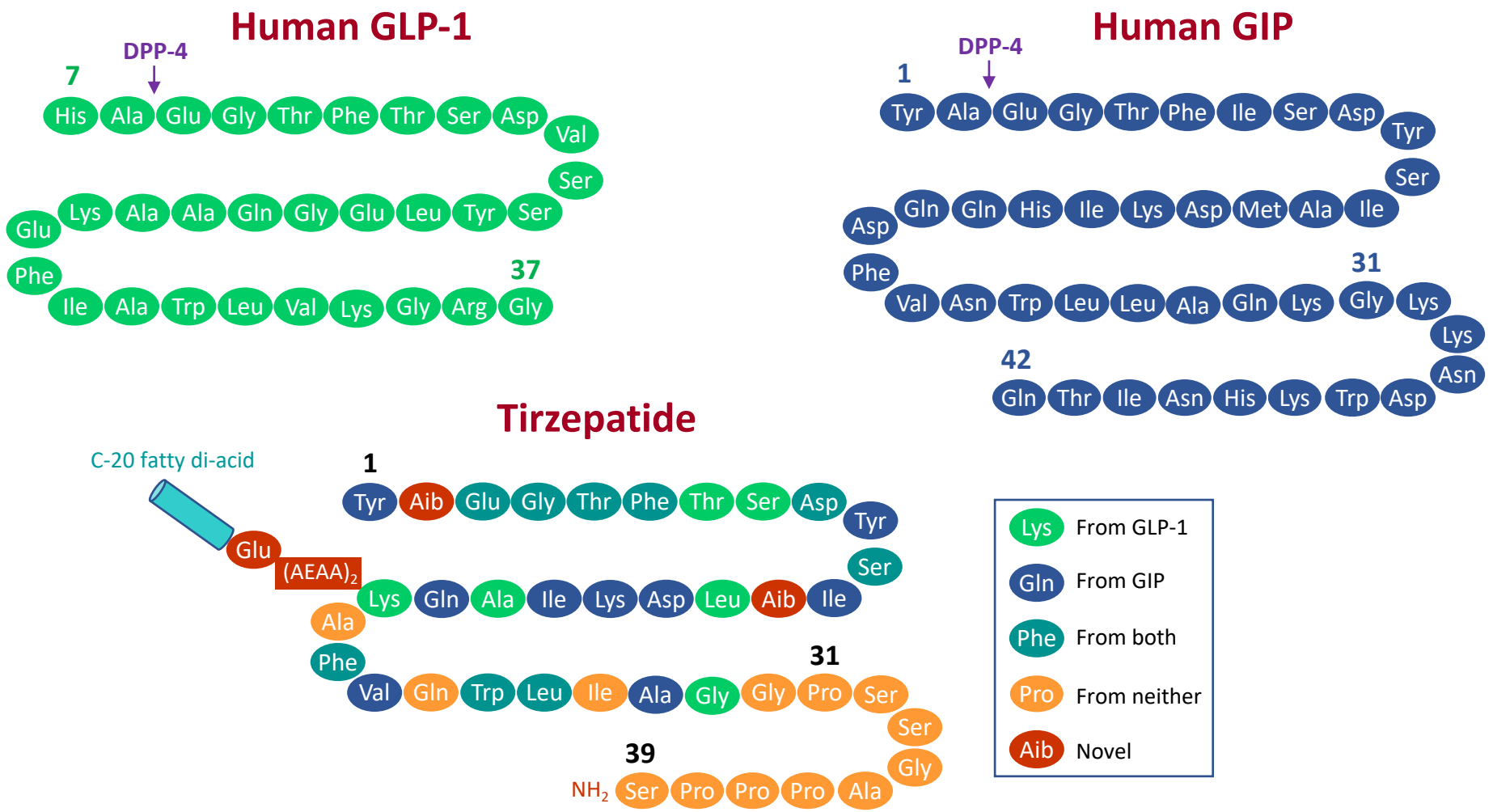
# Tirzepatide – a peptide chimera dual GLP-1 / GIP agonist




GIP = glucose-dependent insulinotropic peptide



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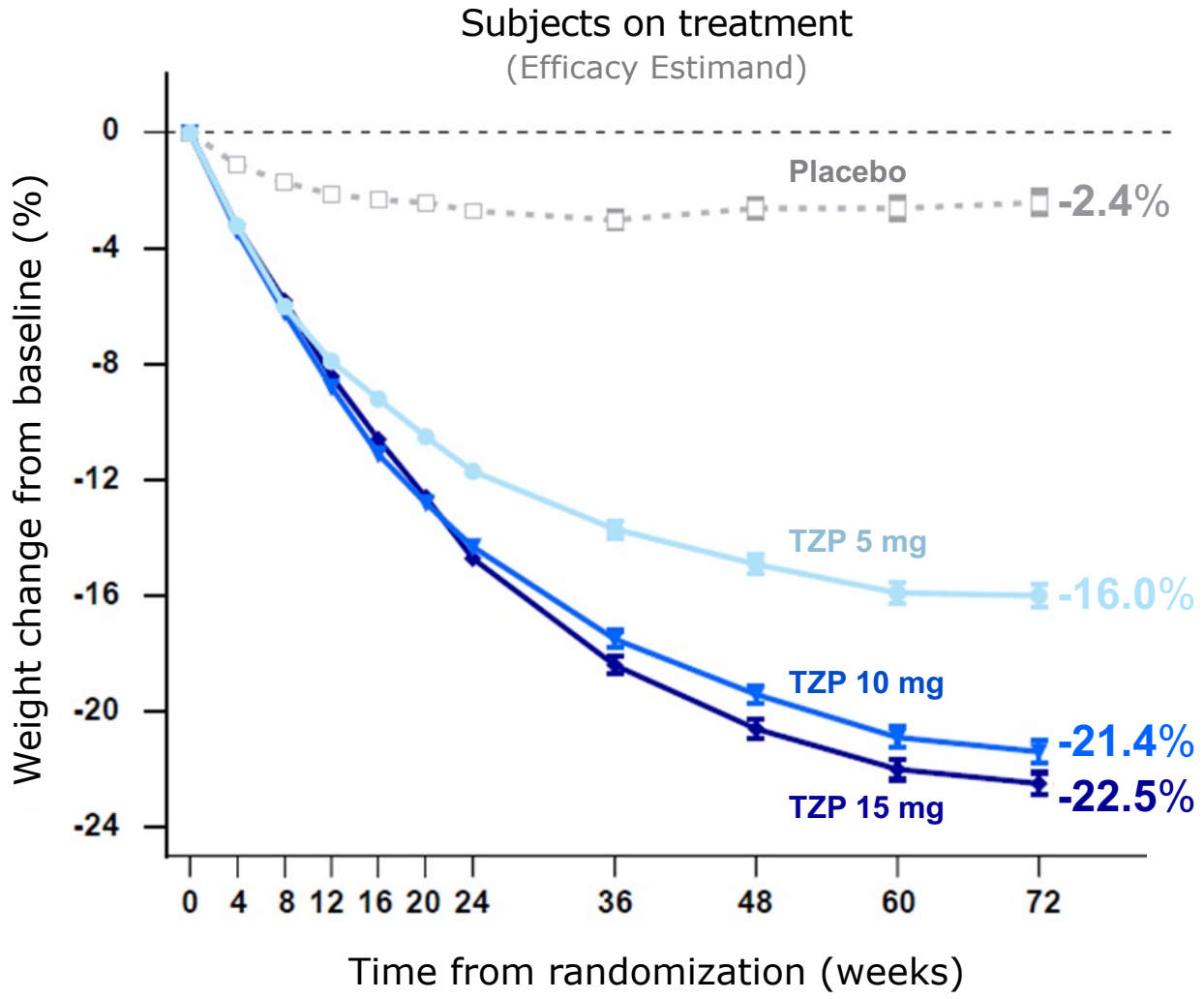
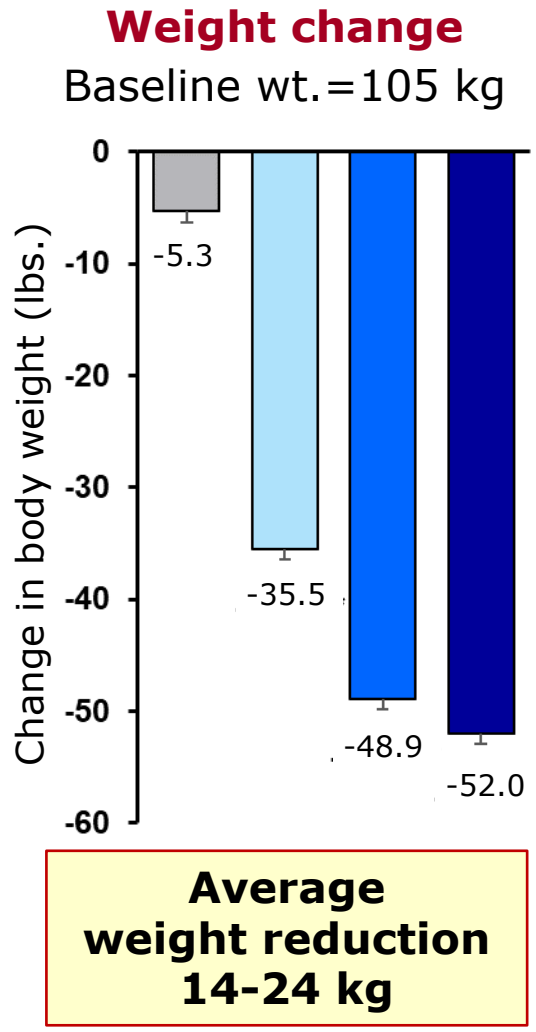
# Weight reduction on tirzepatide* – subjects without diabetes




**Average weight reduction 14-24 kg**

Jastreboff AM *et al*., *NEJM* 2022

*Tirzepatide is not approved for the treatment of obesity

# Dual agonists

- Designer molecules that activate two receptors
- Effective when there is a benefit to activating both receptors in the same cell
- Because of the success of GLP-1 agonists for the treatment of diabetes, obesity and NASH, GLP-1 agonism is the most common component of dual agonists
- The existence of **oxyntomodulin**, a **natural GLP-1/glucagon receptor dual agonist that promotes weight loss,** makes this combination an attractive mechanism



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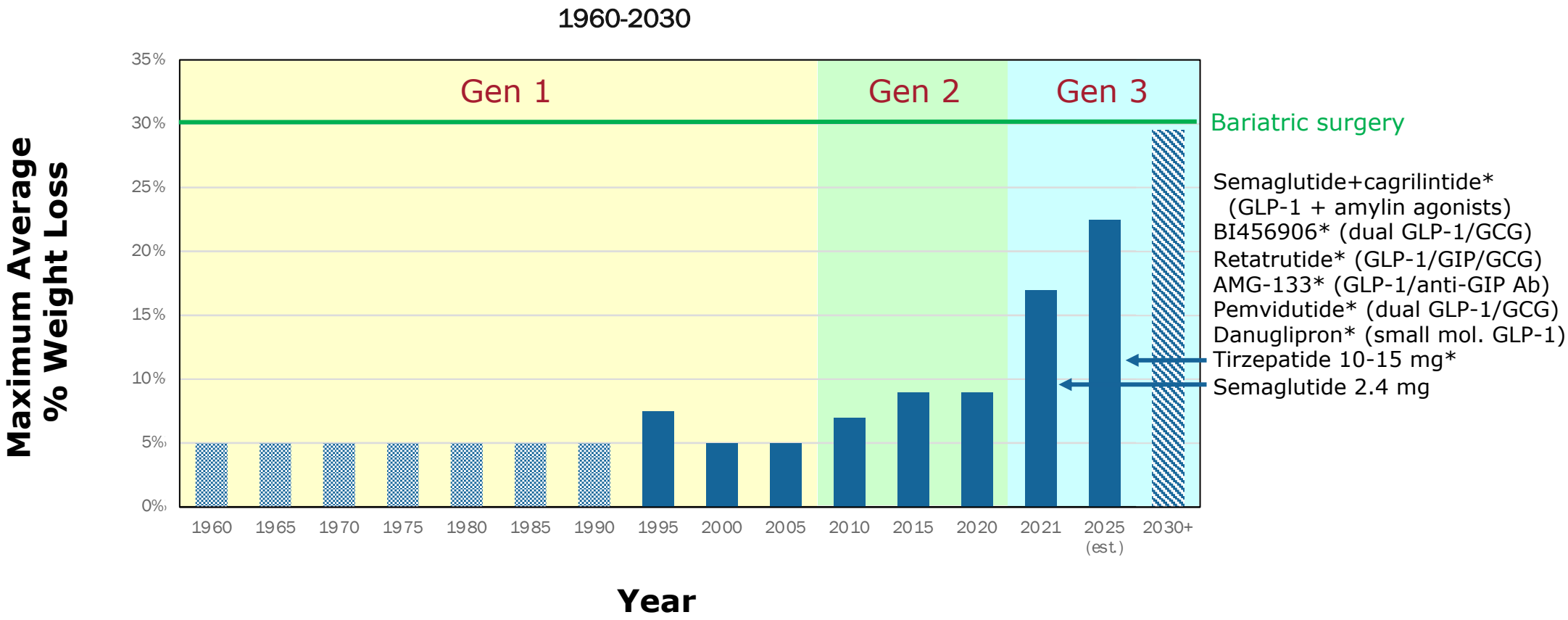
# The 3rd generation of AOMs includes dual and triple agonists




*This medication is not approved for the treatment of obesity

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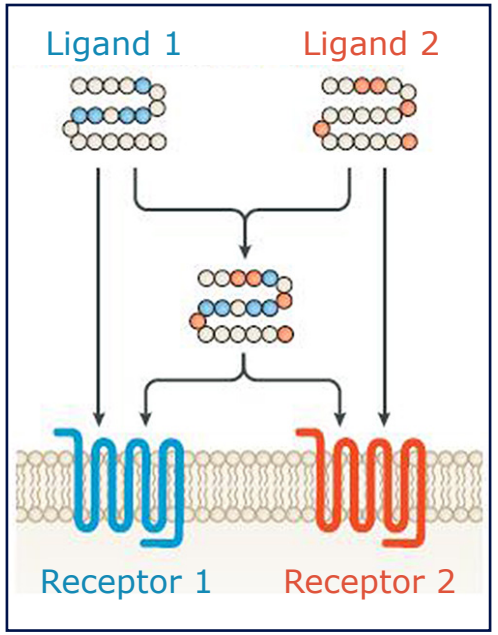


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