

Other Treatment Options in the Pipeline

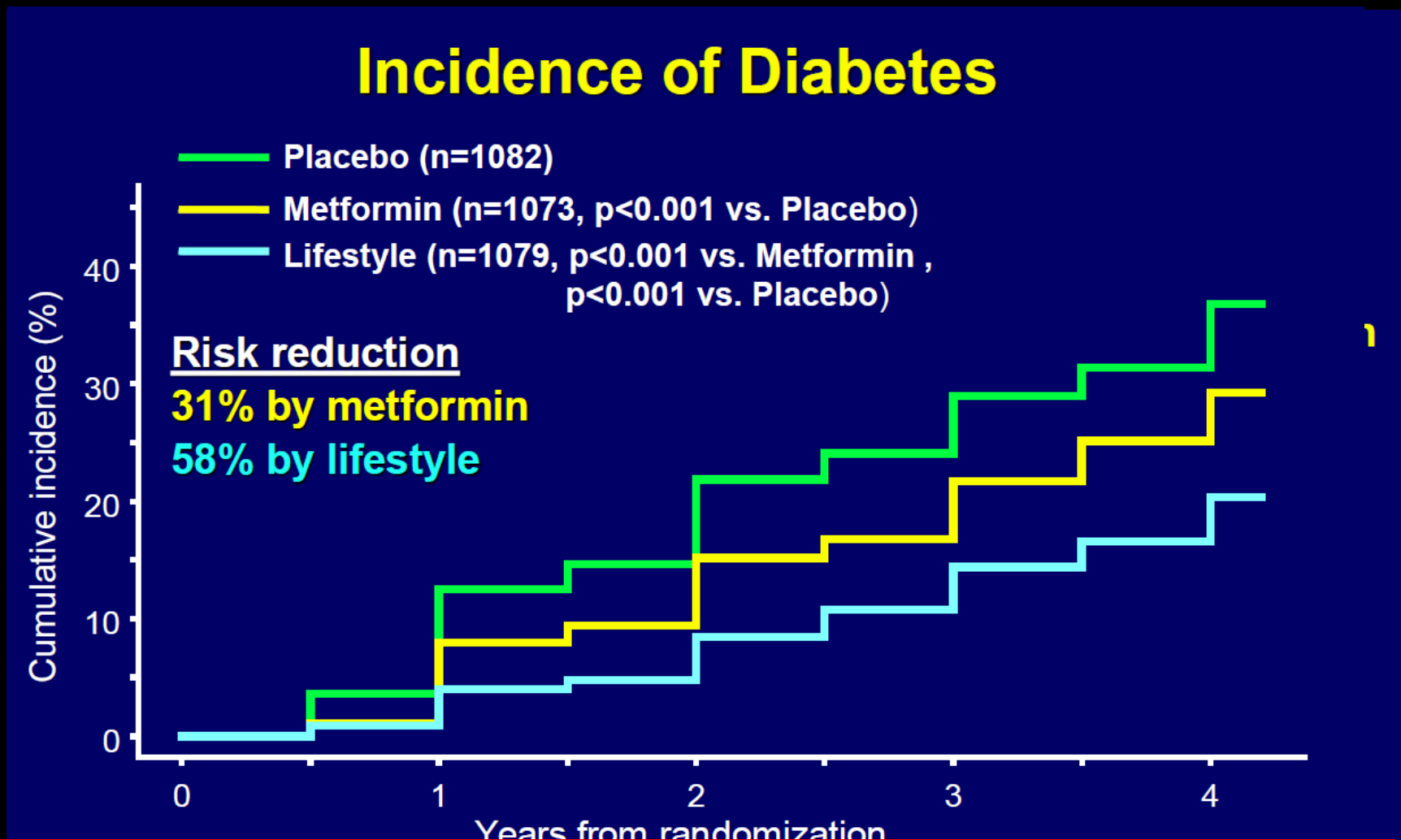
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Diabetes Prevention Program Outcomes



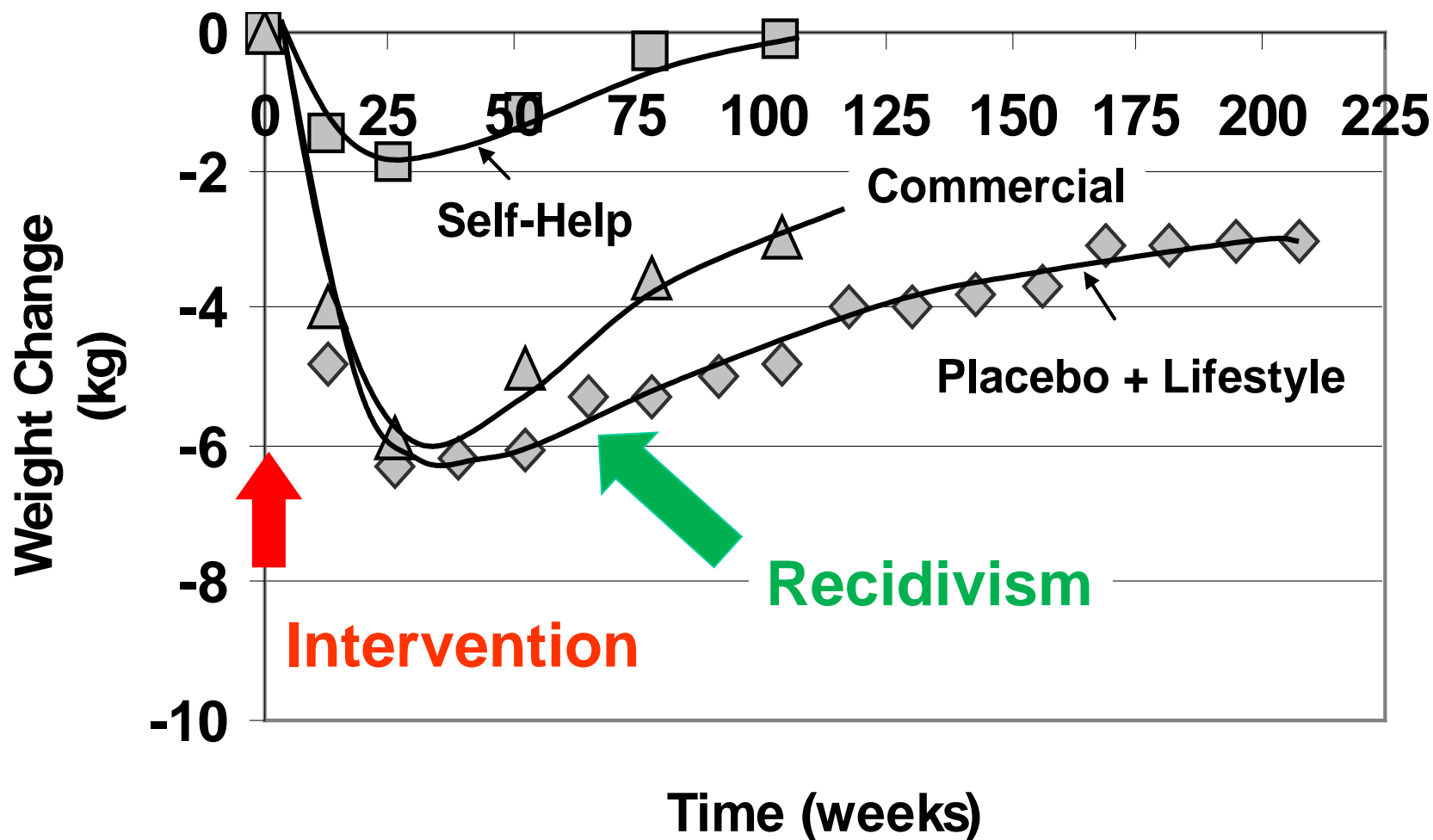
Treatment Goal: Durable 5-10% Weight Loss

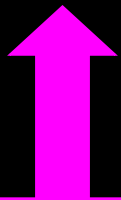
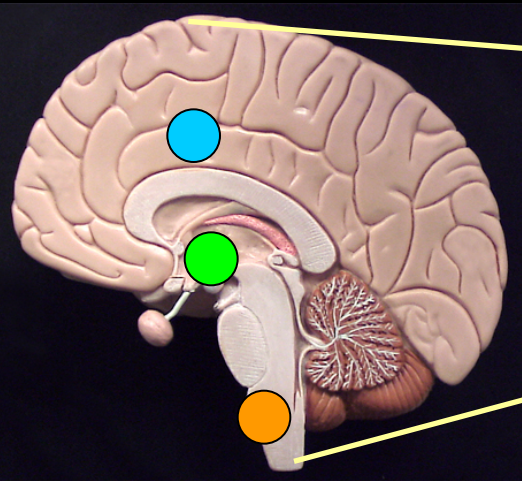
High-intensity Comprehensive Lifestyle Intervention to Achieve & Maintain 5- 10% Body Weight Reduction

Component	Weight Loss	Weight Loss Maintenance
Frequency and duration of treatment contact	14 or more in-person counseling sessions in 6 months with a trained interventionist (individual or group contact). Similarly structured, comprehensive web-based interventions, as well as evidence-based commercial programs may be recommended.	Monthly or more frequent in-person or telephone sessions for ≥1 year with a trained interventionist.
Diet	Low-calorie diet (typically 1200-1500 kcal/d for women, 1500-1800 kcal/d for men), with macronutrient composition based on patient's preferences and health status.	Reduced-calorie diet, consistent with reduced body weight, with macronutrient composition based on patient's preferences and health status.
Physical activity	≥150 min/wk of aerobic physical activity (e.g., brisk walking).	
Behavior therapy	Daily monitoring of food intake and physical activity, facilitated by paper diaries.	
	Weekly monitoring of weight.	
	Structured curriculum of behavior change (e.g., DPP), including goal setting, problem solving, and stimulus control.	
	Regular feedback and support from trained interventionist.	

- Primary Care Setting
- Certification Programs
- YMCAs
- Commercial Programs
- Phone-delivered
- Web-based
- Smart Phone Apps

Early Weight Loss-Limited Long-Term Effectiveness





- NPY5R antagonist ●
- MC4R agonist ●
- CB1R antagonist ●
- 5-HT_{2c} agonist ★
- CCK-A agonist ●
- (dex) Fenfluramine ●
- Axokine (CNTF) ●
- Topiramate ★
- Zonisamide ●
- Sibutramine ●
- Amphetamine ●
- [Phentermine
Ephedrine, PPA] ★
- Bupropion ★
- Fluoxetine ●
- Ecopipam ●
- Tesofensine ●

- SGLT2
- ★ Orlistat

- β₃ AR agonist
- DNP
- Thyroid H.



- GLP1 agonist ★
- Amylin ●
- PYY₃₋₃₆ ●
- Oxyntomodulin ●
- Leptin ●

Δ Energy Storage = E_{intake} - E_{output}

FDA-Approved Medications

Drug	Mechanisms	Dose	Study Duration (weeks)	Mean weight loss (kg (%)) PSWL-MA [‡] (kg)	Common Side Effects Contraindications
Orlistat (Xenical)	Pancreatic and gastric lipase inhibitor; resulting fat malabsorption reduces net energy intake.	120 mg before meals (TID)	52	Drug: 8.8 kg (8.8%) Placebo: 5.8 kg (5.8%) PSWL-MA: 2.6 kg	SE: Oily spotting, flatus with discharge, fecal
Lorcaserin (Belviq)	Selective 5HT _{2c} receptor agonist; promotes satiety and reduces food intake.	10 mg BID	52	Drug: 5.8 kg (5.8%) Placebo: 2.2 kg (2.2%) PSWL-MA: 3.2 kg	
Liraglutide (Saxenda)	GLP-1 agonist; delays gastric emptying & reduces food intake.	Starting dose: 0.6 mg subcutaneous; titrate dose weekly by 0.6 mg as tolerated to	56	Drug: 8.4 kg (8.0%) Placebo: 2.8 kg (2.6%) PSWL-MA: 5.3 kg	
Phentermine (Lomaira)		8 mg (TID)			
Phentermine/Topiramate (Qsymia)	receptor modulation; decreases appetite and reduces food intake.	Recommended dose: 7.5/46 mg Maximum dose: 15/92 mg		Drug: 7.5 mg/46 mg: 8.1 kg (7.8%) 15 mg/92 mg: 10.2 kg (9.8%) Placebo: 1.4 kg (1.2%) PSWL-MA: 8.8 kg	
Naltrexone/Bupropion (Contrave)	Opioid antagonist/dopamine and norepinephrine reuptake inhibitor; acts on CNS pathways to reduce food intake.	8 mg/90 mg tablet wk 1; increase by 1 tablet/d each week until maintenance dose of 2 tablets BID at week 4	56	Drug: 6.2 kg (6.4%) Placebo: 1.3 kg (1.2%) PSWL-MA: 5.0 kg	withdrawal, MAOIs, chronic opioid use, pregnancy

Lipase Inhibitor

Orlistat

5HT_{2c} Agonist

Lorcaserin

GLP-1 Agonist

Liraglutide

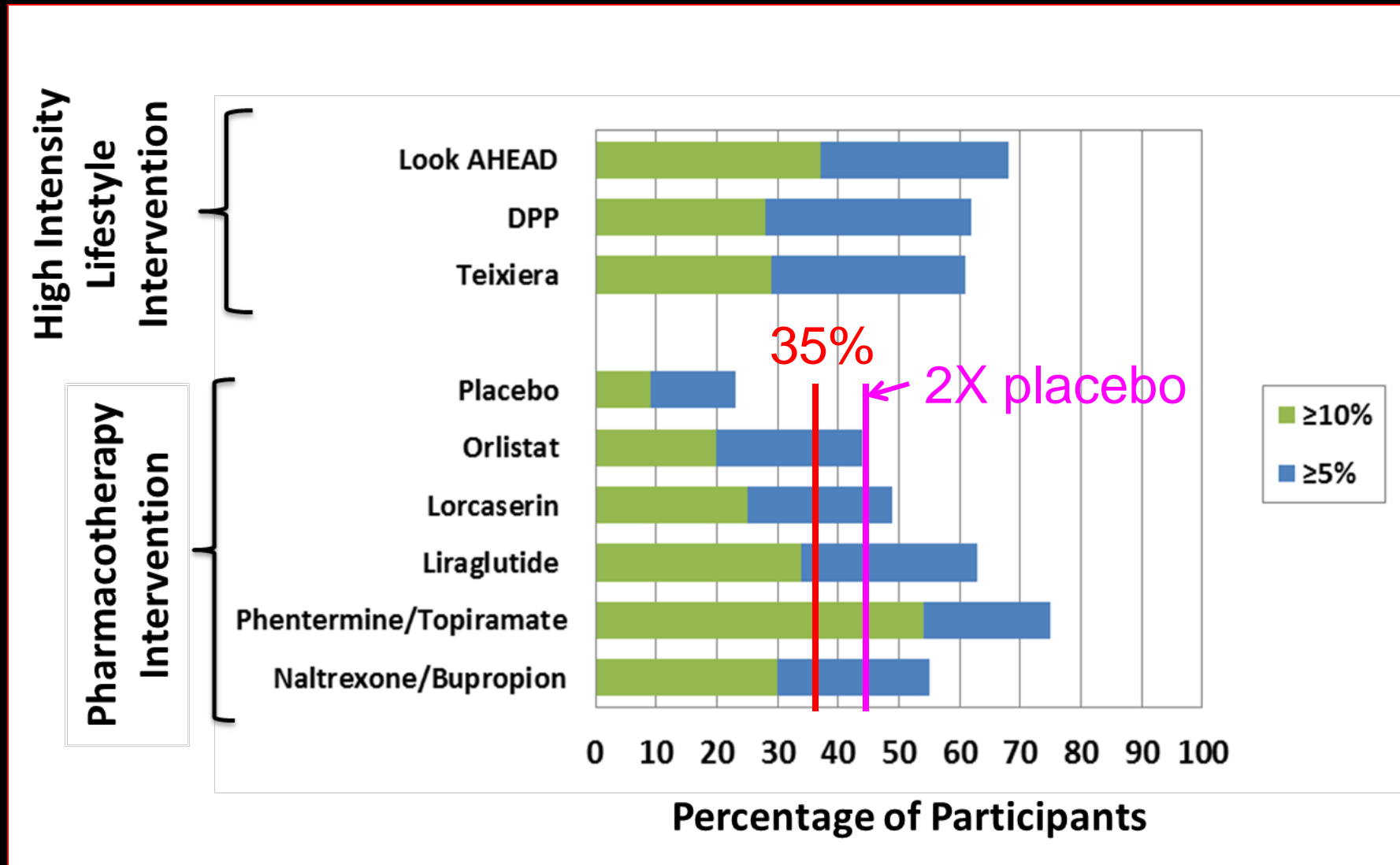
Sympath/GABA

Phen/Topx

μ-opioid ant/NE reupt inhib

Naltrax/Bupr

Comparative Effectiveness of Lifestyle & Pharmacologic Interventions

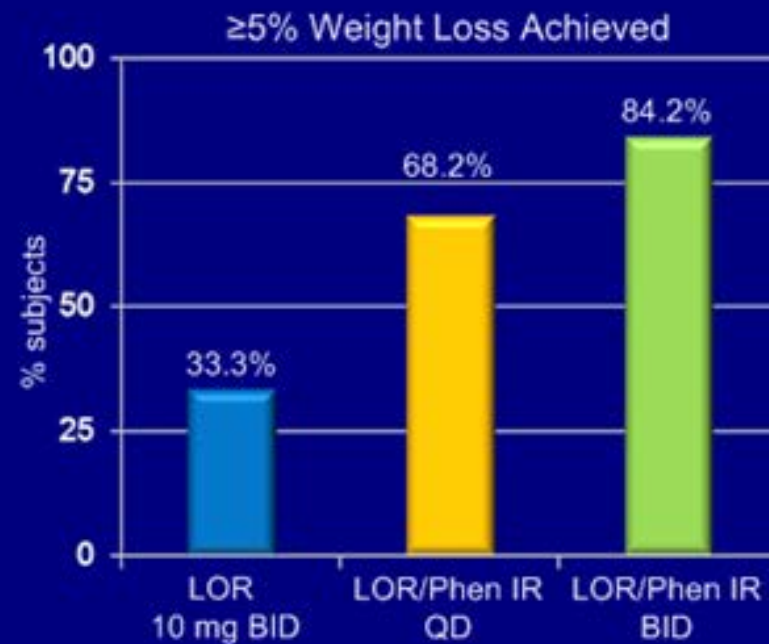
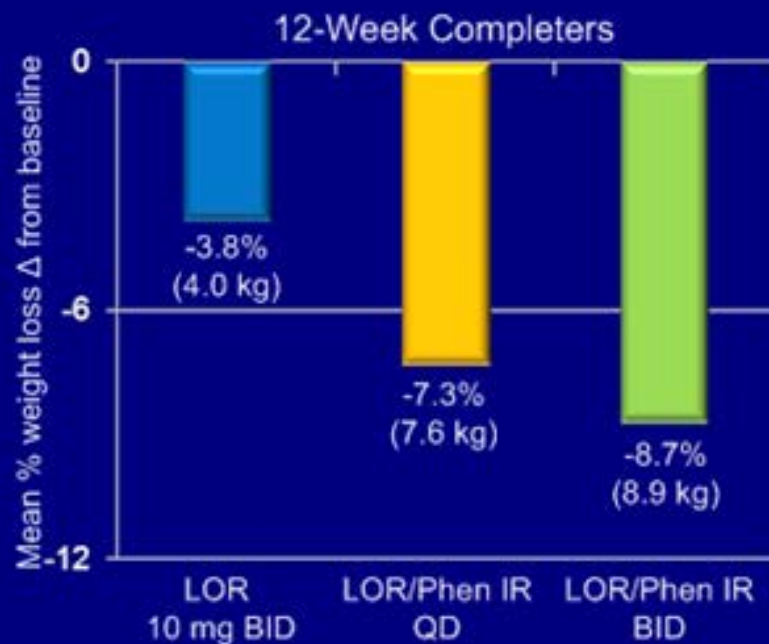


DPP, Diabetes Prevention Program

5-HT_{2C} Combinations



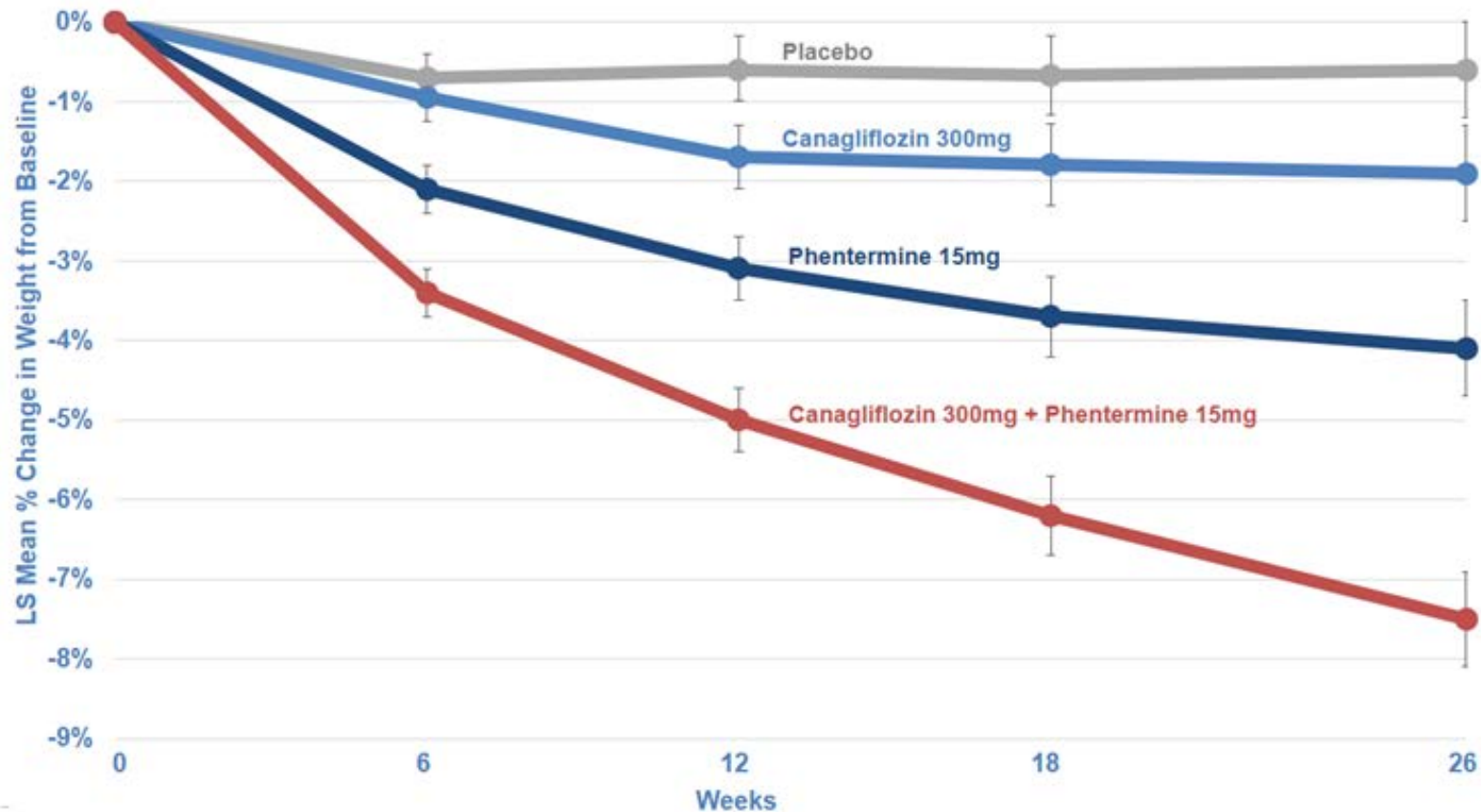
Weight Loss With Combined Lorcaserin + Phentermine Among Overweight or Obese Subjects



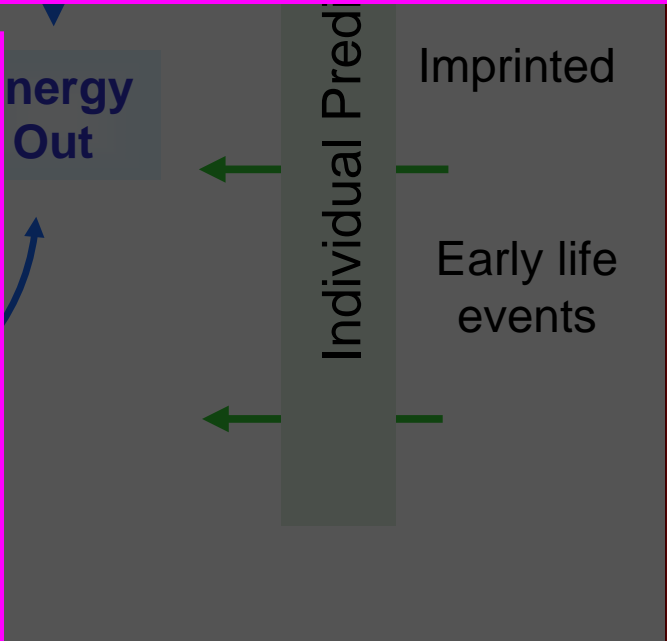
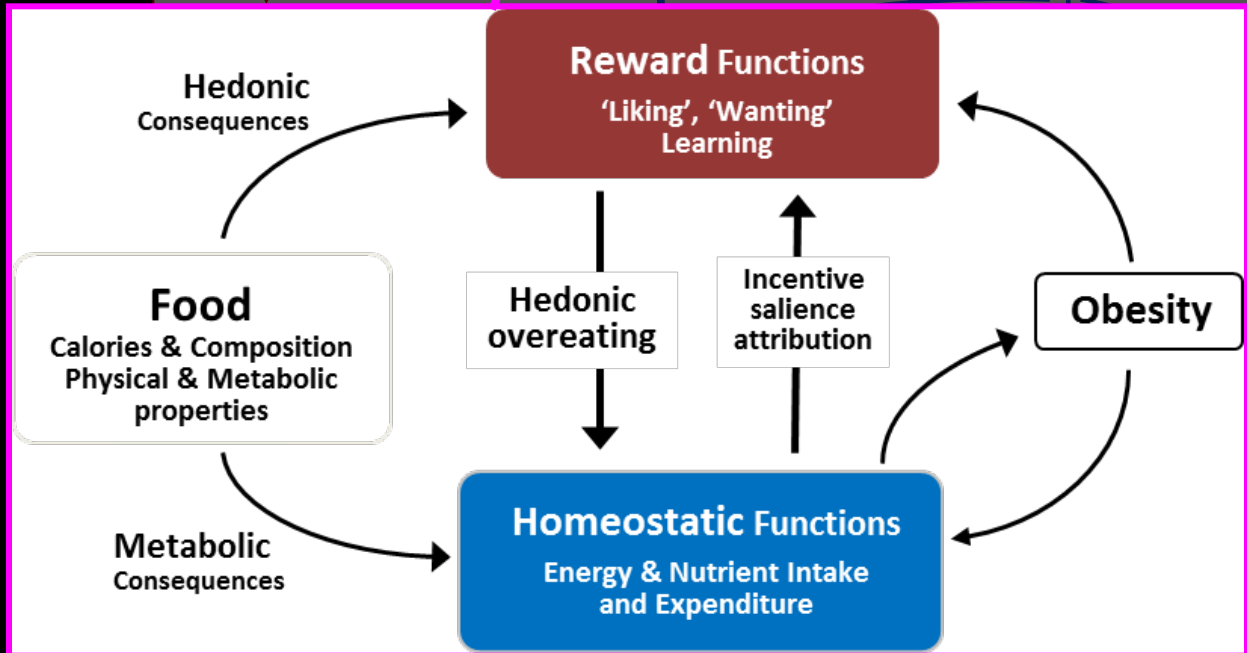
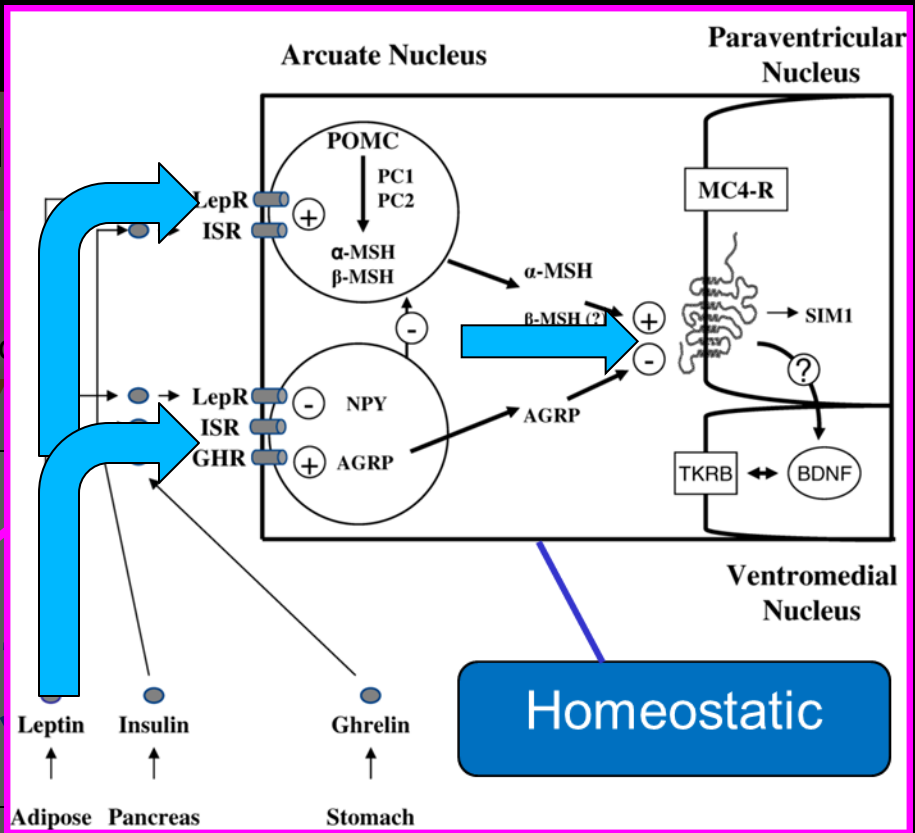
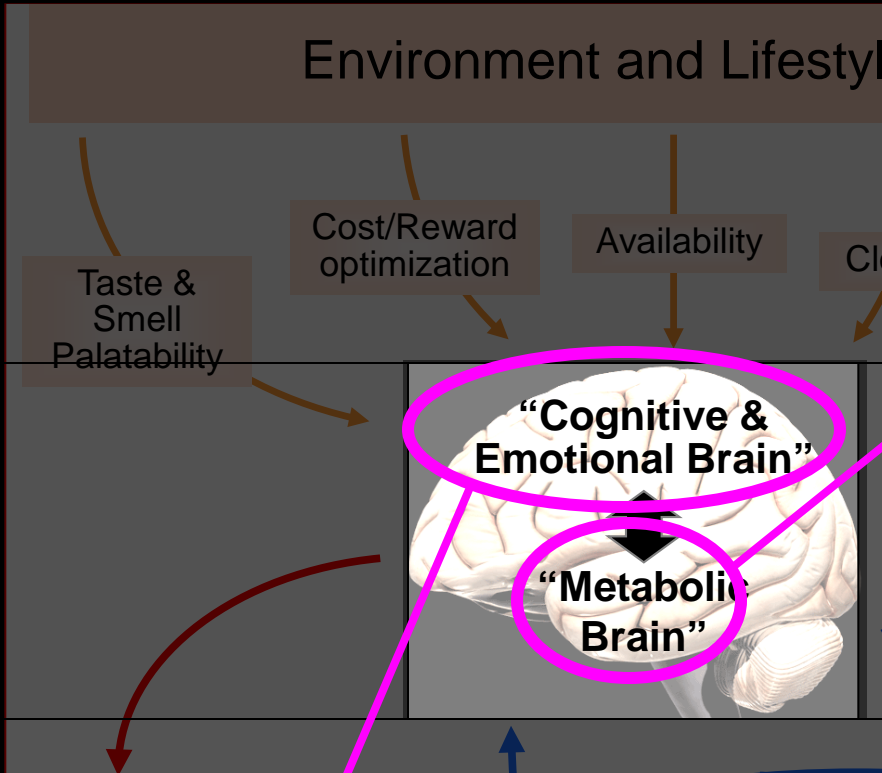
Phentermine, 15 mg

SGLT-1 & 2 Inhibitors/Combinations

Phase II Weight Loss Efficacy Canagliflozin/Phentermine Combination

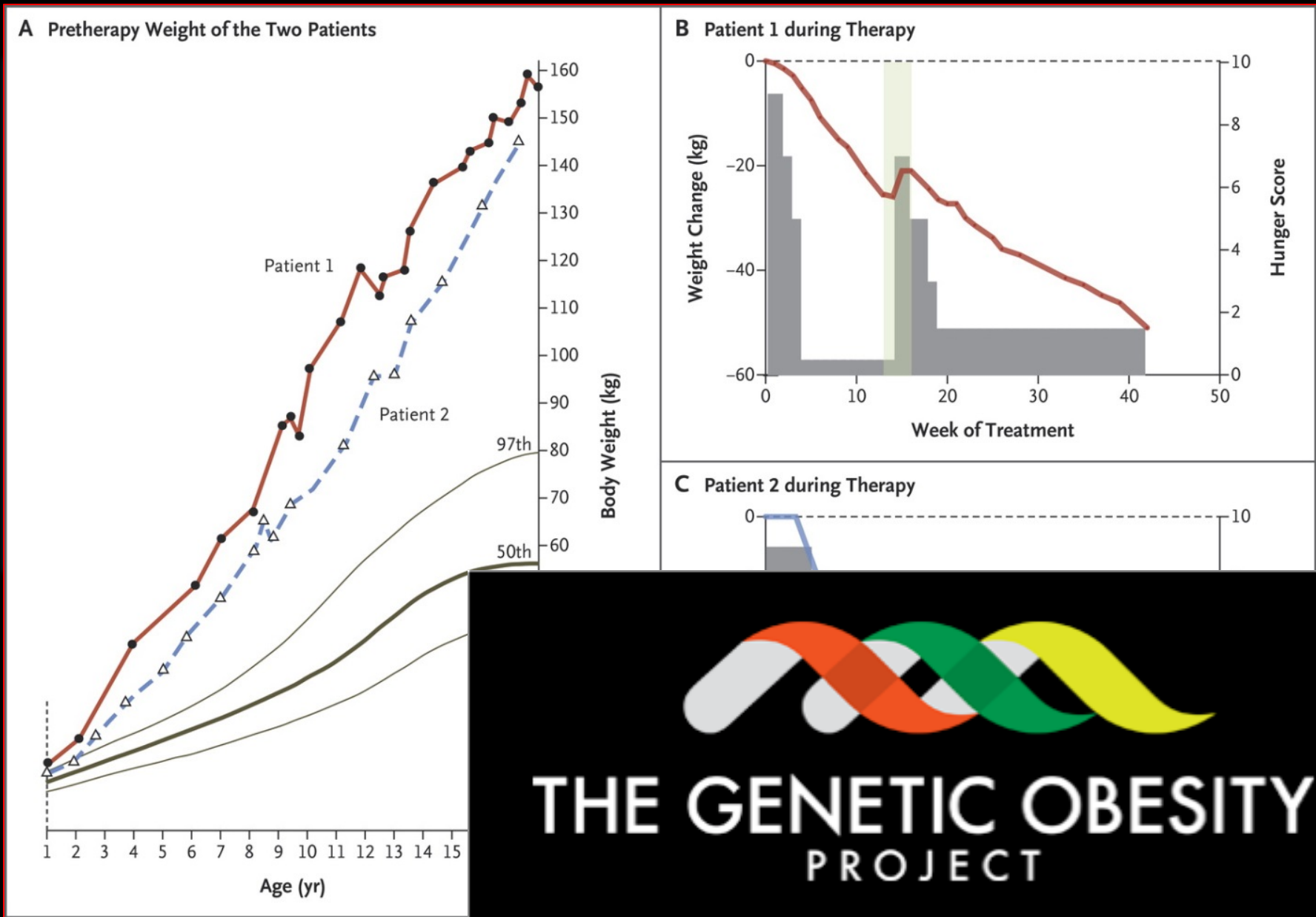


Hollander et al, 2016.06.12, ADA 76th Scientific Sessions, abstract 319-LB

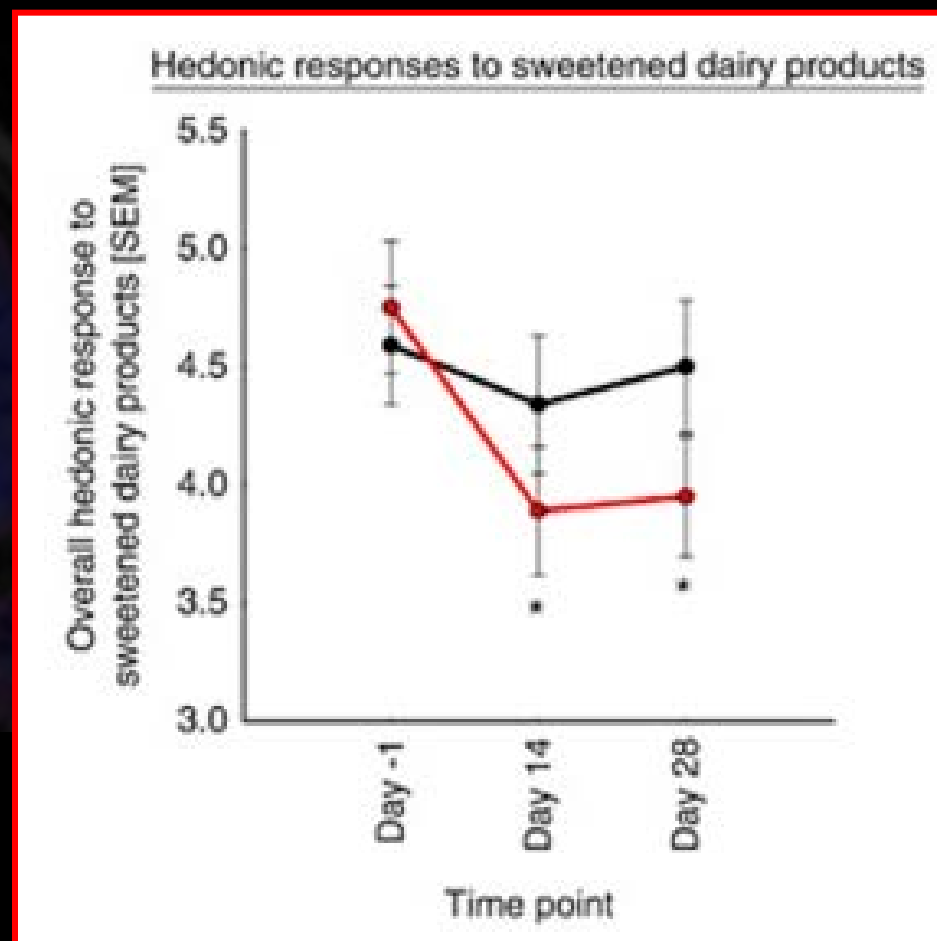
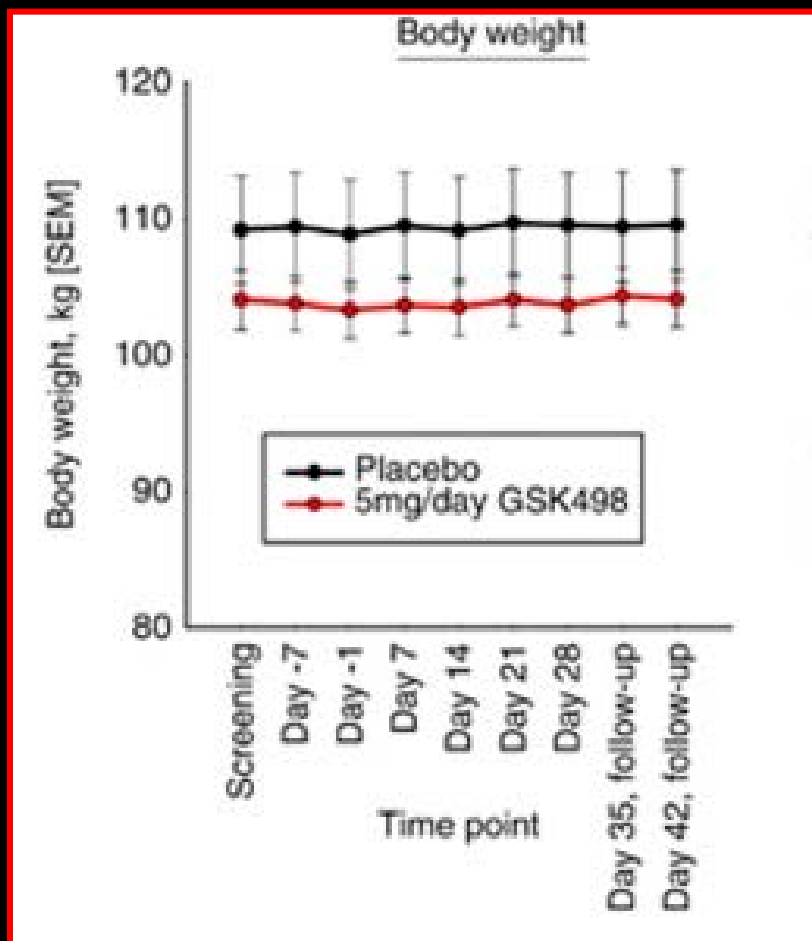


Courtesy HR Berthoud

POMC Deficiency Response to MC4R Agonist



Hedonic Effects of μ -opioid Receptor Antagonism



Peptides in Development

Peptide YY analog 3 compounds
With GLP-1 agonist

Neuropeptide Y analogs

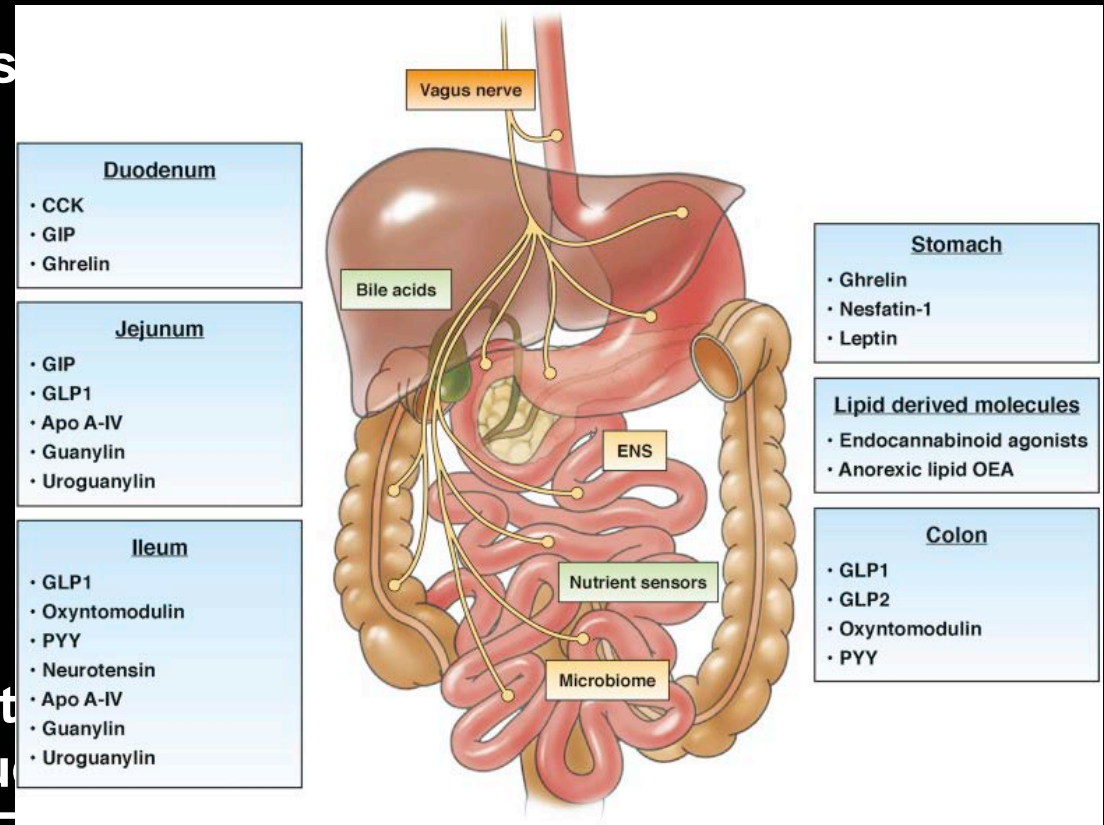
Ghrelin 3 compounds

Amylin analogs (+ Calcitonin)
Long-acting compounds

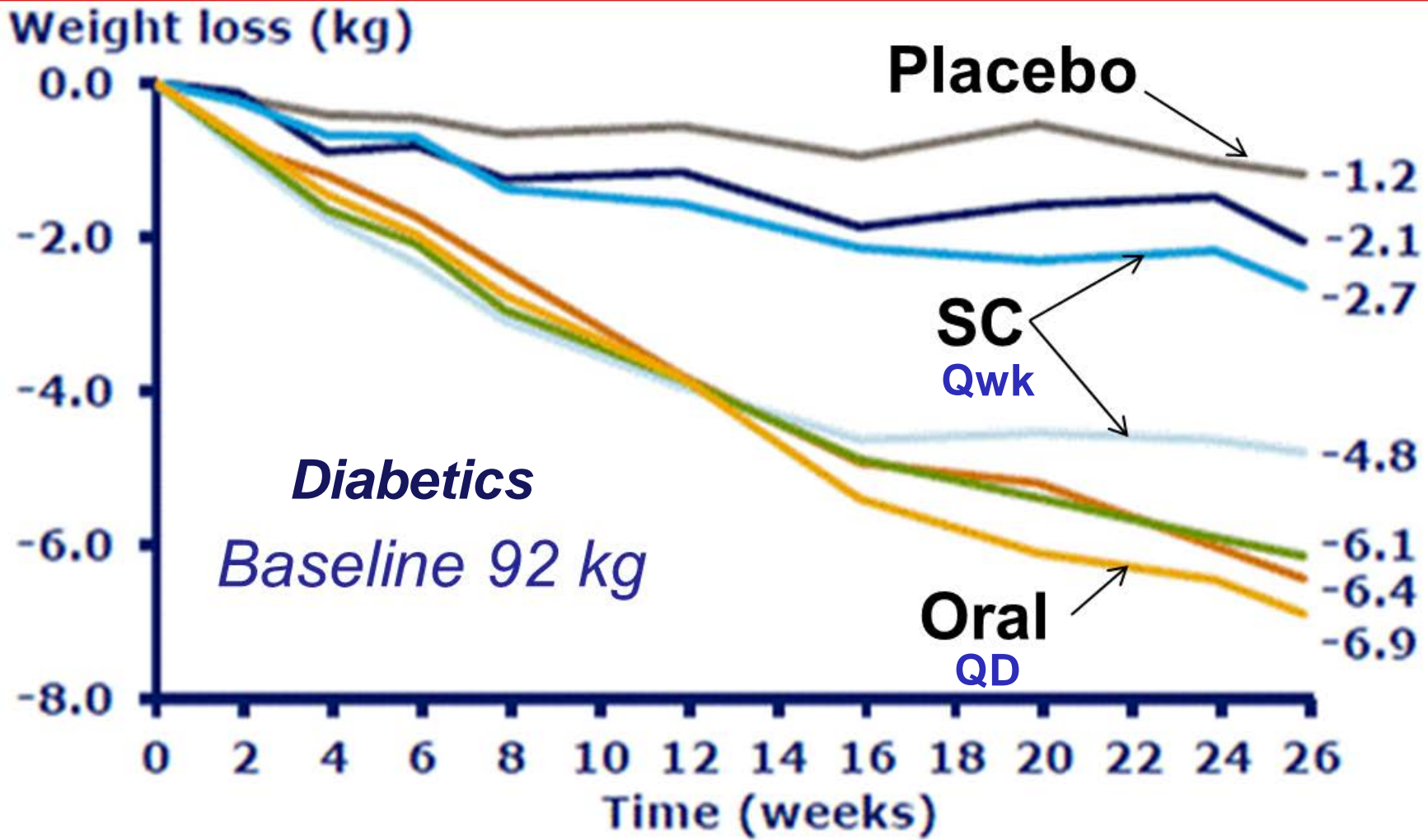
23+ GLP-1 agonists in various stages
Oxyntomodulin (GLP-1/glu)
GLP-1-Fc-FGF21; also FGF21 alone
GLP-1-GIP

With glucagon analog (3)
Long-acting preparations

Semaglutide (Novo Nordisk)



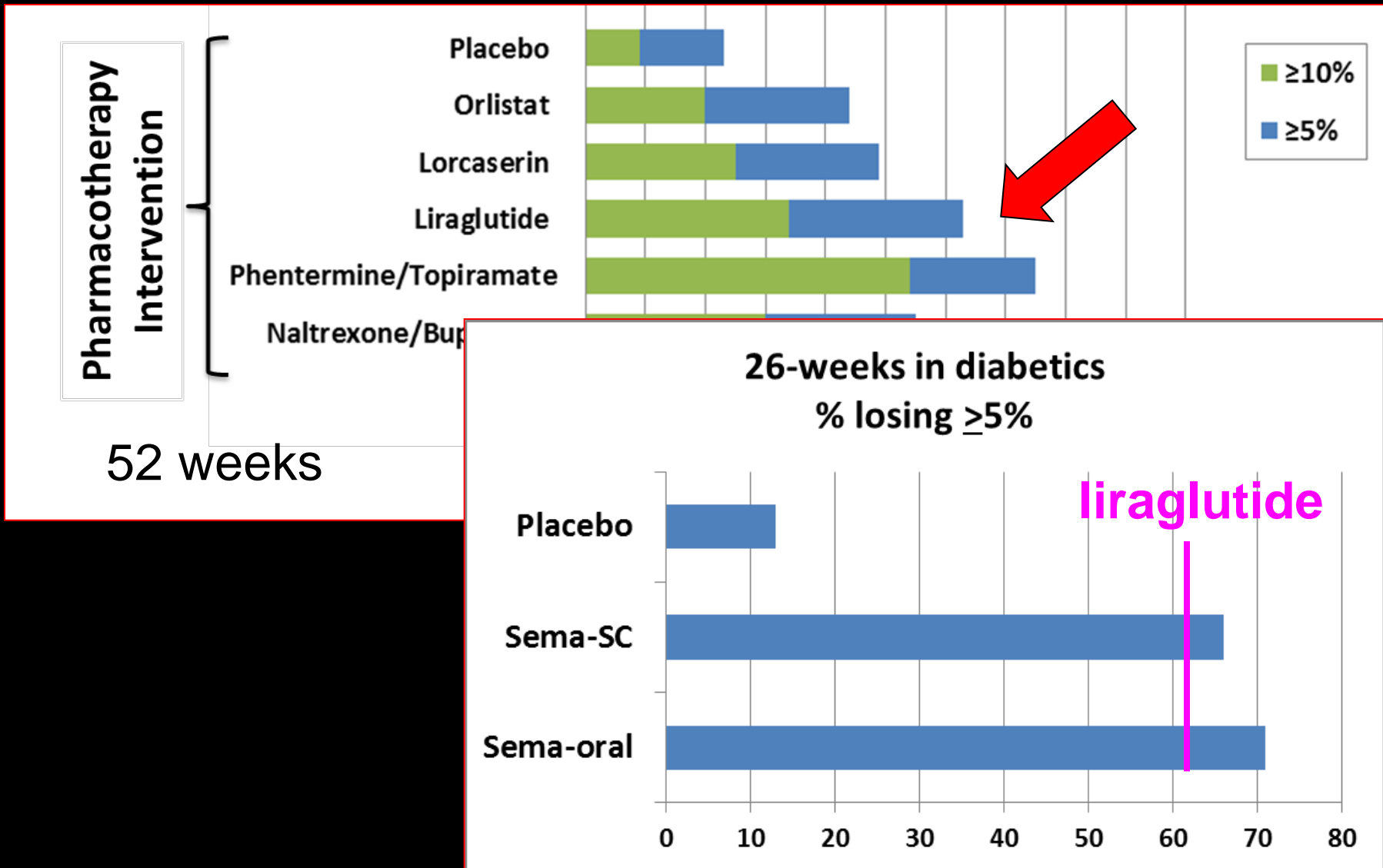
GLP-1 Agonist: Semaglutide



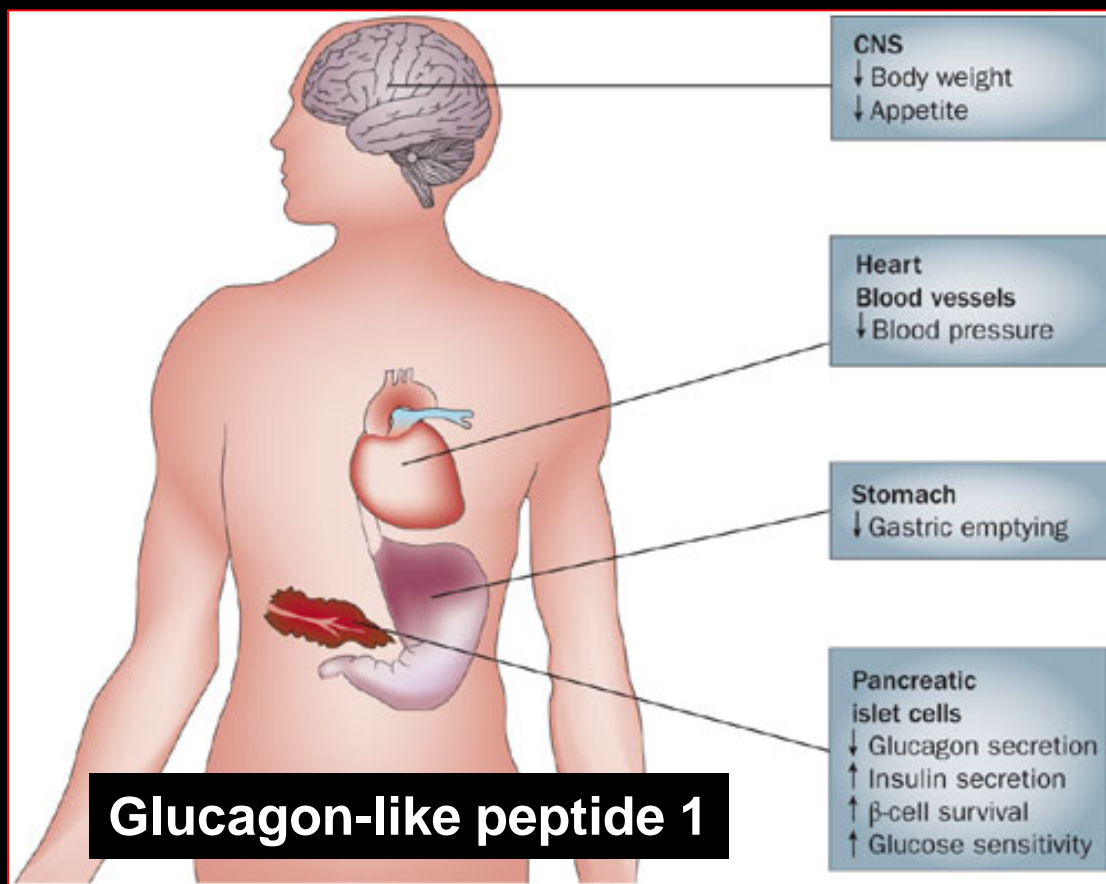
degradation

— Placebo — Sema 2.5 mg — Sema 5 mg — Sema 10 mg — Sema 20 mg — Sema 40 mg — Sema 1 mg sc

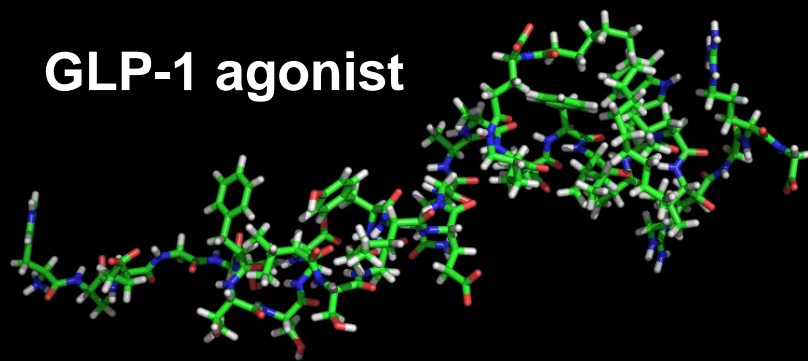
Semaglutide: Relative Efficacy



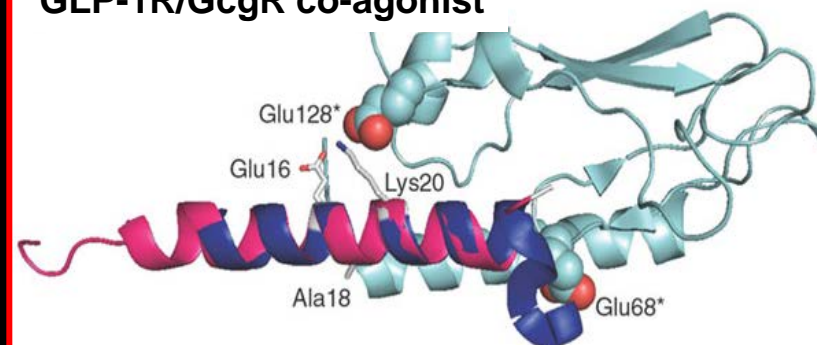
Combination Peptides



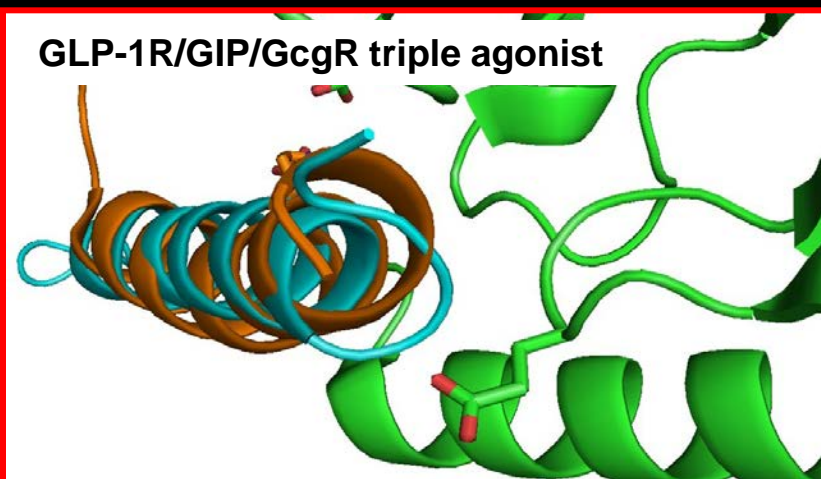
GLP-1 agonist



GLP-1R/GcgR co-agonist



GLP-1R/GIP/GcgR triple agonist

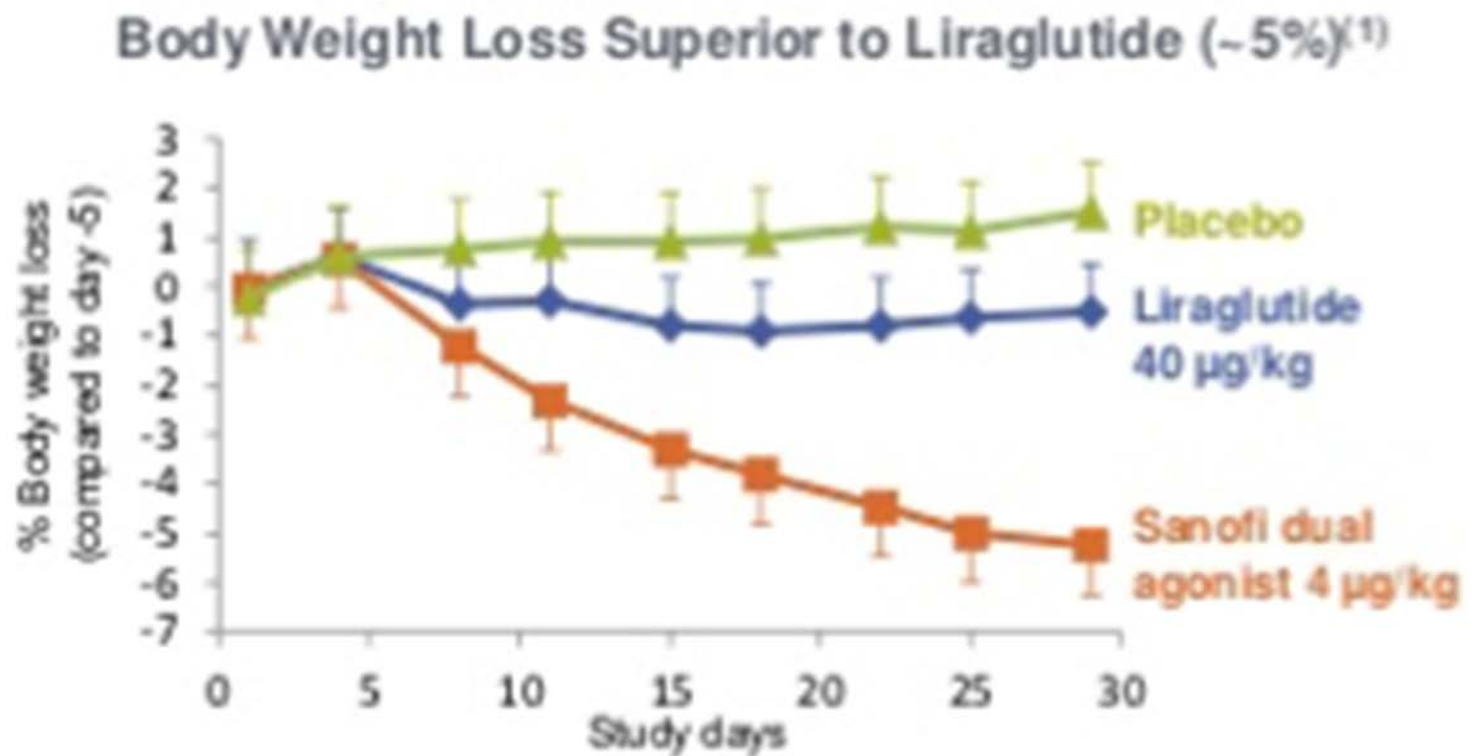


ZP2929: GLP-1/GCG dual agonist

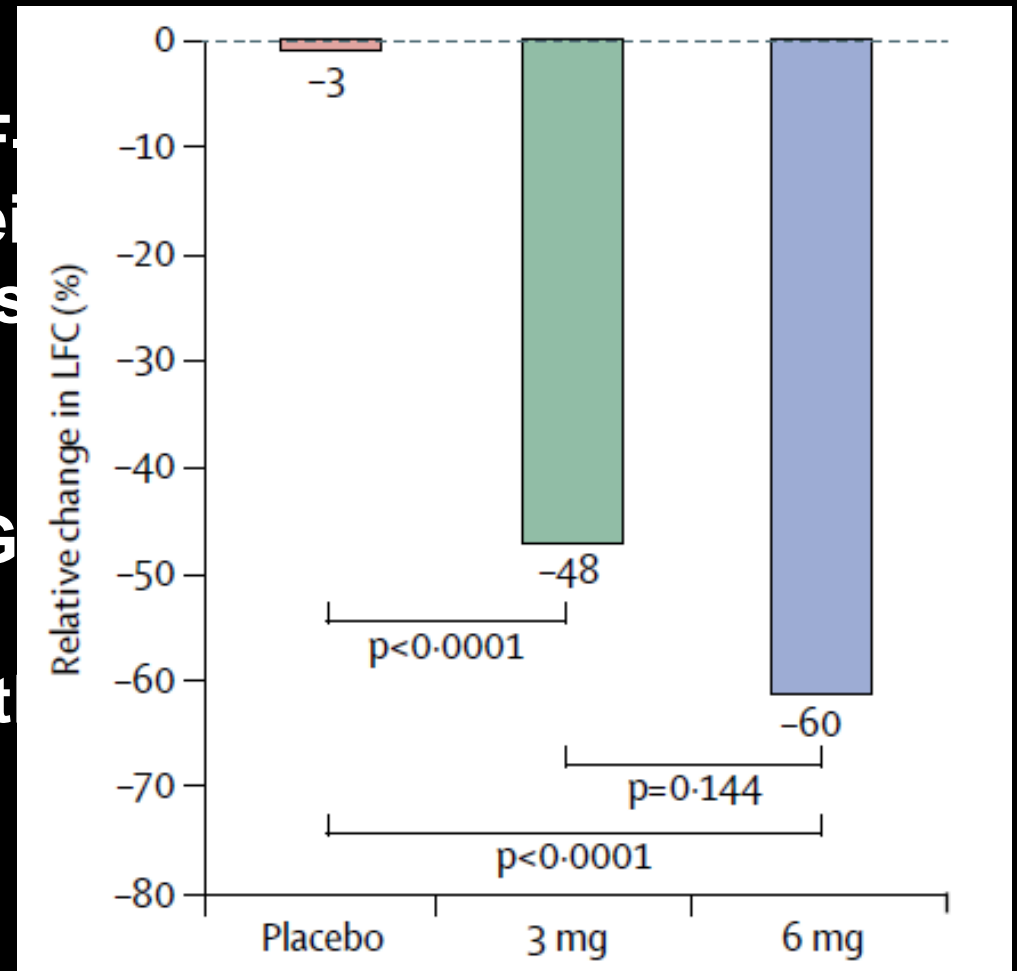
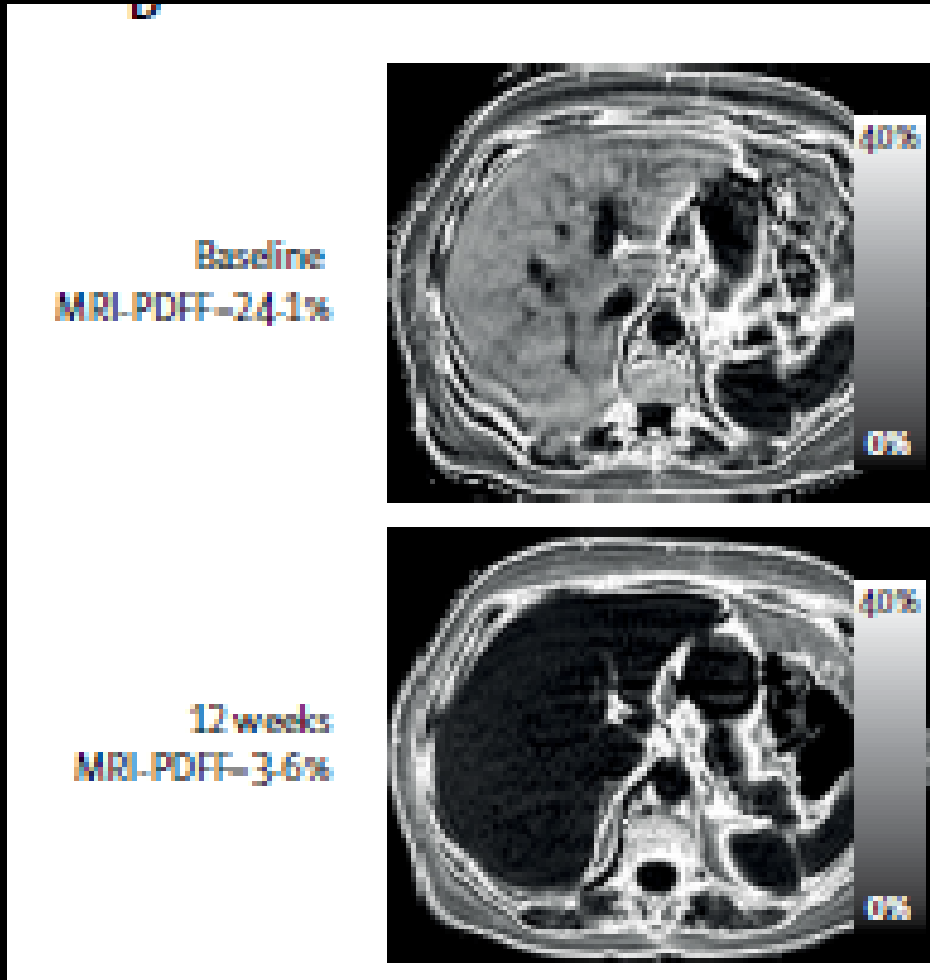
Diet-Induced Obesity Model

SAR425899: GLP-1/GCG dual agonist

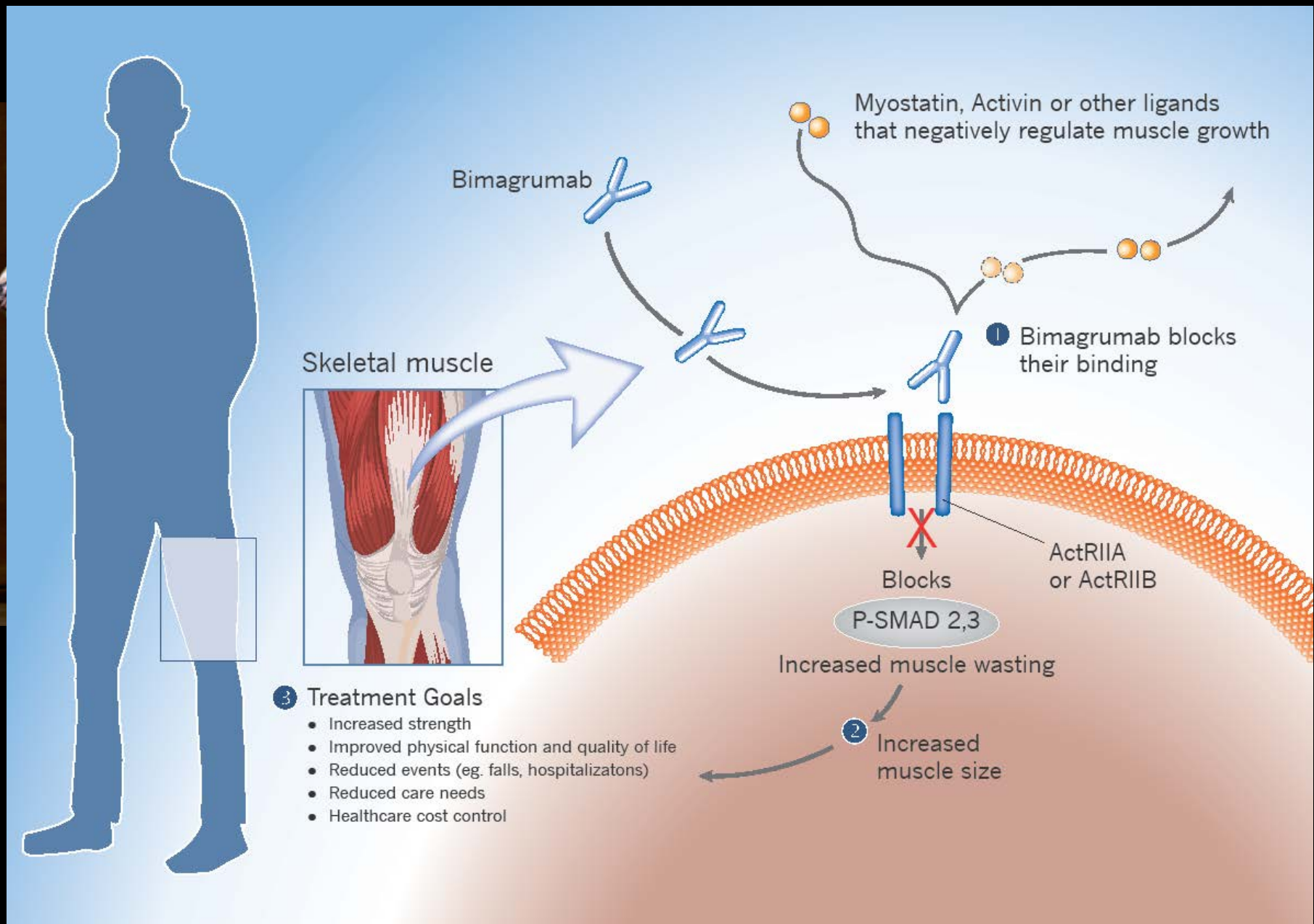
Body Weight Gain (g)



NGM282: FGF-19 Agonist for NASH



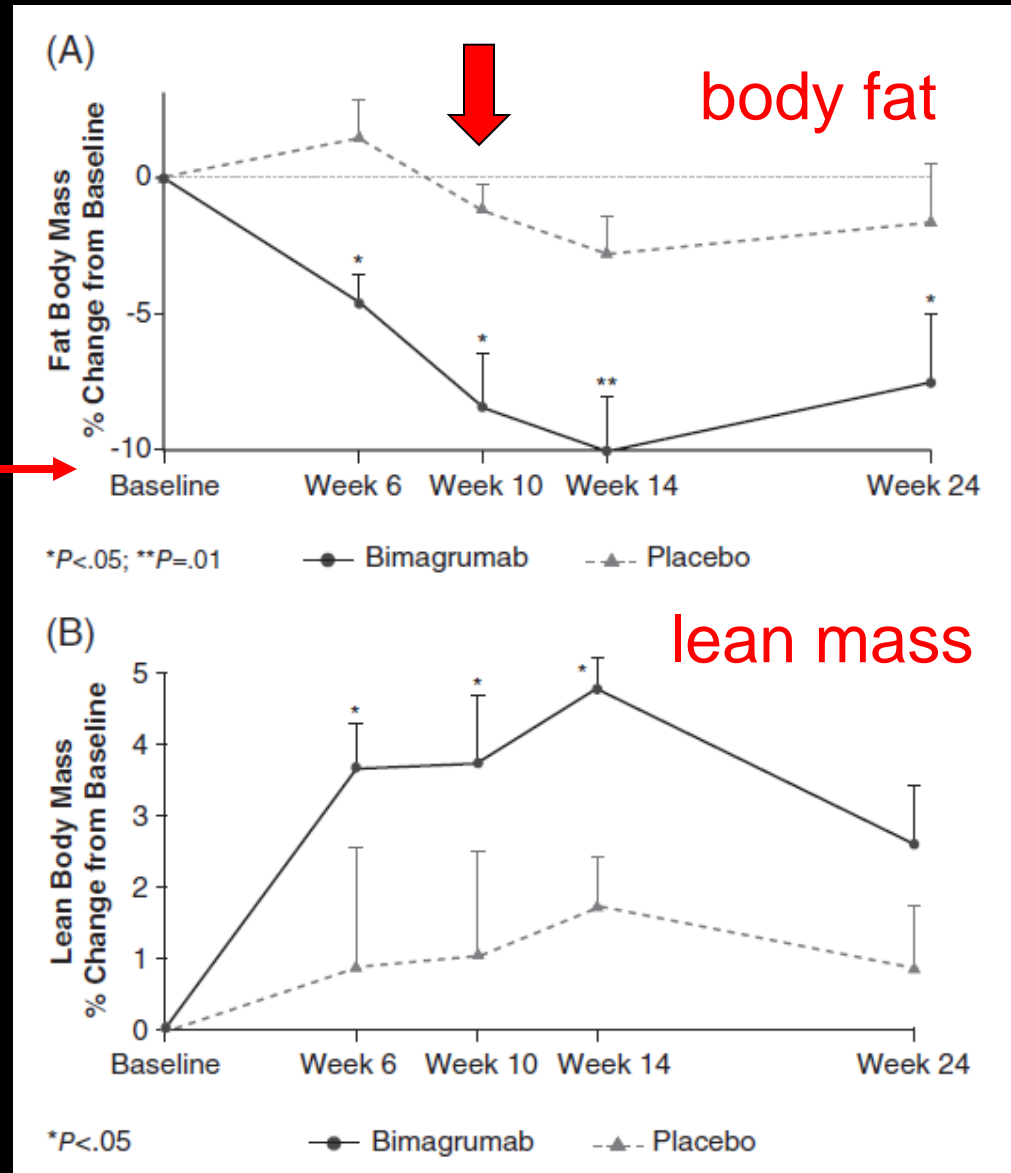
Bimagrumab: Partitioning Adipose Tissue and Skeletal Muscle



Bimagrumab: Body Composition Effects

Patients with Insulin Resistance

Single iv dose →



Δ -7.9%

Δ 2.7%

Bimagrumab: HbA1c Effects

