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# Incretin-Based Therapies: The Past, Present, and Future of Weight Loss Drugs

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Associate Professor
SWOSU College of Pharmacy

The Walter P. Scheffe Continuing Pharmaceutical Education Series
October 29, 2023

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## Financial Disclosure and Resolution

2

Under guidelines established under the Standards for Integrity and Independence in Accredited Continuing Education, disclosure must be made regarding relevant financial relationships with ineligible companies within the last 24 months.

**Jeremy L. Johnson**

I have no relevant financial relationships with ineligible companies to disclose

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# Experimental or Off-Label Drug/Therapy/Device Disclosure

I will be discussing experimental or off-label drugs, therapies and/or devices that have not been approved by the FDA.

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# Professional Practice Gap

- Overweight and obesity are at an all time high in the US. Recent clinical trials have shown GLP-1 and GIP/GLP-1 receptor agonists can safely reduce weight with greater efficacy than past prescription drugs. Newer incretin analog products are emerging as potential weight-loss drugs as well.
- Pharmacists may not be aware of these recent findings and may not yet appreciate how to recommend or counsel on these therapies. The lay public has heard these drugs are great for weight loss and are asking for them.
- Pharmacists need to know how to discuss, recommend, and counsel on the use of GLP-1 and GIP/GLP-1 receptor agonists for weight loss. They need to know the findings of clinical trials and appreciate the complications of supply issues and costs.

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# Learning Objectives

At the completion of this activity, pharmacists will be able to:

1. Interpret findings from select trials regarding incretin analogues and weight loss
2. Identify which incretin analogue products are approved for weight loss
3. Apply evidence of weight loss with incretin analogues to patient case scenarios

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## What is the expected loss of body weight from traditional pharmacologic weight loss therapies, phentermine/topiramate ER, naltrexone/burpropion ER, phentermine, orlistat?

5%

11%

18%

25%

Start the presentation to see live content. For screen share software, share the entire screen. Get help at **pollev.com/app**

6

When poll is active, respond at **pollev.com/ou321**
Text **OU321** to **37607** once to join

**What is the expected loss of body weight from liraglutide 3.0 mg use according to data from the SCALE Obesity trial?**

8%
10%
16%
24%

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When poll is active, respond at **pollev.com/ou321**
Text **OU321** to **37607** once to join

**What is the expected loss of body weight from dulaglutide 4.5 mg use according to data from the AWARD-11 trial?**

5%
12%
20%
25%

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When poll is active, respond at **pollev.com/ou321**
Text **OU321** to **37607** once to join

**What is the expected loss of body weight from semaglutide 2.4 mg use according to data from the STEP-4 trial?**

6%
11%
17%
24%

Start the presentation to see live content. For screen share software, share the entire screen. Get help at **pollev.com/app**

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When poll is active, respond at **pollev.com/ou321**
Text **OU321** to **37607** once to join

**What is the expected loss of body weight from tirzepatide 15 mg use according to data from the SURMOUNT-1 trial?**

5%
11%
18%
23%

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# Overweight/Obesity Defined

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- Body weight that is higher than what is considered healthy for a given height is described as overweight or obesity.
- Body Mass Index (BMI) is a screening tool for overweight and obesity.
  - Does not measure body fat directly and does not diagnose the body fatness or health of an individual
  - Moderately correlated with more direct measures of body fat
    - skinfold thickness measurements
    - bioelectrical impedance
    - underwater weighing
    - dual energy x-ray absorptiometry (DXA) and other methods
  - Strongly correlated with various adverse health outcomes consistent with these more direct measures of body fatness


https://www.cdc.gov/obesity. Accessed 3/12/2023.

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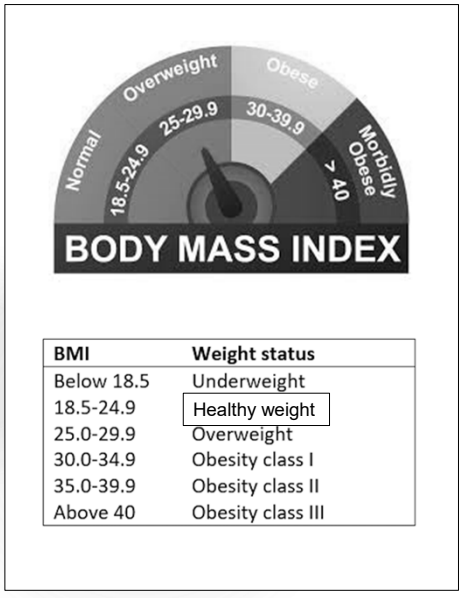


| BMI | Weight status |
|---|---|
| Below 18.5 | Underweight |
| 18.5-24.9 | Healthy weight |
| 25.0-29.9 | Overweight |
| 30.0-34.9 | Obesity class I |
| 35.0-39.9 | Obesity class II |
| Above 40 | Obesity class III |

# BMI Ranges and Categories

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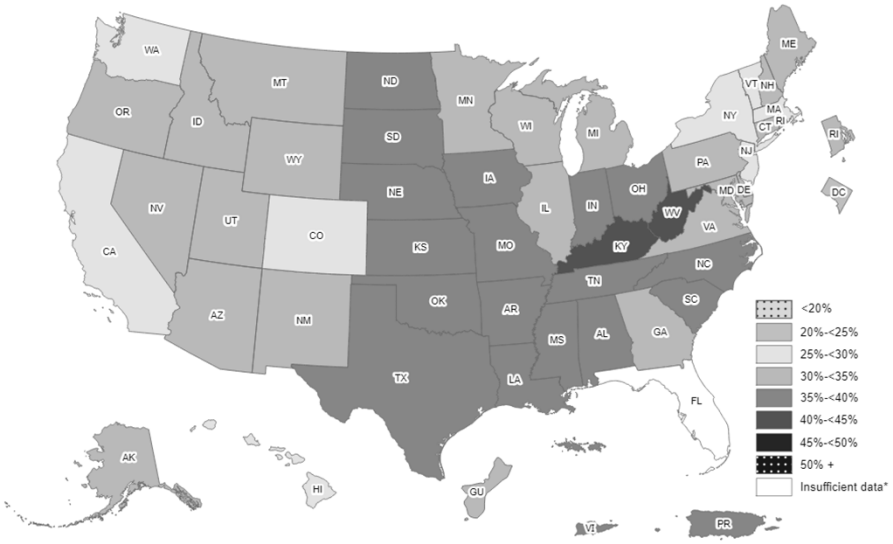
- Use “Healthy Weight” instead of “Normal Weight”
- “Morbidly Obese” is an older term for “Severe Obesity”
- Obesity is divided into 3 classes

12

# Statistics: Overall obesity among US adults




https://www.cdc.gov/obesity. Accessed 3/12/2023.

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# Obesity Statistics

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- The US obesity prevalence was 41.9% (2017 – March 2020)
- From 1999 –2000 through 2017 –March 2020, US obesity prevalence increased from 30.5% to 41.9%
  - During the same time, the prevalence of severe obesity increased from 4.7% to 9.2%
- Obesity prevalence by age
  - 39.8% among adults aged 20 to 39 years
  - 44.3% among adults aged 40 to 59 years
  - 41.5% among adults aged 60 and older
- Obesity prevalence by race
  - Non-Hispanic Black adults (49.9%)
  - Hispanic adults (45.6%)
  - Non-Hispanic White adults (41.4%)
  - Non-Hispanic Asian adults (16.1%)

Annual obesity-related medical care costs in the United States, in 2019 dollars, were estimated to be nearly $173 billion

https://www.cdc.gov/obesity. Accessed 3/12/2023.
NHANES, 2021.

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# Causes of Obesity

15

- Eating patterns
- Physical activity levels
- Sleep routines
- Social determinates of health
- Genetics
- Other health conditions
- Medications

Impact


- Changes in human populations occur too slowly to be responsible for the obesity epidemic
- Variants may increase hunger and food intake
- Rarely causes a clear pattern of inherited obesity within a family

- Cushing's Disease
- Hypothyroidism
- etc

- Steroids
- Antidepressants
- Insulin
- etc

https://www.cdc.gov/obesity. Accessed 3/12/2023.

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# Risks of Obesity

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- Obesity in children and adults increases the risk for the following health conditions
  - High blood pressure and high cholesterol which are risk factors for heart disease
  - Type 2 diabetes
  - Breathing problems, such as asthma and sleep apnea
  - Joint problems such as osteoarthritis and musculoskeletal discomfort
  - Gallstones and gallbladder disease
- Childhood obesity is also associated with:
  - Psychological problems such as anxiety and depression
  - Low self-esteem and lower self-reported quality of life
  - Social problems such as bullying and stigma
  - Obesity as adults
- Adults with obesity have higher risks for stroke, many types of cancer, premature death, and mental illness such as clinical depression and anxiety

https://www.cdc.gov/obesity. Accessed 3/12/2023.

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# Treatment of Obesity

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- Nutrition
- Physical activity
- Behavioral counseling
- Pharmacotherapy
- Metabolic surgery

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# US Obesity Treatment Guidelines

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Gastroenterology 2022;163:1198–1225

**GUIDELINES**

## AGA Clinical Practice Guideline on Pharmacological Interventions for Adults With Obesity

**Eduardo Grunvald**,[1,*] **Raj Shah**,[2,*] **Ruben Hernaez**,[3,4,5,*] Apoorva Krishna Chandar,[6] Octavia Pickett-Blakely,[7] Levi M. Teigen,[8] Tasma Harindhanavudhi,[9] Shahnaz Sultan,[10] Siddharth Singh,[11] and Perica Davitkov,[6,12] on behalf of the AGA Clinical Guidelines Committee

- American Gastroenterological Association (AGA) November 2022
- In adults with obesity or overweight with weight-related complications, who have had an inadequate response to lifestyle interventions, the AGA recommends adding pharmacological agents to lifestyle interventions over continuing lifestyle interventions alone.

Grunvald. Gastroenterology 2022;163:1198-1225.

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# FDA-Approved Pharmacotherapy for Obesity

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- Phentermine/topiramate ER — 3rd line
- Naltrexone/bupropion ER — 4th line
- Phentermine — 5th line
- Orlistat — Not recommended
- Diethylpropion — Last line
- GLP-1 receptor agonists or GIP/GLP-1 receptor agonists???
  - Semaglutide 2.4 mg (Wegovy) — 1st line
  - Liraglutide 3.0 mg (Saxenda) — 2nd line

**Chronic use is needed.**

**Selection of the medication should be based on comorbidities, patient preference, cost, and access to the therapy.**

Grunvald. Gastroenterology 2022;163:1198-1225.

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# Total Body Weight Loss efficacy

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- Phentermine/topiramate ER
- Naltrexone/bupropion ER
- Phentermine
- Orlistat

5-6%

Maybe a little better at 6.8-8.8%

Pharmacotherapy options are prioritized based on weight loss efficacy vs potential harm. While each recommended agent has moderate to high efficacy and low harm risk, favorability of GLP-1 receptor agonists in these regards make them initially preferred agents.

Grunvald. Gastroenterology 2022;163:1198-1225.
Bray GA. Lancet. 2016;387(10031):1947-1956.
Bessesen DH. Lancet Diabetes Endocrinol. 2018;6(3):237-248.
Khera R. JAMA. 2016;315(22):2424-2434.

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Glucagon-like peptide-1 receptor agonists (GLP-1 RA)

Glucose-Dependent Insulinotropic Polypeptide / GLP-1 receptor agonists (GIP/GLP-1 RA)

**DRUG INFORMATION AND CLINICAL TRIAL DATA**

**LIRAGLUTIDE** **DULAGLUTIDE** **SEMAGLUTIDE**

**TIRZEPATIDE**

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# Drug Information
# GLP-1 RA and GIP/GLP-1 RA

- GLP-1 and GIP are incretin hormones secreted by the gut
- GLP-1 RA and GIP/GLP-1 RA mimic the actions of a natural incretins to:
  - increase glucose-dependent insulin secretion
  - decrease glucagon secretion
  - increase beta-cell growth/replication

  → Glucose control
  - delay gastric emptying
  - increase satiety thus decreasing food intake

  → Weight loss
- Adverse effects
  - Primarily GI: nausea, diarrhea, ↓ appetite, vomiting, constipation, dyspepsia, and abdominal pain
- Warnings/Contraindications
  - Pancreatitis, gastroparesis, certain thyroid tumors, retinopathy, gall bladder dz, AKI

Fanshier AV. Clin Diabetes. 2023. https://doi.org/10.2337/cd22-0060.

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# Dosing Information
# GLP-1 RA and GIP/GLP-1 RA

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| | | Indication |
|---|---|---|
| • Liraglutide (Victoza) | 0.6, 1.2, 1.8 mg SQ daily | Diabetes |
| • Liraglutide (Saxenda) | 0.6, 1.2, 1.8 3.0 mg SQ daily | Weight Loss |
| • Dulaglutide (Trulicity) | 0.75, 1.5 mg SQ weekly | Diabetes |
| • Dulaglutide (Trulicity) | 3.0, 4.5 mg SQ weekly | Diabetes |
| • Semaglutide (Rybelsus) | 3, 7, 14 mg po daily | Diabetes |
| • Semaglutide (Ozempic) | 0.25, 0.5, 1.0 mg SQ weekly | Diabetes |
| • Semaglutide (Ozempic) | 0.25, 0.5, 1.0, 2.0 mg SQ weekly | Diabetes |
| • Semaglutide (Wegovy) | 0.25, 0.5, 1.0, 1.7 2.4 mg SQ weekly | Weight Loss |
| • Tirzepatide (Mounjaro) | 2.5, 5, 7.5, 10, 12.5, 15 mg SQ weekly | Diabetes |

Victoza, Saxenda, Trulicity, Rybelsus, Ozempic, Wegovy, Mounjaro [prescribing information].

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# Trials Addressing Weight Loss

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- Liraglutide SCALE Diabetes, SCALE Obesity
- Dulaglutide AWARD-11
- Semaglutide STEP-4
- Tirzepatide SURPASS trials, SURMOUNT-1-4

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# SCALE Diabetes: liraglutide 3.0 mg

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Original Investigation

## Efficacy of Liraglutide for Weight Loss Among Patients With Type 2 Diabetes

### The SCALE Diabetes Randomized Clinical Trial

Melanie J. Davies, MD; Richard Bergenstal, MD; Bruce Bode, MD; Robert F. Kushner, MD; Andrew Lewin, MD; Trine Vang Skjøth, MD; Arne Haahr Andreasen, MSc; Christine Bjørn Jensen, MD; Ralph A. DeFronzo, MD; for the NN8022-1922 Study Group

- Objective: To investigate efficacy and safety of liraglutide vs placebo for weight management in adults with overweight or obesity and type 2 diabetes.
- Design: 56-week randomized, double-blind, placebo-controlled, parallel-group trial
  - BMI ≥27, age ≥18, A1c 7-10%, taking 0-3 oral DM drugs
  - 3 arms: liraglutide 3.0 mg, liraglutide 1.8 mg, placebo
- Primary Outcomes: relative change in weight, proportion of participants losing 5% or more, or more than 10%, of baseline weight at week 56.

Davies MJ. JAMA. 2015;314(7):687-699.

25

# SCALE Diabetes: liraglutide 3.0 mg

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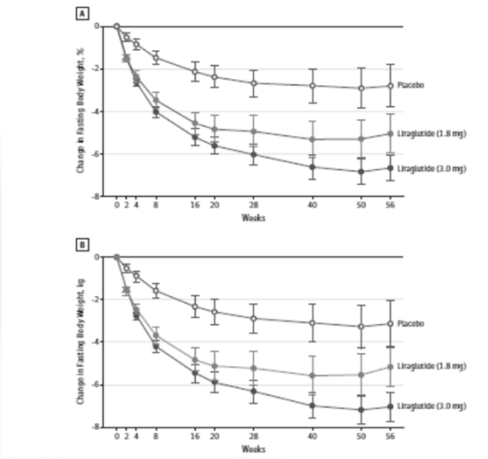
Figure 2. Time Course of Body Weight Loss From Baseline to Week 56 for Liraglutide (3.0 mg), Liraglutide (1.8 mg), and Placebo




Results:

- Body weight loss:
  - Liraglutide 3.0 mg: ↓ **6.0% (6.4 kg or 14 lb)**
  - Liraglutide 1.8 mg: ↓ 4.7% (5.0 kg or 11 lb)
  - Placebo: ↓ 2.0% (2.2 kg or 4.8 lb)
    - Difference vs placebo: all p<0.001
- ≥5% body weight loss:
  - Liraglutide 3.0 mg: 54.3% (p<0.001 vs placebo)
  - Liraglutide 1.8 mg: 40.4% (p<0.001 vs placebo)
  - Placebo: 21.4%
- ≥10% body weight loss:
  - Liraglutide 3.0 mg; 25.2% (p<0.001 vs placebo)
  - Liraglutide 1.8 mg: 15.9% (p<0.006 vs placebo)
  - Placebo: 6.7%

Davies MJ. JAMA. 2015;314(7):687-699.

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# SCALE Obesity: liraglutide 3.0 mg

27

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 2, 2015 VOL. 373 NO. 1

A Randomized, Controlled Trial of 3.0 mg of Liraglutide in Weight Management

Xavier Pi-Sunyer, M.D., Arne Astrup, M.D., D.M.Sc., Ken Fujioka, M.D., Frank Greenway, M.D., Alfredo Halpern, M.D., Michel Krempf, M.D., Ph.D., David C.W. Lau, M.D., Ph.D., Carel W. le Roux, F.R.C.P., Ph.D., Rafael Violante Ortiz, M.D., Christine Bjørn Jensen, M.D., Ph.D., and John P.H. Wilding, D.M., for the SCALE Obesity and Prediabetes NN8022-1839 Study Group

- Objective: To investigate the efficacy of liraglutide 3.0 mg vs placebo for weight management in adults with overweight or obesity but without type 2 diabetes
- Design: 56-week randomized, double-blind, placebo-controlled trial
  - BMI ≥30 or ≥27 with HTN or dyslipidemia, age ≥18, without diabetes (could include prediabetes)
  - 2 arms: liraglutide 3.0 mg, placebo
- Primary Outcomes: change in body weight, proportion of participants losing 5% or more, or more than 10%, of baseline weight at week 56

Sunyer XP. N Engl J Med. 2015;373:11-22.

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# SCALE Obesity: liraglutide 3.0 mg

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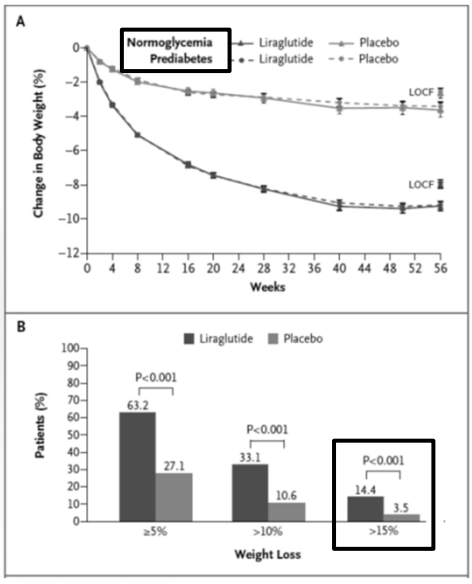


Results:

- Body weight loss:
  - Liraglutide 3.0 mg: ↓ **8.0% (8.4 kg or 18.5 lb)**
  - Placebo: ↓ 2.6% (2.8 kg or 6.2 lb)
    - Difference vs placebo: p<0.001
- ≥5% body weight loss:
  - Liraglutide 3.0 mg: 63.2% (p<0.001 vs placebo)
  - Placebo: 27.1%
- ≥10% body weight loss:
  - Liraglutide 3.0 mg; 33.1% (p<0.001 vs placebo)
  - Placebo: 10.6%

Sunyer XP. N Engl J Med. 2015;373:11-22.

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# AWARD-11: Dulaglutide 4.5 mg

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Efficacy and Safety of Dulaglutide 3.0 mg and 4.5 mg Versus Dulaglutide 1.5 mg in Metformin-Treated Patients With Type 2 Diabetes in a Randomized Controlled Trial (AWARD-11)

Juan P. Frias,[1] Enzo Bonora,[2] Luis Nevarez Ruiz,[3] Ying G. Li,[4] Zhuoxin Yu,[4] Zvonko Milicevic,[4] Raleigh Malik,[4] M. Angelyn Bethel,[4] and David A. Cox[4]

Diabetes Care 2021;44:765–773 | https://doi.org/10.2337/dc20-1473

- Objective: To compare efficacy and safety of dulaglutide at doses of 3.0 and 4.5 mg versus 1.5 mg in patients with type 2 diabetes inadequately controlled with metformin
- Design: 36- and 52-week randomized, double-blind, parallel-arm trial
  - BMI ≥25, age ≥18, A1c 7.5-11%, with type 2 diabetes on metformin
  - 3 arms: dulaglutide 1.5 mg, dulaglutide 3.0 mg, dulaglutide 4.5 mg
- Primary Outcome: change in A1c from baseline
- Secondary Outcome: change in weight from baseline

Frias JP. Diabetes Care. 2021;44:765–773.

29

# AWARD-11: Dulaglutide 4.5 mg

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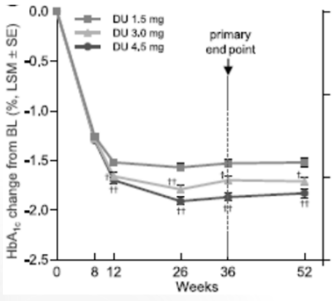


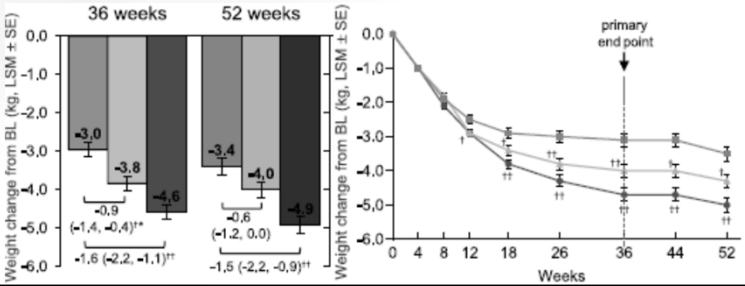


Results:

- Change in A1c:
  - 1.5 mg = -1.54%
  - 3.0 mg = -1.64% (p=0.096 vs 1.5 mg [not significant])
  - 4.5 mg = -1.77% (p<0.001 vs 1.5 mg)
- Change in weight:

| | 36 weeks | 52 weeks |
|---|---|---|
| 1.5 mg | -3.0 kg (-3%) | -3.4 kg (-4%) |
| 3.0 mg | -3.8 kg (-4%) | -4.0 kg (-4%) |
| 4.5 mg | -4.6 kg (-5%) | -4.9 kg (-5%) |

Dulaglutide 4.5 mg: 5% weight loss

Frias JP. Diabetes Care. 2021;44:765–773.

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# STEP-4: Semaglutide 2.4 mg

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JAMA | Original Investigation

Effect of Continued Weekly Subcutaneous Semaglutide vs Placebo on Weight Loss Maintenance in Adults With Overweight or Obesity
The STEP 4 Randomized Clinical Trial

Domenica Rubino, MD; Niclas Abrahamsson, MD; Melanie Davies, MD; Dan Hesse, PhD; Frank L. Greenway, MD; Camilla Jensen, MSc; Ildiko Lingvay, MD, MPH, MSCS; Ofri Mosenzon, MD; Julio Rosenstock, MD; Miguel A. Rubio, MD; Gottfried Rudofsky, MD; Sayeh Tadayon, MD; Thomas A. Wadden, PhD; Dror Dicker, MD; for the STEP 4 Investigators

- Objective: To compare semaglutide 2.4 mg with switch to placebo for weight maintenance in adults with overweight or obesity but without type 2 diabetes after a 20-week run-in with SQ semaglutide titrated to 2.4 mg weekly
- Design: 68-week randomized, double-blind, withdrawal trial
  - BMI ≥30 (or ≥27 with at least 1 weight-related comorbidity), age ≥18, without diabetes
  - All patients titrated to semaglutide 2.4 mg by week 16 and maintained to week 20
  - At week 20: randomized to either placebo or maintained on semaglutide 2.4 mg for 48 weeks
- Primary Outcomes: % change in body weight from week 20 to week 68, absolute change in body weight in kg

Rubino D. JAMA. 2021;325(14):1414-1425.

31

# STEP-4: Semaglutide 2.4 mg

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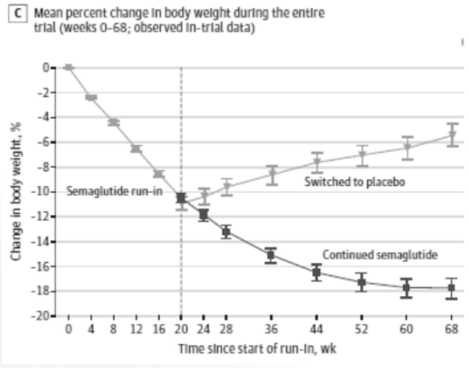


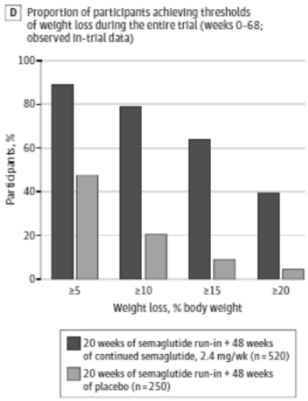


- Week 20 mean weight loss: -10.6%
- Week 68 % weight loss: -17.4% semaglutide
- Week 68 kg weight loss: -18.7 kg (41 lb) semaglutide
- Week 68 % weight loss: -5% placebo

Rubino D. JAMA. 2021;325(14):1414-1425.

Semaglutide
- ≥5% weight loss: 88.7%
- ≥10% weight loss: 79%
- ≥15% weight loss: 63.7%
- ≥20% weight loss: 39.6%

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# Tirzepatide
# The SURPASS Trials

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Weight loss was a secondary outcome measure

- SURPASS-1: T2DM, drug naïve; tirzepatide vs placebo
  - Weight loss: 5mg (-7.0kg), 10mg (-7.8kg), 15mg (-9.5kg)
- SURPASS-2: T2DM, on metformin; tirzepatide vs semaglutide1.0 mg
  - Weight loss: 5mg (-7.6kg), 10mg (-9.3kg), 15mg (-11.2kg)
- SURPASS-3: T2DM, on metformin ± SGLT2 inhibitor; tirzepatide vs insulin degludec
  - Weight loss: 5mg (-7.5kg), 10mg (-10.7kg), 15mg (-12.9kg)
- SURPASS-4: T2DM and ↑CVD risk, on metformin ± SGLT2 inhibitor/SU; tirzepatide vs insulin glargine
  - Weight loss: 5mg (-7.1kg), 10mg (-9.5kg), 15mg (-11.7kg)
- SURPASS-5: T2DM, on insulin glargine ± metformin; tirzepatide vs placebo
  - Weight loss: 5mg (-5.4kg), 10mg (-7.5kg), 15mg (-8.8kg)

Fanshier AV. Clin Diabetes. 2023. https://doi.org/10.2337/cd22-0060.

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# Tirzepatide
# The SURPASS Trials

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- Weights were still decreasing at the end of the trials and never plateaued
- Across all 5 trials:
  - Patients in treatment groups averaged weight loss of 5.44-11.34 kg (12-25 lb)
  - Patients on 5 mg lost 5.4-7.6 kg (11.91-16.7 lb) OR 5.64-8.22% body weight
  - Patients on 10 mg lost 7.5-10.7 kg (16.53-23.59 lb) OR 7.93-10.71% body weight
  - Patients on 15 mg lost 8.8-12.0 kg (19.4-28.44 lb) OR 9.17-13.7% body weight

Fanshier AV. Clin Diabetes. 2023. https://doi.org/10.2337/cd22-0060.

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# Tirzepatide: SURMOUNT-1

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The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

## Tirzepatide Once Weekly for the Treatment of Obesity

Ania M. Jastreboff, M.D., Ph.D., Louis J. Aronne, M.D., Nadia N. Ahmad, M.D., M.P.H., Sean Wharton, M.D., Pharm.D., Lisa Connery, M.D., Breno Alves, M.D., Arihiro Kiyosue, M.D., Ph.D., Shuyu Zhang, M.S., Bing Liu, Ph.D., Mathijs C. Bunck, M.D., Ph.D., and Adam Stefanski, M.D., Ph.D., for the SURMOUNT-1 Investigators*

- Objective: To investigate the efficacy and safety of tirzepatide vs placebo for weight management in adults with overweight or obesity but without type 2 diabetes
- Design: 72-week randomized, double-blind, placebo-controlled trial
  - BMI ≥30 or ≥27 with at least 1 weight-related complication, age ≥18, without diabetes
  - 4 arms: tirzepatide 5 mg, 10 mg, 15 mg, or placebo
- Primary Outcomes: % change in body weight, proportion of participants losing 5% at 72 weeks; Secondary: participants losing 10%, 15% or 20% of baseline weight at week 72

Jastreboff AM. N Engl J Med 2022; 387:205-216.

35

# Tirzepatide: SURMOUNT-1

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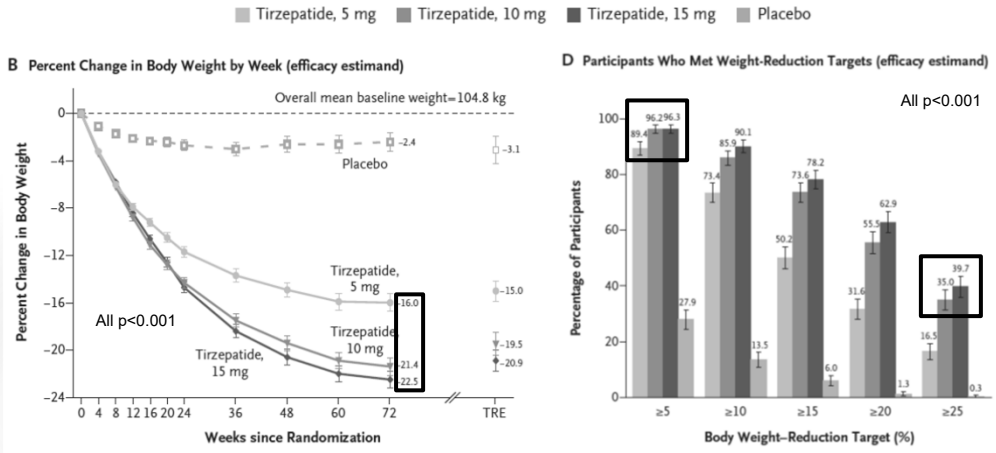


- Mean % weight loss: 5mg (-16%), 10mg (-21.4%), 15mg (-22.5%)
- Those with 22.5% weight reduction lost up to 24kg or 52 lb

Jastreboff AM. N Engl J Med 2022; 387:205-216

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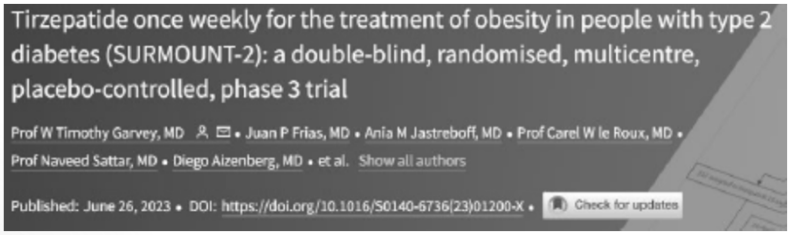
# Tirzepatide: SURMOUNT-2

37

Published June 26, 2023


Tirzepatide once weekly for the treatment of obesity in people with type 2 diabetes (SURMOUNT-2): a double-blind, randomised, multicentre, placebo-controlled, phase 3 trial

Prof W Timothy Garvey, MD • Juan P Frias, MD • Ania M Jastreboff, MD • Prof Carel W le Roux, MD • Prof Naveed Sattar, MD • Diego Aizenberg, MD • et al. Show all authors

Published: June 26, 2023 • DOI: https://doi.org/10.1016/S0140-6736(23)01200-X • Check for updates

- Objective: To investigate the efficacy and safety of tirzepatide vs placebo for weight management in adults with overweight or obesity and with type 2 diabetes
- Design: 72-week randomized, double-blind, placebo-controlled trial
  - BMI ≥27 with at least 1 weight-related complication, age ≥18, with diabetes, and A1c 7-10%
  - 3 arms: tirzepatide 10 mg, 15 mg, or placebo
- Primary Outcomes: % change in body weight; proportion of participants losing 5% at 72 weeks

Garvey T. Lancet. 2023; 402(10402);613-626.

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# Tirzepatide: SURMOUNT-2

38

- Results:
  - 938 participants
    - Mean age: 54.2 years; 51% female; 76% White; 60% Hispanic/Latino
    - Baseline mean bodyweight: 100.7kg; BMI 36·1 kg/m$^2$; A1c 8.02%
  - Percent change in bodyweight at week 72:
    - Placebo: -3.2%
    - Tirzepatide 10 mg: -12.8% (p<0.0001)
    - Tirzepatide 15 mg: -14.7% (p<0.0001)
  - More participants treated with tirzepatide versus placebo met bodyweight reduction thresholds:
    - ≥5%: 79–83% vs 32%; ≥15%: 40-48% vs 3%
  - Adverse effects similar to other incretin weight-loss therapies

Garvey T. Lancet. 2023; 402(10402);613-626.

38

# Tirzepatide: SURMOUNT-3

39

To be published and presented at the ObesityWeek conference in October 2023

- Objective: To investigate the efficacy and safety of tirzepatide vs placebo for 72 weeks after a 12-week intensive lifestyle intervention lead-in period in adults with obesity or overweight with weight-related comorbidities, excluding type 2 diabetes
- Design: 72-week randomized, double-blind, parallel, placebo-controlled trial
  - BMI ≥27 with at least 1 weight-related complication, age ≥18
  - 12-week lead-in of intensive lifestyle interventions to achieve ≥5% body weight reduction, then
  - Randomized to tirzepatide or placebo for 72 weeks
- Primary Outcomes: % change in body weight from randomization time; proportion of participants achieving ≥5% body weight loss at 72 weeks

Lilly News Release July 27, 2023. https://investor.lilly.com/news-releases/news-release-details/tirzepatide-demonstrated-significant-and-superior-weight-loss

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# Tirzepatide: SURMOUNT-3

40

- Results:
  - Lead-in phase:
    - At study entry, mean body weight was 109.5 kg (241.4 lbs)
    - After the 12-week lead-in, mean body weight loss was 6.9%
  - After randomization and 72-week intervention:
    - Percent weight change: Placebo = +3.3% vs Tirzepatide = -21.1%
    - Additional ≥5% body weight loss at 72 weeks: Placebo = 10.7% vs Tirzepatide = 94.4%
    - Tirzepatide total mean weight loss: 26.6%

Lilly News Release July 27, 2023. https://investor.lilly.com/news-releases/news-release-details/tirzepatide-demonstrated-significant-and-superior-weight-loss

40

# Tirzepatide: SURMOUNT-4

41

To be published and presented at the European Association for the Study of Diabetes Annual Meeting in October 2023

- Objective: To investigate the efficacy and safety of tirzepatide vs placebo in adults with obesity or overweight with weight-related comorbidities, excluding type 2 diabetes
- Design: 88-week randomized, double-blind, parallel, placebo-controlled trial
  - BMI ≥27 with at least 1 weight-related complication, age ≥18
  - 36-week open-label lead-in with all patients taking tirzepatide, then
  - Randomized to 56 weeks of continued tirzepatide or switch to placebo
- Primary Outcomes: % change in body weight from randomization time at 88 weeks

Lilly News Release July 27, 2023. https://investor.lilly.com/news-releases/news-release-details/tirzepatide-demonstrated-significant-and-superior-weight-loss

41

# Tirzepatide: SURMOUNT-4

42

- Results:
  - Lead-in phase:
    - Mean body weight was 107.3 kg (236.6 lbs)
    - After the 36-week tirzepatide lead-in, mean body weight loss was 21.1%
  - After randomization and 52-week intervention:
    - Percent weight change: Placebo = +14.8% vs Tirzepatide = -6.7% (additional loss)
    - Tirzepatide total mean weight loss: 26.0%

Lilly News Release July 27, 2023. https://investor.lilly.com/news-releases/news-release-details/tirzepatide-demonstrated-significant-and-superior-weight-loss

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# Tirzepatide

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- Expected to be approved for obesity by the end of 2023

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# Oral Semaglutide

Rybelsus

44

- Approved for T2DM at doses of 7 mg and 14 mg once daily
- Investigational for obesity at doses of 25 mg and 50 mg once daily
- Must be taken on an empty stomach without food or drink for 30 minutes

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# Oral Semaglutide: OASIS-1

45

Weight Loss Trial

- Objective: To investigate the efficacy, safety, and tolerability of high-dose (25, 50 mg) oral semaglutide vs standard dose oral semaglutide (7, 14 mg) placebo in overweight adults with T2DM
- Design: 68-week randomized, double-blind, placebo-controlled phase 3 superiority trial
  - BMI ≥30 or , ≥27 with bodyweight-related complications/comorbidities, age ≥18, without T2DM
  - Randomized to placebo or oral semaglutide escalated to 50 mg daily
- Primary Outcomes: % change in body weight and proportion of participants achieving ≥5% bodyweight 68 weeks
- Results:
  - Percent bodyweight change: 50 mg = 15.1% vs placebo = 2.4% (p<0.0001)
  - Percent achieving target bodyweight loss:
    - ≥5% = 85% vs 26%; OR 12.6, 8.5-18.7; p<0.0001
    - ≥10% = 69% vs 12%; OR 14.7, 9.6-22.6
    - ≥15% = 54% vs 6%; OR 17.9, 10.4-30.7
    - ≥20% = 34% vs 3%; OR 18.5, 8.8-38.9

Knop FK. Lancet. 2023; 402(10403);705-719.

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46

# Potential Upcoming Therapies

IN PHASE 2 TRIALS

46

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# NON-Peptide Oral GLP-1 Receptor Agonists

ORFORGLIPRON

DANUGLIPRON

47

# Oral GLP-1 Receptor Agonists

48

- Injectable GLP-1 RA are large-molecule peptides that must be injected because they cannot endure the acidity of the stomach.
- One oral peptide GLP-1 RA is available; oral semaglutide 7 and 14 mg once daily
  - A peptide that is co-formulated with a gastric mucosal permeation enhancer, salcaproate sodium, that helps protect semaglutide from proteolytic degradation and enhances its absorption across the gastric epithelium
  - It should be taken in a fasting state and no food, liquid, or other medication should be ingested for at least 30 min after its intake
- "Gliprons" are oral NON-peptide GLP-1 RA currently being investigated for T2DM and obesity
  - These are small-molecule products that are not proteins and can be taken orally without protection
  - They may be taken without regard to food and seem to have comparable efficacy and tolerability to injectable GLP-1 RA products

Frias JP. Lancet. 2023 published online. https://doi.org/10.1016/ S0140-6736(23)01302-8

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# Orforglipron – Obesity Trial

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ORIGINAL ARTICLE

## Daily Oral GLP-1 Receptor Agonist Orforglipron for Adults with Obesity

Sean Wharton, M.D., Thomas Blevins, M.D., Lisa Connery, M.D., Julio Rosenstock, M.D., Sohini Raha, Ph.D., Rong Liu, Ph.D., Xiaosu Ma, Ph.D., Kieren J. Mather, M.D., Axel Haupt, M.D., Deborah Robins, M.S., Edward Pratt, M.D., Christof Kazda, M.D., and Manige Konig, M.D., Ph.D., for the GZGI Investigators*

- Objective: To evaluate the efficacy and safety of orforglipron in adults with obesity, or with overweight plus at least one weight-related coexisting condition, and without diabetes
- Design: Phase 2, randomized, double-blind trial
  - Orforglipron at one of four doses (12, 24, 36, or 45 mg) or placebo once daily for 36 weeks
- Primary End Points: The percentage change from baseline in body weight was assessed at week 26 (primary end point) and at week 36 (secondary end point)

Wharton S. N Engl J Med. 2023 published online. DOI: 10.1056/NEJMoa2302392

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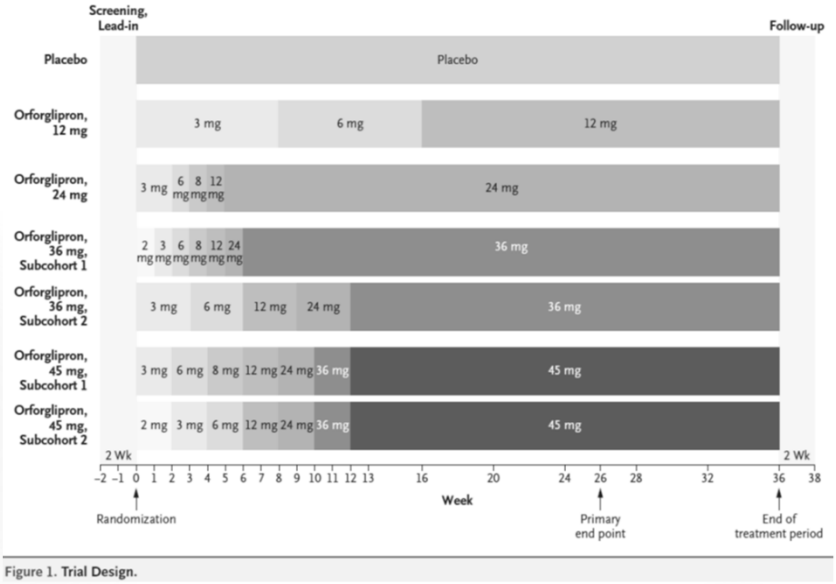


Figure 1. Trial Design.

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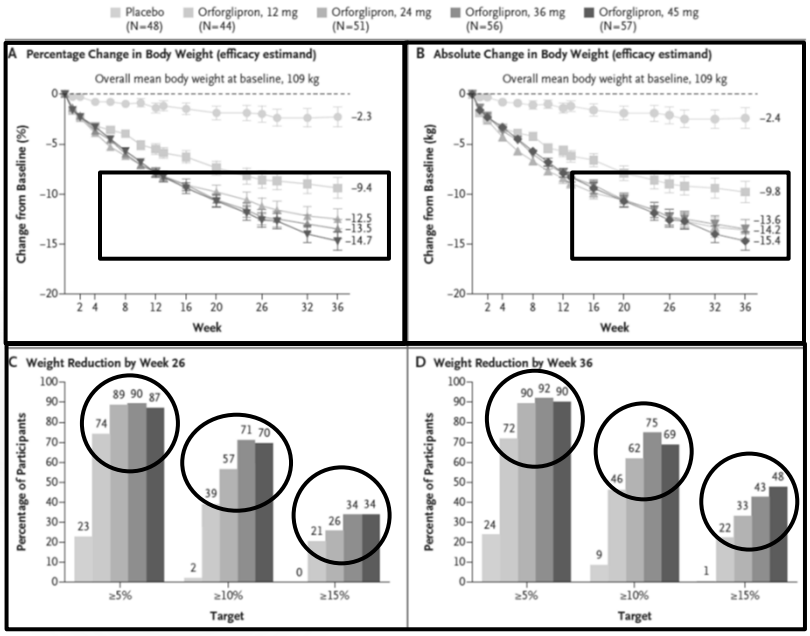


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# Orforglipron – Obesity Trial

Results:

- Change in % weight at 36 wk
  - 24, 36, and 45 mg: -12.5 to -14.7%
- Change in kg at 36 wk
  - 24, 36, and 45 mg: -13.6 to -15.4 kg
- Attainment of wt loss targets
  - See figure
- Weight loss had not plateaued at week 36, implying more loss with more time

Wharton S. N Engl J Med. 2023 published online. DOI: 10.1056/NEJMoa2302392

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# Orforglipron

52

- Findings suggest that lower starting doses and slower dose escalation are indicated for reducing gastrointestinal events and reaching the target dose; useful for phase 3 trials
- The safety profile of orforglipron was consistent with that of the GLP-1 receptor agonist class.
- Liraglutide (3.0 mg once daily) and semaglutide (2.4 mg once weekly) are the only GLP-1 receptor agonists that have been approved for weight management; both are peptide-based injectables
- Phase 3 trials of liraglutide (the SCALE trial) and semaglutide (the STEP 1 trial) showed significant weight reduction at 56 weeks and 68 weeks, respectively, with a mean reduction of 9.2% with liraglutide and 16.9% with semaglutide.
- This phase 2 trial of orforglipron showed weight reduction ranging from 8.6% to 12.6% at 26 weeks and ranging from 9.4% to 14.7% at 36 weeks.

Wharton S. N Engl J Med. 2023 published online. DOI: 10.1056/NEJMoa2302392

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# Other Oral Non-peptide GLP-1 RA

53

- Danuglipron
- Lotiglipron: no longer in development due to adverse effect (LFT)
  - Pfizer will abort lotiglipron to focus on danuglipron

53

# Triple Agonist: GLP-1/GIP/Glucagon
# Dual Agonist: GLP-1/Glucagon

54

- Dual GLP-1 Glucagon Agonists
  - In development
    - Survodutide (BI-456906), pemvidutide, cotadutide, SAR425899, and mazdutide
- Triple GLP-1/GIP/Glucagon Agonists
  - In development
    - HM15211, SAR441255, retatrutide (LY3437943)
- Reports suggest that the ratio of glucagon versus GLP-1 activity is an important determinant of the efficacy and safety profile of GLP-1 and glucagon agonists
- Preclinical evidence for the GIP, GLP-1, and glucagon receptor agonist retatrutide suggests that such balance has been accomplished

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# Role of Glucagon

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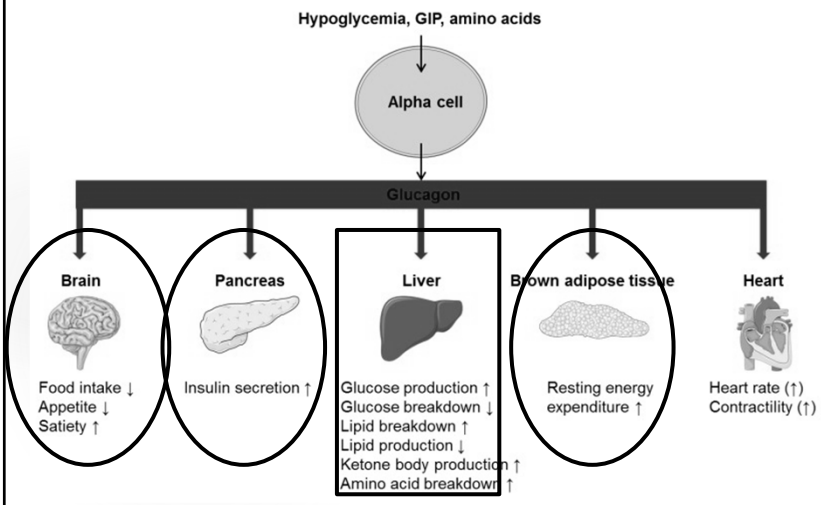


- Glucagon increases glucose levels……right?
- However, it also:
  - Increases insulin secretion
  - Decreases energy intake
  - Increases energy expenditure
- At extraphysiologic doses, these may explain the mechanism for **glucose lowering and weight loss**
- But mechanisms are uncertain

Rix I. Glucagon Physiology. [Updated 2019 Jul 16]. In: Feingold KR. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK279127/

55

# Retatrutide

56

Triple Agonist: GLP-1/GIP/Glucagon

- Once-weekly single peptide SQ injection
- Retatrutide is more potent at GIP receptors and less potent at glucagon and GLP-1 receptors
- Preclinical models
  - Retatrutide treatment reduced food intake and also increased energy expenditure, an effect attributable to glucagon receptor agonism
- Phase 1 trial
  - Retatrutide showed robust reductions in glucose and bodyweight
- Safety profile
  - Consistent with the GLP-1 receptor agonist and GIP and GLP-1 receptor agonist classes, with mild-to-moderate and transient gastrointestinal adverse events being the most commonly reported

Rosenstock J. Lancet 2023; 402: 529–44.

56

# Retatrutide – Obesity Trial

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The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

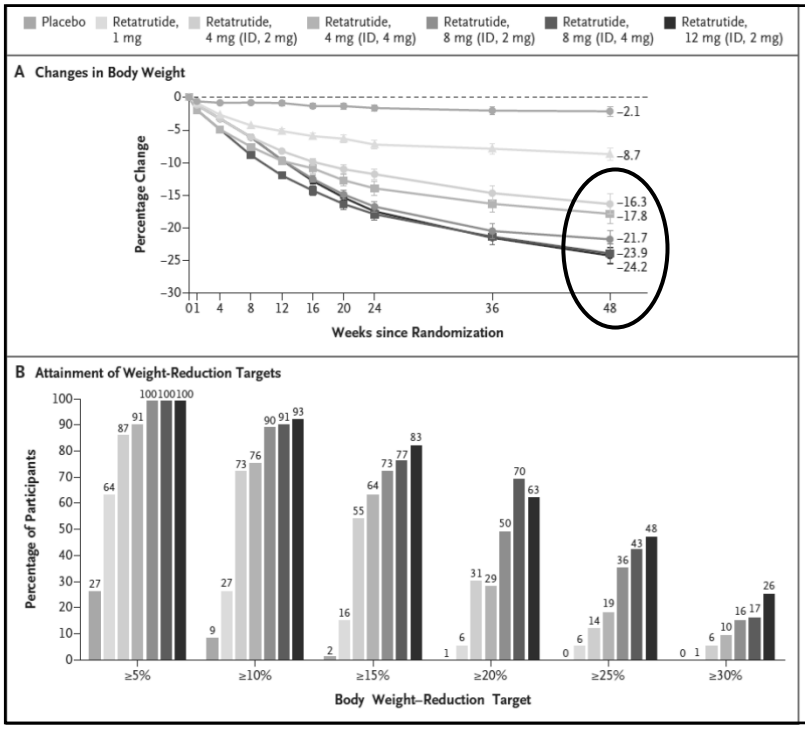
## Triple–Hormone-Receptor Agonist Retatrutide for Obesity — A Phase 2 Trial

Ania M. Jastreboff, M.D., Ph.D., Lee M. Kaplan, M.D., Ph.D., Juan P. Frías, M.D., Qiwei Wu, Ph.D., Yu Du, Ph.D., Sirel Gurbuz, M.D., Tamer Coskun, M.D., Ph.D., Axel Haupt, M.D., Ph.D., Zvonko Milicevic, M.D., and Mark L. Hartman, M.D., for the Retatrutide Phase 2 Obesity Trial Investigators*

- Objective: assess weight loss among adults who had a BMI of 30 or higher or who had a BMI of 27 to less than 30 plus at least one weight-related condition on retatrutide vs placebo
- Design: a phase 2, double-blind, randomized, placebo-controlled trial
  - Intervention: SQ injection 1 mg, 4 mg [initial dose, 2 mg], 4 mg [initial dose, 4 mg], 8 mg [initial dose, 2 mg], 8 mg [initial dose, 4 mg], 12 mg [initial dose, 2 mg]) or placebo once weekly for 48 weeks
- Primary End Points: percentage change in body weight from baseline to 24 weeks
  - Secondary end points included the percentage change in body weight from baseline to 48 weeks and a weight reduction of 5% or more, 10% or more, or 15% or more

Jastreboff AM. N Engl J Med 2023; DOI: 10.1056/NEJMoa2301972.



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# Retatrutide – Obesity Trial – Results

- Change in body weight:
  - Top 3 doses: mean > -20%
- Attainment of weight-loss targets:
  - 5-10% is typical expectation for drugs and 10-15% is considered therapeutic/beneficial
  - See figure
- Safety:
  - Very similar to GLP-1 RA

Jastreboff AM. N Engl J Med 2023; DOI: 10.1056/NEJMoa2301972.

# Retatrutide

59

- Excitement over the A1c reduction
- Even more publicity over the weight loss
  - The most weight loss ever seen with a therapeutic agent to date

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# Survodutide

60

Dual Agonist – GLP-1/Glucagon

- Once-weekly SQ injection
- Investigational for weight loss, T2DM, non-alcoholic steatohepatitis, liver fibrosis
- Phase 2 trial for T2DM is complete
- Phase 2 trial for weight loss is complete
- Currently undergoing another phase 2 trial for T2DM

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# Survodutide

## Phase 2 Obesity Trial

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OR: CLINICAL THERAPEUTICS—INCRETIN-BASED THERAPIES | JUNE 23 2023

**51-OR: A Phase 2, Randomized, Double-Blind, Placebo-Controlled, Dose-Finding Study of BI 456906 in People with Overweight/Obesity** FREE

CAREL LE ROUX; OREN STEEN; KATHRYN J. LUCAS; ELENA STARTSEVA; ANNA UNSELD; ANITA M. HENNIGE

Check for updates

*Diabetes* 2023;72(Supplement_1):51-OR
https://doi.org/10.2337/db23-51-OR

- Objective: This dose-finding study tested efficacy and safety of survodutide in adults with overweight/obesity (with BMI ≥27 kg/m$^2$) without diabetes
- Design: Randomized, double-blind, placebo-controlled study
  - Weekly SQ survodutide (0.6, 2.4, 3.6, 4.8 mg) or placebo for 46 weeks (20-week rapid, bi-weekly dose escalation then 26-week maintenance)
- Primary End Point: weight change (%) from baseline at week 46
  - Secondary endpoints included proportion of patients reaching ≥5, ≥10 or ≥15% weight loss at week 46

Le Roux C. Diabetes 20 June 2023; 72 (Supplement_1): 51–OR. https://doi.org/10.2337/db23-51-OR

61

# Survodutide

## Phase 2 Obesity Trial

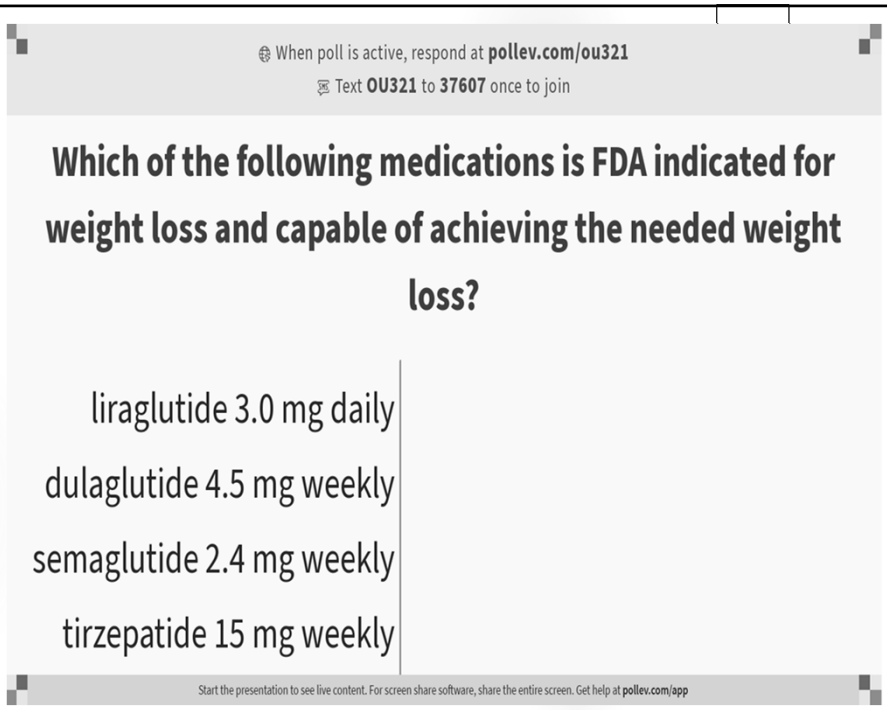
62

- Results:
  - At 46 weeks, the results showed the average reduction in body weight:
    - Placebo (no treatment): 2.0%
    - Survodutide 0.6 mg: 6.2%
    - Survodutide 2.4 mg: 12.5%
    - Survodutide 3.6 mg: 13.2%
    - Survodutide 4.8 mg: 14.9% and continued to 18.7%
  - Percent attainment of weight loss by patients on 4.8 mg survodutide (high dose):
    - ≥5%: 82.8%,
    - ≥10%: 68.8%
    - ≥15%: 54.7%
    - ≥20%: 40% ( on either 3.6 or 4.8 mg)
  - At 46-weeks, weight loss had not yet leveled off, suggesting greater reductions with longer treatment
  - No unexpected adverse effect concerns

Le Roux C. Diabetes 20 June 2023; 72 (Supplement_1): 51–OR. https://doi.org/10.2337/db23-51-OR

62

**A 42yo woman with a history of obesity, hypertension, and dyslipidemia presents to the clinic with a BMI of 34 kg/m$^2$. She has been working on her diet for several months and has adopted a routine exercise regimen, but her weight loss has stagnated. She has heard there are some new safe medications that may help her to lose more weight. She and her provider turn to the clinic pharmacist to recommend an appropriate medication to assist her in losing at least 12 kg.**

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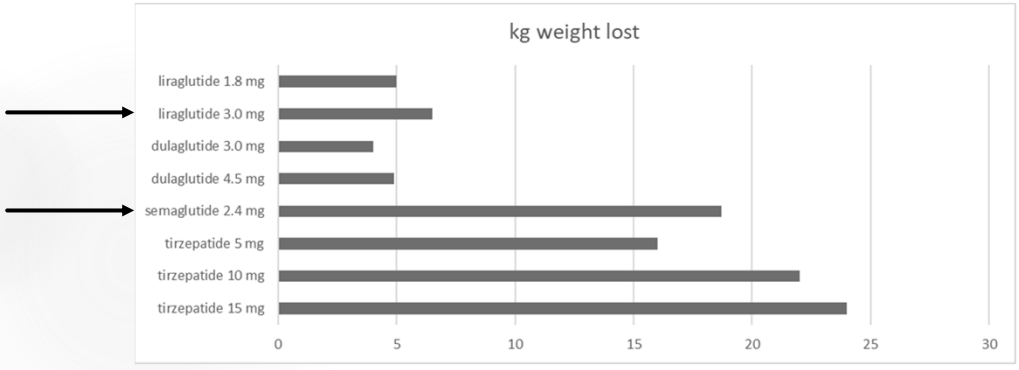
## Comparative Weight Loss in kg Across Trials

64

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# Conclusion and Clinical Pearls

65

- GLP-1 RA and GIP/GLP-1 RA have become very popular for weight loss
- Only liraglutide 3.0 mg (Saxenda) and semaglutide 2.4 mg (Wegovy) are currently FDA indicated for weight loss
- Tirzepatide trials have compelling evidence for weight loss and the SURMOUNT trials will likely lead to an indication for weight loss
- Phentermine/topiramate ER, naltrexone/bupropion ER, phentermine, orlistat:
  - Reduce body weight 5-6%
- Liraglutide 3.0 mg: reduces body weight 6-8%
- Dulaglutide 4.5 mg: reduces body weight 5%
- Semaglutide SQ 2.4 mg : reduces body weight 17%
- Semaglutide po 50 mg: reduces body weight 15%
- Tirzeaptide 15 mg: reduces body weight 23%-26.6%

65

**What changes do you intend to make in your practice as a result of this activity?**

66

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**What is the expected loss of body weight from traditional pharmacologic weight loss therapies, phentermine/topiramate ER, naltrexone/burpropion ER, phentermine, orlistat?**

5%
11%
18%
25%

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**What is the expected loss of body weight from liraglutide 3.0 mg use according to data from the SCALE Obesity trial?**

8%
10%
16%
24%

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**What is the expected loss of body weight from dulaglutide 4.5 mg use according to data from the AWARD-11 trial?**

5%
12%
20%
25%

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**What is the expected loss of body weight from semaglutide 2.4 mg use according to data from the STEP-4 trial?**

6%
11%
17%
24%

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**What is the expected loss of body weight from tirzepatide 15 mg use according to data from the SURMOUNT-1 trial?**

5%

11%

18%

23%

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# Additional Resources

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- Managing Overweight and Obesity in Adults. Systematic Evidence from the Obesity Expert Panel, 2013 [PDF-5.89MB] — US Department of Health and Human Services. National Institutes of Health.
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# Incretin-Based Therapies: The Past, Present, and Future of Weight Loss Drugs


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The Walter P. Scheffe Continuing Pharmaceutical Education Series
October 29, 2023

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