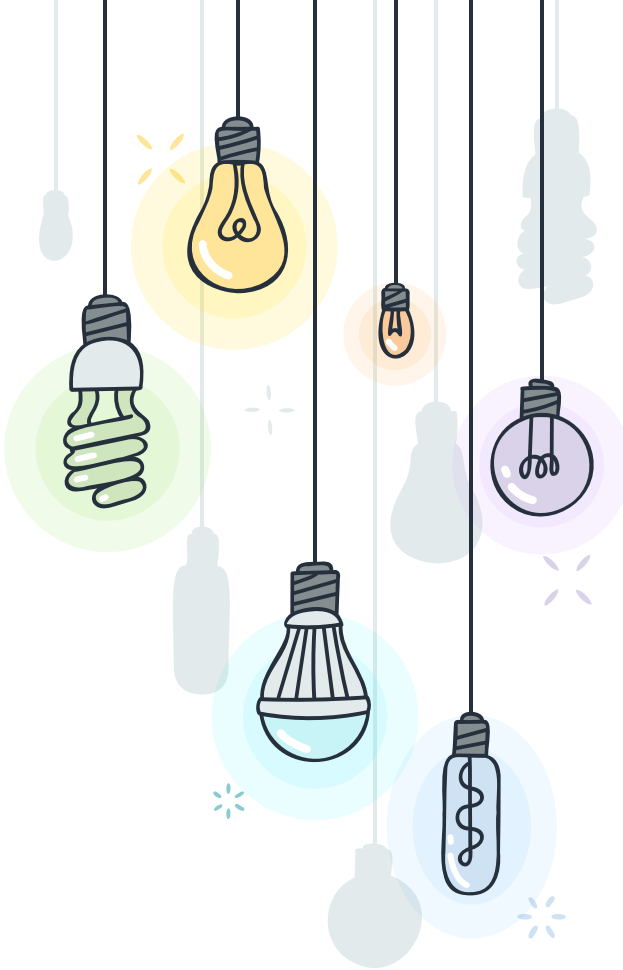
Mounjaro (tirzepatide)

Objectives

- Examine Tirzepatide
- Review primary literature available
- Determine how this could impact future practices



1

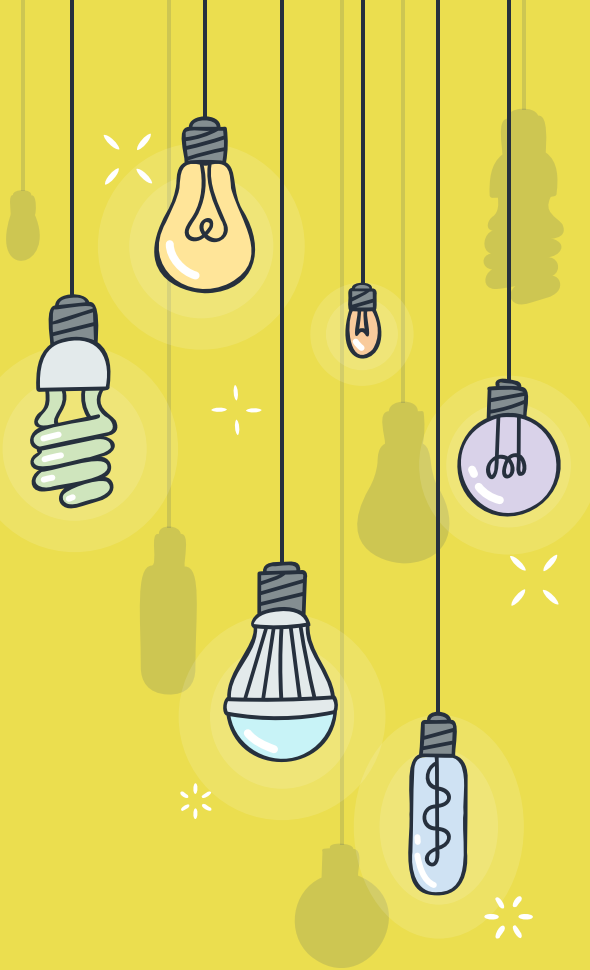
Introduction

Why are we talking about tirzepatide?

On May 13, 2022 the FDA approved Mounjaro to improve blood sugar control in adults with Type 2 diabetes along with diet and exercise.

”Given the challenges many patients experience in achieving their target blood sugar goals, today’s approval of Mounjaro is an important advance in the treatment of type 2 diabetes”

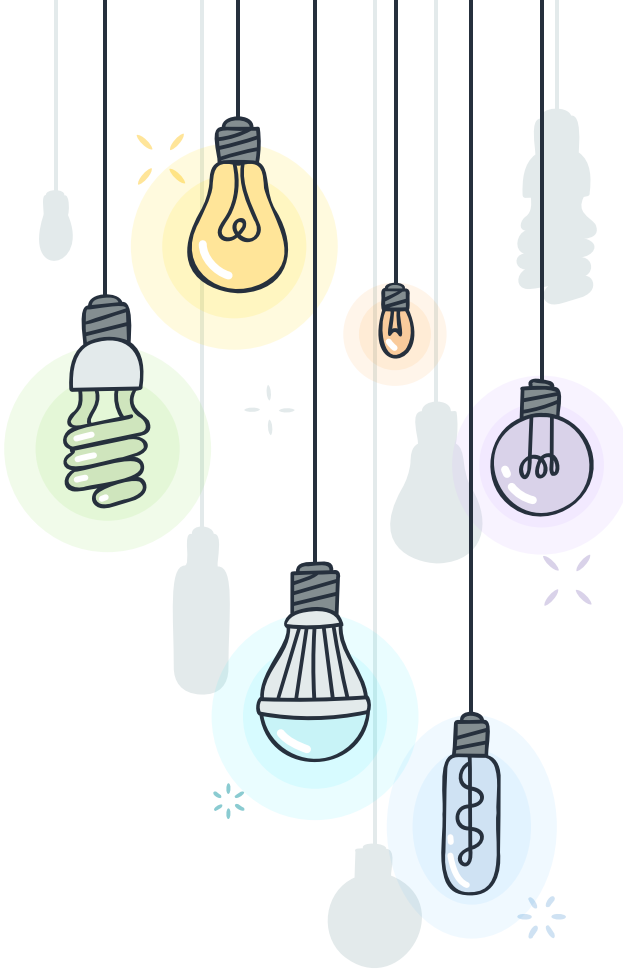
- Patrick Archdeacon, M.D., associate director of the Division of Diabetes, Lipid Disorders and Obesity in the FDA’s Center for Drug Evaluation in Research



Mechanism of Action

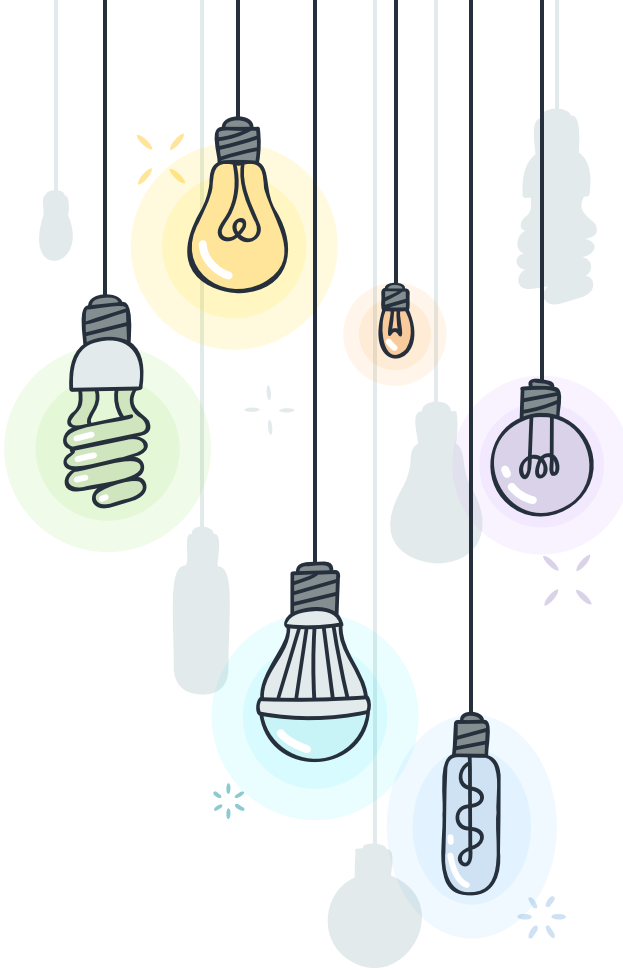
Dual Mechanism:

- (GLP-1) Glucagon-Like Peptide Receptor Agonist
- (GIP) Glucose- Dependent Insulinotropic Polypetide

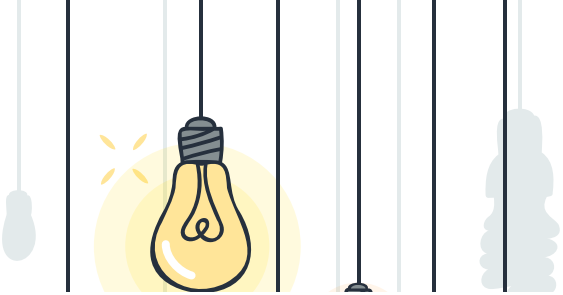


Mechanism of Action

- GLP-1 and GIP are released in response to nutrient intake to cause the incretin effect.
- The incretin effect is the increase in release of insulin after a meal to help the body control post prandial sugars.
- GIP is proposed to be responsible for 2/3 of this effect while GLP-1 only contributes about 1/3



Mechanism of Action



Comparison of Proposed Actions of GIP And GLP-1[5]

Brain

GIP Activity
- ⬇ Reduced food intake

GLP-1 Activity
- ⬇ Reduced food intake
- ⬆ Increased satiety

Whole-Body

GIP Activity
- ⬆ Increased insulin sensitivity

Pancreas

GIP Activity
- ⬆ Increased insulin
- ⬆ Increased glucagon

GLP-1 Activity
- ⬆ Increased insulin
- ⬇ Reduced glucagon

Stomach

GLP-1 Activity
- ⬇ Reduced gastric emptying

Indication

- Currently only approved for Type 2 Diabetes Treatment (SURPASS trials)

- Also being studied for weight loss, but not yet an approved indication (SURMOUNT trials)

Contraindications

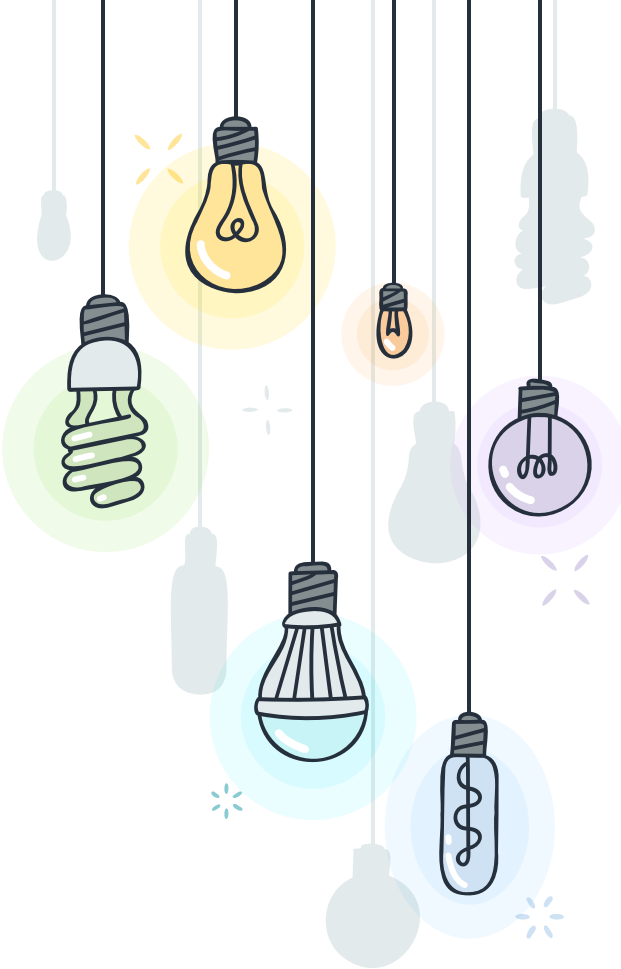
- Hypersensitivity to tirzepatide or any components
- A personal or family history of medullary thyroid carcinoma (Black Box Warning)
- Patients with Multiple Endocrine Neoplasia Syndrome Type 2 (MEN 2)

Warnings/ Precautions

- Bariatric Surgery
  - Dehydration may cause acute or chronic kidney failure. Fluid intake/ Nausea are common after gastric surgeries.
  - Excessive GLP-1 exposure – Pancreatitis
- Delayed Gastric Emptying
- Not recommended in patients with gastroparesis or severe GI disease
- Not studied in patients with a history of pancreatitis

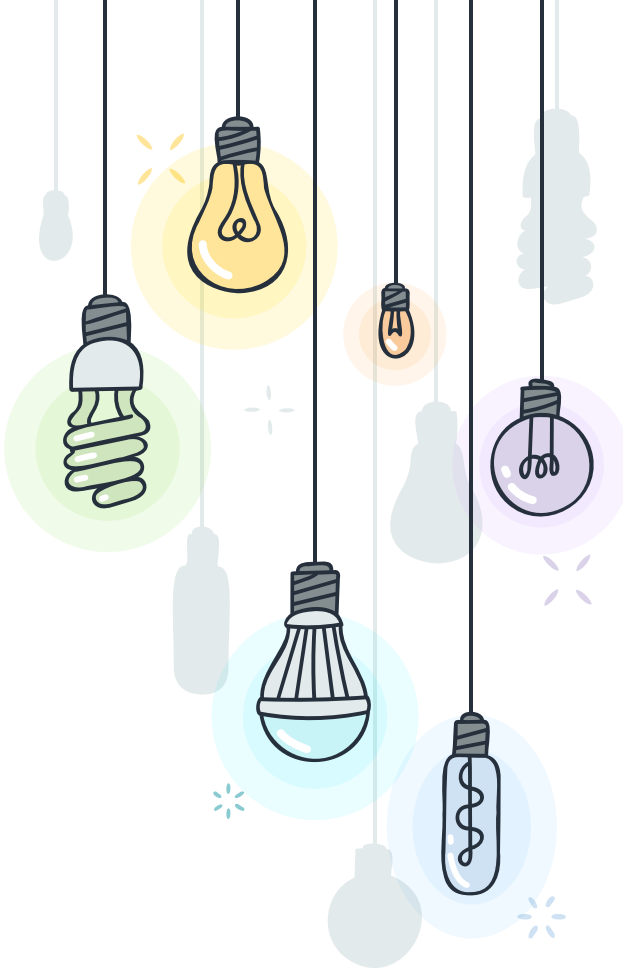
Adverse Effects (Significant)

- AKI (dehydration)
- Diabetic Retinopathy
- Gallbladder Disease
- GI Symptoms
- Hypersensitivity Reactions
- Increase Heart Rate
- Medullary Thyroid Carcinoma
- Pancreatitis



Adverse Effects

- Decreased Appetite (5-11%)
- Diarrhea (12-17%)
- Increased serum amylase (33-38%)
- Increased serum lipase (31-42%)
- Nausea (12-18%)

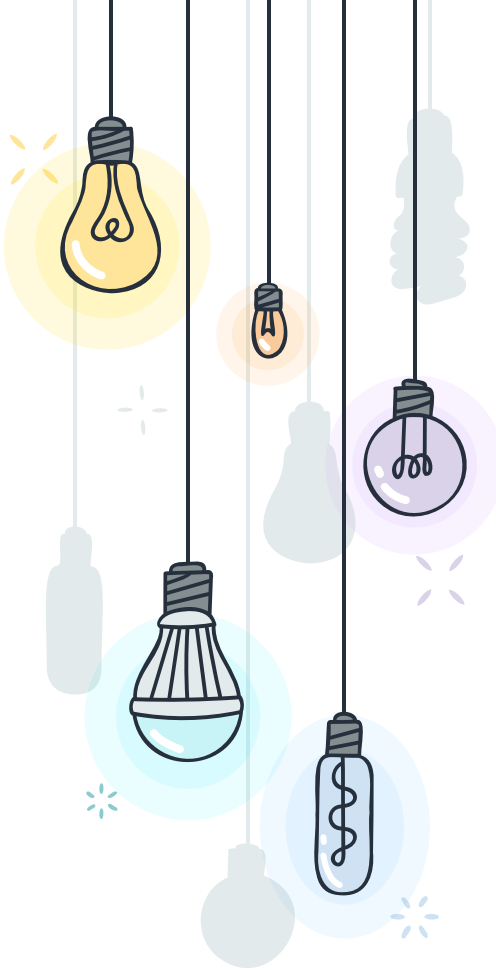


Dosing/ Renal dosing

- Initial: 2.5mg/ week x 4 weeks, then increase to 5mg/ week
- The dose can be titrated by 2.5mg/ week every 4 weeks if further control is needed.
- Maximum dose: 15mg/ week
- No renal dose adjustment/ cutoff

*2.5mg/ week is not a therapeutic dosing regimen

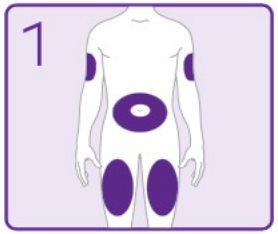
**Allow at least 72 hours between doses when changing days of the week



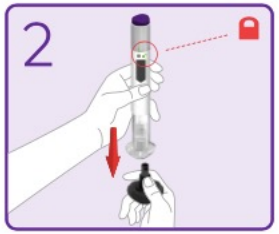
Available Formulations

May be stored at room temperature for up to 21 days

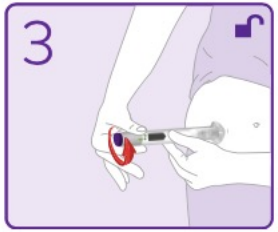
How to use it



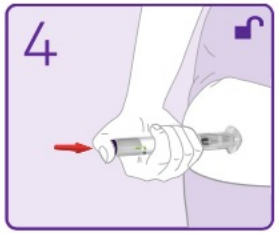
Choose your injection site. Your healthcare provider can help you choose the injection site that is best for you. You or another person can inject the medicine in your stomach, thighs, or the back of your upper arms. Another person should give you the injection in the back of your upper arm.



Pull off the base cap.



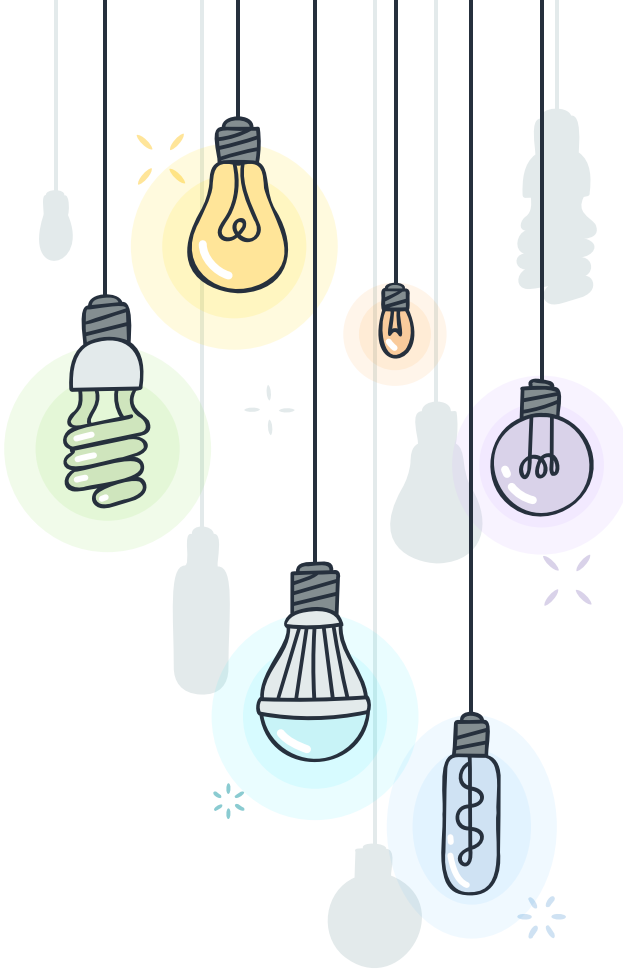
Place the base flat on your skin, then unlock.



Press and hold the button for up to 10 seconds. **Listen** for the first click. It means the injection has started. The second click means that the injection is complete.‡

Pricing

- Prices similar no matter what strength
- Cost is about 6x the cost of Ozempic



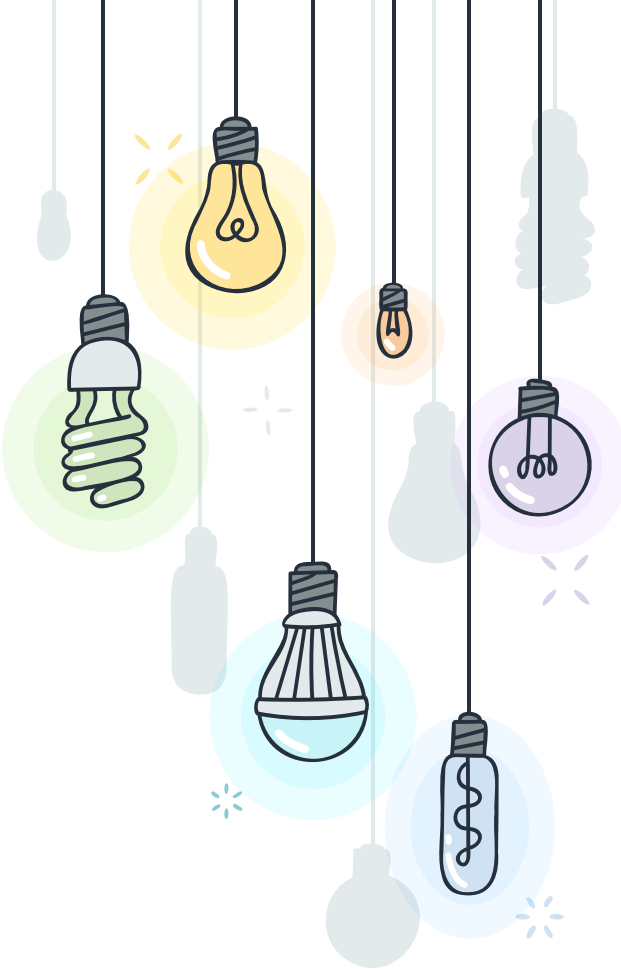
2

Clinical Studies

What evidence is there?

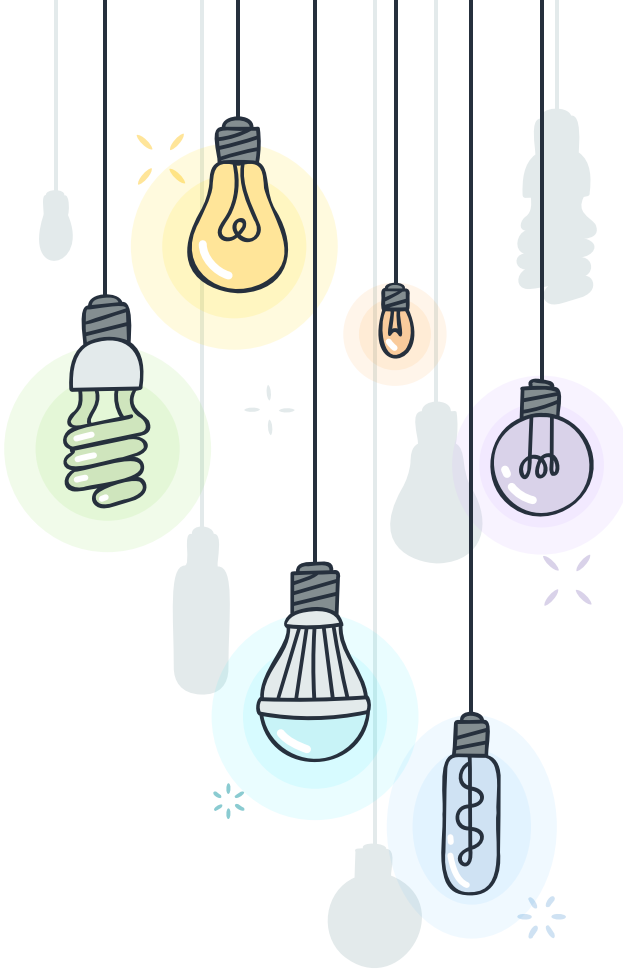
Clinical Trials:

- SURPASS-1: Tirzepatide was compared to placebo at 3 different doses to measure mean change in A1c. Investigators found clinically significant decreases in A1c with tirzepatide.
- SURPASS-2: Tirzepatide was compared to semaglutide using mean change in A1c. Tirzepatide was found to be noniferior and superior to semaglutide.
- SURPASS-3: Tirzepatide was compared to insulin degludec using change in A1c. Tirzepatide was found to be superior to insulin degludec with less risk of hypoglycemia



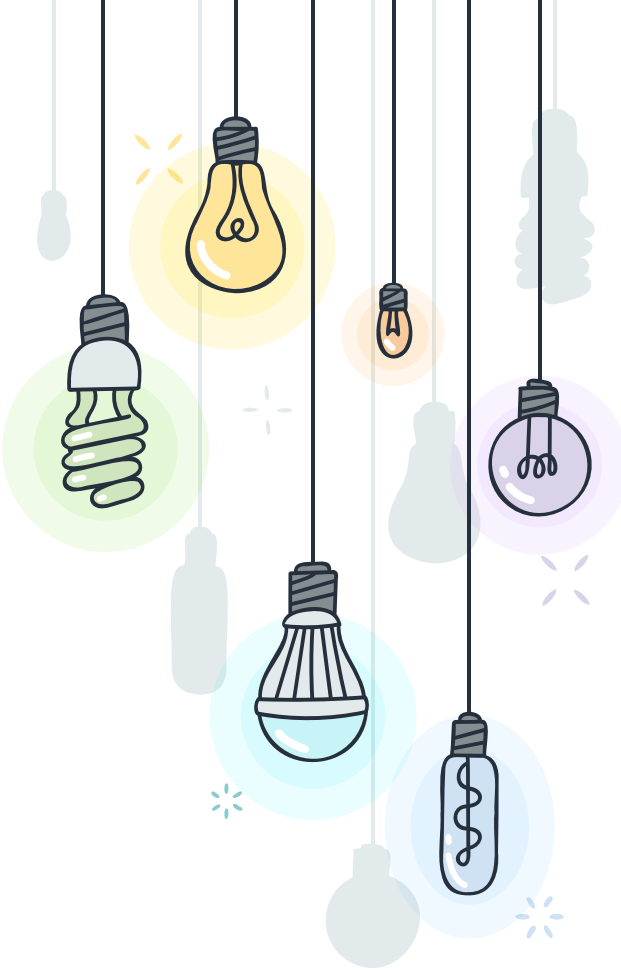
Clinical Trials

- SURPASS-4: Tirzepatide was compared to insulin glargine using change in A1c in patients with increased risk of cardiovascular events. Tirzepatide was found to be have a greater reduction in A1c with less risk of hypoglycemia. An exploratory analysis of this trial also found that tirzepatide slowed progression of CKD.
- SURPASS-5: When added to titrated insulin glargine, tirzepatide was compared to placebo using change in mean bodyweight and A1c. A significantly higher number of patients in the combination group reached an A1c goal of <7%



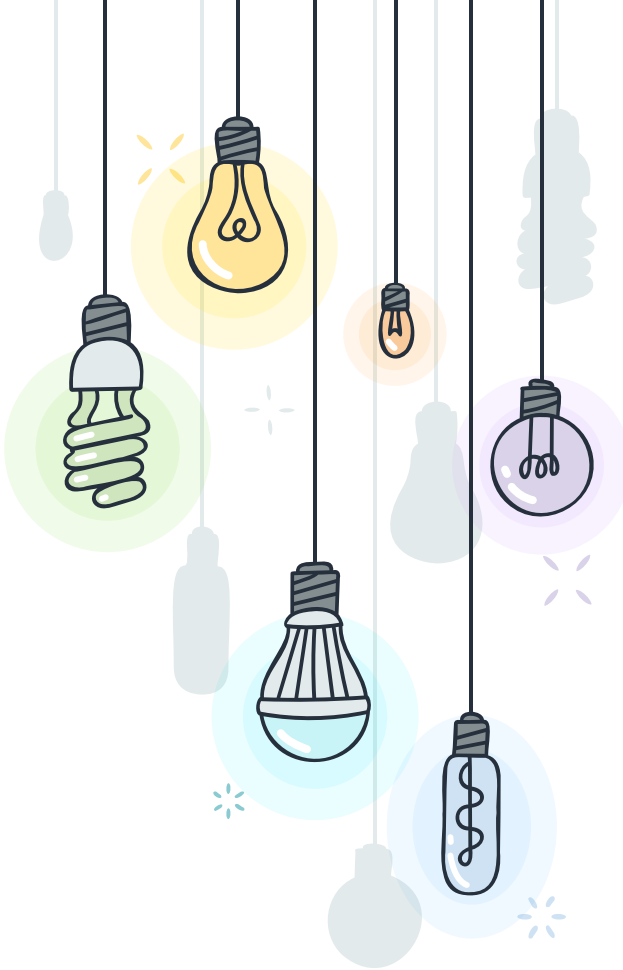
SURPASS-1 Trial design

- 40 week, double blind, multi-center RCT
- Patients were assigned (1:1:1:1) once weekly tirzepatide 5 mg, 10 mg, or 15 mg or placebo.
- N=478 patients
- Mean A1c: 7.9%
- Mean BMI: 31.9



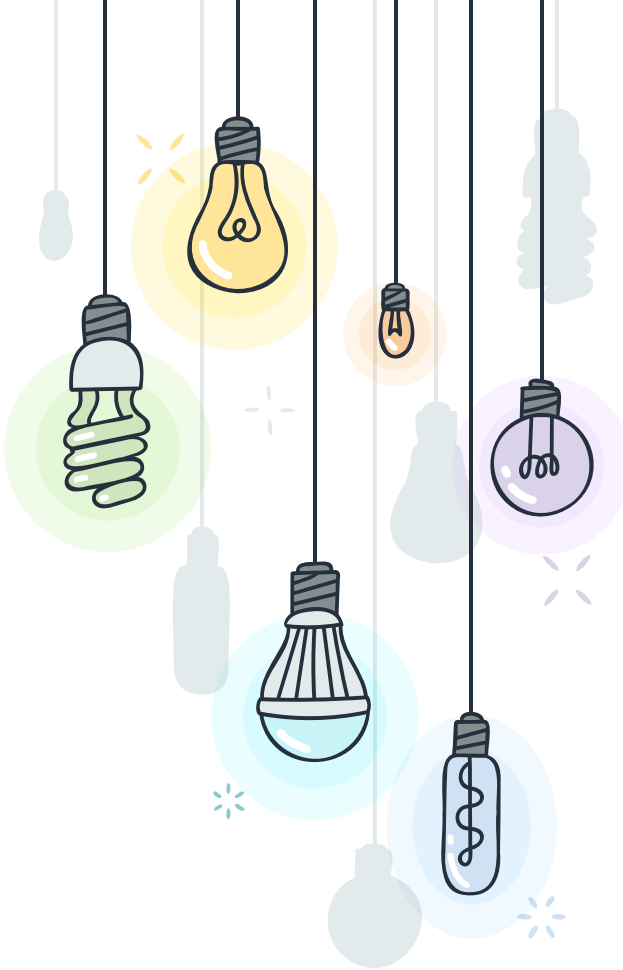
SURPASS-1 TRIAL DESIGN

- Primary outcome: mean change in A1c from baseline at 40 weeks.
- Key Secondary outcomes:
  - Mean change from baseline in fasting serum glucose
  - Proportion of patients at A1c target less than 7% and 5.7%
  - Mean change from baseline in body weight.



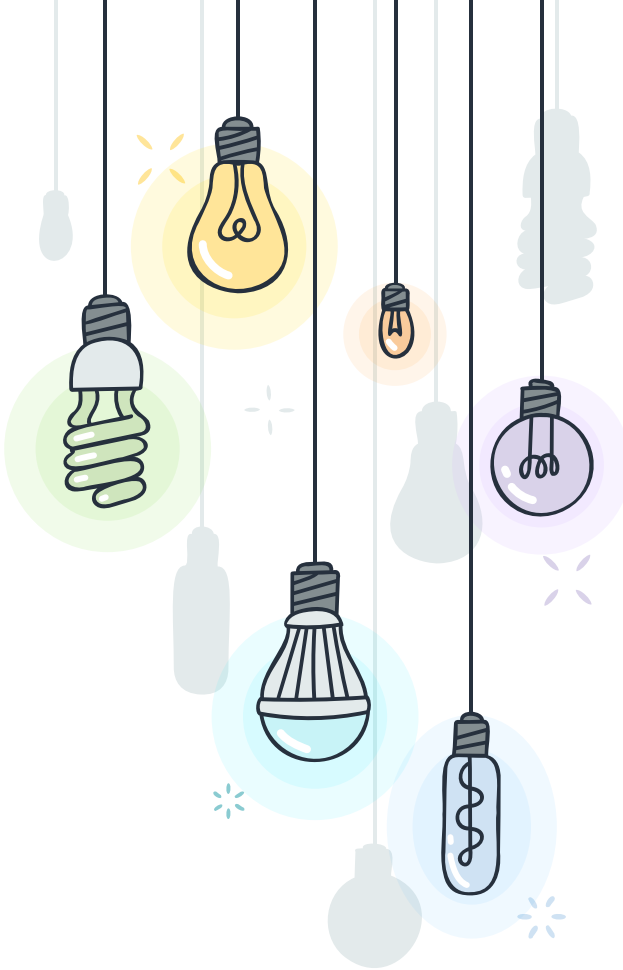
SURPASS-1 Inclusion Criteria

- ≥ 18 years old
- Type 2 diabetes not controlled with diet and exercise alone
- Naïve to injectable therapy
- A1c of 7% -9.5%
- BMI ≥ 23 kg/m^2
- Stable weight within the last 3 months (± 5%)
- Agreement to not start diet and exercise during the program with the intent to lose weight other than\ that required for DM treatment.



SURPASS-1 Exclusion criteria

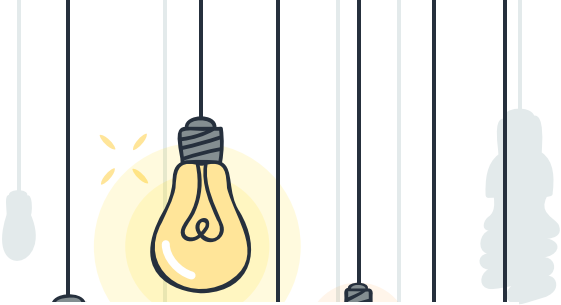
- Type 1 diabetes
- History of pancreatitis
- History of proliferative diabetic retinopathy, diabetic maculopathy or non proliferative diabetic retinopathy that required acute treatment.
- eGFR <30 mL/min per 1.73m^2
- Use of any oral antihyperglycemic 3 months prior to screening.

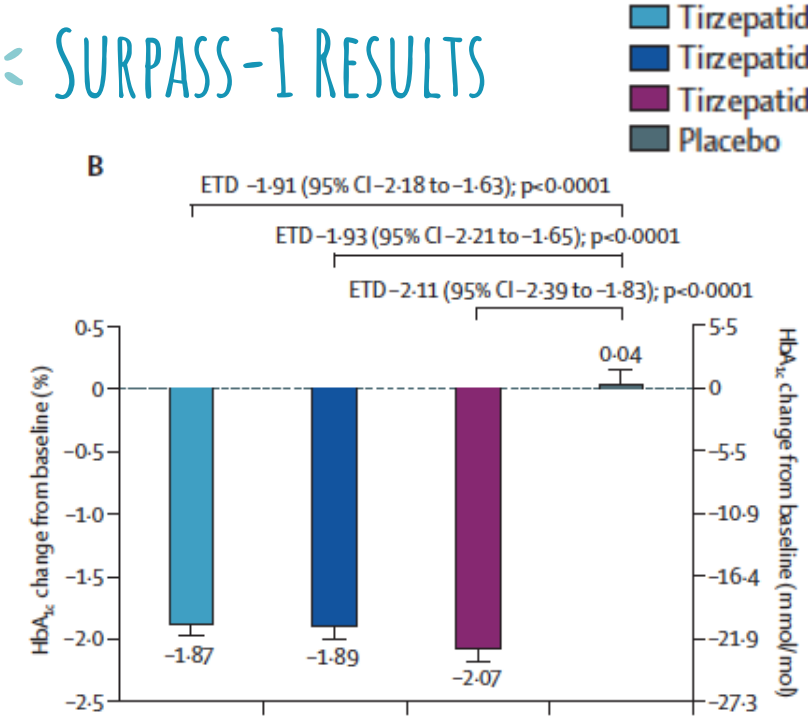


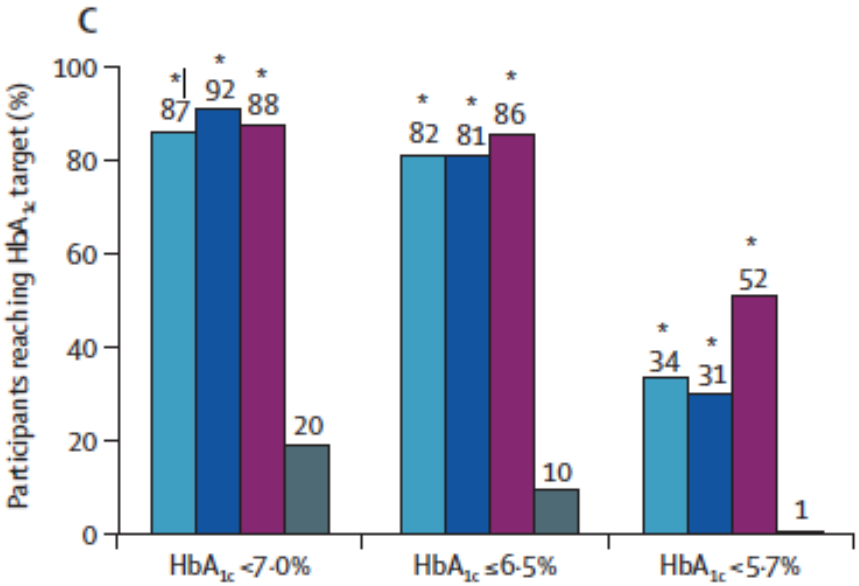
SURPASS-1 RESULTS

- Tirzepatide was found to be superior to placebo:
  - Mean changes in A1c were -1.87% (5mg), -1.89% (10mg), -2.07% (15mg), and +0.04% (placebo).
  - 87-92% of patients reached an A1c of less than 7% while taking tirzepatide compared to 20% with placebo.
  - 34-52% of patients reached an A1c of less than 5.7% compared to 1% with placebo.
  - FSG decreased by 43.6 (5mg), 45.9 (10mg), 49.3 (15mg) and increased by 12.9 with placebo.
  - A dose dependent weight loss from 7-9.5 kg was found.

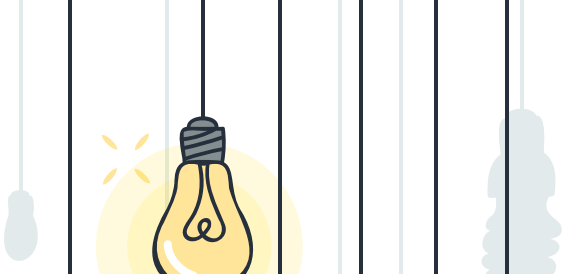
SURPASS-1 RESULTS

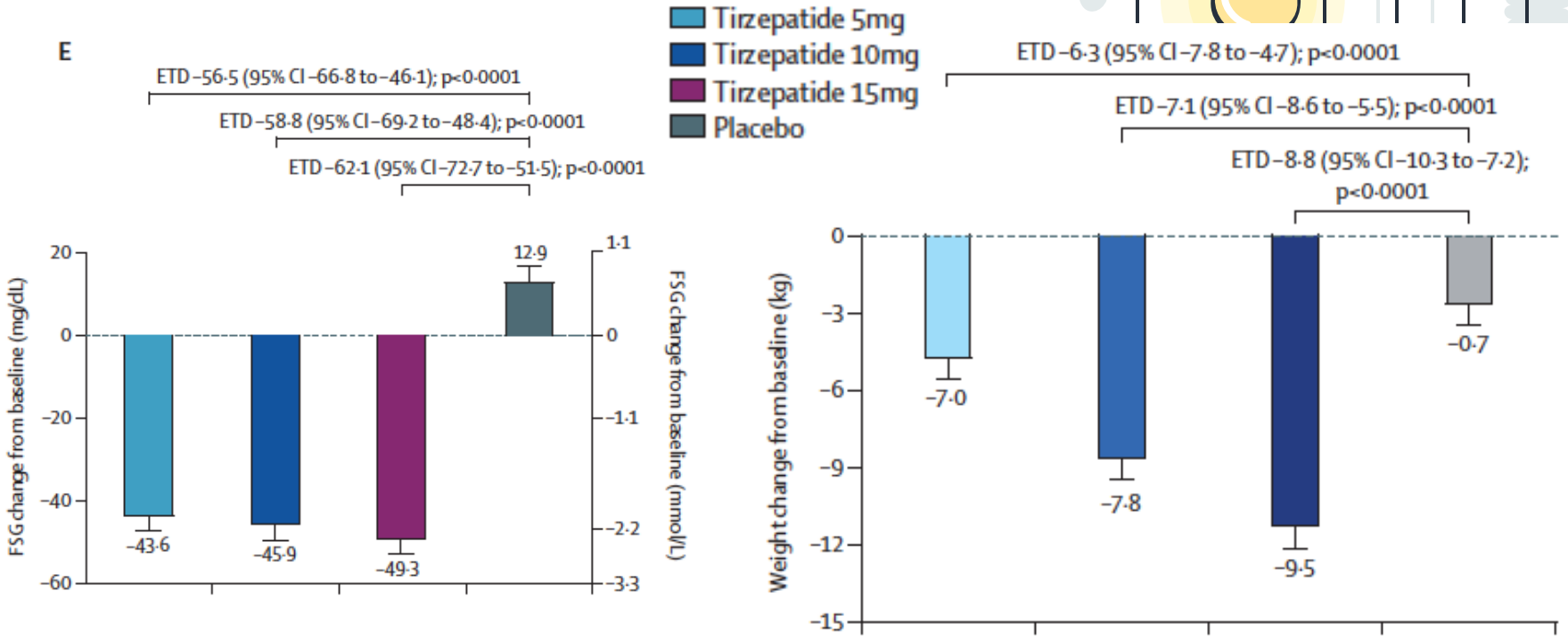






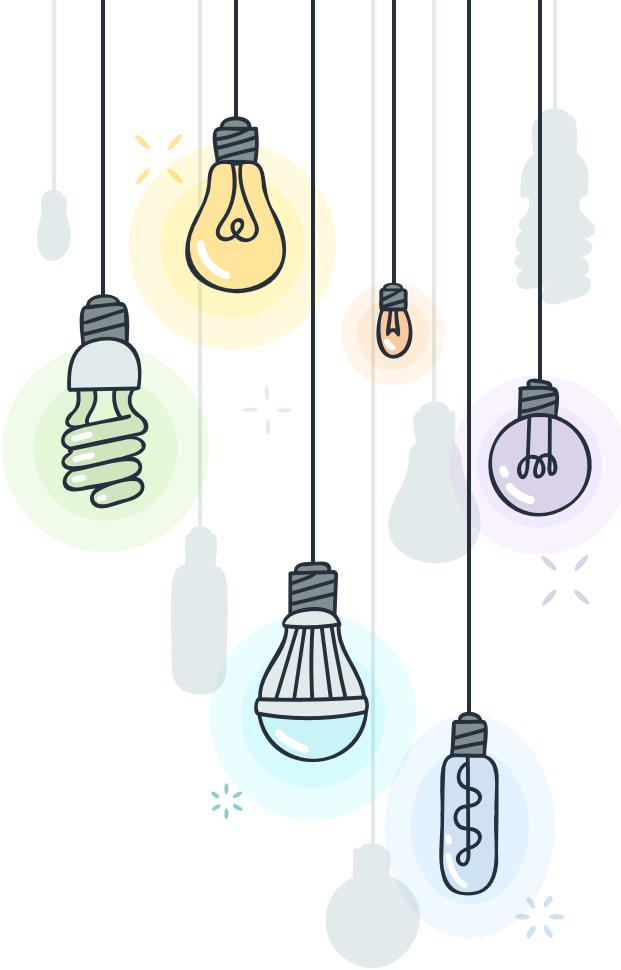
SURPASS-1 RESULTS





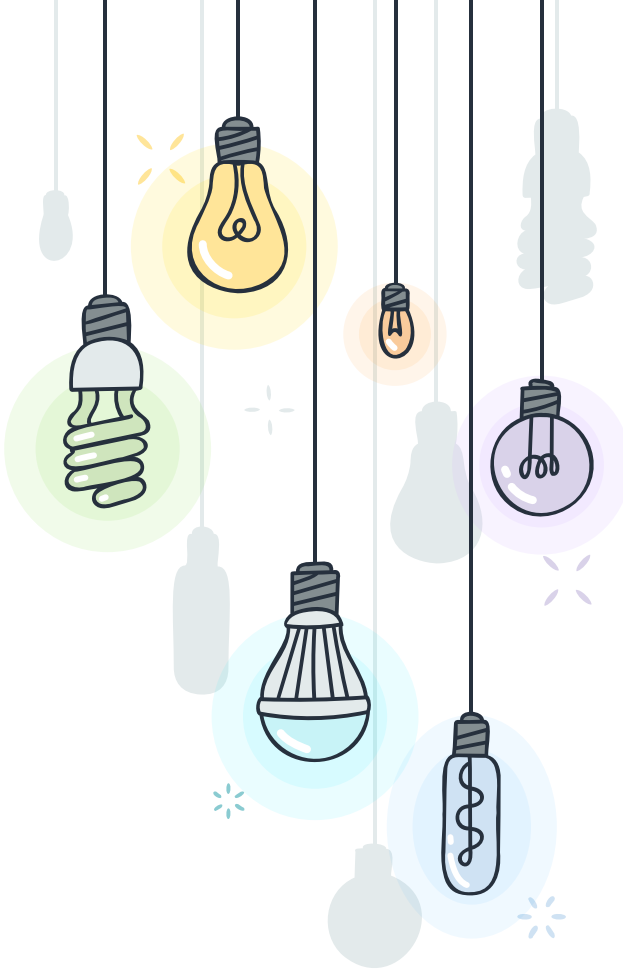
SURPASS-2 TRIAL DESIGN

- 40 week, open label, parallel group RCT
- Multicenter (128 sites)
- Patients were assigned once weekly (1:1:1:1) tirzepatide 5mg, 10mg, 15mg, or 1 mg of semaglutide
- N= 1879 patients
- Mean A1c: 8.28%



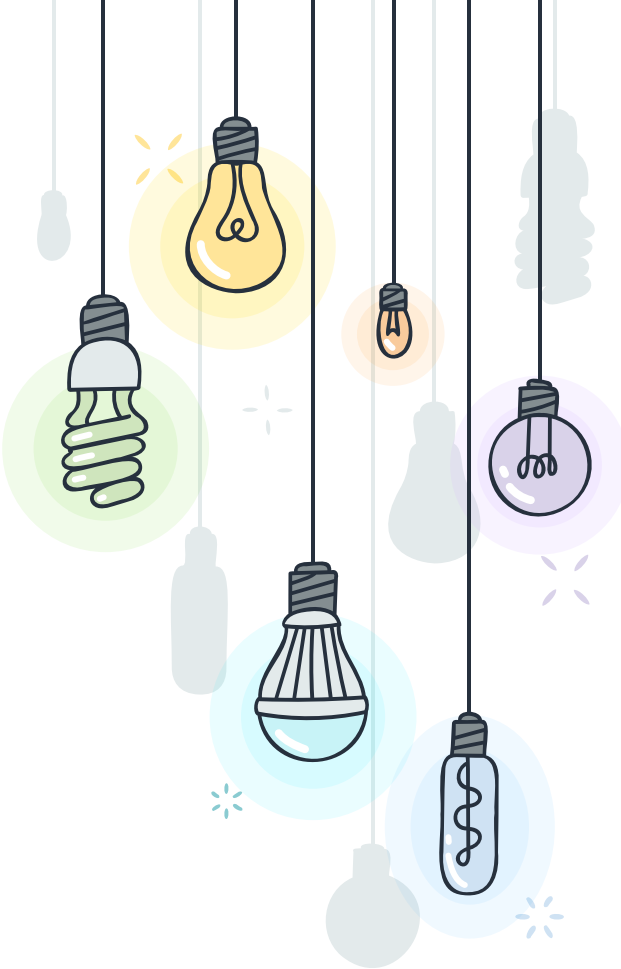
SURPASS-2 TRIAL DESIGN

- Primary outcome: mean change in A1c from baseline at 40 weeks
- Key Secondary outcomes:
  - change in body weight from baseline to week 40
  - Attainment of A1c less than 7% and 5.7%



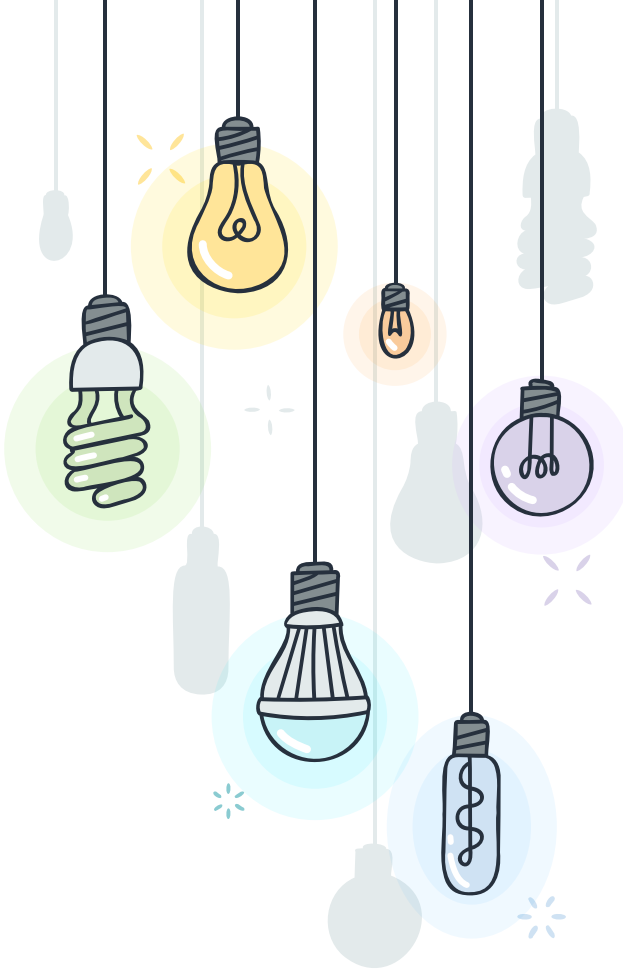
SURPASS-2 Inclusion criteria

- ≥ 18 years old
- Type 2 diabetes not controlled by at least 1500mg of metformin daily
- A1c 7%-10.5%
- BMI ≥ 25 kg/m^2
- Stable weight during the previous 3 months (±5%)



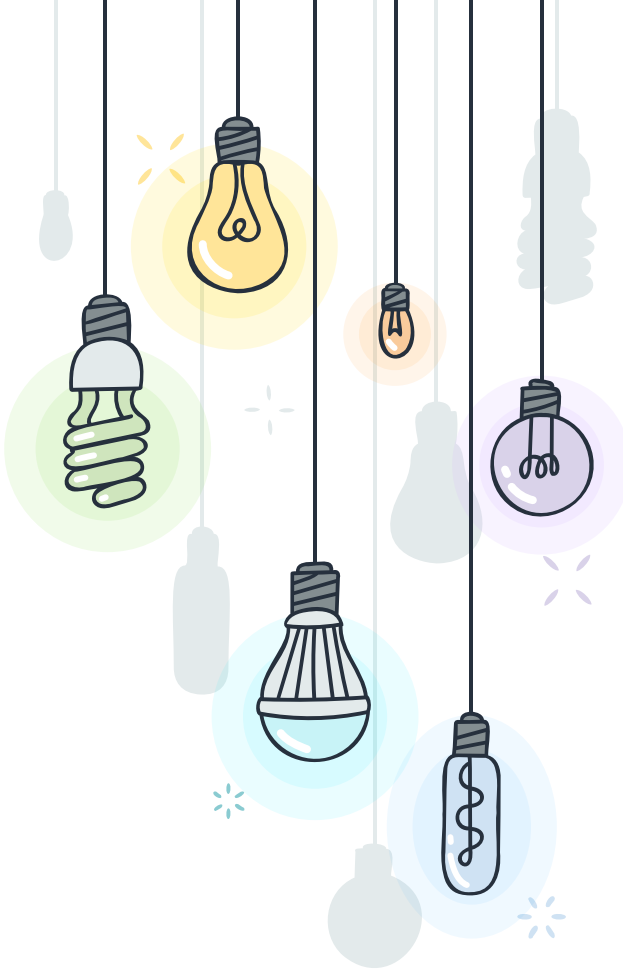
SURPASS-2 Exclusion criteria

- Type 1 diabetes
- eGFR <45 ml/min per 1.73m^2
- History of pancreatitis
- History of proliferative diabetic retinopathy, diabetic maculopathy or non proliferative diabetic retinopathy that required acute treatment.

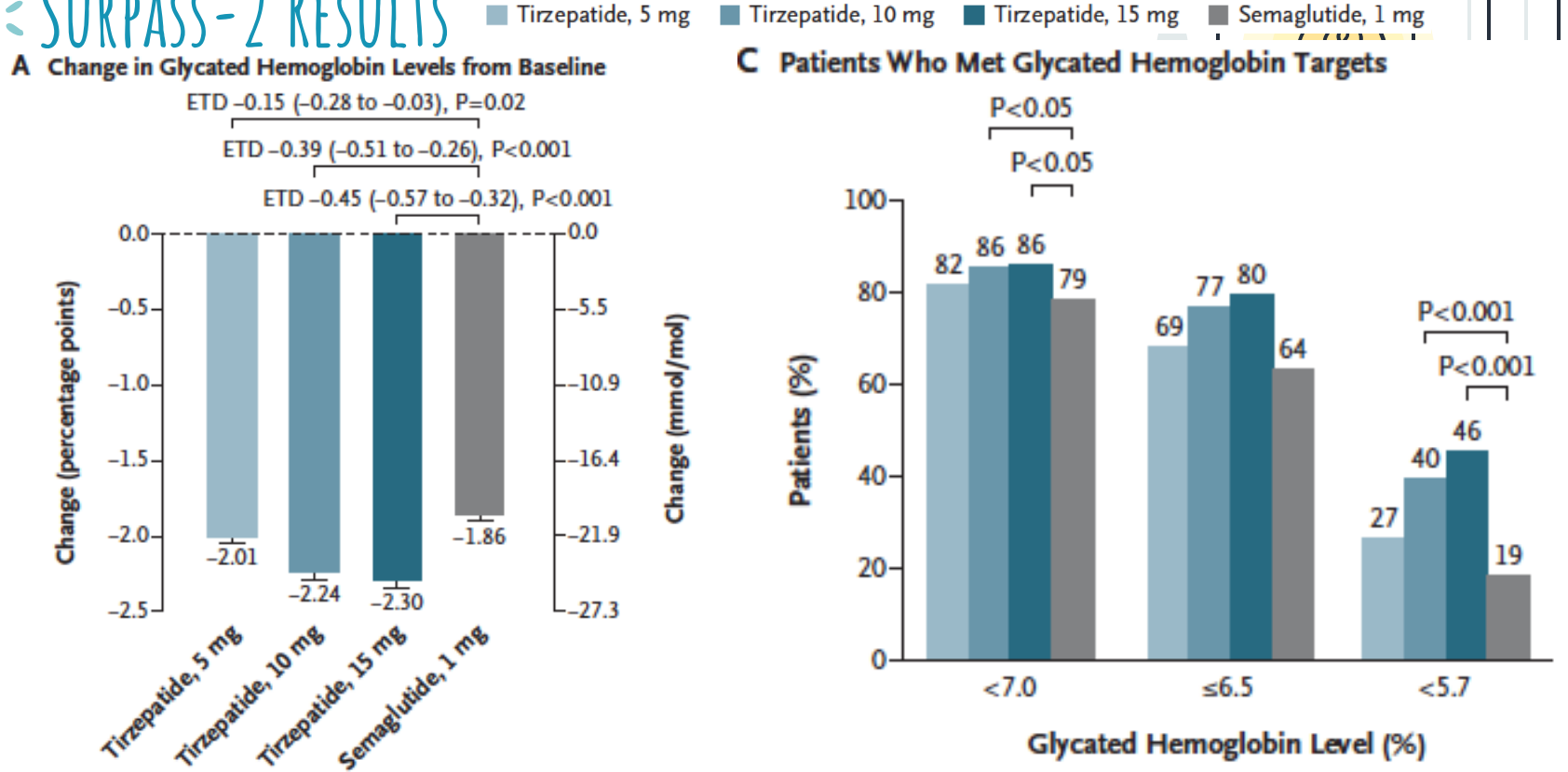


SURPASS-2 RESULTS

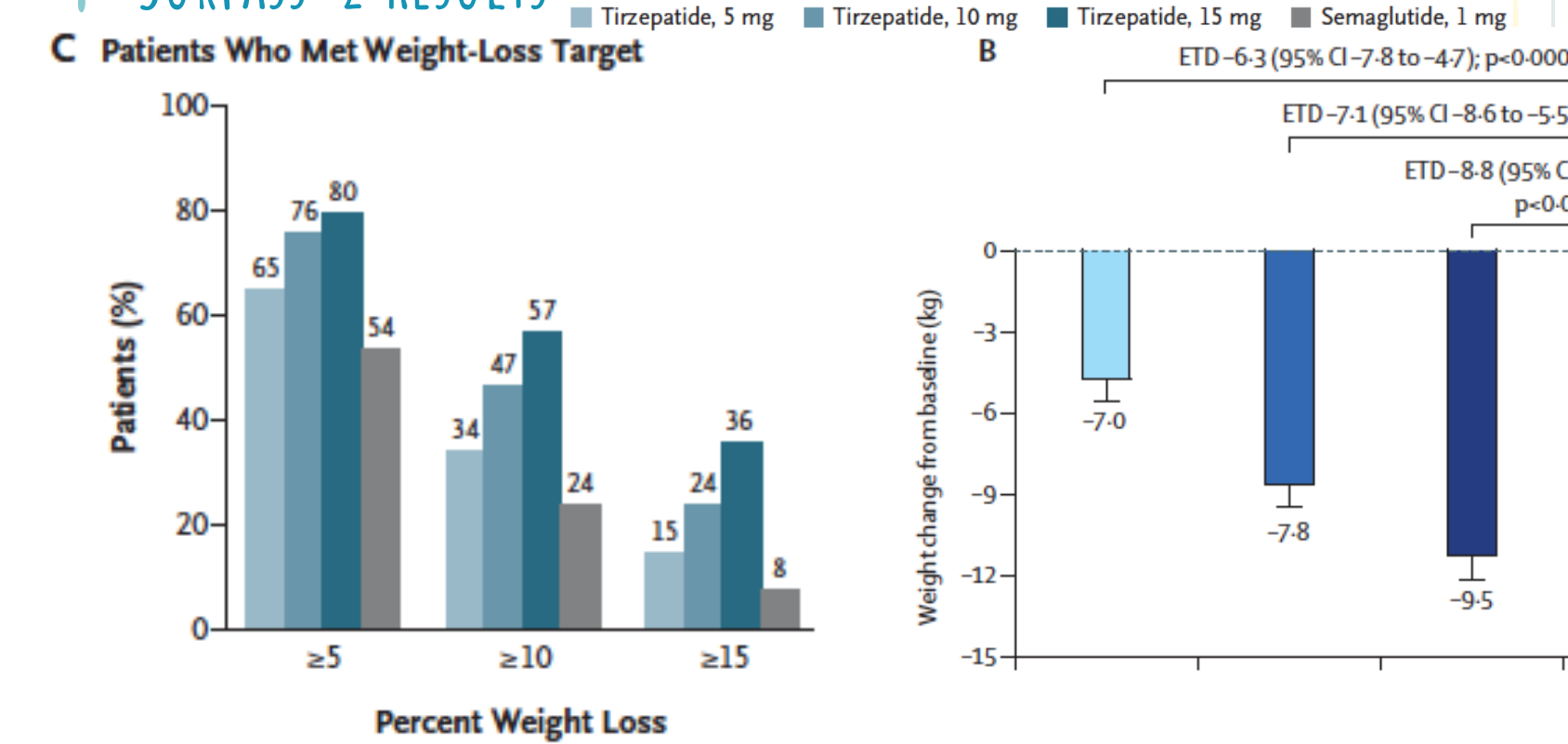
- Tirzepatide was found to be noninferior and superior to semaglutide at all doses:
- Mean changes in A1c were -2.01% (5mg), -2.24% (10mg), -2.30% (15mg) and 1.86 (Ozempic)
- Mean changes in weight were -1.9kg (5mg), -3.6kg (10mg), and -5.5kg (15mg) more than with Ozempic
- 82-86% of patients achieved an A1c <7% as compared to 79% with Ozempic
- 27-46% of patients achieved an A1c of <5.7 was compared to 19% with Ozempic



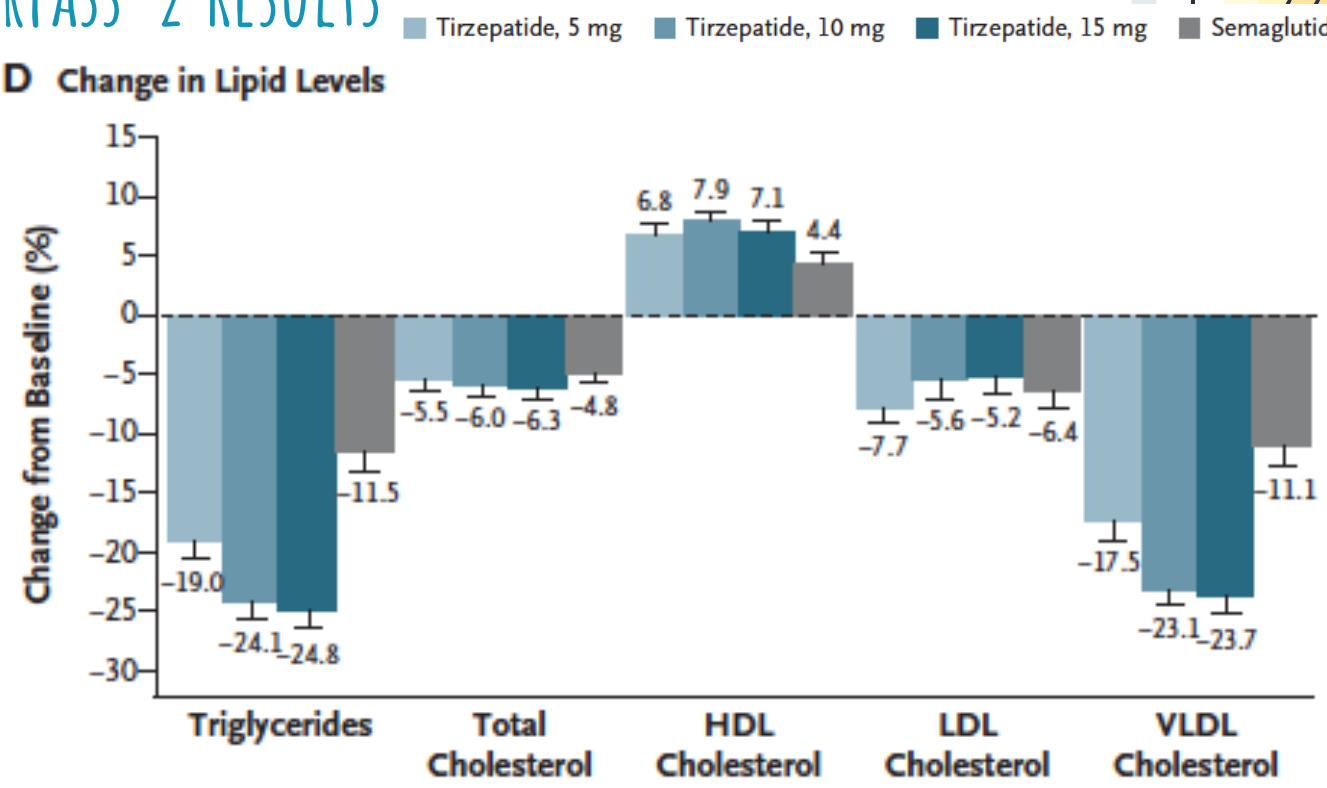
SURPASS-2 RESULTS



SURPASS-2 RESULTS



SURPASS-2 RESULTS



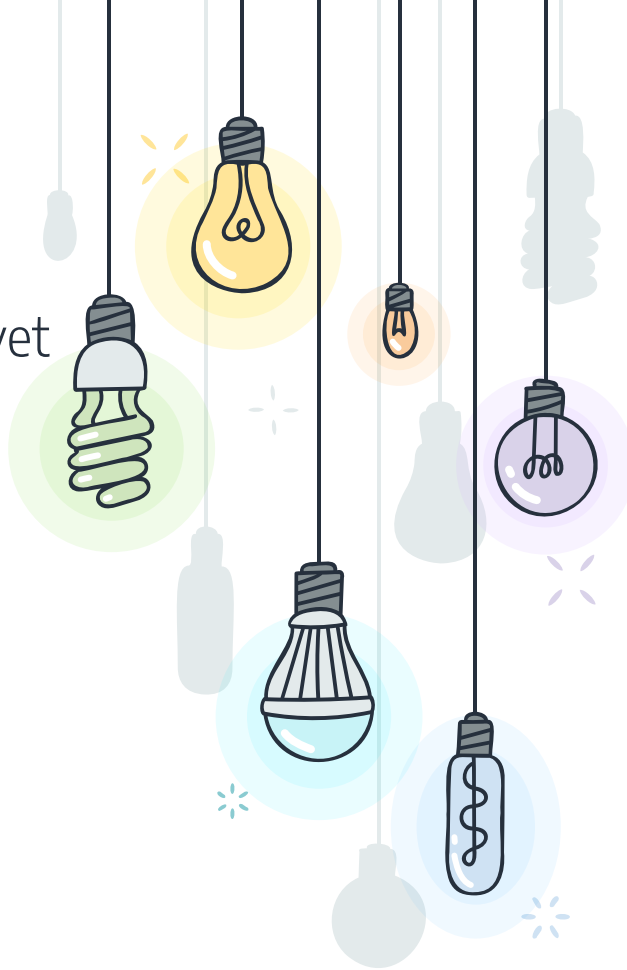
3

Place in practice

How do we use it?

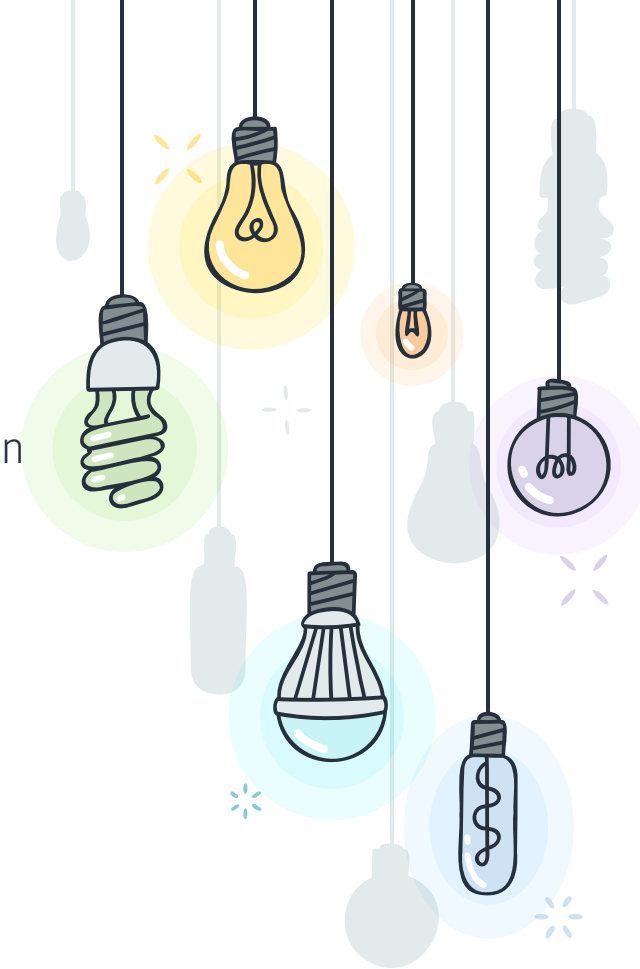
Food for thought

- Currently approved for Type 2 Diabetes, but not yet approved as weight loss therapy.
- SURMOUNT trials currently being conducted
- No mention in ADA or KDIGO guidelines yet



Cardiovascular benefits?

- Whether Mounjaro reduces cardiovascular events in Type 2 diabetes has not yet been measured
- SURPASS-4 focused on the comparison of Mounjaro to insulin glargine in patients at increased cardiovascular risk.
- The main focus of the trial was reduction in A1c, however, MACE-4 events were measured as a secondary outcome.
- The data gathered indicated that risk for MACE-4 was not increased, but did not necessarily indicate they were decreased. (data was not statistically significant)
- SURPASS- CVOT ending Oct. 2024



Thanks!

Any questions?

Cathrine.bauchman@ihs.gov