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The Future is Now: The Next Decade of New Diabetes Treatments, Mechanisms, and Benefits is Here!

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2023 OSHP Fall Meeting
September 22, 2023

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Financial Disclosure and Resolution

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

- The incidence of type 1 diabetes, type 2 diabetes, and obesity are at an all time high in the US and increasing. New treatments are available or being studied that can treat these diseases effectively and safely.
- 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 will have questions and want to know about these new drugs.
- Pharmacists need to know how to discuss, recommend, and counsel on the use of these new drugs and classes. 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. Recognize newly approved and upcoming diabetes therapies and their mechanisms, safety, and efficacy.
2. Interpret findings from select phase 2 and 3 trials used to support approval of new therapies.
3. Apply evidence of new therapies to patient case scenarios.

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Type 1 Diabetes (T1DM)

- Type 1 diabetes (due to autoimmune β -cell destruction, usually leading to absolute insulin deficiency)
- Three stages have been identified
- Stage 3 requires insulin replacement

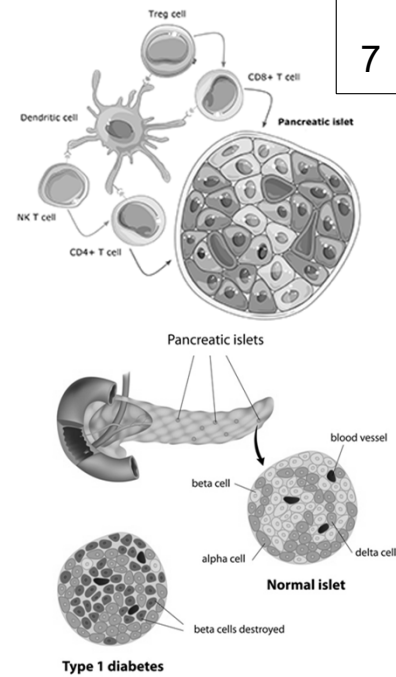
ADA. 2023 Standards of Care in Diabetes. Diabetes Care 2023;46(Suppl. 1):S19–S40

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T1DM

Pathophysiology

- Once triggered, the immune system attacks the β -cells
- As β -cell mass diminishes, exogenous insulin is required



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Stages of T1DM

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Table 2.1—Staging of type 1 diabetes (12,16)

	Stage 1	Stage 2	Stage 3
Characteristics	• Autoimmunity • Normoglycemia • Presymptomatic	• Autoimmunity • Dysglycemia • Presymptomatic	• Autoimmunity • Overt hyperglycemia • Symptomatic
Diagnostic criteria	• Multiple islet autoantibodies • No IGT or IFG	• Islet autoantibodies (usually multiple) • Dysglycemia: IFG and/or IGT • FPG 100–125 mg/dL (5.6–6.9 mmol/L) • 2-h PG 140–199 mg/dL (7.8–11.0 mmol/L) • A1C 5.7–6.4% (39–47 mmol/mol) or $\geq 10\%$ increase in A1C	• Autoantibodies may become absent • Diabetes by standard criteria

FPG, fasting plasma glucose; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; 2-h PG, 2-h plasma glucose.

ADA. 2023 Standards of Care in Diabetes. Diabetes Care 2023;46(Suppl. 1):S19–S40

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Treatment of T1DM

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- Classically, only insulin is used to treat T1DM
- Technically, amylin analogues may be used; this is rare
- Insulin doses may be administered via vial and syringe, insulin pens, or insulin pumps
- Several doses may be needed daily
- Proper technique and knowhow is required to avoid dangerous hypoglycemia

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New NON-Insulin Therapies

TEPLIZUMAB

DONISLECEL

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Teplizumab-mzwv

Approved November 17, 2022

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Delays T1DM

- Trade Name: Tziel
- Indication
 - Teplizumab is a CD3-directed antibody indicated to delay the onset of Stage 3 type 1 diabetes in adults and pediatric patients aged 8 years and older with Stage 2 type 1 diabetes
- MOA
 - Anti-CD3 monoclonal antibody
 - Modifies CD8+ T lymphocytes—effector cells that kill beta cells—by decreased activation, signaling, and gene cell expression
 - Reduces autoimmune destruction of pancreatic beta cells
 - Slows decline of C-peptide
 - Prolongs insulin production
 - Delays progression from Stage 2 to Stage 3 Type 1 Diabetes

Tziel [prescribing information]
Evans EL US Pharm. 2022;47(11):24-26

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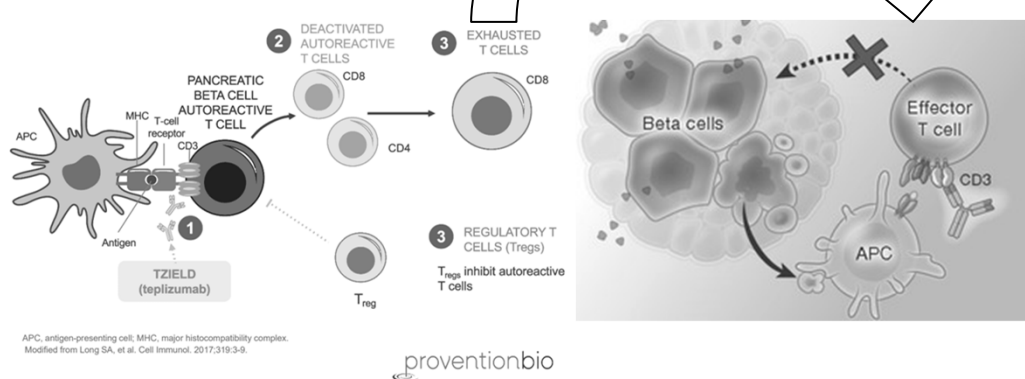
Teplizumab-mzwv: MOA

Immunomodulatory Mechanism of Action of TZIELD (teplizumab)

1. Teplizumab-mzwv binds to CD3 molecules on the surface of both CD4+ and CD8+ T cells during treatment, with internalization of the teplizumab-mzwv/CD3 complex from the surface of T cells

2. The mechanism of action may involve partial agonistic signaling and deactivation of pancreatic beta cell autoreactive T cells

3. TZIELD leads to an increase in the proportion of regulatory T cells and of exhausted CD8+ T cells in peripheral blood



<https://nanome.ai/blog/diabetes-treatment-is-about-to-change-forever/> . Accessed August 30, 2023.
N Engl J Med 2019; 381:603-613. DOI: 10.1056/NEJMdo005563.

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Teplizumab-mzwv

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- Dosing/Administration
 - Preparation
 - Confirm Stage 2 type 1 diabetes
 - ≥ 2 positive pancreatic islet cell autoantibodies, dysglycemia without hyperglycemia
 - Confirm no history of type 2 diabetes
 - Obtain CBC and LFT
 - Administer all age-appropriate vaccinations prior
 - Live-attenuated at least 8 weeks prior
 - Inactive or mRNA at least 2 weeks prior
 - Premedicate prior to infusion for the first 5 treatments:
 - NSAID or APAP, antihistamine, and/or antiemetic

Tzield [prescribing information]

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Teplizumab-mzwv

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- Dosing/Administration
 - **IV infusion** (over a minimum of 30 minutes), using a body surface area-based dosing, **once daily for 14 consecutive days** as follows:
 - Day 1: 65 mcg/m²
 - Day 2: 125 mcg/m²
 - Day 3: 250 mcg/m²
 - Day 4: 500 mcg/m²
 - Days 5 through 14: 1,030 mcg/m²
 - Do not administer two doses on the same day.



Tzield [prescribing information]

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Teplizumab-mzwv

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- Adverse Effects/Warnings
 - Cytokine Release Syndrome
 - Premedicate with antipyretics, antihistamines, antiemetics
 - Monitor LFT (discontinue if over 5 times ULN)
 - Serious Infections
 - Not recommended with serious or chronic infection
 - Lymphopenia
 - Most recover 5 days after treatment completion
 - Monitor CBC, WBC, hemoglobin, neutrophils, and platelets
 - Hypersensitivity
 - Monitor for serum sickness, angioedema, urticaria, rash, vomiting and bronchospasm

Tzield [prescribing information]

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TN-10 Trial

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The NEW ENGLAND
JOURNAL of MEDICINE

ESTABLISHED IN 1812

AUGUST 15, 2019

VOL. 381 NO. 7

An Anti-CD3 Antibody, Teplizumab, in Relatives at Risk
for Type 1 Diabetes

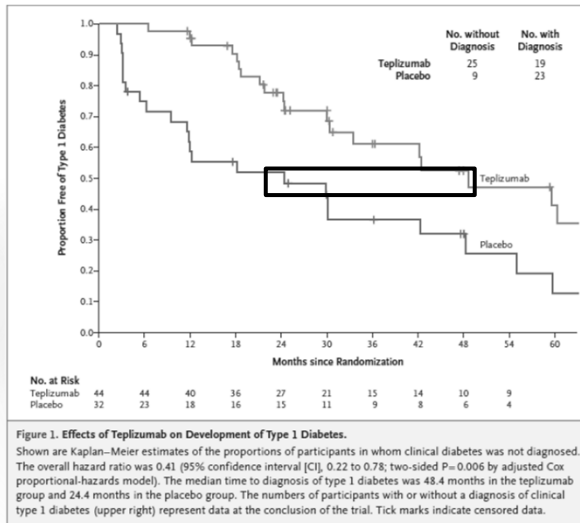
- Objective: Determine whether teplizumab would prevent or delay onset of clinical T1DM in those at high risk for clinical disease vs placebo
- Design: Phase 2, randomized, placebo-controlled, double-blind trial
 - 2 arms: 14-day course of teplizumab or placebo
 - OGTT at 3 months, then every 6 months to determine if clinical disease
- Primary Outcomes: elapsed time from randomization to the clinical diagnosis of diabetes

Herold KC. N Engl J Med 2019;381:603-13.

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TN-10 Trial

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Herold KC. N Engl J Med 2019;381:603-13.

Results:

Efficacy:

- Median time to T1DM diagnosis
 - 48.4 months with teplizumab
 - 24.4 months with placebo
 - HR 0.41; 95%CI, 0.22-0.78; **P=0.006**
- Diagnosed with T1DM
 - 43% on teplizumab
 - 72% on placebo

Safety

- Expected adverse effects of rash and transient lymphopenia

Teplizumab delays T1DM by 2-3 years!

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Teplizumab

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- TN-10 Trial implications:
 - teplizumab received Priority Review and Breakthrough Therapy designations for this indication
 - FDA granted the approval of Tzield to Provention Bio
 - FDA still wants Phase 3 trials completed
 - STOP-T1D Prevention Study began early 2023
- There is a need for early T1DM screening for those at high risk

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Donislecel

Islet transplant

Approved June 28, 2023

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- Indication/Usage:

- Treatment of adults with type 1 diabetes who are unable to approach target HbA1c because of current repeated episodes of severe hypoglycemia despite intensive diabetes management and education.
- Use in conjunction with concomitant immunosuppression.

- MOA:

- The active ingredient is allogeneic pancreatic islets of Langerhans derived from a deceased donor pancreas
 - Pancreatic islets regulate blood glucose levels through secretion of multiple hormones in response to increases and decreases in blood glucose.
 - The primary mechanism of action is believed to be secretion of insulin by infused (transplanted) β - cells.
- May remove need for exogenous insulin injections

Lantidra [prescribing information]

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Donislecel

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- Dosage/Administration:

- The recommended minimum dose is 5,000 equivalent islet number (EIN) per kg patient body weight for initial infusion (transplant) and 4,500 EIN/kg for subsequent infusions (same recipient)
- Administer cells through the hepatic portal vein
- The estimated tissue volume should not exceed 10 cc per transplant infusion
- Total number of islets packaged for infusion is reported on the container label and associated documents

- Subsequent Doses

- A second infusion may be performed if the patient does not achieve independence from exogenous insulin within one year of infusion or within one year after losing independence from exogenous insulin after a previous infusion. A third infusion may be performed using the same criteria as for the second infusion.
- There are no data regarding the effectiveness or safety for patients receiving more than three infusions.

Lantidra [prescribing information]

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Donislecel

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- Pre-medicate:
 - Non-depleting monoclonal anti-interleukin-2 (anti-IL-2) receptor antibody
 - Calcineurin inhibitor
 - Mammalian target of rapamycin (mTOR) inhibitor
 - Tumor necrosis factor (TNF) blocker
 - Perioperative antibiotic prophylaxis
- Warnings:
 - Risks from concomitant immunosuppression
 - Procedural complications
 - Liver laceration, hemorrhage and intra-abdominal bleeding
 - Elevation in portal blood pressure
 - Portal vein branch thrombosis
 - Increased risk of islet graft rejection
 - Transmission of Donor-Derived Infections
 - Panel Reactive Antibodies (PRA)

Lantidra [prescribing information]

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Donislecel

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- Adverse effects:
 - Ninety percent (90%) of subjects had at least one serious adverse reaction. The major causes were attributed to:
 - Infusion procedure
 - liver laceration/hematoma, hemorrhage, and intra-abdominal bleeding (13%)
 - elevation of portal pressure (7%)
 - Immunosuppression
 - Infection (87%)
 - Malignancy (37%)
 - Limitations of Use:

When considering the risks associated with the infusion procedure and long-term immunosuppression, there is no evidence to show a benefit of administration of donislecel in patients whose diabetes is well controlled with insulin therapy or patients with hypoglycemic unawareness who can prevent current repeated severe hypoglycemic events using intensive diabetes management.

Lantidra [prescribing information]

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Donislecel Clinical Trials

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- Two unpublished clinical trials from prescribing information labeled
 - Study 1 and Study 2
 - Non-randomized, prospective, open-label, single-arm
 - A combined 30 subjects with T1DM and hypoglycemia unawareness received 1-2 infusions of donislecel
 - Median age 46.5 (range: 21 – 67) years, 80% female, 100% White, 97% non-Hispanic
 - 11 subjects received 1 infusion
 - 4 were insulin-independent, 3 did not have a donor, and 4 were intolerant to immunosuppression or withdrew from the study within 6 months
 - 19 subjects received 2 infusions
 - 6 were insulin-independent at the time of their second infusion
 - 7 subjects received 3 infusions
 - 0 were insulin-independent

Lantidra [prescribing information]

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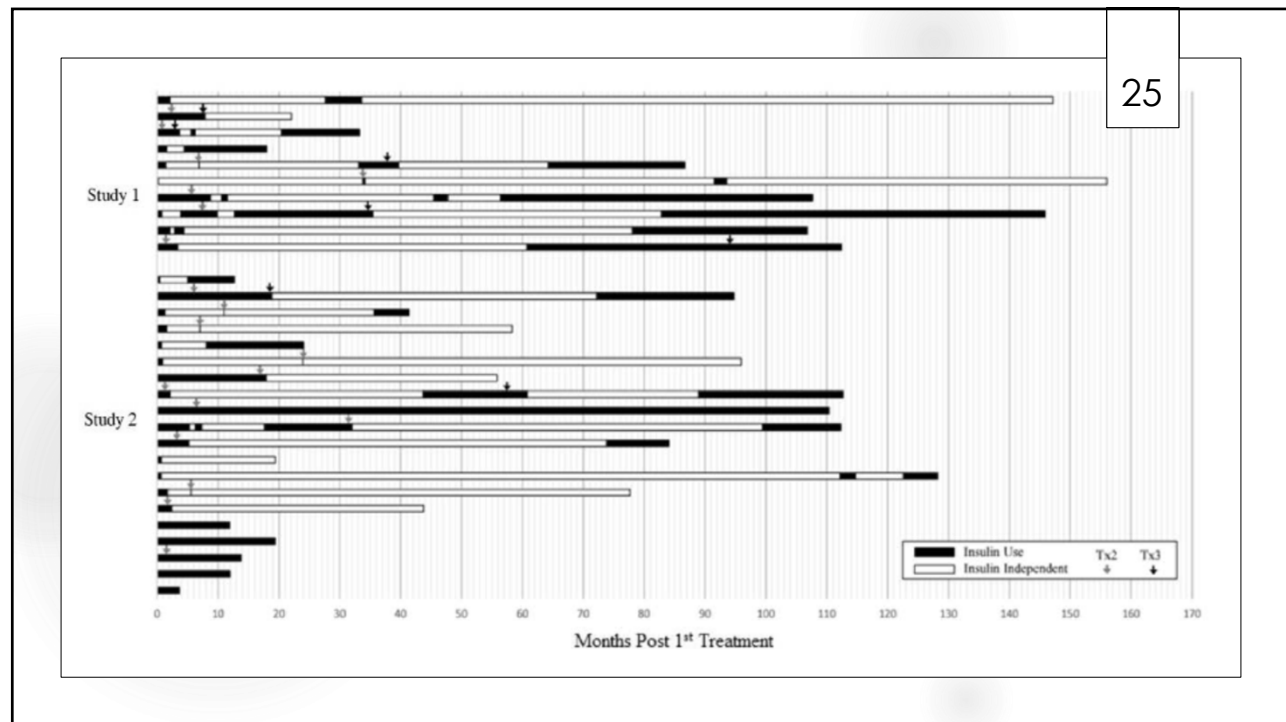
Donislecel Clinical Trials

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- Five subjects had no days of insulin independence
- The 25 subjects who achieved insulin independence
 - 4 subjects (13.3%) were insulin independent for less than one year
 - 12 subjects (36.7%) for 1 to 5 years
 - 9 subjects (33.3%) for greater than 5 years

Lantidra [prescribing information]

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Donislecel

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- The Biologics License Application for donislecel was the subject of an April 21, 2021 meeting of the FDA's Cellular, Tissue, and Gene Therapies Advisory Committee. This meeting concluded with a 12-4 vote in favor of the clinical value of donislecel based on the risk-benefit profile.
- The product was approved despite concerns from the American Society of Transplant Surgeons, the American Society of Transplantation, and an organization of more than 50 transplant surgeons — the Islets for US Collaborative — whose members argue that cadaver-derived (allogeneic) pancreatic islets should be regulated as transplanted organs rather than as biologic drugs, as is done in many other parts of the world.

<https://www.hcplive.com/view/fda-approves-donislecel-lantidra-an-allogeneic-cellular-therapy-for-type-1-diabetes>
Medscape. June 30, 2023.

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

A 12yo boy is screened for T1DM because his older sister was recently diagnosed with it. He is found to have 2 autoantibodies present. He has no pertinent symptoms, and his fasting plasma glucose is 112 mg/dL. What may be the most appropriate next step?

Nothing at this time. He is clearly not in Stage 3 T1DM
Start basalbolus insulin
Start teplizumab to delay progression of Stage 2 T1DM
Start donislecel so the patient will not require insulin therapy

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

Which of the following is appropriate?

A 26-year-old woman with a 19-year history of T1DM presents to her PCP with questions about new T1DM treatments she heard about. She uses an insulin pump. Her A1c has been stable around 6.2%. Her blood glucose Time In Range is >80%. She has not had to deal with significant hypoglycemia for several years and is able to feel symptoms if present and reacts appropriately.

Nothing at this time. She has good control.
Start teplizumab to delay further progression of T1DM.
Start donislecel so this patient may stop her insulin therapy.
Hold insulin. An occasional drug holiday can rejuvenate the pancreas.

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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Type 2 Diabetes (T2DM)

- Type 2 diabetes (due to a non-autoimmune progressive loss of adequate β -cell insulin secretion frequently on the background of insulin resistance and metabolic syndrome)
- T2DM is progressive and will worsen without lifestyle interventions and/or pharmacologic therapy
- T2DM is often accompanied by overweight/obesity

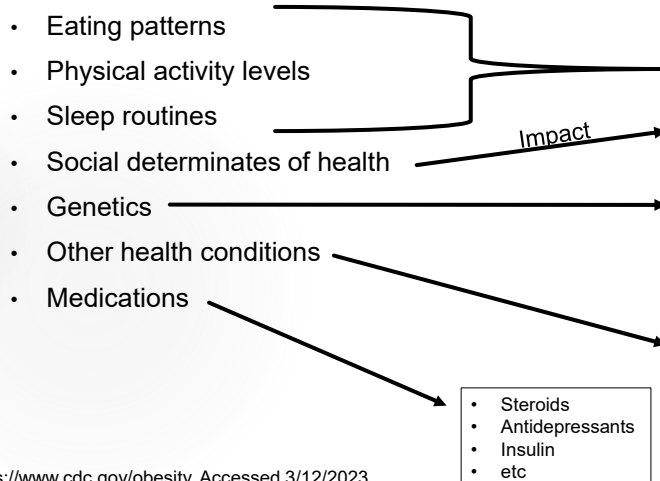
ADA. 2023 Standards of Care in Diabetes. Diabetes Care 2023;46(Suppl. 1):S19–S40

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Causes of Obesity

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



- 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

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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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Risks of Obesity

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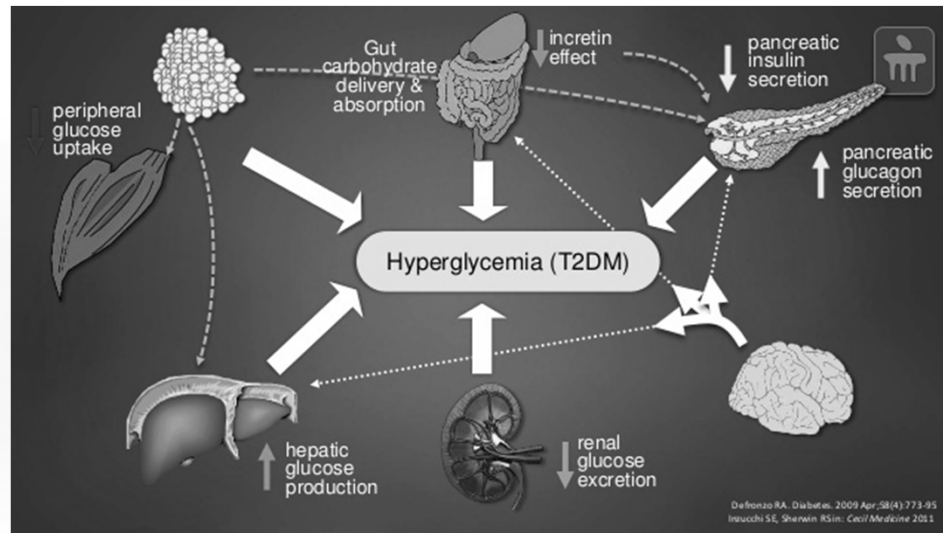
- Obesity in children and adults increases the risk for the following health conditions
 - High blood pressure and high cholesterol which are risk factors for heart disease
 - Type 2 diabetes
 - Breathing problems, such as asthma and sleep apnea
 - Joint problems such as osteoarthritis and musculoskeletal 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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T2DM Pathophysiology

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T2DM Treatments

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- Insulin
- Biguanides
- Sulfonylureas
- Thiazolidinediones
- Alpha glucosidase inhibitors
- Amylin analogues
- DPP-4 inhibitors
- SGLT2 Inhibitors
- GLP-1 Receptor Agonists
- GLP-1/GIP Receptor Agonists

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A NEW Insulin Option

INSULIN ICODEC

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Insulin Icodec

Once Weekly Basal Insulin

- Approval expected in April 2024 for Novo Nordisk
- Modified amino acid structure allows for permanent albumin binding
- Half-life to 196 hours (approximately 7 days).
- Dosed once weekly at 7 times the dose of a once-daily basal insulin

<https://www.drugs.com/medical-answers/what-insulin-icodec-3574279/>

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Icodec ONWARDS 1

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THE NEW ENGLAND JOURNAL OF MEDICINE

ORIGINAL ARTICLE

Weekly Icodec versus Daily Glargine U100 in Type 2 Diabetes without Previous Insulin

Julio Rosenstock, M.D., Stephen C. Bain, F.R.C.P., Amoolya Gowda, M.D.,
 Esteban Jódar, M.D., Ph.D., Bo Liang, M.D., Ph.D.,
 Ildiko Lingvay, M.D., M.P.H., M.S.C.S., Tomoyuki Nishida, M.Sc.,
 Roberto Trevisan, M.D., Ph.D., and Ofri Mosenzon, M.D.,
 for the ONWARDS 1 Trial Investigators*

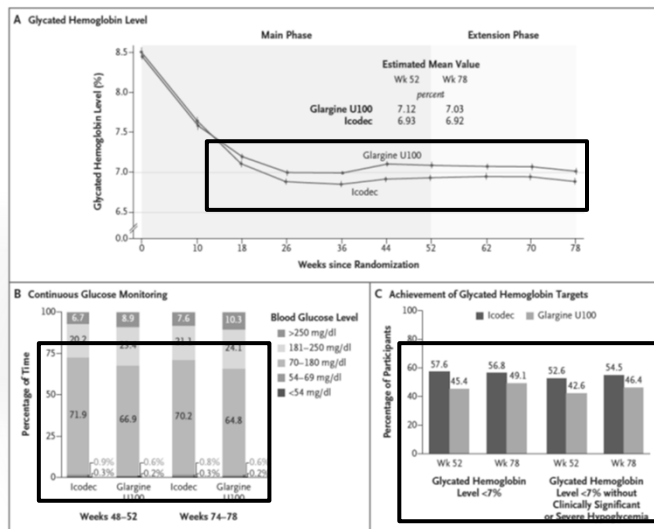
- **Objective:** Determine change in A1c among adults with type 2 diabetes (A1c, 7 to 11%) treated with icodec vs glargine who had not previously received insulin.
- **Design:** 78-week randomized, open-label, treat-to-target phase 3a trial (including a 52-week main phase and a 26-week extension phase, plus a 5-week follow-up period)
 - 2 arms: once-weekly icodec or once daily glargine U100
- **Primary End Points:** change in A1c from baseline to week 52
 - Secondary end point was the percentage of time spent in the glycemic range of 70 to 180 mg/dL in weeks 48 to 52.
 - Hypoglycemic episodes (from baseline to weeks 52 and 83) were recorded.

Rosenstock J. N Engl J Med. 2023. DOI: 10.1056/NEJMoa2303208

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Icodec ONWARDS 1

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Rosenstock J. N Engl J Med. 2023. DOI: 10.1056/NEJMoa2303208

Results:

- Change in A1c at 52 weeks
 - Icodec: from 8.50% to 6.93%
 - Glargine: from 8.44% to 7.12%
 - Estimated between-group difference (-0.19 percentage points; 95% CI, -0.36 to -0.03) confirmed the noninferiority ($P < 0.001$) and superiority ($P = 0.02$) of icodec
- CGM Time in Range 70-180 mg/dL
 - 71.9% vs. 66.9%; estimated between-group difference, 4.27 percentage points [95% CI, 1.92 to 6.62]; $P < 0.001$, confirmed superiority
- Level 2 Hypoglycemia < 54 mg/dL
 - No significant difference between treatments
 - Estimated treatment ratio, 1.27; 95% CI, 0.94 to 1.71

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Icodec ONWARDS 3

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JAMA | Original Investigation

Once-Weekly Insulin Icodec vs Once-Daily Insulin Degludec in Adults With Insulin-Naive Type 2 Diabetes The ONWARDS 3 Randomized Clinical Trial

Ildiko Lingvay, MD, MPH, MSCS; Marisse Asong, MD, MSC; Cyrus Desouza, MBBS; Pierre Gourdy, MD, PhD; Soumitra Kar, MSC; André Vianna, MD, PhD; Tina Vilsbøll, MD, DMSc; Siri Vinther, MD, PhD; Yiming Mu, MD

- **Objective:** Determine safety and efficacy among adults with type 2 diabetes (A1c, 7 to 11%) treated with icodec vs degludec who had not previously received insulin.
- **Design:** 26-week randomized, double-masked, noninferiority, treat-to-target, phase 3a trial (including a 5-week follow-up period)
 - 2 arms: once-weekly icodec or once daily degludec
- **Primary End Points:** change in A1c from baseline to week 26
 - Change in fasting plasma glucose, mean weekly insulin dose during the last 2 weeks of treatment, body weight change
 - Level 2 (clinically significant; glucose level <54mg/dL) and level 3 (severe; requiring external assistance for recovery) hypoglycemic episodes

Lingvay I. JAMA. 2023. doi:10.1001/jama.2023.11313

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Icodec ONWARDS 3

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Table 2. Summary of Key Efficacy and Safety End Points

Outcome	Once-weekly icodec (n = 294)			Once-daily degludec (n = 294)			Estimated treatment difference in icodec vs degludec (95% CI)	P value ^a
	Baseline	Week 26	Change from baseline to week 26	Baseline	Week 26	Change from baseline to week 26		
Primary end point								
HbA _{1c} , %	8.6	7.0	-1.6 percentage points	8.5	7.2	-1.4 percentage points	-0.2 (-0.3 to -0.1) percentage points	<.001 ^b ; .002 ^c
Key secondary end points								
Fasting plasma glucose, mg/dL	187	127	-54	176	127	-54	0 (-6 to 5)	.90
Mean insulin dose from week 24 to 26, U/week	69	204		70	186		Estimated treatment ratio, 1.10 (0.98 to 1.22)	.09
Mean body weight, kg	85.8	87.3	2.8	83.2	86.8	2.3	0.46 (-0.19 to 1.10)	.17

Table 3. Hypoglycemia and Other Adverse Events in the Safety Analysis Set

Key secondary safety end points	Once-weekly insulin icodec (n = 293)			Once-daily insulin degludec (n = 294)			Estimated rate ratio (95% CI)	P value
	Participants, No. (%)	Events	Rate per patient-year of exposure	Participants, No. (%)	Events	Rate per patient-year of exposure		
Level 2 hypoglycemic episodes^a								
Baseline to week 31 ^b	26 (8.9)	53	0.31	17 (5.8)	23	0.13	2.09 (0.99-4.41)	.05
Baseline to week 26 ^c	24 (8.2)	50	0.35	13 (4.4)	17	0.12	3.12 (1.30-7.51)	.01
Level 3 hypoglycemic episodes^a								
Baseline to week 31 ^b	0	0		2 (0.7)	2	0.01		
Baseline to week 26 ^c	0	0		0	0			
Level 2 or level 3 hypoglycemic episodes								
Baseline to week 31 ^b	26 (8.9)	53	0.31	18 (6.1)	25	0.15	1.82 (0.87-3.80)	.11
Baseline to week 26 ^c	24 (8.2)	50	0.35	13 (4.4)	17	0.12	3.12 (1.30-7.51)	.01

Lingvay I. JAMA. 2023. doi:10.1001/jama.2023.11313

Results:

- Change in A1c at 26 weeks
 - Icodec; non-inferior and superior
- Fasting plasma glucose: no diff
- Mean insulin dose: no diff
- Mean body weight: no diff
- Significant hypoglycemia
 - More level 2 and combined levels 2 and 3 hypoglycemia events with icodec at 26 weeks, but not 31 weeks

Icodec looks promising

Watch data on hypoglycemia

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Hormone-related Therapy: Incretins and Beyond

T2DM and/or Weight Loss

- GLP-1 Receptor Agonists
- GLP-1/GIP Receptor Agonists (Twincretin)
- GLP-1/GIP/Glucagon Receptor Agonists (Triple agonist)
- GLP-1/Glucagon Receptor Agonists
- Non-peptide GLP-1 Receptor Agonists
- High-dose oral-GLP-1 Receptor Agonists

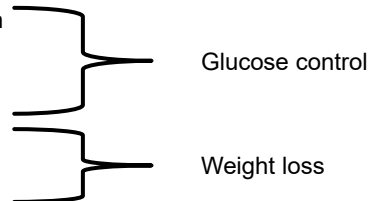
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Drug Information

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
 - delay gastric emptying
 - increase satiety thus decreasing food intake
- 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



Fanshler AV. Clin Diabetes. 2023. <https://doi.org/10.2337/cd22-0060>.

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Tirzepatide – dual agonist; GIP/GLP-1

The SURPASS Trials

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Primary outcome of glucose control

- SURPASS-1: T2DM, drug naïve; tirzepatide vs placebo
 - Compared with a mean A1c reduction of 0.04% from a baseline of 7.94% with placebo, tirzepatide 5-, 10-, and 15-mg doses reduced A1c 1.87, 1.89, and 2.07%, respectively (all P <0.0001).
- SURPASS-2: T2DM, on metformin; tirzepatide vs semaglutide 1.0 mg
 - Compared with a mean A1c reduction of 1.86% from a baseline of 8.28% with semaglutide, tirzepatide 5-, 10-, and 15-mg doses reduced A1c 2.01, 2.24, and 2.30%, respectively (all statistically significant)
- SURPASS-3: T2DM, on metformin ± SGLT2 inhibitor; tirzepatide vs insulin degludec
 - Compared with a mean A1c reduction of 1.34% from a baseline of 8.17% with insulin degludec, tirzepatide 5, 10, and 15 mg reduced A1c by 1.93, 2.2, and 2.37%, respectively (all P <0.001).
- SURPASS-4: T2DM and ↑CVD risk, on metformin ± SGLT2 inhibitor/SU; tirzepatide vs insulin glargine
 - From a mean baseline A1c of 8.52%, tirzepatide 5 mg lowered A1c by 2.24%, 10-mg lowered A1c by 2.43%, and the 15-mg dose lowered A1c by 2.58%; all statistically significant vs glargine
- SURPASS-5: T2DM, on insulin glargine ± metformin; tirzepatide vs placebo
 - From the mean baseline A1c of 8.31%, tirzepatide 5 mg lowered A1c by 2.11%, 10 mg lowered A1c by 2.40%, and 15 mg lowered A1c by 2.34%; all statistically significant vs placebo

Fanshler AV. Clin Diabetes. 2023. <https://doi.org/10.2337/cd22-0060>.

43

Tirzepatide

The SURPASS Trials

44

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 semaglutide 1.0 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)

Fanshler AV. Clin Diabetes. 2023. <https://doi.org/10.2337/cd22-0060>.

44

Triple Agonist: GLP-1/GIP/Glucagon

Dual Agonist: GLP-1/Glucagon

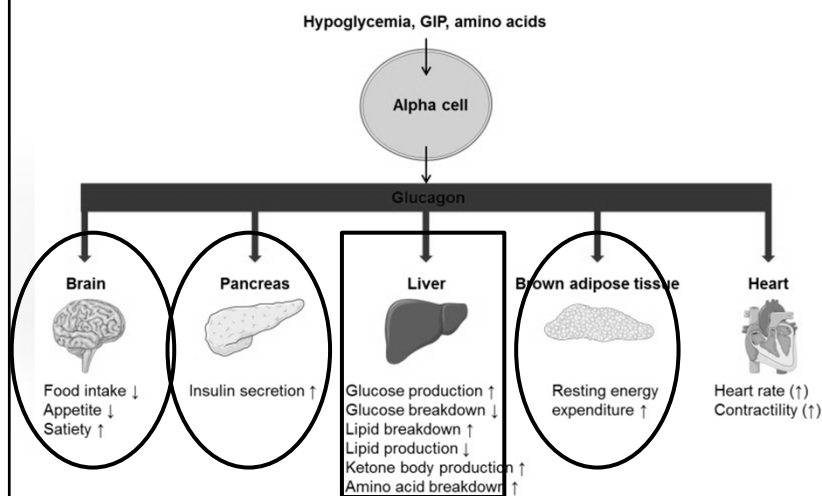
45

- 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

45

Role of Glucagon

46



- 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/>

46

Retatrutide

47

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.

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Retatrutide –T2DM Trial

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Retatrutide, a GIP, GLP-1 and glucagon receptor agonist, for people with type 2 diabetes: a randomised, double-blind, placebo and active-controlled, parallel-group, phase 2 trial conducted in the USA



Julio Rosenstock, Juan Frias, Ania M Jastreboff, Yu Du, Jitong Lou, Sirel Gurbuz, Melissa K Thomas, Mark L Hartman, Axel Haupt, Zvonko Milicevic, Tamer Coskun

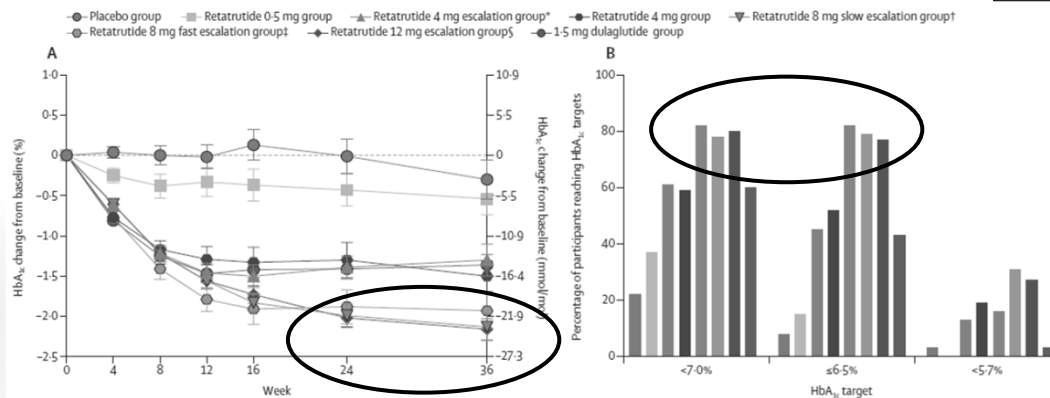
- **Objective:** to examine the efficacy and safety of retatrutide in adults with type 2 diabetes (A1c 7–10.5%; BMI 25–50 kg/m² across a range of doses vs dulaglutide 1.5 mg and placebo)
- **Intervention:** once-weekly injections of placebo, 1.5 mg dulaglutide, or retatrutide maintenance doses of 0.5 mg, 4 mg (starting dose 2 mg), 4 mg (no escalation), 8 mg (starting dose 2 mg), 8 mg (starting dose 4 mg), or 12 mg (starting dose 2 mg)
- **Primary End Points:** change in HbA1c from baseline to 24 weeks
 - Secondary endpoints: change in HbA1c and bodyweight at 36 weeks

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

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Retatrutide – T2DM Trial: Results

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• Change in A1c at 36 wk: (all $P < 0.0001$)

- 8 mg slow: -2.13%
- 8 mg fast: -1.93%
- 12 mg: -2.16%

• Percent A1c target attainment:

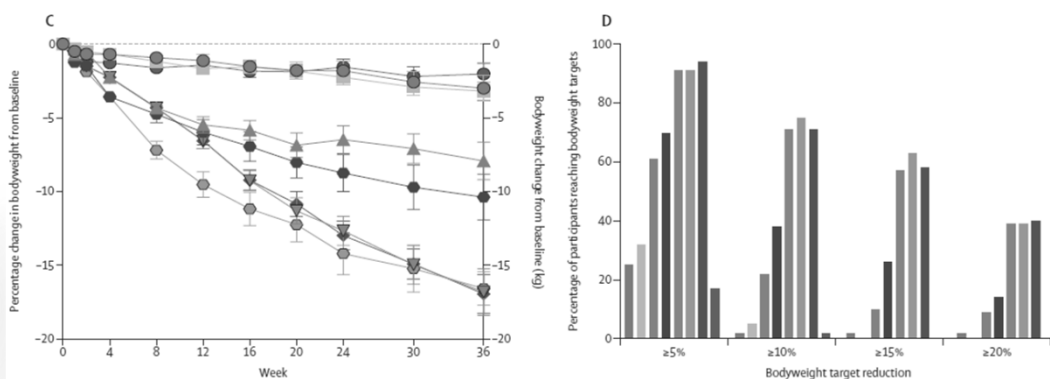
- <7%: ~80% for 8 mg(s), 8 mg(f), 12 mg
- <6.5%: ~80% for 8 mg(s), 8 mg(f), 12 mg
- <5.7%: ~25% for 8 mg(f), 12 mg

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

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Retatrutide – T2DM Trial: Results

50



• Change in weight at 36 wk: (all $P < 0.0001$)

- 8 mg slow: -17%
- 8 mg fast: -17%
- 12 mg: -17%

• Percent weight loss target attainment:

- ≥5%: ~90% for 8 mg(s), 8 mg(f), 12 mg
- ≥10%: ~71-75% for 8 mg(s), 8 mg(f), 12 mg
- ≥15%: ~57-63% for 8 mg(s), 8 mg(f), 12 mg
- ≥20%: ~40% for 8 mg(s), 8 mg(f), 12 mg

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

50

Retatrutide – Obesity Trial

51

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

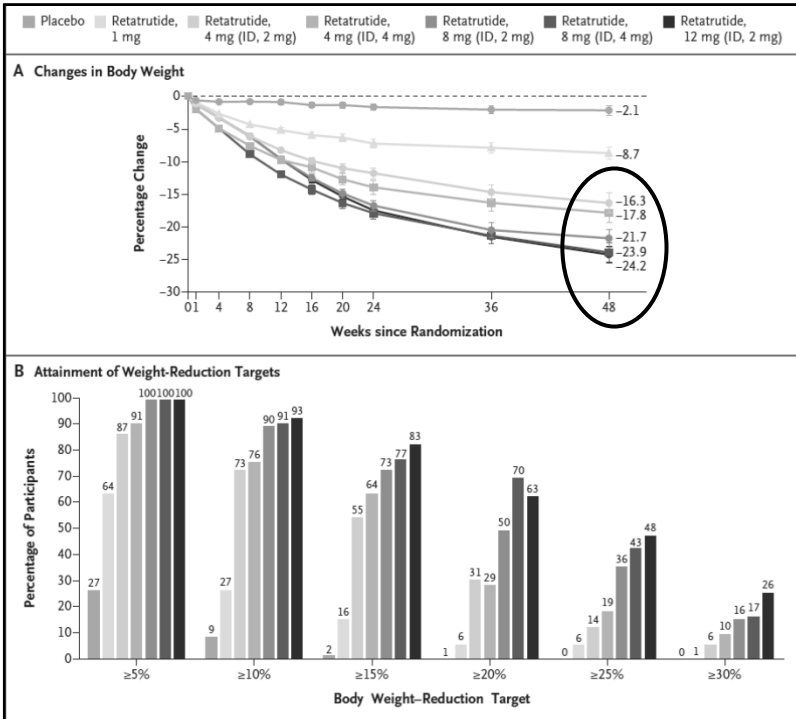
Triple–Hormone-Receptor Agonist Retatrutide for Obesity — A Phase 2 Trial

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.

51



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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.

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Retatrutide

53

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

53

Survodutide

54

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 T2DM trial

55

- Previous phase 2 trial for T2DM by Rosenstock et al, presented at 58th EASD Annual Meeting of the European Association for the Study of Diabetes, 2022.
 - Dose-finding Phase 2 blinded study to assess efficacy and safety vs placebo (PBO) using the weekly GLP-1R agonist semaglutide as an open reference in adults with T2D (A1c 7-10%; BMI 25-50kg/m²)
 - Survodutide up to 0.3, 0.9, 1.8 or 2.7 mg once weekly, or 1.2 or 1.8 mg twice weekly, or placebo, or open-label semaglutide (up to 1.0 mg weekly) for 16 weeks
 - Primary End Point: absolute change from baseline in A1c

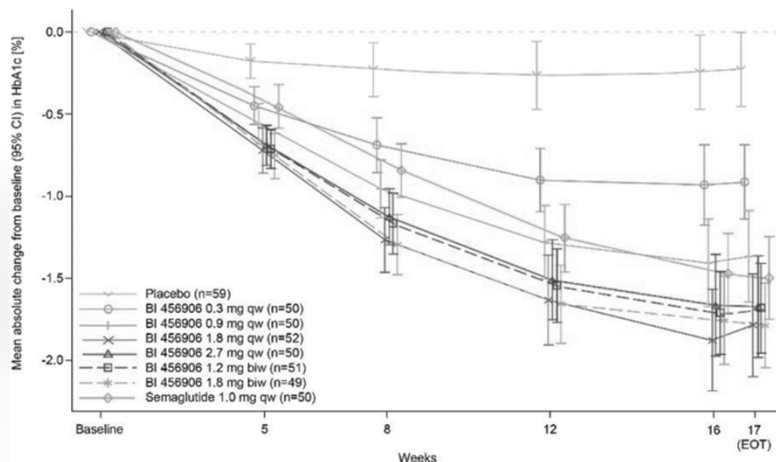
Rosenstock J. 58th EASD Annual Meeting of the European Association for the Study of Diabetes, 2022.
<https://link.springer.com/article/10.1007/s00125-022-05755-w#Sec94>

55

Survodutide

Phase 2 T2DM trial – Results

56



- Change in A1c after 16 weeks
 - Survodutide 1.8 mg weekly
 - -1.88% A1c reduction
- Adverse effects were as expected and GI related
 - AEs were less frequent in bi-weekly dosing groups with slower dose-escalation, compared with weekly dosing

Rosenstock J. 58th EASD Annual Meeting of the European Association for the Study of Diabetes, 2022.
<https://link.springer.com/article/10.1007/s00125-022-05755-w#Sec94>

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Survodutide

Phase 2 Obesity Trial

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Volume 72, Issue
Supplement_1
June 2023



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/m²) 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 $\geq 15\%$ 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>

57

Survodutide

Phase 2 Obesity Trial

58

- **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):
 - $\geq 5\%$: 82.8%,
 - $\geq 10\%$: 68.8%
 - $\geq 15\%$: 54.7%
 - $\geq 20\%$: 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>

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NON-Peptide Oral GLP-1 Receptor Agonists

ORFORGLIPRON

DANUGLIPRON

59

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Oral GLP-1 Receptor Agonists

- 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](https://doi.org/10.1016/S0140-6736(23)01302-8)

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Orforglipron – T2DM Trial

Oral non-peptide GLP-1 RA

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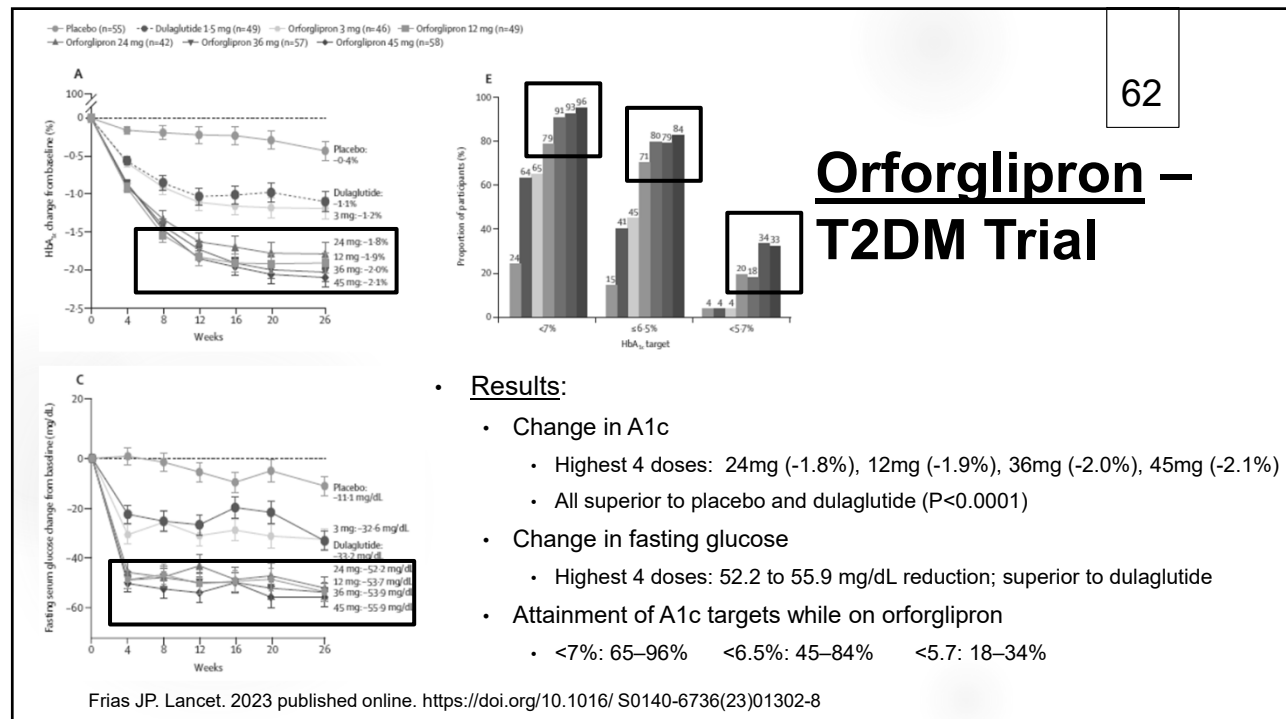
Efficacy and safety of oral orforglipron in patients with type 2 diabetes: a multicentre, randomised, dose-response, phase 2 study

Juan P Frias, Stanley Hsia, Sarah Eyde, Rong Liu, Xiaosu Ma, Manige Konig, Christof Kazda, Kieren J Mather, Axel Haupt, Edward Pratt, Deborah Robins

- **Objective:** to assess the efficacy and safety of orforglipron versus placebo or dulaglutide in adults with type 2 diabetes (A1c 7.0–10.5%, and stable BMI ≥ 23 kg/m²)
- **Design:** 26-week, phase 2, double-blind, randomized, multicenter study
 - placebo, dulaglutide 1.5 mg weekly, or orforglipron 3 mg, 12 mg, 24 mg, 36 mg (group 1), 36 mg (group 2), 45 mg (group 1), or 45 mg (group 2) daily with no food or water restrictions.
- **Primary End Points:** Mean change in A1c from baseline after 26 weeks
 - Secondary end points included change in weight after 26 weeks and adverse effects

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

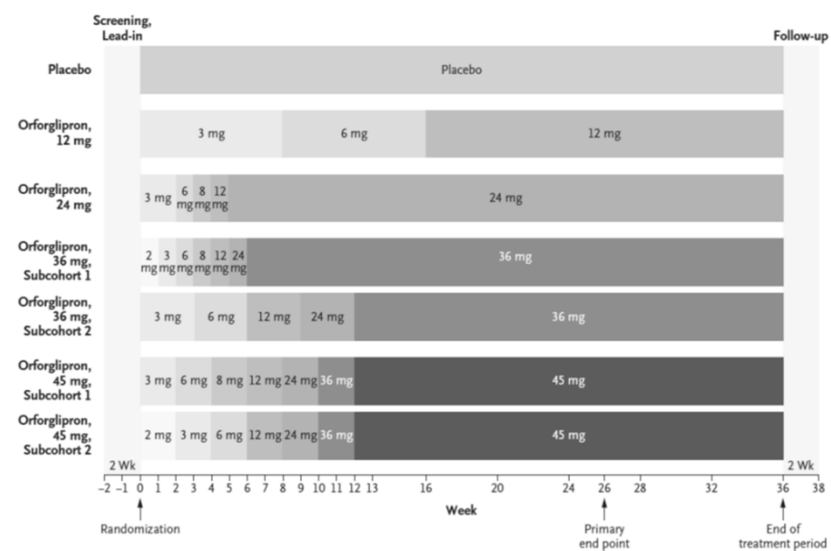
Sean Wharton, M.D., Thomas Blevins, M.D., Lisa Connery, M.D.,
Julio Rosenstock, M.D., Sohini Raha, Ph.D., Rong Liu, Ph.D., Xiaosu Ma, Ph.D.,
Kieren J. Mather, M.D., Axel Haupt, M.D., Deborah Robins, M.S.,
Edward Pratt, M.D., Christof Kazda, M.D., and Manige Konig, M.D., Ph.D.,
for the GZGI Investigators*

- **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)

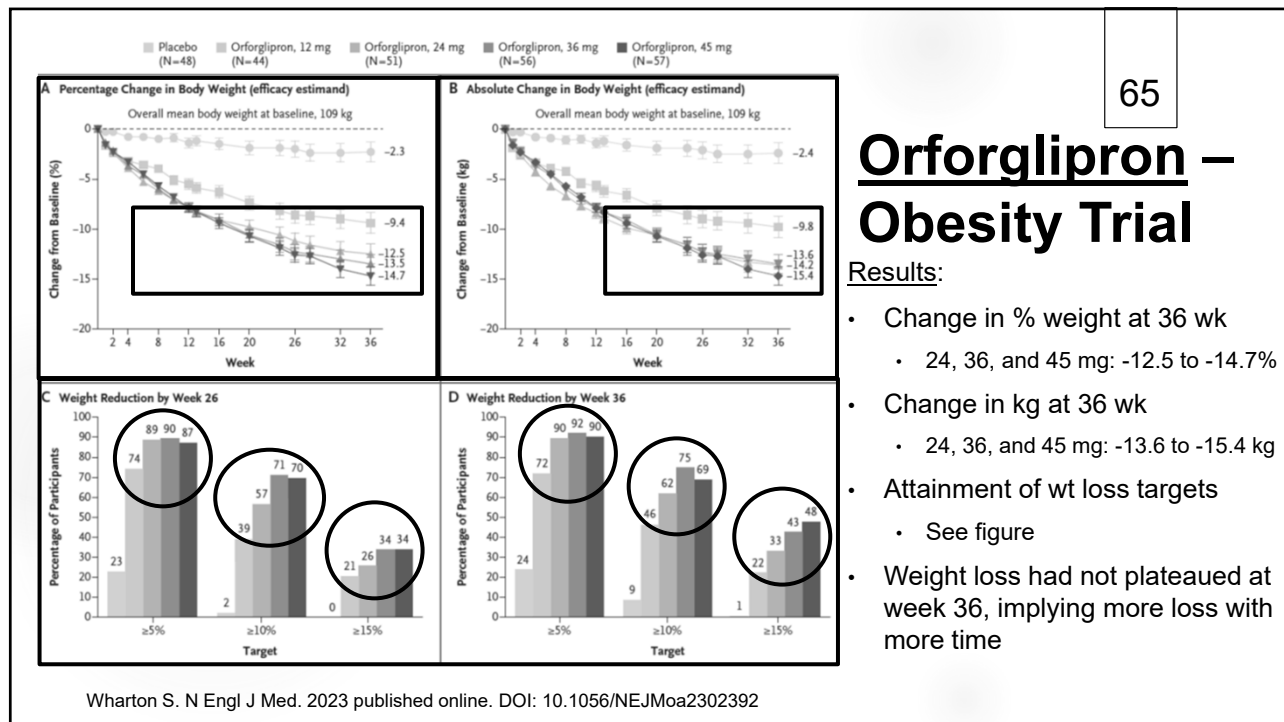
Wharton S. N Engl J Med. 2023 published online. DOI: 10.1056/NEJMoa2302392

63

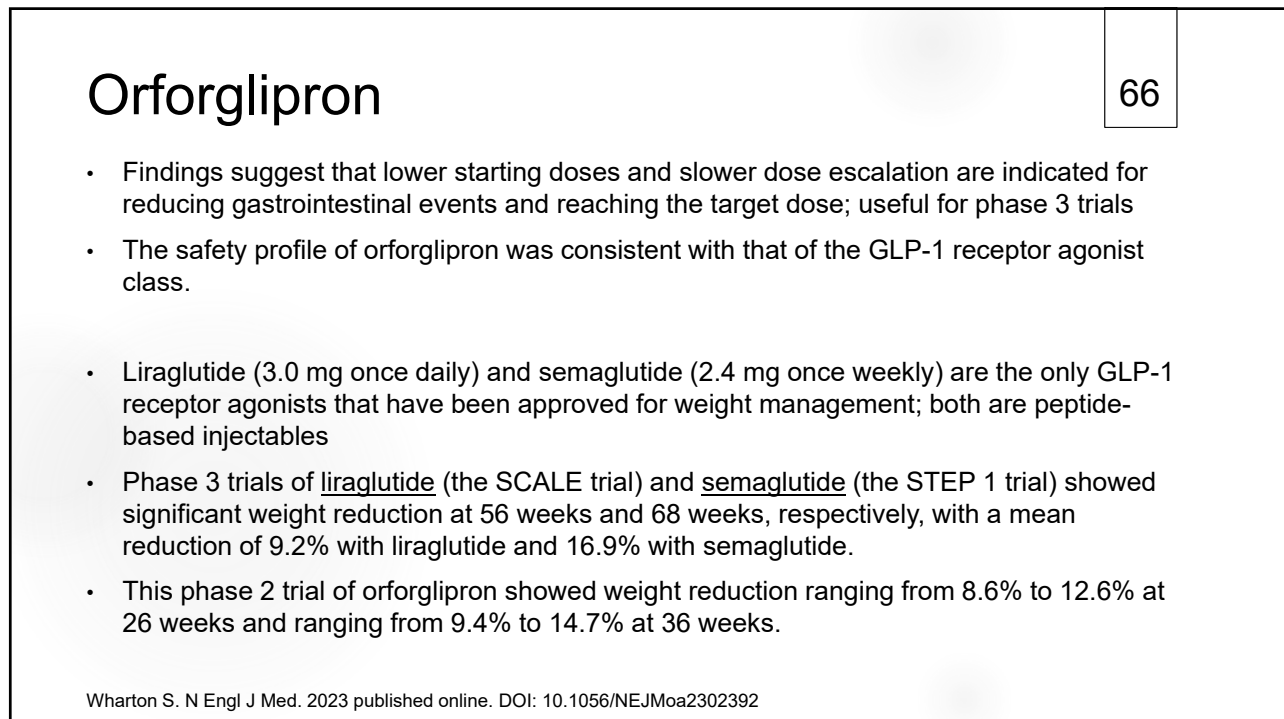
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Other Oral Non-peptide GLP-1 RA

67

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

67

High-dose oral semaglutide PIONEER PLUS and OASIS 1

68

- These trials support the use of oral semaglutide at doses of 25 mg and 50 mg daily for T2DM and Obesity
- For details:
 - PIONEER PLUS: Lancet. DOI: [https://doi.org/10.1016/S0140-6736\(23\)01127-3](https://doi.org/10.1016/S0140-6736(23)01127-3)
 - OASIS 1: Lancet. DOI: [https://doi.org/10.1016/S0140-6736\(23\)01185-6](https://doi.org/10.1016/S0140-6736(23)01185-6)

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

If approved, which of the following could be the first triple agonist for GLP-1/GIP/Glucagon?

survodontide

orforglipron

retatrutide

tirzepatide

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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A 42-year-old woman with a history of T2DM, obesity, hypertension, and dyslipidemia presents to the clinic with a BMI of 34 kg/m². She can use injectables if absolutely necessary, but strongly wishes to stay on oral medications as long as possible. Her A1c is not currently at goal. She has been using oral semaglutide for several months, but struggles to take them in the morning without eating or drinking for 30 minutes. She admits to missing several doses per week.

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

If approved, which of the following drugs would be appropriate to switch to?

survodontide

orforglipron

retatrutide

tirzepatide

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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Conclusion and Clinical Pearls

71

- This is a very exciting time in the development of diabetes treatments
- A delay of stage 3 T1DM can buy precious time for the patient and caregivers to learn about diet planning and insulin dosing so they are better prepared once insulin becomes necessary
- New treatments for T2DM provide new options that may increase adherence and better aid in weight loss
- Only teplizumab, donislecel, and tirzepatide are currently FDA approved
- Watch for phase 3 trial results for the others

71

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

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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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.
- Grunvald E, Shah R, Hernaez R. AGA Clinical Practice Guideline on Pharmacological Interventions for Adults With Obesity. *Gastroenterology* 2022;163:1198-1225.
- Garvey WT, Mechanick JL, Brett EM, et al. AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS AND AMERICAN COLLEGE OF ENDOCRINOLOGY COMPREHENSIVE CLINICAL PRACTICE GUIDELINES FOR MEDICAL CARE OF PATIENTS WITH OBESITY. *Endocrine Practice*. 2016;22(Supplement 3):1-203. doi:10.4158/ep161365.gl.
- Alexis V. Fanshler, Brianne K. Crews, Madison C. Garrett, Jeremy L. Johnson; Tirzepatide: A Novel Glucose-Dependent Insulinotropic Polypeptide/Glucagon-Like Peptide 1 Receptor Agonist for the Treatment of Type 2 Diabetes—The First Twincretin. *Clin Diabetes* 2023; cd220060. <https://doi.org/10.2337/cd22-0060>.
- Obesity and Weight Management for the Prevention and Treatment of Type 2 Diabetes: Standards of Care in Diabetes—2023. *Diabetes Care* 2023;46(Suppl. 1):S128–S139 | <https://doi.org/10.2337/dc23-S008>.
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- OASIS 1: *Lancet*. DOI: [https://doi.org/10.1016/S0140-6736\(23\)01185-6](https://doi.org/10.1016/S0140-6736(23)01185-6)
- Danuglipron: https://www.endocrinologyadvisor.com/home/topics/diabetes/type-2-diabetes/danuglipron-reduces-hba1c-levels-fasting-plasma-glucose-in-type-2-diabetes/?utm_source=eloqua&utm_medium=email&utm_campaign=NWLTR_END_UPDT_RSS-Proclivity-8449_071223_AF&hmEmail=CyDSV8MDufuFeRVGzJRiZlitu%2FqAJ79ugqbP1HaB5Io%3D&sha256email=dab78a308e997f9b6f02d7fb5b79bd9deec879baf42018db8d3c265a15a75d72&hmSubId=&NID=&elqTrack=True

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The Future is Now: The Next Decade of New Diabetes Treatments, Mechanisms, and Benefits is Here!

Jeremy L. Johnson, PharmD, BCACP, CDCES, BC-ADM

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SWOSU College of Pharmacy
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2023 OSHP Fall Meeting
September 22, 2023