2024 Medication Update

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Conflict of Interest

Dr. Trueman has no conflicts of interest to disclose

Objectives

1. Summarize and apply the 2024 American Diabetes Association guideline updates
2. Discuss hot topic issues related to diabetes management
3. Identify novel therapies in phase II and III clinical trials

Abbreviations

- **ACE-I**: angiotensin-converting enzyme
- **ADA**: American Diabetes Association
- **AE**: adverse event
- **ALT**: alanine transaminase
- **AOMs**: anti-obesity medications
- **ARB**: angiotensin II receptor blocker
- **ASCVD**: atherosclerotic cardiovascular disease
- **AWP**: average wholesale price
- **BMI**: body mass index
- **CB1R**: cannabinoid receptor-1
- **CGM**: continuous glucose monitor
- **CGMP**: Current Good Manufacturing Practice
- **CKD**: chronic kidney disease
- **CMS**: Centers for Medicare & Medicaid Services
- **CRL**: complete response letter
- **CVD**: cardiovascular disease
- **DM**: diabetes mellitus
- **DPP-4i**: dipeptidyl peptidase 4 inhibitor
- **eGFR**: estimated glomerular filtration rate
- **FAERS**: FDA Adverse Event Reporting System
- **FDA**: Food & Drug Administration
- **FIB-4**: fibrosis-4
- **FRAX**: Fracture-Risk Assessment Tool
- **GCGR**: glucagon receptor
- **GI**: gastrointestinal
- **GIP**: glucose-dependent insulinotropic polypeptide
- **GLP-1 RA**: glucagon-like peptide-1 receptor agonist

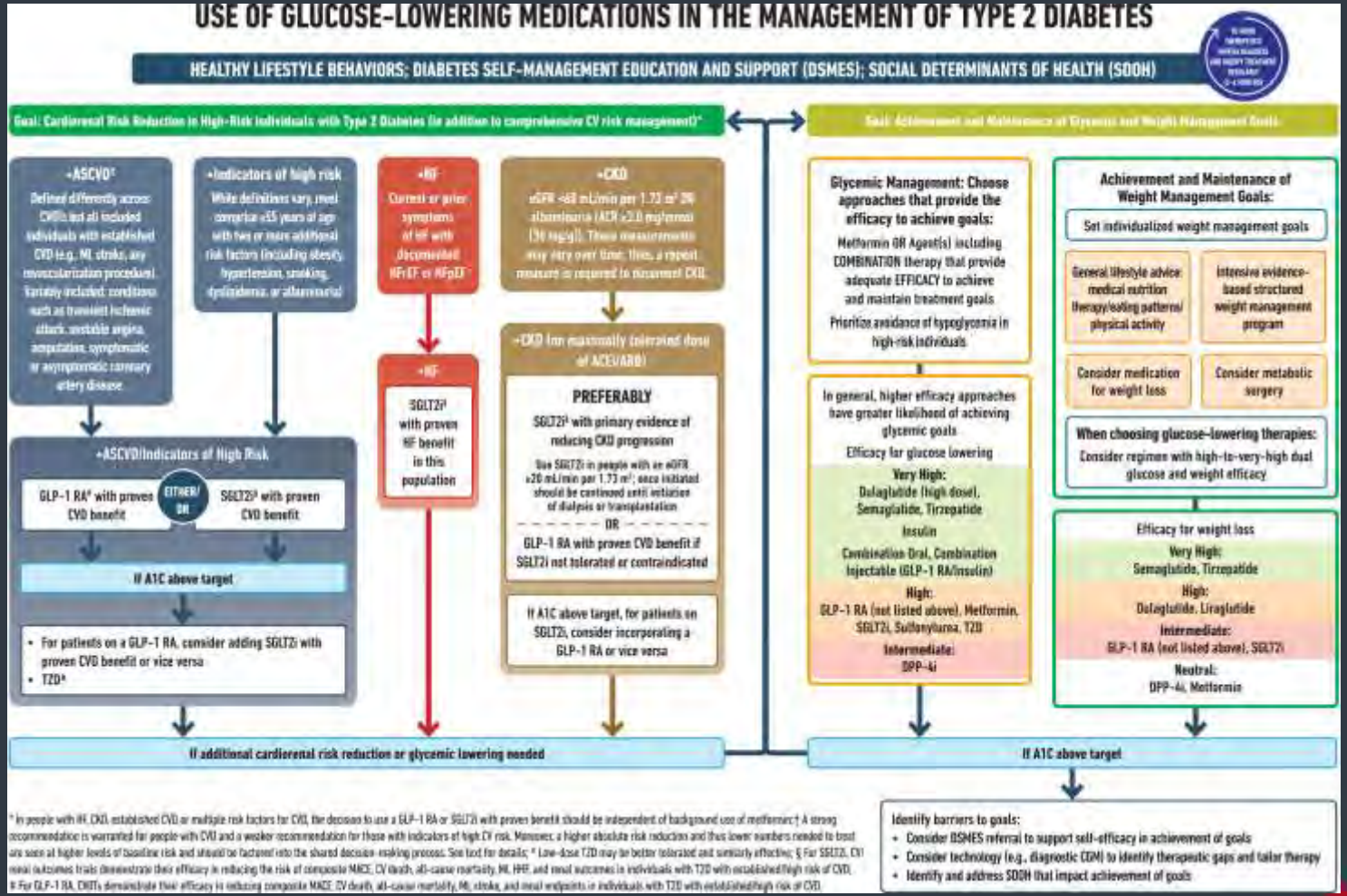
Abbreviations, cont.

- **HF**: heart failure
- **HFmrEF**: heart failure with mildly reduced ejection fraction
- **HFpEF**: heart failure with preserved ejection fraction
- **HHC**: hepatocellular carcinoma
- **HLD**: hyperlipidemia
- **HR**: hazard ratio
- **HTN**: hypertension
- **KCCQ – CSS**: Kansas City Cardiomyopathy Questionnaire – Clinical Summary Score
- **LVEF**: left ventricle ejection fraction
- **LFTs**: liver function tests
- **MACE**: major adverse cardiovascular events
- **MASH**: metabolic dysfunction-associated steatohepatitis
- **MDI**: multiple daily injections
- **MI**: myocardial infarct
- **MRA**: mineralocorticoid receptor antagonist
- **NAFLD**: nonalcoholic fatty liver disease
- **NAS**: NAFLD Activity Score
- **NNT**: number needed to treat
- **OOP**: out of pocket
- **OSA**: obstructive sleep apnea
- **PA**: prior authorization
- **QL**: quantity limit
- **SGLT-1/2i**: sodium-glucose cotransporter-1& 2 inhibitor
- **SGLT-2i**: sodium-glucose cotransporter-2 inhibitor
- **SU**: sulfonylurea
- **T1D**: type 1 diabetes mellitus
- **T2D**: type 2 diabetes mellitus
- **UACR**: urinary albumin creatinine ratio

Guideline Review

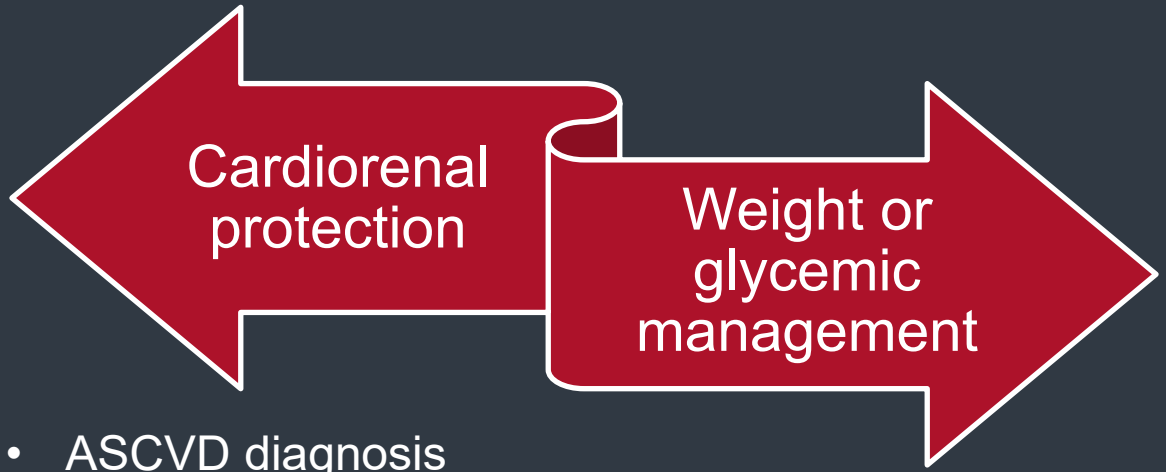
2024 ADA T2D Guidelines

Nebraska Medicine



American Diabetes Association. 9. *Diabetes Care*. 2024; 47(Suppl_1): S158–S178.

2024 ADA Guideline Recommendations



- ASCVD diagnosis or at risk for ASCVD
- Heart failure
- Chronic Kidney Disease

American Diabetes Association. 9. *Diabetes Care*. 2024; 47(Suppl_1): S158–S178.

2024 Guidelines - Cardiorenal

Established ASCVD and at increased risk for ASCVD

- GLP-1 RA or SGLT-2i with proven cardiovascular benefit

A1c above goal

- Add agent not in use
- Thiazolidinedione

Risk Factors

Age ≥ 55 years old PLUS 2 additional risk factors:

- Obesity
- HTN
- Smoking
- HLD
- Albuminuria

Heart Failure

- SGLT-2i with proven benefit

A1c above goal

Follow recommendations for other cardiorenal reduction or move to glycemic lowering

American Diabetes Association. 9. *Diabetes Care*. 2024; 47(Suppl_1): S158–S178.

2024 Guidelines - Cardiorenal

Chronic Kidney Disease

- *In setting of max tolerated ACE-I/ARB*
- SGLT-2i with primary evidence of reducing CKD progression
- GLP-1RA with proven CVD benefit if SGLT-2i not tolerated or contraindicated

A1c above goal

For patient on SGLT-2i, add GLP-1RA and vice versa

Definition

- eGFR < 60 $^{mL}/_{min}$ OR
- Albuminuria *(UACR ≥ 30 mg/g)*

Glycemic management for advanced CKD *(eGFR <30 $^{mL}/_{min}$)*: GLP-1 RA is preferred

Use SGLT-2i in patients with eGFR ≥ 20 mL/min

- Once initiated, should be continued until initiation of dialysis or transplantation
- Glycemic benefits reduced at eGFR < 45 mL/min

Baseline UACR ≥ 300: reduction of ≥ 30% in mg/g recommended to slow CKD progression

**Medications titrated to achieve this goal*

American Diabetes Association. 9. *Diabetes Care*. 2024; 47(Suppl_1): S158–S178.
American Diabetes Association. 11. *Diabetes Care* .2024; 47(Suppl_1): S219–S230.

2024 Guidelines - Cardiorenal

Finerenone

- Reduction of cardiovascular events, including hospitalizations from heart failure
- Reduction of kidney disease progression in patients with CKD + albuminuria

*Reduction in worsening heart failure events and death from cardiovascular causes in HFmrEF or HFpEF in patients without DM

REMEMBER:

- *Use with ACE-I/ARB**
- Do not initiate if serum K > 5.0 mEq/L
  - Monitor K levels 4 weeks after initiation
- Starting dose based on eGFR
- Small initial decrease in eGFR within 4 weeks, then stabilizes

Solomon SD, et al. *NEJM*. 2024.
Finerenone. Package insert. Bayer, Inc; 2022.
American Diabetes Association. 9. *Diabetes Care*. 2024; 47(Suppl_1): S158–S178.
American Diabetes Association. 11. *Diabetes Care* .2024; 47(Suppl_1): S219–S230.

2024 Guidelines – Weight Management

Weight Management

- Lifestyle advice
- **Careful selection of additional glucose-lowering agents** if needed
- If weight loss goals not achieved, additional interventions recommended:
  - Intensive evidence-based structured weight-loss program
  - Pharmacological agents
  - Metabolic surgery

Efficacy for Weight Loss

Very high:
Semaglutide, tirzepatide

High:
Dulaglutide, liraglutide

Intermediate:
GLP-1 RA *(not listed above)*, SGLT-2i

Neutral:
DPP-4i, metformin

Education to patient on need to continue medication to maintain weight loss

American Diabetes Association. 9. *Diabetes Care*. 2024; 47(Suppl_1): S158–S178.

Reminders about Weight Loss

Use of weight-based medications in adults in outpatient setting is rare

Reduction of weight may require dose reduction of other medications

Particularly, medications that play a role in cardiometabolic disease

Examples include:
- o Antihypertensives, including diuretics
- o Antihyperglycemics
- o Levothyroxine
- o Warfarin

2024 ADA Guidelines – Glycemic Management

Glycemic Management

- Metformin OR agents(s) with adequate efficacy to achieve and maintain goals
- May require combination therapy

Very high:
Dulaglutide (high dose), semaglutide, tirzepatide
Insulin
Combination oral, combination injectable (GLP-1RA/Insulin)

High:
GLP-1 RA (not listed above), metformin, SGLT-2i, sulfonylurea, thiazolidinedione

Intermediate:
DPP-4i

American Diabetes Association. 9. *Diabetes Care*. 2024; 47(Suppl_1): S158–S178.

GLP-1 RA & SGLT-2i Indications

ASCVD	HF	CKD
GLP-1 RA: dulaglutide, liraglutide, semaglutide (*Ozempic*) **SGLT-2i**: canagliflozin, empagliflozin	**GLP-1 RA**: N/A **SGLT-2i**: canagliflozin, dapagliflozin, empagliflozin, ertugliflozin **SGLT-1/2i**: sotagliflozin	**GLP-1 RA**: dulaglutide, liraglutide, semaglutide (*Ozempic*) • Renal benefit from CVOTs *(driven by albuminuria)* **SGLT-2i**: canagliflozin, dapagliflozin, empagliflozin
GLP-1 RA: dulaglutide, liraglutide, semaglutide *(Ozempic)* **SGLT-2i**: canagliflozin, empagliflozin	**GLP-1 RA**: N/A **SGLT-2i**: None specified, although reduced risk noted	**GLP-1 RA**: dulaglutide, semaglutide (*Ozempic*) **SGLT-2i**: canagliflozin, dapagliflozin, empagliflozin

**Role of tirzepatide remains under investigation*

American Diabetes Association. 9. *Diabetes Care*. 2024; 47(Suppl_1): S158–S178.

Semaglutide (Ozempic) in CKD

Double-blind, randomized, placebo-controlled, multinational trial

- Event driven
- Intention to treat

Patient Population

- T2D
- CKD
  - eGFR 50 – 70 mL/min + UACR 300 – 5000 mg/g
  - eGFR 25 – 50 mL/min + UACR 100 – 5000 mg/g

Additional noteworthy patient characteristics

- Able to continue MRA, SGLT-2i use
  - Stratified by SGLT-2i use at baseline
- Followed labeled titration up to 1mg with extension, pauses allowed based on AE

Primary Outcome = Major Kidney Disease Events

- Onset of kidney failure (dialysis, transplantation, eGFR < 15 mL/min)
- ≥ 50% reduction in eGFR from baseline
- Death from kidney-related or cardiovascular causes

Perkovic V, et al. *NEJM*. 2024;391:109-121.

Semaglutide (Ozempic) in CKD

Baseline Characteristics

- Average age: 66.6 years, primarily men (69.7%)
- Mean eGFR = 47 mL/min, UACR 567.6
- 68% at high risk for primary outcome
- SGLT-2i use was low: 15.6%

Primary Outcome = Major Kidney Disease Events

- Completed early due to efficacy
- HR: 0.76; CI 0.66 – 0.88; p = 0.0003
- NNT: 20 patients (treated for 3 years)

Primary Outcome Components

- Kidney-specific components: HR: 0.79; CI 0.66 – 0.94

Confirmatory Secondary Outcomes

- Mean annual rate of change in eGFR – not clinically significant
- 22% decrease in risk of major cardiovascular event
- 20% decrease in risk of death from any cause

At 104 weeks, UACR reduced by 12% in placebo, 40% in semaglutide group

Perkovic V, et al. *NEJM*. 2024;391:109-121.

2024 ADA Guideline Recommendations

Major Changes

- Highlighted importance of early combination therapy
- Glucagon for patients taking insulin or at risk of hypoglycemia
- Bone health screenings

Nonalcoholic Fatty Liver Disease/Metabolic Dysfunction-Associated Steatotic Liver Disease

American Diabetes Association. *Diabetes Care*. 2024; 47(Suppl_1): S5–S10.

Adjusting Our Mindsets – Insulin

Insulin can be first line

- Signs of catabolism, severe hyperglycemia present
  - Works much faster than other pharmacotherapies
- A1c ≥ 1.5% above goal requires dual-combination therapy

But it doesn't need to be forever

- "Switch out" with therapy targeted at addressed comorbid disease states

Insulin doesn't need to replace anything

- Rec 9.25: continue previous agents for ongoing glycemic and/or metabolic benefits

American Diabetes Association. 9. *Diabetes Care*. 2024; 47(Suppl_1): S158–S178.

Adjusting Our Mindsets – Clinical Goals

A1c vs Risk Factor Reduction

HISTORICALLY: → Adjust pharmacotherapy to target A1c

NOW: → Add pharmacotherapy to target comorbid, hypoglycemia risk reduction

Switching Agents

If A1c at/ close to goal: → De-intensify therapies, particularly in geriatrics or high hypoglycemia-risk populations

Don't forget about comorbid risks

Geriatric ≠ forgetting about additional pharmacotherapy benefits

American Diabetes Association. 9. *Diabetes Care*. 2024; 47(Suppl_1): S158–S178.

Glucagon Prescribing

6.13 Glucagon should be prescribed for <u>all individuals taking insulin or at high risk for hypoglycemia.</u>

RISK FACTORS

Clinical/Biological

<u>MAJOR</u>:

- Recent *(within the past 3–6 months)* level 2 or 3 hypoglycemia
- Intensive insulin therapy*
- Impaired hypoglycemia awareness
- End-stage kidney disease
- Cognitive impairment or dementia

<u>OTHER</u>:

- Multiple recent episodes of level 1 hypoglycemia
- Basal insulin therapy*
- Age ≥75 years
- Female sex
- High glycemic variability
- Polypharmacy
- CVD, CKD
- Neuropathy
- Retinopathy
- Major depressive disorder

Social, Cultural, Economic

<u>MAJOR</u>:

- Food insecurity
- Low-income status
- Homelessness
- Fasting for religious or cultural reason

<u>OTHER</u>:

- Low health literacy
- Alcohol or substance use disorder

American Diabetes Association. 6. *Diabetes Care*. 2024; 47(Suppl_1): S111–S125.

Glucagon Prescribing

Family, friends, caregivers, school staff, etc. should be trained on it's use and be aware of its location

Pre-mixed products preferred

Providers should regularly assess **access**, understanding, use of glucagon

Patients don't administer glucagon themselves

2-22% of patients indicated for use are prescribed

**Rates listed as per 1,000 person years*

Overall fill rate: 2.28

Highest risk populations:
T1D : 36.76
Short-acting insulin: 16.63
H/o severe hypoglycemia: 20.12

Herges JR, et al. *Diabetes Care*. 2023;46(3):620-627.
American Diabetes Association. 6. *Diabetes Care*. 2024; 47(Suppl_1): S111–S125.

Bone Health – Screening

DEXA SCREENING

Traditional:
> 65 years old

Type 2 Diabetes:
> 5 years post-diagnosis with additional risk factors

Repeat every 2-3 years based on results, risk factors

Results

FRAX score:
Subtract 0.5 from t-score

Initiating Treatment:
Consider with T-score of -2.0 *(instead of -2.5)*

Traditional Risk Factors

- Prior osteoporotic fracture
- Age > 65
- Low BMI
- Sex
- Malabsorption
- Recurrent falls
- Glucocorticoid use
- Family history
- Alcohol/tobacco abuse
- Rheumatoid arthritis

Diabetes-Specific Risk Factors

- Lumbar spine or hip T-score ≤ -2.0
- Frequent hypoglycemia
- Diabetes duration > 10 years
- Insulin, TZD, SU
- A1c > 8%
- Peripheral, autonomic neuropathy
- Retinopathy and nephropathy

American Diabetes Association. 4. *Diabetes Care* .2024; 47(Suppl_1): S52–S76.

Bone Health – Treatment

DIABETES

Maintaining glucose control

- 8% ↑ fracture risk per 1% rise in A1c

Pharmacotherapy choices

- Avoid thiazolodinediones
- DPP-4, GLP-1 RA considered “bone neutral”
  - Tirzepatide may prevent bone loss associated with weight loss
- SGLT-2i considered safe

Minimizing hypoglycemia

- Limiting use of sulfonylureas, insulin use

OSTEOPOROSIS

Non-pharmacologic

- Aerobic and weight-bearing exercises

Building blocks

- Calcium *(age-specific recommendations)*
- Optimization of vitamin D level

Osteoporosis Pharmacotherapy

- Same as general population
- Limit utilization of romosozumab *(higher risk of MI/stroke)*

American Diabetes Association. 4. *Diabetes Care* .2024; 47(Suppl_1): S52–S76.

T2D and Liver Disease

NAFLD changed to **M**etabolic dysfunction-**A**ssociated **S**teatotic **L**iver **D**isease (MASLD)

Reflect etiology of disease

Why screen?

+ NAFLD: >70% of T2D patients

Clinically significant fibrosis: 12 – 20% of T2D patients

Cirrhosis ± liver decompensation

HHC

Liver transplant

Cardiovascular mortality

Liver-related mortality

American Diabetes Association. 4. *Diabetes Care* .2024; 47(Suppl_1): S52–S76.

T2D and Liver Disease - Screening

Which T2D patients to screen?

- Obesity
- Cardiometabolic risk factors OR established CVD
- LFTs elevated > 6 months

How to screen?

$$\text{FIB-4} = \frac{\text{Age (years)} \times \text{AST Level (U/L)}}{\text{Platelet Count } (10^9/\text{L}) \times \sqrt{\text{ALT (U/L)}}}$$

< 1.3	If LFTs elevated, evaluate for other causes	If LFTs normal, reassess in 2-3 years
1.3 – 2.67	Intermediate → Fibroscan or blood markers	Intermediate or high? Refer to GI Low risk? Repeat in 2-3 years
> 2.67	High risk → Fibroscan or blood markers	Remains intermediate or high risk? Refer to GI

American Diabetes Association. 4. *Diabetes Care*. 2024; 47(Suppl_1): S52–S76.

T2D and Liver Disease – Treatment

Nonpharmacologic

Lifestyle changes that promote weight loss

Structured nutrition plan with physical activity program

Bariatric surgery targeting MASH treatment and cardiometabolic benefits

Pharmacologic

Preferred: pioglitazone or GLP-1 RA

If overweight: GLP-1 RA with demonstrated NASH benefits as ADJUNCT to lifestyle

- Use of other pharmacotherapies as indicated
- Insulin preferred in T2D with decompensated cirrhosis

Comprehensive Cardiometabolic Risk Management ± Statins

American Diabetes Association. 4. *Diabetes Care*. 2024; 47(Suppl_1): S52–S76.

Other Hot Topics in Guidelines

Therapeutic Inertia

Treatment at diagnosis

Complications Prevention

American Diabetes Association. 9. *Diabetes Care*. 2024; 47(Suppl_1): S158–S178.

Medication Changes and Updates

New/Updated Approvals

Insulin Icodec – Follow-Up

Tirzepatide & Semaglutide Trials

Nebraska Medicine

Liraglutide Updates

Label expansion: Saxenda

- Data submitted to expand weight loss indication to 6-12 years old with obesity
- Based on 56-week trial

Authorized generic: Victoza

- Manufactured by Teva
- 3x3mL box AWP:
  - Brand: $978.32
  - Generic: $929.41

Teva announces launch of authorized generic of Victoza® in the U.S. Published June 24, 2024. Accessed September 22, 2024
Fick, M. Novo's older obesity drug is safe and effective for children, study finds- *Reuters* - Sep 10, 2024. Accessed September 15, 2024.

FDA Approval Updates

Semaglutide (Wegovy)

- *Reduction of the risk of major adverse cardiovascular events, including cardiovascular death, non-fatal heart attack or non-fatal stroke in adults with established cardiovascular disease*

Tirzepatide (Zepbound)

- *Adjunct to a reduced-calorie diet and increased physical activity for **chronic** weight management in adults with an initial BMI of:*
  - *30 kg/m^2 (obesity)*
  - *27 kg/m^2 (overweight) with at least 1 weight-related comorbidity*

Resmetirom

- *Treat noncirrhotic non-alcoholic steatohepatitis with moderate to advanced liver scarring*

Dapagliflozin

- *T2D in patients **10 years** and older*

Insulin Icodec

- *Decision pending "requests related to the manufacturing process and the type 1 diabetes indication"*

Insulin Icodec

ONWARDS 1
Noninferior A1c reduction compared to daily glargine

ONWARDS 2
Superior A1c reduction compared to daily degludec

ONWARDS 3
Superior A1c reduction compared to daily degludec

ONWARDS 4
Noninferior A1c reduction compared to daily glargine *(+ bolus)*

ONWARDS 5
Superior A1c reduction compared to daily glargine *(U100 or U300)*

ONWARDS 6
Noninferior A1c reduction compared to degludec

UPDATE:

- July 2024: FDA issued CRL → additional information requested related to manufacturing process, type 1 indication before review can be completed
- Novo unable to complete requests during 2024
- Committee did not discuss T2D indication

Lingvay I, et al. *JAMA*. 2023;330(3):228-237.
Philis-Tsimikas A, et al. *Lancet*. 2023;11(6):414-425.
Rosenstock J, et al. *N Engl J Med*. 2023;389:297-308.
Mathieu C, et al. *Lancet*. 2023; 401(10392):1929-1940.
Bajaj HS, et al. *Ann Intern Med*. 2023;176(11):1476-1485.
Russell-Jones D, et al. *Lancet*. 2023;402(10413):1636-1647.
Novo Nordisk receives Complete Response Letter in the US for once-weekly basal insulin icodec. Accessed September 15, 2024.

Insulin Icodec – Upcoming

ONWARDS 9

- 26 week open-label, single arm trial for insulin naïve patients
- A1c reduction using CGM-based dose titration
- Completed April 2024

- Phase 1 trial: children and teenagers

ICO-SEMA

COMBINE 1

- 52 week randomized, open-label, active control trial for patients not controlled on basal insulin
- A1c reduction comparing IcoSema vs icodec
- Completed April 2024

COMBINE 2

- 52 week randomized, open-label, parallel group trial for insulin naïve on stable dose of GLP-1 RA
- A1c reduction comparing IcoSema to semaglutide
- Completed January 2024

COMBINE 2. Clinical Trials.gov. Updated July 19, 2024. Accessed September 15, 2024. https://clinicaltrials.gov/study/NCT05259033.
COMBINE 1. Clinical Trials.gov. Updated June 25, 2024. Accessed September 15, 2024. https://clinicaltrials.gov/study/NCT05352815.
ONWARDS 9. Clinical Trials.gov. Updated April 18, 2024. Accessed September 15, 2024. https://clinicaltrials.gov/study/NCT05823948.

Semaglutide (Wegovy)

SELECT

Trial Population
Adults 45+ years old with previous MI, stroke or symptomatic peripheral arterial disease and BMI ≥ 27 without diabetes

Intervention
Semaglutide 2.4mg

Comparator
Placebo

Primary Outcome
Superior to placebo for 20% reduction in 3-point MACE events

NNT = 67 patients

March 2024 CMS Ruling

AOMs that receive FDA approval for an additional medically accepted indication → AOM can be considered Part D drug for that specific use

CMS will evaluate FDA labeling and updated treatment guidelines when reviewing formularies for upcoming year

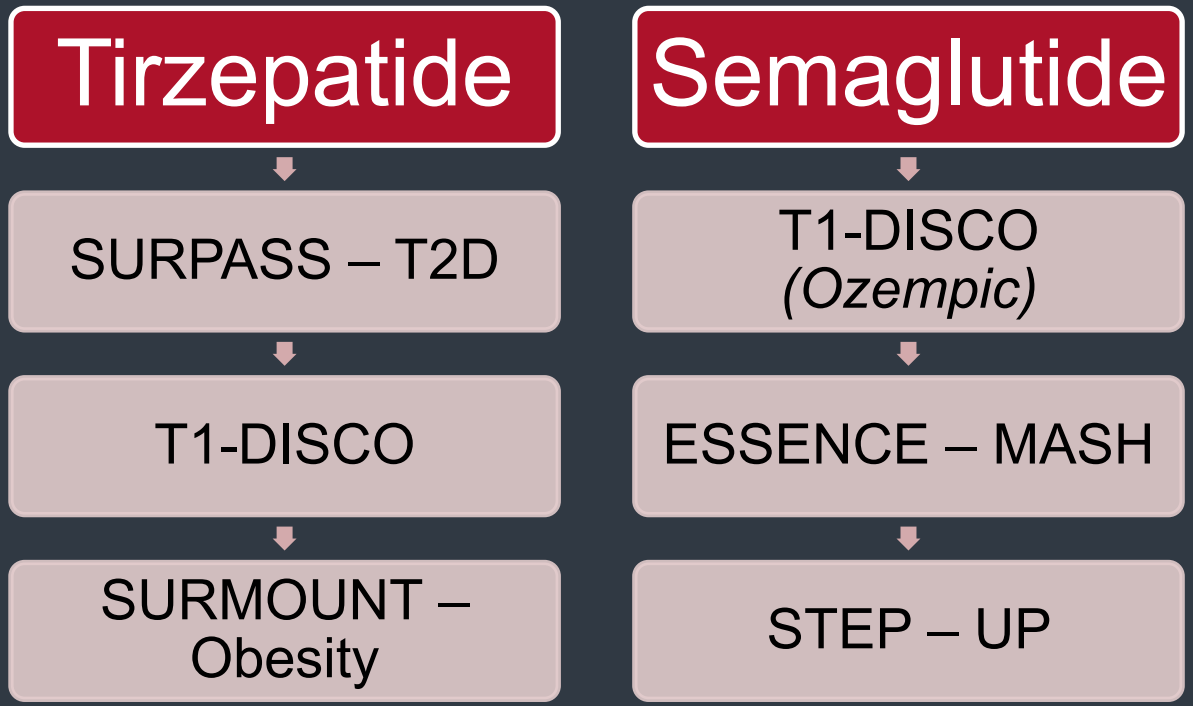
Coverage not provided if patient does not have additional medically accepted indication → Consider use of PAs to ensure medications being used for "medically accepted indication."

May use step therapy, QL requirements as well

Part D sponsors **may** include on their formularies, but not required

Lincoff AM, et al. *NEJM*. 2023;389(24):2221-2232.
Part D coverage of anti-obesity medications with medically accepted indications. CMS. Published March 20, 2024. Accessed September 22, 2024.

IN PROCESS


Tirzepatide
SURPASS – T2D
T1-DISCO
SURMOUNT – Obesity
Semaglutide
T1-DISCO (Ozempic)
ESSENCE – MASH
STEP – UP

Tirzepatide – Diabetes Trials

SURPASS – EARLY	SURPASS – CVOT	SURPASS – PEDS
Trial Population Adults with T2D diagnosed within the last 4 years taking metformin	**Trial Population** Adults with T2D, confirmed ASCVD, and BMI ≥ 25	**Trial Population** Children aged 10-17 years with T2D, BMI > 85th percentile, taking metformin ± insulin
Intervention Tirzepatide @ max tolerated dose	**Intervention** Tirzepatide @ max tolerated dose	**Intervention** Tirzepatide
Comparator Intensified conventional care dose	**Comparator** Dulaglutide 1.5mg	**Comparator** Placebo
Primary Outcome Change in A1c *(104 weeks)*	**Primary Outcome** Time to 3-pt MACE	**Primary Outcome** Change in A1c *(30 weeks)*
Expected Completion November 2027	**Expected Completion** Extended to June 2025	**Expected Completion** Moved up to February 2025

SURPASS-CVOT. Clinical Trials.gov. Updated May 9, 2024. Accessed August 24, 2024. https://clinicaltrials.gov/study/NCT04255433.
SURPASS-PEDS. Clinical Trials.gov. Updated July 23, 2024. Accessed August 24, 2024. https://clinicaltrials.gov/study/NCT05260021.
SURPASS-EARLY. Clinical Trials.gov. Updated August 29, 2024. Accessed September 22, 2024. https://clinicaltrials.gov/study/NCT05433584.

Tirzepatide – Diabetes Trials

TZP-T1D	Investigational Doses
Trial Population Adults with T1D *(treated only with insulin)* and BMI ≥ 27	**Trial Population** Adults with T2D taking metformin ONLY, BMI ≥ 35
Intervention Tirzepatide 15mg	**Intervention** 2 “high doses” Tirzepatide
Comparator No intervention	**Comparator** Tirzepatide, placebo
Primary Outcome % change in body weight *(32 weeks)*	**Primary Outcome** % change in body weight *(44 weeks)*
Expected Completion May 2026	**Expected Completion** October 2026

TZP-T1D. Clinical Trials.gov. Updated June 3, 2024. Accessed September 29, 2024. https://clinicaltrials.gov/study/NCT06180616.
A study of investigational tirzepatide doses. Clinical Trials.gov. Updated September 26, 2024. Accessed September 29, 2024. https://clinicaltrials.gov/study/ NCT06037252.

Tirzepatide – Obesity Trials

SURMOUNT – 5

Trial Population
Adults with BMI ≥ 30 OR BMI ≥ 27 with related comorbidity

Intervention
Tirzepatide

Comparator
Semaglutide 2.4mg

Primary Outcome
% change in body weight
No. with ≥ 5% body weight reduction

Expected Completion
Moved up to November 2024

SURMOUNT – MMO

Trial Population
Adults with BMI ≥ 27 with related ASCVD comorbidity or ASCVD risk factors

Intervention
Tirzepatide

Comparator
Placebo

Primary Outcome
Time to *(modified)* MACE+

Expected Completion
October 2027

SURMOUNT - ADOLESCENTS

% change in body weight in patients 12-17 y/o + ≥ 95th percentile OR BMI 85th – 95th percentile with 1 weight-related comorbidity

Completion: October 2026

SURMOUNT - MAINTAIN

% maintenance of body weight reduction in adults with BMI ≥ 30 OR BMI ≥ 27 with related comorbidity

Completion: May 2026

SURMOUNT-5. Clinical Trials.gov. Updated August 28, 2024. Accessed September 22, 2024. https://clinicaltrials.gov/study/NCT05822830.
SURMOUNT-MAINTAIN. Clinical Trials.gov. Updated July 22, 2024. Accessed September 22, 2024. https://clinicaltrials.gov/study/NCT06047548.
SURMOUNT-MMO. Clinical Trials.gov. Updated September 4, 2024. Accessed September 22, 2024. https://clinicaltrials.gov/study/NCT05556512.
SURMOUNT-ADOLESCENTS. Clinical Trials.gov. Updated September 19, 2024. Accessed September 29, 2024. https://clinicaltrials.gov/study/NCT06075667.

Tirzepatide – The Sky is the Limit

TOGETHER – PsA
Symptom improvement in patients with Psoriatic arthritis + BMI ≥ 27
Tirzepatide + Ixekizumab
Completion: August 2026

TOGETHER – PsO
Symptom improvement in patients with moderate to severe plaque psoriasis + BMI ≥ 27
Tirzepatide + Ixekizumab
Completion: May 2026

TREASURE – CKD
Change in kidney oxygenation in patients with CKD, BMI > 27, +/- T2D
Completion: February 2026

STOP KNEE-OA
% of patients that undergo knee replacement with BMI ≥ 30, moderate-to-severe knee osteoarthritis
Completion: May 2027, 2037

IDEAL COR
Change in coronary lipid burden in patients with BMI ≥ 27 *(excluded DM)*
Completion: August 2028

IDEAL-COR. Clinical Trials.gov. Updated September 23, 2024. Accessed September 29, 2024. https://clinicaltrials.gov/study/NCT06606821.
STOP KNEE-OA. Clinical Trials.gov. Updated September 23, 2024. Accessed September 29, 2024. https://clinicaltrials.gov/study/NCT06191848.
TOGETHER-PsA. Clinical Trials.gov. Updated September 19, 2024. Accessed September 29, 2024. https://clinicaltrials.gov/study/NCT06588296.
TOGETHER-PsO. Clinical Trials.gov. Updated September 19, 2024. Accessed September 29, 2024. https://clinicaltrials.gov/study/NCT06588283.
TREASURE-CKD. Clinical Trials.gov. Updated September 19, 2024. Accessed September 29, 2024. https://clinicaltrials.gov/study/NCT05536804.

Semaglutide – "Diabetes" Trials

HIGH-Dose	T1-DISCO	Triple Therapy in T1D
Trial Population Adults with T2D, BMI ≥ 30	**Trial Population** Adults < 50 years old with T1D, BMI 20-45	**Trial Population** Adults with T1D on 0.5u/kg MDI or 0.4u/kg CSII AND well-versed in carb counting
Intervention Semaglutide 7.2mg	**Intervention** Semaglutide	**Intervention** Semaglutide OR semaglutide + dapagliflozin
Comparator Semaglutide 2.4mg, placebo	**Comparator** Placebo	**Comparator** Placebo, standard of care
Primary Outcome % change in body weight	**Primary Outcome** Change in central, peripheral arterial stiffness	**Primary Outcome** Change in A1c at 6 months
Expected Completion December 2024	**Expected Completion** December 2026	**Expected Completion** May 2025

T1-DISCO. Clinical Trials.gov. Updated May 16, 2024. Accessed September 29, 2024. https://clinicaltrials.gov/study/NCT05819138.
Triple therapy in T1D. Clinical Trials.gov. Updated January 3, 2024. Accessed September 30, 2024. https://clinicaltrials.gov/study/NCT03899402.
Research study to see how semaglutide helps… Clinical Trials.gov. Updated September 27, 2024. Accessed September 30, 2024. https://clinicaltrials.gov/study/NCT0564913.

Semaglutide – Other Trials

ESSENCE

Trial Population
Histologic evidence of MASH + fibrosis stage 2 or 3 + histological NAS score ≥ 4

Intervention	Comparator
Semaglutide	Placebo

Primary Outcome
Part 1: resolution of steatohepatitis and no worsening of fibrosis
Part 2: Cirrhosis-free survival

Expected Completion
Part 1: Complete
Part 2: April 2029

BARI-STEP

% change in weight in patients > 1 year post-surgery with < 20% weight loss
Semaglutide 2.4mg
Completion: September 2025

STEP-UP

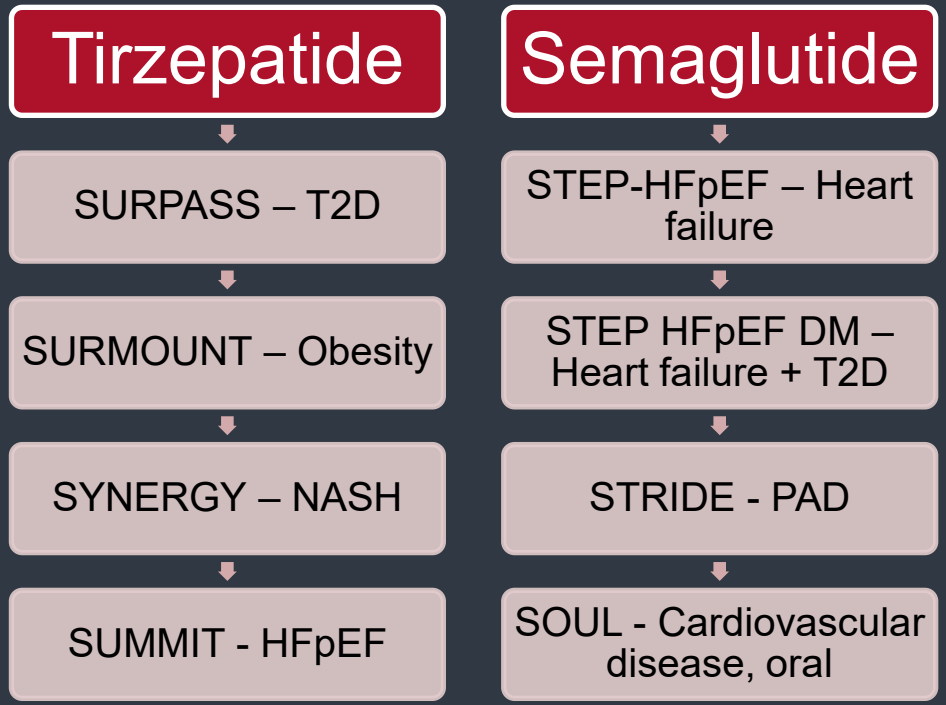
% change in weight in patients with BMI ≥ 30
Semaglutide 7.2mg
Completion: November 2025

EVOKE-PLUS

Change in Clinical Dementia rating in adults 55-85 y/o with mild cognitive impairment
Oral semaglutide
Completion: October 2026

STEP-UP. Clinical Trials.gov. Updated September 27, 2024. Accessed September 30, 2024. https://clinicaltrials.gov/study/NCT05646706.
EVOKE-PLUS. Clinical Trials.gov. Updated August 22, 2024. Accessed September 30, 2024. https://clinicaltrials.gov/study/NCT04777409.
BARI-STEP. Clinical Trials.gov. Updated November 11, 2023. Accessed September 30, 2024. https://clinicaltrials.gov/study/NCT05646706.
ESSENCE. Clinical Trials.gov. Updated September 27, 2024. Accessed September 29, 2024. https://clinicaltrials.gov/study/NCT04822181.

COMPLETED


Tirzepatide
SURPASS – T2D
SURMOUNT – Obesity
SYNERGY – NASH
SUMMIT - HFpEF
Semaglutide
STEP-HFpEF – Heart failure
STEP HFpEF DM – Heart failure + T2D
STRIDE - PAD
SOUL - Cardiovascular disease, oral

Tirzepatide – Diabetes Trials

SURPASS – 6	SURPASS – SWITCH	SURPASS – SWITCH-2
Trial Population Adults with T2D taking insulin ± metformin	**Trial Population** Adults with T2D, taking a stable dose of dulaglutide (0.75mg or 1.5mg) for ≥ 6 months	**Trial Population** Adults with T2D, taking a stable dose of listed GLP-1 RA for ≥ 3 months
Intervention Tirzepatide 5, 10, 15mg + glargine	**Intervention** Tirzepatide	**Intervention** Tirzepatide 5mg
Comparator Lispro	**Comparator** Dulaglutide 3 & 4.5mg	**Comparator** None; previously on liraglutide, dulaglutide, semaglutide
Primary Outcome Superiority in A1c reduction (-2.1% vs -1.1%) at 52 weeks	**Primary Outcome** Change in A1c *(40 weeks)*	**Primary Outcome** - 0.43% mean change in A1c; -2.15kg change in body weight
	Completed August 2024	

Jabbour S, et al. *Endocr Pract.* 2024;30(8):701-709.
Rosenstock J, et al. *JAMA.* 2023;330(17):1631-1640.
SURPASS-SWITCH. Clinical Trials.gov. Updated August 16, 2024. Accessed September 22, 2024. https://clinicaltrials.gov/study/NCT05564039.

Tirzepatide – Obesity Trials

SURMOUNT – OSA

Trial Population
Adults with BMI ≥ 30 and OSA without PAP usage

Intervention
Maximum tolerated dose of tirzepatide (10mg or 15mg)

Comparator
Placebo

Primary Outcome
Apnea-Hypopnea Index: -25.3 events/hr vs -5.3 events/hr

SURMOUNT – 1 *104-week Extension*

Trial Population
Adults with BMI ≥ 30 OR BMI ≥ 27 with related comorbidity

Intervention
Tirzepatide 5mg, 10mg, 15mg

Comparator
Placebo

Primary Outcome
Average 22.9% body weight reduction compared to 2.1% with placebo *(over 176 weeks)*

Secondary Outcome
-94% reduced risk of progression from pre-diabetes to diabetes
17 week off-treatment follow-up: -88% reduced risk of progression

Published Results?
November 3-6 *(ObesityWeek 2024)*

Malhorta A, et al. *NEJM*. 2024. online ahead of print.
Tirzepatide reduced the risk of developing type 2 diabetes by 94% in adults with pre-diabetes and obesity or overweight. 2024. Accessed August 24,2024

Tirzepatide – Other Comorbidities

SYNERGY - NASH

Trial Population
Adults with BMI between 27 and 50 with NASH *(MASH)* stage 2 or 3

Intervention	Comparator
Tirzepatide 5, 10, 15mg	Placebo

Primary Outcome
% of patients with NASH *(MASH)* resolution without worsening of fibrosis: 44-62% vs 10% placebo

Side effects
92% vs 83% placebo group
96% of GI AE were mild/moderate

Phase 3 Trials?

SUMMIT

Trial Population
Adults with BMI ≥ 30, stable HF with LVEF ≥ 50%

Intervention	Comparator
Tirzepatide 5, 10, 15mg	Placebo

Primary Outcome
Reduce risk of composite endpoint of time-to-first occurrence of urgent HF visit, HF hospitalization, oral diuretic intensification, CV death
Change in KCCQ-CCS score

Completed
Results pending
Safety data consistent with previous studies

Loomba R, et al. *NEJM*. 2024;391:299-310.
Lilly's tirzepatide successful in phase 3 study showing benefit in adults with HFpEF and obesity. Published August 1, 2024. Accessed September 29, 2024.

Semaglutide *(Wegovy)* Updates

STEP HFpEF	STEP HFpEF DM	Pooled Anaylsis
Trial Population Adults with symptomatic HFpEF and BMI ≥ 30 without diabetes	**Trial Population** Adults with symptomatic HFpEF and BMI ≥ 30 **AND** diabetes	**Trial Population** STEP HFpEF + STEP HFpEF DM AND Patients with investigator-reported history of HFpEF from FLOW + SELECT
Intervention Semaglutide 2.4mg	**Intervention** Semaglutide 2.4mg	**Intervention** Semaglutide 1.0mg (FLOW) & 2.4mg
Comparator Placebo	**Comparator** Placebo	**Comparator** Placebo
Primary Outcome* Change in KCCQ-CCS score: 16.6 points vs 8.7 with placebo	**Primary Outcomes** Change in KCCQ-CCS score: 13.7 points vs 6.4 with placebo Change in body weight: -9.8% vs -3.4% with placebo	**Primary Outcome** Risk of combined endpoint of cardiovascular death or heart failure events: 5.4% vs 7.5% in placebo

Kosiborod MN, et al. *NEJM*. 2023;389:1069-1084.
Kosiborod MN, et al. *NEJM*. 2024;390:1394-1407.
Kosiborod MN, et al. *Lancet*. 2024;404(10456):949-961.

Semaglutide – Diabetes Trials

STRIDE	SOUL
Trial Population T2D with symptomatic PAD with intermittent claudication	**Trial Population** T2D + ≥ 50 years old + ASCVD *(Coronary HD, cerebrovascular disease, symptomatic PAD, CKD)*
Intervention Semaglutide 1mg *(subq)*	**Intervention** Semaglutide 14mg *(oral)*
Comparator Placebo	**Comparator** Placebo
Primary Outcome Change in maximum walking distance on a constant load treadmill test	**Primary Outcome** Time to MACE
Completed July 2024	**Completed** August 2024

SOUL. Clinical Trials.gov. Updated September 19, 2024. Accessed September 29, 2024. https://clinicaltrials.gov/study/ NCT03914326.
STRIDE. Clinical Trials.gov. Updated September 19, 2024. Accessed September 28, 2024. https://clinicaltrials.gov/study/NCT04560998.

Semaglutide, oral

OASIS – 1	OASIS – 4
Trial Population Adults with BMI ≥ 30 or a BMI ≥ 27 with related comorbidity *Excluded if 5kg weight change in 90 days prior to study period*	
Intervention Oral semaglutide **50mg**	**Intervention** Oral semaglutide **25mg**
Comparator Placebo	**Comparator** Placebo
Primary Outcome Change in body weight at 68 weeks: -15.1% vs -2.4% with placebo	**Primary Outcome** Change in body weight at 72 weeks
	Completed May 2024

Knop FK, et al. *Lancet.* 2023;23:01185-6.
OASIS-4. Clinicaltrials.gov. Updated July 12, 2024. Accessed September 29, 2024. https://clinicaltrials.gov/study/NCT05564117.

Upcoming FDA Approvals?

Tirzepatide *(Zepbound)*

- OSA – submitted to FDA late spring 2024
- HFpEF?

Semaglutide *(Ozempic)*

- Renal disease progression prevention
- Decision anticipated in January 2025

Semaglutide *(Wegovy)*

- Obesity-related HFpEF
  - Europe: recommended inclusion to reduce symptoms and improve physical limitations
- MASH – potentially in later 2025

Wegovy recommended by European regulatory authorities for label update to reflect reduced HF symptoms and improved physical function. 2024. Accessed September 28,2024.

Hot Topics – GLP-1 RA

GLP-1 RA & Generics
GLP-1 RA & Management Tips
GLP-1 RA & Compounding
GLP-1 RA & Diabetic Retinopathy
GLP-1 RA & Suicidal Ideation

Nebraska Medicine

GLP-1 RAs & Generics

Generic Dulaglutide

- US patent: September 2027

Generic Liraglutide

- Now available: Teva
- Coming: Sandoz, Viartis
- Patent expired

Generic Semaglutide

- Sandoz
- Available in Canada in 2026
- US patent expires in March 2026

Generic Tirzepatide

- “Composition of Matter:” January 2026
- “Formulation:” June 2039

Gregerson E. *Beckers Hospital Review.* Published September 3, 2024. Accessed September 28, 2024.

GLP-1 RAs & GLP-1/GIP RA

Evaluation and Monitoring of Weight Loss

- Goal: 5% weight loss at 12 weeks
- Ensure appropriate nutrition
- Rapid weight loss = NOT GOOD
- Evaluate doses of other medications

Drug Interactions

- Related to changes in digestion
- PROSPERO Study: changes in pharmacokinetics of certain medications
  - Warfarin, oral contraceptives, acetaminophen, ACE inhibitors, statins, digoxin
  - No clinically significant changes noted, but studied population was overall healthy
- Real-world experience: tacrolimus, oral contraceptives
- Weight-related “interactions” as well

Calvarysky B, et al. *Drug Saf.* 2024;47(5):439-451.

GLP-1 RAs & Compounding

During periods of medication shortages, compounding of GLP-1 RA may be legal under federal law

- Meet criteria noted in the Federal Food, Drug and Cosmetic Act
  - Active ingredient produced by facility registered with the FDA

Outsourcing facilities

- Comply with CGMP
- Inspected by FDA
- Other criteria, including adverse event reporting, reporting on product source to FDA

Once shortages are over, no longer legal for outsourcing facilities to produce compounded products

Compounded products are **NOT** FDA-approved for safety, efficacy, or purity

- Potential for contamination
- Potential for incorrect amount of active ingredients
- Potential for addition of other ingredients that change medication properties

MANY adverse events reported to FDA with compounded semaglutide, including serious infection and 7 deaths

Compounding when Drugs are on FDA's Drug Shortages List. Updated September 24, 2024. Accessed September 28, 2024.

GLP-1 RAs & Compounding

After discussing risk vs benefit, if a patient would still like to proceed with using compounded GLP-1, it's important to follow these steps

Confirm the facility the product came from

Note: there are currently NO facilities registered to compound tirzepatide

- Olympia Pharmacy
  Orlando, FL 32811
- PQ Pharmacy LLC
  Brookville, FL 34604
- ProRx LLC
  Exton, PA 19341

If not one of the these, do not use

Confirm the ingredients

Products containing other substances *(Vitamin B12, Vitamin D, etc.)* do not come from outsourcing facilities

Semaglutide salts ≠ Semaglutide base *(active ingredient in Ozempic or Wegovy)*

Confirm the dose

Avoid doses above what has been studied

Education on dose – how many mL/units?
**Reports of patients administering 5-20x more than intended dose*

Injection education

Access to appropriately sized syringes

Compounding when Drugs are on FDA's Drug Shortages List. Updated September 24, 2024. Accessed September 28, 2024.
FDA alerts health care providers, compounders and patients of dosing errors associated with compounded injectable semaglutide products. Updated July 26, 2024. Accessed September 28,

GLP-1 RAs & Diabetic Retinopathy

Historical Perspective

ANY rapid improvement in blood sugars appears to worsen retinopathy

Package Labeling

Dulaglutide, semaglutide: rapid improvement in glucose control associated with temporary worsening of diabetic retinopathy

Updated Evidence

American Society of Retina Specialists Annual Meeting *(August 2024)*

Retrospective, observational study evaluating overall risk of requiring treatment for diabetic macular edema or proliferative diabetic retinopathy

SGLT-2i: lower risk

GLP-1 RA: no increase in risk

Recommendation

Close monitoring in patients with history of diabetic retinopathy

Clinical practice:

- Avoid certain agents
- Evaluate stability of retinopathy

Await results of FOCUS trial *(2027)*

Semaglutide vs placebo with pre-existing T2D up to 5 years evaluating evidence of retinopathy progression

Davis C, et al. *WJPR*. 2023;12(12):140-166.
FOCUS. Clinical Trials.gov. Updated August 14, 2024. Accessed September 28, 2024. https://clinicaltrials.gov/study/NCT03811561.
Callari M. Research promises better diabetic retinopathy management – Medscape. Published August 16, 2024. Accessed September 28, 2024

GLP-1 RAs & Suicidal Ideation

History…

FDA label requirement for ALL **weight management** medications

"Patients treated with *** should be monitored for the emergence or worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior. Discontinue *** in patients who experience suicidal thoughts or behaviors. Avoid *** in patients with a history of suicidal attempts or active suicidal ideation.

Europe	July 2023	European Medicines Agency launches investigation for multiple GLP-1 RAs • Dulaglutide, exenatide, liraglutide*, lixisenatide, semaglutide*
U.S.	Late 2023	FDA launches investigation for all GLP-1 RAs • Based on 265 reports received since 2010 *(potential for duplicates)* • 113 narratives

Lipanovic D. *Pharmaceutical Journal.* 2024; 312(7981).
EMA statement on ongoing review of GLP-1 receptor agonists. European Medicines Agency. Published July 11, 2023. Accessed October 3, 2023.

GLP-1 RAs & Suicidal Ideation

FDA

1/11/24: preliminary evaluations have not found evidence that use of these medicines causes suicidal thoughts/actions

Evaluated FAERS, clinical trials

Continue to investigate due to small numbers of events seen in both active & control groups
- Includes meta-analysis of all GLP-1 RA trials

EMA

4/12/24: final decision

"Available evidence does not support a causal association between GLP-1 RA and suicidal and self-injurious thoughts and actions."

Reviewed multiple large database studies, non-clinical studies, clinical trials, post-marketing surveillance

Mental Health Reminders

CDC study: 29.2% of diabetes vs 17.9% without

Moderate and severe depressive symptoms and antidepressant use associated with increased obesity

Recommendations:

Monitor for and advise patients using agents to report new or worsening depression, suicidal thoughts, or any unusual changes in mood or behavior

Report side effects to MedWatch

Koyama AK, et al. *Prev Chronic Dis*. 2023;20:220407.
Pratt LA, et al. NCHS data brief, no 167. Hyattsville, MD: National Center for Health Statistics. 2014.
Meeting highlights from the PRAC 8-11 April 2024. EMA. Published April 12, 2024. Accessed September 28, 2024.
Update on FDA's ongoing evaluation of reports of suicidal thoughts or actions in patients taking... FDA. Published March 8, 2024. Accessed September 28, 2024.

Hot Topics

Inflation Reduction Act – Price Negotiations
Inflation Reduction Act – 2025 Part D Updates

Nebraska Medicine

The Why: Top 25 Prescription Drug Expenditures, 2023

1. Semaglutide
- $38.6 billion
- ↑ 100.1%

4. Dulaglutide
- $16.3 billion
- ↑ 5.1%

5. Empagliflozin
- $15.9 billion
- ↑ 34%

8. Tirzepatide
- $13.2 billion
- ↑ 373.1%

13. Insulin glargine
- $8.9 billion
- ↓ 4.6%

15. Dapagliflozin
- $7.9 billion
- ↑ 41.8%

17. Insulin aspart
- $5.8 billion
- ↓ 3.4%

19. Sitagliptin
- $5.7 billion
- ↓ 9.4%

23. Insulin lispro
- $5.3 billion
- ↓ 1.8%

= **$117.6 BILLION**

Tichy EM, et al. *AJHP*. 2024;81(14):583-598.

Inflation Reduction Act

First round of price negotiations:
Negotiations end in Aug 2024 → Maximum fair prices published in Sept 2024 → prices take effect in 2026

2026 Discounts:
- 38-79% discounted
- $6 billion in 2023 federal government Medicare savings
- Once effective: $1.5 billion in enrollee savings

Apixaban	Empagliflozin	Rivaroxaban	Sitagliptin	Dapagliflozin
Sacubitril-valsartan	Etanercept	Ibrutinib	Ustekinumab	Aspart *(Fiasp)* & Detemir

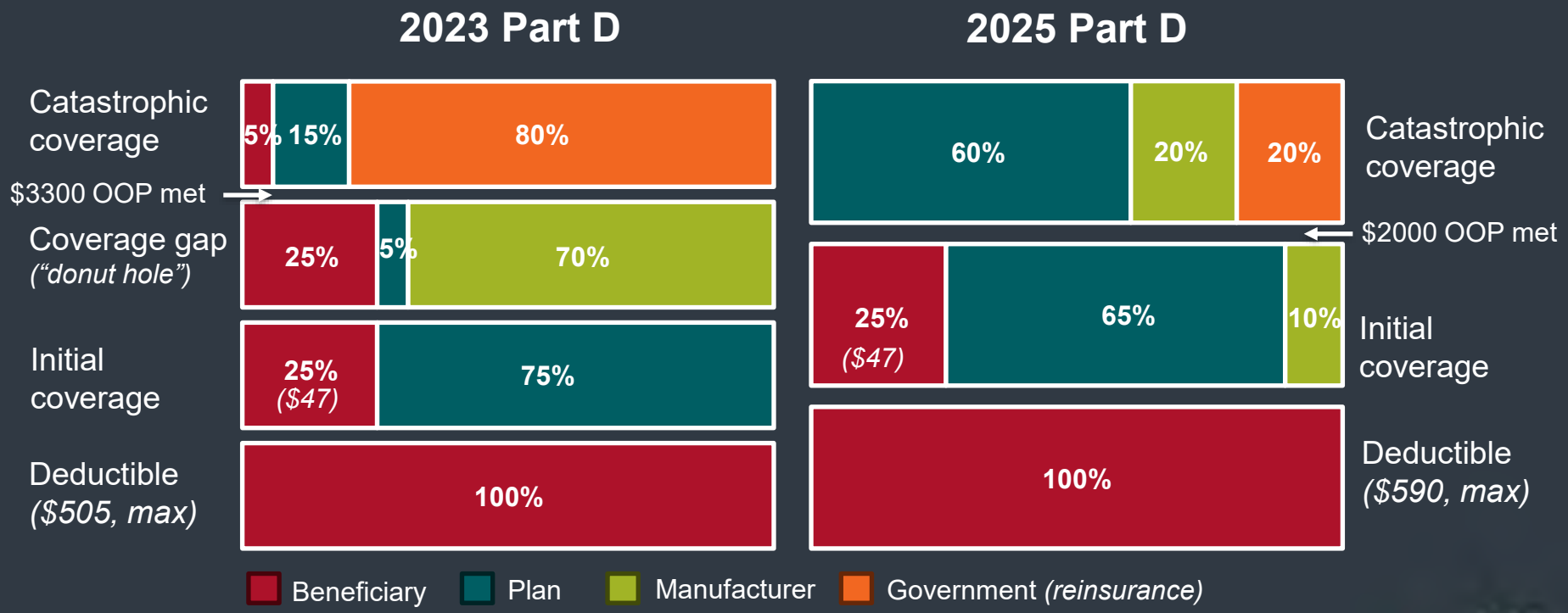
Cubanski J, et al. *KFF*. Published January 24, 2023. Accessed September 22, 2023.

Inflation Reduction Act - Nebraska

	No. of Patients	2023 List Cost	Negotiated Cost
Empagliflozin	7,000 patients	$573	$197 *(↓66%)*
Sitaglipitin	3,000 patients	$527	$113 *(↓79%)*
Dapagliflozin	3,000 patients	$556	$178 *(↓68%)*
Aspart *(Fiasp)* & Detemir	5,000 patients	$495	$119 *(↓76%)*

Gregerson E, et al. *Becker's Hospital Review*. Published August 20, 2024. Accessed September 28, 2024.
Inflation reduction act research series: Medicare use & OOP expenditures for drugs selected for negotiation under drug price negotiation program. (Fact sheet no. HP-2023-21). August 2023.

Medicare Part D Redesign



Despite redesign, limited changes to premiums expected

Centers for Medicare and Medicaid. Accessed October 3, 2024. https://www.cms.gov/newsroom/fact-sheets/final-cy-2025-part-d-redesign-program-instructions-fact-sheet.

Medicare Prescription Payment Plan

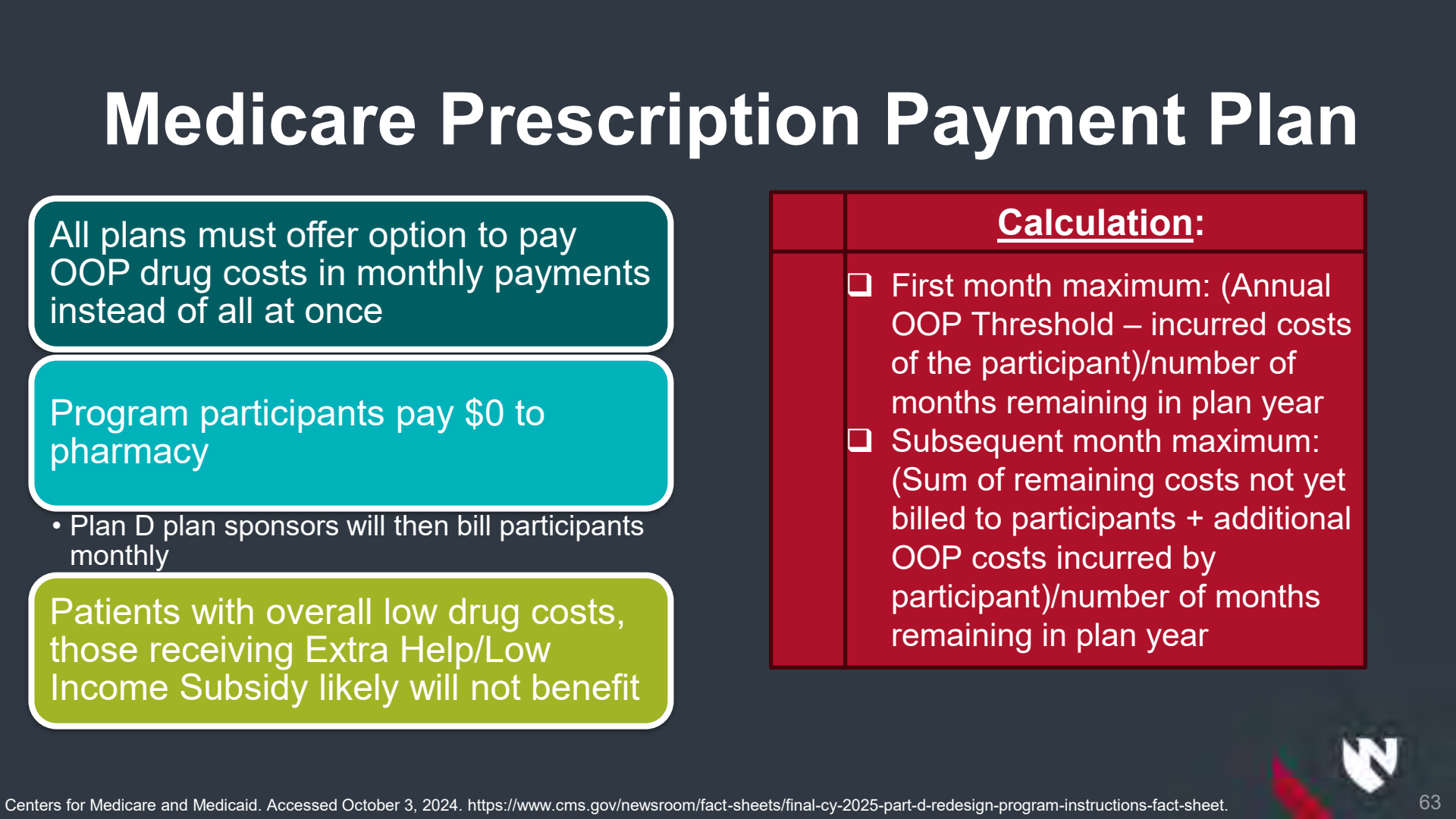
All plans must offer option to pay OOP drug costs in monthly payments instead of all at once

Program participants pay $0 to pharmacy

- Plan D plan sponsors will then bill participants monthly

Patients with overall low drug costs, those receiving Extra Help/Low Income Subsidy likely will not benefit

	Calculation:
	❑ First month maximum: (Annual OOP Threshold – incurred costs of the participant)/number of months remaining in plan year ❑ Subsequent month maximum: (Sum of remaining costs not yet billed to participants + additional OOP costs incurred by participant)/number of months remaining in plan year



Centers for Medicare and Medicaid. Accessed October 3, 2024. https://www.cms.gov/newsroom/fact-sheets/final-cy-2025-part-d-redesign-program-instructions-fact-sheet.

Medicare Prescription Payment Plan

1 Maximum Possible Payment

$2,000 *[annual OOP maximum]* – $0 = $2,000/12 *[remaining months in the year]* = **$166.67**

2 Compare total OOP cost

If total OOP cost for fill > maximum possible payment, then **$166.67** is billed

3 Subsequent Months

$333.33 *[remaining balance]*
+$500 [new costs]
=$833.33

$833.33/11 *[remaining months]*
= $75.76

4 Once max OOP met *(April)*

$1131.81 *[remaining balance]*
+$500 [new costs]
=$1631.81

$833.33/9 *[remaining months]*
= $181.31

Month	Suzie's Drug Cost	Suzie's Monthly Cost
January	$500	$167.67
February	$500	$75.76
March	$500	$125.76
April	$500	$181.31
May – Dec.	$0	$181.31

= $2,000

Low Cost Copays

$80/month x 12 months = $960

Centers for Medicare and Medicaid. Accessed October 3, 2024. https://www.medicare.gov/prescription-payment-plan/examples.

Investigational Drugs

Insulin Efsitora Alfa
Investigational Products
Investigational Phase 3 Products
Investigational Phase 2 Products

Nebraska Medicine

Insulin Efsitora Alfa

QWINT 1

- 52 week randomized, open-label trial
- Insulin naïve
- Noninferior A1c reduction compared to glargine
- Lower rates of hypoglycemia

QWINT 2

- 52 week randomized, parallel-design, open-label, treat-to-target trial
- Insulin naïve
- Noninferior A1c reduction compared to degludec
- No severe hypoglycemia noted with efsitora alfa

QWINT 3

- 78 week randomized, parallel-design, open-label trial
- Previously on 10-110 units of basal insulin
- Noninferiorr A1c reduction compared to degludec
- Showed numerically higher rates of severe hypoglycemia *(<54 $^{mg}/_{dL}$)*

Wysham C, et al. *NEJM*. 2024; online ahead of print.
In a first-of-its-kind fixed dose study, once weekly insulin efsitora alfa leads to A1c reduction similar to daily insulin. Accessed September 15, 2024.

Insulin Efsitora Alfa

QWINT 4

- 52 week randomized, parallel-design, open-label trial
- Previously on ≥ 10 units of basal & 2+ prandial doses daily
- Noninferior A1c reduction compared to glargine *(both groups on lispro)*
- Completed, not published

QWINT 5

- 60 week randomized, parallel-design, open-label trial
- T1D
- Noninferior improvement in A1c compared to degludec
- Higher rates of combined level 2 or level 3 hypoglycemia

FDA?

- Unclear when Lilly will submit

Bergenstal RM, et al. *Lancet*. 2024;404(10458):1132-1142
With once-a-week dosing, insulin efsitora alfa delivers A1c reduction and safety profile consistent with daily insulin. Accessed September 22, 2024.

New Investigational Products

morphic

Stanford University

GE

novo nordisk®

RESET *(EndoBarrier)*

- Gut liner sleeve inserted via 1-hr endoscopy in the first 60 cm of small intestine
- Results in changes in metabolism of glucose, nutrients, gut hormones
- Obesity and T2D
- STEP-1 currently recruiting

Polymer-nanoparticle *(PNP)* hydrogel

- Mesh of polymers & nanoparticles dissolve over time
- Goal: Q3 months
- Obesity and T2D
- Pig models currently, human trials in mid/late 2025

Peripheral focused ultrasound *(PFUS)*

- Specifically regulate metabolic function
- T2D and Obesity

STEP-1. Clinical Trials.gov. Updated July 18, 2024. Accessed September 15, 2024. https://clinicaltrials.gov/study/NCT04101669.
GE HealthCare and Novo Nordisk to collaborate to advance novel non-invasive treatment for T2D and obesity with ultrasound. Published October, 2023. Accessed September 28, 2024.
New drug delivery system could reduce daily diabetes shots to just three a year. Stanford University School of Engineering. News Release. November 22, 2023. Accessed September 15, 2024.

Investigational Phase 3 Drugs

Retatrutide

GLP-1, GIP & glucagon receptor agonist (triple agonist)

Diabetes: TRANSCEND-T2D *1-3*
Trials completed Q2/Q4 2026, Q1 2027

Obesity: TRIUMPH 1–4, OUTCOMES
Trials completed Q1 – Q2 2026; Q1 2029

Orforglipron

Daily oral **nonpeptide** GLP-1 receptor agonist

Diabetes: ACHIEVE 1–5
Trials completed Q3-Q4 2025

Obesity: ATTAIN 1, 2, 4, MAINTAIN
Trials completed Q4 2025, Q1 2026

Survodutide

GLP-1 & glucagon receptor agonist

Obesity: SYNCHRONIZE 1, 2, CVOT
Trials completed Q1 2026

NASH: one phase 3 trial
Trials completed Q1 2026

CagriSema

Weekly GLP-1 RA *(Sema)* + dual amylin and calcitonin RA *(Cagri)*

Type 2 Diabetes	Obesity
Phase 3 trials: REIMAGINE	Phase 3 trials: REDEFINE
Primary outcome: Change in A1c	Primary outcome: % change in body weight at PLUS # of patients achieving 5%+ weight reduction; weight change after stopping; MACE
Baseline DM medications: no previous treatment; metformin +/- SGLT-2i; basal insulin	Comparators: placebo; semaglutide alone; cagrilintide alone; tirzepatide
Comparators: placebo; semaglutide alone; tirzepatide	REDEFINE 3: CVOT with 3-point MACE; include DM and non-DM

REIMAGINE-2. Clinical Trials.gov. Updated September 24, 2024. Accessed September 29, 2024. https://clinicaltrials.gov/study/NCT06065540.

New Investigational Drugs

Monlunabant
- Oral CB1R inverse agonist
- T2D & Obesity

NN9650
- Monthly GLP-1/GIP
- T2D & Obesity

Eloralintide
- Weekly amylin agonist
- Obesity (+ T2D?)

Mazdutide
- GLP-1/GCGR
- Obesity

MariTide
- GLP-1 RA/GIP
- Obesity & T2D
- *Potential for injecting less than weekly?*

Monlunabant

Oral CB1R inverse agonist/receptor blocker

Diabetic Kidney Disease	Obesity & Metabolic Syndrome
Phase 2: 2 doses vs placebo	Phase 2: 3 doses vs placebo
Primary outcome: Change in UACR at 16 weeks	Primary outcome: body weight at 16 weeks
Secondary: change in eGFR	Secondary: change in waist circumference; change in lipid panel; change in glucose control *(A1c, c-peptide)*; change in total body fat and skeletal muscle mass
Completed September 2024	Primary study completed June 2024; extension expect March 2025

Phase 2 of INV-202. Clinical Trials.gov. Updated September 19, 2024. Accessed September 29, 2024. https://clinicaltrials.gov/study/NCT05514548.
Study of INV-202 in obesity and metabolic syndrome. Clinical Trials.gov. Updated August 29, 2024. Accessed September 29, 2024. https://clinicaltrials.gov/study/NCT05891834.

Eloralintide & Mazdutide

Weekly amylin agonist	Weekly GLP-1R/GCGR agonist
Obesity	Obesity
Phase 2: 6 doses vs placebo	Phase 2: 3 doses vs placebo
Primary outcome: % change in body weight Secondary: % of patients with 5%, 10% body weight reductions; % change in BMI	Primary outcome: % change in body weight Secondary: % change in BMI; % change in weight; change in liver fat content
Inclusion: BMI ≥ 27 without DM	Inclusion: BMI ≥ 27 with weight-related comorbidities (excluded DM)
Estimated Completion: September 2025	Estimated Completion: May 2025

Study of LY3305677. Clinical Trials.gov. Updated September 19, 2024. Accessed September 29, 2024. https://clinicaltrials.gov/study/NCT06124807.
Study of LY3841136 compared with placebo. Clinical Trials.gov. Updated September 27, 2024. Accessed September 29, 2024. https://clinicaltrials.gov/study/NCT06230523.
Study of LY3841136 compared with tirzepatide. Clinical Trials.gov. Updated September 19, 2024. Accessed September 29, 2024. https://clinicaltrials.gov/study/NCT06603571.

MariTide *(Maridebart Cafraglutide)*

GLP-1 receptor agonist/GIP receptor antagonist

Obesity	+/- Diabetes
Phase 2: 3 total doses	
Cohort A = 7 dose regimens vs placebo	Cohort B = 4 doses regimens vs placebo

Primary outcome: % change in body weight

Inclusion:	
BMI ≥ 30 OR BMI ≥ 27 with weight-related comorbidities	T2D treated with metformin, SU or SGLT-2i

Estimated Completion: January 2026

Dose-ranging study to evaluate AMG 133. Clinical Trials.gov. Updated August 7, 2024. Accessed September 29, 2024. https://clinicaltrials.gov/study/NCT05669599.

Phase 3: Mechanisms of Action

Brain	Whole Body	Pancreas	Stomach	New Agents
GIP ↓ food intake	GIP ↑ insulin sensitivity	GIP ↑ insulin ↑ glucagon		Retatrutide GIP / GLP-1 / Glucagon
GLP-1 ↓ food intake ↑ satiety		GLP-1 ↑ insulin ↓ glucagon	GLP-1 ↓ gastric emptying	Orforglipron GLP-1
	Glucagon ↑ energy expenditure			Survodutide GLP-1 / Glucagon
Amylin ↓ food intake ↑ satiety		Amylin ↓ glucagon	Amylin ↓ gastric emptying	CagriSema GLP-1 / Amylin

Nauck MA, et al. *Diabetes Metab J.* 2021;23(S3):5-29.
Ascanio AM, et al. *Cardiol Rev.* 2024;32(1):83-90.

Phase 2: Mechanisms of Action

Brain	Whole Body	Pancreas	Stomach
GIP ↓ food intake	GIP ↑ insulin sensitivity	GIP ↑ insulin ↑ glucagon	
GLP-1 ↓ food intake ↑ satiety		GLP-1 ↑ insulin ↓ glucagon	GLP-1 ↓ gastric emptying
	Glucagon ↑ energy usage		
Amylin ↓ food intake ↑ satiety		Amylin ↓ glucagon	Amylin ↓ gastric emptying
CB1 ↑ satiety	CB1 ↑ energy usage		

New Agents

- Monlunabant: CB1
- Eloralintide: Amylin
- Mazdutide: GLP-1, Glucagon
- MariTide: GLP-1, GIP

Nauck MA, et al. *Diabetes Metab J.* 2021;23(S3):5-29.
Ascanio AM, et al. *Cardiol Rev.* 2024;32(1):83-90.

Medications Coming in the Not So Near Future

Type 1 Diabetes Grand Challenge

- Diabetes UK
- Breakthrough T1D
- Steve Morgan Foundation

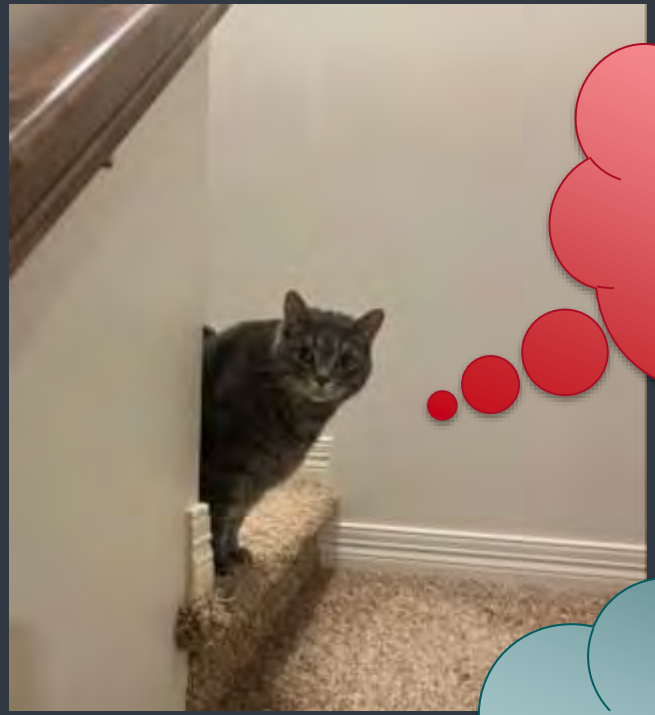
$64 million

Type 1 Diabetes Research

$19 million for 6 projects:

- 4 aimed at glucose-responsive “smart” insulins
- 1 aided at ultrafast-acting insulin
- 1 aimed at combining insulin and glucagon

Tucker, M. ‘New era’ in insulin possible if research successful - *Medscape* - Aug 15, 2024. Accessed September 15, 2024.



Is it snack time yet?

QUESTIONS?

Nebraska Medicine