SHIELDS
HEALTH SOLUTIONS

Weighing the Evidence

Clinical Updates on GLP-1 and Incretin-Based Therapies

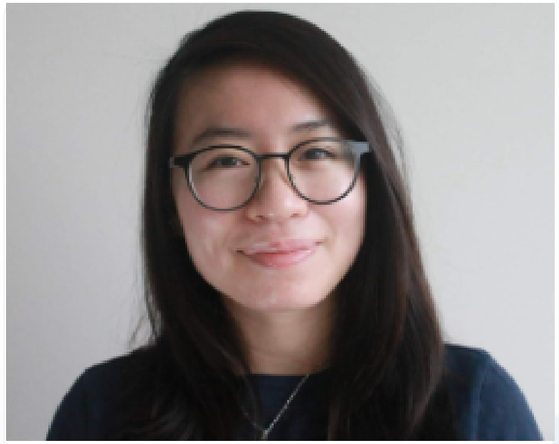
Meet the Shields Team

Dr. Cody Gao

PharmD
Ambulatory Clinical Pharmacist
cgao@shieldsrx.com

Dr. Elliot Ogorek

PharmD
Ambulatory Clinical Pharmacist
eogorek@shieldsrx.com



Dr. Sharon Zhu

PharmD, BCGP
Ambulatory Clinical Pharmacist II
szhu@shieldsrx.com

GLP-1 Clinical Updates

Objectives

01

CURRENT LANDSCAPE

Review the current landscape of Glucagon-Like Polypeptide-1 Receptor Agonist (GLP-1 RA) and GLP- 1RA/Glucose-dependent Insulinotropic Polypeptide (GIP) therapies, including Food and Drug Administration (FDA)-approved formulations and approved clinical indications.

02

FUTURE INDICATIONS

Identify future indications for currently FDA-approved GLP-1 RA and GLP-1 RA/GIP therapies, with a focus on anticipated or expanded uses.

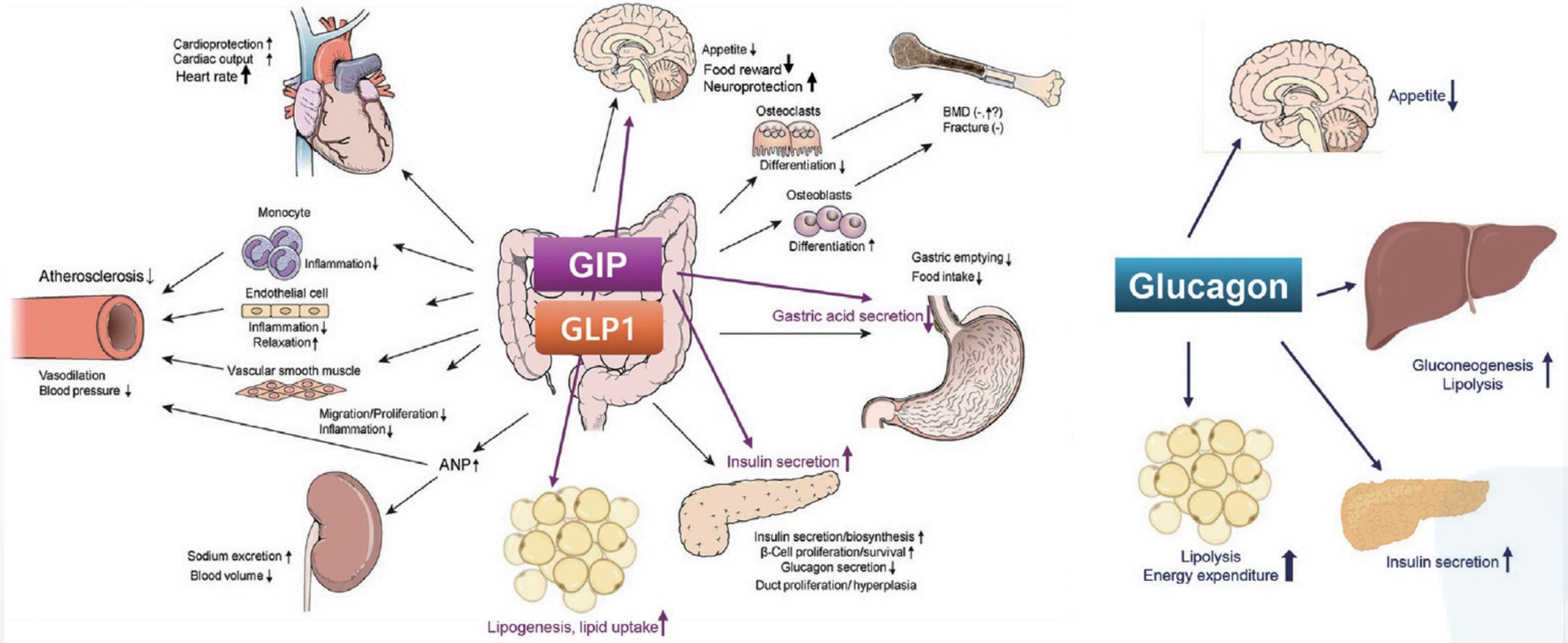
03

EMERGING THERAPIES

Explore emerging incretin therapies in the development pipeline.

Photo: ©iStock/Jay Pierstorff
https://www.research.va.gov/research in action/Diabetes-drug-from-Gila-monster-venom.cfm

GLP-1 RA Mechanism of Action



Son JW, Lim S. Son JW, Lim S. Glucagon-Like Peptide-1 Based Therapies: A New Horizon in Obesity Management. Endocrinol Metab (Seoul). 2024

Current GLP-1 RA Landscape

Type 2 Diabetes

- Semaglutide (Ozempic, Rybelsus)
- Liraglutide (Victoza)
- Dulaglutide (Trulicity)
- Tirzepatide (Mounjaro)
- Exenatide (Byetta, Bydureon)

Obesity

- Semaglutide (Wegovy)
- Tirzepatide (Zepbound)
- Liraglutide (Saxenda)
- Orforglipron (Foundayo)

Zepbound (tirzepatide) KwikPen

Dosing

- 1 pen = 4 weekly doses
- Available in all 6 strengths
  - 2.5 mg/0.6 mL
  - 5 mg/0.6 mL
  - 7.5 mg/0.6 mL
  - 10 mg/0.6 mL
  - 12.5 mg/0.6 mL
  - 15 mg/0.6 mL

Pen Needles

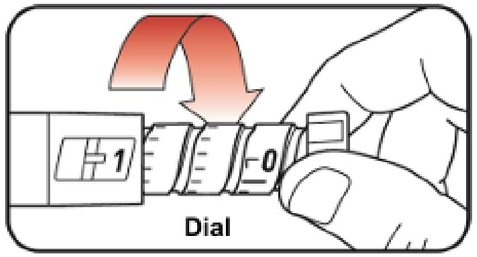
- **NOT INCLUDED**
- Compatible with ISO 11608-2 compliant pen needles from brands such as Embecta (formerly BD), Novo Nordisk, and Terumo, in any length and gauge combination:
  - Lengths: 4mm, 5mm, 6mm, 8mm, 12.7mm
  - Gauge: 29G, 30G, 31G, 32G, 33G, 34G

Priming

- **Weekly** with every dose
- Turn knob to “prime” symbol and push until a drop appears

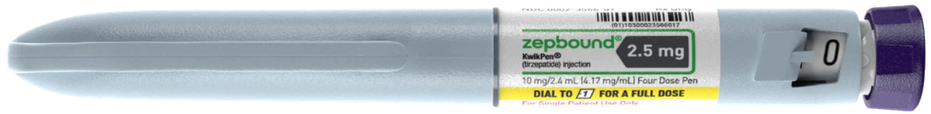
Selecting Dose

- Turn knob until “1” symbol



Storage

- Unused: refrigerator between 2°C and 8°C
- In Use: at room temperature up to 30°C for up to 30 days



1. Zepbound® KwikPen® Instructions for Use. Eli Lilly Canada Inc.

Wegovy HD (semaglutide) Injection

Table 4. Adverse Reactions (2% and Greater Than WEGOVY® 2.4 mg and Placebo) in WEGOVY® 7.2 mg Injection-treated Adults with Obesity for Weight Reduction

	Placebo N=303 %	WEGOVY® Injection (2.4 mg once weekly) N=304 %	WEGOVY® Injection (7.2 mg once weekly) N=1,311 %
Nausea	13	35	39
Vomiting	6	16	22
Dysesthesia[a]	0	6	22
Constipation	8	19	20
Abdominal pain[b]	7	9	12
Fatigue[c]	5	9	11
Headache	7	8	9
Dizziness[d]	1	5	6
Hair loss	1	3	6
Flatulence	2	2	4

[a] Includes allodynia, burning sensation, dysesthesia, hyperesthesia, hyperpathia, pain of skin, paresthesia, sensitive skin, skin burning sensation, skin discomfort, and skin sensitization.
[b] Includes abdominal pain, abdominal pain upper, abdominal pain lower, gastrointestinal pain, abdominal tenderness, abdominal discomfort and epigastric discomfort.
[c] Includes fatigue and asthenia.
[d] Includes dizziness and dizziness postural.

Current Doses

- 0.25 mg
- 0.5 mg
- 1 mg
- 1.7 mg
- 2.4 mg

New Dose

- 7.2 mg (FDA approved on March 19th 2026)

wegovy.com

Trial: STEP UP

	Semaglutide 7.2 mg (n=1005)	Semaglutide 2.4 mg (n=201)	Placebo (n=201)	Treatment comparison: semaglutide 7.2 mg vs specified comparator
Coprimary Endpoints				
Change in bodyweight, %	**−18.7%** (0.4); n=950	**−15.6%** (0.7); n=189	**−3.9%** (0.6); n=171	Estimated treatment difference (ETD) vs 2.4 mg: **−3.1%** (−4.7 to −1.6); p<0.0001 ETD vs placebo: **−14.8%** (−16.2 to −13.4); p<0.0001
Proportion of participants with bodyweight reduction ≥ 5%	862/950 (90.7%)	170/189 (89.9%)	63/171 (36.8%)	Odds Ratio (OR) vs 2.4 mg: **1.2** (0.8 to 2.0); p=0.47 OR vs placebo: **12.1** (8.3 to 17.6); p<0.0001

1. Wharton S et al. Lancet Diabetes Endocrinol. 2025;13(11):949-963.
2. Wegovy. Package insert. Novo Nordisk Inc; 2026.

Wegovy (semaglutide) Tablets

New Doses

- 1.5 mg
- 4 mg
- 9 mg
- 25 mg

R2 Formulation

- Increased bioavailabilty

SNAC technology

- Co-formulated with **s**odium **N**-(8-[2-hydroxybenzoyl] **a**mino) **c**aprylate **(SNAC)** to enable absorption in the stomach

Administration based on PK study

- Take with ≤ 120 mL (4 oz) of water
- Empty stomach, ≥ 30 minutes before food or drink
- Absorption not clinically significant between 50 mL and 120 mL of water
- Longer post-dose fasting period improved absorption

wegovy.com

Trial: OASIS 4

Participants	Intervention	Comparison	Outcomes		Pearls
n = 307 participants with **overweight or obesity without diabetes**	Semaglutide 25 mg PO once daily (n = 205)	Placebo (n = 102)	Percent change in body weight:		Demonstrated safety & tolerability at 25 mg
			Semaglutide: -13.6%	Placebo: -2.2%	
			Estimated difference, −11.4 percentage points; 95% confidence interval, −13.9 to −9.0; P<0.001		

1. Wharton S et al. N Engl J Med. 2025;393(11):1077-1087.
2. Nielsen MS et al. Diabetes Ther. 2025 Feb;16(2):269-287. doi: 10.1007/s13300-024-01674-8.

Foundayo (orforglipron) Tablets


lilly.com

Doses

- 0.8 mg
- 2.5 mg
- 5.5 mg
- 9 mg
- 14.5 mg
- 17.2 mg

Formulation

- Non-peptide small molecule

Administration

- Take 1 tablets by mouth once daily
- **With or without food**
- Swallow whole. Do not break, crush, or chew tablet
- If a dose is missed, take missed dose as soon as possible

Drug Interactions

- **Strong CYP3A4 Inhibitors**: max dose of Foundayo is **9 mg once daily**. Avoid concomitant use with strong CYP3A4 inhibitors that also inhibit OATP1B.
- **CYP3A4 Inducers:**
  - strong inducers: **Avoid**
  - moderate inducers: **Monitor**
- Simvastatin: **Do not exceed simvastatin 20 mg once daily** when used concomitantly with Foundayo

Difference between orforglipron and oral semaglutide

	Indication	Chemistry	Fasting	Timing	Liquid	Concurrent medications	ACHIEVE-3 trial	
							A1c[1]	**Weight**[1]
Orforglipron tablets	(1) To reduce excess body weight and maintain weight reduction	Non-peptide (small molecule)	Not required	Flexible	No water restrictions	No restrictions	orforglipron 36 mg: -2.16%	orforglipron 36 mg: -9.2% (-19.7 lbs)
Semaglutide tablets	(1) + (2) To reduce risk of MACE	SNAC Peptide (large molecule)	Required	Morning	Up to 4 oz. (120 mL) of plain water only	Must wait 30 minutes	semaglutide 14 mg: -1.45%	semaglutide 14 mg: -5.3% (-11 lbs)

[1]Efficacy estimand

1. Rosenstock J et al. Lancet. 2026;407(10534):1147-1160.
2. Eli Lilly. (September 17, 2025). Lilly's oral GLP-1, orforglipron, superior to oral semaglutide in head-to-head trial. https://investor.lilly.com/news-releases/news-release-details/lillys-oral-glp-1-orforglipron-superior-oral-semaglutide-head\
3. Foundayo. Package insert. Eli Lilly and Company; 2026.
4. Wegovy. Package insert. Novo Nordisk Inc; 2026.

Foundayo (orforglipron) Tablets

Trial: ATTAIN-1

Participants	Intervention	Comparison	Outcomes		Pearls
n = 3,127 • adults with **obesity** (BMI ≥30 or 27-30 and at least one obesity-related complication) • **without diabetes**	Orforglipron: • 6 mg PO once daily (n = 625) • 12 mg PO once daily (n = 630) • 36 mg PO once daily (n = 639)	Placebo (n = 768)	Percent change in body weight from baseline to week 72:		Treatment with all 3 doses was associated with greater reduction in body weight and BMI than with placebo
			Orforglipron: • 6 mg: **-7.5%** (95% CI, -8.2 to –6.8) • 12 mg: **-8.4%** (95% CI, −9.1 to −7.7) • 36 mg: **-11.2%** (95% CI, −12.0 to −10.4)	Placebo: −2.1% (95% CI, −2.8 to −1.4)	

Average Weight at Baseline and ATTAIN-MAINTAIN Results

	Wegovy[iii] to Orforglipron	Zepbound[iii] to Orforglipron
Starting weight[i] (at start of SURMOUNT-5)	113.5 kg (250.2 lbs)	115.8 kg (255.3 lbs)
Weight at switch to oral[i] (at start of ATTAIN-MAINTAIN)	95.0 kg (209.4 lbs)	90.9 kg (200.4 lbs)
Weight after 52 weeks of oral maintenance[ii] (at end of ATTAIN-MAINTAIN)	95.9 kg (211.4 lbs)	95.9 kg (211.4 lbs)

[i]Observed mean based on efficacy estimand data set
[ii]Mixed Model for Repeated Measures (MMRM) based on efficacy estimand data set
[iii]Treatment was at maximum tolerated doses of either 1.7 mg or 2.4 mg (Wegovy) or 10 mg or 15 mg (Zepbound)

1. Wharton S et al. N Engl J Med. 2025;393(18):1796-1806.
2. Eli Lilly. (December 18, 2025). Lilly's orforglipron helped people maintain weight loss after switching from injectable incretins to oral GLP-1 therapy in first-of-its-kind Phase 3 trial. https://investor.lilly.com/news-releases/news-release-details/lillys-orforglipron-helped-people-maintain-weight-loss-after

Chronic Kidney Disease

Trial: FLOW

Participants	Intervention	Comparison	Outcomes	Pearls
n = 3533 Participants: • **T2DM** (A1c ≤10%) • **CKD** (GFR 50-75 mL/min2 and urinary albumin-to-creatinine ratio of >300 and <5,000 OR an eGFR of 25 - <50 mL/min/1.73m^2 and a urinary albumin-to-creatinine ratio of >100 and <5,000)	Semaglutide 1 mg SC once weekly (n = 1766)	Placebo (n = 1766)	Major kidney disease events Semaglutide: 331 events | Placebo: 410 events Hazard ratio (HR), 0.76; 95% confidence interval, 0.66-0.88; P=0.0003) Composite of onset of kidney failure Semaglutide: 218 events | Placebo: 260 events HR, 0.79; 95% CI, 0.66-0.94 A sustained (for ≥28 days) 50% reduction in the eGFR from baseline Semaglutide: 165 events | Placebo: 213 events HR, 0.73; 95% CI, 0.59 to 0.89 Death from kidney-related cardiovascular causes Semaglutide: 123 events | Placebo: 169 events HR, 0.71; 95% CI, 0.56-0.89	**Trial was stopped early due to efficacy** Semaglutide 1 mg SC once weekly: ↓ risk of major kidney disease by 24% ↓ reduced risk of major cardiovascular events and death from any cause Slowed annual loss of kidney function by mean of 1.16 mL/min/1.72m^2

1. Perkovic V et al. N Engl J Med. 2024;391(2):109-121.

Obstructive Sleep Apnea

Trial: SURMOUNT-OSA

<table>
<tr><th>Participants</th><th>Intervention</th><th>Comparison</th><th>Outcomes</th><th>Pearls</th></tr>
<tr>
<td rowspan="7">n = 469

Adults with:
• moderate-to-severe OSA (apnea-hypopnea index (AHI) ≥15 events per hour)
• obesity (BMI ≥30)

Trial 1: participants not receiving positive airway pressure (PAP) at baseline

Trial 2: participants receiving PAP</td>
<td rowspan="7">Tirzepatide 10 mg or 15 mg SC once weekly
(n = 234)</td>
<td rowspan="7">Placebo
(n = 235)</td>
<td colspan="2">Change in the apnea-hypopnea index (AHI) from baseline</td>
<td rowspan="7">Tirzepatide:
↓AHI
↓body weight
↓hypoxic burden
↓high sensitivity c-reactive protein concentration
↓systolic blood pressure

Improved sleep related patient reported outcomes</td>
</tr>
<tr><td colspan="2">Trial 1</td></tr>
<tr><td>Tirzepatide: -25.3 events per hour (95% CI, 29.3 to -21.2)</td><td>Placebo: -5.3 events per hour (95% CI, -9.4 to -1.1)</td></tr>
<tr><td colspan="2">Estimated treatment difference of -20.0 events per hour (95% CI, -9.9 to -1.2) (P<0.001)</td></tr>
<tr><td colspan="2">Trial 2</td></tr>
<tr><td>Tirzepatide: -29.3 events per hour (95% CI, -33.2 to -25.4)</td><td>Placebo: -5.5 events per hour (95% CI, -9.9 to -1.2)</td></tr>
<tr><td colspan="2">Estimated treatment difference of -23.8 events per hour (95% CI, -29.6 to -17.9) (P<0.001)</td></tr>
</table>

1. Malhotra A et al. N Engl J Med. 2024;391(13):1193-1205.

Non-cirrhotic Metabolic Dysfunction-Associated Steatohepatitis

Trial: ESSENCE

<table>
<tr><th>Participants</th><th>Intervention</th><th>Comparison</th><th colspan="2">Outcomes</th><th>Pearls</th></tr>
<tr><td rowspan="6">n = 1197

Participants age ≥18 years with:
• biopsy-defined MASH
• fibrosis stage 2 or 3, according to Nonalcoholic Steatohepatitis Clinical Research Network (NASH CRN)
• nonalcoholic fatty liver disease activity score (NAS) of 4 or more</td><td rowspan="6">Semaglutide 2.4 mg SC once weekly (n = 534)</td><td rowspan="6">Placebo (n = 266)</td><td colspan="2">Resolution of steatohepatitis without worsening of liver fibrosis</td><td rowspan="6">1st GLP1-RA with specific MASH indication for fibrosis

Efficacy in patients with cirrhosis has not been established, screen for cirrhosis and treat</td></tr>
<tr><td>Semaglutide: 62.9% of 534 patients</td><td>Placebo: 34.4% of 266 participants</td></tr>
<tr><td colspan="2">Estimated difference 28.7 percentage points; 95% CI, 21.1-36.2; P < 0.0001</td></tr>
<tr><td colspan="2">Reduction in liver fibrosis without worsening of steatohepatitis</td></tr>
<tr><td>Semaglutide: 36.8%</td><td>Placebo: 22.4%</td></tr>
<tr><td colspan="2">Estimated difference 14.4 percentage points; 95% CI 7.5-21.3; P<0.001</td></tr>
</table>

1. Sanyal AJ et al. N Engl J Med. 2025;392(21):2089-2099.

Major Adverse Cardiovasulcar Events

Trial: SELECT

<table>
<tr><th>Participants</th><th>Intervention</th><th>Comparison</th><th colspan="2">Outcomes</th><th>Pearls</th></tr>
<tr><td rowspan="3">n = 17,604

Participants age 45 years or older:
• preexisting CV disease
• BMI 27 or greater (overweight or have obesity)
• NO history of T2DM</td><td rowspan="3">Semaglutide 2.4 mg SC once weekly (n = 8,803)</td><td rowspan="3">Placebo (n = 8,001)</td><td colspan="2">Composite of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke</td><td rowspan="3">Semaglutide 2.4 mg SC once weekly
↓incidence of death for CV causes, nonfatal MI, or nonfatal stroke</td></tr>
<tr><td>Semaglutide: 569 events (6.5%)</td><td>Placebo: 701 events (8%)</td></tr>
<tr><td colspan="2">Hazard ratio: 0.80; 95% CI, 0.72-0.90; p<0.001)</td></tr>
</table>

1. Lincoff AM et al. N Engl J Med. 2023;389(24):2221-2232.

Major Adverse Cardiovasulcar Events

Trial: SOUL

<table>
<tr><th>Participants</th><th>Intervention</th><th>Comparison</th><th colspan="2">Outcomes</th><th>Pearls</th></tr>
<tr><td rowspan="3">n = 9560

Participants aged ≥50 years
• T2DM (A1c 6.5-10%)
• ASCVD (at least one of the following conditions: CAD, cerebrovascular disease, symptomatic PAD, CKD)</td><td rowspan="3">Semaglutide 14 mg PO daily
(n = 4825)</td><td rowspan="3">Placebo
(n = 4825)</td><td colspan="2">Time to first occurrence of MACE, a composite outcome consisting of CV death, nonfatal MI, nonfatal stroke</td><td rowspan="3">Semaglutide 14 mg PO daily:
↓ risk of MACE</td></tr>
<tr><td>Semaglutide: 579/4825 participants (12% incidence, 3.1 events per 100 person years)</td><td>Placebo: 668/4825 participants (13.8% incidence, 3.7 events per 100 person years)</td></tr>
<tr><td colspan="2">Hazard ratio, 0.86; 95% confidence interval, 0.77 - 0.96; P = 0.006)</td></tr>
</table>

1. McGuire DK et al. N Engl J Med. 2025;392(20):2001-2012.

Summary

Trials	Medication	Primary population	Outcomes
STEP UP (March 2026)	Semaglutide injection high dose	Obesity	**-18.7% weight loss** with semaglutide 7.2 mg SC once weekly
OASIS 4 (Sep. 2025)	Oral semaglutide	Obesity/Overweight	**-13.6% weight loss** with semaglutide 25 mg PO once daily
ACHIEVE-3 (Feb. 2026)	Orforglipron vs. oral semaglutide	Type 2 diabetes	**Head-to-head:** Orforglipron 36 mg significantly better than oral semaglutide for A1c reduction (-2.16%) and weight loss (-9.2%)
ATTAIN-1 (April 2026)	Orforglipron	Obesity/Overweight	**-11.2% weight loss** with orforglipron 36 mg PO daily
ATTAIN-MAINTAIN (Jan. 2026)	Orforglipron	Obesity	Participants who lost weight with injectable GLP1-RA maintained their previously achieved weight loss when switching to oral orforglipron
FLOW (May 2024)	Semaglutide	T2DM + CKD	**↓risk of major kidney disease by 24%** Trial stopped early due to effiacy
SURMOUNT-OSA (June 2024)	Tirzepatide	Obesity + sleep apnea	Participants in both trials who received tirzepatide had significant reductions in AHI and in sleep apnea-specific hypoxic burden
ESSENCE (Nov. 2025)	Semaglutide	MASH	**63% resolution of steatohepatitis** **37% improvement in fibrosis**
SELECT (Nov. 2023)	Semaglutide	CVD + Obesity	**20% ↓incidence of death for CV causes, nonfatal MI, or nonfatal stroke** with semaglutide 2.4 mg SC once weekly
SOUL (Dec. 2025)	Oral semaglutide	T2DM + ASCVD/CKD	**14%↓risk of MACE** with semaglutide 14 mg PO daily

Landscape of Emerging GLP-1 Research

Evidence Readiness

Preclinical / Mechanistic	Phase 1–2 RCTs Underway	Phase 2–3 Promising Data	Phase 3 / Pivotal Trials
Epilepsy / Seizures	PCOS	Alcohol Use Disorder	~~Alzheimer's Disease (EVOKE / EVOKE+)~~ Failed
Prader-Willi Syndrome	IBD / Crohn's	Opioid Use Disorder	Heart Failure (HFpEF)
Fibromyalgia	Psoriasis	Sarcopenia	Prediabetes prevention
	Asthma / COPD	Smoking Cessation	Osteoarthritis
	Type 1 Diabetes		Peripheral Artery Disease
	Parkinson's Disease		

Emerging Evidence

Alzheimer's Disease & Dementia

What the research shows:

JAN 2025

VA/U.S. Veterans

Class Wide

~2.5M
patients studied

Lower dementia risk vs. other diabetes drugs

AUG 2024

Lancet eClinical

Semaglutide

100M+
patient records

Linked to lower cognitive risk

JAN 2026

ELAD

Liraglutide

204
patients studied

Tied to slower cognitive decline in key brain regions + less brain shrinkage

NOV 2025

EVOKE / EVOKE +

Oral Semaglutide

Failed
n=3,808 * 2 years

Biomarkers improved; no slowing of clinical decline

1. Xie Y et al. Nat Med. 2025;31(3):951-962.
2. Wang, W et al. Alzheimer's Dement. 2024;20(12):8661-8672.
3. Edison P et al. Nat Med. 2026;32(1):353-361.
4. Cummings JL et al. Alzheimer's Res Ther. 2025;17(1):14.

Emerging Evidence

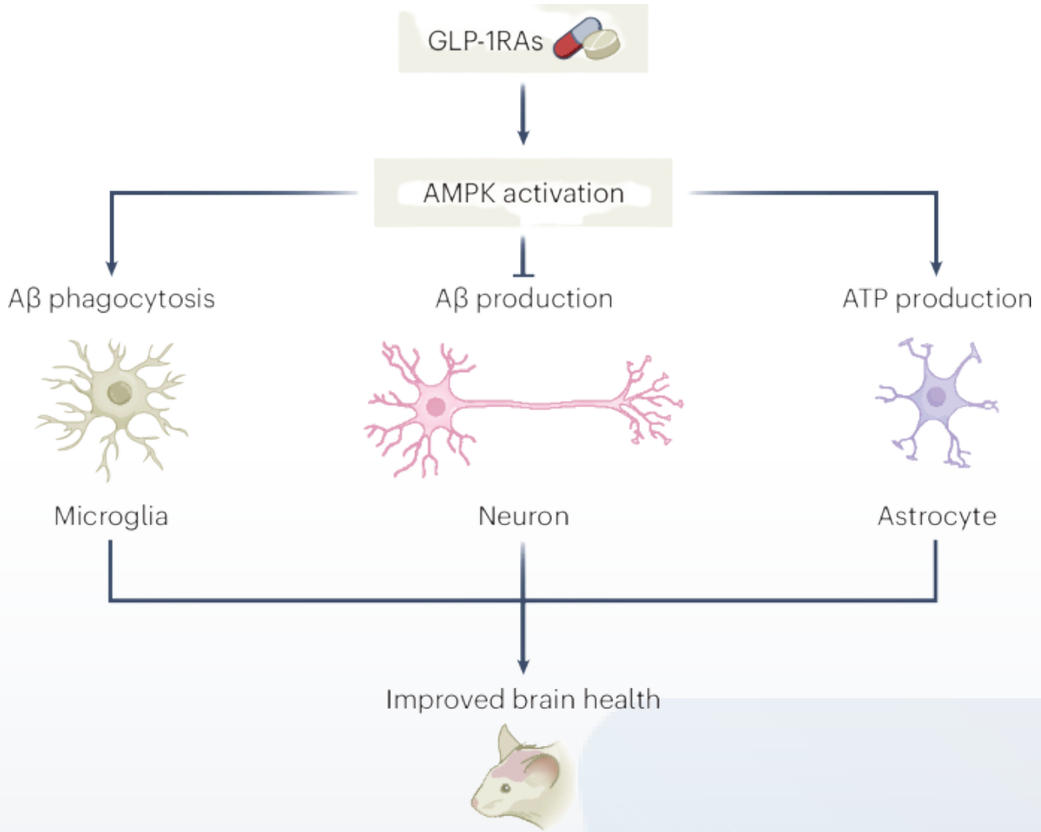
Alzheimer's Disease & Dementia

The setback:

- Nov 2025 — Novo Nordisk's EVOKE/EVOKE+ Phase 3 trials: No cognitive benefit for semaglutide in patients with existing mild cognitive impairment or dementia

Where things stand:

- Emerging consensus is that GLP-1s may work for prevention rather than treatment of established disease
- Combination approaches (GLP-1 + anti-amyloid) may be the next trial design
- Mechanistic rationale remains compelling
- New studies targeting pre-symptomatic patients are now being designed



1. Cummings JL et al. Alzheimers Res Ther. 2025;17(1):14.

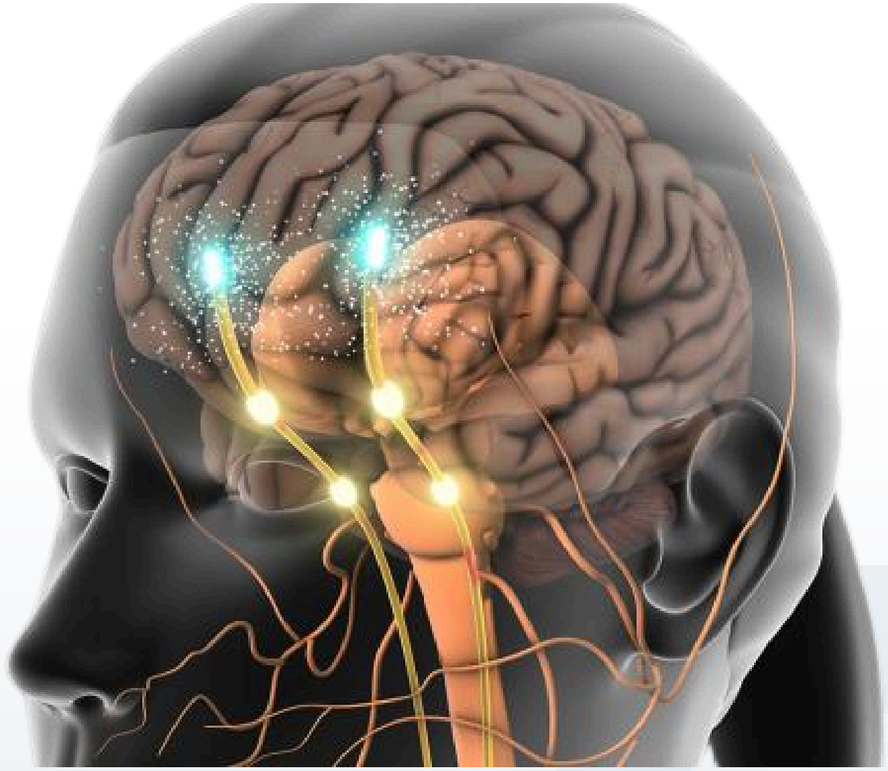
Addiction & Substance Use Disorders

Alcohol Use Disorder

The mechanism: GLP-1 receptors exist in the brain's reward pathways — GLP-1 drugs may dampen dopamine activity and reduce cravings for addictive substances

Exenatide once weekly for AUD investigated in a randomized, placebo-controlled clinical trial (Mette Klausen)
October 10, 2022, PMID: 36066977

- Objective: Evaluate efficacy of exenatide on AUD in terms of heavy drinking days and brain scans
- Population: 127 patients diagnosed with AUD
- Results: reduced heavy drinking days only in obese patients (p=0.03) and showed significant improvement in cue reactivity regions of the brain (p<0.05).



Semaglutide for Alcohol Use Disorder: A Randomized Clinical Trial
February 12, 2025, PMID: 39937469

- N=48
- Laboratory component, 2 hours access to preferred beverage. Reduced intake by ~2 drinks; 57% reduction in average BAC (p=0.03).
- Self reported: Reduced drinks per drinking day (p=0.04), cravings (p=0.01), and heavy drinking days (p=0.04). Did not reduce number of drinking days (NS).

1. Klausen MK et al. JCI Insight. 2022;7(19):e159863.
2. Hendershot CS et al. JAMA Psychiatry. 2025;82(4):395-405.

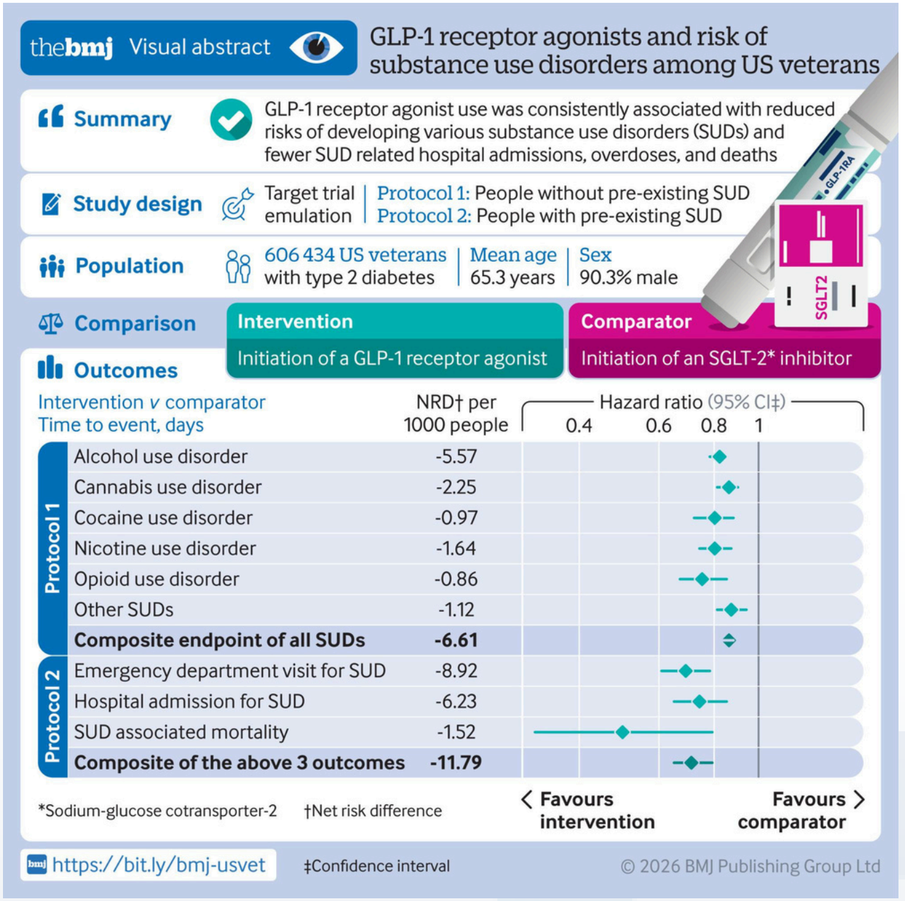
Emerging Evidence

Addiction & Substance Use Disorders

Substance Use Disorders

Glucagon-like peptide-1 receptor agonists and risk of substance use disorders(SUD) among US veterans with type 2 diabetes: cohort study

- GLP-1 RA use was associated with lower incident alcohol, cocaine, cannabis, opioid, and nicotine use disorders.
- In patients with baseline SUD, GLP-1 RA initiation correlated with 30% reduction in ED visits, 25% reduction in hospitalizations, 40% reduction in overdose, and 50% reduction in drug-related deaths, compared to SGLT-2.
- Composite SUD endpoint: HR 0.86 (95% CI 0.82-0.89).
- The study also found a 25% reduction in suicidal ideation among GLP-1 users, a significant finding given earlier concerns that the drugs might increase suicide risk.



1. Cai M et al. BMJ. 2026;392:e086886.

Emerging Evidence

Osteoarthritis & Inflammation

Key trial — STEP-9 (NEJM, Oct 2024):

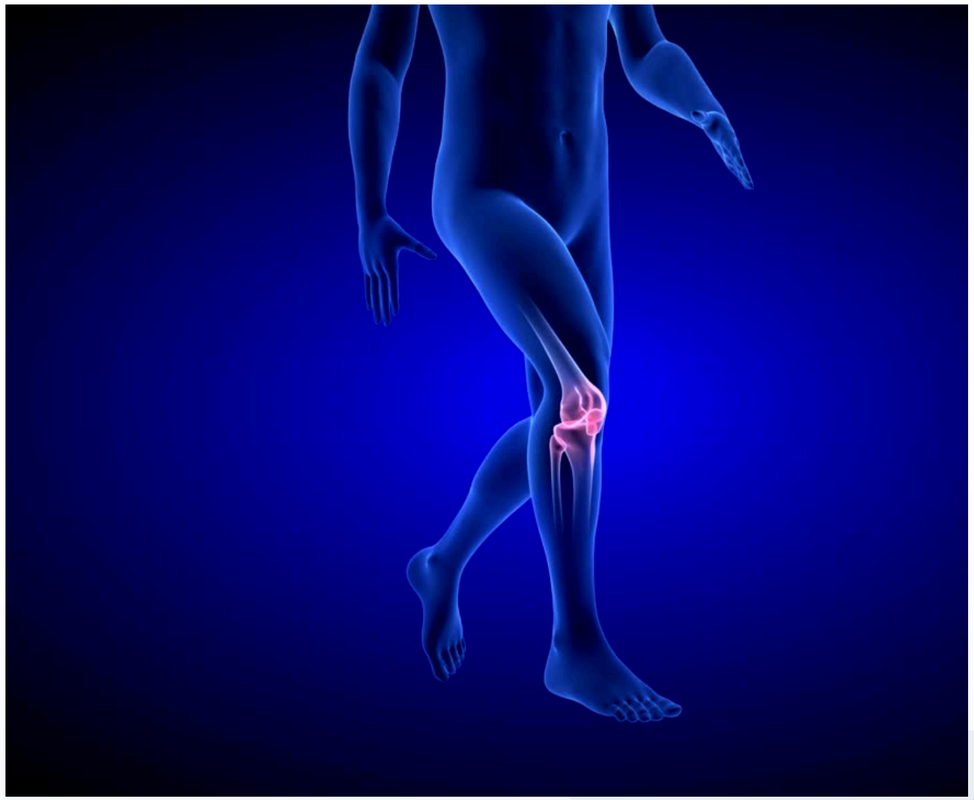
- n = 407 adults with obesity (BMI ≥30) and moderate-to-severe knee OA
- Semaglutide 2.4 mg weekly vs. placebo over 68 weeks
- WOMAC pain score: −41.7 (semaglutide) vs. −27.5 (placebo); p<0.001
- Weight reduction: −13.7% vs. −3.2%

Open question: Is the pain benefit driven by weight loss, or does semaglutide have a direct anti-inflammatory effect on joint tissue? The trial was not designed to separate these mechanisms. Did have both counseling on diet and physical activity as part of the protocol for both arms.

Supporting signals:

- Obesity Science & Practice (May 2024): Semaglutide associated with reduced risk of developing knee OA in claims data
- J Clinical & Translational Endocrinology (June 2024): Small studies show improvements in psoriasis, pericardial fat, clotting risk, and renal function — potentially via systemic inflammation reduction

Broader picture: Eli Lilly is actively investigating GLP-1 mechanisms across a wide range of inflammatory diseases, including Crohn's disease and severe skin and lung disorders



1. Bliddal H et al. N Engl J Med. 2024;391(17):1573-1583.
2. Baser O et al. Obes Sci Pract. 2024;e762.
3. Yaribeygi H et al. J Clin Transl Endocrinol. 2024;36:100340.

Theoretical

Asthma

The mechanism: GLP-1 receptors are expressed throughout bronchial epithelium and airway smooth muscle. Anti-inflammatory actions, including reducing eosinophil activity and systemic cytokine levels, provide biological rationale for symptom benefit independent of weight loss.

What the evidence shows:

- UK observational study (April 2025): ~60,000 patients including ~10,000 GLP-1 users with obesity and asthma
  - GLP-1 users had meaningfully better asthma **symptom control**
  - However: **no measurable improvement in lung function** (FEV1/FVC)
- Researchers conclude: anti-inflammatory effects, not direct airway effects, are the likely driver

Where things stand: No dedicated Phase 3 RCT for asthma exists. Signal is promising but mechanism remains unproven in humans. More targeted trials are needed before clinical recommendations can be made.

1. Kaplan A et al. Adv Ther. 2025;42(6):2950-2956.

Theoretical

Cancer

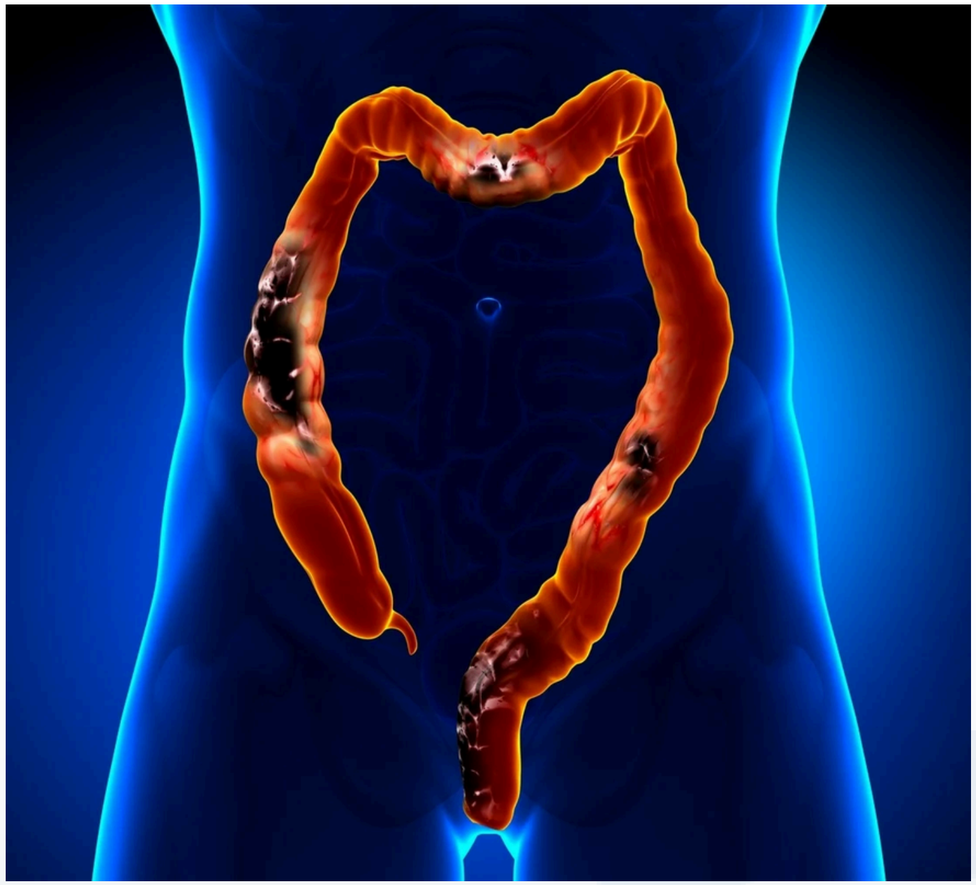
Early signals (not proven causation):

- JAMA Oncology (Dec 2023, 101.2M T2DM patient records): Retrospective analysis of 101.2 million T2DM patient records found GLP-1 users had markedly reduced risk of colorectal cancer vs. non-users. Authors note the association is strong enough to warrant prospective study but do not claim causation.
- Obesity journal (May 2023): Small study, semaglutide may enhance natural killer cell activity, which plays a role in suppressing tumor proliferation

Active research:

- Nature Cancer review (Jan 2026): Dozens of GLP-1 clinical trials underway — including endometrial, breast, and prostate cancer

Note: Medullary thyroid cancer (MTC) boxed warning for GLP-1 RAs is still in place



1. Wang L et al. JAMA Oncol. 2024;10(2):256-258.
2. De Barra C et al.Obesity (Silver Spring). 2023;31(7):1787-1797.
3. Yabut JM et al. Nat Cancer. 2026;7(2):260-271.

Theoretical

PCOS

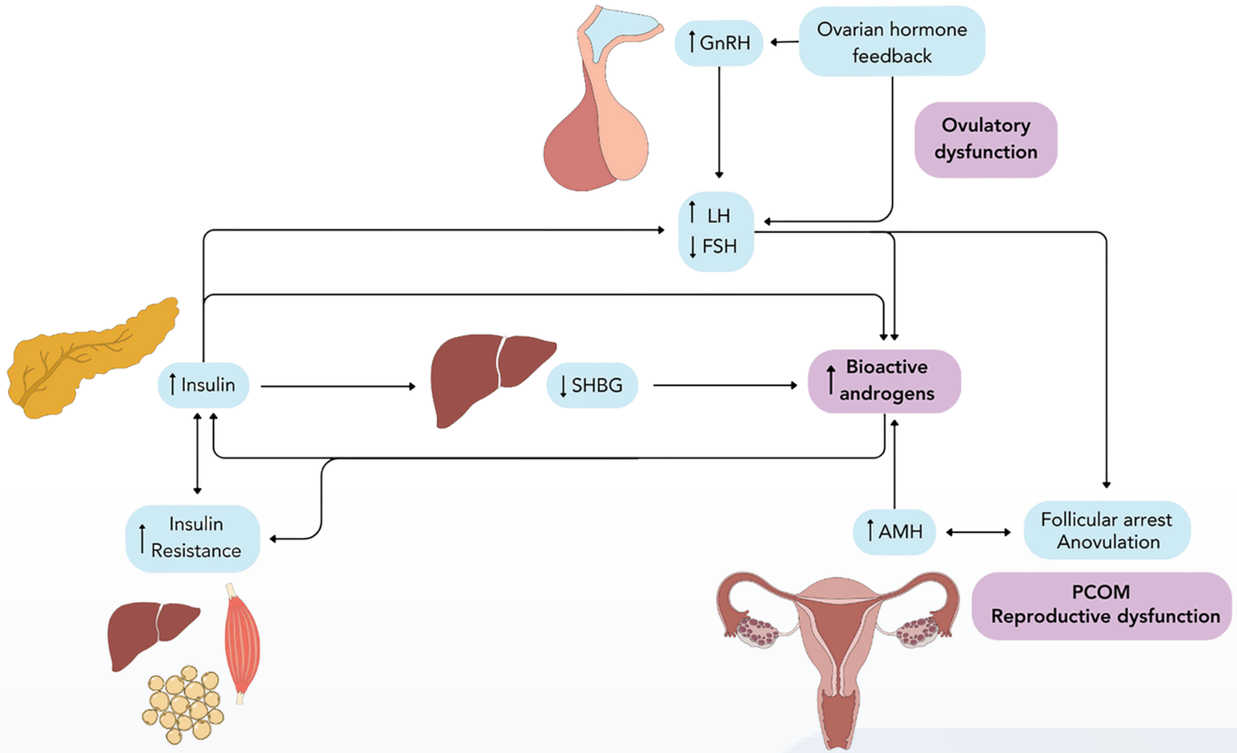
Why it makes sense: PCOS involves excess testosterone, insulin resistance, irregular periods, and infertility, all areas where GLP-1s have overlapping effects on metabolism and hormones

Early data:

- Journal of Clinical Medicine (Sept 2023): Low-dose semaglutide reduced body weight in ~80% of obese PCOS patients who hadn't responded to prior treatment, and **menstrual cycles normalized**
- At least **12 studies** on GLP-1 use in PCOS + obesity are currently underway

Important caveats:

- No large RCTs yet
- Off-label prescribing is happening now
- Metformin has been a standard off-label treatment for PCOS for decades
- Must be stopped before pregnancy — counsel patients accordingly



1. Carmina E et al. J Clin Med. 2023;12(18):5921.
2. Houston EJ et al. J Endocrinol. 2025;265(2):e240269.

More than Diabesity

GLP-1 receptor agonists are now under investigation across neurodegeneration, addiction, chronic inflammation, and oncology with mechanisms that extend well beyond metabolic pathways.

Most indications remain early-phase. Expect off label use.

Manufacturer	Drug Name	Formulation + Frequency	Indication	Where in pipeline	Mechanism of Action (MOA)
Amgen (Thousand Oaks, CA)	**MariTide** (maridebart cafraglutide)	Subcutaneous injection - once **monthly**	Weight management	Phase 3	GLP-1 **agonist** + GIP **antagonist**
Bloom Science (San Diego, CA)	**BL-001**	Oral capsule - once daily	Weight management	Phase 1b	Live Biotherapeutic Product (LBP) designed to replicate the metabolic effects of the ketogenic diet w/out any dietary restriction
Boehringer Ingelheim (Ingelheim, Germany)	**Survodutide**	Subcutaneous injection - once weekly	Weight management, MASH and fibrosis	Phase 3	GLP-1 agonist + glucagon agonist
Eli Lilly (Indianapolis, IN)	**Eloralintide**	Subcutaneous injection - once weekly	Weight management	Phase 3	Selective **amylin** receptor agonist
Sciwind Biosciences (Hangzhou, China)	**Ecnoglutide**	Subcutaneous injection - once weekly	Weight management, T2DM	Approved by China's National Medical Products Administration (NMPA) in January 2026 for T2DM	cAMP-biased GLP-1 receptor agonist

1. https://www.novonordisk.com/content/nncorp/global/en/news-and-media/news-and-ir-materials/news-details.html?id=916

Retatrutide

- Once weekly subcutaneous injection
- **Triple hormone receptor agonist that activates receptors for: GLP-1, GIP, and glucagon - - - “GLP-3”**

- Currently in Phase 3 trials for T2DM, obesity, knee osteoarthritis pain, moderate-to-severe OSA, chronic low back pain, cardiovascular and renal outcomes, and MASH

- Two Phase 3 trials completed:
  - **TRIUMPH-4**: adults with obesity or overweight and knee osteoarthritis, and without T2DM, as an adjunct to healthy diet and physical activity (1)
    - Results: average weight loss of **28.7%** of their body weight at 68 weeks (taking retatrutide 12 mg); significant reduction in pain scores and improved measures of physical function

  - **TRANSCEND-T2D-1**: adults with T2DM and inadequate glycemic control with diet and exercise alone (2)
    - Results: participants **lowered A1c by an average of 1.7% to 2%** at 40 weeks; **average weight loss of 16.8%** (taking retatrutide 12 mg); **no observable weight loss plateau**
      - very difficult to achieve weight loss in patients with T2DM while also lowering A1c!

Possible release in late 2026/early 2027

1. Eli Lilly & Company. (December 11, 2025). Lilly's triple agonist, retatrutide, delivered weight loss of up to an average of 71.2 lbs along with substantial relief from osteoarthritis pain in first successful Phase 3 trial. PR Newswire. https://www.prnewswire.com/news-releases/lillys-triple-agonist-retatrutide-delivered-weight-loss-of-up-to-an-average-of-71-2-lbs-along-with-substantial-relief-from-osteoarthritis-pain-in-first-successful-phase-3-trial-302638804.html
2. Eli Lilly & Company. (March 19, 2026). Lilly’s triple agonist, retatrutide, demonstrated significant reductions in A1C and weight in first Phase 3 trial for treatment of type 2 diabetes. PR Newswire. https://investor.lilly.com/news-releases/news-release-details/lillys-triple-agonist-retatrutide-demonstrated-significant

CagriSema

- Once-weekly subcutaneous injection

- GLP-1 **(semaglutide)** and amylin receptor (**cagrilintide**) agonists
  - Amylin: secreted with insulin from the pancreas to reduce food intake and improve glucose metabolism; helps regulate satiety after eating
- **Filed for FDA approval** (for weight management) on 12/18/25

- Phase 3 trials:

  - **REDEFINE-4**: 84 week trial comparing weight loss between participants given once weekly injected CagriSema (2.4 mg cagrilintide and 2.4 mg semaglutide) or tirzepatide (15 mg)
    - **CagriSema failed to demonstrate non-inferiority to tirzepatide in weight reduction**
    - After 84 weeks, patients taking CagriSema had **23%** weight reduction while those taking tirzepatide had **25.5%** weight reduction

- **REIMAGINE-2**: 68 week trial comparing A1c reduction and weight loss between patients taking CagriSema, semaglutide monotherapy, cagrilintide monotherapy, or placebo
  - After 68 weeks, patients taking CagriSema experienced 1.91% reduction in A1c vs. semaglutide monotherapy patients who experienced 1.76% reduction
  - Patients taking CagriSema experienced a 14.2% weight loss vs. semaglutide monotherapy patients who experienced 10.2% reduction

1. https://www.novonordisk.com/content/nncorp/global/en/news-and-media/news-and-ir-materials/news-details.html?id=916

PF-08653944

- Weekly/**monthly** subcutaneous injection
- **Ultra-long acting** GLP-1 agonist
- Ten Phase 3 trials expected in 2026
- **VESPER-3**: an ongoing Phase 2b trial in adults with obesity or overweight without T2DM for 64 weeks
  - Endpoints: Demonstrate PF'3944 could achieve continued weight loss when switching from weekly to monthly subcutaneous injections and maintain its efficacy while reducing the dosing frequency four-fold
    - Demonstrate PF'3944 could switch to a four-fold equivalent monthly dose while maintaining a well-tolerated and favorable safety profile
  - **Weekly dosing until week 12, then monthly dosing to week 28**
  - Results: continuous weight loss after switching to monthly dosing, no plateau observed at week 28, continued weight loss expected through week 64
  - Participants were randomized across four titration protocols:
    - Arm 1 (0.4 mg QW/ 0.8 mg QW/ 3.2 mg QM);
    - Arm 2 (0.8 mg QW/ 3.2 mg QM);
    - Arm 3 (0.4 mg QW/ 0.8 mg QW/ 1.2 mg QW / 4.8 mg QM);
    - Arm 4 (0.6 mg QW/ 1.2 mg QW/ 4.8 mg QM); or
    - Arm 5 (placebo)

1.Pfizer. (February 3, 2026). Pfizer's Ultra-Long-Acting Injectable GLP-1 RA Shows Robust and Continued Weight Loss with Monthly Dosing in Phase 2b Trial. https://www.pfizer.com/news/press-release/press-release-detail/pfizers-ultra-long-acting-injectable-glp-1-ra-shows-robust

AbbVie Clinical Trials

WHAT ARE THE CLINICAL TRIAL PHASES?

SAFETY

Is the investigational medication/treatment safe?

- Are there side effects?
- How does it affect or move through the body?
- Is it safe to use at the same time as other medications?

Who's in it?
Small group of healthy people—generally less than 100

Lasts several months to 1 year

PHASE 1

EFFICACY

Is the investigational medication/treatment effective in treating the targeted condition?

- Does it relieve, reverse or stop the progression of the condition?
- How safe is it?
- What is the most effective dosage?

Who's in it?
Generally 100-300 people with the exact condition being studied

Lasts 1 to 2 years

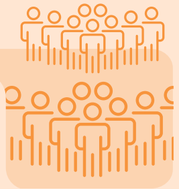
PHASE 2

FOLLOW UP

After the investigational medication/ treatment is approved, how does it work for other patients with the condition?

- More safety/efficacy information is gathered
- Are there long-term benefits?
- Are there long-term risks?

Who's in it?
Often several thousand people who have been prescribed the investigational medication



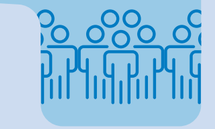
PHASE 4

CONFIRMATION

How does the investigational medication/ treatment compare to the standard treatment for the condition?

- More effective, less effective, or the same?
- Longer-term adverse effects?
- How does it affect quality of life, or survival?
- How might it be used along with existing treatments?

Who's in it?
Often 300-3,000 people with the exact condition being studied



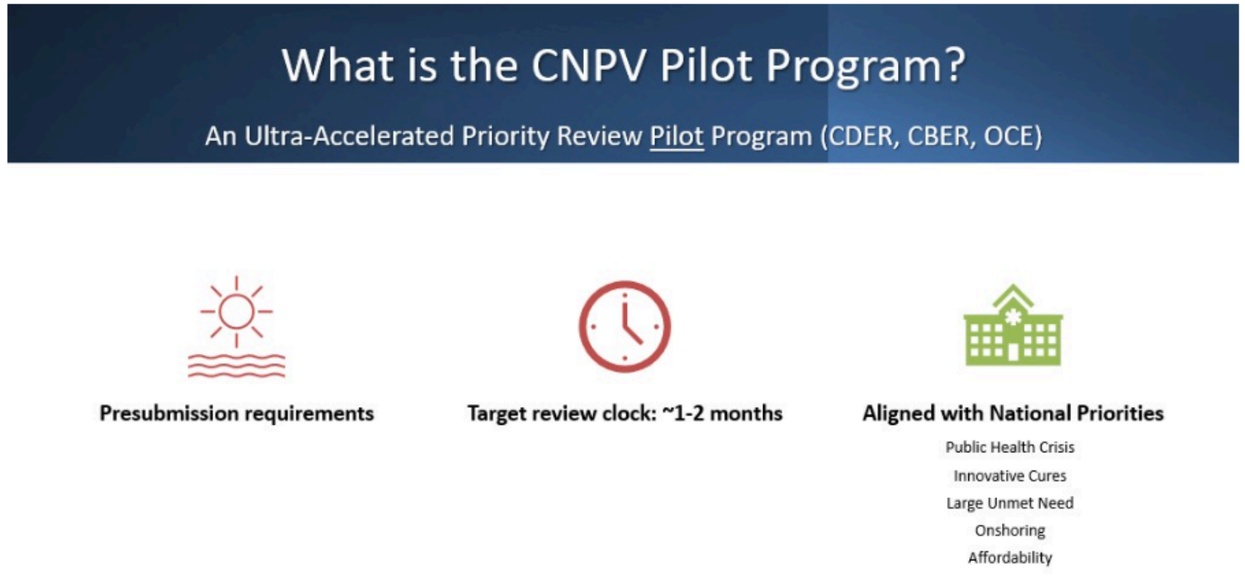
Lasts 1 to 4 years

PHASE 3

Visit AbbvieClinicalTrials.com | Visit ClinicalTrials.gov | Talk to your healthcare provider

FDA Accelerated Approval Program

- **C**ommissioner's **N**ational **P**riority **V**oucher (**CNPV**) pilot program - announced in June 2025
  - Can shorten a drug's review time by the FDA from 10-12 months to 1-2 months after submitting a New Drug Application (NDA)



CNPV Compared To Other FDA Priority Review Programs

- Ultra-fast timeline – 1-2 months target vs. 6+ months
- Nontransferable vouchers
- Enhanced presubmission requests to facilitate expedited rolling review
- Multidisciplinary "tumor board-style" discussion between review team and senior agency leadership

1. https://www.fda.gov/drugs/nda-and-bla-approvals/accelerated-approval-program

FDA Accelerated Approval Program

Which drugs can participate:

This innovative program uses a collaborative tumor board-style review process to accelerate review and approval of products that align with one of five critical U.S. national health priorities:

Public health crisis response

- Products addressing urgent/emerging threats or significant population impact.

Innovative breakthrough therapies

- Transformative treatments with novel mechanisms that fundamentally change disease management.

Large unmet medical needs

- Therapies for conditions where existing treatments inadequately address patient outcomes.

Onshoring and supply chain resilience

- Onshoring drug development/manufacturing to strengthen U.S. domestic capacity, reduce foreign dependencies, and improve national security.

Affordability

- Approaches that improve overall value through reduced costs to the healthcare system or that enhance access to important products.

*****Receipt of a voucher does not impact the likelihood of approval.*****

1. https://www.fda.gov/drugs/nda-and-bla-approvals/accelerated-approval-program

FDA Accelerated Approval Program

First voucher recipients under CNPV pilot program announced October 16, 2025

- **Pergoveris** for infertility
- **Teplizumab** for Type I diabetes
- **Cytisinicline** for nicotine vaping addiction
- **DB-OTO** for deafness
- **Cenegermin-bkbj** for blindness
- **RMC-6236** for pancreatic cancer
- **Bitopertin** for porphyria
- **Ketamine** for domestic manufacturing of a critical drug for general anesthesia
- **Augmentin XR** for domestic manufacturing of a common antibiotic

Second voucher recipients under CNPV pilot program announced November 6, 2025

- **Zongertinib** for HER2 lung cancer
- **Bedaquiline** for drug-resistant tuberculosis in young children
- **Dostarlimab** for rectal cancer
- **Casgevy** for sickle cell disease
- **Wegovy for obesity and related health conditions**
- **Orforglipron for obesity and related health conditions**

These voucher recipients will receive a decision within 1-2 months after filing a complete application
Otherwise, this process takes a standard of 10-12 months

1. https://www.fda.gov/drugs/nda-and-bla-approvals/accelerated-approval-program

Recent CNPV approvals

Wegovy HD (semaglutide, 7.2mg injection)

- Approval of already existing drug
- The approval was granted just **54 days after filing**, compared with the standard 10- to 12-month review timeline

Foundayo (orforglipron, tablet)

- First new molecular entity approved under CNPV program
- FDA approval issued **50 days after filing** — and 294 days before the application's PDUFA date of January 20, 2027
  - PDUFA: (Prescription Drug User Fee Act) date is the FDA's goal date for making a final decision—approval or rejection—on a new drug application

1. https://www.fda.gov/news-events/press-announcements/fda-approves-first-new-molecular-entity-under-national-priority-voucher-program

What happens when you stop?

Maintenance Therapy

WHAT IS ALREADY KNOWN ON THIS TOPIC

The development of highly effective weight management medications (WMMs) has transformed the treatment of obesity

Real world observations estimate that around 50% of people with obesity discontinue WMMs within 12 months

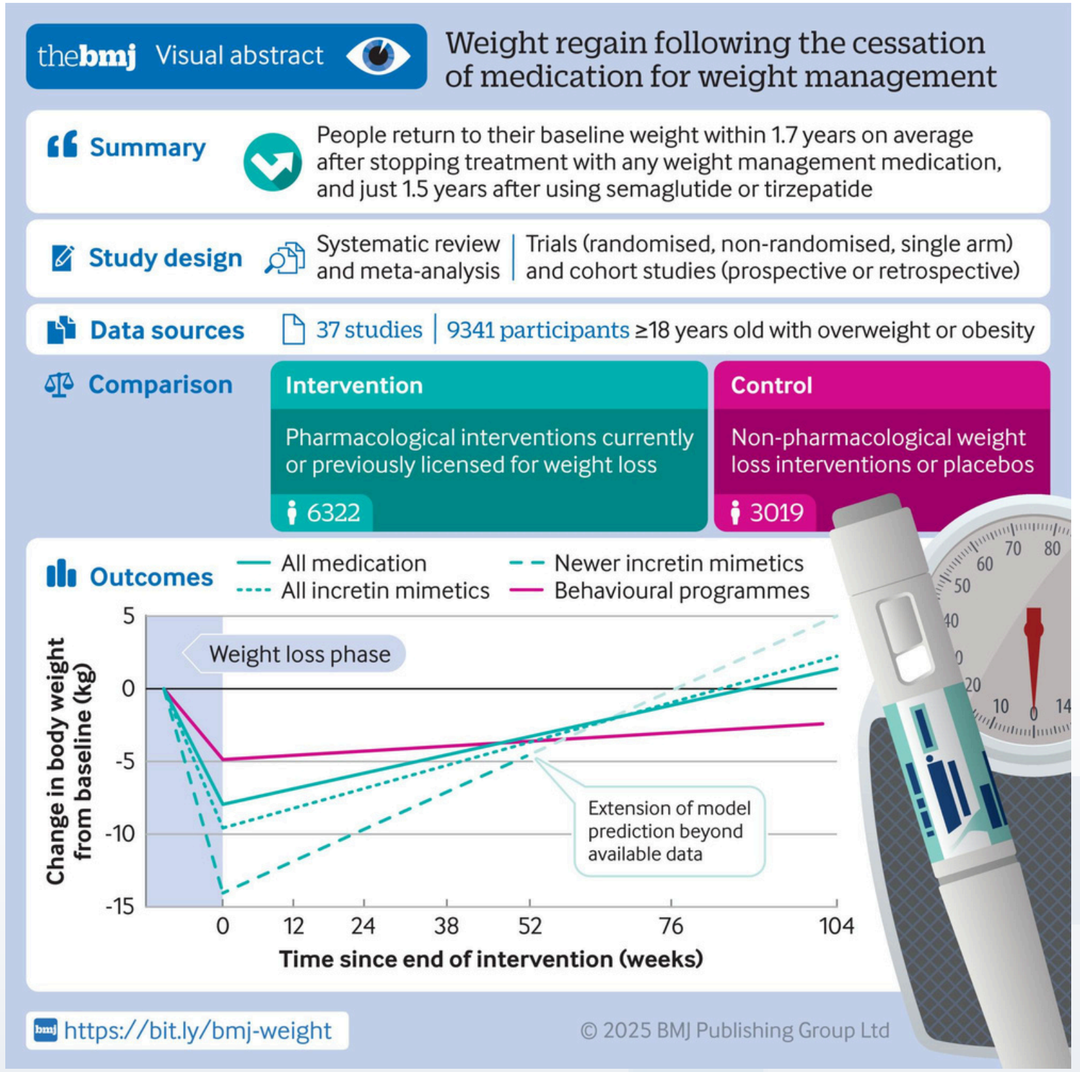
A previous systematic review quantified and compared the rate of weight regain with behavioural weight management programmes (BWMPs)

WHAT THIS STUDY ADDS

People on average regain weight at a rate of 0.4 kg/month after cessation of WMMs, leading to a projected return to baseline weight after 1.7 years

Although weight loss resulted in improvements in HbA_{1c}, fasting glucose, total cholesterol, triglycerides, systolic and diastolic blood pressure, all markers returned to baseline within 1.4 years of treatment cessation

The rate of weight regain after the cessation of WMMs was faster than after the cessation of BWMPs, independent of the amount of weight lost during treatment



1. West S, Scragg J, Aveyard P, et al. Weight regain after cessation of medication for weight management: systematic review and meta-analysis. BMJ. 2026;392:e085304. Published 2026 Jan 7. doi:10.1136/bmj-2025-085304

Key Takeaways

The GLP-1 RA landscape is evolving rapidly — from new formulations and higher doses to entirely new therapeutic entities.

What's here now: Wegovy HD (7.2 mg injection), oral Wegovy tablets, and Foundayo (orforglipron), the first oral, non-peptide GLP-1 RA, have all reached the market, with FDA-approved indications spanning obesity, T2DM, MACE risk reduction, CKD, OSA, and MASH.

What's coming: Retatrutide (triple agonist), CagriSema (GLP-1 + amylin), and monthly-dosed options like Pfizer's PF-08653944 are in late-stage development and could reshape treatment paradigms within the next 12 to 18 months.

What to watch for: Emerging research in addiction, Alzheimer's prevention, osteoarthritis, asthma, cancer, and PCOS suggests GLP-1 RA mechanisms extend well beyond metabolic disease, though most remain early-phase and off-label.

THANK YOU

QUESTIONS?

Cody Gao: cgao@shieldsrx.com
Elliot Ogorek: eogorek@shieldsrx.com
Sharon Zhu: szhu@shieldsrx.com