EMERGING PHARMACOLOGIC MEDICATIONS FOR THE TREATMENT OF OBESITY

From appetite suppression to multi-receptor metabolic therapeutics

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Internal Medicine

Critical Care Medicine

Diplomat of American Board of Obesity Medicine

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COI Disclosures (Dr. Stephen Glazer)

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- Novo Nordisk, Eli Lilly, Bausch Health, Idorsia, Ontario Bariatric Network
- **Other**:
- Medical Director Bariatric Medical and Surgical Program Humber River Hospital.

FINANCIAL BIAS

MITIGATE BIAS

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THE OPENING ARGUMENT

A vast clinical need is becoming a major therapeutic market

Prevalence, economic burden and drug demand are rising together.

890M

adults living with obesity worldwide (2022)

$4.32T

annual global impact projected by 2035

$105B

2030 obesity-drug sales estimate

$190B

2035 diabetes + obesity GLP-1 market

WHY NEED WILL OUTRUN SUPPLY

- Only a minority of eligible patients currently receive evidence-based pharmacotherapy
- Long-term persistence, affordability and equitable access remain limiting
- **Next wave competes on efficacy, convenience, tolerability, outcomes—and manufacturability**

Sources: WHO 2025; World Obesity Federation 2023/2025; Reuters Feb 2026; Morgan Stanley Apr 2026.

A USEFUL MAP

The pipeline is solving four different problems

Efficacy is only one dimension of innovation.

MORE SIGNALS

Retatrutide
Survodutide

GLP-1 + GIP/glucagon

Clinical question →

Can efficacy exceed 25%?

AMYLIN SYNERGY

CagriSema
Amycretin

Satiety + incretin

Clinical question →

Can satiety be amplified?

EASIER DELIVERY

Orforglipron

Oral, no food/water restriction

Clinical question →

Can pills broaden access?

LESS FREQUENT

MariTide

Monthly injection potential

Clinical question →

Can persistence improve?

Benchmarks: semaglutide and tirzepatide are established therapies, not the focus of this emerging-agent review.

MECHANISM & SITE OF ACTION

TRIPLE AGONIST

Retatrutide

Satiety, insulinotropic and energy-expenditure pathways in one peptide

RECEPTOR / SIGNAL	PRINCIPAL SITES	PHYSIOLOGIC EFFECT
GLP-1 receptor	Brain • pancreas • GI	Satiety; glucose-dependent insulin; slower gastric emptying
GIP receptor	Pancreas • adipose • CNS	Insulinotropic and central satiety signaling
Glucagon receptor	Liver • adipose • CNS	Energy expenditure and hepatic lipid mobilization

NON–WEIGHT-LOSS BENEFITS / SIGNALS

- **HbA1c reduction up to ~1.9 points in phase 3 T2D data**
- Marked liver-fat, lipid and blood-pressure improvements
- Less knee-OA pain and better function in TRIUMPH-4; partly weight mediated

Sources: NEJM 2023; Nature Medicine 2024; Lilly phase 3 disclosures, 2025–2026.

PHASE 3 • INVESTIGATIONAL

WEEKLY SC

Retatrutide

Once-weekly GLP-1/GIP/glucagon receptor triple agonist

EVIDENCE

TRIUMPH-1 & TRIUMPH-4

Phase 3; adults with obesity (TRIUMPH-1) and obesity + knee OA (TRIUMPH-4).

28.3% at 80 wk

TRIUMPH-1, 12 mg efficacy estimand; 45.3% achieved ≥30%.
TRIUMPH-4: 28.7% at 68 weeks plus improved OA pain.

CLINICAL PEARLS

1. **First phase 3 program to show mean weight reduction in the high-20% range.**
2. Glucagon activity may raise energy expenditure—but may also shape heart-rate and tolerability monitoring.
3. Topline company data: await full peer review, regulatory review and long-term outcomes.

Sources: Lilly, TRIUMPH-1 (21 May 2026) and TRIUMPH-4 (11 Dec 2025); phase 2 NEJM 2023.

MECHANISM & SITE OF ACTION

AMYLIN + GLP-1

CagriSema

Amylin satiety signaling plus GLP-1 incretin biology

RECEPTOR / SIGNAL	PRINCIPAL SITES	PHYSIOLOGIC EFFECT
Amylin receptor	Area postrema • hindbrain	Satiation; smaller meals; slower gastric emptying
GLP-1 receptor	Brain • pancreas • GI	Appetite reduction; insulin ↑; glucagon ↓
Combined signal	Brain–gut–pancreas axis	Complementary satiety and metabolic control

NON–WEIGHT-LOSS BENEFITS / SIGNALS

- **HbA1c reduction 1.91 points in REIMAGINE 2**
- Systolic BP fell 10.9 mmHg in REDEFINE 1 analysis
- hsCRP and modeled CV-risk improved; outcomes remain unproven

Sources: NEJM 2025; Hypertension 2026; Novo Nordisk REIMAGINE 2, Feb 2026.

PHASE 3 • INVESTIGATIONAL

WEEKLY SC

CagriSema

Fixed-dose cagrilintide (amylin analogue) + semaglutide (GLP-1 RA)

EVIDENCE

REDEFINE 1

Phase 3, n≈3,400; obesity/overweight without diabetes; 68 weeks.

22.7% at 68 wk

If adherent: 22.7% vs 16.1% semaglutide, 11.8% cagrilintide, 2.3% placebo. Treatment-policy: 20.4% vs 3.0%.

CLINICAL PEARLS

1. **Amylin + GLP-1 is complementary satiety biology, not simply “more GLP-1.”**
2. Only 57.3% reached the maximum dose—dose flexibility and real-world tolerability matter.
3. Use the correct estimand: 22.7% assumes adherence; 20.4% reflects treatment policy.

Source: Garvey et al., NEJM 2025, REDEFINE 1; Novo Nordisk disclosures.

MECHANISM & SITE OF ACTION

SELECTIVE AMYLIN AGONIST

Eloralintide

Selective amylin-receptor agonism activates hindbrain satiety pathways

RECEPTOR / SIGNAL	PRINCIPAL SITES	PHYSIOLOGIC EFFECT
Amylin receptor →	Area postrema • NTS →	Satiation; smaller meals; reduced food intake
Downstream signaling →	Hypothalamic circuits • GI →	Appetite regulation and gastric-emptying effects
Selective pathway →	Hindbrain–hypothalamus axis →	Reduced intake through non-incretin satiety biology

NON–WEIGHT-LOSS BENEFITS / SIGNALS

- **Waist circumference and cardiometabolic markers improved**
- Weight reduction was driven predominantly by fat-mass loss
- Distinct pathway may complement future incretin combinations

Source: Briere et al., DOM 2025; Billings et al., Lancet 2025; Lilly updates.

PHASE 3 • INVESTIGATIONAL

WEEKLY SC

Eloralintide

Once-weekly selective, long-acting amylin receptor agonist

EVIDENCE

PHASE 2

Phase 2, n=263 adults without diabetes; 48 weeks.

Up to 20.1% at 48 wk

9 mg regimen vs 0.4% placebo; dose-responsive reduction.

CLINICAL PEARLS

1. **Selective amylin agonism offers a non-incretin approach to appetite regulation.**
2. Slower dose escalation improved tolerability; nausea and fatigue were usually mild to moderate.
3. Phase 3 is underway; no regulatory approval has been granted.

Source: Billings et al., Lancet 2025; ClinicalTrials.gov; Lilly updates.

MECHANISM & SITE OF ACTION

ORAL GLP-1 RA

Orforglipron (Foundayo)

Oral small-molecule activation of GLP-1 receptors

RECEPTOR / SIGNAL		PRINCIPAL SITES		PHYSIOLOGIC EFFECT
GLP-1 receptor	→	Hypothalamus • hindbrain	→	Hunger reduction and greater satiation
GLP-1 receptor	→	Pancreatic β/α cells	→	Glucose-dependent insulin ↑; glucagon ↓
GLP-1 receptor	→	Stomach • vagal axis	→	Slower gastric emptying, especially early

NON–WEIGHT-LOSS BENEFITS / SIGNALS

- **HbA1c reductions up to ~1.8 points in phase 3 T2D trials**
- Improved BP, waist and atherogenic lipid measures
- Unrestricted oral administration may broaden access and persistence

Sources: NEJM 2025; FDA Foundayo prescribing information 2026; ATTAIN/ACHIEVE trials.

APPROVED IN US • EMERGING ROLLOUT

DAILY ORAL

Orforglipron

Once-daily oral, nonpeptide small-molecule GLP-1 receptor agonist

EVIDENCE

ATTAIN-1

Phase 3, n=3,127; obesity/overweight without diabetes; 72 weeks.

12.4% at 72 wk

36 mg efficacy estimand vs 0.9% placebo; 39.6% achieved ≥15%.
GI events drove dose-related discontinuation.

CLINICAL PEARLS

1. **No injection and no food/water timing restriction: a scalability and access play.**
2. Efficacy is below leading injectables, but convenience may improve initiation and reach.
3. Do not confuse formulation convenience with absence of class GI effects or contraindications.

Source: Wharton et al., NEJM 2025 (ATTAIN-1); current regulatory status checked Aug 2026.

MECHANISM & SITE OF ACTION

GLP-1 ↑ • GIP-R ↓

MariTide

Sustained GLP-1 agonism paired with GIP-receptor antagonism

RECEPTOR / SIGNAL	PRINCIPAL SITES	PHYSIOLOGIC EFFECT
GLP-1 agonism	CNS • pancreas • GI	Satiety; insulin ↑; glucagon ↓; gastric emptying ↓
GIP-R antagonism	Adipose • pancreas • CNS	Modulates GIP signaling and energy storage
Antibody conjugate	Systemic • ~21-day half-life	Sustained exposure for monthly dosing

NON–WEIGHT-LOSS BENEFITS / SIGNALS

- **Improved HbA1c and fasting glucose in participants with T2D**
- Improved BP, lipids and cardiometabolic risk markers
- Monthly dosing may improve adherence; outcomes unproven

Sources: NEJM 2025; Amgen phase 2 ADA presentation 2025; MARITIME program.

PHASE 3 • INVESTIGATIONAL

MONTHLY SC

MariTide

Long-acting GLP-1 agonism + GIP receptor antagonism

EVIDENCE

Phase 2 MariTide study

Randomized phase 2; obesity with and without type 2 diabetes; 52 weeks.

≈20% at 52 wk

Without diabetes: up to ~20% vs 2.6% placebo; with diabetes: up to ~17% vs 1.4%. No plateau at week 52.

CLINICAL PEARLS

1. **The mechanistic twist is GIP antagonism—opposite direction from tirzepatide—paired with GLP-1 agonism.**
2. Monthly dosing could improve persistence, but early nausea/vomiting and dose escalation remain important.
3. Long half-life may be a benefit for adherence and a challenge if adverse effects occur.

Sources: Jastreboff et al., NEJM 2025; Amgen phase 2 presentation, June 2025.

MECHANISM & SITE OF ACTION

DUAL AGONIST

Survodutide

GLP-1 appetite signaling plus glucagon-driven hepatic metabolism

RECEPTOR / SIGNAL	PRINCIPAL SITES	PHYSIOLOGIC EFFECT
GLP-1 receptor	Brain • pancreas	Satiety and glucose-dependent insulin secretion
Glucagon receptor	Liver	Lipid oxidation and increased energy expenditure
Dual signal	Brain–liver axis	Reduced intake plus increased metabolic flux

NON–WEIGHT-LOSS BENEFITS / SIGNALS

- **Large liver-fat and visceral-fat reductions in phase 3 imaging**
- Improved HbA1c in obesity with T2D
- MASH benefit is plausible and under dedicated study

Sources: Lancet Diabetes Endocrinol 2024; SYNCHRONIZE-1/2 disclosures 2026.

PHASE 3 • INVESTIGATIONAL

WEEKLY SC

Survodutide

Once-weekly GLP-1/glucagon receptor dual agonist

EVIDENCE

SYNCHRONIZE-1

Phase 3; obesity/overweight without diabetes; 76 weeks.

16.6% at 76 wk

Top dose, actual treatment: 16.6% vs 2.6% placebo; substantial visceral and liver-fat reductions reported.

CLINICAL PEARLS

1. **Glucagon biology may be particularly relevant when obesity coexists with MASLD/MASH.**
2. Body-composition and liver-fat signals may matter beyond the scale.
3. Phase 3 efficacy is meaningful but below triple-agonist topline results; outcomes and phenotype may differentiate it.

Sources: Boehringer Ingelheim phase 3 disclosure Apr/Jun 2026; le Roux et al., Lancet D&E 2024.

MECHANISM & SITE OF ACTION

UNIMOLECULAR DUAL

Amycretin

A single molecule co-activates GLP-1 and amylin receptors

RECEPTOR / SIGNAL		PRINCIPAL SITES		PHYSIOLOGIC EFFECT
GLP-1 receptor	→	Brain • pancreas • GI	→	Appetite reduction and glucose-dependent insulin
Amylin receptor	→	Area postrema • hindbrain	→	Satiation; meal-size reduction; gastric emptying ↓
Combined molecule	→	Brain–gut–pancreas axis	→	Synchronized dual signaling; SC and oral programs

NON–WEIGHT-LOSS BENEFITS / SIGNALS

- **HbA1c reduction about 1.8 points in phase 2 T2D study**
- Up to 89.1% achieved HbA1c <7% in 2026 program data
- Oral and weekly-SC options are being developed

Sources: Lancet 2025; Novo Nordisk phase 2 T2D disclosure 2025 and ADA 2026 update.

ADVANCING TO PHASE 3 • INVESTIGATIONAL

WEEKLY SC / ORAL

Amycretin

Single molecule with GLP-1 receptor + amylin receptor agonism

EVIDENCE

Phase 1b/2a

Small, dose-escalation studies; adults with overweight/obesity; up to 36 weeks.

22.0% at 36 wk

SC 20 mg cohort: estimated 22.0% loss vs 2.0% gain with placebo. Early oral program also supports dual-route development.

CLINICAL PEARLS

1. **Unimolecular design may simplify dual-hormone delivery versus co-formulation.**
2. The striking efficacy signal comes from small, early-phase cohorts—uncertainty remains high.
3. Watch dose selection, tolerability, durability and whether oral exposure can match injectable performance.

Sources: Dahl et al., Lancet 2025; Novo Nordisk phase 1b/2a disclosure Jan/Jun 2025.

MECHANISM & SITE OF ACTION

VK2735

DUAL AGONIST

Dual GLP-1/GIP agonism in injectable and oral development

RECEPTOR / SIGNAL	PRINCIPAL SITES	PHYSIOLOGIC EFFECT
GLP-1 receptor	Brain • pancreas • GI	Satiety; insulin ↑; glucagon ↓; gastric emptying slows
GIP receptor	Pancreas • adipose • CNS	Glucose-dependent insulin and complementary central signaling
Dual signal	Brain–gut–pancreas axis	Coordinated appetite and glycemic effects

NON–WEIGHT-LOSS BENEFITS / SIGNALS

- **Improved fasting glucose and cardiometabolic markers in early trials**
- Oral and injectable formulations may broaden treatment choice
- Phase 3 VANQUISH program is evaluating durability and safety

Sources: Bays et al., Obesity 2026; Viking VENTURE and VANQUISH updates, 2024–2026.

PHASE 3 • INVESTIGATIONAL

WEEKLY SC / ORAL

VK2735

Dual GLP-1/GIP agonism in injectable and oral development

EVIDENCE

VENTURE

Phase 2, n=176; adults with obesity; weekly SC treatment for 13 weeks.

14.7% at 13 wk

Highest dose; placebo-adjusted reduction up to 13.1%. No weight-loss plateau observed.

CLINICAL PEARLS

1. **Rapid early efficacy is promising, but 13 weeks is too short to predict long-term outcomes.**
2. Oral phase 2 achieved up to 12.2% at 13 weeks; GI tolerability and discontinuation require attention.
3. VANQUISH phase 3 will establish durability, broader safety and real-world relevance.

Sources: Bays et al., Obesity 2026; Viking VENTURE and VANQUISH updates, 2024–2026.

MECHANISM & SITE OF ACTION

GLP-1 + GLP-2

Dapiglutide

Dual GLP-1/GLP-2 agonism links appetite regulation with intestinal biology

RECEPTOR / SIGNAL	PRINCIPAL SITES	PHYSIOLOGIC EFFECT
GLP-1 receptor	**Brain • pancreas • GI**	Satiety; insulin ↑; glucagon ↓; gastric emptying slows
GLP-2 receptor	**Intestinal epithelium • gut**	Trophic and barrier effects; altered nutrient handling
Dual signal	**Brain–gut axis**	Appetite suppression plus intestinal signaling

NON–WEIGHT-LOSS BENEFITS / SIGNALS

- **Potential intestinal-barrier and mucosal effects remain mechanistic hypotheses**
- Early glycemic and cardiometabolic signals were exploratory
- Program paused in 2025; no demonstrated outcomes benefit

Sources: Zealand Pharma phase 1b reports, 2024–2025; Nielsen et al., eClinicalMedicine 2026.

PROGRAM PAUSED • PHASE 2–READY

WEEKLY SC

Dapiglutide

Dual GLP-1/GLP-2 agonism links appetite regulation with intestinal biology

EVIDENCE

Phase 1b dose escalation

Small early-phase cohorts; weekly dosing for 13–28 weeks; predominantly male participants.

11.6% at 28 wk

Highest escalation cohort to 26 mg; no lifestyle intervention. Program later paused.

CLINICAL PEARLS

1. **GLP-2 biology differentiates dapiglutide, but its added clinical value in obesity is unproven.**
2. The 28-week result came from a small, 95%-male cohort without a concurrent placebo arm.
3. Current status matters: Zealand paused development in 2025 amid a crowded pipeline.

Sources: Zealand Pharma phase 1b reports, 2024–2025; Nielsen et al., eClinicalMedicine 2026.

MECHANISM & SITE OF ACTION

ACTRII ANTIBODY

Bimagrumab

Activin type II receptor blockade acts directly on skeletal muscle and adipose tissue

RECEPTOR / SIGNAL	PRINCIPAL SITES	PHYSIOLOGIC EFFECT
ActRIIA / ActRIIB blockade →	Skeletal muscle →	Myostatin/activin signaling ↓; anabolic lean-mass effect
ActRII / ALK7 pathway →	Adipose tissue →	Lipid mobilization and fat-mass reduction
With GLP-1 therapy →	Muscle–adipose–brain →	Appetite reduction plus preferential adiposity loss

NON–WEIGHT-LOSS BENEFITS / SIGNALS

- **Preserved or increased lean mass while reducing adiposity**
- Reduced visceral and intrahepatic fat in phase 2 studies
- Potentially higher-quality weight loss; physical-function benefit unproven

Source: Heymsfield et al., Nature Medicine 2026; BELIEVE NCT05616013.

PHASE 2 • INVESTIGATIONAL

IV / SC DEVELOPMENT

Bimagrumab

Activin type II receptor blockade acts directly on skeletal muscle and adipose tissue

EVIDENCE

BELIEVE

Phase 2, n=507; bimagrumab, semaglutide, combinations or placebo; 48–72 weeks.

22.1% at 72 wk

High-dose combination; fat mass −45.7%, lean mass −2.9% vs −7.4% with semaglutide alone.

CLINICAL PEARLS

1. **This is a body-composition strategy—not an appetite suppressant.**
2. At week 72, 92.3% of combination weight loss was fat mass versus 71.1% with semaglutide.
3. DXA lean mass is not muscle strength: functional benefit still needs direct demonstration.

Source: Heymsfield et al., Nature Medicine 2026; BELIEVE NCT05616013.

MECHANISM & SITE OF ACTION

DUAL AGONIST

Mazdutide

Dual GLP-1/glucagon agonism targets appetite and hepatic energy metabolism

RECEPTOR / SIGNAL	PRINCIPAL SITES	PHYSIOLOGIC EFFECT
GLP-1 receptor	Brain • pancreas • GI	Satiety; insulin ↑; glucagon modulation; gastric emptying slows
Glucagon receptor	Liver • adipose	Lipid oxidation, energy expenditure and hepatic-fat reduction
Dual signal	Brain–liver axis	Reduced intake plus increased metabolic flux

NON–WEIGHT-LOSS BENEFITS / SIGNALS

- **Beneficial changes across prespecified cardiometabolic measures**
- Substantial liver-fat reductions reported in GLORY-1 imaging analyses
- Improved glycemic control in T2D phase 3 studies

Source: Ji et al., NEJM 2025 (GLORY-1); Innovent regulatory and phase 3 updates.

APPROVED IN CHINA • 2025

WEEKLY SC

Mazdutide

Dual GLP-1/glucagon agonism targets appetite and hepatic energy metabolism

EVIDENCE

GLORY-1

Phase 3, n=610 Chinese adults with overweight/obesity; 48 weeks.

14.0% at 48 wk

Mazdutide 6 mg vs 0.3% placebo; 49.5% achieved ≥15% weight reduction.

CLINICAL PEARLS

1. **GLP-1/glucagon biology may be attractive when obesity coexists with MASLD or dysglycemia.**
2. GLORY-1 provides published phase 3 evidence, but generalizability beyond the Chinese population needs study.
3. Approved in China in 2025; regulatory status differs internationally.

Source: Ji et al., NEJM 2025 (GLORY-1); Innovent regulatory and phase 3 updates.

Move from “Which causes most weight loss?” to “Which creates durable health gain?”

1

OUTCOMES

CV, kidney, OSA, OA, MASH—not weight alone

2

TOLERABILITY

Slow titration, GI burden, discontinuation, reversibility

3

BODY COMPOSITION

Preserve muscle, strength and function during treatment

4

PERSISTENCE

Route, frequency, cost, coverage and supply

5

LIFE COURSE

Chronic treatment, weight regain, pregnancy planning, older age

TAKE-HOME

Five conclusions for the next era of obesity pharmacotherapy

01 Efficacy is approaching bariatric territory for selected multi-agonists.

02 Oral and monthly options may expand reach more than another few efficacy points.

03 Amylin and glucagon pathways are now central, not peripheral to the pipeline.

04 Estimands, adherence and trial phase matter when interpreting headline percentages.

05 **The next differentiator is durable complication reduction with preserved function.**

The future is not one “best” drug but it is precision, persistence and proven outcomes.

Key sources: WHO; World Obesity Federation; NEJM/Lancet pivotal publications; sponsor phase 3 disclosures through 31 Aug 2026.