

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

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COI Disclosures (Dr. Stephen Glazer)

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- Medtronic, Bariatric Advantage, Leo Pharmaceuticals

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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**

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

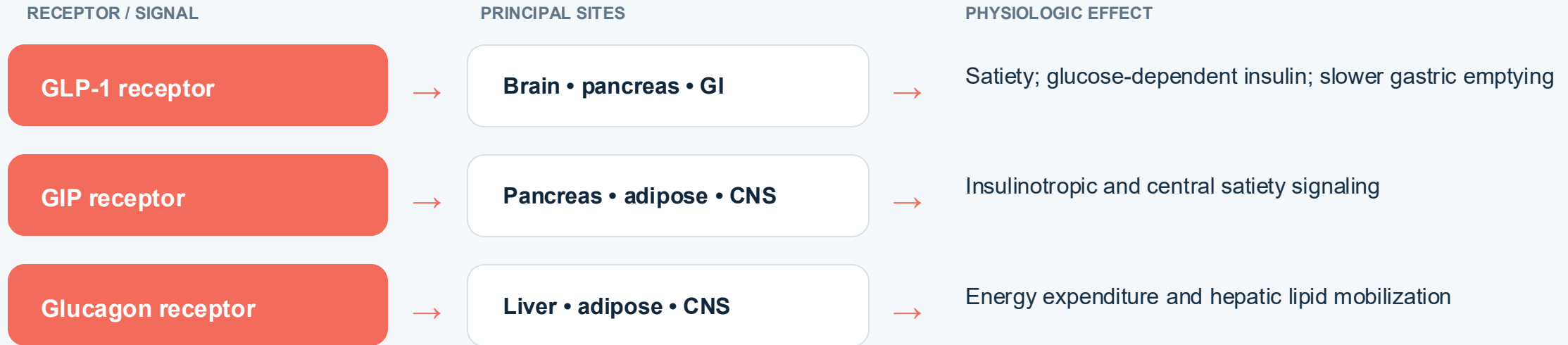
Monthly injection potential

Clinical question →

Can persistence improve?

Retatrutide

Satiety, insulinotropic and energy-expenditure pathways in one peptide



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

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 $\geq 30\%$.
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

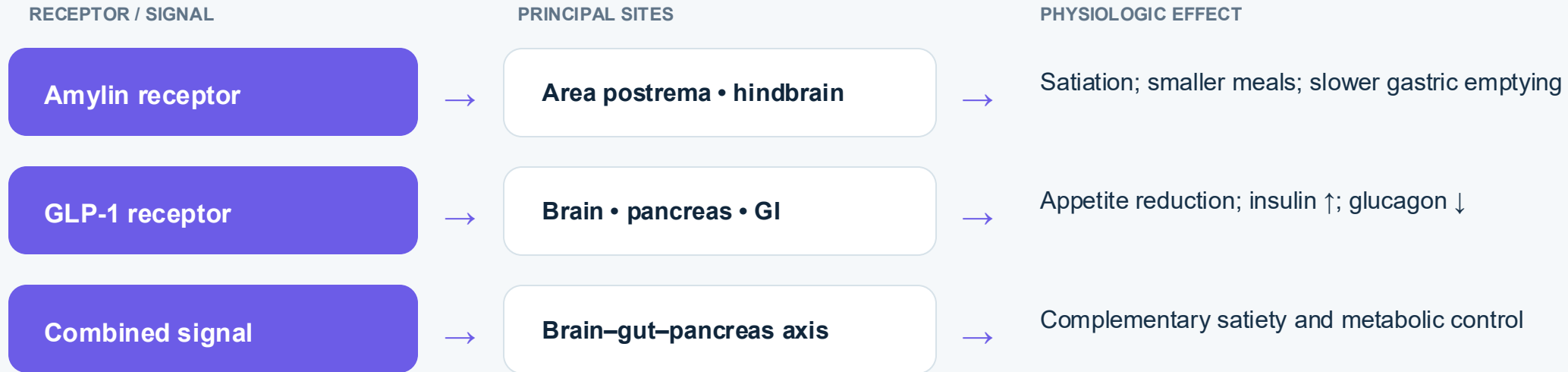
Glucagon activity may raise energy expenditure—but may also shape heart-rate and tolerability monitoring.

3

Topline company data: await full peer review, regulatory review and long-term outcomes.

CagriSema

Amylin satiety signaling plus GLP-1 incretin biology



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

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

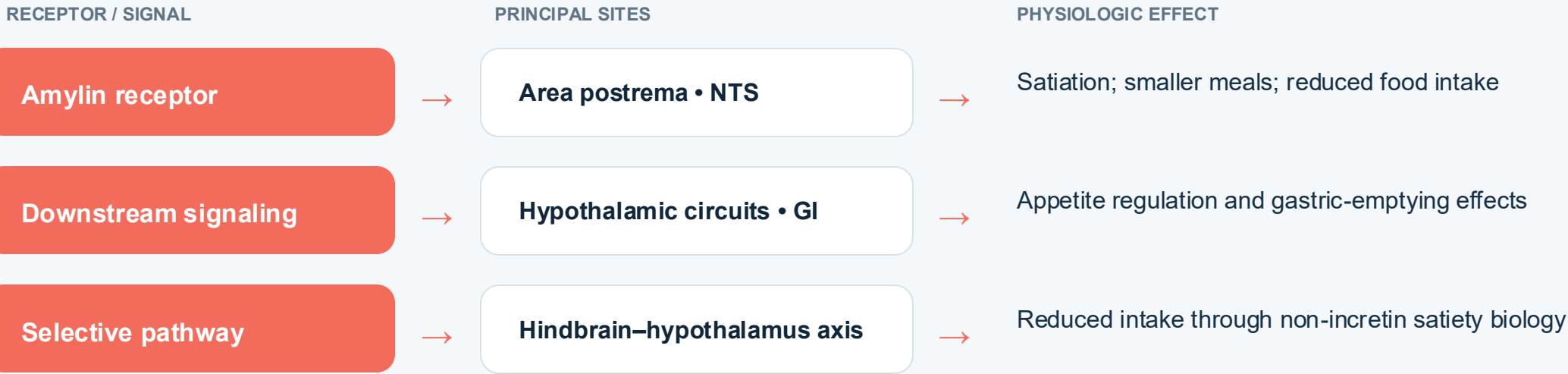
Only 57.3% reached the maximum dose—dose flexibility and real-world tolerability matter.

3

Use the correct estimand: 22.7% assumes adherence; 20.4% reflects treatment policy.

Eloralintide

Selective amylin-receptor agonism activates hindbrain satiety pathways



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

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

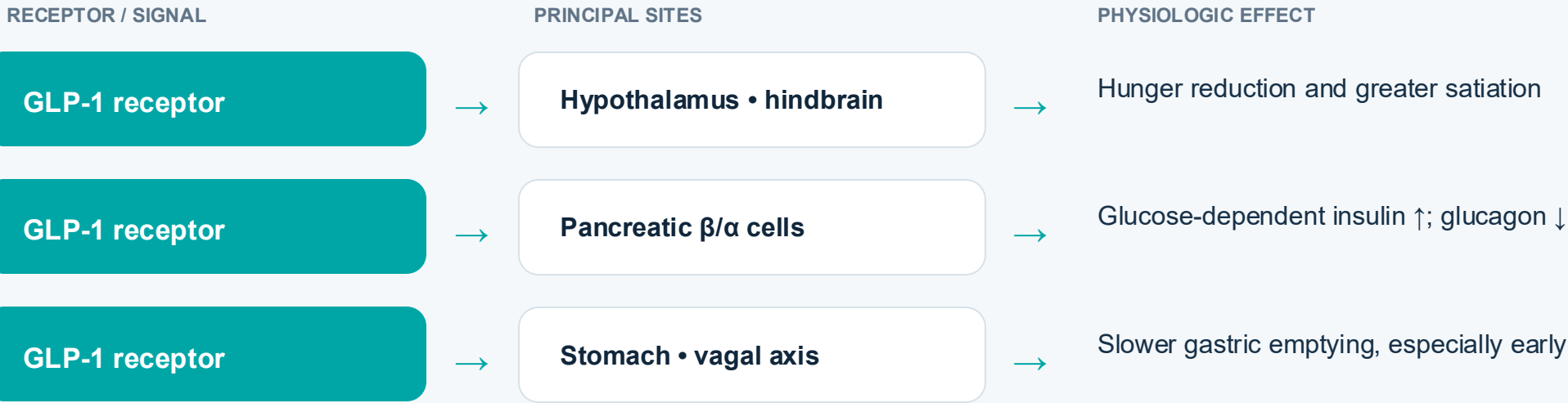
Slower dose escalation improved tolerability; nausea and fatigue were usually mild to moderate.

3

Phase 3 is underway; no regulatory approval has been granted.

Orforglipron (Foundayo)

Oral small-molecule activation of GLP-1 receptors



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

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 $\geq 15\%$.
GI events drove dose-related discontinuation.

CLINICAL PEARLS

1

No injection and no food/water timing restriction: a scalability and access play.

2

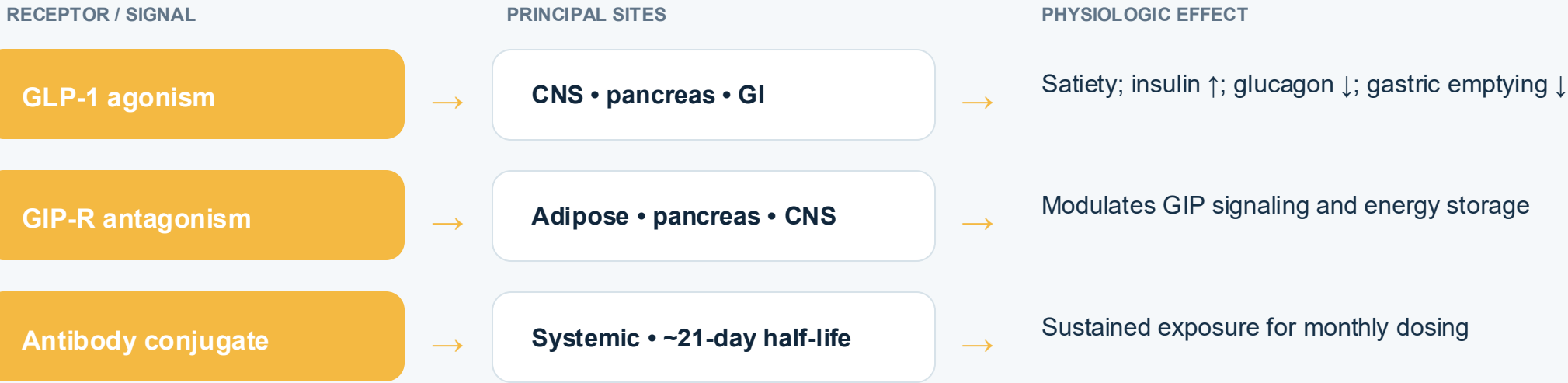
Efficacy is below leading injectables, but convenience may improve initiation and reach.

3

Do not confuse formulation convenience with absence of class GI effects or contraindications.

MariTide

Sustained GLP-1 agonism paired with GIP-receptor antagonism



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

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.

Survodutide

GLP-1 appetite signaling plus glucagon-driven hepatic metabolism



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

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

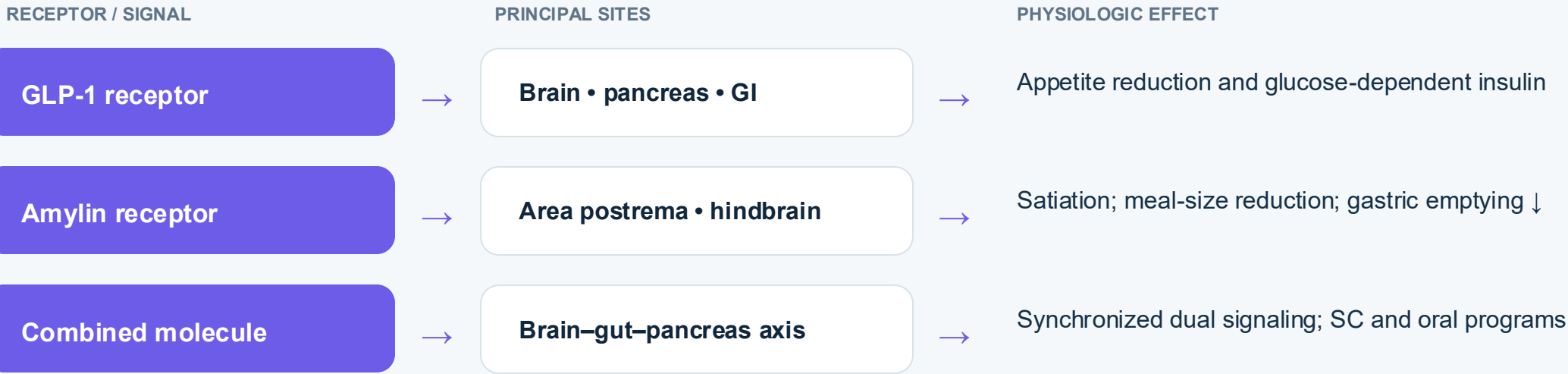
Body-composition and liver-fat signals may matter beyond the scale.

3

Phase 3 efficacy is meaningful but below triple-agonist topline results; outcomes and phenotype may differentiate it.

Amycretin

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



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

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

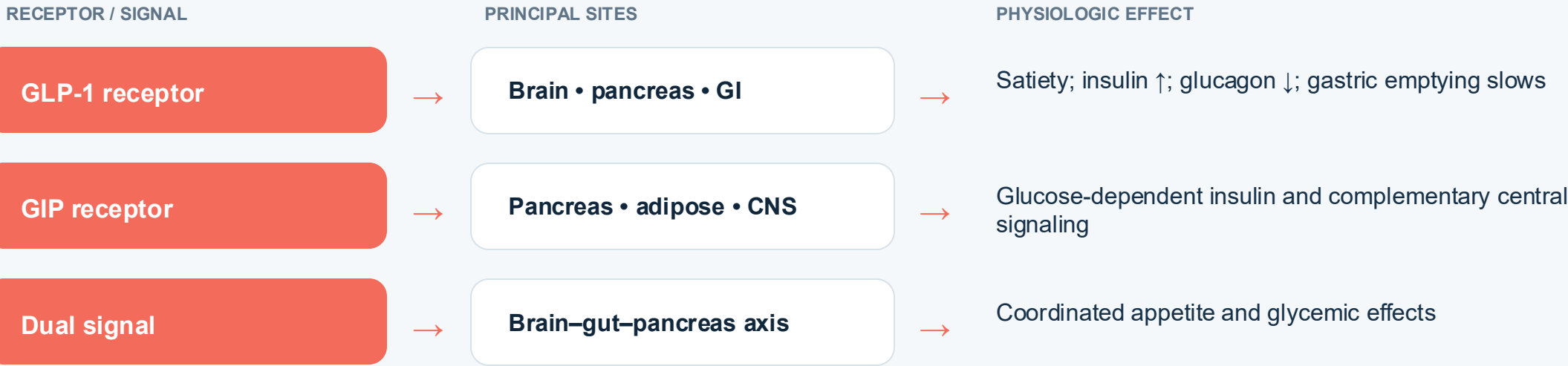
The striking efficacy signal comes from small, early-phase cohorts—uncertainty remains high.

3

Watch dose selection, tolerability, durability and whether oral exposure can match injectable performance.

VK2735

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



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

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

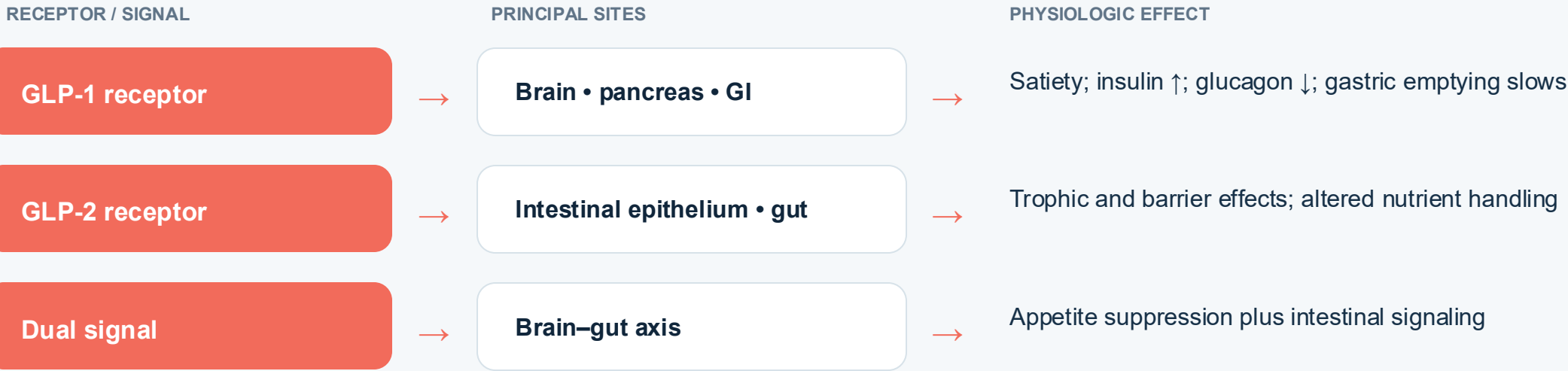
Oral phase 2 achieved up to 12.2% at 13 weeks; GI tolerability and discontinuation require attention.

3

VANQUISH phase 3 will establish durability, broader safety and real-world relevance.

Dapiglutide

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



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

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

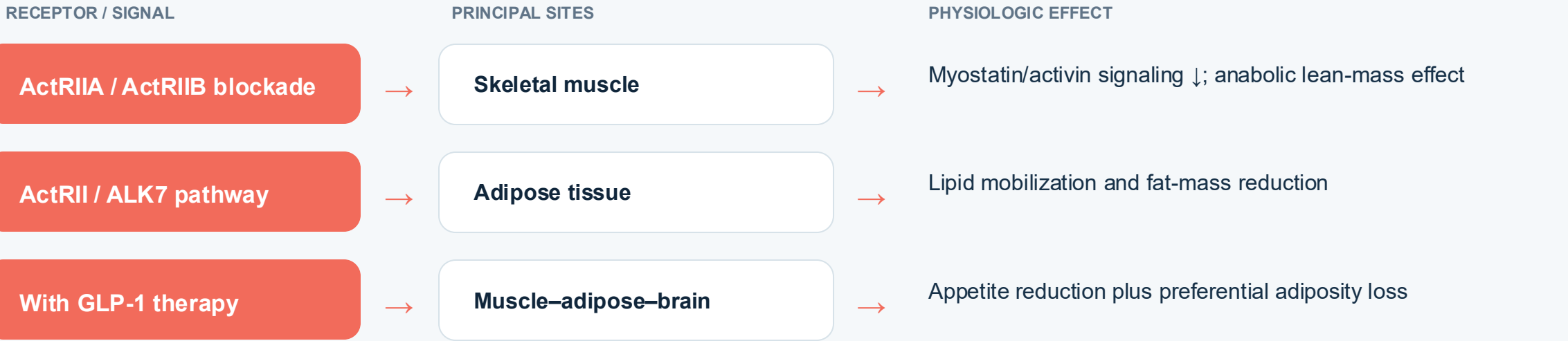
The 28-week result came from a small, 95%-male cohort without a concurrent placebo arm.

3

Current status matters: Zealand paused development in 2025 amid a crowded pipeline.

Bimagrumab

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



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

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

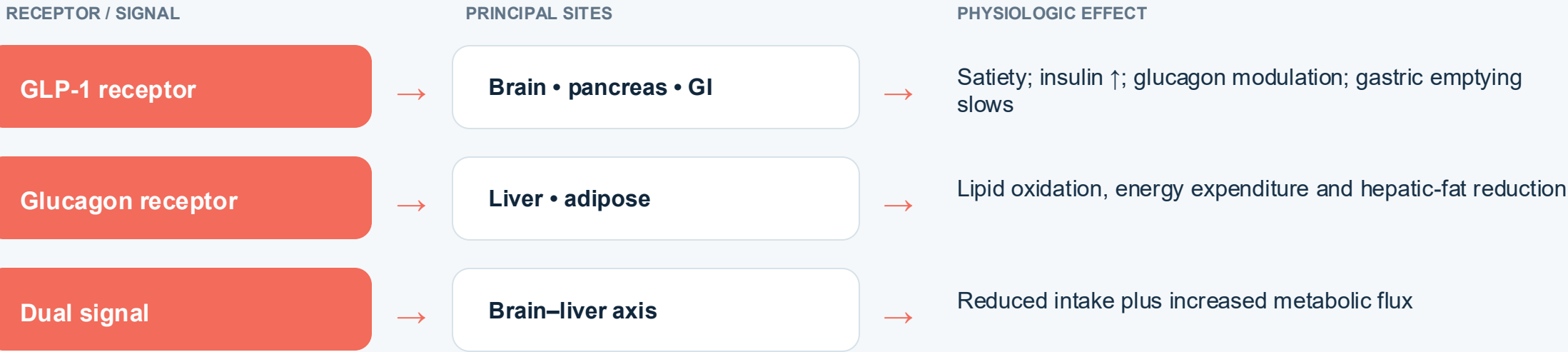
At week 72, 92.3% of combination weight loss was fat mass versus 71.1% with semaglutide.

3

DXA lean mass is not muscle strength: functional benefit still needs direct demonstration.

Mazdutide

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



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

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 $\geq 15\%$ 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.

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

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.