



GLP-1s and beyond

The commercial success of GLP-1 receptor agonists has reshaped the biopharma investment landscape at a speed and scale with few modern parallels. The global GLP-1 market is estimated at \$50–90 billion in 2025, depending on scope and methodology. That commercial signal has pulled capital in at every level, with individual licensing agreements now reaching \$5–6 billion, and the Pfizer/Metsera acquisition valued a single clinical-stage company at approximately \$10 billion. More than 150 companies are now active in the GLP-1 drug ecosystem,¹ developing next-generation incretin therapies, combining GLP-1 receptor agonism with additional hormonal pathways, including glucose-dependent insulinotropic polypeptide (GIP), glucagon, and amylin signaling. At the same time, the industry is exploring how oral medicines will fit into the injectable obesity market.

As illustrated in Figure 1, successive generations of peptide agents have steadily increased average weight-loss efficacy, with newer multi-agonist approaches pushing beyond 20% reductions in body weight. The competitive landscape now includes hundreds of obesity assets spanning a wide range

of modalities, creating one of the most crowded therapeutic fields in drug development.

This whitepaper explores emerging differentiation strategies and asks where innovation is likely to create value in an increasingly crowded landscape. Throughout this review, we use the term “GLP-1 space” broadly to include adjacent incretin and metabolic approaches that are frequently developed alongside or in combination with GLP-1 receptor agonism, including GIP-based therapies, glucagon-containing multi-agonists, amylin analogs, and combination strategies designed to improve treatment outcomes, such as reducing lean muscle loss. We do not, however, attempt to comprehensively review all obesity-related therapeutic mechanisms, including approaches targeting leptin, melanocortin signaling, inflammation, cannabinoid receptors, thermogenesis, gut microbiome modulation, or other emerging non-incretin pathways. Instead, our focus is on understanding how the GLP-1 revolution has reshaped the treatment landscape and where the next wave of differentiation may emerge.

WEIGHT LOSS IN OBESITY

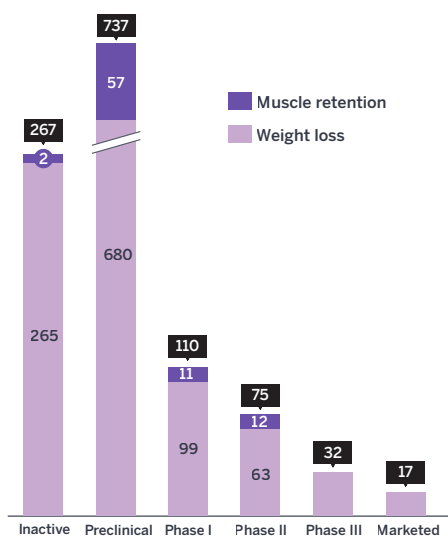
● Agonist ● Antagonist

MARKETED

LATE STAGE DEVELOPMENT

Asset, Company	Highest Phase	GLP1R	GIPR	GCGR	AMYR	RoA	Frequency	Modality	Weight Loss	Time	Source
Semaglutide 7.2 mg, Novo Nordisk	Mrk	●				SC	QW	Peptide	20.7%	72w	PhIII STEP UP
Tirzepatide, Eli Lilly	Mrk	●	●			SC	QW	Peptide	20.2%	72w	PhIII SURMOUNT-1
Semaglutide oral, Novo Nordisk	Mrk	●				PO	QD	Peptide	16.6%	64w	PhIII OASIS-4
Semaglutide 2.4 mg, Novo Nordisk	Mrk	●				SC	QW	Peptide	15%	68w	PhIII STEP 1
Orforglipron, Eli Lilly	Mrk	●				PO	QD	SMOL	12.4%	72w	PhIII ATTAIN-1
Retatrutide, Eli Lilly	PhIII	●	●	●		SC	QW	Peptide	28.3%	80w	PhIII TRIUMPH-1
CagriSema, Novo Nordisk	Pre-Reg	●			●	SC	QW	Peptide	22.7%	68w	PhIII REDEFINE-1
Enicepatide/CT-388, Roche	PhIII	●	●			SC	QW	Peptide	22.5%	48w	PhII
Eloralintide, Eli Lilly	PhIII	●			●	SC	QW	Peptide	20.1%	48w	PhII
Ribupatide, Hengrui & Kailera	PhIII	●	●			SC	QW	Peptide	19.2%	48w	PhIII in China
Survodutide, Boehringer Ingelheim	PhIII	●		●		SC	QW	Peptide	16.6%	76w	PhIII SYNCHRONIZE-1
Maridebart, Amgen	PhIII	●	●			SC	QM	Peptide-Ab	16.2%	52w	PhII
VK2735, Viking Therapeutics	PhIII	●	●			SC	QW	Peptide	14.7%	13w	PhII VENTURE
Aleniglipron, Structure Therapeutics	PhIII	●				PO	QD	SMOL	12.1%	36w	PhIb ACCESS
Elecoglipron, AstraZeneca	PhIII	●				PO	QD	SMOL	11.8%	36w	PhII VISTA
HRS-7535, Hengrui & Kailera	PhIII	●				PO	QD	SMOL	11.1%	50w	PhIII in China
Petrelintide, Roche	PhIII				●	SC	QW	Peptide	10.7%	42w	PhIb ZUPREME-1

FULL OBESITY PIPELINE



MUSCLE RETENTION PIPELINE

■ MSTN ■ ActA ■ ACTRIIA/B ■ ACVR1C ■ INHBE ■ AR ■ APJ ■ CRHR2 ■ MAS1L ■ Alternative Targets

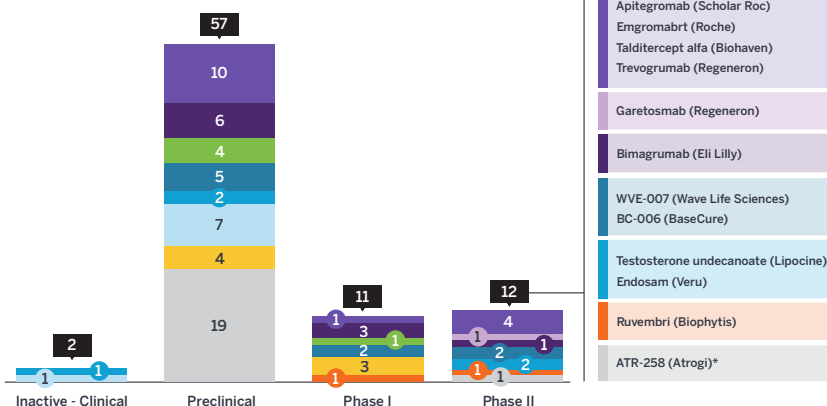


Figure 1: GLP-1 Related Development in Obesity

Panel A: Weight Loss in Obesity

The figure depicts a selected, non-exhaustive list of assets in the space, compared by reported weight loss. Only trials conducted in obesity/overweight populations are shown. Trials in type 2 diabetes are not included. Each asset is specified by development stage, mechanism of action (GLP1R, GIPR, GCGR and AMYR agonism or antagonism), route of administration, dosing frequency and modality. It is intended as an illustrative overview of the field rather than a comprehensive catalogue. Weight-loss values are not perfectly comparable across rows, as figures depend on which estimand is reported and on whether they are placebo-adjusted. Numbers quoted elsewhere may therefore differ slightly.

Panel B: Obesity Pipeline

The left panel depicts the obesity pipeline by highest development stage, split into weight-loss and muscle-retention focused strategies. Assets with an unspecified strategy are bucketed under weight loss. Note the axis break on the preclinical bar. The right panel shows the muscle-retention pipeline split by target, with assets and their companies indicated for the latest development stage reached (Phase II). "Alternative targets" groups mechanisms not shown individually. *Atrig's ATR-258 in Phase II is a β 2-adrenoceptor agonist.

ActA: activin A; **ACTRIIA/B:** activin receptor type IIA/IIB; **ACVR1C:** activin A receptor type 1C (ALK7); **AMYR:** amylin receptor; **APJ:** apelin receptor; **AR:** androgen receptor; **CRHR2:** corticotropin-releasing hormone receptor 2; **GCGR:** glucagon receptor; **GIPR:** glucose-dependent insulinotropic polypeptide receptor; **GLP1R:** glucagon-like peptide-1 receptor; **INHBE:** inhibin subunit beta E (activin E); **MAS1L:** MAS1-like G-protein-coupled receptor; **Mrk:** marketed; **MSTN:** myostatin; **Peptide-Ab:** peptide-antibody conjugate; **PO:** oral; **Pre-Reg:** pre-registration; **QD:** once daily; **QM:** once monthly; **QW:** once weekly; **RoA:** route of administration; **SC:** subcutaneous; **SMOL:** small molecule; **Data updated as of August 2026.**

Differentiating Strategies

The discovery of GLP-1 transformed our understanding of metabolic regulation. Identified in the 1980s as an incretin hormone that stimulates glucose-dependent insulin secretion, GLP-1 quickly emerged as an attractive therapeutic target for diabetes. Yet despite the biological promise, early attempts to harness the pathway faced a fundamental obstacle: native GLP-1 was practically undruggable. Following secretion from the gut, the peptide is rapidly degraded by dipeptidyl peptidase-4 (DPP-4) and cleared by the kidneys, resulting in a circulating half-life of only one to two minutes.² The history of GLP-1 therapeutics is, therefore, largely a story of pharmacokinetic engineering. The field progressed through a series of innovations designed to extend drug exposure. The first approved GLP-1 receptor agonist (GLP-1RA) was exenatide, a synthetic version of a 39-mer peptide isolated from the saliva of Gila monster that is more resistant to DPP-4 degradation.³ Unfortunately, its circulatory half-life remained relatively short requiring twice-daily subcutaneous injections. Subsequent generations introduced amino acid substitutions and fatty-acid conjugation strategies that increased albumin binding and prolonged circulation. These advances extended half-life from minutes to hours and eventually to days, enabling the once-weekly administration schedules that define today's leading products. What began as a challenge in peptide chemistry ultimately laid the foundation for one of the most commercially successful therapeutic classes in modern medicine.

Although GLP-1RAs were initially developed for type 2 diabetes (T2D), weight loss rapidly emerged as a clinically meaningful effect. Early agents such as exenatide and liraglutide demonstrated modest reductions in body weight, but the field's understanding of what was pharmacologically achievable shifted with dose. Astrup et al.'s 2009 phase II dose-ranging trial of liraglutide in non-diabetic individuals with obesity was the first study designed explicitly to interrogate the dose-weight loss relationship.⁴ It was established that 3.0 mg produced meaningfully greater weight loss than the 1.8 mg diabetes dose. That finding prompted the SCALE phase III program and the eventual approval of liraglutide 3.0 mg as Saxenda.⁵ Unfortunately, Saxenda's impact was limited. Approximately 8% weight loss over 56 weeks was clinically meaningful but not transformative, and a demanding daily injection schedule compounded the barrier to uptake.

Semaglutide's data reframed what GLP-1 receptor agonists could be. Initial data from the seminal STEP1 trial of semaglutide 2.4 mg showed body weight reduction by 12.4% relative to placebo in people with obesity without T2D.⁶ For the first time, pharmacological interventions produced levels of weight loss previously associated primarily with bariatric

surgery. These data led to its FDA approval for chronic weight management in 2021 as an adjunct to a reduced-calorie diet and increased physical activity, about seven years after the approval of liraglutide (Saxenda).⁷ Efficacy then improved to 20.7% with the 7.2 mg dose, earning another FDA approval in 2026.⁸ Now clinical trials routinely report double-digit percentage reductions in body weight, transforming obesity from a therapeutic area characterized by repeated disappointments into one of the most attractive opportunities in the pharmaceutical industry. Today, obesity has overtaken oncology as the largest contributor to late-stage pharmaceutical pipeline value, highlighting how rapidly the field has evolved from scientific curiosity to commercial powerhouse.⁹

Yet despite this remarkable progress, the field appears increasingly constrained, not by a lack of efficacy, but by a different question: how much weight loss is enough, and when does more stop being better? While incremental improvements remain possible, the relationship between efficacy and clinical value is becoming less straightforward. Increasingly potent therapies are often accompanied by higher rates of gastrointestinal adverse events, treatment discontinuation, and concerns regarding the consequences of rapid or extreme weight reduction.^{10,11} As weight-loss percentages approach levels once thought unattainable with medicine, simply maximizing efficacy no longer represents the most meaningful measure of therapeutic success. This raises a broader strategic question for the field: if greater weight loss alone is unlikely to define the next generation of winners, which strategies will set therapies apart? Several potential answers are beginning to emerge.

One area of increasing interest addresses a challenge that remains largely unresolved: what happens after successful weight loss? Long-term maintenance of weight reduction remains difficult,^{12,13} and dedicated maintenance therapies may ultimately become a distinct opportunity separate from weight-loss induction itself. A second approach focuses on improving side effects and limitations of existing therapies, especially regarding gastrointestinal (GI) tolerability and the quality of weight loss achieved. Body composition studies consistently show that a substantial proportion of weight lost during therapy is lean tissue rather than adipose tissue alone.¹⁴ It is worth noting that clinical evidence directly linking this lean mass loss to adverse functional outcomes remains limited. The concern is biologically plausible and warrants attention, but it has not yet been proved to be detrimental, particularly in adults under 65. Substantial effort is nonetheless being directed toward preserving skeletal muscle and other components of lean body mass while maintaining the metabolic benefits of weight reduction. A third strategy seeks

to expand the utility of GLP-1-based therapies beyond obesity itself. Researchers are evaluating the role of these agents across a growing range of indications, including cardiovascular, liver, and chronic kidney disease, as well as neurodegenerative, neuropsychiatric, and numerous other disorders.¹⁵

The Unsolved Problem of Weight Maintenance

Professional guidance has converged on a single conclusion: obesity is a chronic, relapsing disease requiring indefinite management rather than a finite course of therapy. The 2025 American Association of Clinical Endocrinology consensus statement puts it without qualification, describing adiposity-based chronic disease as a condition that necessitates long-term treatment and care.¹⁶ But real-world practice looks different. In a large US cohort of prescribed GLP-1RA, more than half discontinued within one year and nearly three-quarters within two years.¹³ Tolerability, injection burden, cost, coverage restrictions, and unresolved questions around indefinite exposure all contribute to discontinuation. The result is a mismatch at the center of obesity care: chronic therapy in principle, interrupted treatment in practice. And despite this reality, there are still no widely established, evidence-based protocols designed specifically to prevent or manage weight regain after GLP-1 discontinuation. That gap, more than the depth of initial weight loss, may become the defining problem of the next phase of obesity treatment.

Weight regain is not an exception; it is an expected trajectory. In Novo Nordisk's STEP 1 extension (company-sponsored), participants who stopped semaglutide regained roughly two-thirds of their lost weight within one year, with cardiometabolic improvements in blood pressure, lipids, and glycemia reversing in parallel.¹² Eli Lilly's SURMOUNT-4 trial (company-sponsored) showed the same pattern with tirzepatide (GLP-1RA x GIPRA): patients switched to placebo regained 14.0% of body weight over the following year, while those continuing therapy lost an additional 5.5% and 89.5% maintained at least 80% of their lead-in weight loss.¹⁷ A 2026 systematic review and meta-regression further reinforced the pattern, finding that weight regain begins soon after GLP-1RA cessation and, at one year, averages around 60% of the weight lost during treatment.¹⁸ Two observations are worth emphasizing. First, weight gain is rarely complete within the follow-up periods studied, with patients retaining at least a portion of their initial weight loss. Second, the trajectory of regain is highly heterogeneous, varying by agent, treatment duration, magnitude of initial weight loss, and likely by underlying patient biology and behavior.

Why does the weight come back?

One explanation could be biological counter-regulation. From decades of calorie-restriction studies, we know that weight loss can trigger a durable defense response: appetite increases, satiety signals weaken, and energy expenditure falls below what would be predicted by body size alone. Sumithran and colleagues showed that one year after diet-induced weight loss, appetite-regulating hormones, including leptin, peptide YY, cholecystokinin, insulin, ghrelin, and gastric inhibitory polypeptide, remained shifted in a direction favoring regain, while subjective hunger remained elevated.¹⁹ Adaptive thermogenesis is similarly persistent, still measurable six years after substantial weight loss.²⁰ Bariatric surgery reinforces the same point but also complicates it. Surgery remains more durable than current pharmacotherapy, yet regain still occurs. In the Swedish Obese Subjects cohort, gastric bypass produced maximal weight loss of 32% at one to two years, settling at 25% at ten years.²¹ This shows that even anatomical restriction can be partly overridden.

Yet a purely biological explanation is incomplete. Behavior also measurably alters the trajectory. In the Danish S-LiTE program, regain one year after treatment discontinuation was higher in patients on liraglutide (GLP-1RA) alone versus liraglutide combined with exercise,²² and dietary restraint and physical activity independently predicted less regain.²³ One additional concern cuts across both biology and behavior: a meaningful fraction of weight lost on incretin monotherapy is lean mass (see section on Lean Mass Loss), and because muscle contributes to resting energy expenditure and functional reserve, poor body composition could plausibly increase regain risk.¹⁴

Biology and behavior are not competing explanations. Weight regain after GLP-1 discontinuation likely reflects the interaction between these various aspects. Current withdrawal trials show us that regain happens. They do not yet tell us how much is driven by endocrine rebound, metabolic adaptation, reduced adherence to lifestyle change, loss of medication access, or simple removal of the drug's active appetite-suppressive effect.

A further unanswered question concerns not how much weight returns, but what kind of tissue it is. While substantial attention has focused on the proportion of lean mass lost during incretin-induced weight loss, there are very limited data on the composition of the regained weight after treatment discontinuation. Determining whether patients primarily regain fat mass, lean mass, or a combination of both could have major implications for maintenance strategies, muscle-preserving therapies, and future obesity drug development.

What can be done to address weight regain?

Three opportunities are emerging. First, muscle-sparing combinations that aim to preserve lean mass while maximizing fat loss, potentially improving long-term durability if body composition influences regain risk.²⁴ Preserving muscle addresses the composition problem directly and, if the energy-expenditure link holds, may reduce regain propensity as well. Related activin and myostatin pathway agents are moving through development on the same thesis. The second is amylin-based combinations, which aim for deeper, potentially better-composed loss. Amylin biology is associated with reduced metabolic adaptation and lean-mass sparing, though dedicated maintenance data are still absent. The third is maintenance-specific therapy: agents or regimens designed not to maximize initial loss but to hold a reduced set-point, ideally orally, at low cost, and with side effects mild enough for years of use. This space remains largely empty, but the first data are beginning to appear. The phase IIb ATTAIN-MAINTAIN trial showed that patients could be switched from injectable incretins to oral orforglipron (a small-molecule GLP-1RA) and hold their loss, with those coming off semaglutide maintaining all but 0.9 kg, and 75–79% maintaining weight against 38–49% on placebo.²⁵ Dedicated maintenance trials are also running for monthly dosing and for amylin-based regimens. What remains genuinely uncontested is novel maintenance mechanisms: structured step-down protocols, non-incretin approaches to energy expenditure, and fixed-duration induction followed by a cheaper, less toxic maintenance agent.

For researchers, the open question is mechanistic: what drives weight regain after pharmacological weight loss, and does the answer differ by drug class, patient biology, or treatment duration? For biopharma and investors, this is the less crowded problem. The initial weight-loss market is increasingly contested, while durable maintenance remains largely unaddressed: partly because maintenance trials are harder to design and longer to run, and partly because the field has not yet agreed on what maintenance even requires biologically. The companies that solve durability, not just efficacy, will define the next generation of obesity care.

Gastrointestinal Tolerability as a Bottleneck

As drugmakers look for ways to prevent weight regain and extend the duration of treatment for patients on GLP-1-based therapies, one issue increasingly demands attention because of how directly it contributes to discontinuation: gastrointestinal side effects such as nausea, vomiting, and diarrhea. This is not an isolated or drug-specific concern. It is a safety signal detected consistently across the majority of trials in the GLP-1 space and confirmed by multiple independent meta-analyses. A 2025 network meta-analysis of 39 trials and more than 33,000 non-diabetic patients with overweight or

obesity found that every therapy evaluated, including amylin-based agents within the broader GLP-1 space as defined earlier in this paper, significantly increased nausea risk, with relative risks ranging from roughly 2.3-fold for cagrilintide (a long-acting amylin analogue) to nearly 4.8-fold for orforglipron relative to placebo; vomiting, diarrhea, and constipation followed similar, drug-dependent patterns.²⁶ A 2026 umbrella review spanning 1,751 randomized trials and 3.6 million patients reached the same conclusion at a far larger scale: GLP-1 therapy carries roughly 2.5 times the odds of nausea, 2.8 times the odds of vomiting, and twice the odds of diarrhea relative to control, the single most consistent, highest-certainty safety finding across the entire drug class.²⁷

The biology behind these effects, while still being actively investigated, is coming into focus. Some of the beneficial effects of GLP-1 therapies are mediated through peripheral signaling in the gastrointestinal tract itself, but a substantial share of the drugs' efficacy depends on direct action in the central nervous system: by engaging receptors in the hypothalamus and hindbrain, GLP-1 suppresses appetite signaling and slows gastric emptying. The same drugs, however, also act on a separate brain region, the area postrema, believed to drive the aversive, nausea-producing responses that underlie many of the observed GI effects.^{2,28} That these effects appear to arise from at least partially distinct neural circuits is what has opened the door to the mitigation strategies described below: if satiety and aversion can be pharmacologically dissociated, so, in principle, can efficacy and tolerability.

Several patterns in the clinical data are now well established. GI adverse events scale with dose, and they appear largely independent of route of administration: oral and subcutaneous semaglutide show statistically indistinguishable GI tolerability once differences in circulating drug exposure are accounted for.²⁸ Symptoms are also not confined to treatment initiation. While GI adverse events peak during the first weeks of therapy and around each dose escalation, a meaningful share of patients continues to report gastrointestinal symptoms for as long as they remain on treatment.²⁹ The consequence is measurable in real-world adherence: as many as 20% of patients discontinue GLP-1 therapy specifically because of GI side effects,²⁶ and more than half of all patients discontinue treatment of any kind within a year of starting, with tolerability being one of several contributing factors alongside cost and patients reaching their personal weight goals.^{2,14} Because discontinuation is also the strongest predictor of subsequent weight regain, GI tolerability issues are not only a burden in their own right; they feed directly into the weight maintenance problem described in the preceding section.

Finding ways to deal with GI toxicity

Two mitigation strategies are currently being pursued to tackle GI toxicity associated with GLP-1 therapies. The first, already standard clinical practice, is pharmacokinetic: slower, more gradual dose titration measurably reduces GI adverse events without compromising eventual efficacy once the full therapeutic dose is reached, though a meaningful fraction of patients still report tolerability issues even with optimized titration.² The second targets the receptor biology itself. Co-agonism at the GIP receptor, alongside the GLP-1 receptor, has shown promising effects in reducing GI toxicity, particularly nausea and vomiting. Preclinical mechanistic work suggests that GIP-receptor-expressing neurons in the area postrema may inhibit the very circuits responsible for the aversive GLP-1 signal.^{2,29} The clearest causal test of the hypothesis comes from a controlled study that added a selective long-acting GIPR agonist on top of a fixed dose of liraglutide: relative to adding a placebo, this reduced total GI adverse events by roughly 16% and nausea by roughly 15%, with no comparable effect on diarrhea.³⁰ Consistent with this, the dual GLP-1R x GIPR agonist tirzepatide has shown an improved tolerability profile in its pivotal SURMOUNT-1 trial, even at the highest tested dose relative to single-target semaglutide in its pivotal STEP1 trial, with lower rates of nausea (31% vs. 44%), vomiting (12% vs. 25%), and diarrhea (23% vs. 32%).^{6,31} However, the picture might not always be as clear as it may seem. Despite substantial differences in the adverse event profile between tirzepatide and semaglutide in their pivotal studies, a direct head-to-head comparison between the two compounds in patients with obesity found a meaningful difference in GI-related adverse events only for vomiting (15% vs. 21%) but not for nausea (44% vs. 44%) or diarrhea (24% vs. 23%).³²

Evidence from other GLP1-RA x GIP dual agonists now in development is directionally supportive but not uniform. Kailera's ribupatide (GLP1RA x GIP) illustrates how much titration matters on its own: in a titrated phase II trial of the oral formulation, nausea ranged from 11.9% to 22.7% and vomiting from 2.4% to 11.4% across doses, at or below what is typically reported for GLP-1 monoagonists.³³ A separate phase I study that gave a single subcutaneous dose without any titration told a very different story: nausea in 61.5% of participants and vomiting in 35.9%, with the planned dose escalation curtailed early after several participants met a stopping rule for moderate-or-greater nausea.³⁴ Even a favorably positioned dual agonist can look poorly tolerated without proper titration, underscoring that dosing strategy remains at least as important as target selection. Roche's CT-388 showed a clearly dose-dependent GI and appetite effect in its small first-in-human phase I study, with nausea and reduced appetite reported in most participants at the highest dose tested, though on a sample of only six patients per

cohort; the company has separately reported a more favorable 5.9% adverse-event-driven discontinuation rate from a larger, not-yet-published phase II trial.^{35,36} Viking Therapeutics' VK2735, by contrast, showed a clearly dose-dependent rise in GI adverse events across its four tested doses, with nausea reaching 63% and vomiting 29% at the highest dose, compared with 20% and 0% respectively on placebo, and adverse-event-driven discontinuation reaching 20% at the top dose versus none on placebo.³⁷ Potency balance between the two receptors, dose, and titration schedule appear to matter as much as the mere presence of GIP agonism.

Whether through fixed-dose combinations or through rational drug design, varying the agonistic profile of incretin-based therapies remains one of the most active areas of the obesity development pipeline, though the accumulating evidence suggests that adding a GIP component is not by itself a guarantee of better tolerability, and a growing number of assets are entering the clinic to test how much of a differentiator it actually proves to be.

The Challenge of Lean Mass Loss

Although gastrointestinal problems may be the best-characterized side effects of GLP-1-based weight loss, another effect of these treatments has come into focus in recent years and is already sparking considerable clinical development and investment. As noted briefly above, a substantial share of the weight lost on therapies across the GLP-1 space is not fat but lean body mass, or skeletal muscle. As GLP-1 adoption has grown, so has scrutiny of that trade-off from physicians and drug developers alike. This section takes up the question in full: how large the effect is, why it happens, and what is being developed to counter it.

The signal was there from the earliest pivotal trials. In the phase III STEP 1 trial of once-weekly semaglutide, the study that underpinned Wegovy's approval for weight loss, a dual-energy X-ray absorptiometry (DEXA) sub-study found that total lean body mass fell by close to 10% after 68 weeks.³⁸ Popular and clinical commentary has since converged on a widely repeated estimate: up to 40% of the weight lost on semaglutide can come from lean mass, with the remainder from fat.^{6,39} A similar pattern emerged in the phase III SURMOUNT-1 trial of the GLP-1 x GIP dual agonist tirzepatide, where a DEXA sub-study measured a 10.9% reduction in lean mass after 72 weeks, alongside a 33.9% drop in fat mass.⁴⁰ Real-world data confirm this is not a trial artifact. A 2026 analysis of body-composition records from close to 8,000 patients on semaglutide or tirzepatide found the same pattern outside the trial setting. It also reported a functional correlation. Patients who lost 5% or more of their lean mass over a year were meaningfully more likely to show reduced exercise tolerance than those

who lost less. The gap was about seven percentage points on semaglutide (45.6% vs. 38.4%) and 11 percentage points on tirzepatide (33.3% vs. 22.2%).⁴¹ The analysis has not yet been peer reviewed, so its conclusions remain preliminary. It nonetheless frames the question the field has yet to answer: whether the lean mass lost on these therapies translates into lasting functional decline.

Manufacturers point out that the proportion of lean mass relative to total body weight tends to hold steady or even improve during treatment, since fat is lost preferentially.³⁸ However, proportional stability does not mean the absolute loss is clinically irrelevant. Skeletal muscle is a metabolically active tissue that drives a meaningful share of resting energy expenditure. Losing it during pharmacological weight loss means that weight regained after stopping or tapering therapy may return disproportionately as fat, the so-called yo-yo effect, compounding metabolic dysfunction rather than reversing it. The concern is not only metabolic. Muscle loss also accelerates frailty, and that risk grows as older adults become a larger share of the treated population for whom rebuilding lost muscle is substantially harder than for younger patients.

An emerging pipeline to address muscle loss

Weight loss driven by a large caloric deficit is understood to trigger muscle loss through several overlapping catabolic pathways. The best-validated of these is the Activin Receptor Type II (ActRII) pathway, and particularly the ActRIIB receptor. Under normal physiology, ActRIIB is activated by ligands from the TGF-beta superfamily, mainly myostatin and activin A, and this signaling restrains muscle growth, preventing uncontrolled hypertrophy and keeping muscle mass within a stable homeostatic range.^{42,43} During rapid, calorie-restriction-driven weight loss, this brake is thought to be one of the pathways that tips toward net muscle breakdown. Blocking it, either by neutralizing its ligands or by antagonizing the receptor itself, has been shown to slow or reverse muscle loss and, in principle, to support muscle growth even while a patient continues to lose weight.^{44,45}

The pipeline response is visible (Figure 1). ActRII biology is now attracting dedicated programs in obesity, though clinical validation remains early. Myostatin-selective antibodies lead the development: Roche's emugrobar and Regeneron's trevogrumab are both in phase II, as is Scholar Rock's apitegromab. Alongside trevogrumab, Regeneron is developing garetosmab, an antibody against activin A specifically. Biohaven is in phase II with talditercept alfa, a bivalent anti-human myostatin adnectin-Fc fusion protein that inhibits the myostatin/activin pathway, which it repurposed for obesity after licensing the molecule from Bristol Myers Squibb (BMS-986089 had previously failed to hit its primary endpoint in

Duchenne muscular dystrophy and, subsequently, spinal muscular atrophy). Eli Lilly, through its 2023 acquisition of Versanis Bio, holds bimagrumab,⁴⁶ an antagonistic antibody against both the A and B subunits of ActRII. Arrowhead Pharmaceuticals and Rona Therapeutics have taken a different modality entirely, using RNA interference to knock down expression of INHBE and ALK7, two proteins in the activin signaling network, through ARO-INHBE, ARO-ALK7, and RN3161, respectively. Other, earlier-stage targets under exploration include the androgen receptor, the apelin receptor, and the Mas-related G-protein coupled receptor MRGPRX. A separate, more ambitious set of preclinical programs is looking past add-on therapies altogether, hunting for a new weight-loss mechanism that combines efficacy with muscle-sparing body composition from the outset. Those efforts are still early and face a steep climb against entrenched, and soon-to-be genericized, incretins.

Clinical proof of concept has arrived from multiple directions over the past year. Scholar Rock's phase II EMBRAZE trial added the anti-myostatin antibody apitegromab to tirzepatide in 102 patients with obesity or overweight⁴⁷ and found that, over 24 weeks, apitegromab preserved 54.9% of the lean mass otherwise lost on tirzepatide alone (a difference of 1.9 kg, $p=0.001$).⁴⁷ This shifted the composition of weight loss from roughly 70% fat / 30% lean on tirzepatide alone to 85% fat / 15% lean with apitegromab added. Total weight loss was statistically similar between arms (12.3% vs. 13.4%), meaning the drug changed the quality of weight loss rather than its magnitude. Adverse event rates were similar between arms (76% vs. 71%), with one serious adverse event in each group.

Regeneron's phase II COURAGE trial told a similar story but with a twist.⁴⁸ In patients on semaglutide alone, about a third of weight loss came from lean mass. Adding the anti-myostatin antibody trevogrumab cut that loss roughly in half while increasing fat loss and modestly boosting total weight loss. A triplet arm adding the anti-activin A antibody garetosmab went further. It preserved 80.9% of the lean mass that would otherwise have been lost on semaglutide alone, and lifted total weight loss to 13.4% of body weight versus 10.6%. The trade-off was safety. Discontinuations reached 28.3% against 4.6%, and two deaths were reported in the triplet arm.⁴⁹ Regeneron has stated it found no causal association between treatment and either event. The pattern nonetheless suggests that stacking activin-pathway blockers raises risk alongside efficacy. A June 2026 subgroup analysis found the lean-mass benefit across all baseline muscle levels, but it was roughly twice as large in patients who started with low lean mass.⁵⁰ The subgroups were small, yet the direction suggests that the patients most vulnerable to muscle loss may benefit most from the intervention.

Data from Eli Lilly's phase II BELIEVE trial of its anti-ActRIIA/B antibody bimagrumab arguably made the strongest case yet for targeting the receptor rather than a single ligand.²⁴ When combined with semaglutide, bimagrumab achieved 22.1% total body weight loss, with 92.8% of that from fat, vs. 15.7% weight loss with semaglutide alone, only 71.8% of which was fat. The combination also produced a 58% reduction in visceral fat, versus 36% with semaglutide alone. Most strikingly, bimagrumab given without any GLP-1 produced 10.8% weight loss that was entirely attributable to fat, with lean mass increasing by 2.5%. That result positions the activin pathway as a weight-loss target in its own right, not merely a rescue therapy for GLP-1-induced muscle loss.

Does the muscle actually work?

Encouraging as these data are, one readout has been largely absent: whether the lean mass being preserved is functional. The gap matters, for reasons rooted in where these drugs came from. Many of the myostatin and activin pathway drugs now being tested in obesity were developed first for muscle-wasting diseases such as Duchenne muscular dystrophy and spinal muscular atrophy, where results often disappointed, and where functional benefit was never guaranteed, given that the underlying disease has distinct, often genetic, drivers. That track record is a reason for caution, not a deal-breaker, but it does mean that a DEXA scan showing preserved lean tissue is not, by itself, proof that a patient can climb stairs, rise from a chair, or avoid a fall more easily.

Veru's enobosarm, a small-molecule selective androgen receptor modulator, has shown a body-composition benefit in the same range as the antibody programs above. In its phase IIb QUALITY trial, adding enobosarm to semaglutide reduced the lean-mass share of total weight loss to under 10% compared with more than 30% for semaglutide alone, with fat accounting for the rest.⁵¹ Enobosarm has so far been the only asset in this space to report a functional endpoint alongside the body composition data. The same trial reduced the proportion of patients who lost 10% or more of their stair-climb power by roughly 46% relative to semaglutide alone. Veru has since moved into a second phase IIb trial, PLATEAU, that enrolls adults aged 65 and older, on the premise that this is the population for whom muscle and bone loss carry the highest stakes, tracking physical function, mobility, and bone mineral density through 2027.⁵² Physical-function measures are already part of the ongoing programs. Scholar Rock built exploratory physical-function endpoints into EMBRAZE itself, and Regeneron's COURAGE trial tracks physical function among its secondary endpoints alongside lean mass. Lilly's bimagrumab trials have so far tracked quality of life and muscle volume. Data reported on these readouts, however, have been sparse.

A young field attracting serious capital

Lean mass loss as a side effect of GLP-1-based weight loss treatment has only been widely acknowledged for a few years, so the field addressing it is still in its early stages. But the pace of investment suggests conviction is building faster than the data is maturing. Biohaven's decision to license a myostatin/activin asset that had already failed in two separate neuromuscular indications and pivot it into obesity, and Eli Lilly's roughly \$1.9 billion acquisition of Versanis Bio in 2023 for bimagrumab,⁵³ both look, in hindsight, like early moves rather than one-offs. Analysts at TD Cowen have projected that muscle-preserving therapies paired with GLP-1s could generate more than \$30 billion in sales by 2035, and roughly a dozen companies are now active in the space.⁵⁴ Notably, large incretin franchises, such as Novo Nordisk and Amgen, do not yet have a late-stage muscle-preservation asset of their own in the clinic. If the ongoing phase II and III programs continue to read out positively, that gap looks like exactly the kind of opportunity these companies, and the investors backing challengers to them, will be watching closely. Developments in this space will be closely watched not only by the weight-loss community, but also by other therapeutic areas that historically have received less attention and financial investments, such as sarcopenia or (cancer) cachexia. Advancements in the area of muscle preservation therapies in the context of GLP-1 treatment might therefore also benefit other patient populations with equally high, if not higher, unmet needs.

GI side effects may be the best-characterized side effects of GLP-1-based weight loss, whereas lean mass loss has recently come into focus and is already drawing substantial capital, but they are not the only ones. Effects on bone density, ocular safety, a risk for thyroid C-cell tumors identified in rodent studies, as well as questions of aesthetics and dermatology are among the other open questions, some of them generating their own, earlier-stage waves of development, worth watching as the broader safety and durability story around GLP-1 therapy continues to unfold.

Beyond Diabetes and Obesity: Mapping GLP-1's Next Frontier

The previous section examined two of the costs of GLP-1's success in obesity: GI tolerability and the lean mass lost alongside fat, and the industry is now racing to address them. That a drug class this established is only now confronting questions of durability and side effects is itself a measure of how fast it has moved. The GLP-1 space has gone from a niche treatment for T2D to a franchise whose sales projections climb with every new indication.⁵⁵ Drug developers are now looking to extend the same underlying mechanisms into a wider set of disease areas, encouraged by a large and still-growing body of academic literature testing GLP-1s across an expanding list of disease models (Figure 2). Much of that early-stage data

Approved as standalone
 Approved with comorbidity
 Explored

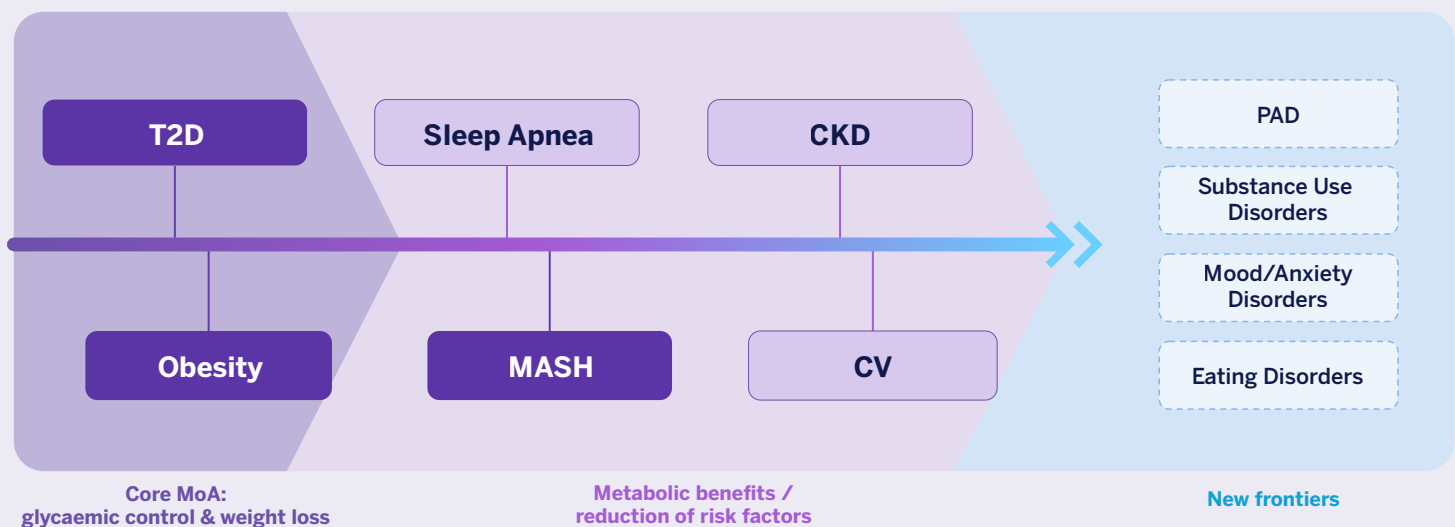


Figure 2: Mapping GLP-1's Expansion: From Core Metabolic Control to New Therapeutic Frontiers

Approved indications for GLP-1-based therapies have expanded from the foundational metabolic indications, type 2 diabetes and obesity, into a growing set of comorbidity-gated and standalone indications, with additional areas under active investigation. Dark purple mark indications approved as standalone, without requiring another qualifying condition: type 2 diabetes and obesity, and metabolic dysfunction-associated steatohepatitis (MASH), independent of obesity or diabetes status. Medium purple boxes mark indications approved only in patients who also meet a defined comorbidity criterion: obstructive sleep apnea (approved specifically for adults with obesity), chronic kidney disease (approved for adults with type 2 diabetes), and cardiovascular risk reduction (approved for adults with established cardiovascular disease and obesity or overweight). Boxes with a dashed blue border mark indications currently in clinical exploration, including peripheral artery disease, substance use disorders, mood and anxiety disorders, and eating disorders.

CKD: chronic kidney disease; **CV:** cardiovascular; **GLP-1:** glucagon-like peptide-1; **MASH:** metabolic dysfunction-associated steatohepatitis; **MoA:** mechanism of action; **PAD:** peripheral artery disease; **T2D:** type 2 diabetes

deserves some caution, given flaws in experimental design or comparability that limit how much weight any single preclinical or retrospective finding can carry, but that has not stopped drug developers from following the signals into their own company-sponsored trials. This chapter surveys where that expansion is furthest along, where it has already stumbled, and where the evidence remains too early to call.

Sleep apnea: The first new label

The clearest sign that GLP-1s have already moved beyond diabetes and obesity is obstructive sleep apnea, a condition mechanistically tied to excess weight through fat deposition around the upper airway. In December 2024, the FDA approved Eli Lilly's Zepbound (tirzepatide) for moderate-to-severe obstructive sleep apnea in adults with obesity, the first drug ever approved for this indication and, unlike the MASH approval that followed it the next year, a standard rather than accelerated approval.⁵⁶ The pivotal phase III SURMOUNT-OSA trials, in 469 patients, found that tirzepatide reduced the apnea-hypopnea index by 25.3 events per hour in patients not using positive airway pressure (PAP) therapy and by 29.3 events per hour in those already on it, compared with

reductions of roughly five events per hour on placebo in each group. On a prespecified secondary measure of disease resolution (an apnea-hypopnea index below five, or between 5 and 14 with minimal residual daytime sleepiness), 43.0% of patients in the non-PAP trial and 51.5% of those already on PAP therapy met that threshold on the highest tirzepatide dose after a year, a benchmark the sponsor has described as approximating disease resolution.⁵⁷ Sleep apnea is a useful marker for how GLP-1 expansion is likely to proceed elsewhere. The indication required no new biology, only a direct, mechanistically obvious consequence of weight loss, made official once a company ran the dedicated trial.

Cardiovascular, liver, and kidney disease

Beyond sleep apnea, another area of expansion sits close to GLP-1's core metabolic mechanism: disease of the heart, liver, and kidney. Semaglutide's label already reflects part of this reach. The phase III SELECT trial found that semaglutide reduced major adverse cardiovascular events by 20% relative to placebo (6.5% vs. 8.0%) in patients with established cardiovascular disease and overweight or obesity but without diabetes, supporting a March 2024 FDA label

expansion for cardiovascular risk reduction.^{58,59} In August 2025, Novo Nordisk added a new type of indication altogether: accelerated approval of Wegovy for non-cirrhotic MASH with moderate-to-advanced liver fibrosis, a standalone histology-based indication granted independently of the weight-related comorbidity requirements attached to Wegovy's original obesity label.⁶⁰ As with other accelerated approvals, continued marketing depends on confirming clinical benefit in an ongoing trial, but the approval may still be only the first of several new therapeutic areas GLP-1 and other incretin therapies enter over the coming years.

The pivotal data behind that approval, from the phase III ESSENCE trial of once-weekly semaglutide, showed a meaningfully higher fraction of patients achieving resolution of steatohepatitis without worsening fibrosis (62.9% vs. 34.3% on placebo), improvement in liver fibrosis without worsening steatohepatitis (36.8% vs. 22.4%), and the combination of both endpoints (32.7% vs. 16.1%).⁶¹ Other drugmakers are following closely. Eli Lilly's phase II SYNERGY-NASH trial of tirzepatide reported a positive readout in 2024, with as much as 73.3% of patients on the highest dose achieving steatohepatitis resolution without worsening fibrosis, compared with 13.2% on placebo.^{62,63} Lilly has since launched a phase III program, SYNERGY-Outcomes, testing both tirzepatide and retatrutide against placebo in roughly 4,500 patients, with primary completion expected around 2030.⁶⁴ Boehringer Ingelheim's dual GLP-1R/GCGR agonist survodutide has advanced into phase III with LIVERAGE, in patients with moderate-to-advanced (F2/F3) liver fibrosis due to MASH, and a companion trial, LIVERAGE-Cirrhosis, in patients with compensated MASH cirrhosis, with both expected to complete around 2031.^{65–67}

A similar pattern is playing out in kidney and vascular disease. Novo Nordisk led the way with the phase III FLOW trial, in which once-weekly semaglutide reduced the risk of major kidney disease events, a composite of substantial kidney function decline, kidney failure, and death from kidney or cardiovascular causes, by 24% relative to placebo in patients with T2D and chronic kidney disease, supporting an updated Ozempic label in January 2025.^{68,69} Semaglutide has also shown benefit in peripheral artery disease (PAD): the phase IIb STRIDE trial found that once-weekly semaglutide significantly improved maximum walking distance and quality of life in patients with T2D and symptomatic PAD.^{70,71} Novo Nordisk submitted a label extension application to the FDA based on those results, but unlike the CKD indication, this application appears to have been withdrawn rather than approved, according to industry pipeline trackers; EU regulators, by contrast, recommended a positive label update for the PAD indication around mid-2025. The divergence is a reminder that positive trial data does not always travel evenly across regulators. Eli Lilly is

running its own phase III cardiovascular and kidney outcomes trial, TRIUMPH-Outcomes, testing retatrutide in roughly 10,000 adults with obesity and established atherosclerotic cardiovascular disease or chronic kidney disease, with primary completion expected around 2029.⁷² AstraZeneca's oral small-molecule GLP-1RA efcoglipron only recently moved into phase III under the company's ELUMINATE program; one trial in that program, ELUMINATE-4, is testing the drug on top of the SGLT2 inhibitor dapagliflozin in patients with T2D and chronic kidney disease, though results are still several years away.^{73,74}

Heart failure with preserved ejection fraction

Not every cardiometabolic readout has translated into an approval. Heart failure with preserved ejection fraction (HFpEF), common among patients with obesity, has produced two data sets that were positive on their own terms but were not enough to secure registration. Eli Lilly's phase III SUMMIT trial found that tirzepatide cut the rate of worsening heart failure events to 8.0%, vs. 14.2% on placebo, a 46% relative risk reduction,⁷⁵ but Lilly withdrew the resulting FDA application in May 2025 after the agency requested an additional confirmatory trial.⁷⁶ Novo Nordisk's phase III STEP-HFpEF trial produced similarly positive results in obese patients with HFpEF, and Novo also filed for approval, then withdrew the application in August 2024 following discussions with the FDA, at the time stating an intention to resubmit early the following year.⁷⁷ Novo did resubmit, in January 2025, and the FDA acted on that submission in November 2025, but the outcome was narrower than a standalone HFpEF indication: the agency added a description of heart-failure hospitalization as an additional endpoint within the existing cardiovascular-risk-reduction label, while explicitly noting that an effect on heart failure itself has not been established.⁷⁸ As of mid-2026, Wegovy is still not approved for HFpEF as a distinct indication in the US, even though EU regulators went further and recommended a label update reflecting reduced heart-failure symptoms. The HFpEF experience illustrates that positive phase III data alone do not guarantee a path to approval, particularly for symptom- and hospitalization-based endpoints of the kind used in heart failure trials, and that US and EU regulators do not always reach the same conclusion from the same data.

Crossing the blood-brain barrier

A more ambitious frontier lies beyond the blood-brain barrier, in disorders of the central nervous system, most prominently Alzheimer's and Parkinson's disease. (Public) interest here was fueled in large part by retrospective cohort studies, including a 2025 analysis of nearly 216,000 US Department of Veterans Affairs patients treated with GLP-1 RAs, compared with more than 1.2 million patients on other antihyperglycemic therapies, which found a reduced risk of neurocognitive disorders overall (hazard ratio 0.95), driven by a lower risk

of dementia (0.92) and Alzheimer's disease specifically (0.88).⁷⁹ In parallel to these retrospective cohort studies, Novo Nordisk had already been testing oral semaglutide in two large phase III trials, EVOKE and EVOKE+, enrolling close to 3,800 patients with early symptomatic Alzheimer's disease. Results reported in late 2025 and published in full in 2026 showed that semaglutide did not slow clinical progression relative to placebo, despite producing meaningful reductions in several disease-associated biomarkers.⁸⁰ Novo has not announced a formal exit from the space, but it did terminate the trials' planned one-year open-label extension following the results,⁸¹ and no other large pharmaceutical company currently runs a comparably sized neurodegeneration program in the clinic, leaving the field, for now, mostly to smaller investigator-led trials and early-stage biotech.

Some of the enthusiasm that followed the original cohort studies looks, in hindsight, premature, for a reason that coverage at the time often underplayed: these are retrospective comparisons of patients who happened to be prescribed a GLP-1 against those who were not, not direct evidence of a treatment effect on neurodegeneration itself. Every patient in the Veterans Affairs (VA) analysis had T2D, a condition independently associated with higher dementia risk, and similar reductions in Alzheimer's and Parkinson's risk have also been reported for other diabetes drug classes, including sodium-glucose cotransporter 2 (SGLT2) inhibitors. That leaves open how much of the original signal reflected a direct effect of GLP-1 receptor agonism on the brain, as opposed to better control of an underlying metabolic disease that itself drives cognitive risk. EVOKE's null result does not resolve that distinction.

Substance use and neuropsychiatric disorders

Not everything to emerge from these retrospective cohort studies is destined to follow the same disappointing path as Alzheimer's disease. That same VA cohort analysis also reported reduced risk across a cluster of neuropsychiatric outcomes among GLP-1-treated patients, including alcohol use disorder (hazard ratio 0.89), cannabis use disorder (0.88), opioid use disorder (0.87), and suicidal ideation or self-harm (0.90).⁷⁹ Of these, alcohol use disorder has drawn the most attention from large pharma to date. At the end of July, Altimmune reported topline data from its phase II RECLAIM trial of pemvidutide, its dual GLP-1 x glucagon receptor agonist, in patients with alcohol use disorder: over 24 weeks, pemvidutide reduced heavy drinking days by 4.2 per week from baseline, compared with 2.75 per week on placebo, and produced a higher proportion of patients achieving a two-level reduction in WHO Risk Drinking Level, a registrational endpoint recognized by the FDA.⁸² Altimmune is now seeking an end-of-phase-II meeting with the FDA to design a pivotal phase III program. It is the first positive alcohol use disorder

data to come out of a company-sponsored trial, though not the first positive signal for the indication overall: investigators at the Psychiatric Centre Copenhagen at Rigshospitalet have separately tested exenatide and semaglutide in more than 200 combined patients with alcohol use disorder. Exenatide missed its primary endpoint overall but showed benefit in the subgroup of patients with obesity,⁸³ while semaglutide reduced heavy drinking days by 41.1 percentage points, compared with 26.4 percentage points on placebo.⁸⁴

Eli Lilly is running two distinct programs in the same indication. Mazdutide, a GLP-1R x GCGR dual agonist Lilly co-develops with Innovent Biologics, which is already approved in China for obesity and diabetes, is in a phase II proof-of-concept trial in alcohol use disorder that began enrolling in early 2025, with results not yet reported.⁸⁵ Separately, and further along in development, brenipatide, a GLP-1R x GIPR dual agonist in the same mechanistic class as tirzepatide, has already moved into two parallel phase III trials, RENEW-ALC-1 and RENEW-ALC-2, enrolling roughly 1,100 patients each, without a public phase II alcohol use disorder readout preceding that decision.⁸⁶ ⁸⁷ This is a more aggressive development approach than is typical at this stage, advancing to phase III on the strength of a mechanistic rationale rather than indication-specific proof of concept, and whether it proves prescient or premature will become clearer once the RENEW-ALC trials read out.

Preclinical and smaller studies point to potential benefit in other substance use disorders, including nicotine, cannabis, and opioid dependence, as well as in eating disorders such as binge eating disorder, but company-sponsored proof of concept in these areas is still pending and, alcohol use disorder aside, is not currently being actively pursued by large pharma. The trials that do exist are almost entirely investigator-led and draw a mixed picture: some report meaningful benefit, others do not, and differences in trial design and choice of endpoint make many hard to compare directly. Confirmation, where it comes, will likely require larger, company-run randomized trials of the kind Altimmune and Lilly are now running in alcohol use disorder. Given how recently that data turned positive, it may only be a matter of time before other large pharmaceutical companies follow the same path into neuropsychiatric indications beyond alcohol.

Sleep apnea, cardiometabolic disease, liver and kidney disease, heart failure, neurodegeneration, and neuropsychiatric disorders each illustrate a different stage of GLP-1's expansion beyond diabetes and obesity: an approved and marketed indication, an established beachhead, a stumble at the regulatory finish line, a high-profile retreat, and an early, genuinely uncertain wager, respectively. For an industry whose growth has so far been overwhelmingly a story about weight loss, that range is itself notable. Not every one of these bets

will pay off, and some, as heart failure and Alzheimer's disease already show, will not. But the number of therapeutic areas in which large pharmaceutical companies are now willing to run their own trials suggests the industry sees GLP-1 and incretin biology as a platform rather than a single-indication franchise, and the next several years of company-sponsored trial readouts will do more to define its real ceiling than anything published so far.

Deals and Investment Landscape

The GLP-1 deal wave has outpaced the modalities discussed in our earlier white papers in both scale and speed. Across the curated list of strategic transactions tracked here, roughly \$54 billion in disclosed value has been committed since 2024, with individual licensing agreements reaching \$5–6 billion and one acquisition at \$10 billion (Figure 3). That \$10 billion price tag was set by a public bidding war between Pfizer and Novo Nordisk, which Novo entered with a \$9 billion counteroffer before withdrawing.⁸⁸ This, together with the queue of large caps paying billions for assets, shows how scarce differentiated obesity assets have become. That ceiling now sits above the largest deals in previously discussed modalities: targeted protein degradation peaked at Monte Rosa/Novartis' \$5.7 billion,⁸⁹ and in vivo CAR-T at Kelonia/Lilly's \$7 billion.⁹⁰ The GLP-1 space has now cleared that mark, and it has done so repeatedly, with multiple multibillion-dollar transactions across a broader range of acquirers within a compressed timeframe.

Unsurprisingly, Novo Nordisk and Eli Lilly remain the most active dealmakers, each extending an established franchise. Novo has spread its bets across oral small molecules and delivery formats (Vivtex \$2.1 billion;⁹¹ Lexicon, \$1.1 billion⁹²), whereas Lilly has targeted discovery platforms and long-acting formats (Camurus, \$870 million;⁹³ Superluminal, \$1.3 billion⁹⁴). Alongside them, acquirers without such an established obesity franchise are buying their way in: Pfizer most aggressively with Metsera, followed by Roche, AstraZeneca, AbbVie, Merck, Regeneron, and GSK.

China has become a major source of GLP-1 deal flow. At least 10 of the strategic transactions originate with Chinese biotechs. It began with the \$6.0 billion Hengrui/Kailera agreement,⁹⁵ which licensed a de-risked Chinese incretin portfolio, and it has since been replicated by AstraZeneca/CSPC,⁹⁶ Merck/Hansoh,⁹⁷ Regeneron/Hansoh,⁹⁸ Pfizer/YaoPharma,⁹⁹ and others. For large pharma's arriving late to obesity, in-licensing a phase II or phase III Chinese asset has become the fastest route to a competitive clinical position.

What they are paying for has shifted with each recent deal toward three mechanisms. The first is amylin: Roche's \$5.3 billion deal centered on Zealand's amylin analog petrelintide,¹⁰⁰ Pfizer's Metsera acquisition was anchored by the monthly amylin analog MET-233i alongside a long-acting GLP-1,¹⁰¹ and Verdiva's \$2.47 billion Sciwind license brought a once-weekly oral amylin analog.¹⁰² The second is multi-receptor agonism spanning dual and triple combinations. Regeneron's Hansoh in-license⁹⁸ and AstraZeneca's lead CSPC Pharmaceutical Group asset SYH2082⁹⁶ are dual GLP-1 x GIP receptor agonists, whereas Novo Nordisk's Hengqin collaboration centers on UBT251, a GLP-1 x GIP x glucagon triple agonist.¹⁰³ The third is oral small molecules. Novo/Septerna,¹⁰⁴ Nimbus/Lilly,¹⁰⁵ and Madrigal/CSPC¹⁰⁶ all represent bets on replacing injectable formats entirely, opening obesity treatment to a far broader patient population than weekly pen injectors can reach. Running across all three is a pull toward longer dosing intervals. The market has moved decisively away from another weekly GLP-1 injectable. The premiums now attach to amylin biology, multi-agonist mechanisms, oral administration, and once-monthly or less-frequent dosing.

The venture layer reflects the same thesis driving the strategic deals, but with wider experimental variation. Notably, the same names turn up on the cap tables. Large pharma is not merely acquiring late-stage assets, but it is seeding the venture layer in parallel, often through its corporate venture and holding arms. Lilly appears in BioAge, OrsoBio, Verdiva, SaneGene, and Juvena, whereas Novo Holdings invests in Tanai, Antag, Sidera, and Alveus. By topic, next-generation incretins and multi-agonists dominate the largest raises, e.g., Kailera, Verdiva, Metsera, Alveus, but other adjacent bets recur. As in the strategic deals, one recurring bet is oral formulation and novel delivery. CORXEL raised \$287 million in a Series D,¹⁰⁷ and Syntis Bio closed \$38 million in a Series A,¹⁰⁸ both for oral GLP-1s, while Anodyne raised \$12.6 million in a Series A for a GLP-1 patch.¹⁰⁹ Another is the quality of weight loss rather than its magnitude. This is clearest at Juvena, whose \$33.5 million Series B,¹¹⁰ with Lilly among the investors, backs regenerative biologics aimed at muscle health and body composition, the venture-stage expression of the same thesis Lilly and Regeneron are pursuing through licensing. A further cluster is genetic medicine, mainly siRNAs. SaneGene, with a first-in-class INHBE siRNA program, raised \$110 million in Series B,¹¹¹ whereas Junevity closed a \$20 million seed round for its broader siRNA platform.¹¹²

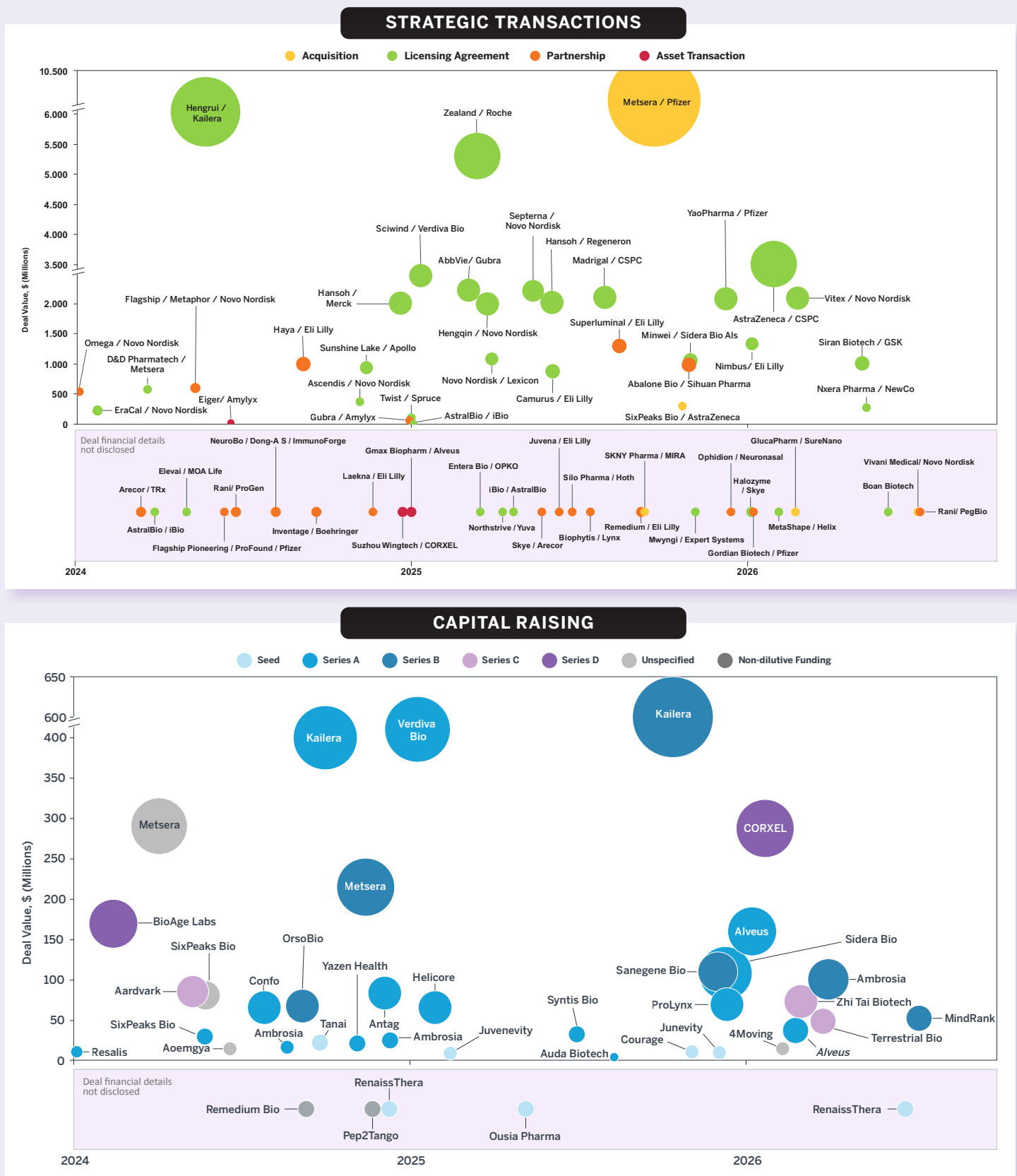


Figure 3. Recent Deal Activity in “GLP-1 Space”

Strategic transactions and capital-raising events from January 2024 to August 2026. Each bubble represents a single deal. Bubble size is proportional to deal value (USD millions). The x-axis indicates deal date and the y-axis deal value. Deals with undisclosed financial terms are plotted below the axis break. Bubble color denotes deal type: strategic transactions include partnerships, acquisitions, licensing agreements and asset transactions, while capital-raising events are categorized by round type (Non-dilutive Funding, Pre-seed, Seed, Series A through D, and Unspecified). Venture capital extension rounds are labelled in italics.

Deal data are sourced from GlobalData, filtered on deal years 2024 to 2026, global geography, and four deal types: mergers and acquisitions, strategic alliances, private equity and venture financing. Two complementary searches were run across all four deal types and combined. The first filtered by molecular target, covering GLP-1R, GIP, GIPR, GCR, amylin together with the muscle-retention targets MSTN, ACVR1C, ACTA, ACTRI, ACTRII, ACTRIIB, INHBE, APJ, CRHR2 and MAS1L. The second filtered by indication (obesity), restricted to the broad “GLP-1 space” as defined in the scope of this paper. As with the pipeline figures, this is not intended to be a comprehensive list; it is designed to convey the scale and direction of deal activity rather than to capture every transaction in the space. Data are current as of August 2026.

Closing Remarks

GLP-1-targeted therapies have revolutionized the treatment of patients living with T2D, but it was their application to weight loss in patients with obesity or overweight that transformed them into one of the largest revenue generators in modern pharmaceutical history. Large enough that obesity has now overtaken oncology as the single biggest contributor to late-stage industry pipeline value. Given this success, it comes as no surprise that the space is bursting with competition, with companies chasing differentiation in a field that grows more crowded by the day. As achievable weight loss appears to be approaching a ceiling of what is healthily possible, pharmaceutical companies and investors are racing to identify and build out the next sources of growth and revenue around GLP-1 biology.

This white paper covered three such areas: the maintenance of weight loss once treatment ends, the emerging side effects of GLP-1 therapy and the search for ways to mitigate them, and the expansion of incretin-based medicine into indications and therapeutic areas well beyond obesity and metabolic disease. Investment and deal activity are already moving in the same direction: more than \$50 billion in disclosed GLP-1-related deal value since 2024 suggests the market has recognized that this is no longer a race to build the single best weight-loss drug, but a broader platform opportunity spanning durability, tolerability, and disease scope. It is likely only a matter of time before GLP-1 therapies extend their success story well beyond obesity. Maintenance, tolerability, and how far the underlying biology can truly reach, maybe even in a preventative setting against age-related diseases—all remain as open questions. The companies and capital that move first to answer them will shape where the field goes next.

Abbreviations

AAACE: American Association of Clinical Endocrinology, **ActRII:** activin receptor type II, **ActRIIB:** activin receptor type IIB, **ALK7:** activin receptor-like kinase 7, **CAR-T:** chimeric antigen receptor T-cell, **CKD:** chronic kidney disease, **DEXA:** dual-energy X-ray absorptiometry, **DPP-4:** dipeptidyl peptidase-4, **FDA:** US Food and Drug Administration, **GCGR:** glucagon receptor, **GI:** gastrointestinal, **GIP:** glucose-dependent insulinotropic polypeptide, **GIPR:** GIP receptor, **GIPRA:** GIP receptor agonist, **GLP-1:** glucagon-like peptide-1, **GLP-1R:** GLP-1 receptor, **GLP-1RA:** GLP-1 receptor agonist, **HFpEF:** heart failure with preserved ejection fraction, **INHBE:** inhibin subunit beta E, **MASH:** metabolic dysfunction-associated steatohepatitis, **MGRPRX:** Mas-related G-protein coupled receptor X, **NASH:** nonalcoholic steatohepatitis, **PAD:** peripheral artery disease, **PAP:** positive airway pressure, **RNA:** ribonucleic acid, **SGLT2:** sodium-glucose cotransporter-2, **siRNA:** small interfering RNA, **T2D:** type 2 diabetes, **TGF-beta:** transforming growth factor beta, **WHO:** World Health Organization.

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