OBESITY DRUG DEVELOPMENT

Still room to grow

A watershed moment as GLP-1s revolutionised obesity care. Novo Nordisk's Wegovy (semaglutide) and Eli Lilly's Zepbound (tirzepatide) Glucagon Like Peptide (GLP-1) agonists quickly captured the attention of the biopharma industry in the early 2020s, launching on the backs of impressive clinical weight loss data. The significant clinical benefit has led to blockbuster sales, in the order of USD8.1bn and USD4.9bn, respectively, in 2024. Four years into the launch of the current generation of GLP-1s in obesity, Novo Nordisk and Eli Lilly continue to jockey for market position, with extensive post-marketing clinical studies to differentiate their products. Moreover, there are a variety of assets making their way through clinical trials, from the next-generation GLP-1s to well-known mechanisms re-cast in light of the renewed interest in obesity and innovative novel approaches. In this report, we explore the current clinical and market needs in the GLP-1 space as well as the directions taken by pharma, investors and academia searching for the next obesity breakthrough.

Physicians still see room for improvement. In a proprietary physician survey, DNB // Back Bay asked 50 physicians treating obesity patients in the US about their perspective on current GLP-1 use, unmet needs, and where they see the market heading. While heralding GLP-1s as a 'game changer' for obesity patients, the physicians still saw an opportunity to improve efficacy and tolerability, noting that approximately one-third of their patients discontinued treatment after six months. Beyond these issues, the physicians also highlighted cost and availability as key barriers to patient access.

Capital flows substantiate physician sentiment. Deal-making in the obesity space has accelerated in the past two years, with 41 strategic deals struck over 2023–2024 (compared with 19 over 2019–2022). Notably, ~40% of these deals involved a GLP-1 agonist monotherapy or combination approach. Novo Nordisk and Eli Lilly led the charge in deal-making, with 13 and eight deals, respectively, deploying ~USD3bn in upfront payments over the past five years. Quick to see the potential in this renewed commercial market and biopharma appetite, VCs poured nearly USD1.8bn into private companies in this space during 2024. Similar to strategic consolidators, private capital has been largely focused on GLP-1 assets, with more than USD2bn committed to companies advancing GLP-1 or GLP-1 combination approaches over the past four years. While the market leaders have a first-mover advantage, strategic and private money clearly sees an opportunity to develop a product with a competitive edge.

In search of the next big thing. The mechanism by which the GLP-1s exert their effect is multi-fold but largely the result of appetite suppression. Indeed, there is a flurry of ongoing late-stage clinical trials for complementary mechanisms such as GIP, glucagon and amylin, among others, which are believed to increase the therapeutic window for obesity medications. The push for convenience is evident, with over half of industry deals focusing on oral formulations to replace weekly injections. While a substantial portion of industry efforts seems to be focused on improving GLP-1s, we note US National Institutes of Health (NIH) funding has supported a diverse array of targets to date, in search of the next obesity breakthrough.

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Contents

Introduction

Novo Nordisk's Wegovy (semaglutide) and Eli Lilly's Zepbound (tirzepatide) quickly reached blockbuster status within their first year on the market, with consensus forecasts indicating USD46bn in combined sales by 2031[1]. The adoption of GLP-1 drugs in the US has catapulted them into public awareness, sparking speculation about their potential to reshape national weight trends and eating habits, with ripple effects reaching unexpected sectors from fast food to airlines[2]. Furthermore, it has captured the attention of other large companies such as Amgen, AstraZeneca, and Merck, which have entered the space and/or refocused their obesity efforts in recent years, leading to a flurry of deal-making activity. In this piece, we highlight the feedback from a proprietary physician survey, as well as the scope and focus of biopharma licensing/M&A interest, and determine which targets are garnering interest from private and public funding.

Given the commercial success of approved GLP-1s, there has been a clear uptick in strategic and investor interest in the space. However, in contrast to other areas of active biopharma and VC interest, there has yet to be a clear coalescing around specific targets outside of GLP-1s and similar mechanisms (known as incretins). While there are a number of targets of interest in the fields of oncology and autoimmunity beyond market-leading products, there are few consensus mechanisms of interest outside of first- and second-generation approaches such as incretins and muscle-sparing agents. We briefly review the commercial and late-stage mechanistic approaches in obesity, how physicians view the current treatment options, and where pharma, biotech, venture capital and even academia are focusing their interest.

Target universe and diversity

Wegovy (semaglutide) and Eli Lilly's Zepbound (tirzepatide) are Glucagon Like Peptide (GLP-1) agonists that stimulate the production of insulin, which underpins their established role in the ability to control blood sugar/HbA1c in type 2 diabetes (T2D). This hormone is mainly produced in the gut and secreted into the bloodstream following the consumption of food containing fat. It targets a diverse range of tissues, including the liver, gut, muscle, brain, and pancreas[3]. Some of the first GLP-1 agonists available were Byetta (exenatide) and Victoza (liraglutide), which were indicated to treat T2D. Victoza was notable as the first GLP-1 to show benefits on cardiovascular outcomes, which led to a surge in utilisation and piqued broader interest in the GLP-1 mechanism. It also showed a weight loss benefit in clinical trials in diabetes – generally 2–3kg on average. While the prevailing hypothesis is that they induce weight loss by lowering energy intake, newer GLP-1s have shown an association with reduced food cravings, which was not seen with earlier GLP-1s like liraglutide. This may be due to GLP-1 involvement in vagal nerve stimulation and signalling, as well as in overall gastrointestinal (GI) motility and gastric emptying[4]. While there is more to learn on how GLP-1 works in weight loss specifically, the clinical results – generally thought to be in the range of a 15–20% loss in body weight with a corresponding benefit to cardiovascular outcomes – are clear.

In addition to GLP-1 activity, Zepbound is a gastric inhibitory polypeptide (GIP) agonist. Like GLP-1, GIP is secreted into circulation following nutrient ingestion and acts on the GIP receptor (GIPR) on pancreatic beta-cells to stimulate insulin secretion. Furthermore, GIPR is expressed on neurons in the hypothalamus and activating those neurons results in reduced food intake and body weight. The potential benefits of GIP agonism on top of GLP-1 are beginning to emerge from clinical data. For example, in the Eli Lilly-sponsored SURMONT-5 trial, patients on Zepbound lost 20.2% of their weight after 72 weeks of treatment, while patients given Novo Nordisk's Wegovy lost only 13.7% of their weight[5]. However, we note higher levels of Wegovy (7.2mg versus the FDA-labelled dosage of 2.4mg) achieved weight loss >20%[6]. Given SURMONT-5 was an open-label study, a comparison of cardiovascular benefits has yet to be

[1] Visible Alpha
[2] Ozempic Could Crush the Junk Food Industry, But it Is Fighting Back – https://www.nytimes.com/2024/11/19/magazine/ozempic-junk-food.html
[3] Holst JJ. The physiology of glucagon-like peptide 1. Physiol Rev. 2007 Oct;87(4):1409-39. doi: 10.1152/physrev.00034.2006. PMID: 17928588
[4] Brierley DI, de Lartigue G. Reappraising the role of the vagus nerve in GLP-1-mediated regulation of eating. Br J Pharmacol. 2022 Feb;179(4):584-599. doi: 10.1111/bph.15603. Epub 2021 Jul 31. PMID: 34185884; PMCID: PMC8714868
[5] https://www.lilly.com/en-CA/news/press-releases/2024.12.4-tirzepatide-surmount-5-h2h
[6] https://www.fiercepharma.com/pharma/novo-nordisk-touts-superior-weight-loss-results-study-high-dose-wegovy

determined. Several other organisations are advancing GIP agonists with or without GLP-1 activity. Data from Viking's Phase 2 VENTURE study of its VK-2735 GLP-1/GIP agonist was released in 2024, showing statistically significant weight loss compared to placebo[7]. Notably, Viking is also advancing an oral version of this dual agonist. In addition to Viking, Roche, Zealand, and Amgen are all developing assets targeting the GIP pathway. Amgen's MariTide targets GLP-1 while antagonising, not activating, the GIPR through an antibody. Amgen released data in 2024 showing efficacy in line with current injectables with a less frequent dosing regimen (once monthly profile)[8].

In addition to GLP-1 and GIP, glucagon is a pancreatic peptide hormone secreted in response to low blood glucose and acts on glucagon receptors (GCGR), most abundantly found in the liver. During a hypoglycaemic event, the pancreas releases glucagon, which in turn stimulates the release of stored glucose from the liver to raise blood sugar[9]. Thus, the prevailing hypothesis is that in the context of GLP-1 agonism, glucagon may stimulate lipolysis, leading to fat tissue shrinkage. A number of companies are considering dual (GLP-1 and GCGR) or triple targeting (GLP-1, GIP, GCGR) programmes in obesity, such as Zealand's survodutide (GLP-1/GCG), Altimmune's pemvidutide (GLP-1/GCG) and Eli Lilly's retatrutide (GIP, GLP, glucagon). In Zealand's Phase 2 obesity study, patients treated with once-weekly survodutide 4.8mg achieved a mean weight loss of 18.7% versus placebo at 2%[10]. Similarly, in a Phase 2 study, retatrutide achieved up to a 17.5% mean weight reduction at 24 weeks and 24.2% at 48 weeks in adults with obesity or overweight[11].

Amylin is a pancreatic hormone that works as a satiety signal, reducing the 'reward' feeling associated with food by acting in the brain. Amylin also slows gastric emptying and suppresses the release of glucagon to control blood sugar[12]. Interestingly, agents targeting amylin are not new to the market. Symlin was approved in 2005 for patients with type 1 or type 2 diabetes as an adjunct to mealtime insulin for achieving improved glycaemic control. The adoption of Symlin has been poor, mostly owing to its lack of potency and insufficient pharmacokinetic properties. Nevertheless, newer amylin analogues are making their way through the clinic. Notably, Novo Nordisk released data for CagriSema's GLP-1/amylin combination approach. The REDEFINE 1 trial assessed a combination of 2.4mg cagrilintide (amylin analogue) and 2.4mg semaglutide versus cagrilintide monotherapy, semaglutide monotherapy, and placebo in 3,417 adults with obesity or overweight with one or more comorbidities and without type 2 diabetes. For those patients adherent to the regimen, CagriSema achieved a weight loss of 22.7% after 68 weeks[13]. With Novo Nordisk utilising a flexible trial protocol (patients could modify their dosage throughout the trial), only 57.3% of patients reached the highest dose (2.4mg/2.4mg). To prove increased efficacy beyond 25% weight loss, Novo Nordisk has started a new two-year Phase 3 trial at the maximum dose of CagriSema, with expected completion in August 2028. In addition to CagriSema, Zealand's petrelintide is a peptide amylin analogue intended for once-weekly administration, which in early clinical studies has achieved ~5–9% weight loss reduction after 16 weeks of treatment. Most recently, Novo Nordisk's amycretin showed an impressive 22% weight loss at 36 weeks in a Phase 1b/2a study[14]. However, the study included only 125 patients and tolerability data with amycretin has not yet been released, increasing the anticipation around future data releases and clinical studies.

[7] https://ir.vikingtherapeutics.com/2024-02-27-Viking-Therapeutics-Announces-Positive-Top-Line-Results-from-Phase-2-VENTURE-Trial-of-Dual-GLP-1-GIP-Receptor-Agonist-VK2735-in-Patients-with-Obesity

[8] https://www.amgen.com/newsroom/press-releases/2024/11/amgen-announces-robust-weight-loss-with-maritide-in-people-living-with-obesity-or-overweight-at-52-weeks-in-a-phase-2-study

[9] Pedersen C, Kraft G, Edgerton DS, Scott M, Farmer B, Smith M, Laneve DC, Williams PE, Moore LM, Cherrington AD. The kinetics of glucagon action on the liver during insulin-induced hypoglycemia. Am J Physiol Endocrinol Metab. 2020 May 1;318(5):E779-E790. doi: 10.1152/ajpendo.00466.2019. Epub 2020 Mar 24. PMID: 32208001; PMCID: PMC7272728

[10] Kosiborod MN, Platz E, Wharton S, le Roux CW, Brueckmann M, Ajaz Hussain S, Unseld A, Startseva E, Kaplan LM; SYNCHRONIZE–CVOT Trial Committees and Investigators. Survodutide for the Treatment of Obesity: Rationale and Design of the SYNCHRONIZE Cardiovascular Outcomes Trial. JACC Heart Fail. 2024 Dec;12(12):2101-2109. doi: 10.1016/j.jchf.2024.09.004. Epub 2024 Oct 23. PMID: 39453356

[11] Ania M. Jastreboff, M.D., Ph.D., Lee M. Kaplan, M.D., Ph.D., Juan P. Frías, M.D. https://orcid.org/0000-0001-9486-1255, Qiwei Wu, Ph.D., Yu Du, Ph.D., Sirel Gurbuz, M.D., Tamer Coskun, M.D., Ph.D., Axel Haupt, M.D., Ph.D., Zvonko Milicevic, M.D., and Mark L. Hartman, M.D. Triple–Hormone-Receptor Agonist Retatrutide for Obesity — A Phase 2 Trial

[12] Mietlicki-Baase EG. Amylin-mediated control of glycemia, energy balance, and cognition. Physiol Behav. 2016 Aug 1;162:130-40. doi: 10.1016/j.physbeh.2016.02.034. Epub 2016 Feb 27. PMID: 26922873; PMCID: PMC4899204

[13] https://www.novonordisk.com/news-and-media/news-and-ir-materials/news-details.html?id=915082

[14] https://www.novonordisk.com/news-and-media/news-and-ir-materials/news-details.html?id=915251

One issue brought into focus alongside GLP-1 weight loss is that in addition to body fat, patients also lose muscle/lean body mass[15]. Despite this, most patients still see an increase in the percentage of lean body mass relative to total body mass, and while the clinical need to address muscle loss in all patient types has been debated, there are a number of late clinical-stage assets trying to mitigate the loss of muscle mass. Myostatin and activin are TGF-beta ligands that play a role in skeletal muscle mass, bone, and erythropoiesis[16]. Preclinical models suggest that inhibition of some TGF-beta superfamily members has tissue-building and stimulatory effects on skeletal muscle. The most notable industry-sponsored assets are likely Eli Lilly/Versanis' bimagrumab, a Type II Receptor (ActRII) antagonist, and Regeneron's antibody trevogrumab, a myostatin inhibitor, in combination with garetosmab, an antibody that inhibits activin A. Additional names in this space include Biohaven (taldefgrobep alfa) and Scholar Rock, which are also progressing assets targeting myostatin.

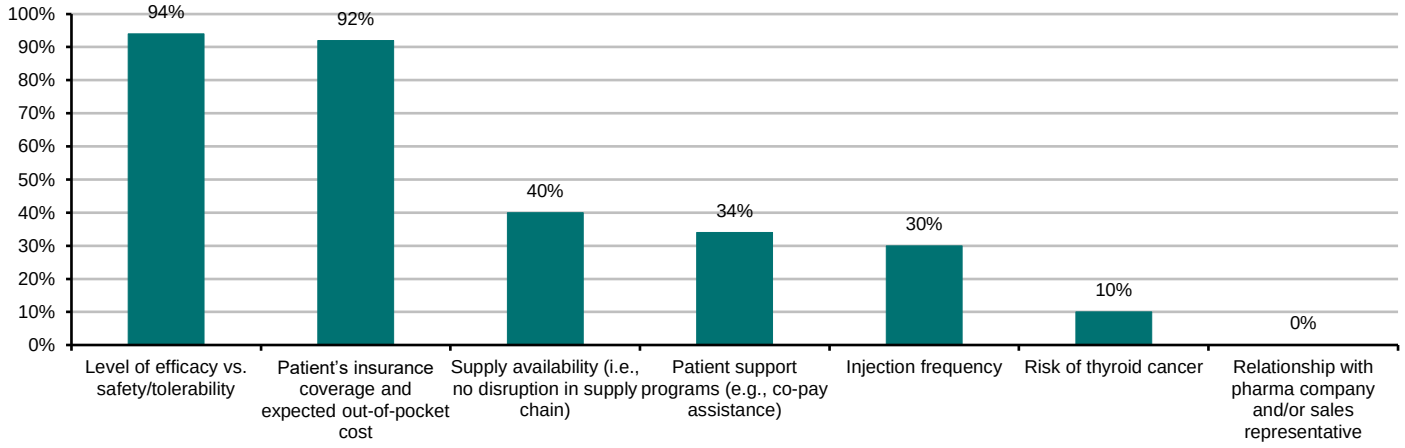
Beyond these late-stage programmes, there are a variety of earlier-stage programmes and assets addressing efficacy, tolerability, and comorbidities associated with obesity. Categorising mechanisms in this field into clear categories or buckets is difficult, as even traditionally gut-acting hormones are increasingly appreciated as having an effect beyond the pancreas, gut and liver, such as peripheral or central nervous system activity. Nevertheless, there are a variety of overlapping and/or complementary approaches to extend the efficacy already seen with the approved and late-stage obesity targets discussed above. Given the importance of energy intake to survival, there are a variety of neuronal pathways that control appetite as well as energy expenditure that are under investigation in the clinic, among others Cannabinoid Receptor 1 (CB1) and agouti-related peptide (AgRP). While commercial and late-stage assets are largely thought to decrease appetite, the addition of medicines that increase energy expenditure has been hypothesised to complement the efficacy of GLP-1s. Targets such as PPAR, AMPK, and FGF21, among others, fall into this category – all of which have seen interest from the biopharma space.

Efficacy and access – drivers of current use

With this development landscape as a backdrop, we conducted a survey of 50 endocrinologists and primary care physician specialists in the US (in Q4 2024) to understand their perspective on clinical needs within the obesity space. The physicians surveyed treated a median of 325 patients with obesity on an annual basis. When considering the most critical factors in choosing a GLP-1, efficacy was key for the physicians, with 94% ranking it among the top three factors in their choice and 66% rating it as the number one factor. In addition to efficacy, the physicians were also concerned with access, with patients' insurance, out-of-pocket expenses and supply availability ranking highly in determining their choice of treatment.

[15] Neeland IJ, Linge J, Birkenfeld AL. Changes in lean body mass with glucagon-like peptide-1-based therapies and mitigation strategies. Diabetes Obes Metab. 2024 Sep;26 Suppl 4:16-27. doi: 10.1111/dom.15728. Epub 2024 Jun 27. PMID: 38937282
[16] Rodgers BD, Ward CW. Myostatin/Activin Receptor Ligands in Muscle and the Development Status of Attenuating Drugs. Endocr Rev. 2022 Mar 9;43(2):329-365. doi: 10.1210/endrev/bnab030. PMID: 34520530; PMCID: PMC8905337

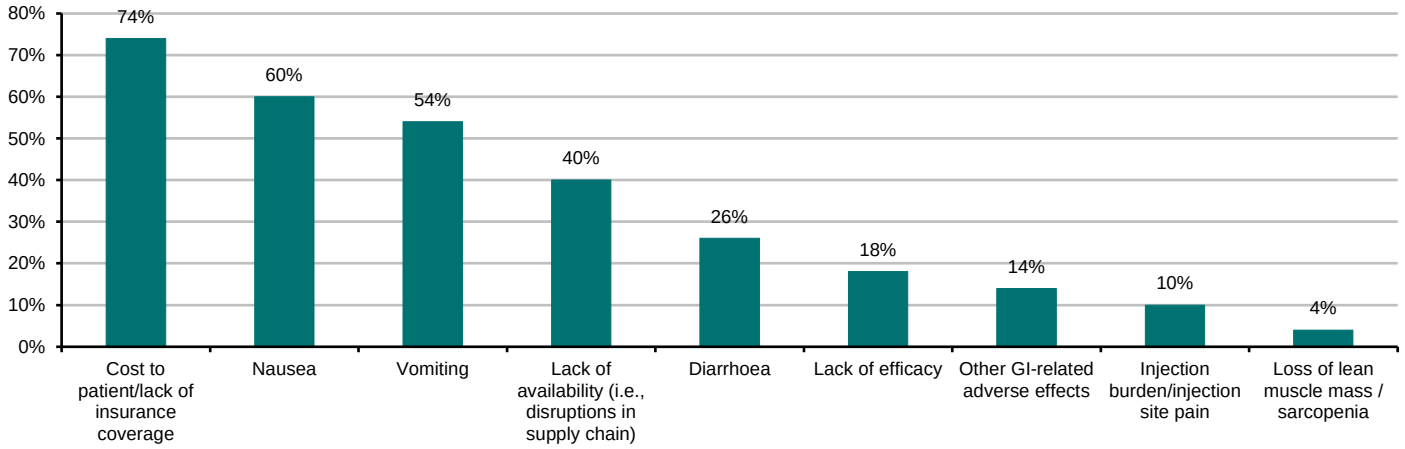
Figure 1: Most important factors in prescribing a GLP-1 (% ranked in top three), n=50



Source: DNB // Back Bay physician survey (Q4 2024)

Despite the efficacy of GLP-1 medicines, patient discontinuation remains an important commercial question as the GLP-1 field evolves. In our survey, physicians reported an average 33% of patients discontinuing treatment after an average of six months on therapy. Among the reasons for discontinuation therapy, cost/access and nausea side effects were the most common. While the side effect profile of these medicines is being addressed with newer combination regimens, as described above, the question of access and availability remains in the field. It is notable that 54% of the physicians ranked lack of coverage as the number one reason for patient discontinuation, while drug availability ranked highly in the common reasons for discontinuation, with 40% of the physicians ranking it among the top three considerations. While issues of demand were out of the scope of this review, our data suggests the market is poised for growth, not solely based on improved efficacy/safety of medicines alone.

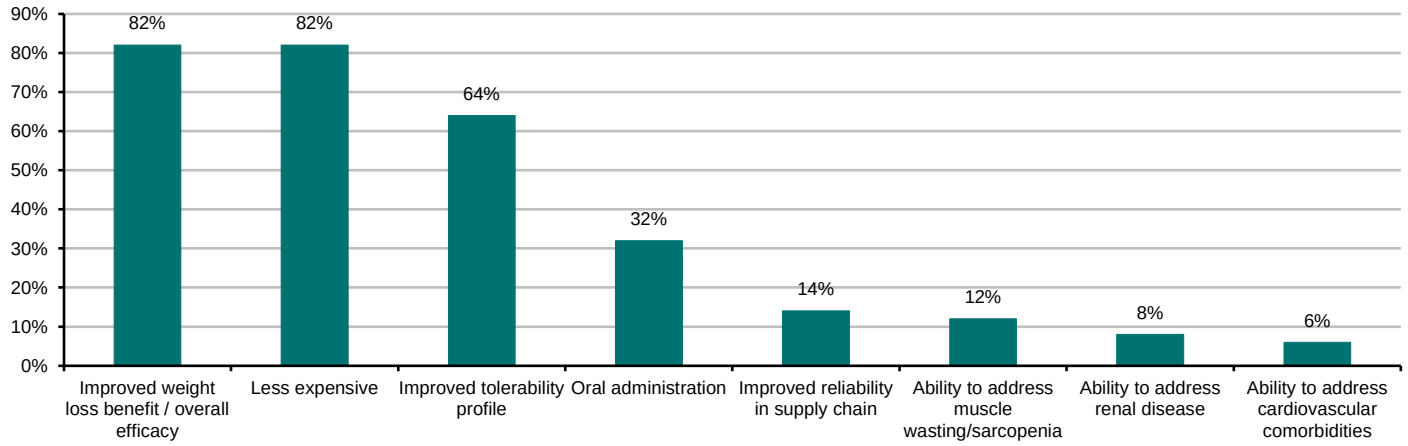
Figure 2: Most common reasons for discontinuation (% ranked in top three), n=50



Source: DNB // Back Bay physician survey (Q4 2024)

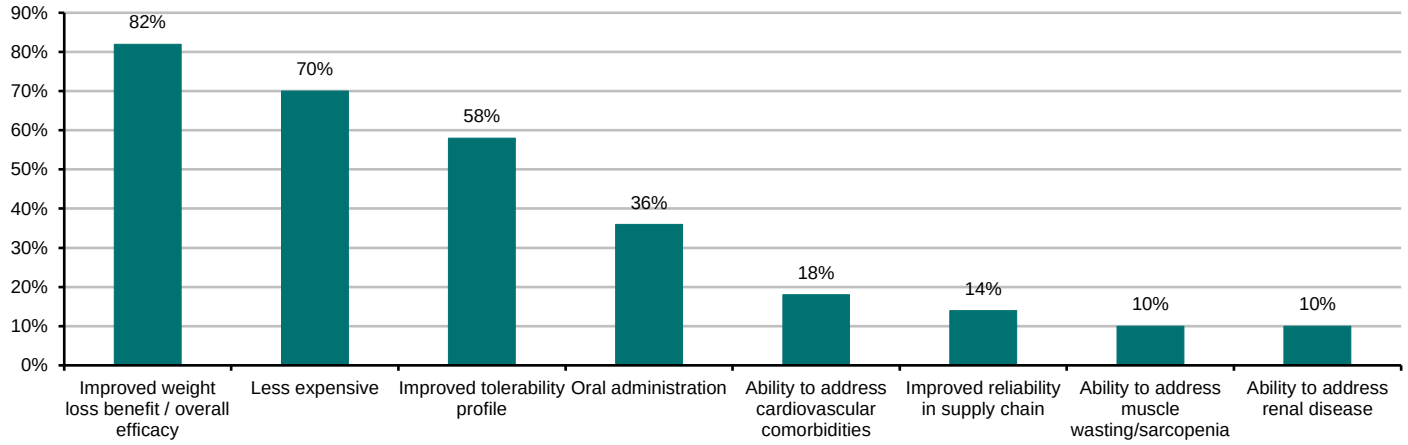
When considering both GLP-1 and non-GLP-1 assets in the pipeline, the physicians overwhelmingly desired medicines that were more efficacious with reduced out-of-pocket cost for patients.

Figure 3: Considerations in switching to a newer GLP-1 agent (% ranked in top three), n=50



Source: DNB // Back Bay physician survey (Q4 2024)

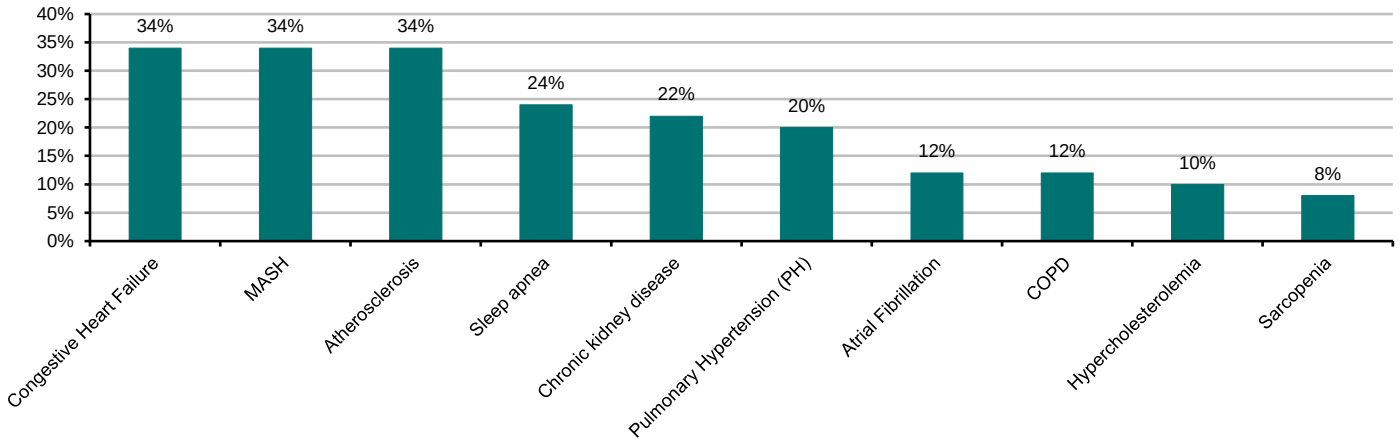
Figure 4: Considerations in switching to a non-GLP-1 agent (% ranked in top three), n=50



Source: DNB // Back Bay physician survey (Q4 2024)

GLP-1 sponsors continue to release data on the ability of these medicines to not only reduce a patient's weight but affect common obesity-related complications, including cardiovascular and renal disease. Consistent with the view that comorbidity management is a lower priority in obesity management, the physicians highlighted no single individual co-morbidity as particularly difficult to manage within their patients on incretin therapy, with heart failure, metabolic disease associated steatohepatitis (MASH) and atherosclerosis the indications of greatest need.

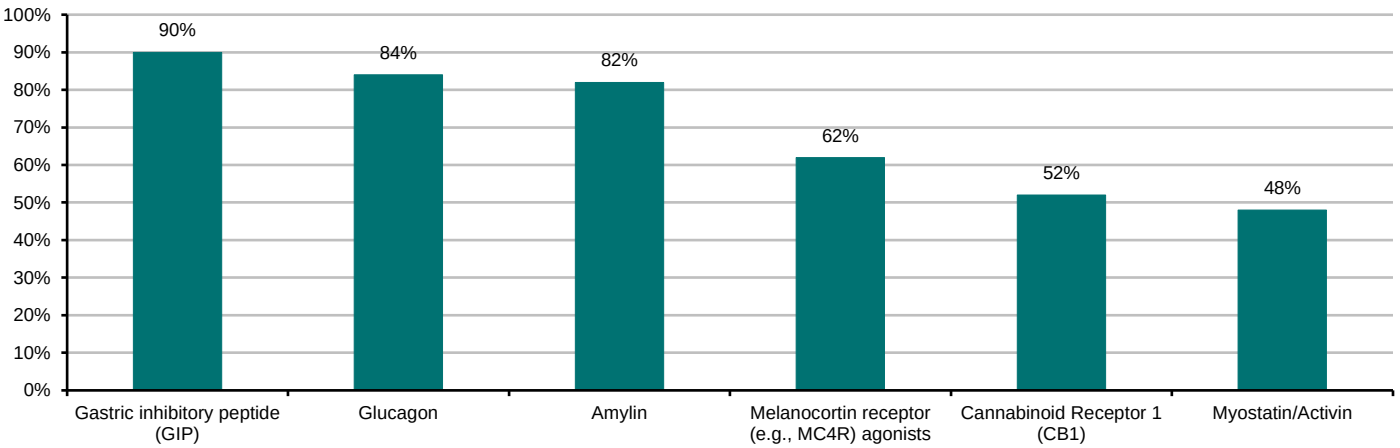
Figure 5: Leading comorbidity not addressed with GLP-1s (% rated as the most important comorbidity), n=50



Source: DNB // Back Bay physician survey (Q4 2024)

Finally, we assessed the familiarity of clinical stage targets among the physicians, with >80% aware of GIP, glucagon, and amylin. Interestingly, less than half the physicians were familiar with novel myostatin/activin approaches in development.

Figure 6: Familiarity with clinical stage targets (% of physicians familiar with the target)

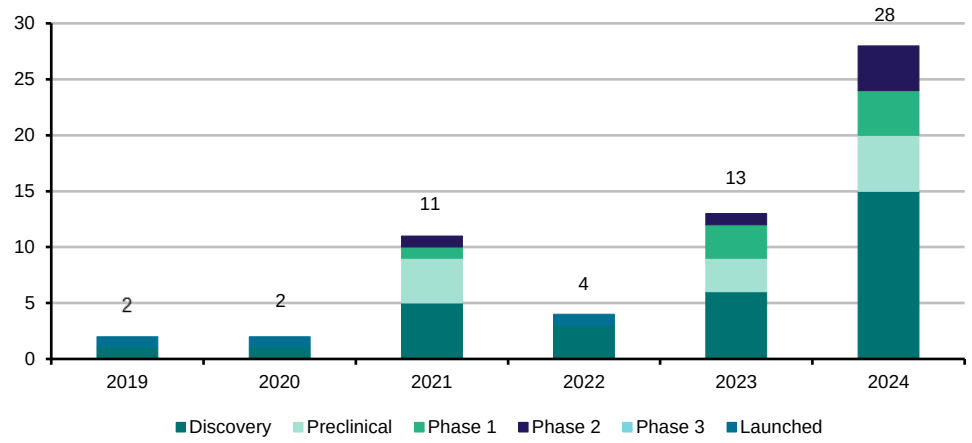


Source: DNB // Back Bay physician survey (Q4 2024)

Strategic deals within the obesity space

Biopharma deal activity (licensing, partnering, co-development, M&A, etc.) in the obesity space has accelerated since the approval of Wegovy in June 2021. The number of strategic transactions in 2024 alone matched the volume of the previous three years combined. Furthermore, the stage of dealmaking has been relatively early, with discovery and pre-clinical stage agreements making up ~72% of overall deal flow. This is likely a result of lagging investment in this space prior to the 2020s, as active obesity drug development had been concentrated in a relatively small set of companies.

Figure 7: Obesity deals by phase of transaction, n=60, (January 2019–December 2024)

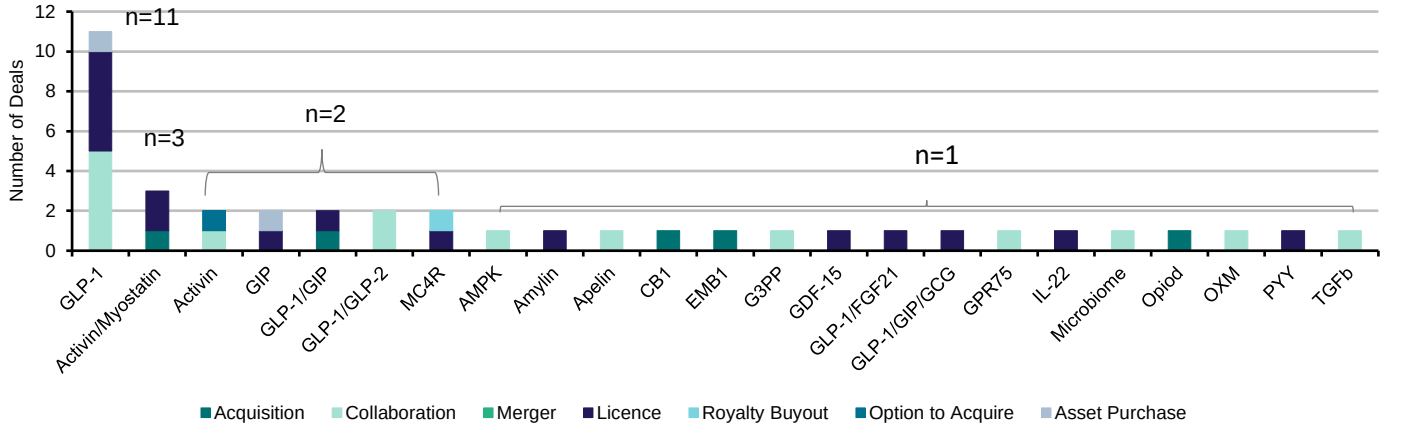


Source: Cortellis

Despite the increase in the total number of deals in 2024, there was reduced capital deployed to obesity companies/assets relative to 2023. The greater capital spending in 2023 was primarily due to three large >USD1bn M&A deals, with no obesity-related M&A in 2024. The largest obesity deal to date has been Roche's acquisition of Carmot Therapeutics for ~USD2.7bn in December 2023, which was driven by the latter's lead Phase-2 ready, dual GLP-1/GIP agonist. Among the larger licensing deals in 2024 was Merck's preclinical licensing agreement with Hansoh Pharma to develop its preclinical oral GLP-1, for USD112m upfront and USD1.9bn in milestones.

From a target perspective, the majority of transactions centred around GLP-1 agonist mechanisms, accounting for 28% of all deals. Consistent with physician feedback, this signals a belief by pharma in the potential to build upon the clinical profile of the current GLP-1 assets. Furthermore, combo deals involving assets combining GLP-1 agonism with an additional target mechanism encompassed four of the 40 with disclosed targets (January 2019–December 2024). Beyond GLP-1, five of the 40 deals involved the activin and/or myostatin pathways. While these pathways are of significant interest, as shown by Eli Lilly's USD1.9bn acquisition of Versanis and its activin/myostatin targeting asset bimagrumab, the optimal patient population where these mechanisms will be deployed remains to be seen.

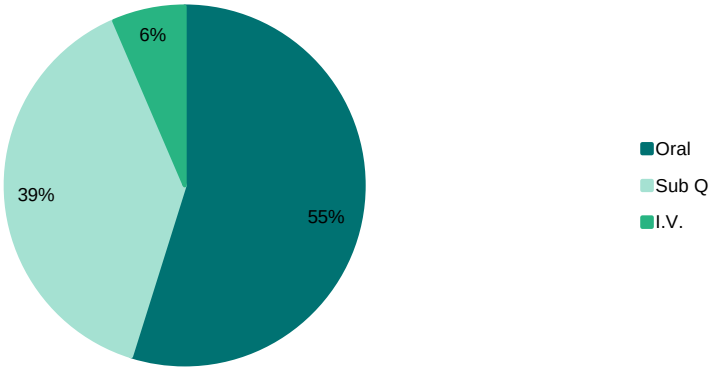
Figure 8: Obesity deals with disclosed targets by deal type, n=40 (January 2019–December 2024)



Source: Cortellis

Given that the currently approved GLP-1s are administered subcutaneously once weekly and many of the late-stage assets are also injectable, there is considerable interest in developing oral options to forgo the burden of weekly injections. Indeed, for deals relating to assets with a known route of administration, over half involved oral options.

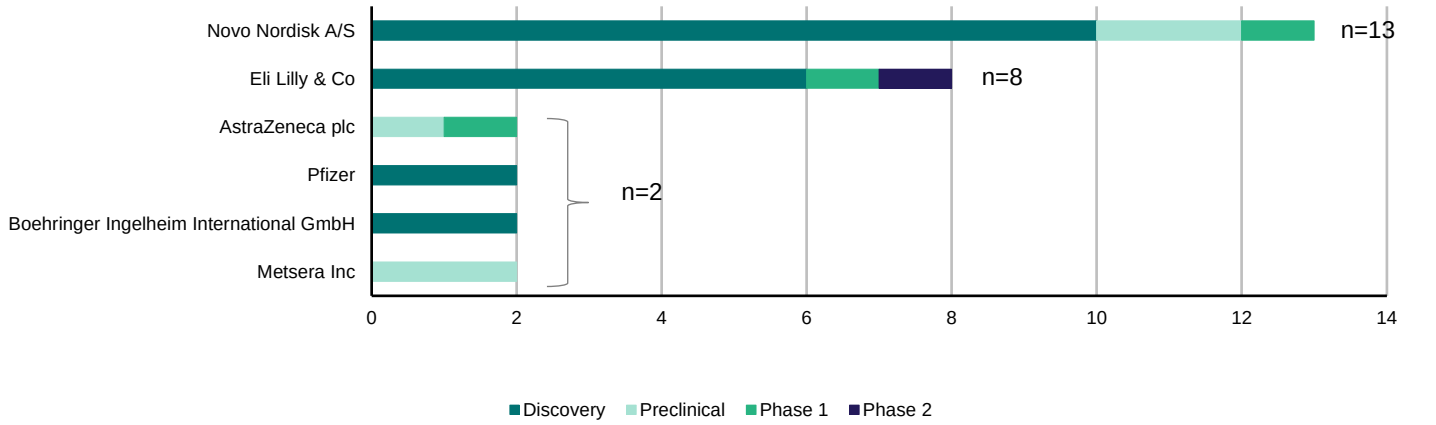
Figure 9: Obesity deals by disclosed route of administration (RoA), n=13 (January 2019–December 2024)



Source: Cortellis

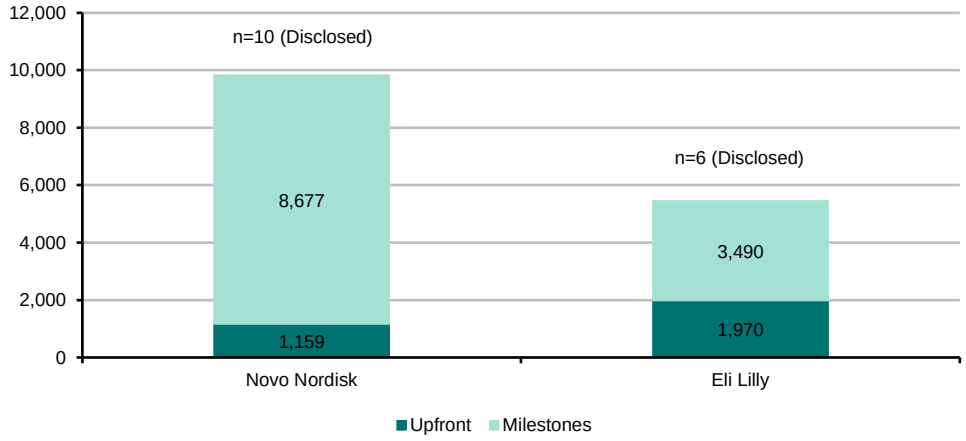
While deal flow has accelerated (January 2019–December 2024), a substantial volume is concentrated among a small number of global companies. Of the 60 deals in the past five years, 21 (35%) have involved Novo Nordisk and Eli Lilly. With duelling commercial obesity products, these companies have sought to expand their pipelines across a variety of mechanisms. Both Novo Nordisk and Eli Lilly have invested heavily in novel target discovery (~75% of both companies' deal flow). Between them, the two companies have deployed ~USD3bn in upfront deal payments, with >USD10bn committed in milestones. Novo Nordisk's largest milestone-based transaction was with Valo Health in September 2023 for its AI drug discovery capabilities, at USD60m upfront and up to USD2.7bn for up to 11 cardiometabolic programmes. In January 2025, Novo Nordisk elected to expand the scope of the original agreement to up to 20 programmes, offering USD190m upfront and up to USD4.6bn in milestones.

Figure 10: Active obesity consolidators with two or more deals (January 2019–December 2024)



Source: Cortellis

Figure 11: Invested in obesity deals by Novo Nordisk and Eli Lilly (USDm) (January 2019–December 2024)



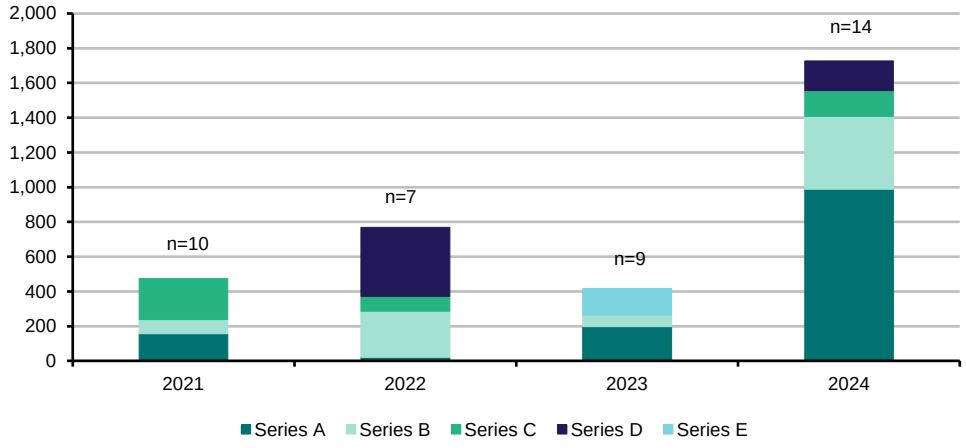
Source: Cortellis

VC financing and early-stage investments

Consistent with the recent spike in biopharma deal-making, the total number of companies funded by the VC community doubled in 2024 compared to 2022. In 2023, strategics led in capital deployed for obesity assets, while 2024 saw a major increase in venture funding for obesity companies. In 2024, not only did the total capital deployed increase, but the average raise increased dramatically to ~USD123m (USD46m in 2023).

VCs have primarily invested in companies developing GLP-1s, which account for ~30% of venture deals and 36% of capital invested in obesity companies. Following GLP-1 on its own, the second most funded target is another commercial target, GLP-1/GIP. Between them, the two commercial targets account for 62% of all capital flow from VCs in the past four years. Of all targets financed, 34% had only one private company raising money to pursue clinical development, with the average raise of those companies being ~USD58m, which compares to USD100m (on average) for companies with a GLP-1 asset.

Figure 12: Venture funding by year and round (USDm), n=40, (January 2021–December 2024)

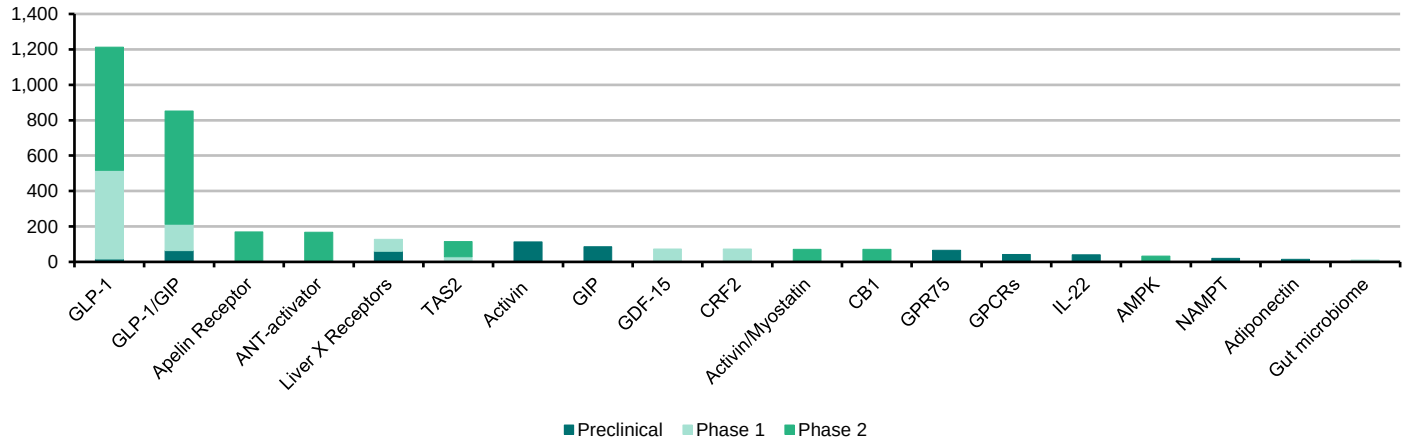


Source: Pitchbook

In 2024's biotech funding landscape of over 100 mega-rounds (>USD100m raised), three obesity companies – Kailera Therapeutics, Metsera, and BioAge Labs – distinguished themselves among capital-rich life science firms by securing substantial investments. Kailera commanded the largest raise in one round, coming out of stealth mode with a USD400m financing, securing capital from notable investors, including Bain Capital Life Sciences, RTW Investments, Atlas Venture, and

Lyra Capital. It was built upon four licensed GLP-1 drug candidates from Hengrui for USD110m upfront and up to USD5.9bn in milestones. The lead asset in the transaction was an injectable GLP-1/GIP RA, HRS9531 (now rebranded as KAI-9531) that had completed Phase 2 trials for obesity and T2D in China. Metsera raised two mega-rounds in 2024, with plans to file an IPO in early 2025. It launched in April 2024 with USD350m based on a Phase 1 GLP-1 asset and a preclinical pipeline consisting of a dual amylin/calcitonin receptor agonist, a GGG (GLP-1, GIP, glucagon) asset, and two IND ready candidates from its oral peptide delivery platform, with a total of over USD500m in VC funding to date. Finally, BioAge Labs raised a USD170m Series D in February 2024 to initiate a Phase 2 trial of its apelin receptor agonist used in combination with Eli Lilly's Zepbound. Just seven months later in September 2024, the company successfully executed a ~USD198m IPO on the NASDAQ.

Figure 13: Venture funding per target (USDm), n=40 (January 2021–December 2024)



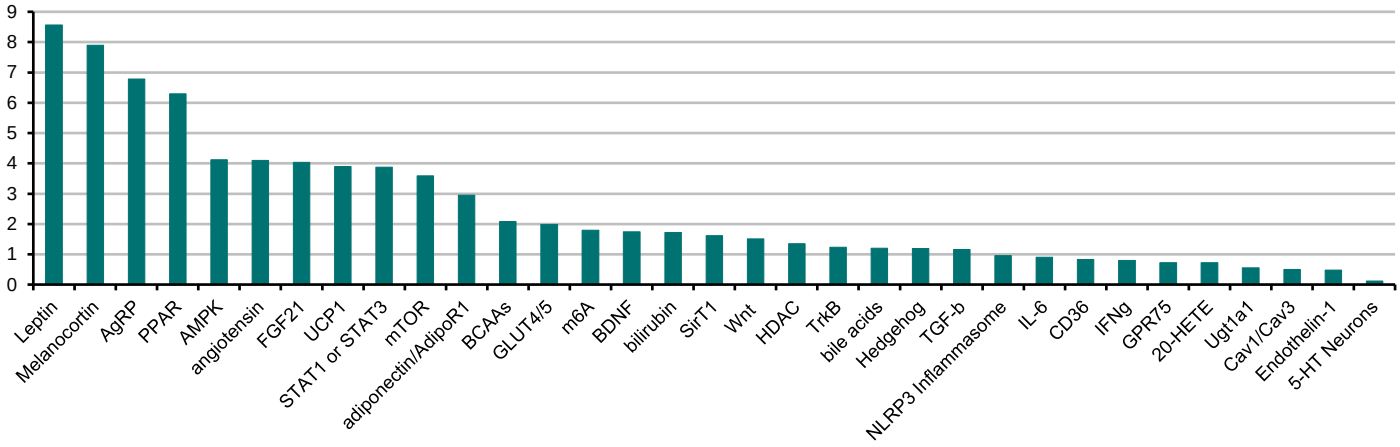
Source: Pitchbook

Moving beyond company formation, we look at the focus of very early-stage research within obesity at the academic level by assessing active grant funding activity within the US National Institutes of Health (NIH) RePORTER system as of July 2024. Within our data set, there was considerably more target funding parity relative to the venture funding environment. The top funded targets constitute a variety of mechanisms from appetite regulators to energy expenditure pathways to renal disease mediators. Despite the interest of academics, many of these targets have a long history of clinical and commercial development. Considering leptin alone, Myalept (Chiesi Farmaceutici) was approved in 2014 for lipodystrophy, Regeneron's REGN4461 is awaiting an FDA decision in lipodystrophy, while ERX Pharmaceuticals completed a Phase 1 clinical trial in 2023 for its leptin sensitiser.

Interestingly, Takeda had a leptin targeting asset (Pramlintide/Metreleptin) in development for obesity, which it discontinued in 2011. Beyond Leptin, Rhythm Pharmaceuticals has an approved melanocortin (MCR4) asset, Imcivree, used to treat rare genetic forms of obesity (Bardet-Biedl syndrome, deficiencies of POMC, leptin receptor, and PCSK1), while Palatin Technologies is currently conducting a Phase 2 trial in obese patients with its melanocortin targeting asset, bremelanotide, in combination with tirzepatide, with results expected in Q1 2025. While of interest in obesity, Peroxisome proliferator-activated receptors (PPAR) targeting assets are approved for numerous indications, including hypercholesterolemia and primary biliary cholangitis. AMP-activated protein kinase (AMPK) is the main target in this category actively being investigated by large pharma companies. In October 2022, Eli Lilly signed a USD490m structured deal with Nimbus to discover novel therapeutics against a specific isoform of AMPK, with the lead asset now in the lead optimisation stage. Angiotensin type 2 receptor (AT2R) and Fibroblast growth factor 21 (FGF21) are associated with the browning of white

adipose tissue and fatty acid oxidation/lipid metabolism, respectively[17] [18]. Both have been tested in areas outside of obesity, with no currently active programmes in the clinic.

Figure 14: Grant funding per target, July 2024 (USDm), n=186



Source: NIH RePORTER

Figure 15: Targets with USD4m+in active grant funding

Target	Key role in obesity	Selected corporate interest
Leptin	Appetite regulation and satiety	Chiesi, Regeneron, ERX Pharmaceuticals
Melanocortin	Appetite regulation/energy expenditure/renal implications	Rhythm Pharmaceuticals, Cosette Pharmaceuticals,
AgRP	Appetite regulation and satiety/energy expenditure	N/A
PPAR	Lipid and glucose metabolism	N/A
AMPK	Cellular energy homeostasis	Eli Lilly/Nimbus, Amplifier Therapeutics
Angiotensin	Adipose tissue function and insulin sensitivity/renal implications	N/A
FGF21	Energy expenditure and metabolism	N/A

Source: Back Bay

Conclusions

The commercial traction for GLP-1 therapies has reignited industry interest in obesity, with a shift from it being a neglected 'lifestyle' disease to a prime focus alongside other metabolic disorders like diabetes. Still, the field remains largely focused on GLP-1 assets, with much of the deal-making and investment focused on improving this class of drug. Despite Novo Nordisk and Eli Lilly's intense four-year rivalry in the GLP-1 market since Wegovy's launch in 2021, the industry's narrow focus on GLP-1 and GLP-1 combination therapies appears inconsistent with the potential for diverse approaches to obesity treatment. Nevertheless, feedback from our physician survey underscores a clear demand for improved GLP-1 safety and tolerability, signalling that investment capital is strategically aligning with critical market needs.

Beyond the clinical needs in the incretin class, we note another top-of-mind issue for the physicians: access and availability. Cost and insurance coverage play an outsized role in guiding the choice of physicians and patients between GLP-1 options. For some, this is an even more important consideration than clinical efficacy. Additionally, the availability of the drug product itself remains a concern for the treating physicians. Much has recently been written about supply shortages and Novo Nordisk's and Eli Lilly's investments in manufacturing capabilities. We note that many of the deals in this space are early-stage licensing deals coming with little, if any, manufacturing infrastructure capabilities. Among clinical-stage obesity targets beyond GLP-1, the physicians were most commonly aware of GIP, glucagon, and amylin, while fewer than half were aware of myostatin/actin.

[17] Han A, Xu S, Li R, Leow MK, Sun L, Chen P. Angiotensin type 2 receptor activation promotes browning of white adipose tissue and brown adipogenesis. Signal Transduct Target Ther. 2017 Jun 23;2:17022. doi: 10.1038/sigtrans.2017.22. Erratum in: Signal Transduct Target Ther. 2018 Apr 19;3:10. doi: 10.1038/s41392-018-0014-9. PMID: 29263921; PMCID: PMC5661636
[18] Fisher FM, Chui PC, Antonellis PJ, Bina HA, Kharitonenkov A, Flier JS, Maratos-Flier E. Obesity is a fibroblast growth factor 21 (FGF21)-resistant state. Diabetes. 2010 Nov;59(11):2781-9. doi: 10.2337/db10-0193. Epub 2010 Aug 3. PMID: 20682689; PMCID: PMC2963536

With a variety of late-stage clinical studies assessing improved GLP-1s with or without complementary mechanisms moving toward pivotal readouts, we have also looked earlier in the development life cycle. In the realm of academic research, there is a greater diversity of targets – notably some that take a fundamentally different approach to many of the late-stage products in development. While GLP-1s and their ilk suppress appetite and act on the GI tract, targets such as AgRP, AMPK, PPAR, etc. target tissues as diverse as the CNS, fat (adipose) tissue, and the immune system. However, many of the targets being investigated have checkered clinical histories in obesity and adjacent indications, further highlighting the dearth of novel targets beyond GLP-1 and incretins mechanisms.

The clinical burden of obesity is multifactorial, and as such, affecting weight loss should mitigate multiple associated health complications/comorbidities. Indeed, Wegovy and Zepbound have labelled claims for the prevention of major cardiovascular events (e.g. heart attack and stroke) and improvement in sleep apnoea, respectively – with emerging data generation in renal disease and even evidence highlighting possible neuroprotective mechanisms. As such, the field could be just beginning to scratch the surface of what is possible with a renewed and concerted effort from academia, biopharma, and clinicians.

Appendix

Questions asked in DNB // Back Bay's physician survey (Q4 2024)

1 What factors are most important for you in deciding between prescribing currently available GLP-1 agonist therapies for management of obesity? Please rank the options listed below from first to last, where 1 is most important and 7 is least important.

- 1.1 Level of efficacy versus safety/tolerability.
- 1.2 Risk of thyroid cancer.
- 1.3 Injection frequency.
- 1.4 Patient's insurance coverage and expected out-of-pocket cost.
- 1.5 Patient support programmes (e.g. co-pay assistance).
- 1.6 Supply availability (i.e. no disruption in supply chain).
- 1.7 Relationship with pharma company and/or sales representative.

2 For your patients currently on a GLP-1 agonist therapy for weight loss, what are the most common factors that drive treatment discontinuation? Please rank the options listed below from first to last, where 1 is most common and 9 is least common.

- 2.1 Lack of efficacy.
- 2.2 Injection burden/injection site pain.
- 2.3 Nausea.
- 2.4 Diarrhoea.
- 2.5 Vomiting.
- 2.6 Other GI-related adverse effects.
- 2.7 Loss of lean muscle mass/sarcopenia.
- 2.8 Cost to patient/lack of insurance overage.
- 2.9 Lack of availability (i.e. disruptions in supply chain).

3 Thinking about GLP-1 therapies that are currently in clinical trials – which would be the most important considerations in your willingness to replace existing GLP-1s (i.e. Wegovy (semaglutide), Zepbound (tirzepatide)). Please rank the factors below from 1 (most important) to 8 (least important).

- 3.1 Oral administration.
- 3.2 Improved weight loss benefit/overall efficacy.
- 3.3 Improved tolerability profile.
- 3.4 Less expensive.
- 3.5 Improved reliability in supply chain.
- 3.6 Ability to address cardiovascular comorbidities.
- 3.7 Ability to address muscle wasting/sarcopenia.
- 3.8 Ability to address renal disease.

4 For non-GLP-1 therapies in development – which would be the most important considerations in your willingness to add on to existing GLP-1s. Please rank the below, with 1 being most important and 8 being least important.

- 4.1 Oral administration.

4.2 Improved weight loss benefit/overall efficacy.

4.3 Improved tolerability profile.

4.4 Less expensive.

4.5 Improved reliability in supply chain.

4.6 Ability to address cardiovascular comorbidities.

4.7 Ability to address muscle wasting/sarcopenia.

4.8 Ability to address renal disease.

5 For your patients currently on a GLP-1 agonist therapy for weight loss, please rate the following comorbidities based on your opinion of the level of clinical need for additional treatment in addition to their GLP-1 regimen on a 1-to-5 scale where 1 means there is a significant and urgent clinical need and 5 means there is minimal clinical need.

5.1 Congestive heart failure.

5.2 Atrial fibrillation.

5.3 Atherosclerosis.

5.4 Hypercholesterolemia.

5.5 Sleep apnoea.

5.6 Chronic obstructive pulmonary disease (COPD).

5.7 Pulmonary hypertension (PH).

5.8 Sarcopenia.

5.9 Chronic kidney disease/failure.

5.10 Metabolic-disease associated steatohepatitis (MASH).

6 Which of the following late clinical-stage mechanisms are you aware of?

6.1 Gastric inhibitory peptide (GIP).

6.2 Glucagon.

6.3 Amylin.

6.4 Myostatin/Activin.

6.5 Cannabinoid Receptor 1 (CB1).

6.6 Melanocortin receptor (e.g. MC4R) agonists.

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