Obesity: Key Pipeline Developments and Clinical Trial Insights

IQVIA Pipeline Link/Trial Link — September 2024

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Obesity is a chronic complex disease defined by excessive fat deposits that can impair health. Obesity heightens the risk of type 2 diabetes (T2DM), heart disease and certain cancers. It can impact bone health, reproduction, morbidity, disability, and quality of life.[1] The 2019 Global Burden of Disease study estimates that obesity contributed to approximately 5 million deaths globally.[2] Over the years, several anti-obesity medications (AOM) have reached the market but failed after widespread use due to serious adverse effects, including cardiovascular events, suicidality, abuse, dependence, and cancer. Advancements have been made in elucidating the role of entero-pancreatic hormones in the regulation of feeding, appetite and glycemia that has led to the development of glucagon-like peptide-1 receptor (GLP1R) agonists as safe and effective treatments for T2DM and obesity.

The first GLP1R agonist to reach the market since 2014 for obesity was Novo Nordisk's semaglutide (WEGOVY), which was approved by the US FDA in June 2021. Semaglutide quickly emerged as a blockbuster, reaching sales of USD 7.73 billion in 2023. Later two other drugs were approved for the treatment of obesity — Lilly's tirzepatide (ZEPBOUND), a glucose-dependent insulinotropic polypeptide receptor (GIPR)/GLP1R co-agonist, and Rhythm Pharmaceuticals' setmelanotide (IMCIVREE), a melanocortin 4 receptor (MC4R) agonistic peptide.[3]

This article provides an update on current treatment options for obesity and outlines the latest development activities, including ongoing clinical trials of key experimental drugs with data sourced from IQVIA Pipeline Link and IQVIA Trial Link.

Over the years, several anti-obesity medications have reached the market but failed after widespread use due to serious adverse effects, including cardiovascular events, suicidality, abuse, dependence, and cancer.

Obesity measurement and prevalence

Overweight and obesity are commonly measured using the Body Mass Index (BMI). BMI thresholds for obesity vary by age and gender in infants, children, and adolescents. Obesity arises from an energy imbalance due to diet, physical activity, medications, diseases, and genetic factors. According to the World Health Organization, a BMI of 25 or more is considered overweight, and 30 or more is defined as obesity in adults. In 2022, 16% of adults (18 years and older) and 8% of children and adolescents (5 to 19 years) were affected by obesity.[4]

Treatment options for obesity

As obesity is a chronic condition with associated morbidity and mortality, prompt diagnosis and treatment are essential. Therapeutic options include lifestyle modifications (yielding up to 10% weight loss), pharmacotherapy and bariatric surgery.[5] Bariatric surgery consists of small incisions to modify the stomach to a smaller size and bypass a portion of the intestine; however, it is not widely applicable and carries risks of complications. Pharmacotherapy can be considered alongside with lifestyle changes for individuals with a BMI greater than 30 kg/m^2 or a BMI of 27 to 29.9 kg/m^2 in the presence of weight-related complications.[6] While a 5 to 10% weight loss is beneficial, more may be needed to alleviate obesity complications. Pharmacotherapy options include GLP1R agonists, GIPR and GLP1R dual agonists, pancreatic lipase inhibitors, sympathomimetics, combination drugs, including sympathomimetic/anticonvulsant and opioid receptor antagonist/dopamine and noradrenaline reuptake inhibitors.

Semaglutide and liraglutide, both GLP1R agonists, act centrally and peripherally to promote satiety, decrease hunger, delay gastric emptying, and ultimately reduce food intake. Tirzepatide, a GIPR and GLP1R dual agonist, acts similarly to GLP1R agonists and orlistat, a pancreatic lipase inhibitor, reduces fat absorption. Phentermine and diethylpropion, both sympathomimetics works by increasing satiety and energy expenditure through central nervous system actions. Phentermine/topiramate is a sympathomimetic/anticonvulsant combination, while naltrexone/bupropion is a combination of the opioid receptor antagonist/dopamine and noradrenaline reuptake inhibitor.[7]

Novo Nordisk's semaglutide was initially approved as a 2.4 mg once weekly subcutaneous injection in June 2021 for use as an adjunct to diet and exercise for chronic weight management in adults with obesity or who are overweight with at least one weight-related comorbidity. In March 2024, it was further approved to reduce the risk of cardiovascular death, heart attack and stroke in adults with cardiovascular disease and obesity or overweight. The approval was based on the SELECT Phase III trial (NCT03574597), which showed that semaglutide treatment resulted in a significant reduction in the risk of major adverse cardiovascular events in 6.5% of participants compared with 8% of participants receiving placebo. Semaglutide lowers mean body weight by approximately 15% after 68 weeks of treatment relative to 2.4% in placebo controls.[8,9] Additionally, a once-daily tablet formulation is being evaluated in the OASIS-3 Phase III trial (NCT05890976) which is expected to complete in February 2025.

Lilly became the first to obtain approval for an AOM that activates both incretin hormone receptors, GIP and GLP-1, following the US FDA's approval of tirzepatide in November 2023 for chronic weight management in adults. The approval was based on data from the SURMOUNT-1 (NCT04184622) and SURMOUNT-2 (NCT04657003) Phase III trials.[10] In the SURMOUNT-1 trial, patients treated with tirzepatide achieved average weight reductions of 16% to 22.5% compared with 2.4% for those on placebo.[11] In the SURMOUNT-2 trial, patients on tirzepatide achieved average weight reductions of 13.4% to 15.7% compared with 3.3% in patients administered placebo. Tirzepatide was later approved in the EU in March 2024.

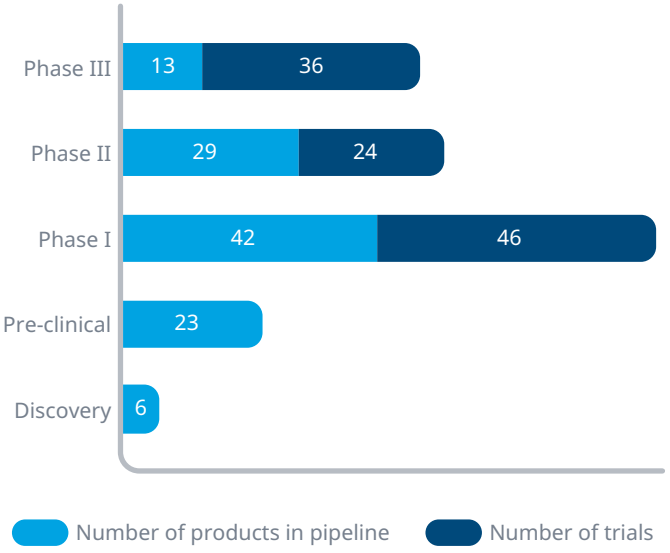
Rhythm Pharmaceuticals' setmelanotide (IMCIVREE) is the first-ever therapy approved by the US FDA (November 2020) for chronic weight management in adult and pediatric patients aged 6 years and older with obesity due to proopiomelanocortin (POMC), proprotein convertase subtilisin/kexin type I (PCSK1) or leptin receptor (LEPR) deficiency confirmed by genetic

testing. In June 2022, setmelanotide was approved for monogenic or syndromic obesity due to Bardet-Biedl syndrome. Additionally, the EMA broadened the marketing authorization for setmelanotide to cover children aged 2 to 6 years. The approval was based on Phase III data, which showed that 80% of patients with POMC or PCSK1 deficiency and 45.5% of patients with LEPR deficiency achieved over 10% weight loss after one year of treatment with setmelanotide.[12] A weekly depot formulation of setmelanotide has been evaluated in a Phase III trial (NCT05194124), and this formulation is predicted to launch in Q3 2025 according to IQVIA Pipeline Link.

Obesity pipeline insights: Overview on molecule type and target

As of August 2024, IQVIA's Pipeline Link and Trial Link listed 107 total clinical programs in development with different mechanism of actions.

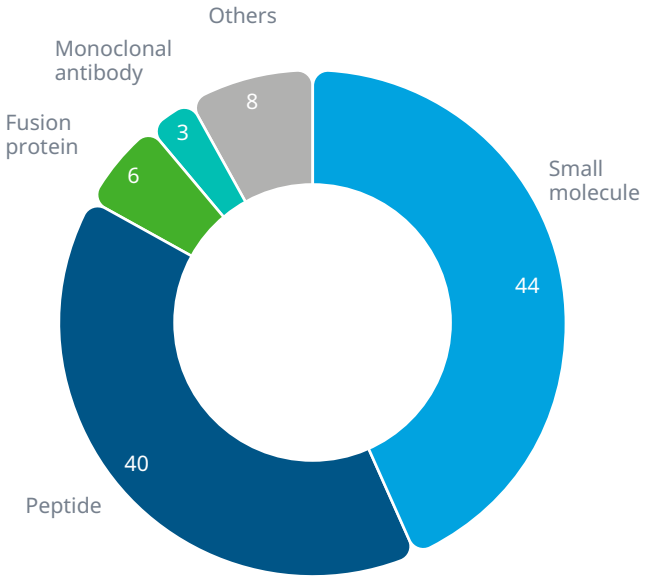
Figure 1: Phase-wise distribution of obesity pipeline assets and ongoing trials by current stage of development



Source: IQVIA Pipeline Link/Trial Link.

The majority of drugs in development are small molecules and peptides. Additional molecule types being developed include fusion proteins, monoclonal antibodies and lipopeptides. The obesity pipeline is dominated by GLP1R agonists followed by drugs targeting CALCR, dual agonists of GIPR and GLP1R, and MC4R.

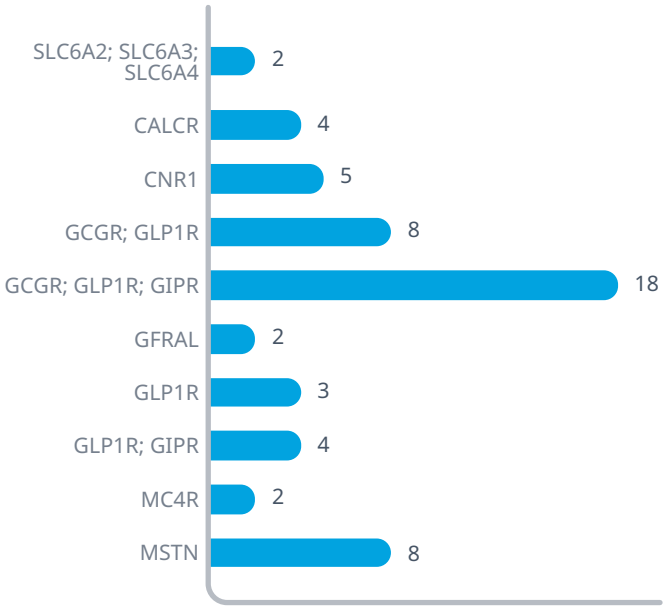
Figure 2: Molecule types in development for obesity



Source: IQVIA Pipeline Link/Trial Link.

In 2022, 16% of adults (18 years and older) and 8% of children and adolescents (5 to 19 years) were affected by obesity.

Figure 3: Targets in development for obesity



Source: IQVIA Pipeline Link/Trial Link.

LATE-STAGE PIPELINE PRODUCTS

Tesofensine

SANIONA is developing tesofensine (NS-2330), a triple monoamine reuptake inhibitor that modulates brain activity by increasing the level of serotonin, dopamine, and noradrenaline for the treatment of hypothalamic obesity.[13] In December 2019, Saniona's partnered company Medix submitted an NDA to the Mexican health authority, COFEPRIS,[14] and in Q1 2023, the agency expressed favorable opinion for approval and the company is targeting to launch the product in 2024.[15] The TIPO-1 trial (NCT00394667) demonstrated that a daily oral dose of 0.50 mg of tesofensine resulted in significant weight loss. Additionally, Phase III trials have validated its effectiveness and safety for treating obesity.

Mazdutide

Innovent's mazdutide (IBI362; LY3305677), a once weekly subcutaneous injection, is a dual agonist of the GLP-1 and glucagon receptors (GCGR). In February 2024, China's NMPA accepted to review an NDA of mazdutide for chronic weight management in adults with obesity or overweight.[16] The Phase III GLORY-1 trial (NCT05607680) showed promising results, meeting all primary and secondary endpoints in reducing liver fat content and improving multiple cardiometabolic risk factors.[17] Mazdutide at 4 mg and 6 mg doses led to significant weight loss of approximately 15% at week 48, which was comparable to semaglutide.[18] The product is predicted to launch in Q3 2025 according to IQVIA Pipeline Link.

Obesity clinical trial landscape

As of August 2024, Trial Link lists 106 ongoing clinical trials (active, not recruiting and recruiting), including 60 trials in Phase II and III development with selected trials listed in the table below.

Table 1: List of ongoing clinical trials involving obesity therapies

DRUG/ TARGET	COMPANY	HIGHEST PHASE	ROA DOSAGE)	NCT ID (ENROLLMENT)	STUDY START DATE	ESTIMATED PCD	PREDICTED LAUNCH DATE	NUMBER OF SITES (COUNTRIES)
LIRAGLUTIDE (SAXENDA) GLP1R	NOVO NORDISK	Phase III	VIAL	NCT04775082 (78)	4-Mar-2021	1-Aug-2023	Q2 2025	26(USA+7)
SEMAGLUTIDE (WEGOVY) GLP1R	NOVO NORDISK	Phase III	PRE-FILLED SYRINGE (once weekly; 7.2mg)	NCT05646706 (1407)	4-Jan-2023	20-Sep-2024	Q4 2025	99(USA+11)
				NCT05649137 (513)	4-Jan-2023	4-Oct-2024		66(USA+7)
SEMAGLUTIDE (NN9932) GLP1R	NOVO NORDISK	Phase III	ORAL ORDINARY (once daily)	NCT05890976 (230)	13-May-2023	14-Feb-2025		15(China)
ECNOGLUTIDE (XW003) GLP1R	SCIWIND	Phase III	PRE-FILLED SYRINGE	NCT05813795 (664)	5-Apr-2023	20-Jun-2024	Q1 2026	1(China)
CAGRILINTIDE + SEMAGLUTIDE (CAGRISEMA) CALCR; GLP1R	NOVO NORDISK	Phase III	PRE-FILLED SYRINGE	NCT05567796 (3400)	1-Nov-2022	21-Oct-2024	Q1 2026	222(USA+22)
				NCT05394519 (1200)	1-Feb-2023	11-Dec-2024		169(USA+12)
				NCT05813925 (330)	3-Apr-2023	27-Jan-2025		22(Japan+1)
				NCT05996848 (300)	15-Aug-2023	18-Feb-2025		39(China)
				NCT06388187 (300)	24-Jun-2024	27-Feb-2026		24(USA+4)
				NCT06131437 (800)	27-Nov-2023	27-Aug-2025		50(USA)

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* The trials highlighted in blue are pivotal trials.

Table 1: List of ongoing clinical trials involving obesity therapies *continued*

DRUG/ TARGET	COMPANY	HIGHEST PHASE	ROA DOSAGE)	NCT ID (ENROLLMENT)	STUDY START DATE	ESTIMATED PCD	PREDICTED LAUNCH DATE	NUMBER OF SITES (COUNTRIES)
TIRZEPATIDE (ZEPBOUND) GLP1R; GIPR	LILLY	Phase III	PRE-FILLED SYRINGE	NCT05556512 (15374)	11-Oct-2022	7-Oct-2027	Q2 2026	682(USA+26)
				NCT06047548 (400)	20-Sep-2023	22-May-2026		20(USA)
				NCT05822830 (700)	21-Apr-2023	6-Nov-2024		32(USA+1)
				NCT06439277 (300)	3-Jun-2024	31-May-2027		70(USA+10)
				NCT06075667 (150)	16-Oct-2023	1-Oct-2026		38(USA+7)
ORFORGL-IPRON (LY3502970) GLP1R	LILLY	Phase III	ORAL ORDINARY	NCT05803421 (2620)	3-Apr-2023	24-Apr-2025	Q3 2026	391(USA+15)
				NCT05869903 (3000)	5-Jun-2023	12-Sep-2025		138(USA+9)
				NCT05872620 (1500)	5-Jun-2023	30-Jun-2025		136(USA+10)
				NCT05931380 (236)	31-Jul-2023	30-Jun-2025		16(Japan)
HRS9531 GLP1R; GIPR	JIANGSU HENGRUI	Phase III	VIAL	NCT06396429 (540)	13-May-2024	30-Jul-2025	Q4 2026	1(China)
SURVODUTIDE (BI 456906) GCGR; GLP1R	BOEHRINGER INGELHEIM; ZEALAND PHARMA	Phase III	PRE-FILLED SYRINGE	NCT06066515 (726)	15-Nov-2023	19-Dec-2025	Q2 2027	118(USA+13)
				NCT06077864 (4935)	17-Nov-2023	12-Mar-2026		544(USA+ 35)
				NCT06066528 (755)	15-Nov-2023	19-Dec-2025		143(USA+18)
				NCT06176365 (272)	19-Dec-2023	12-Nov-2025		28 (Japan)
				NCT06214741 (300)	15-Jan-2024	26-Dec-2025		31(China)
				NCT06309992 (160)	13-Mar-2024	16-Feb-2026		23(USA)
RETATRUTIDE (LY3437943) GCGR; GLP1R; GIPR	LILLY	Phase III	PRE-FILLED SYRINGE	NCT05882045 (1800)	30-May-23	20-Jan-2026	Q2 2027	166(USA+9)
				NCT05929066 (2100)	10-Jul-2023	15-Apr-2026		133(USA+11)
				NCT05931367 (405)	1-Aug-2023	6-Feb-2026		49(USA+5)
				NCT05929079 (1000)	11-Jul-2023	3-May-2026		100(USA+7)
				NCT06383390 (10000)	30-Apr-2024	28-Feb-2029		704(USA+24)
MARIDEBART CAFRAGL-UTIDE (MARITIDE) GLP1R; GIPR	AMGEN	Phase II	PRE-FILLED SYRINGE	NCT05669599 (592)	18-Jan-2023	4-Oct-2024	Q4 2030	78(USA+11)

Source: IQVIA Pipeline Link and Trial Link

* The trials highlighted in blue are pivotal trials.

Novel therapies in early development

In recent years, advancements in understanding obesity's emerging drug targets have expanded treatment possibilities. Research efforts are increasingly focused on discovering novel targets for drug development, aiming to create more effective and precise pharmacological treatments.

Bimagrumab

Lilly's bimagrumab (LY3985863), a monoclonal antibody targeting ActRIIA/ActRIIB, is currently in Phase II development. In a 48-week Phase II trial, patients with T2DM and obesity who were treated with bimagrumab experienced a placebo-adjusted 22% reduction in total body fat mass and a 4.5% increase in lean mass, with minimal impact on caloric intake.[19] Notably, there was no weight regain for 12 weeks after stopping treatment, unlike the rapid rebound often seen with incretin therapies. Another Phase II trial, BELIEVE (NCT05616013), is ongoing to evaluate bimagrumab's effects in obesity without T2DM and is expected to complete in June 2025.

S-309309

Shionogi is developing S-309309, a novel monoacylglycerol transferase 2 (MGAT2) inhibitor, for obesity. In May 2024, Shionogi completed a Phase II trial (NCT05925114) evaluating once-daily oral S-309309 capsules in obese adults in the USA. The primary endpoint was the percent change in body weight from baseline at week 24 and the data from this trial are anticipated in Q3 2024. In preclinical studies of high-fat diet-induced obese mice, treatment with S-309309 resulted in over 10% weight loss per year.[20]

Monlunabant

Monlunabant (INV-202), a selective cannabinoid receptor (CB1R) inverse agonist developed by Inversago Pharma (now a subsidiary of Novo Nordisk), is designed for once-daily oral use in obesity treatment. Monlunabant is currently in being evaluated in a Phase II trial (NCT05891834) in adults with obesity, with an estimated study completion date of March 2025.[21]

LY3541105

LY3541105 is an investigational DACRA (Dual amylin and calcitonin receptor agonist) targeting amylin and calcitonin receptors to regulate appetite and energy expenditure. LY3541105 is in a Phase I trial (NCT05380323) to evaluate its safety, tolerability, and pharmacokinetics in healthy and overweight participants following subcutaneous administration.[22]

DA-1726

DA-1726 is a novel dual oxyntomodulin analog that functions as a GLP1R and GCGR agonist, developed for treating obesity. Based on data from preclinical studies in murine models, DA-1726 showed superior weight loss compared with semaglutide and cotadutide. DA-1726 also demonstrated similar weight reduction while consuming more food compared with tirzepatide. The Phase I trial (NCT06252220) is expected to conclude by June 2025, with top-line data anticipated in Q1 2025.[23]

Pemvidutide

Altimmune's pemvidutide (ALT-801) is a peptide-based dual agonist for the GLP-1R and GCGR being developed for obesity. In the Phase II MOMENTUM trial (NCT04881760), pemvidutide demonstrated a significant mean weight loss of 15.16% at the 2.4 mg dosage, and more than 30% of subjects lost 20% body weight (2.4 mg dosage) at week 48.[24]

Summary

In recent years, significant progress has been made in treating obesity. The approval of GLP-1R and GIPR agonists has greatly improved weight management and related comorbidities, helping many patients lead healthier lives. The treatment landscape is evolving, with promising results from products in advanced development stages. Metabolic modulators are now a primary focus, including dual agonists targeting both GLP-1R and GIPR to enhance metabolic rate and reduce appetite. Additionally, MC4R agonists offer solutions for genetic obesity, while myostatin inhibitors aim to increase muscle mass. These innovative approaches represent a comprehensive strategy to manage and potentially alleviate obesity-related morbidities.

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