Obesity Review: Peter Charlish

New formulations and mechanisms drive obesity R&D

Against a background of intense competition in the anti-obesity medicines sector, the past few weeks have seen the publication of significant new findings relating to products based on GLP-1 (glucagon-like peptide-1) agonists. Notable among these were the results of the Phase 3b SURMOUNT-5 trial, which compared the two market-leading products in this sector, Novo Nordisk A/S's Wegovy (semaglutide) and Eli Lilly & Co's Zepbound (tirzepatide). Published in *The New England Journal of Medicine*, the study found that treatment with tirzepatide was superior to treatment with semaglutide with respect to reduction in body weight and waist circumference[1].

In the US and elsewhere, semaglutide is marketed as Wegovy for overweight and as Ozempic for diabetes. In the US, tirzepatide is marketed as Zepbound for overweight and as Mounjaro for diabetes, but in the EU tirzepatide is marketed as Mounjaro for both indications. The two products differ slightly in their pharmacology: while semaglutide is a pure GLP-1 receptor agonist (GLP-1 RA), tirzepatide is a dual GLP-1 and GIP (gastric inhibitory polypeptide) receptor agonist.

Following the *NEJM* report, a study published in *eClinical Medicine* suggested that, in patients receiving first-generation GLP-1 RAs for diabetes and weight loss, the products do not increase the risk of obesity-related cancer (both obesity and diabetes are associated with an increased risk of certain types of cancer)[2]. The study also suggested that GLP-1 RAs may contribute to a decreased risk of obesity-related cancer by a mechanism other than simple weight loss, possibly by reducing inflammation. However, further studies are needed to confirm these findings and understand their underlying mechanisms, the study's authors concluded.

Limitations of the medicines

Despite the overall efficacy and safety of the current generation of anti-obesity medications based on GLP-1 RAs, use of the products still has certain limitations. For instance, they must be given by subcutaneous injection via a pre-filled pen, which must be refrigerated prior to use. This requirement is compounded by the fact that many users obtain these products from online pharmacies, necessitating the maintenance of a low temperature during transit. A major objective of companies marketing GLP-1 RAs has therefore been to develop a version which is more patient-friendly. This article will look at recent progress in this direction, as well as discussing other developments in the anti-obesity space.

A landmark event occurred in May 2025 when the US Food and Drug Administration formally accepted Novo Nordisk's New Drug Application (NDA) submission for a once-daily oral formulation of Wegovy for chronic weight management in obese or overweight adults with one or more comorbidities, and for reduction of the risk of major adverse cardiovascular events in overweight or obese adults with established cardiovascular disease. If the NDA is approved, Wegovy could become the first oral formulation of a GLP-1 RA indicated for chronic weight management (an oral formulation of semaglutide, Rybelsus, is already available in several markets, including the US, the EU and Japan, for type 2 diabetes management).

Novo Nordisk's NDA is based on results from the OASIS 4 trial, a 64-week Phase 3 placebo-controlled study which evaluated the safety and efficacy of once-daily oral semaglutide in 307 obese or overweight adults with one or more comorbidities (but not diabetes). The trial period included a 12-week dose escalation and a seven-week off-treatment follow-up period. According to results presented at the ObesityWeek conference in San Antonio, Texas, in November 2024, mean weight loss was 13.6% in the oral semaglutide group compared with 2.2% in the control group. A greater proportion of participants achieved various specific levels of weight loss in the semaglutide group than in the control group. Semaglutide also outperformed placebo in terms of improvement in cardiometabolic risk factors.

While semaglutide may become the first GLP-1 RA to be approved for oral use, Novo Nordisk is not putting all its eggs in one basket. The company is carrying out advanced clinical trials of CagriSema, a fixed-dose combination of semaglutide and the amylin analogue cagrilintide intended for once-weekly subcutaneous treatment. In March 2025, the company reported that, in the Phase 3 REDEFINE 2 trial, the product elicited a statistically significant and superior weight loss at 68 weeks compared with placebo. Novo Nordisk says it expects to file for the first regulatory approval of CagriSema in the first quarter of 2026.

Novo Nordisk is also developing amycretin, a long-acting co-agonist of GLP-1 and amylin intended for weekly subcutaneous or daily oral treatment of obesity. A Phase 1 trial of the oral formulation was completed in 2024, which found a 13.1% weight loss after 12 weeks.

More recently, a Phase 1b/2a study of amycretin in subjects with overweight or obesity found that it was associated with a higher mean body weight change than subjects receiving placebo. A high frequency of gastrointestinal side effects was reported, but rates were similar to those seen in early-phase studies of other GLP-1 and amylin agonists.

In addition, the Danish company is exploring potential anti-obesity products that act as cannabinoid receptor 1 (CB1) inverse agonists, and which are effective when given orally (an inverse agonist binds to the same receptor as an agonist but elicits the opposite response). Furthest ahead in the development pipeline is monlunabant, which as INV-202, was part of the acquisition of Inversago Pharmaceuticals Inc in August 2023. In September 2024, Novo Nordisk announced headline results from a Phase 2a

clinical trial of monlunabant in individuals with obesity and metabolic syndrome: after 16 weeks of treatment, subjects receiving a once-daily 10 mg dose of monlunabant reported an average weight loss of 7.1 kg, compared to a reduction of 0.7 kg with placebo. A related compound, INV-347, a "next-generation" oral small molecule CB1 receptor blocker, entered Phase 1 trials in January 2024.

Most recently, in May 2025, Novo Nordisk announced a planned collaboration with Septerna Inc, which is based in South San Francisco, California,US, to discover, develop and commercialise oral small molecule medicines for obesity, type 2 diabetes and other cardiometabolic diseases. Initially this will involve four development programmes for G protein-coupled receptor targets, including GLP-1, GIP and glucagon (GCG) receptors. The companies will jointly conduct research activities from discovery through to candidate selection, after which Novo Nordisk will have sole responsibility for all development and commercialisation activities.

Developments at Lilly

Meanwhile, over at Lilly, there are no plans to develop an oral formulation of tirzepatide; rather, the company is actively developing orforglipron, a GLP-1 RA that can be administered by mouth, for the treatment of both obesity and diabetes. Positive results from the ACHIEVE-1 Phase 3 trial of the product in diabetes were announced in April 2025, while Phase 3 studies of the product in obesity are still underway. However, in June 2023 the company announced Phase 2 data for once-daily oral orforglipron in adults with obesity or overweight, with at least one weight-related comorbidity. At the 26-week primary endpoint, orforglipron showed statistically significant dose-dependent body weight reductions of up to 12.6% for all doses, compared with 2.0% for placebo. Among the orforglipron group, body weight continued to decrease at 36 weeks with body weight reductions of up to 14.7%.

Also in Phase 3 trials at Lilly is retatrutide (LY3437943), a triagonist for the GIP receptor, the GLP-1 receptor and the GCG receptor. It is being studied for the treatment of obesity, osteoarthritis and obstructive sleep apnoea, with a planned simultaneous submission strategy. Retatrutide is administered once-weekly by subcutaneous injection. In Phase 2 studies published in 2023, retatrutide demonstrated a mean weight reduction up to 17.5% at 24 weeks in participants living with obesity or overweight without diabetes, and a mean weight reduction up to 24.2% at the end of 48 weeks.

Lilly also has a number of potential anti-obesity agents currently undergoing Phase 2 trials. These include:

- Bimagrumab (LY3985863), a monoclonal antibody that binds the activin/myostatin type II receptors ActRIIA and ActRIIB and blocks ligand binding;
- Eloratinide (LY3841136), a selective amylin receptor agonist;
- LY3549492, a GLP-1 RA; and
- Mazdutide (LY3305677), an analogue of another gut hormone, oxyntomodulin, that acts as a GLP-1R/GCGR dual agonist. It is being developed simultaneously in China by Innovent Biologics Co Ltd for both obesity (NDA submitted) and type 2 diabetes (currently in Phase 3). Innovent recently commenced a Phase 3 study comparing mazdutide with semaglutide in Chinese adults with overweight or obesity and metabolic dysfunction-associated fatty liver disease.

Also active in the GLP-1 RA space is Boehringer Ingelheim GmbH, which is developing survodutide (BI 456906), a long-acting GCG/GLP-1 receptor dual agonist for once-weekly subcutaneous administration, under licence from Zealand Pharma A/S. Boehringer Ingelheim is evaluating survodutide in global Phase 3 trials for people living with overweight and obesity, as well as key sub-populations. These include SYNCHRONIZE-1 and SYNCHRONIZE-2, which focus on people living with comorbidities, including those without and with type 2 diabetes, respectively. The SYNCHRONIZE-CVOT trial focuses on people living with cardiovascular disease, chronic kidney disease, or those at risk of cardiovascular disease. Additionally, Boehringer Ingelheim is evaluating survodutide in regional Phase 3 clinical trials in Japan (SYNCHRONIZE-JP) and China (SYNCHRONIZE-CN) for sub-populations of people living with obesity.

Zealand Pharma itself is also developing petrelintide, an investigational long-acting amylin analogue for once-weekly subcutaneous administration. It is being evaluated in a Phase 2 clinical programme in people living with overweight or obesity: ZUPREME-1 is for people without type 2 diabetes, while ZUPREME-2 is for people with type 2 diabetes. In March 2025, Zealand Pharma and Roche Holding AG formed a partnership to develop and market petrelintide as a potential foundational therapy for overweight and obese individuals.

Other companies with potential anti-obesity products undergoing Phase 2 trials include Altimmune Inc and Amgen Inc. Altimmune's candidate is pemvidutide, a GLP-1/GCG dual receptor agonist which recently completed the 48-week MOMENTUM Phase 2 trial in individuals with obesity and at least one obesity-related comorbidity. Mean weight loss on a 2.4 mg dose of pemvidutide was 15.6%, with over 30% of subjects achieving 20% or more weight loss. Amgen's candidate is MariTide (maridebart cafraglutide, AMG 133), a peptide-antibody conjugate that activates the GLP-1 receptor and antagonises the GIP receptor. A Phase 2 chronic weight management study is ongoing in adults living with overweight or obesity, with or without type 2 diabetes: data readout is predicted for the second half of 2025. Meanwhile, two Phase 3 trials are currently enrolling patients: MARITIME-1 involves adults with overweight or obesity but not diabetes, while MARITIME-2 includes adults with overweight or obesity together with type 2 diabetes.

Other mechanisms of weight control

Anti-obesity agents based on gut-derived hormones whose normal function is to help regulate food intake, known as incretins, are not the only kids on the block, with some companies pursuing other mechanisms of weight control. One such company is Rhythm Pharmaceuticals Inc, headquartered in Boston, Massachusetts, US, which focuses on the development of medicines for previously untreatable or undertreated neuroendocrine diseases. Rhythm was founded in 2008 and went public in 2017.

Rhythm's lead candidate is Imcivree (setmelanotide), a melanocortin-4 receptor (MC4R) agonist designed to treat severe obesity caused by impairment of the MC4R pathway (see box). Imcivree has been approved for various MC4R pathway diseases in the US, Europe, the UK and several other countries. In addition, the company is advancing a comprehensive clinical research programme for subcutaneous setmelanotide in MC4R pathway diseases, including the TRANSCEND Phase 3 trial in patients with acquired hypothalamic obesity. In April 2025, Rhythm announced that the trial had met its primary endpoint, with a statistically significant and highly clinically meaningful reduction in body mass index with setmelanotide in both adult and paediatric patients compared with placebo.

The MC4R pathway

Certain relatively uncommon types of obesity are caused by genetic variations in a key signalling pathway within the brain which is responsible for regulating hunger, food intake, satiety and energy expenditure. This pathway is known as the melanocortin-4 receptor (MC4R) pathway.

The MC4R pathway is mediated by the release of the hormone leptin from peripheral fat cells, which acts as a signal to the brain regarding how much fat is stored in the body. In the arcuate and paraventricular nuclei of the hypothalamus, leptin promotes signalling in the MC4R pathway by binding to specific receptors, referred to as LEPR. This stimulates production of pro-opiomelanocortin (POMC), a protein precursor of several biologically active peptides, including ACTH, various melanocyte-stimulating hormones (MSH), and beta-endorphin. MSH activates MC4 receptors, which results in reduced appetite and increased energy expenditure.

However, this pathway may be disrupted by loss-of-function mutations in key genes upstream of MC4R. Such variants may occur in genes encoding LEPR, or POMC, or one of some 30 or so other genes. Disruption of the pathway can cause persistent hyperphagia in early childhood, leading to rapid weight gain and obesity. Mutations of the MC4R gene itself are the most common form of monogenic obesity and have been implicated in 1% to 6% of early-onset severe obesity.

Rhythm is also carrying out the Phase 3 EMANATE trial of setmelanotide in patients with obesity and at least one specific gene variant in the MC4R pathway, with study completion scheduled for the end of this year. At the same time, Rhythm is developing the investigational MC4R agonists bivamelagon (LB54640) and RM-718. Bivamelagon is the subject of the Phase 2 SIGNAL trial in patients with hypothalamic obesity; unlike setmelanotide, it can be administered orally. RM-718 is still in Phase 1 studies and can also be given by mouth, but appears to offer a less frequent dosing schedule than bivamelagon.

Interestingly, as of April 2025 Pfizer Inc was developing an MC4R antagonist, PF-07258669, for the treatment of appetite loss malnutrition, although few details are available. The same month, Pfizer announced the decision to discontinue development of danuglipron (PF-06882961), an oral GLP-1 RA, which was being investigated for chronic weight management.

Elsewhere, Palatin Technologies Inc is currently conducting a Phase 2 clinical trial in obese patients with the MC4R agonist bremelanotide in combination with tirzepatide. The company says that while GLP-1 agonists to treat obesity are highly effective, as many as two-thirds of patients discontinue use in the first year because of side-effects and a plateau effect. This often results in patients regaining significant weight. The highly selective MC4R agonists being developed by Palatin could potentially play a vital role in treating obesity as monotherapy and/or combination therapy, the company states.

Saniona AB, a Danish company, is taking a different approach. The company is developing tesofensine, an orally active monoamine reuptake inhibitor that increases the levels of dopamine, serotonin and noradrenaline in the brain. These neurotransmitters are involved in the regulation of appetite, food-seeking behaviour and metabolism. Tesofensine's weight-reducing effect in obese patients was confirmed in a six-month Phase 2 clinical trial (the TIPO-1 trial) in which tesofensine led to a weight loss of at least 10%, which the company says is comparable to some GLP-1 RAs.

Diverse drug candidates

Saniona's partner Productos Medix SA has submitted a new drug application to the Mexican food and drug administration, COFEPRIS, for approval of tesofensine for the treatment of patients with obesity. Medix has completed a Phase 3 evaluation of oral tesofensine which effectively confirmed the safety and effectiveness profile observed in Saniona's Phase 2 studies.

Meanwhile the Japanese company Shionogi & Co Ltd is conducting Phase 2 trials of S-309309, an orally active anti-obesity drug that inhibits the enzyme monoacylglycerol acyltransferase 2, a novel mechanism. The trial, which is being carried out in the US, is evaluating S-309309's efficacy and safety in adults with a BMI of 30 or greater. Three doses are being tested to determine the maximum drug effect, designed to provide proof of concept and inform a global Phase 3 study. Shionogi says that S-309309 is one of its highest priority items and is being developed "at top speed".

It was mentioned earlier that Novo Nordisk is carrying out trials of a fixed-dose combination of semaglutide and cagrilintide (CagriSema), and other companies are also looking at the potential of combination therapies. One such company is Ascletis Pharma Inc, a Chinese company listed on the Hong Kong Stock Exchange. The company recently commenced a US Phase 2 study to evaluate the safety and preliminary efficacy of single-dose, ultra-long-acting, subcutaneously administered ASC47 in combination with semaglutide in participants with obesity who do not have type 2 diabetes (the ASC47-103 study). ASC47 is a small molecule agonist that selectively targets the thyroid hormone receptor beta in adipose tissue. In animal studies, the combination achieved a 57% greater reduction in body weight with muscle preservation compared with semaglutide monotherapy. The company says topline data from the ASC47-103 study are expected in the fourth quarter of 2025.

Another drug candidate showing potential for clinical use in combination with a GLP-1 RA is NodThera's NT-

0796, an oral NLRP3 inflammasome inhibitor. The NLRP3 inflammasome is involved in detecting damaged cells and eliciting an immune response. Preclinical data published in April 2025 showed that combined dosing with NT-0796 and semaglutide led to greater weight loss than monotherapy with either compound alone in an animal model of obesity. According to NodThera, treatment with NT-0796, which is able to penetrate the brain and appears to act centrally, also reduced weight regain following the cessation of treatment with semaglutide. The company is planning to initiate a Phase 2 trial of NT-0796 in obese individuals.

In summary, vigorous efforts to improve upon existing obesity treatments, including products with more convenient routes of administration and new mechanisms of action, are continuing. In addition, growing recognition of the benefits of weight reduction, including cancer risk reduction, improved cardiovascular health and improvement in co-morbidities such as sleep apnoea, are all combining to drive this dynamic, and lucrative, sector.

References:

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Interview: NodThera Ltd

Targeting the inflammasome to treat obesity

The Philadelphia, US-based biotech company NodThera Ltd has started dosing patients in a trial of a small molecule drug for obesity that targets a protein in an inflammasome complex in the brain. The Phase 2 study will enrol 160 patients who are obese and may or may not also have type 2 diabetes. The trial will be carried out over 24 weeks with headline data expected in the second quarter of 2026. Although it is small, the trial is being positioned to test a relatively new concept: whether it is possible to change the course of obesity by correcting underlying metabolic dysfunction.

In an interview on 6 June, Alan Watt, chief scientific officer of NodThera, said the company is positioning itself to treat chronic, low-grade inflammation that can arise as people age or follow unhealthy lifestyles. This is to be distinguished from inflammation that arises from an infection or injury. Obesity is one result of low-grade inflammation. Certain neurodegenerative diseases are another. NodThera has already tested its small molecule drug, NT-0796, in a Phase 1b/2 Parkinson's disease study where it showed evidence of reducing neuroinflammatory and inflammatory biomarkers in elderly patients. That was in 2024.

Now the company is shifting its priorities to put more resources into obesity against a background of rising disease prevalence and the demand for new treatments.

"Parkinson's is still a priority, but obesity is coming first," the executive commented.

In May, NodThera raised $50 million from investors to expand its clinical studies in obesity which, in addition to the recently initiated Phase 2 for NT-0796, will feature a combination study of NT-0796 and Novo Nordisk's semaglutide. This study is expected to start in the early autumn. Semaglutide is a glucagon-like peptide-1 drug which has been approved for the treatment of obesity under the name Wegovy. Wegovy has achieved weight loss of as much as 18.2% but also has shortcomings, one of which is the loss of lean body mass. The upcoming combination trial will attempt to find out whether it's possible to improve the weight loss profile. "We will be asking the question: can we ameliorate some of the side effects of the GLP-1s," Dr Watt said.

NodThera was launched in 2016 by Epidarex Capital, a private equity firm, on the basis of research conducted by Selvita SA, a service company in Poland. Its first venture round in 2018 was co-led by Sofinnova Partners and 5AM Ventures.

The science concept is to develop small molecule inhibitors of the NLRP3 inflammasome, one of several protein complexes that is a critical component of the innate immune system, triggering the release of pro-inflammatory cytokines to fight disease. Over-activity of the NLRP3 inflammasome is implicated in a wide range of diseases.

"The diseases we have been interested in from the onset of the company are diseases that have a commonality and that commonality is chronic, low-grade inflammation. So what we see is that cardiovascular disease, metabolic disease, obesity, arthritis and neurodegeneration, they all have a common aetiology," the executive said.

This article was written by the *MedNous* editor on the basis of an interview with the NodThera chief scientific officer, Alan Watt, on 6 June.