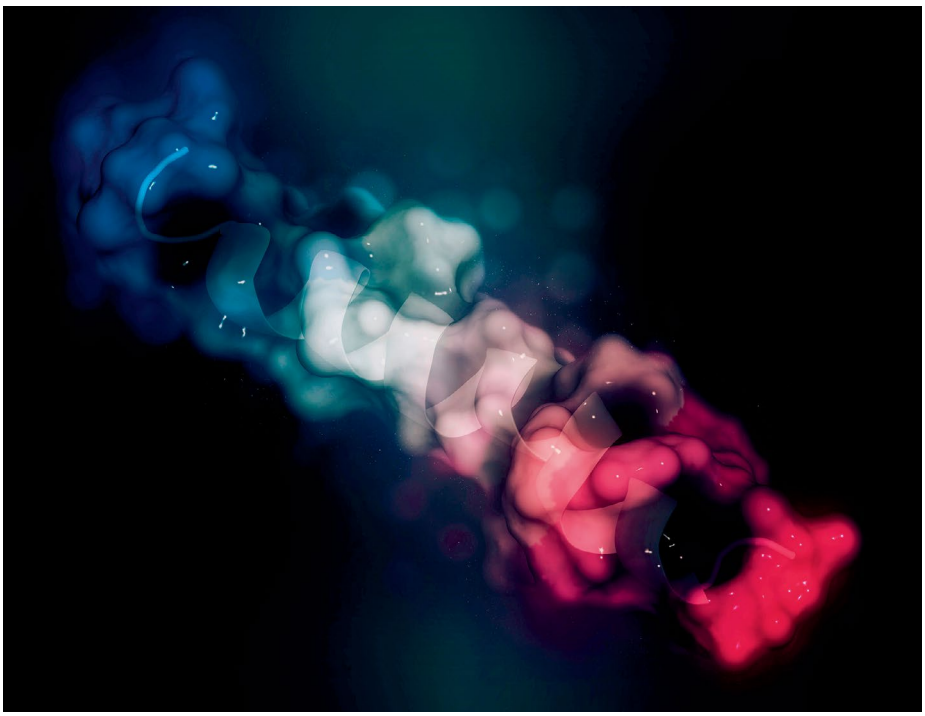
After GLP-1, what's next for weight loss?

The GLP-1 agonist Wegovy has re-energized the hunt for obesity treatments. Alternatives – ranging from bitter taste compounds to lean muscle boosters and bacteria – are already in the clinic.

By Melanie Senior



GLP-1 analogs mimic the action of a natural gut hormone.

Wegovy (semaglutide) is the most successful weight-loss drug in history. When Novo Nordisk launched the drug in mid-2021, it caused a sensation. Citizens and celebrities scrambled to access the therapy, triggering supply shortages – and a social media storm – that confirmed huge pent-up demand. Yet Wegovy could soon be upstaged by Eli Lilly's diabetes drug Mounjaro (tirzepatide), whose latest phase 3 weight loss data were released in April. Both drugs are expected to generate billions of dollars in annual sales and have re-kindled excitement in a field more often associated with setbacks than with success.

Wegovy, like Mounjaro, started out as an antidiabetic drug, with weight loss a welcome added benefit. Wegovy mimics the effects of glucagon-like peptide 1 (GLP-1), a hormone released by the gut's L cells in response to food. GLP-1 stimulates pancreatic cells to release insulin and lower blood glucose, sends satiety signals to the brain via the vagus nerve, and slows stomach emptying, making people feel full for longer. Mounjaro, approved for diabetes in May 2022, activates GLP-1 receptors and those of a second incretin (insulin-stimulating gut hormone) called glucose-dependent insulinotropic polypeptide (GIP).

Targeting both mechanisms – GLP-1 and GIP – with Mounjaro could lead to even more weight loss than GLP-1 agonism alone: in the 72-week phase 3 SURMOUNT-1 obesity trial, patients on the highest dose lost 17.8% more body weight on average than those taking placebo. The weight reduction experienced by participants in the Wegovy trial was 12.4% more than that with placebo, though, in the absence of head-to-head trials, direct comparisons are difficult. Some analysts peg peak annual sales for Mounjaro in obesity at over $10 billion, and Wegovy at about $8 billion.

Physicians are delighted with these new treatment options. Yet GLP-1 agonists aren't suitable for everyone, says Fatima Cody Stanford, an obesity medicine physician at Harvard Medical School. Although long-term safety data for the class are reassuring (the first GLP-1 agonist, Amylin's Byetta (exenatide), was approved in 2005 for diabetes), some patients don't respond to the drugs. In the Wegovy STEP trials, a quarter of participants who did respond experienced nausea and diarrhea or vomiting, though these effects were mostly mild and tended to dissipate. That the drug needs to be injected may also be a barrier. Plus, Wegovy costs over $1,300 per month and requires chronic administration to keep weight off: a year after stopping the drug, patients regained two-thirds of their previous weight loss. This motivates the hunt for alternatives (Table 1).

The next wave of weight-loss drugs aims at improving first-generation agents' efficacy, convenience or tolerability. Novo is trialling higher doses of its oral semaglutide (approved as Rybelsus for diabetes); top-line phase 3a results show similar weight loss after 68 weeks as that seen with the injectable version. Pfizer and Sosei Heptares' oral GLP-1 receptor agonist danuglipron also led to significant weight reduction in a phase 2 study, although at twice-daily dosing.

Others are following Lilly down the combination route, pairing GLP-1 agonism with GIP-modulating effects. GIP is secreted by K cells in the small intestine in response to food. It potentiates the insulin response from pancreatic beta cells. Viking Therapeutics is among those with an early-stage dual GLP-1/GIP agonist; on 28 March the biotech reported phase 1 results for its subcutaneous program and the initiation of a phase 1 trial for an oral once-daily formulation.

GLP-1 and GIP aren't simply additive, though. These incretins work together to regulate appetite, food intake and energy expenditure, but they need to be carefully balanced. Paradoxically, both GIP agonists and GIP antagonists have been shown to potentiate the weight reduction obtained with GLP-1 agonists. Amgen's bispecific antibody AMG 133, for instance, combines GLP-1 agonism and GIP antagonism. This combination triggered a weight loss of 14.5% in a phase 1 trial of 110 people with obesity.

Yet GIP has long been considered an obesogenic incretin because it stimulates

Table 1 | Beyond Wegovy: selected non-GLP1-targeted obesity therapies in clinical trials

Company	Approach	Stage of development
Aardvark Therapeutics	TAS2R agonist: bitter taste receptor agonists	Phase 2
Aphaia Pharma	Reawakening nutrient-sensing in intestinal lining cells using glucose capsules	Phase 2
Rivus Pharmaceuticals	HU6: mitochondrial uncoupler (DNP pro-drug)	Phase 2a/b
Versanis Bio	Activin type II receptor agonist: increases lean muscle mass	Phase 2b
Ysopia Bioscience	Xia1: single-strain biotherapy based on gut bacterium *Christensenella minuta*, found to limit weight gain and normalize metabolic markers	Phase 2
LG Chem	Oral melanocortin 4 receptor (MC4R) agonist: hypothalamic target	Expected to start phase 2/3 for rare genetic obesity in 2023
Scohia	Agonist of GPR40 (free fatty acid receptor 1): regulates insulin, GIP and GLP-1 secretion	Phase 2-ready
Shionogi	Oral monoacylglycerol acyltransferase 2 (MOGAT2) inhibitor: inhibits fat absorption and suppresses appetite via GLP-1 and other gut peptide release	Phase 1
Inversago Pharma	Peripheral cannabinoid receptor 1 (CB1R) small-molecule blocker for metabolic syndrome complicated by obesity and diabetic kidney disease	Phase 1
Novo Nordisk	LAGDF15 (growth differentiation factor 15) agonist: reduces food intake via central mechanism	Phase 1
Kallyope	Gut-restricted small molecules that act via the gut–brain axis to elicit a systemic response	Phase 1
Xeno Biosciences	XEN-101: delivers oxygen to the lower gut, mimicking microbiota changes induced by gastric bypass surgery per 'air hypothesis': surgery means more oxygen gets to gut, leading to more aerobic microbes	Approaching phase 1

Sources: websites; scientific literature; clinicaltrials.gov.

lipogenesis and enhances insulin-driven incorporation of fatty acids into triglycerides. In some circumstances, it triggers pancreatic alpha cells to release glucagon, which, although it raises blood sugar, may also enhance energy expenditure. Biopharma companies including Boehringer Ingelheim/Zealand Pharma, Lilly, AstraZeneca and Altimmune are testing compounds that hit glucagon receptors directly, alongside GLP-1, seeking to harness that energy effect. Preclinical and early human studies are also exploring whether triple incretins – unimolecular agonists of GLP-1, GIP and glucagon receptors – could achieve even greater metabolic outcomes while mitigating against the diabetogenic risk of glucagon stimulation.

Other hormones and signaling molecules that regulate appetite and energy balance are under investigation too. For instance, Novo Nordisk is testing semaglutide with cagrilintide, an analog of amylin, which, like GLP-1, curbs appetite and delays gastric emptying; the combination is in phase 3. A once-weekly synthetic peptide YY (PYY), another appetite-cutting gut hormone that may also boost fat oxidation and energy expenditure, is in phase 2 at Novo Nordisk. Scohia is among those looking to regulate insulin and GLP-1 secretion by activating GPR40, also called free fatty acid receptor-1; Shionogi's program inhibits monoacylglycerolacyltransferase, an enzyme that catalyzes triglyceride production and thereby influences gut incretin release.

Then there are those, such as Aardvark Therapeutics, looking to reawaken the natural gut hormones that are disrupted in obesity. The biotech uses chemical compounds with an extremely bitter taste, which target specific receptors in the mouth and also in the gut, where they trigger appetite-suppressing hormones like GLP-1, GIP, PYY and cholecystokinin. Aardvark's taste receptor type 2 (TAS2R) agonist is taken orally but acts, and stays, almost exclusively in the gut. The compound, ARD-101, is a salt of denatonium, a bitter chemical used in antifreeze and other products to prevent ingestion. "We're tricking the body into thinking it's being challenged with a toxin," says CEO Tien Lee. ARD-101 has completed phase 2 trials in obesity and after bariatric surgery. Results are still unpublished, but Lee claims that even low doses led to positive metabolic changes, with no serious side effects. The compound also reduces the inflammation associated with obesity, which GLP-1 agonists don't address. Aardvark is in phase 2 testing in Prader–Willi syndrome, a rare genetic condition characterized by constant hunger, obesity and diabetes.

A different approach, pursued by Zug, Switzerland-based Aphaia Pharma, is to reawaken nutrient-sensing cells in the distal gut that become less responsive in obesity. This loss may be due to changes in gut motility and greater food absorption in the upper intestine, which deprives lower gut cells of contact with nutrients, and may be exacerbated by inflammation. By delivering glucose directly to these cells using specially formulated capsules, Aphaia aims to restore a normal food response. "GLP-1 agonists don't target the nerve endings or their ability to sense nutrients," says CSO Steffen-Sebastian Bolz, alluding to the full range of signals – not only endocrine, but also neuroendocrine and neuronal – that control appetite, satiety and energy use. Bolz suggests that Aphaia's approach may complement GLP-1 agonists by helping maintain weight loss. Early trials in humans point to standalone benefits, too. Unpublished phase 1 data from 20 patients with obesity showed therapeutically relevant release of GLP-1, PYY, oxyntomodulin (which activates GLP-1 and glucagon), glicentin and other enteric hormones. The response was comparable to that seen after gastric bypass surgery, one of the most effective weight loss tools. A 150-patient phase 2 trial of the drug candidate, APH-012, is enrolling.

Lean muscle mass is the focus for Versanis Bio. This approach, in addition to driving fat loss, has several metabolic benefits, including reduced insulin resistance and higher basal metabolic rate. The monoclonal antibody bimagrumab, originally developed by Novartis for sarcopenia, targets activin type II receptors. This antibody blocks the muscle-degrading

impact of myostatin and activin and reduces fat mass, though the mechanisms aren't clearly understood. It is in a phase 2b trial as a monotherapy (given intravenously) and in combination with semaglutide in 450 patients who are overweight or have obesity. An earlier phase 2 randomized study helped patients with diabetes who are also either overweight or obese lose 22% fat mass and gain 4.5% lean mass relative to placebo; all participants were also on a calorie-restricted diet. Wegovy does cause muscle loss alongside weight reduction, but it improves the overall lean-to-fat mass ratio. Bimagrumab will need to better that; its sponsors also hope it will avoid the weight rebound associated with incretin therapies.

Others are attempting to boost energy expenditure, suppress fat absorption or use helpful gut bacteria to induce weight loss (Table 1). Rivus Pharmaceuticals harnesses mitochondrial uncoupling, a natural process that dissipates energy from fat and sugar oxidation as heat rather than generating ATP. An unpublished phase 2 study with Rivus's lead oral compound, HU6, reduced liver, visceral and total body fat and conserved muscle mass without changes to diet or exercise. Cardiovascular and metabolic health indicators also improved.

Larger, longer trials are required to determine the safety and efficacy of these approaches. Obesity drug development is littered with failures. Uncoupling agent 2,4-dinitrophenol (DNP), used for weight loss until the mid-twentieth century, caused fever, hyperthermia and death. Sanofi's appetite-curbing rimonabant, a cannabinoid receptor antagonist, was withdrawn from the European market in 2008, two years after launch, owing to severe mood disorders. Humans have evolved multiple compensatory pathways and regulatory mechanisms to protect feeding and energy expenditure, which rodent models don't always fully capture.

EraCal Therapeutics uses a zebrafish-based discovery platform to screen potential antiobesity compounds early. The Schlieren, Switzerland-based company's 'whole organism' approach picks up many more of the wide-ranging physiological and behavioral effects of potential drugs than traditional reductionist screening methods using cell lines or organoids, the company argues. The platform detected rimonabant's lack of behavioral selectivity — that it impacts other behaviors, beyond appetite — and has generated potentially more selective, and potent, oral appetite suppressors. Preclinical ERA 379 targets an undisclosed liver protein to change peripheral nutrient sensing. Unlike incretins, ERA 379 doesn't rely on the vagus nerve connecting the gut to the brain; it may therefore act synergistically with GLP-1 agonists. EraCal has a research deal with Novo Nordisk to find new obesity drug targets and another with Nestlé Health Sciences to uncover metabolically helpful nutraceuticals.

Multiple treatments and combinations are required in the fight against obesity, a complex, heterogenous condition that scientists are only just beginning to unravel — and which was only recently recognized as a disease rather than poor lifestyle choice. "Obesity is the new hypertension," says Louis Aronne, a physician specializing in metabolic diseases at Weill-Cornell Medical College. The arrival of GLP-1 agonists is "just the very beginning," he continues. Other approaches will emerge — including medicines that can be taken more intermittently. "I wouldn't exclude any idea at this point." With an estimated 650 million people affected worldwide, "we need everything we have to win this. We must learn from each other," says Aphaia's Bolz.

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