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Review article

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GLP-1-based therapies for diabetes, obesity and beyond

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Abstract

Glucagon-like peptide 1 (GLP-1)-based therapies, such as semaglutide and tirzepatide, represent highly effective treatment options for people with type 2 diabetes and obesity, enabling effective control of glucose and weight loss, while reducing cardiovascular and renal morbidity and mortality. The success of these medicines has spurred development of next-generation GLP-1-based drugs, promising greater weight loss, improved tolerability and additional options for the route and frequency of dosing. This Review profiles established and emerging GLP-1-based medicines, discussing optimization of pharmacokinetics and tolerability, engagement of new therapeutically useful pathways and safety aspects. Structurally unique GLP-1-based medicines that achieve substantially greater and rapid weight loss may impact musculoskeletal health, providing a rationale for therapeutics that more selectively target adipose tissue loss while preserving muscle mass and strength. Ongoing clinical trials in peripheral vascular disease, neuropsychiatric and substance use disorders, metabolic liver disease, arthritis, hypertension and neurodegenerative disorders may broaden indications for GLP-1-based therapeutics.

Sections

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Introduction

Glucagon-like peptide 1 (GLP-1), rapidly released from intestinal L cells in response to food intake, was first described as a hormone that stimulates pancreatic insulin secretion[1–3]. This finding was subsequently followed by observations that GLP-1 also inhibits pancreatic glucagon secretion and gastric emptying. Together, these findings instigated the development of a new class of GLP-1-based medicines as glucose-lowering therapeutics for type 2 diabetes (T2D)[4]. Subsequent preclinical studies in rats and mice demonstrated that GLP-1 also reduces food intake by influencing brain regions involved in the regulation of feeding[5–7], actions requiring the canonical G-protein-coupled GLP-1 receptor (GLP-1R)[7], enabling weight loss. This weight loss effect was later demonstrated in humans with sustained administration of GLP-1 (ref. 8). The related gut-derived insulin stimulating hormone, glucose-dependent insulinotropic polypeptide (GIP; produced by enteroendocrine K cells), was found to be less effective in lowering glucose and body weight in humans, but manipulating GIP receptor (GIPR) signalling proved effective when combined with GLP-1 in next-generation therapies for T2D and weight loss[9].

The early development of GLP-1 therapies (see Fig. 1) faced several challenges. These included the degradation of both GLP-1 and GIP by dipeptidyl peptidase-4 (DPP-4) and rapid clearance of native GLP-1 via the kidney, together with substantial gastrointestinal adverse events that developed quickly if therapeutic doses of GLP-1 receptor agonists (GLP-1RAs) were administered too rapidly, resulting in high drug levels within hours of administration[4]. Remarkably, the first GLP-1RA approved for T2D in 2005 was twice-daily exenatide, a GLP-1-related peptide discovered in the venom extracted from the *Heloderma suspectum* lizard. Although exendin-based medicines such as twice-daily or once-weekly exenatide are relatively resistant to enzymatic inactivation by DPP-4 due to a position 2 glycine, they exhibit only 53% amino acid identity relative to native GLP-1, and elicit greater immunogenicity[10]. However, the development of high-titre anti-exendin antibodies has not proven to meaningfully impact the clinical response to therapy or the safety of these exendin-based medicines[11].

The first human GLP-1RA, liraglutide – a long-acting human GLP-1RA – contained a 16-carbon lipid side chain to enable non-covalent binding to albumin. This modification extended the circulating half-life ($t_{1/2}$), conferred partial resistance to DPP-4 and delayed renal clearance. Liraglutide was approved for T2D in 2010, exhibiting an extended 24 h pharmacokinetic profile suitable for once-daily administration (Table 1). The first once-weekly drug introduced for T2D, an extended-release form of exenatide, was approved in 2012, followed in 2014 by once-weekly dulaglutide, an immunoglobulin-based GLP-1RA (Fig. 1). Liraglutide was the first GLP-1 medicine studied for weight loss and was approved in 2014 for treatment of people with overweight (body mass index (BMI) 27 kg m^{-2}) and one or more weight-related comorbidities, or obesity[12]. Modern-day GLP-1 medicines, exemplified by semaglutide, containing a C18 octadecanedioic acid moiety attached to Lys26, and the GIPR–GLP-1R co-agonist tirzepatide, containing a C20 eicosanedioic acid lipid moiety, are approved for both T2D and obesity (Table 1). These peptides feature a slower time to the circulating maximal drug concentration, (C_{Max}), are resistant to degradation by DPP-4 and are also lipidated, enabling non-covalent binding to albumin and an extended pharmacokinetic profile suitable for once-weekly administration. Although doses of semaglutide ranging from 0.5 mg to 2 mg once weekly are approved for treatment of T2D, a higher dose of 2.4 mg once weekly is approved for weight loss in people with overweight or obesity. In contrast, a similar range of tirzepatide doses, from 5 mg to 15 mg weekly, is approved for both T2D and weight loss[13].

Current GLP-1 drug development for obesity and related complications is focused on molecules that may provide greater weight

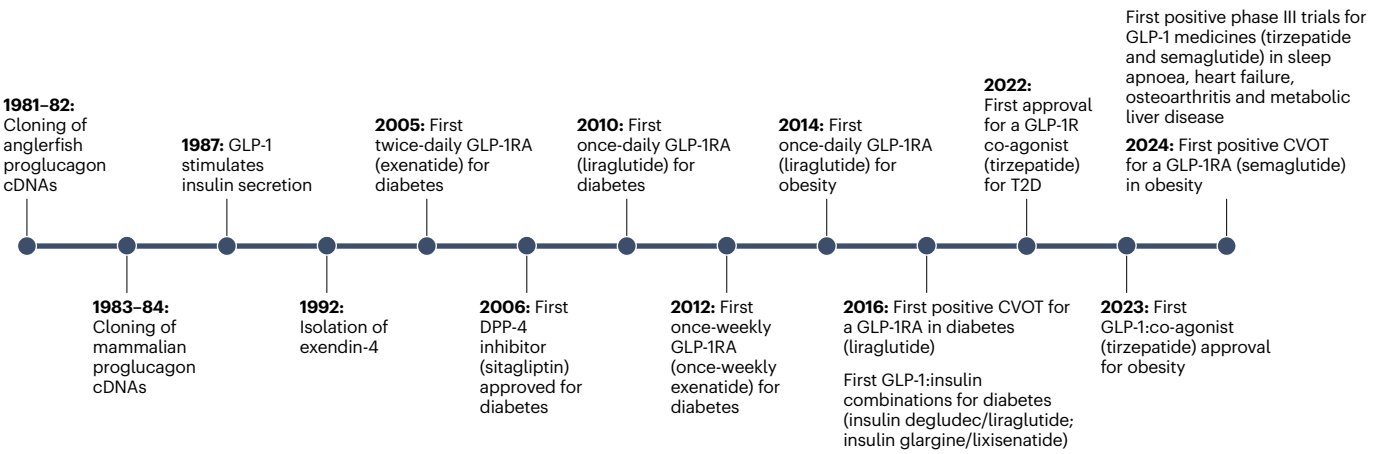


Fig. 1 | Timeline for GLP-1-based therapeutics. Key events include the first cloning of anglerfish proglucagon cDNAs revealing the identification of a glucagon-like peptide 1 (GLP-1) sequence[146], the cloning of the first mammalian proglucagon cDNAs and genes[147,148], the first demonstration that GLP-1 directly stimulates insulin biosynthesis and secretion from islet β-cells in a glucose-dependent manner[1]. The isolation of exendin-4 in 1992 (refs. 149,150) ultimately led to the approval of synthetic exendin-4, designated as exenatide, as the first GLP-1 medicine approved for the treatment of type 2 diabetes (T2D)[150]. Sitagliptin, the first dipeptidyl peptidase-4 (DPP-4) inhibitor, was approved in 2006 (ref. 151); the first once-weekly GLP-1 medicine, once-weekly exenatide[10], was approved in 2012; and the first approval of a GLP-1 medicine for weight loss in obesity, liraglutide, was approved in 2014 (ref. 152). Two fixed-ratio GLP-1-insulin formulations were approved in 2016: insulin degludec/liraglutide and insulin glargine/lixisenatide[153]. The first GLP-1 receptor agonist (GLP-1RA) outcome trial, with liraglutide, was reported in 2016 (ref. 154), and the first GLP-1 co-agonist, tirzepatide, was approved in 2022 for T2D (ref. 155) and in 2023 for weight loss (ref. 156). Landmark clinical trials expanding the indications for GLP-1 medicines include the SELECT cardiovascular outcomes trial with semaglutide[108], the tirzepatide obstructive sleep apnoea trials[122], semaglutide and, separately, tirzepatide for heart failure outcomes[113,157], and semaglutide for osteoarthritis and metabolic liver disease[121,126].

Table 1 | Approved GLP-1 based therapies

Drug	Target	Indication	Administration	Dose	Key trial	Year of approval
Exenatide	GLP-1R	T2D	Twice daily subcutaneously	10 µg twice daily	AMIGO	2005
Exenatide once weekly	GLP-1R	T2D	Once weekly	2 mg once weekly	EXSCEL	2012
Lixisenatide	GLP-1R	T2D	Once daily	20 µg daily	ELIXA	2016
Liraglutide	GLP-1R	T2D	Once daily	1.8 mg daily	LEADER	2010
		Obesity		3 mg daily	SCALE	2014
Dulaglutide	GLP-1R	T2D	Once weekly	4.5 mg weekly	REWIND	2014
Semaglutide	GLP-1R	T2D	Once weekly	1–2 mg weekly	SUSTAIN-6	2017
		Obesity		2.4 mg weekly	SELECT	2021
		T2D	Oral daily	14 mg daily	PIONEER-6 SOUL	2019
Tirzepatide	GLP-1R /GIPR	T2D	Once weekly	15 mg weekly	SURPASS CVOT	2025
		Obesity			SURMOUNT MMO	2027

GIPR, glucose-dependent insulinotropic polypeptide receptor; GLP-1, glucagon-like peptide 1; GLP-1R, glucagon-like peptide 1 receptor; T2D, type 2 diabetes.

loss, improved tolerability, less frequent administration and, ideally, lower manufacturing costs. GLP-1 medicines under development include small molecules and peptides, as well as antibody-based GLP-1RAs. Although some of these activate the GLP-1R alone, there is considerable activity in developing GLP-1-based multi-agonists including GIPR–GLP-1R co-agonists, glucagon receptor (GCGR)–GLP-1R co-agonists, GCGR–GIPR–GLP-1R triple agonists, amylin receptor (AMLNR)–GLP-1R co-agonists and GIPR antagonists–GLP-1RAs.

This Review will first briefly highlight the profiles of currently approved GLP-1-based therapies such as semaglutide and tirzepatide, and then focus on the characteristics of emerging therapeutics in clinical development, including novel GLP-1RAs and GLP-1-based multi-agonists. Considerations for the use of GLP-1-based therapies and potential future indications are discussed.

Characteristics of approved GLP-1-based therapies

The field of GLP-1-based medicines has evolved from the initial approval of short-acting medicines such as exenatide twice daily and lixisenatide, to longer-acting therapies, such as liraglutide once daily, and once-weekly therapies, such as exenatide once weekly and dulaglutide. Modern GLP-1-based medicines, such as semaglutide and tirzepatide, provide enhanced glucose control and greater weight loss, and are approved for the treatment of both T2D and overweight with one or more weight-related complications, or obesity[14,15]. The attributes of current GLP-1-based medicines are outlined below, highlighting efficacy, safety and opportunities for differentiation of next-generation therapies.

Mechanisms of action

GLP-1 stimulates insulin and inhibits glucagon secretion and gastric emptying, enabling effective reduction of glycaemia in people with T2D. Insulin sensitivity may be improved indirectly with weight loss[16]. The pancreatic islet actions of GLP-1 are glucose-dependent, contributing to a low rate of hypoglycaemia in the absence of concomitant use of sulfonylureas or insulin. The inhibition of gastric emptying is subject to tachyphylaxis, although some individuals continue to experience clinically significant slowing of gastrointestinal transit with sustained use of GLP-1 medicines. Interpretation of the effects of GLP-1 medicines on gastric emptying is challenged by the suboptimal validity of using acetaminophen absorption, commonly deployed as a surrogate for gastric emptying, rather than more rigorous techniques such as scintigraphy or stable isotope breath tests[17]. Notably, reports of gastrointestinal adverse events correlate poorly with the rate of gastric emptying in people treated with GLP-1 medicines, and the extent of weight loss achieved with GLP-1 medicines such as semaglutide and tirzepatide does not reflect the presence or absence of gastrointestinal adverse events[18,19]. Weight loss is primarily achieved through a reduction of hunger and decreased food intake, reflecting engagement of multiple anatomically distinct populations of GLP-1R$^+$ neurons in the hypothalamus, brainstem and additional regions of the central nervous system (CNS)[13]. There is little evidence to support a role for currently utilized GLP-1 medicines in the augmentation or relative preservation of energy expenditure in humans[20].

Pharmacokinetic and efficacy profiles

The first GLP-1 medicine approved in 2005, exenatide, exhibited a very short $t_{1/2}$ of ~2.4 h, requiring twice-daily administration to achieve reductions in HbA1c of 0.6–0.8%, with a modest 1–2% weight loss[21]. Lixisenatide is an exenatide derivative containing amino acid modifications at the carboxy terminus to enhance stability that exhibits a circulating $t_{1/2}$ of 3 h; lixisenatide was non-inferior (20 µg once daily) to exenatide 10 µg twice daily for glucose control in people with T2D (ref. 22). Exenatide once weekly is administered as a microsphere-encapsulated exenatide poly-(D,L-lactide-co-glycolide) mixture injected subcutaneously, with extended release of exenatide exhibiting greater efficacy for glucose control and comparable weight loss relative to twice-daily exenatide[10]. Liraglutide, a human GLP-1 analogue administered once daily at doses of 1.2 mg or 1.8 mg, was approved in 2010 for T2D (Fig. 1) and exhibits a circulating $t_{1/2}$ of 13–15 h via non-covalent binding to albumin; liraglutide has a sustained pharmacokinetic profile, enabling 24 h activation of the GLP-1R after once-daily administration. In a head-to-head randomized trial, liraglutide produced a greater reduction in HbA1c and more weight loss compared with exenatide once weekly, associated with more gastrointestinal adverse events in liraglutide-treated subjects, over 26 weeks[23]. Dulaglutide is an immunoglobulin Fc-based

molecule containing two modified GLP-1 peptides, with a pharmacokinetic profile suitable for once-weekly administration[24]. A head-to-head trial demonstrated dulaglutide 1.5 mg once weekly was non-inferior to liraglutide 1.8 mg daily for HbA1c reduction, but weight loss (2.9 kg versus 3.61 kg for dulaglutide versus liraglutide, respectively) was greater with liraglutide over 26 weeks in people with T2D (ref. 25). Progressively greater weight loss was observed with development of newer GLP-1 medicines — 1–2% with exenatide twice daily, 2–4% with exenatide once weekly and dulaglutide[23,26], and 3–4% with liraglutide[25] — in trials for 26–52 weeks in people with T2D.

Next-generation GLP-1 medicines, exemplified by semaglutide and tirzepatide (Fig. 2), are long-acting peptides administered once weekly, and are more effective for glucose control and weight loss than older molecules, likely reflecting enhanced receptor engagement and optimized pharmacokinetics. The superior efficacy of tirzepatide presumably reflects engagement of both GIPRs and GLP-1Rs and a possible contribution from biased receptor signalling, favouring cAMP generation over β-arrestin recruitment[27].

Semaglutide 1 mg weekly produced a greater reduction in HbA1c and body weight relative to dulaglutide at 1.5 mg once weekly over 40 weeks in people with T2D (ref. 28). In contrast, all three doses of tirzepatide (5 mg, 10 mg and 15 mg once weekly) were more effective in lowering HbA1c and reducing body weight over 40 weeks compared with treatment with semaglutide 1 mg once weekly[29]. The two leading GLP-1 medicines, semaglutide and tirzepatide, have been extensively studied in people with T2D and people with overweight/obesity. The glucose-lowering efficacy of semaglutide 1 mg once weekly was studied in the SUSTAIN trials in people with T2D and in the STEP trials (2.4 mg once weekly) in people with overweight and one or more weight-related comorbidities, or obesity. These trials demonstrated superior HbA1c reduction for semaglutide versus older GLP-1 medicines and insulin. A direct comparison of semaglutide versus insulin glargine therapy over 30 weeks in subjects with suboptimal glycaemic control on either metformin alone or in combination with a sulfonylurea demonstrated greater reductions of HbA1c and body weight with less hypoglycaemia in subjects treated with semaglutide[30]. Higher doses of semaglutide, up to 2 mg once weekly, were more effective for glucose control and weight loss relative to 1 mg once weekly in people with T2D and were subsequently approved for T2D in many regions[31].

In the STEP weight loss clinical trial programme, semaglutide 2.4 mg once weekly achieved 10–17% weight loss across a range of study populations, with up to 40% of subjects experiencing 20% weight loss in some trials[13,32]. Evaluation of higher doses of semaglutide, 7.2 mg once weekly, in people with overweight or obesity revealed up to 20.7% weight loss (18.3% placebo-subtracted) after 72 weeks in the STEP UP trial, compared with 15.1% placebo-subtracted

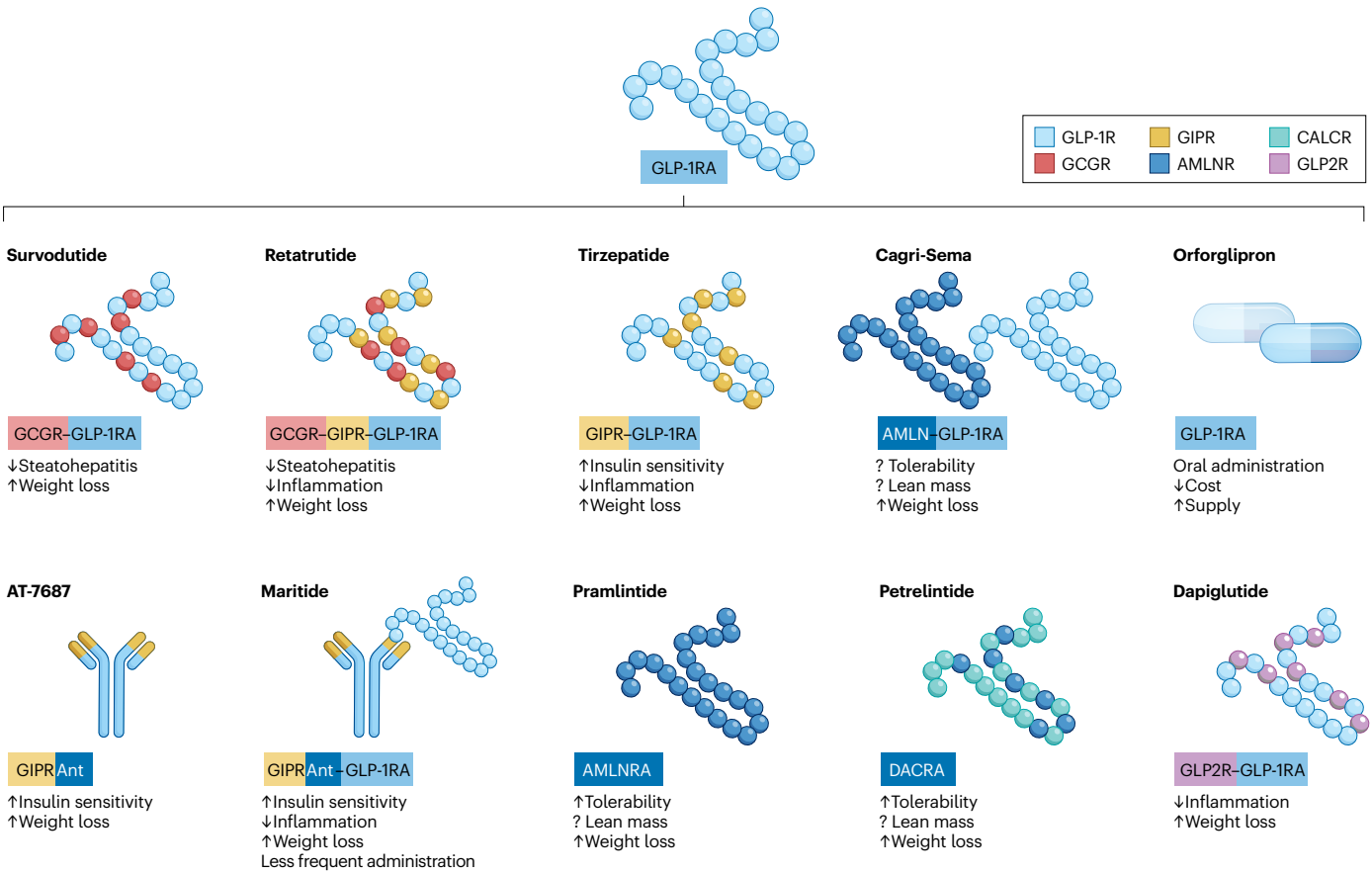


Fig. 2 | New classes of GLP-1-related therapies in clinical development. Representative examples of new medicines with their envisioned beneficial attributes indicated below each drug class. AMLNR, amylin receptor; AMLNRA, amylin receptor agonist; CALCR, calcitonin receptor; DACRA, dual amylin and calcitonin receptor agonist; GCGR, glucagon receptor; GIP, glucose-dependent insulinotropic polypeptide; GIPR, GIP receptor; GIPRAnt, GIPR antagonist; GLP-1, glucagon-like peptide 1; GLP-1R, GLP-1 receptor; GLP-1RA, GLP-1 receptor agonist; GLP2R, glucagon-like peptide 2 receptor.

weight loss with semaglutide 2.4 mg once weekly (https://www.novonordisk.com/news-and-media/news-and-ir-materials/news-details.html?id=915087); 33% of trial subjects achieved >25% weight loss with semaglutide 7.2 mg, with adverse events numerically similar to those reported for the semaglutide 2.4 mg once-weekly cohort.

The first clinically approved GIPR–GLP-1R dual agonist, tirzepatide, is a 39 amino acid acylated peptide containing a C20 fatty diacid connected via a linker to the lysine at position 20 (ref. 33). Tirzepatide exhibits a $t_{1/2}$ of ~5 days, with a time to C_{max} of 24–48 h[33]. Tirzepatide potentiates insulin secretion via activation of both the GIPR and the GLP-1R in human islets[34]. Tirzepatide preferentially activates GIPR versus GLP-1R (approximately fivefold weaker at the GLP-1R (ref. 33)) and is also biased at the GLP-1R, favouring cAMP generation versus recruitment of β-arrestin[27]. Prior to the success of tirzepatide, two structurally distinct GIPR–GLP-1R co-agonists were tested clinically in subjects with T2D and were not clearly superior to GLP-1RAs for reduction of HbA1c or body weight[35,36]. Support for the concept that GIPR agonism alone produces favourable metabolic benefits derives from studies of LY3537021, a long-acting GIPR agonist that produces 2.7 kg (placebo-subtracted) weight loss after 4 weeks of once-weekly administration to patients with T2D (see Related Links).

The phase III SURPASS clinical trial programme evaluated the effectiveness of tirzepatide in several thousand people with T2D, demonstrating robust, often unprecedented, reductions in HbA1c and body weight across a wide range of individuals. For example, tirzepatide was evaluated against semaglutide over 40 weeks in people with T2D, at doses of 5 mg, 10 mg or 15 mg once weekly[29]. All three dose regimens provided superior reduction in HbA1c and body weight relative to semaglutide 1 mg once weekly. Despite the superior efficacy of tirzepatide, rates of adverse events were comparable in people treated with tirzepatide versus semaglutide. Starting at a mean baseline weight of 93.7 kg, subjects on the highest dose of tirzepatide 15 mg once weekly experienced a mean weight loss of 11.2 kg versus 5.7 kg with semaglutide[29].

The effectiveness of tirzepatide as a weight loss therapy in people with overweight and one or more weight-related comorbidities or people with obesity was studied in multiple clinical trials over 72 weeks in the SURMOUNT programme. Tirzepatide produced robust weight loss in people with or without T2D, resulting in up to 20% placebo-subtracted weight loss at the highest dose tested (15 mg weekly) in people without T2D (ref. 37). Moreover, low rates of discontinuation (6–10%) were observed across the SURMOUNT trial programme[37–40]. The SURMOUNT-2 trial studied the extent of weight loss achievable with tirzepatide in 938 people with T2D, baseline HbA1c of 8.02% and either overweight or obesity (baseline BMI 36.1 kg m^{-2}) with concomitant advice on choice of healthy balanced meals to achieve a 500-kcal deficit reduction, as well as recommendations for moderate physical activity of at least 150 min per week. Trial participants treated with tirzepatide achieved up to 11.6% placebo-subtracted weight loss at the 15 mg once weekly dose[38]. Remarkably, at the end of the 72-week treatment period, the mean HbA1c was 7.5%, 7% and 6.9% for subjects treated with placebo, tirzepatide 10 mg and tirzepatide 15 mg weekly, respectively[38].

The SURMOUNT-5 trial compared the efficacy of maximally tolerated doses of tirzepatide, up to 15 mg once weekly, with semaglutide 2.4 mg once weekly in adults with obesity or overweight and weight-related comorbidities, over 72 weeks. The percentage change in body weight was 20.2% with tirzepatide, versus 13.7% with semaglutide; 31.6% versus 16.1% of subjects treated with tirzepatide versus semaglutide, respectively, achieved at least 25% weight loss (see Related Links). The titration steps required to achieve effective control of glycaemia or meaningful weight loss are simpler for tirzepatide relative to the titration regimen required to attain maximally effective doses of semaglutide.

Current dogma, based in part on substantial weight regain of approximately two-thirds of the previous weight lost observed 1 year following discontinuation of semaglutide in the STEP 1 trial extension[41], highlights the importance of prolonged use of GLP-1 medicines to maintain weight loss for the majority of individuals. After a mean weight loss of 17.3% over 68 weeks with semaglutide in the STEP 1 trial, weight regain of 11.6% occurred over the ensuing 52 weeks resulting in a net loss of 5.6% body weight at the end of the 120-week observation period[41]. In contrast, after once-weekly tirzepatide therapy for 36 weeks in subjects with overweight and obesity studied in the SURMOUNT-4 trial, 46.5% of subjects maintained at least 10% or more of the weight loss 1 year after discontinuation of tirzepatide[39]. Understanding interindividual differences in weight loss achieved as well as the extent, rapidity and distribution of weight gain following discontinuation of GLP-1 medicines is currently limited. For example, analysis of the impact of genetic factors known to affect body weight on the extent of weight loss with GLP-1 medicines or metabolic surgery was undertaken in 10,960 subjects from 9 multi-ancestry biobank studies and 6 countries. Polygenic scores linked to body weight and T2D, as well as missense variants related to GLP-1R signalling, were not found to be associated with the weight loss effects of GLP-1 medicines[42]. Elucidation of factors predicting weight loss or weight regain responses represents an important area for progress towards implementation of personalized medicine approaches in the weight loss clinic (Boxes 1 and 2).

Safety and tolerability profiles

The principal adverse events elicited by all GLP-1 medicines are nausea, diarrhoea, constipation and vomiting, reflecting activation of CNS GLP-1R$^+$ neurons linked to aversive responses, and reduction of gastric emptying[14]. The extent of the adverse events reported reflects individual sensitivity and C_{Max}, and the time to C_{Max}. Interrogation of the CNS sites mediating the actions of GLP-1 reveals that distinct brain regions are responsible for aversive (area postrema) versus anorectic (hypothalamus and hindbrain) responses[43,44], raising the theoretical possibility of selective targeting of GLP-1 medicines to predominantly engage neural circuits enabling weight loss. Preclinical data support a modest anti-aversive activity for GIP, potentially contributing to attenuation of the aversive responses of co-administered GLP-1RAs (ref. 45). Notably, a single dose of the long-acting, selective GIPR agonist LY3537021 administered to predominantly male subjects with overweight or obesity attenuated the gastrointestinal adverse events of once-daily liraglutide up-titrated over a 9-day period to a final dose of 2.4 mg once daily over the last 5 days[46].

Optimized pharmacokinetics with slower time to a greater C_{Max} might enable achievement of greater efficacy and tolerability than that observed with current GLP-1 medicines and represents an important goal for newer GLP-1 medicines, including small-molecule oral GLP-1RAs. Whether the route of administration (oral pill versus parenteral injection) influences tolerability independent of pharmacokinetic profiles is unclear, as the tolerability of oral versus injectable semaglutide was identical when corrected for circulating drug concentrations in the PIONEER and SUSTAIN trials in people with T2D (ref. 47).

If gastrointestinal adverse events are sufficiently severe so as to limit adequate fluid intake, dehydration may ensue, leading to acute kidney injury even in the absence of pre-existing kidney impairment[14].

Box 1 | Achieving healthy weight loss

Concerns have been raised that the emergence of more powerful weight loss medicines achieving 20–25% or even greater weight loss may be associated with disproportionately higher rates of clinically significant sarcopenia, principally reduced muscle mass and strength, known to be associated with adverse outcomes and excess mortality[163], providing therapeutic opportunities to combine muscle-sparing agents with glucagon-like peptide 1 (GLP-1) medicines. Consistent with the goal of achieving healthy weight loss and meaningful outcomes (see Fig. 3), increasing attention is now focused on body composition, muscle strength, functional activity and the proportion of loss of fat mass versus fat-free mass[164,165]. Clinical trial data support the benefits of regular exercise several times a week in potentiation of the effects of reduction of fat mass with liraglutide therapy, while preserving fat-free mass; enduring benefits on the maintenance of body weight and composition were observed 1 year after cessation of the exercise + liraglutide regimens, relative to findings with liraglutide alone[166]. Nevertheless, changes in body composition, muscle strength and ensuing metabolic sequelae observed after medication cessation and subsequent weight regain has not been adequately studied.

Beyond the acknowledged importance of diet (sufficient protein) and resistance exercise, clinical candidates under consideration for preferential sparing of fat-free mass in combination with GLP-1 medicines include growth hormone or growth hormone releasing hormone analogues, urocortin-2/3, bimagrumab, the apelin receptor agonist azelaprag (formerly AMG-986)[167], and antibodies and antagonists targeting activin, myostatin, TGFβ and their respective receptors. A phase II trial studying azelaprag in combination with tirzepatide for weight loss was halted due to concerns of elevated liver enzymes associated with azelaprag exposure (https://ir.bioagelabs.com/news-events/press-releases). Several clinical trials are underway assessing the impact of combining bimagrumab with semaglutide or tirzepatide over 48 weeks on body composition measured by dual-energy X-ray absorptiometry and quality of life (NCT05616013 and NCT06643728). Beyond preservation of fat-free and muscle mass, the ideal end-points for demonstration of compelling functional improvement in muscle mass and overall health have not yet been widely agreed. Although grip strength, 6-min walk time, stair climbing and quality of life measurements are important surrogates, they are not as functionally meaningful as the ability to be mobile and avoid falls, fractures, emergency room visits and hospitalizations. Moreover, registration trials may not be sufficiently powered to detect significant differences in all clinically relevant outcomes, and the validity and utility of surrogates for successful trial outcomes will need to be clarified. Key elements relating to this important emerging area of excess weight loss, clinically significant sarcopenia, and options for monitoring and achieving healthy weight loss are further discussed in refs. 168–170.

Gall bladder adverse events, principally cholecystitis and gallstones, are reported with GLP-1 medicines in trials of people with T2D or obesity, generally in fewer than 1% of the exposed population. The relative risk of biliary tract adverse events reflects the dose and duration of exposure to GLP-1 medicines[48]. Whether the gall bladder adverse events reflect contributions from concomitant weight loss, alterations in biliary tract motility, changes in lithogenic bile composition or other mechanisms remains unclear. Initial concerns raised about the risk of pancreatitis or pancreatic cancer have not been substantiated by clinical trial or real-world data[14]. GLP-1 medicines are contraindicated in people with a history of medullary thyroid cancer or multiple endocrine neoplasia type 2; whether these medicines increase rates of well-differentiated thyroid cancer independent of enhanced ascertainment remains uncertain, and an ongoing registry, now into its second decade, is scrutinizing the potential relationship of GLP-1 medicines and medullary thyroid cancer[14,49].

Novel GLP-1RAs

The currently approved GLP-1RAs are all peptides delivered by subcutaneous injection, except for an oral formulation of semaglutide that is approved for T2D (Box 3). Oral semaglutide is co-formulated with sodium *N*-(8-[2-hydroxybenzoyl] amino) caprylate (SNAC), enabling rapid absorption of semaglutide across the gastric mucosa while simultaneously protecting it from local enzymatic degradation[50]. Although the bioavailability of oral semaglutide remains low, and the tablet must be administered on an empty stomach, it still provides effective glucose control when administered once daily in phase III trials for T2D (ref. 50). The SNAC ingredient is generally recognized as safe (GRAS) and has no known independent side effects. Multiple small-molecule GLP-1RAs are being developed with the aim of providing oral drugs, which would also be less challenging to manufacture in the quantities needed to meaningfully expand the distribution of GLP-1 medicines (Fig. 2). Oral GLP-1RAs do not require a supply of pens, nor the final fill and finish step merging active pharmaceutical ingredients into the pens, and neither would they require a cold chain for distribution. The available data suggest that several of these investigational oral GLP-1RAs exhibit pharmacokinetic and pharmacodynamic profiles suitable for once-daily oral dosing, with the most promising molecules likely to achieve at least 15–20% weight loss in people with obesity.

There is also continued interest in peptide and small-molecule GLP-1RAs and combinations that could improve upon currently marketed drugs, with differentiation possible through attainment of greater weight loss, less frequent administration, greater tolerability or achievement of better outcomes beyond glucose control or weight loss (Fig. 2).

Small molecules

ASC30. ASC30 is a small-molecule GLP-1RA being developed by Ascletis Pharma Inc. that has been studied in two phase I 28-day multiple ascending dose (MAD) trial in subjects with obesity, at doses from 2 mg to 40 mg up-titrated weekly, producing weight loss ranging from 4.3% to 6.3% from baseline at the maximum tolerated dose. Ascletis also intends to develop a once-monthly subcutaneous formulation of ASC30 (see Related Links).

AZD5004. ECC5004, now co-developed with AstraZeneca as AZD5004, is a biased small-molecule GLP-1RA that favours cAMP accumulation without β-arrestin 2 recruitment or receptor internalization.

Once-daily administration of AZD5004 exhibits few pharmacokinetic differences whether administered with or without food, and exhibits dose-proportional pharmacokinetics, with a time to maximal concentration (T_{max}) of 8–12 h and a median elimination $t_{1/2}$ of 10.7–25 h after single-dose administration[51]. Intact AZD5004 is the predominant molecular species detected in plasma, accounting for >90% of drug-related exposure. AZD5004 has been studied in both single ascending dose and MAD studies, at doses ranging from 10 mg to 50 mg once daily over 4 weeks in people with T2D. Up to 5.8% weight reduction was observed over 28 days in subjects exposed to 50 mg daily, the highest dose tested. A range of (not disclosed) doses of AZD5004 is being assessed for weight management in the 26-week phase IIB VISTA trial in 304 people with overweight or obesity without T2D. The phase IIB SOLSTICE trial is evaluating a range of doses of AZD5004 over 26 weeks in subjects with T2D, with HbA1c of 7–10.5%, on a regimen of diet and exercise alone, or on stable metformin or sodium-glucose co-transporter 2 (SGLT-2) inhibitor therapy (see Related Links).

CT-996. Originally discovered by Carmot Therapeutics, CT-996 is a once-daily oral small-molecule GLP-1RA that exhibits biased signalling, with a half-maximal effective concentration (EC_{50}) at the GLP-1R of 0.49 nM, reduction of β-arrestin recruitment and GLP-1R internalization, and a plasma $t_{1/2}$ of 17–22 h, that is now being developed for T2D and obesity by Roche (see Related Links).

CT-996 exhibits a T_{max} of 8-9.6 h and a $t_{1/2}$ of 17.1–21.8 h. In a 4-week multiple ascending phase I trial, once-daily CT-996 achieved up to 6.1% placebo-subtracted weight loss at a final dose of 120 mg daily, with blood levels not impacted by food ingestion and a tolerability profile consistent with the GLP-1 medicine class (see Related Links). Phase II studies are scheduled for 2025.

Danuglipron. The small-molecule GLP-1RA danuglipron was derived through medicinal chemistry efforts primarily focused on optimization of cAMP accumulation, with a subtle bias for cAMP, relative to βArr1 recruitment[52]. Nevertheless, in studies employing diffusion-enhanced resonance energy transfer, danuglipron − but not orforglipron − induced internalization of the GLP-1R (ref. 53). The affinity of danuglipron for the GLP-1R is several-fold higher than that observed for exenatide or liraglutide. Phase I clinical trial testing of danuglipron at single doses ranging from 3 mg to 300 mg once daily revealed dose-proportional pharmacokinetics, with a $t_{1/2}$ ranging from 4.3 h to 6.1 h and time to C_{max} of 2.0–6.0 h[52].

Danuglipron was studied over a range of doses, from 2.5 mg to 120 mg twice daily administered with food, in people with T2D. In subjects aged 18–75 years treated with diet and exercise with or without background metformin therapy, placebo-subtracted reductions in HbA1c from 0.47% to 1.14% were reported for the highest dose of danuglipron, together with up to 4.17 kg placebo-subtracted differences in body weight, over 16 weeks[54]. However, up to 46% of subjects discontinued the medicine on the highest dose, 120 mg twice daily, due to adverse events, predominantly gastrointestinal. Tolerability was also problematic in a second 12-week trial of danuglipron in people with T2D or people with obesity, treated with up to 200 mg twice daily, with discontinuation rates of 27.3–72.7% of study participants across a range of danuglipron doses reflecting high rates of gastrointestinal adverse events[55].

The clearance of a single 20 mg dose of danuglipron does not depend on the estimated glomerular filtration rate (eGFR) in people with T2D (ref. 56), hence it is unlikely that danuglipron dosing would require adjustment in people with renal impairment. Several new formulations of extended-release danuglipron, designed to optimize the pharmacokinetic profile and extend the time to C_{max}, were assessed, however clinical development of Danuglipron was discontinued in April 2025 due to a single case of drug-induced liver injury (see Related Links).

GSBR-1290. Structure Therapeutics is developing GSBR-1290 (aleniglipron), a once-daily small-molecule oral GLP-1RA with biased activation of cAMP and minimal engagement with β-arrestin, with 24 h pharmacokinetic coverage after a single dose (https://ir.structuretx.com/static-files/775ca535-9bd3-455e-a41a-44dea273c90d). GSBR-1290 has been studied as both capsule and tablet formulations, with time to C_{Max} ranging from 3 h to 6 h. GSBR-1290 has been studied at doses up to 120 mg daily in people with overweight and obesity, over 12 weeks. From a mean BMI of 31.5 kg m^{-2}, GSBR-1290-treated subjects achieved a mean placebo-subtracted weight loss of 6.2%, with 67% of trial participants experiencing at least 6% weight loss. A substantial proportion of the 37 study subjects reduced the dose of GSBR-1290 (40.5%) or discontinued the drug (18.9%), perhaps reflecting rates of nausea (89.2%) and vomiting (62.2%). A subsequent study with less aggressive titration regimens reduced the rates of adverse events, with study

Box 2 | Optimal duration of therapy with GLP-1-based therapies

A clinically relevant discussion surrounds the extent and rapidity of weight gain associated with cessation of glucagon-like peptide 1 (GLP-1) medicines in people with type 2 diabetes (T2D) or obesity, as GLP-1 medicines are often stopped and frequently restarted after short durations of therapy, with uncertain consequences for health[168]. Discontinuation of semaglutide 2.4 mg once weekly in the STEP 1 trial after 68 weeks and a mean weight loss of 17.3% (and 2% with placebo) resulted in 11.6% and 1.9% weight regain by week 120, resulting in overall net weight loss of 5.6% and 0.1% for the semaglutide versus placebo arm, respectively[41]. The consequences of discontinuation of tirzepatide were studied in the SURMOUNT-4 trial, where study participants were initially treated for 36 weeks with tirzepatide, followed by participants continuing on tirzepatide or placebo for the next 52 weeks[39]. Remarkably, 46.2% of study subjects maintained at least 10% weight loss, and 25.9% of participants maintained at least 15% weight loss. At the end of the study, by week 88, the mean weight loss achieved was 25.3% for subjects continuously treated with tirzepatide and 9.9% for the tirzepatide/placebo group[39]. Intriguingly, in the small phase I trial of MariTide, some subjects maintained >10% weight loss even 5 months after the last dose of medicine[79]. Prediction, perhaps using a combination of clinical features, biomarkers and/or genetics, of which individuals may benefit from dosing cessation or holidays, versus intermittent therapy, or switching to a different medicine for weight loss maintenance, represents an insufficiently explored area. Whether the extent and duration of therapy should be guided not only by achievement of weight loss outcomes[168], but also by changes in body composition, functional read-outs of muscle quality and strength, and quality of life measurements as discussed above, is worthy of future investigation[39,41,164,166].

Box 3 | Oral delivery of peptide drugs

The quest for oral delivery of proteins and peptides, while simultaneously achieving reasonable bioavailability and therapeutic efficacy, has been challenging[50]. Although administration of once-daily oral insulin I338 was non-inferior to once-daily insulin glargine delivered by subcutaneous injection over 8 weeks in patients with type 2 diabetes (T2D)[171], it seems likely that the high cost of insulin precludes commercial viability of oral delivery, until improvements are realized in bioavailability and in the cost of manufacturing. Although the bioavailability of oral semaglutide formulated with an absorption enhancer is also low (~1%), oral semaglutide was shown to be effective in reduction of HbA1c in a range of clinical trials that include active comparators such as the sodium-glucose co-transporter 2 (SGLT-2) inhibitor empagliflozin and the dipeptidyl peptidase-4 (DPP-4) inhibitor sitagliptin[50]. Oral semaglutide is absorbed predominantly through the stomach and delivers similar reductions in HbA1c and body weight to those achieved with subcutaneously injected semaglutide, when assessed on the basis of comparable circulating levels of semaglutide[47]. Notwithstanding the challenges of low bioavailability and, hence, greater cost of active peptide, higher doses of oral semaglutide delivered through a formulation that enhances bioavailability have been assessed in people with T2D and/or obesity. Compared with the originally marketed version of oral semaglutide, the new higher-dose formulation deleted two excipients: the filler microcrystalline cellulose and the binder povidone K 90. Hence, the new formulation comprises magnesium stearate, semaglutide and the absorption enhancer sodium *N*-(8-[2-hydroxybenzoyl] amino) caprylate (SNAC). Administration of either 25 or 50 mg oral semaglutide once daily to subjects with T2D for 68 weeks produced substantially greater reductions in HbA1c and body weight loss, as well as more gastrointestinal adverse events, relative to trial participants receiving the currently approved dose of 14 mg once daily[172]. The higher-dose formulation, up to 50 mg once daily, was also studied over 68 weeks, in combination with lifestyle modification, in people with overweight or obesity, achieving placebo-subtracted weight loss of 12.7%[173]. Novo Nordisk has indicated their intention to file for approval of oral semaglutide 25 mg daily for weight loss indications.

Effective delivery of oral glucagon-like peptide 1 (GLP-1) peptide-based medicines has also been reported for VK2735, a GLP-1 receptor (GLP-1R)–glucose-dependent insulinotropic polypeptide receptor (GIPR) co-agonist, demonstrating placebo-subtracted reductions in body weight of up to 3.6% with 40 mg once daily, with a very favourable adverse event profile (see Related Links). After 28 days of once-daily oral dosing ranging from 2.5 mg to 100 mg VK2735 in healthy adults with body mass index (BMI) > 30, subjects experienced up to 6.8% placebo-subtracted weight loss — with 100% of VK2735-treated subjects experiencing at least 5% weight loss — with mild to moderate gastrointestinal adverse events, consistent with the GLP-1 class (https://ir.vikingtherapeutics.com/2024-11-04-Viking-Therapeutics-Reports-New-Data-from-VK2735-Obesity-Program-at-ObesityWeek-R-2024).

An oral version of a unimolecular amylin–GLP-1 peptide, designated amycretin, produced up to 12% placebo-subtracted weight loss in a phase I trial, starting from a mean baseline body weight of 89 kg (see Related Links).

discontinuations ranging from 5.% to 11.1%, providing a rationale for further optimization of dose titration using a lower starting dose (5 mg), and 4-week intervals for dose up-titration in a phase IIb trial extending out to 36 weeks, with separate phase II studies testing doses as high as 240 mg daily in people with overweight or obesity (see Related Links).

KAI-7535. KAI-7535 is a small-molecule oral GLP-1RA being developed by Kailera Therapeutics, which has been evaluated in single ascending dose and MAD human studies in healthy volunteers (see Related Links). In the 28-day MAD study, the median T_{Max} was 5.98–10.98 h and the geometric mean $t_{1/2}$ was 6.48–8.42 h on day 28, with a mean reduction of 4.38 kg body weight from a baseline weight of 67.9 kg.

Orforglipron. LY3502970 (now known as orforglipron) is a small-molecule GLP-1RA, originally discovered by Chugai Pharmaceuticals, that acts as a partial agonist at the GLP-1R, biased towards G protein activation relative to negligible recruitment of β-arrestin[57]. The small-molecule versus peptide GLP-1RAs exhibit unique interactions with the GLP-1R, as binding of orforglipron to the GLP-1R is not fully displaced by GLP-1(7–36)amide or danuglipron[53]. Preclinical studies demonstrate that orally administered orforglipron engages the GLP-1R (edited to confer human GLP-1R responsivity) both in islets and CNS neurons, producing pharmacodynamic actions (c-Fos induction, reduction of food intake, body weight and glycaemia) to a similar extent relative to that achieved with peptide GLP-1RAs such as exenatide or semaglutide[53].

Following demonstration of robust efficacy in people with T2D and obesity in phase II studies[58,59], orforglipron is currently being studied in separate phase III trials in T2D and obesity. The phase III programme in obesity includes a trial to assess orforglipron for weight maintenance after achievement of weight loss with tirzepatide (ATTAIN-MAINTAIN; NCT05869903) and a head-to-head trial versus insulin glargine in patients with T2D and overweight or obesity at increased cardiovascular risk (ACHIEVE-4) (see Related Links).

A range of orforglipron doses from 3 mg to 45 mg once daily were assessed over 26 weeks in people with T2D, with a mean baseline HbA1c of 8.1% and BMI of 35.2 kg m^{-2}. An up to 1.67% placebo-subtracted reduction in HbA1c, together with a 7.9 kg placebo-subtracted weight loss, was observed at the highest dose tested – results superior to those achieved using dulaglutide 1.5 mg once weekly as an active comparator[58]. Mild to moderate gastrointestinal adverse events were more common in subjects treated with orforglipron versus dulaglutide, perhaps reflecting inclusion of shorter titration intervals for orforglipron, from 1 to 3 weeks. Orforglipron (12–45 mg once daily) was also assessed over 36 weeks in people with obesity (mean baseline BMI 37.9 kg m^{-2}). Placebo-subtracted weight loss ranged from 7.1% to 12.5%, with discontinuation rates of 10–17% attributed to gastrointestinal adverse events. The phase III trial programmes are assessing longer duration of titration intervals, to improve tolerability. Unlike the requirement for oral semaglutide to be taken in the fasted state to enhance bioavailability, the AUC and C_{max} for orforglipron are approximately 18–24% lower in the fed versus the fasted state, without meaningful differences in T_{max}

and $t_{1/2}$, suggesting the feasibility of dosing without regard to timing of food ingestion[60]. Among the new trials planned for orforglipron are studies in people with obstructive sleep apnoea, and a separate trial in individuals with hypertension. Topline data for orforglipron in the ACHIEVE I phase III 40-week trial demonstrated lowering of A1C by an average of 1.3% to 1.6% from a baseline of 8.0% and up to 7.9% weight loss at the highest dose, 36 mg once daily (see Related Links).

RGT-075. RG-075 is a small-molecule GLP-1RA developed by Regor Therapeutics Group with a peak-trough ratio of <5 that has produced up to 5% placebo-subtracted weight loss in individuals with overweight or obesity when studied over 12 weeks, with an ongoing phase IIB trial examining doses up to 225 mg daily over 36 weeks (see Related Links).

TERN-601. TERN-601 is a small-molecule GLP-1RA with a pharmacokinetic profile suitable for once-daily dosing that has been studied in a 28-day MAD study in healthy adults with overweight or obesity. Placebo-subtracted weight loss of 4.9% was observed at the highest dose tested, 740 mg daily, with 67% of trial subjects losing at least 5% body weight on 740 mg daily. The pharmacodynamic activity of TERN-601 has been postulated to partly reflect its prolonged exposure within the gut mucosa, potentially triggering local GLP-1Rs enabling activation of a gut–brain axis promoting satiety, thereby facilitating 24-h drug coverage despite a $t_{1/2}$ of 4–6 h and C_{Max} of <2 h (see Related Links).

Peptide GLP-1RAs

MET-097. MET-097 is a long-acting lipidated fully biased GLP-1RA with a $t_{1/2}$ of 380 h that may be suitable for once-monthly administration. In phase I studies, MET-097 was evaluated in 125 healthy, non-diabetic, adult participants with overweight or obesity at weekly doses of 0.2–1.2 mg, with a total of five weekly doses administered without up-titration. MET-097 1.2 mg once weekly produced 7.5% weight loss at day 36 and 8.1% weight loss at day 57, 4 weeks after administration of the last dose. Adverse events, predominantly gastrointestinal, were reported as mild to moderate and transient, consistent with data reported for the GLP-1 class. A $t_{1/2}$ of 360 h raises the possibility of less frequent, perhaps once monthly, administration (see Related Links). MET-097i was subsequently assessed over 12 weeks using a range of doses in people with overweight or obesity without T2D, demonstrating placebo-subtracted weight loss up to 11.3%, with future trials planned to explore the feasibility of once-monthly dosing (see Related Links).

Ecnoglutide. Ecnoglutide is a high-affinity, cAMP-biased, DPP-4-resistant acylated GLP-1RA, exhibiting reduced GLP-1R internalization, with a $t_{1/2}$ of 124–138 h, suitable for once-weekly administration. An oral form of ecnoglutide, designated XW004, is also being evaluated in a phase I clinical trial[61]. Ecnoglutide was evaluated in China at three doses up to 1.2 mg once weekly for 20 weeks in subjects with T2D, producing a 2.39% HbA1c reduction from a baseline of 8.67%. From a mean starting BMI of 26.2 kg m^{-2}, up to 2.76% weight loss was observed at the highest dose tested, and two phase III trials are studying ecnoglutide as monotherapy, or as an add on to metformin in people with T2D (ref. 62).

GZR18. GZR18 (Bofanglutide) is a long-acting lipidated investigational GLP-1RA (ref. 63) being assessed in China for the treatment of obesity and T2D. In a phase IIB 30-week trial evaluating weekly and biweekly dosing in subjects with overweight or obesity, weight loss of up to 17.29% and 17.78% was observed with maximally effective doses of 48 mg biweekly and 24 mg weekly, respectively (see Related Links). Bofanglutide at doses of 24 mg or 48 mg administered biweekly is currently being assessed in a phase III trial in Chinese patients with overweight or obesity (see Related Links).

NPM-115. NPM-115 is a long-acting exenatide formulation delivered through a NanoPortal subdermal implant that is being studied in a 17-week trial assessing the safety, tolerability and pharmacokinetic profile, enrolling patients with overweight or obesity. Trial participants will be treated for the first 8 weeks with once-weekly semaglutide, followed by randomization to once-weekly exenatide, semaglutide 1 mg once weekly or an injection of the exenatide-containing implant (see Related Links).

GLP-1-based multi-agonists: finding the ideal partner for GLP-1

Some next-generation GLP-1 therapies are based on co-formulation with additional peptide receptor agonists, such as the combination of cagrilintide (an amylin analogue) and semaglutide (Cagri-Sema), or, more frequently, unimolecular design of GLP-1 medicines, such as tirzepatide, with one or more additional metabolically active peptide epitopes, to achieve simultaneous activation of multiple receptors and superior metabolic outcomes (Fig. 2). Preclinical studies and clinical data demonstrate the utility of engaging multiple mechanisms to provide additional reduction in body weight beyond that achieved with GLP-1R agonism alone[64–66].

GIP

Tirzepatide, the first GIPR–GLP-1R co-agonist, exhibits superior glucose control and weight reduction relative to semaglutide[29,37,67–70]. Of note, tirzepatide is also being assessed in separate trials in combination with the MC4R agonist bremelanotide for weight loss in people with obesity (NCT06565611). A phase I trial has also assessed the efficacy of combining tirzepatide with intravenous administration every 3 weeks of mibavademab, a monoclonal antibody that activates the leptin receptor, revealing an inverse relationship between the degree of weight loss (up to 3.1%) and the baseline levels of circulating leptin[71]. An ongoing phase II trial is assessing the combination of subcutaneously administered mibavademab plus tirzepatide over 24 weeks, followed by re-randomization to assess the impact of continuing treatment with mibavademab and tirzepatide or placebo for an additional 24 weeks (NCT06373146).

In addition to tirzepatide, multiple GIPR–GLP-1R medicines are under development. Some are formulated for once-weekly or once-monthly injections, whereas others are synthesized/formulated either as small molecules or peptides for once-daily oral administration. GIP stimulates glucose-dependent insulin secretion, reduces appetite leading to weight loss with sustained administration, and enhances insulin sensitivity through weight loss-independent mechanisms[9]. GIP also regulates bone formation and bone resorption, raising questions surrounding the putative benefits and safety of sustained gain or diminution of GIPR signalling. Although the available data informing changes in bone density and fractures following long-term use of GLP-1 medicines are limited, and even less is known clinically about sustained manipulation of GIPR activity, analysis of individuals with missense and predicted loss of function mutations in the *GIPR* did not reveal associations with genetic variation in the *GIPR* and reduced bone mineral density or rates of fractures[72].

VK2735. The phase II VENTURE trial studied 176 adults with overweight or obesity treated with a range of doses of the peptide GIPR–GLP-1R co-agonist VK2735, administered subcutaneously at doses ranging from 2.5 mg to 15 mg once weekly for 13 weeks, achieving up to 13.1% placebo-subtracted (14.7% from baseline) weight loss (https://ir.vikingtherapeutics.com/2024-11-04-Viking-Therapeutics-Reports-New-Data-from-VK2735-Obesity-Program-at-ObesityWeek-R-2024). Up to 88% of VK2735-treated subjects experienced at least 10% weight loss, with no plateau observed after 13 weeks. Whether the pharmacokinetic profile of VK2735 would support once-monthly dosing remains uncertain. Viking Pharmaceuticals is also developing an oral formulation of VK2735. In a 28-day MAD study, the oral formulation produced up to 3.3% placebo-subtracted weight loss, with 57% of subjects reporting >5% weight loss. A 13-week phase II trial, VENTURE-Oral, studying VK2735 in patients with overweight or obesity was initiated and completed enrollment in the first quarter of 2025 (see Related Links). Phase III trials for the injectable formulation of VK2735 are planned for 2025.

KAI-9531. Kailera Therapeutics is developing HRS-9531, now renamed KAI-9531, discovered by Jangsu Hengrui Pharmaceuticals Co. This molecule is a dual GIPR–GLP-1R co-agonist with a mean $t_{1/2}$ of ~1 week. HRS-9531 has been studied in separate phase II trials in people with T2D and with obesity. KAI-9531 exhibits a $t_{1/2}$ of 7–8 days in healthy individuals. A 20-week ascending dose trial in people with T2D, BMI 22–40 kg m^{-2}, at doses of 2 mg, 3 mg or 4.5 mg once weekly, produced placebo-subtracted reductions in HbA1c up to 2.2%, from a baseline HbA1c of 8.2%, at the highest dose (4.5 mg once weekly), with 90% of study subjects achieving HbA1c of <6.5%. Placebo-subtracted weight loss of 6.3% was observed in the highest-dose cohort, from a mean baseline weight of 78.7 kg. Significant reductions in systolic blood pressure, triglycerides and urine albumin-to-creatinine ratio (UACR) were also observed in KAI-9531-treated subjects (see Related Links). Adverse events were mild to moderate, and predominantly gastrointestinal, consistent with the GLP-1 class.

The efficacy of KAI-9531 was studied in an independent phase II trial in participants with obesity without T2D, BMI 28–40 kg m^{-2}, at doses up to 6 mg once weekly, with 96% of 240 subjects completing the 24-week trial. Up to 16.7% placebo-subtracted weight loss was observed at week 24 at the highest dose tested, together with reductions in systolic blood pressure, triglycerides and transaminase levels (see Related Links). Updated clinical trial results for the 8 mg once-weekly dose demonstrated a 21.1% placebo-subtracted weight loss after 36 weeks, with 59% of subjects experiencing >20% weight loss (see Related Links).

CT-868. Roche is developing the biased GIPR–GLP-1R agonist CT-868 as a once-weekly therapy for people with T1D and overweight/obesity, and a related molecule, CT-388, for people with obesity with or without T2D (see Related Links). In a phase IB trial, CT-388 22 mg once weekly produced up to 19% weight loss in patients with obesity over 24 weeks, with ongoing studies examining efficacy in subjects with T2D and obesity.

BGM0504. BGM0504 is a dual GLP-1R–GIPR C-terminally acylated, C18 fatty diacid lipidated long-acting co-agonist that exhibits greater potency at both receptors relative to tirzepatide in vitro and in preclinical studies in vivo[73]. The safety, tolerability and pharmacokinetic profile of BGM0504 were evaluated in healthy Chinese volunteers at doses up to 15 mg once weekly, exhibiting a mean $t_{1/2}$ of 4 days and a reduction in body weight of up to 5.4 kg at day 15 (ref. 74).

Maridebart cafraglutide. Intriguingly, both gain-of-function and loss-of-function approaches for the GIPR are being pursued in combination with GLP-1R agonism[75,76]. Loss-of-function mutations in human *GIPR* are associated with favourable cardiometabolic outcomes. A combination of genetic and pharmacological analyses demonstrated that mutations within human *GIPR* variants simultaneously impairing both G_s signalling and β-arrestin 2 recruitment are associated with a lower burden of adiposity-related traits, including reduced BMI[77]. Collectively, genetic data linked to clinical phenotypes and pharmacological data from loss of GIPR activity support development of GIPR antagonist–GLP-1RA combinations, with MariTide demonstrating robust efficacy in preclinical[66,78] and phase I clinical testing[79].

Phase I data for MariTide (AMG-133 or maridebart cafraglutide), a bispecific human GIPR blocking antibody with two linked GLP-1RA peptides and a molecular weight of 153,514 Da, revealed up to 14.6% weight loss after a total of three once-monthly injections in a small MAD study of 140 mg, 280 mg or 420 mg in subjects with obesity; substantial weight loss (up to 11.2%) persisted for up to 5 months following the last injection of the 420 mg dose[79]. A treatment-related increase in circulating free fatty acid levels (~4.5 mmol l^{-1}) was observed in phase I.

Phase II trials for MariTide studied a total of 592 people living with obesity and/or T2D, randomized across 11 different dosing arms. In people with overweight or obesity without T2D, from a mean starting BMI of 38 kg m^{-2}, MariTide produced up to 20% weight loss in subjects, findings associated with reductions in LDL cholesterol (−5%), blood pressure (−11 mmHg) and C-reactive protein (CRP) (−3%) at the highest tested dose of 420 mg, with 98% of trial subjects reporting at least 5% weight loss (see Related Links). In patients living with overweight or obesity and T2D, with a baseline BMI of 36 kg m^{-2}, MariTide (420 mg monthly) produced a mean weight reduction of 17%, associated with a reduction in HbA1c of 2.2%, from a baseline of 7.9%. Remarkably, a much greater reduction in high-sensitivity CRP (72% lower) was detected with MariTide therapy in people with T2D. Gastrointestinal side effects, consistent with the GLP-1 class, were the most common adverse events reported with MariTide. Despite concerns surrounding blockade of GIPR signalling and bone and mineral homeostasis[14], there was no association between exposure to MariTide and changes in bone mineral density in the phase II programme. MariTide will be studied in the phase III MARITIME programme in people with overweight or obesity, as well as in individuals with T2D. Antibodies and small-molecule antagonists or peptides such as AT-7687 (ref. 80) that block GIPR alone are also under early-stage clinical development.

Amylin

Amylin analogues such as cagrilintide and petrelintide are being developed as stand-alone therapeutic options, or for use in combination with GLP-1RAs for additional weight loss (Fig. 2). The first clinically developed aggregation-resistant amylin analogue pramlintide was initially approved for the treatment of T2D and T1D, together with concomitant use of insulin[81], in the United States in 2005, acting to lower blood glucose through central inhibition of gastric emptying and glucagon secretion. Pramlintide also induced satiety, leading to modest weight loss, fostering interest in the use of amylin analogues for weight loss. A trial of pramlintide alone, used at a dose of 360 mg twice daily, or administered together with metreleptin 5 mg twice daily produced meaningful weight loss (8.4% for pramlintide alone versus 12.7% for the combination) in 177 male and female subjects with overweight or obesity, mean BMI 32 kg m^{-2}, studied over a 20-week trial period[82].

These drugs target the AMLNRs, heterodimers of the calcitonin receptor coupled to either receptor amplifying protein (RAMP)1 or RAMP3. Selective agonists targeting the AMLNRs have a lower affinity for the calcitonin receptor, whereas drugs such as cagrilintide target both the amylin and calcitonin receptors and are referred to as dual amylin and calcitonin receptor agonists (DACRAs)[83,84]. StructureTx is developing the oral small-molecule amylin agonist ACCG-2671, a DACRA with nanomolar in vitro binding affinity for both the amylin and calcitonin receptors, to be potentially co-formulated with the small-molecule GLP-1RA aleniglipron (see Related Links).

Cagrilintide. Cagrilintide, a lipidated amylin analogue suitable for once-weekly administration, was studied using a range of doses from 0.3 mg to 4.5 mg weekly in 706 individuals with overweight or obesity, mean baseline BMI 37.8 kg m^{-2}, producing up to 7.8% placebo-subtracted weight loss over 32 weeks[85]. Interestingly, rates of gastrointestinal adverse events were lower with cagrilintide relative to the active comparator of liraglutide 3 mg once daily, and the presence or titre of anti-cagrilintide antibodies did not impact the extent of weight loss.

The efficacy of cagrilintide 2.4 mg once weekly alone or co-administered with 2.4 mg semaglutide once weekly was studied over 32 weeks in 92 subjects with T2D, baseline HbA1c of .4% and BMI 35.5 kg m^{-2}. The extent of HbA1c reduction with Cagri-Sema (2.2%) was not greater than that achieved with semaglutide alone (1.8%), but the rates of gastrointestinal adverse events and the reduction in body weight were greater with Cagri-Sema (15.6%) relative to weight loss with semaglutide (5.1%) or cagrilintide (8.1%) alone[86]. Cagri-Sema is being studied in five trials for people with obesity in the phase III REDEFINE programme, including a CVOT with 7,000 participants and a 72-week head-to-head trial versus tirzepatide (see Related Links). Top-line data for the REDEFINE-1 trial reported weight loss in 3,417 randomized individuals with obesity or overweight with one or more comorbidities and a mean baseline body weight of 106.9 kg. Flexible dosing guidelines enabled 57.3% of study subjects treated with Cagri-Sema to achieve the highest dose versus 82.5% with cagrilintide 2.4 mg and 70.2% with semaglutide 2.4 mg once weekly. Almost 22% weight loss was achieved with trial participants adherent to Cagri-Sema, versus 11.8% and 16.1% with 2.4 mg once weekly of cagrilintide and semaglutide, respectively. Weight loss of 25% was achieved after 68 weeks in 40.4% of trial participants on Cagri-Sema. In the REDEFINE 2 trial studying people with T2D, Cagri-Sema achieved 12.6% placebo-subtracted weight loss, with 61.9% of patients achieving the highest dose after 68 weeks (see Related Links).

Petrelintide. Petrelintide is a 36 amino acid acylated balanced human amylin analogue that activates both amylin and calcitonin receptors and is administered once weekly. Petrelintide has been studied in a phase IB trial of adults (79% male) with overweight or obesity, HbA1c of <6.5%, BMI 27–39 kg m^{-2} and mean BMI 29.2 kg m^{-2}. Once-weekly petrelintide produced a change in body weight of −4.8%, −8.6% and −8.3%, respectively, with 1 mg, 2 mg or 3 mg once weekly, versus −1.7% with placebo over 16 weeks. The proportion of subjects reporting nausea ranged from 16.7% to 33.3%, with one study participant discontinuing trial participation (see Related Links). Petrelintide is currently being studied over 42 weeks as a weekly therapy in people living with overweight or obesity.

Other amylin analogues. AZD6234 is a long-acting amylin analogue with data from preclinical studies supporting preferential loss of fat, rather than fat-free mass. The clinical potential for achievement of meaningful weight loss in subjects with overweight or obesity is being evaluated over 36 weeks in the phase IIB APRICUS trial (see Related Links). A unimolecular amylin–GLP-1 peptide, designated amycretin, is being developed for both oral and parenteral administration, and produced up to 13.1% weight loss, from a baseline weight of 89 kg, after 12 weeks of administration of the once-daily tablet formulation (see Related Links). Subsequent evaluation of amycretin in 125 subjects with overweight or obesity revealed up to 22% weight loss at the highest dose (20 mg once weekly) tested over 36 weeks, from a mean baseline body weight of 92.7 kg, with a safety profile described as consistent with the GLP-1 class (see Related Links).

Eloralintide, an amylin agonist suitable for once-weekly administration, is being studied in several phase II trials with or without tirzepatide in people with T2D or in subjects with overweight or obesity (NCT06345066; NCT06603571).

Glucagon

Glucagon inhibits food intake and promotes weight loss, and targets hepatocytes to directly reduce liver fat[87]. Although classical actions of glucagon entail augmentation of hepatic glucose production leading to an increase in plasma glucose, an appropriate ratio of GLP-1 to glucagon may conserve the glucose-lowering of GLP-1, while retaining the actions of glucagon on liver lipid metabolism and appetite. Whether chronic augmentation of GCGR signalling also contributes to sustained increases or prevention of decreases in energy expenditure, contributing to weight loss in people with T2D or obesity, is not yet clear. Multiple GCGR–GLP-1R co-agonists are in phase II/phase III testing for obesity, metabolic liver disease and T2D (refs. 88,89), and retatrutide, a GCGR–GIPR–GLP-1R triple agonist, is in phase III trials for multiple indications[90,91]. Nevertheless, some GCGR–GLP-1R molecules have been discontinued due to mechanism-based tolerability or safety signals[92]. Some of the glucagon–GLP-1 medicines robustly lower glucose; others, such as efinopegdutide and pemvidutide, do not[88,93].

Pemvidutide. Pemvidutide is a 29 amino acid balanced long-acting GCGR–GLP-1R co-agonist suitable for once-weekly administration due to an 18-carbon diacid alkyl chain attached via a glycosidic linkage, enabling albumin binding. The MOMENTUM trial examined the extent of weight loss achievable with pemvidutide over 48 weeks at doses of up to 2.4 mg once weekly, with placebo-subtracted weight loss of 13.4% at the highest dose tested, and 78.1% of the weight loss attributed to a of fat mass (see Related Links). More than 30% of the subjects achieved at least 20% weight loss at the highest dose tested with 74.1% of pemvidutide-treated subjects completing the study, with the trajectory of body weight predicting ongoing weight loss with additional pemvidutide exposure. Adverse events reported in the MOMENTUM trial were consistent with the class of GLP-1 medicines. Pemvidutide does not meaningfully lower blood glucose independent of its effects on weight loss, reflecting the balanced glucagon–GLP-1 co-agonism. The phase III programme for pemvidutide comprises four trials, including studies of individuals with elevated liver, fat or increased LDL and older individuals with baseline sarcopenia (see Related Links).

Mazdutide. Mazdutide is an acylated GCGR–GLP-1R co-agonist suitable for once-weekly administration being developed primarily in China for the treatment of T2D and obesity. In phase II testing in people with T2D at doses of 3.0 mg, 4.5 mg and 6.0 mg, mazdutide produced

greater percentage weight loss from baseline of 0.9%, 5.0% and 5.4%, respectively, versus 0.9% for 1.5 mg once weekly dulaglutide and 1.1% for placebo[94]. The safety profile was largely similar for mazdutide versus dulaglutide-treated patients. Mazdutide was also studied in a phase II trial of Chinese patients with overweight or obesity, at doses up to 6 mg once weekly, with placebo-subtracted weight loss of 12.3% after 24 weeks at the highest dose tested[95]. Weight loss of at least 10% was achieved by 50.8% of study subjects treated with 6 mg once weekly. A subset of 22 individuals with pretreatment and post-treatment dual-energy X-ray absorptiometry scans revealed a proportionately greater reduction in fat versus lean mass with mazdutide therapy, and adverse effects reported were predominantly mild to moderate gastrointestinal complaints, consistent with the GLP-1 class[95]. A phase III trial studying mazdutide for weight loss in people with overweight or obesity in China at doses of 4 mg or 6 mg once weekly for 48 weeks demonstrated a 14.7% placebo-subtracted weight loss at the highest dose tested, with associated reductions in blood pressure, waist circumference, cholesterol, triglycerides and transaminase levels (see Related Links). An exploratory analysis of subjects with baseline MRI-PDFF ≥10% demonstrated an ~75% placebo-subtracted reduction in liver fat with mazdutide therapy. Mazdutide has been submitted to the National Medical Products Administration review authority in China and is being studied by Eli Lilly in a 28-week trial in people with alcohol dependence disorder (NCT06817356).

Survodutide. Survodutide is a 29 amino acid acylated degradation-resistant GCGR–GLP-1R co-agonist suitable for once-weekly administration that exhibits approximately tenfold lower potency ex vivo against the GCGR and GLP-1R relative to the native peptides. Survodutide produces weight loss through a reduction of food intake and an increase in energy expenditure, actions requiring both the GCGR and the GLP-1R in preclinical studies[96]. In phase II studies 46 weeks in duration, survodutide was studied at doses up to 4.8 mg once weekly, yielding 12.1% placebo-subtracted weight loss at the highest dose studied[89]. Survodutide is currently being assessed in phase III trials for weight loss in people with (NCT06066528) or without (NCT06066515) T2D, at doses of 3.6 mg or 6 mg once weekly. The cardiovascular safety of survodutide 3.6 mg or 6.0 mg once weekly is being assessed in people with overweight and at least two weight-related complications or in people with obesity and a history of cardiovascular or chronic kidney disease in the SYNCHRONIZE-CVOT study. The primary composite end-point incudes cardiovascular death, non-fatal stroke, non-fatal myocardial infarction, ischaemia-related coronary revascularization or heart failure events (NCT06077864).

Retatrutide. Retatrutide is a GCGR–GIPR–GLP-1R triagonist under development for the treatment of obesity as well as T2D and metabolic liver disease. Retatrutide is less potent at the human GCGR and GLP-1R (by a factor of 0.3 and 0.4, respectively) and more potent at the human GIPR (by a factor of 8.9)[97]. A phase II trial evaluated multiple doses of retatrutide, up to 12 mg once weekly, in 338 subjects with overweight or obesity for 48 weeks. Multiple doses of retatrutide produced more than 20% placebo-subtracted weight loss, with 60% of subjects achieving >15% weight loss[90]. At 48 weeks, weight loss was −22.8% in the 8 mg group and −24.2% in the 12 mg group, versus −2.1% in the placebo-treated cohort.

The efficacy of a range of doses of retatrutide, up to 12 mg once weekly, was also examined over 36 weeks in individuals with T2D, duration of diabetes of 6–8 years, age 18–75 years and HbA1c of 7–10.5%, treated with either diet and exercise alone or metformin[91]. A dose-dependent reduction of HbA1c was observed with retatrutide, up to 2.02% with 12 mg once weekly from a baseline of 8.3%, versus 1.41% for the group treated with dulaglutide 1.5 mg once weekly. Remarkably, up to 16.2% weight loss was observed at week 36 with 12 mg retatrutide once weekly, with ~40% of individuals achieving >20% placebo-subtracted weight loss at the three highest doses tested. Adverse events, predominantly mild to moderate gastrointestinal adverse events, were consistent with those described for the GLP-1 class. The safety and efficacy of retatrutide is being examined in a broad phase III programme in people with T2D in the TRANSCEND-T2D programme (NCT06354660; NCT06297603), including a direct comparison with semaglutide (NCT06260722) and in individuals with overweight/obesity in the TRIUMPH programme (NCT06662383; NCT05936151; NCT05929066; NCT05882045; NCT05929079).

The cardiovascular safety of retatrutide is being studied in the TRIUMPH Outcomes trial, enrolling individuals with BMI >27 kg m^{-2} and a history of atherosclerotic cardiovascular and/or kidney disease (NCT06383390), with two primary outcomes encompassing the development of cardiovascular (non-fatal myocardial infarction, non-fatal stroke, cardiovascular death or heart failure events requiring visits to the hospital) as well as renal (≥40% sustained decline in the eGFR, cardiovascular death or renal death) end-points.

Other GCGR–GLP-1R co-agonists. The GCGR–GLP-1R co-agonist efinopegdutide produced competitive reductions in liver fat content (72.7% versus 42.3%) and a reduction in body weight (8.5% versus 7.1%) for efinopegdutide versus semaglutide, respectively[88].

AZD9550 is an earlier stage GCGR–GLP-1R co-agonist being studied in people with metabolic liver disease and individuals with overweight and obesity with or without T2D (NCT06151964). UBT251 is a triple GCGR-GLP-1R-GIPR multi-agonist discovered by United Laboratories, now being co-developed with Novo Nordisk. In a phase IB trial over 12 weeks in people with overweight or obesity, UBT251 produced up to 15.1% weight loss from baseline, at the highest dose tested (https://www.novonordisk.com/content/nncorp/global/en/news-and-media/news-and-ir-materials/news-details.html?id=915958).

Bioglutide (NA-931) is an investigational quadruple receptor peptide agonist that activates the glucagon, GIP, GLP-1 and IGF-I receptors being developed as a once-daily oral formulation (capsule) for chronic weight management, potentially enabling meaningful weight loss and preferential loss of adipose tissue mass with less reduction of muscle mass. Phase I trials demonstrated that bioglutide achieved placebo-subtracted weight loss of 5.1% over 28 days (see Related Links), whereas more prolonged exposure in a 12-week MAD study assessing 150 mg of bioglutide daily achieved up to 10.4% placebo-subtracted weight loss.

GLP-1 receptor-targeted therapeutics

A complementary strategy for activating GLP-1R while simultaneously engaging signalling mechanisms promoting improved glycaemia and reduced body weight involves coupling of metabolically active molecules to GLP-1R ligands, thereby selectively targeting cargo to GLP-1R circuits. Oestrogen was targeted to $GLP\text{-}1R^{+}$ cells through generation of a degradation-resistant GLP-1 molecule covalently coupled to an aromatic oestrogen ester. The GLP-1R–oestrogen conjugate exhibited markedly reduced activity at oestrogen receptor-α and produced greater weight loss in obese mice relative to individual administration of biologically active oestrogen or GLP-1 alone[98]. Notably, the

stable oestrogen–GLP-1 conjugate did not exhibit undesirable oestrogenic activity such as induction of uterine hyperplasia or testicular atrophy and did not alter plasma levels of luteinizing hormone and follicle-stimulating hormone, further highlighting selectivity for targeting oestrogen action to GLP-1R$^+$ cells[98].

Dexamethasone coupled to a GLP-1RA via a disulfide linker enabled selective delivery of glucocorticoids to, and release within, GLP-1R$^+$ cells[99]. The unimolecular dexamethasone–GLP-1 conjugate reduced body weight, improved glucose metabolism and reduced both hypothalamic and systemic inflammation, actions which were eliminated in *Glp1r*$^{-/-}$ mice and partially blunted in mice with neuronal deletion of the GLP-1R (ref. 99). Weight loss was attributed to both a reduction in food intake and an increase in energy expenditure. The GLP-1–dexamethasone conjugate did not impact the hypothalamic–pituitary axis; circulating levels of corticosterone or biomarkers of bone metabolism and the bone mineral density were no different[99].

A hybrid molecule has been designed containing an *N*-methyl-D-aspartate (NMDA) receptor antagonist linked to a GLP-1RA to simultaneously activate the GLP-1R, while inhibiting the glutamate activated ion channel within GLP-1R$^+$ cells[100]. The prototype molecule dizocilpine was coupled to a GLP-1RA via a disulfide linker and exhibited superior activity to reduce body weight and improve glycaemia control relative to dizocilpine or GLP-1R agonism alone, while exhibiting molecular and functional evidence for neuroplasticity in the hypothalamus and brainstem[100]. Notably, the hybrid molecule produced superior weight loss relative to the combined administration of dizocilpine and a GLP-1 analogue, through reduction of food intake and a relative increase in energy expenditure. The metabolic benefits of NMDA receptor antagonism were not observed with dizocilpine coupled to GIP or PYY, indicating the importance of targeting dizocilpine to GLP-1R$^+$ cells while simultaneously activating GLP-1R. Despite the intriguing benefits of the receptor targeting approach in preclinical studies, these molecules have not yet advanced towards clinical evaluation.

Established and new indications for next-generation GLP-1-based therapies

GLP-1-based therapeutics started with the approval of exenatide for T2D in 2005, followed by the first approval of this class of medicines for obesity (liraglutide) in 2014. Over the last decade, GLP-1-based therapies have been approved for multiple new indications (Fig. 3), expanding the clinical indications for GLP-1 therapeutics beyond control of glucose and body weight[101,102]. Our understanding of how direct and indirect GLP-1R-dependent mechanisms improve disease pathology across a diverse range of organ systems is incomplete and still evolving (Fig. 4). GLP-1 medicines are being investigated for a wide range of new indications, many characterized in part by dysregulated inflammation (Figs. 3 and 4). Below we describe recent progress in establishment of clinical evidence broadening the therapeutic utility of GLP-1 medicines.

Cardiovascular disorders

The first definitive evidence for cardioprotection, notably a reduction in non-fatal myocardial infarction, non-fatal stroke and cardiovascular death, was established in 2016 for people with T2D treated with long-acting GLP-1 medicines such as liraglutide in the LEADER trial[103,104] (Figs. 1–3). The cardiovascular safety of semaglutide was demonstrated in the PIONEER-6 and SUSTAIN-6 CVOTs with oral and injectable semaglutide, respectively[105,106]. Safety was further demonstrated in the SOUL trial, demonstrating a 14% reduction in the primary major adverse cardiovascular events (MACE) end-point in 9,650 people with T2D and established cardiovascular disease and/or kidney disease in subjects treated with oral semaglutide (see Related Links and ref. 107). Up to 49% of participants in the SOUL trial received treatment with an SGLT-2 inhibitor at some point during the trial.

The SELECT trial examined the cardiovascular safety of semaglutide 2.4 mg once weekly in 17,604 individuals with a history of atherosclerotic cardiovascular disease and either overweight and one or more weight-related comorbidities or obesity, without T2D. Subjects treated with semaglutide (mean duration of exposure 34.2 months) experienced a 20% reduction in non-fatal myocardial infarction, non-fatal stroke and cardiovascular death, and a 19% reduction in all-cause mortality[108]. Although a mean weight loss of 10.2% was sustained after 4 years of therapy[109], the cardioprotective benefits of semaglutide were reported to be partially independent of weight loss in the SELECT trial (https://easo.org/semaglutide-4-year-weight-loss-and-cardiovascular-benefits/). Despite some baseline differences in age, medication use and prior history of cardiovascular disease,

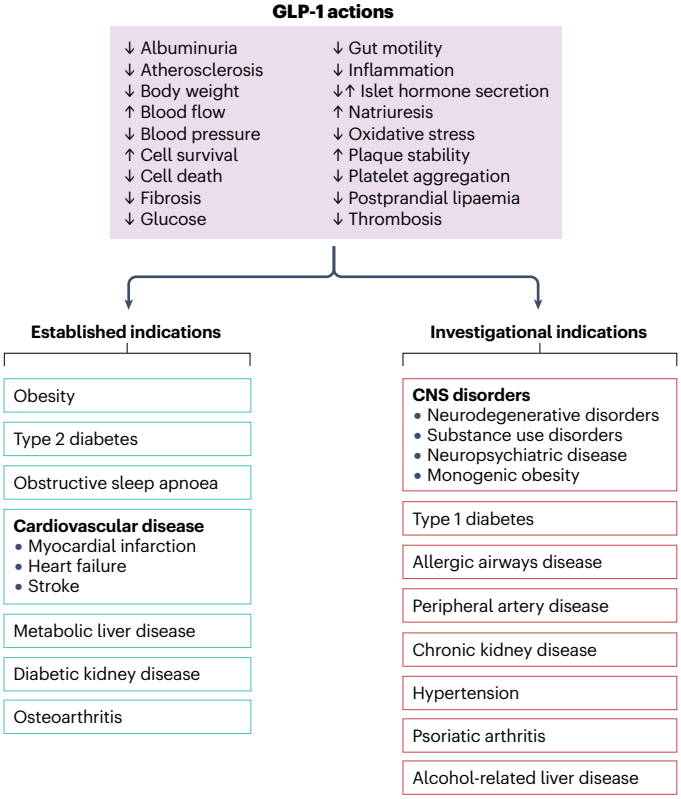
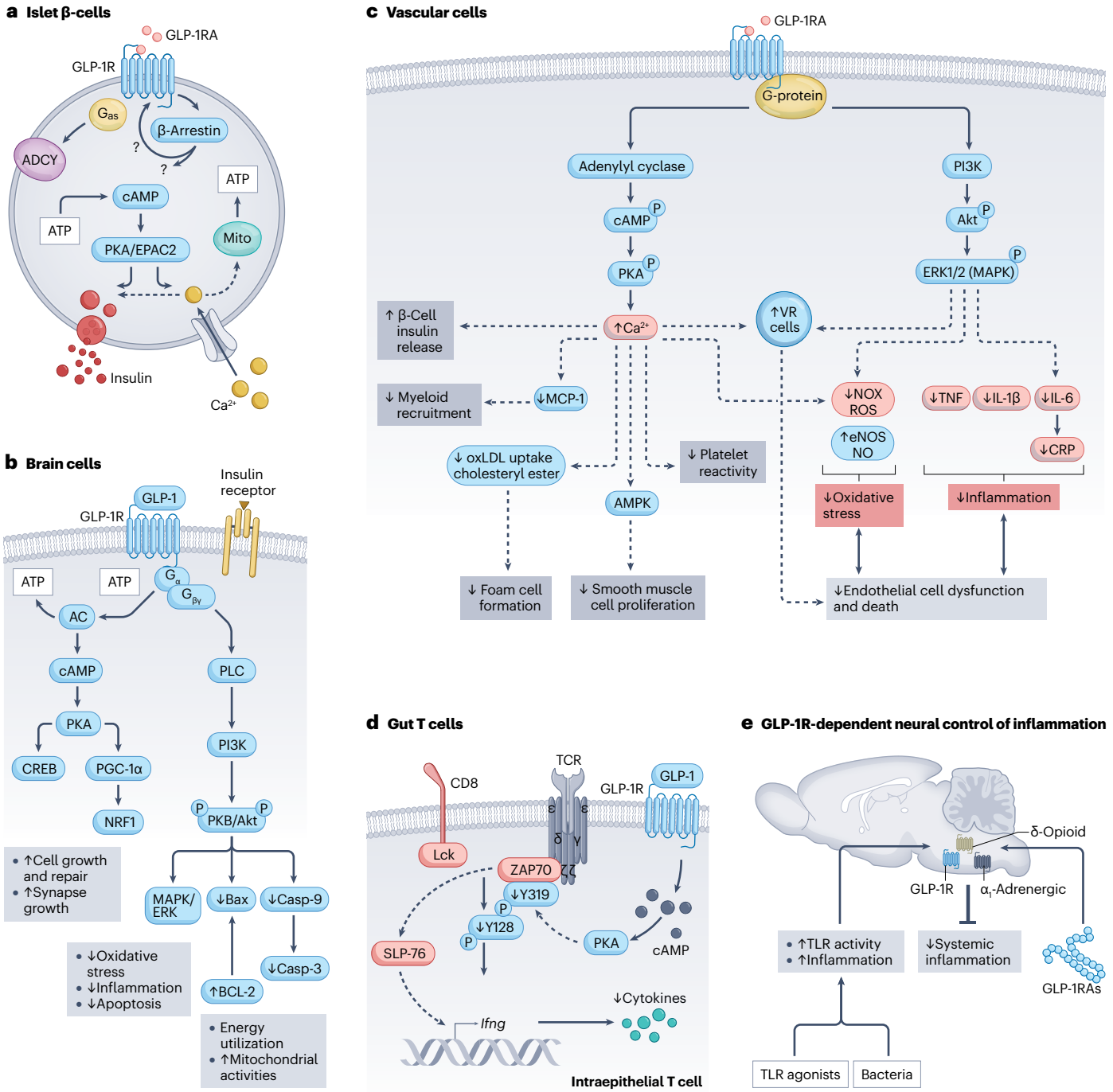


Fig. 3 | Actions and indications for GLP-1-based therapies. Systemic and localized actions of glucagon-like peptide 1 (GLP-1) medicines that contribute to improvement of organ health and the clinical benefits of GLP-1 medicines now established for a range of conditions (top panel): indications and disorders with established benefit identified from clinical trials with one or more GLP-1 medicines in phase III trials (left panel) and indications currently under investigation in clinical trials (right panel). GLP-1 medicines have not yet received a licence for metabolic liver disease, but results from phase III trials such as ESSENCE with semaglutide support this pending indication. CNS, central nervous system.



semaglutide reduced the rates of MACE to a similar extent in males versus females in the SELECT trial[110].

In separate trials (STEP-HFpEF and STEP-HFpEF DM), semaglutide improved symptoms, the 6-min walk time and outcomes such as visits to the emergency room or hospitalization in people with obesity and heart failure with preserved ejection fraction, with and without T2D (refs. 111,112). A pooled analysis of four trials — SELECT, FLOW, STEP-HFpEF and STEP-HFpEF DM — revealed that semaglutide reduced (hazard ratio 0.69) the risk of the combined end-point (heart failure event defined as urgent visit or hospitalization or cardiovascular death)[113], establishing the benefits of semaglutide therapy in this population beyond symptomatic improvement.

The cardiovascular safety of tirzepatide (up to 15 mg weekly) versus dulaglutide 1.5 mg weekly is being evaluated in the SURPASS CVOT trial, in 13,299 people with T2D, age >40 years, baseline HbA1c of 8.4%, mean BMI 32.6 kg m^{-2} and established atherosclerotic cardiovascular disease. At trial enrolment, 65% of subjects had a history of coronary artery disease, including 47.3% with a prior myocardial infarction, 19.15%

Fig. 4 | Direct and indirect mechanisms mediating the benefits of GLP-1-based therapies. Selective mechanisms linking glucagon-like peptide 1 (GLP-1) action to organ protection and the pleiotropic benefits of GLP-1 medicines. Scenarios highlighting GLP-1 receptor (GLP-1R) signalling pathways in different cells/organs are illustrated as selective examples of direct and indirect actions of GLP-1. **a**, GLP-1 acts directly on islet β-cells, δ-cells and a small subset of α-cells to control islet hormone secretion. Canonical GLP-1R signalling proceeds through G protein-mediated augmentation of cAMP accumulation, enabling changes in secretory and transcriptional activity. GLP-1 also potentiates the glucose-stimulated potentiation of membrane-associated voltage-dependent Ca^{2+} channels, augmenting insulin secretion. **b**, Neuronal GLP-1Rs are coupled to activation of cAMP and phosphatidylinositol 3-kinase (PI3K), engaging signalling pathways linked to changes in cell growth, apoptosis, inflammation and oxidative stress. **c**, GLP-1R is expressed in some vascular cells, including subsets of endothelial and smooth muscle cells. As described for neuronal cells, GLP-1R signalling activates cAMP and PI3K pathways in vascular and non-vascular cell types impacting blood vessel pathophysiology through direct and indirect mechanisms, leading to changes in vascular reactivity, blood flow, atherosclerosis, oxidative stress and vascular inflammation. **d**, GLP-1 controls inflammation directly through expression of the GLP-1R in some T cells, best characterized in gut intraepithelial T cells. **e**, GLP-1 also controls some forms of systemic inflammation induced by Toll-like receptor (TLR) ligands indirectly, via the GLP-1R-dependent neural control of systemic inflammation. AC, adenylyl cyclase; BAX, Bcl-2-associated X protein; BCL-2, B cell lymphoma 2; Casp-3, caspase-3; CREB, cAMP response element-binding protein; CRP, C-reactive protein; eNOS, endothelial nitric oxide synthase; EPAC2, exchange protein directly activated by cAMP2; ERK, extracellular signal-regulated kinase; GLP-1RA, GLP-1 receptor agonist; Ifng, interferon-γ; IL-1β, interleukin-1β; LCK, lymphocyte-specific protein tyrosine kinase; MAPK, mitogen-activated protein kinase; MCP-1, monocyte chemoattractant protein 1; NO, nitric oxide; NOX, nicotinamide adenine dinucleotide phosphate (NADPH) oxidase; NRF1, nuclear respiratory factor 1; oxLDL, oxidized low-density lipoprotein; PGC-1α, peroxisome proliferator-activated receptor-β co-activator 1α; PKA, protein kinase A; PLC, phospholipase C; ROS, reactive oxygen species; SLP-76, SH2 domain containing leukocyte protein of 76 kDa; TCR, T cell receptor; TNF, tumour necrosis factor; VR, vascular regenerative; ZAP70, ζ-chain-associated protein kinase 70. Part **a** is adapted with permission from ref. 158, Oxford University Press, parts **b** and **c** are adapted from refs. 159,160, CC by 4.0 (https://creativecommons.org/licenses/by/4.0/), and parts **d** and **e** are adapted from refs. 161,162, Elsevier.

with a history of stroke and 25.3% with peripheral artery disease[114]. The primary composite end-point is non-inferiority for time to three-point MACE (non-fatal myocardial infarction, non-fatal stroke and cardiovascular death), with a superiority analysis to compare the effect of tirzepatide versus dulaglutide. Although very few cardiovascular events were recorded in the phase III SURPASS programme in people with T2D, tirzepatide did not increase the number of cardiovascular events (four-point MACE) or rates of cardiovascular death[68].

The cardiovascular safety of tirzepatide is also being scrutinized in the SURMOUNT MMO trial, in people with overweight and one or more weight-related comorbidities or in people with obesity (NCT05556512). Trial eligibility includes participants older than 40 years of age with established atherosclerotic cardiovascular disease, or older individuals with at least three risk factors for CVD, with a primary outcome of all-cause mortality, non-fatal myocardial infarction, non-fatal stroke, coronary revascularization or heart failure events.

The therapeutic potential of semaglutide 1 mg once weekly versus placebo in 792 symptomatic people with T2D, mean BMI 29.6 kg m^{-2}, with lower extremity peripheral artery disease is being assessed in the STRIDE trial, with a primary end-point of change in maximum walking distance on a constant-load treadmill[115]. At trial enrolment, the median maximum walking distance was 186 m semaglutide improved walking distance by 13% in the STRIDE trial[116].

Renal disease

The FLOW trial studied the safety of semaglutide 1 mg once weekly in 3,533 people with T2D and chronic kidney disease, based on entry criteria of elevated urinary albumin excretion and reduced eGFR[117]. The primary trial composite end-point included reductions in dialysis, transplantation or achievement of an eGFR of <15 ml min^{-1} per 1.73 m^2, or a 50% reduction in eGFR, or death from renal or cardiovascular causes. The FLOW trial was stopped early by the data safety monitoring committee due to a 24% reduction in the primary composite outcome in semaglutide-treated individuals. Trial subjects randomized to semaglutide exhibited reduction in both renal end-points as well as in rates of cardiovascular death. Fewer serious adverse events were reported in semaglutide-treated subjects[118]. The benefits of semaglutide in the FLOW trial were observed independent of the presence or absence of concomitant use of SGLT-2 inhibitors at baseline[119]. A renoprotective benefit of semaglutide was also detected in the absence of T2D, most recently in the SELECT trial. Semaglutide therapy produced a 22% reduction in the rate of the composite kidney end-point (kidney-related death, new requirement for kidney replacement therapy, onset of persistent eGFR <15 ml min^{-1} per 1.73 m^{-2}, persistent ≥50% reduction in eGFR or onset of persistent macroalbuminuria), with rates of 1.8% with semaglutide versus 2.2% with placebo (hazard ratio 0.78)[120]. Based on the results of the FLOW trial, regulatory authorities have now approved the use of semaglutide for the prevention of more severe chronic kidney disease and cardiovascular death in people with T2D and early evidence for chronic kidney disease (Fig. 3).

Osteoarthritis

The STEP-9 trial examined the efficacy of semaglutide in 407 patients with obesity and knee osteoarthritis over 68 weeks, with primary end-points of change in body weight and pain scores[121]. At baseline, the mean age was 56 years, BMI 40.3 kg m^{-2} and 81.6% of subjects were women. Semaglutide therapy produced improvements in pain and physical function scores, associated with a weight loss of 13.7% and 3.2% with semaglutide versus placebo, respectively. Rates of serious adverse events were similar in the two treatment arms, and a greater reduction in use of analgesic agents was reported in the semaglutide-treated subjects[121].

Sleep apnoea

Tirzepatide, administered up to a maximum tolerated dose of 15 mg once weekly, achieved the primary and multiple secondary end-points over 52 weeks when studied versus placebo in 469 people with mild to moderate obstructive sleep apnoea and obesity, previously treated with or without positive airway pressure. At baseline, the mean BMI was 39.1 kg m^{-2} and most subjects (67%) were male, with a mean age of 47.9 years and a mean apnoea hypopnoea index of 51.5 events per hour. Individuals treated with tirzepatide experienced a reduction in the apnoea hypopnoea index, reduced sleep disturbance and hypoxic burden, and lower body weight, blood pressure and circulating levels of high-sensitivity CRP[122]. Based on the results of these two trials, a new indication was granted by the US Food and Drug Administration

(FDA) for tirzepatide as the first medical therapy approved for the treatment of moderate to severe obstructive sleep apnoea in adults with obesity, to be used in combination with an exercise regimen and a reduced-calorie diet.

Metabolic liver disease

Pemvidutide is being assessed in people with metabolic dysfunction-associated steatohepatitis (MASH) and separately in people with obesity. Pemvidutide was studied at doses of 1.2 mg, 1.8 mg and 2.4 mg once weekly in people with overweight or obesity and hepatic fat content >10%. Reductions in liver fat content of up to 68.5% were observed in the pemvidutide-treated cohorts versus 4.4% in placebo-treated individuals, with placebo-subtracted weight loss of up to 4.1%[123]. The most common adverse events were mild to moderate gastrointestinal complaints, predominantly nausea.

Tirzepatide has been evaluated at doses of 5 mg, 10 mg and 15 mg weekly over 52 weeks in participants with MASH and stage F2 or F3 fibrosis (57% women, 58% with T2D, mean BMI 36.1 kg m^{-2}). Substantial resolution of MASH without worsening of fibrosis was seen in up to 62% of trial participants treated with the 15 mg once weekly dose, with at least a one-stage improvement in fibrosis detected in 51% of subjects[124]. Tirzepatide therapy was associated with weight loss of −10.7%, −13.3% and −15.6% with 5 mg, 10 mg and 15 mg weekly, versus −0.8% with placebo. Whether the extent of improvement in liver disease reflects both weight loss-dependent and independent actions of tirzepatide remains uncertain.

Survodutide was studied in 293 subjects with biopsy-confirmed MASH and fibrosis stages F1–F3 over 48 weeks at doses of 2.4 mg, 4.8 mg or 6 mg once weekly[125]. A total of 281 of 293 trial subjects (95.9%) completed the trial, and 219 had paired biopsy samples. Survodutide substantially reduced liver fat and improved MASH without worsening of fibrosis in 47%, 62% and 43% of individuals treated with 2.4 mg, 4.8 mg and 6 mg once weekly, compared with 14% in the placebo arm. A reduction in fibrosis by at least one stage occurred in 34%, 36% and 34%, respectively, versus 22% in placebo-treated individuals. Gastrointestinal adverse events were much more common in survodutide-treated patients[125]. The efficacy of survodutide is being examined in two separate trials in people with MASH, including subjects with moderate to advanced fibrosis (NCT06632444) as well as individuals with MASH and cirrhosis (NCT06632457).

The ESSENCE trial examined the therapeutic efficacy and safety of semaglutide 2.4 mg once weekly in 800 participants with MASH and fibrosis stages F2–F3, mean age 56 years, 57.1% female, BMI 34.6 kg m^{-2}, 55.5% with T2D and the majority with risk factors for cardiovascular disease[126]. Top-line trial results reported for the first 800 subjects after 72 weeks revealed a 37% improvement in fibrosis stage versus 22.5% for placebo, and 62.9% achieved resolution of steatohepatitis without worsening of fibrosis, versus 34.1% for placebo (see Related Links).

The efficacy of retatrutide in people with metabolic liver disease was examined over 48 weeks using magnetic resonance imaging proton density fat fraction assessments in people with metabolic dysfunction-associated steatotic liver disease (MASLD) in a sub-study of individuals in the obesity trial[90]. Liver fat reduction of 81.4% and 82.4% was observed at the two highest doses tested, with most of the reduction detectable within the first 24 weeks of therapy[127]. Retatrutide is being studied in a large phase III programme for T2D, obesity and metabolic liver disease, including a 10,000-person cardiovascular and renal outcomes trial (TRIUMPH OUTCOMES) in people with overweight or obesity, and a small cardiovascular safety trial (1,800 persons) in subjects with obesity and a history of cardiovascular disease (see Related Links).

Other indications

Observations that some of the cardiovascular benefits of GLP-1 medicines may be partially independent of weight loss and improved glucose control (Figs. 2 and 4), together with preclinical data and anecdotal reports of clinical improvement of multiple disorders, has sparked interest in assessing the therapeutic utility of GLP-1 medicines in a range of inflammatory, neurodegenerative and neuropsychiatric disorders (Figs. 3 and 4). Ongoing registration trials are testing the efficacy of GLP-1 medicines in people with peripheral artery disease, Parkinson disease and Alzheimer disease, whereas investigator-initiated trials are testing a much wider range of therapeutic scenarios for GLP-1 medicines, including neuropsychiatric and dependence-related disorders. The putative efficacy of GLP-1 medicines in neurodegenerative disorders may stem, in part, from the direct neuroprotective and indirect anti-inflammatory weight loss-independent mechanisms of action[102].

Substance use disorders. Given the links between the reward systemic, hedonic behaviours and the pathophysiology of dependence disorders, including alcohol, smoking, cocaine, cannabis and narcotic addiction, there is tremendous interest in, and ongoing trials, studying the potential efficacy of GLP-1 medicines in these conditions[128]. Although substantial preclinical data support the premise that GLP-1 medicines modify the extent of addictive behaviours, randomized clinical trial data have not yet shown consistent, compelling and sustained reductions in rates of alcohol use or the extent of smoking cessation in clinical studies[129,130]. Administration of placebo or semaglutide once weekly over 9 weeks, with a final dose of 1 mg semaglutide administered in the last week, to 48 individuals with moderate alcohol use disorder demonstrated that semaglutide reduced the amount of alcohol consumed in a laboratory setting at the end of the study period, while also reducing the number of drinks per day and alcohol craving[131]. Cigarette use was also reduced by semaglutide in a sub-cohort of active smokers[131]. Observational cohort data from Sweden in 227,866 individuals identified with alcohol use disorder from 2006 to 2023 revealed that the use of semaglutide and liraglutide was associated with a decreased risk of hospitalization due to alcohol use disorder in subjects with T2D and/or obesity[132]. Similarly, analysis of a real-world cohort of 215,970 individuals with T2D initiating a GLP-1 medicine in the US Veterans Affairs Health Care system revealed relative reductions in the risk of substance use disorders, as well as decreased rates of neurodegenerative disorders such as Alzheimer disease[133]. Ongoing phase II clinical trials are studying the use of tirzepatide as an adjunct to buprenorphine over 26 weeks in the treatment of opioid use disorder (NCT06651177), and a smaller 4-week trial will study the feasibility of tirzepatide in alcohol use disorder (NCT06727331). Multiple trials are also underway (up to 26 weeks in duration) studying semaglutide therapy in alcohol use disorder (NCT05895643; NCT05520775; NCT06015893; NCT05892432), opioid use disorder (NCT06639464; NCT06548490) and smoking/nicotine intake (NCT05530577).

Central nervous system disorders. GLP-1 medicines reduce rates of stroke in multiple cardiovascular outcome trials in people with T2D (refs. 104,134,135) (Fig. 3). The hazard ratio for reduction of non-fatal stroke with semaglutide in the SELECT trial was 0.93 (ref. 108). Several GLP-1 medicines, principally exenatide or derivatives thereof, have been studied in five randomized control trials in people with Parkinson

disease. Positive results, principally the halting of disease progression, were reported in trials of exenatide twice daily[136], exenatide once weekly[137] and lixisenatide once daily[138]. In contrast, a 36-week trial of NLY01, a pegylated exenatide derivative administered once weekly, to 255 trial subjects randomized to placebo, 2.5 mg or 5 mg of NLY01 (n = 85 per group) failed to show any beneficial effect on Parkinson disease motor or non-motor scores of disease activity[139]. Moreover, the largest longest trial to date studied exenatide once weekly in Parkinson disease over 96 weeks in 194 people aged 25–80 years, with Hoehn and Yahr stage 2.5 or less when on dopaminergic treatment. Study subjects were on dopaminergic treatment for at least 4 weeks before trial enrolment. No benefit of exenatide therapy was detected at 96 weeks on the primary end-point using clinical rating scales to assess changes in motor and non-motor indices of Parkinson disease activity[140].

Evidence from cardiovascular outcome trials and real-world data from analysis of events in people with T2D supports the hypothesis that GLP-1 medicines may reduce deterioration of cognitive dysfunction[133,141–143]. The therapeutic potential of oral semaglutide to reduce rates of cognitive dysfunction is being evaluated in two trials, EVOKE and EVOKE+, in people at risk for cognitive dysfunction with or without concomitant cerebrovascular disease. Trial participants include men and women aged 55–85 years with mild cognitive impairment or mild dementia and a putative diagnosis of Alzheimer disease based on analysis of cerebrospinal fluid biomarkers, or positron emission tomography consistent with evidence for brain amyloid[144].

Summary and conclusions

Substantial progress in the development of more powerful GLP-1 medicines promises to deliver multiple agents capable of achieving 25% weight loss. As each new class of GLP-1 medicines emerges, careful evaluation of the safety and risk–benefit profile will be required. Beyond simply achieving greater weight loss, next-generation GLP-1 medicines ideally should preserve the cardiorenal and metabolic benefits of established GLP-1 medicines[101], while theoretically differentiating in at least one key area to make them therapeutically competitive in an expanding market for metabolic medicines. There is considerable interest in expanding the delivery of GLP-1-based medicines beyond peptides, to include small-molecule orally available tablets or capsules, antibodies, gene or cell-based therapy, RNA interference and even gene editing to activate components of GLP-1R signaling pathways[14].

Notably, despite an understandable focus on achieving greater weight loss, at least some of the benefits of GLP-1 medicines, such as in the cardiovascular system, may be weight loss-independent[102]. Whether newer agents will produce more durable weight loss (following cessation of therapy) and/or be suitable for less frequent administration is not clear. More evidence is required to understand the safety of GLP-1 medicines in special populations such as older individuals, in young children and adolescents, and during pregnancy. It also seems logical and important to explore whether GLP-1 medicines might be safe and effective for reduction of heart and kidney disease in people with T1D. It remains uncertain whether a defined period of treatment with GLP-1 medicines followed by cessation of therapy may be associated with a legacy-like effect of continuing improvements in health, as has been described for glucose-lowering agents in people with diabetes[145]. Remarkably, 40 years after the discovery of GLP-1, new GLP-1 medicines show great potential for conferring substantial benefits leading to improved human health well beyond the original indications of T2D and obesity.

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D.J.D. conceptualized, researched, wrote and edited the manuscript.

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