Novel GLP-1-Based Medications for Type 2 Diabetes and Obesity

Short running title: GLP-1-based weight-loss drugs

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CONFLICT OF INTEREST

JWS serves as an advisory board member for Novo Nordisk and Eli Lilly & Co and has participated in the speakers' bureaus of Novo Nordisk, Eli Lilly & Co, Sanofi, Boehringer Ingelheim, and AstraZeneca. He has also received research funding from Chong Kun Dang Pharma.

ClR reports grants from the EU Innovative Medicine Initiative, Irish Research Council, Science Foundation Ireland, Anabio, and the Health Research Board. He serves on advisory boards and speakers panels of Novo Nordisk, Roche, Herbalife, GI Dynamics, Eli Lilly, Johnson & Johnson, Gila, Irish Life Health, Boehringer Ingelheim, Currax, Zealand Pharma, Keyron, AstraZeneca, Arrowhead Pharma, Amgen, AbbVie, Metsera, Nymble, and Rhythm Pharma. ClR is the Chair of the Irish Society for Nutrition and Metabolism. ClR received stock options as payment for scientific advisory board functions from Metsera and Nymble. ClR provides obesity clinical care in the My Best Weight clinic and Beyond BMI clinic and is a co-owner of these clinics.

MB received honoraria as a consultant and speaker from Abbott, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Daiichi-Sankyo, Lilly, MSD, Novo Nordisk, Novartis and Sanofi.

MAN has been member on advisory boards or has consulted with Boehringer Ingelheim, Eli Lilly & Co., Medtronic, Merck, Sharp & Dohme, Novo Nordisk, Pfizer, Regor, Sun Pharma, and Structure Therapeutics (ShouTi, Gasherbrum). He has received grant support from Merck, Sharp & Dohme. He has also served on the speakers' bureau of Eli Lilly & Co., Menarini/Berlin Chemie, Merck, Sharp & Dohme, Medscape, Medical Learning Institute, Novo Nordisk.

SL is an advisory board member for Novo Nordisk and AstraZeneca and has served on the speakers' bureau of Novo Nordisk, Sanofi, Boehringer Ingelheim, AstraZeneca and Merck, Sharp & Dohme. He has received research funding from Chong Kun Dang and Daewoong Pharma.

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Abstract

The approvals of semaglutide and tirzepatide have set new benchmarks in the treatment of type 2 diabetes and obesity. Building on their success, novel GLP-1-based therapeutics are rapidly advancing. These next-generation agents engage not only GLP-1 receptors but also those for other gastro-entero-pancreatic hormones such as glucose-dependent insulinotropic polypeptide (GIP), glucagon, amylin, and peptide YY (PYY) to enhance energy uptake, storage, and expenditure through synergistic mechanisms.

Both GIP receptor agonism and antagonism, particularly in combination with GLP-1 receptor agonism, have shown promise. Maridebart cafraglutide, combining GLP-1R agonism with GIPR antagonism, exemplifies this innovative approach. Glucagon co-agonists like survodutide and mazdutide have demonstrated significant weight loss and improved glycemic control. Amylin-

based agents, including CagriSema (cagrilintide + semaglutide) and amycretin, enhance satiety and glycemic outcomes through complementary actions.

Further innovation is seen in triple agonists such as retatrutide, which targets GIP, GLP-1, and glucagon receptors to amplify metabolic effects. Meanwhile, the emergence of orally active small-molecule GLP-1 receptor agonists like danuglipron and orforglipron, which are resistant to enzymatic degradation, marks a major advance in patient-friendly drug delivery.

This review explores the mechanisms, clinical development, and therapeutic potential of these novel agents, excluding already approved drugs like liraglutide, semaglutide, and tirzepatide. We highlight how multi-receptor agonists and oral GLP-1-based therapies may reshape the future landscape of obesity and type 2 diabetes treatment by offering more effective and better-tolerated options.

1. Introduction

In 2022, an estimated 828 million people worldwide had diabetes mellitus (1), a condition that markedly increases the risk of complications including cardiovascular disease (CVD), renal failure, vision loss, certain cancers, and infections such as COVID-19 (2). Obesity, affecting over 800 million globally (3,4) and ~42% of U.S. adults (5), is a major driver of this burden, with annual healthcare costs of ~$173 billion in the U.S. alone (6). Excess visceral adipose tissue (VAT) is a key determinant of obesity-related complications and the metabolic syndrome (7). Obesity is now recognized as a chronic, progressive, and relapsing multisystem disease (8-10).

Although lifestyle modification remains central to managing type 2 diabetes (T2D) and obesity, most patients require adjunctive therapy to achieve sustained weight loss. Over the past decade, GLP-1 receptor agonists (GLP-1RAs) have transformed care, with semaglutide and

tirzepatide setting new efficacy benchmarks—achieving ~15% weight loss and improving comorbidities (11-14). Building on this success, the therapeutic landscape is moving toward multi-agonist strategies (e.g., GLP-1 with glucose-dependent insulinotropic polypeptide [GIP], glucagon, or amylin), which enhance insulin secretion, suppress appetite, reduce ectopic fat storage, and increase energy expenditure (15-18). Recent trials show these agents can surpass GLP-1RA monotherapy in weight loss and metabolic benefit (17,19,20). In parallel, advances in oral and small-molecule GLP-1RAs are overcoming limitations of peptide injectables, improving drug stability and patient acceptance.

This manuscript sheds light on emerging GLP-1-based medications targeting obesity and T2D beyond the established agents like semaglutide or tirzepatide. We review their mechanisms of action, clinical trial outcomes, and potential adverse effects, aiming to inform about the current frontier of GLP-1-based therapeutic innovations.

2. Gastro-Entero-Pancreatic Peptide Hormones with Therapeutic Potential Regarding Glucose Homeostasis and Body Weight Regulation: Potential Mechanisms of Action

Recent efforts have focused on modifying GLP-1 or combining it with other gastrointestinal and pancreatic hormones to improve glycemic control and weight reduction while limiting adverse effects. These strategies have yielded dual and triple agonists as well as agonist–antagonist combinations. Terms such as "GLP-1 medicines" (19) overemphasize the GLP-1RA component, whereas "nascent nutrient-stimulated hormone-based therapeutics" (20) is overly broad, as some hormones of interest (e.g., glucagon) are not nutrient-stimulated. We therefore propose the term "gastro-entero-pancreatic peptide hormones with therapeutic potential," which best reflects both their origin and peptide nature.

Fig. 1 illustrates the conceptual framework underpinning the development of these novel pharmacological strategies for obesity and T2D management, highlighting the integration of diverse gastro-entero-pancreatic peptide hormones to optimize efficacy, safety, and clinical outcomes.

(1) Glucagon-like peptide-1 (GLP-1)

Incretins, particularly GLP-1 and GIP, play critical roles in regulation of glucose metabolism independent of body weight. While GIP secretion is generally preserved in T2D, its insulinotropic efficacy is markedly diminished (21). GLP-1 secretion is also preserved in T2D, but it is still able to elicit an insulinotropic response in patients with T2D (21), leading to effective lowering of plasma glucose in the fasting state (22) and after meals (23), positioning the GLP-1 receptor (GLP-1R) as a pivotal target for glucose-lowering therapies (24).

GLP-1 is secreted by L cells in response to nutrient intake, enhancing glucose-dependent insulin secretion without increasing the risk for hypoglycemia (25,26). It also suppresses glucagon secretion during hyperglycemia while allowing glucagon release during hypoglycemia (27). Additionally, GLP-1 reduces appetite (28), delays gastric emptying (23), and promotes weight loss (29). GLP-1RAs can cause gastrointestinal side effects, such as nausea, vomiting, diarrhea, obstipation and others (30,31).

Beyond these classical actions, recent insights have revealed that GLP-1 is also produced in pancreatic α-cells under metabolic stress and in preproglucagon (PPG)-expressing neurons of the brainstem, which project to hypothalamic and autonomic centers, highlighting its neuroendocrine functions beyond classical metabolic regulation (32). The central nervous system mechanisms underlying GLP-1-mediated appetite suppression involve widely distributed GLP-1R-expressing

neuronal populations rather than a single pathway (33). While gut-derived GLP-1 is not essential for normal appetite control (34), brain-derived GLP-1 from preproglucagon neurons in the brainstem plays a critical role, particularly during stress or excess food availability (35).

GLP-1RAs activate multiple sites including the hypothalamic arcuate nucleus, stimulating POMC/CART neurons and inhibiting NPY/AGRP neurons via GABAergic mechanisms, brainstem regions, and diverse areas such as nucleus accumbens, lateral parabrachial nucleus, hippocampus, and lateral septum (36-41). The anorectic effects are predominantly mediated through glutamatergic signaling, as selective disruption of GLP-1Rs in glutamatergic neurons significantly attenuates appetite suppression by liraglutide and semaglutide, while GABAergic neuron-specific deletion has minimal impact (42). This distributed network explains why endogenous GLP-1R signaling importance varies with experimental context, while pharmacological activation consistently reduces appetite across species.

Findings from GLP-1R knockout mice further underscore context-dependent roles in energy homeostasis (26). Global GLP-1R knockout mice show normal food intake and body weight under standard conditions and even exhibit resistance to diet-induced obesity (43,44), initially suggesting GLP-1R signaling may be not essential to case an overt metabolic phenotype. However, global germline GLP-1R knockout mice are characterized by diminished insulin secretion in response to oral glucose challenge (45). Moreover, acute pharmacological blockade with exendin (9-39) consistently increases food intake (33), indicating endogenous GLP-1 actively suppresses feeding under physiological conditions.

Targeted deletion studies resolve this apparent contradiction, as knockdown of GLP-1Rs in the lateral hypothalamus substantially increases food intake and body weight (46), while dorsomedial hypothalamic GLP-1R deletion promotes weight gain and decreases energy

expenditure (47). These findings suggest that developmental compensation and circuit redundancy mask GLP-1R importance in global knockout models, but targeted disruption reveals functionally significant roles for specific GLP-1R populations in appetite control.

At the molecular and cellular level, GLP-1R expression is largely confined to pancreatic β-cells and specific neurons, while it is minimal or absent in cells of peripheral tissues such as hepatocytes, enterocytes, and adipocytes—despite clinical effects observed in these tissues. This has led to growing recognition of indirect mechanisms of action, including vagal neural signaling, δ-cell-mediated somatostatin release, and channeling substrate flow (systemic metabolic crosstalk) (32). These findings challenge the traditional, simple view on incretin function restricted to the stimulation of insulin and suppression of glucagon secretion, and support a more integrated framework in which GLP-1 acts through both direct and indirect inter-organ networks regulating glucose metabolism, energy balance, and cardiovascular function (48,49).

Importantly, GLP-1-based therapies have benefits beyond glucose control. Multiple studies have demonstrated pleiotropic effects of GLP-1 and GLP-1RAs, including anti-inflammatory actions (50,51), improvements in postprandial hyperlipidemia (52,53), improvements in endothelial dysfunction (54), reduction in oxidative stress (55), and preservation of pancreatic β-cell function (56,57).

The earlier GLP-1RAs such as liraglutide (injected once-daily) showed the spectrum of therapeutic effects (glycaemic control, body weight reduction, prevention of CV events and renal functional decline, etc.), but with modest efficacy (58,59). The next-generation compounds such as semaglutide and tirzepatide for once-weekly use are characterized by optimized dose-escalation strategies that lead to better tolerance, lower adverse events rate, and greater efficacy

concerning glycemic control and weight reduction (60,61).

Common side effects of GLP-1RAs include nausea, vomiting, and diarrhea, which are typically transient and can be prevented by a rather low initial dose (relative to the maintenance dose) and gradual dose-escalation with multiple steps. Safety considerations include contraindications for individuals at risk, i.e., with a personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia type 2. Despite earlier suspicions regarding a potential risk, large-scale trials and meta-analyses have not demonstrated a direct association between GLP-1RAs and an increased risk of pancreatitis or pancreatic cancer, a conclusion supported by evaluations from regulatory agencies such as the US FDA and EMA (62,63).

In parallel, emerging insights into GLP-1 biology, ranging from its multiple sites of synthesis to indirect inter-organ signaling pathways, have expanded the conceptual framework beyond classical incretin physiology (64,65). This broader understanding does not only enhance our interpretation of GLP-1's systemic effects, but also provides a strong rationale for the development of multi-agonist therapies (GLP-1/GIP, GLP-1/glucagon, GLP-1/amylin combinations), which leverage synergistic hormonal networks and offer therapeutic benefits beyond conventional monotherapy.

(2) Glucose-Dependent Insulinotropic Polypeptide (GIP)

GIP is secreted by K-cells in the duodenum and jejunum in response to nutrient intake (66). It plays a multifaceted role in metabolism, including the stimulation of insulin secretion ("incretin action") (21) and of glucagon release (especially, when plasma glucose is low) (67), promoting adipose tissue lipogenesis, and improving lipid buffering capacity (68).

Indeed, based on GIP receptor (GIPR) knockout mice, GIP was considered an obesogenic

factor, since GIPR knock-out prevented weight gain with high-energy feeding. Also, the expression of GIPRs in adipose tissue (69), the increase of lipoprotein lipase (LPL) activity in response to GIP (70), and the stimulation of adipose tissue blood flow under the influence of GIP (71) seemed to support an obesogenic role for GIP. In addition, early studies of GIP analogues alone failed to produce meaningful weight loss in humans (72,73). However, the notable weight-reducing efficacy of tirzepatide, a dual GLP-1R/GIPR co-agonist, has renewed interest in GIP's role in body weight regulation (74).

Recent findings suggest that GIPR agonism exerts weight-reducing effects through both central and peripheral mechanisms (75). In the central nervous system, GIPR is expressed in the hypothalamus and hindbrain, where its activation suppresses food intake and reduces body weight through GABAergic neurons in obese rodents (76). These effects persisted in GLP-1R knockout mice but were abolished in animals lacking neuronal GIPR, highlighting the importance of central GIP signaling in appetite regulation (55). Intracerebral administration of long-acting GIP analogs reduced feeding at pharmacologically relevant doses, whereas native GIP was less effective (55).

Emerging evidence indicates GIPR activation attenuates GLP-1R-associated vomiting in shrews (77) and may modulate dietary preferences, specifically reducing the hedonic appeal of energy-dense foods (78). However, human studies have failed to document reduced energy intake in response to exogenous GIP administration (73,79). A head-to-head comparison of tirzepatide (a dual GIPR/GLP-1R co-agonist) and semaglutide (a selective GLP-1RA) demonstrated superior weight loss with tirzepatide, but without measurable differences in appetite, satiation, fullness, or ad libitum energy intake (80). This discrepancy between animal and human studies regarding GIP's influence on energy intake suggests significant species

differences that require further investigation.

In peripheral tissues, GIP's effects are context dependent. Under conditions of hyperinsulinemia, GIP enhances lipid storage by increasing LPL activity via PKB activation and AMPK inhibition, inducing LPL gene transcription through CREB-TORC2 (81,82), promoting adipocyte differentiation, and increasing adipose tissue blood flow, though these effects are attenuated in insulin resistance (71). In contrast, under insulin-resistant or hypoinsulinaemic states, GIP promotes lipolysis and fatty acid oxidation (83). Long-acting GIPR agonists reduce fat mass independently of food intake and suppress adipose tissue inflammation, indicating broader metabolic benefits (84,85). A recent study demonstrated that increased GIPR expression in adipose tissue promoted energy expenditure and led to weight loss through SERCA-mediated futile calcium cycling, independent of sustained reductions in food intake (86).

Paradoxically, preclinical studies suggest that blocking GIP signaling also yields anti-obesity effects (73,75,87). When used in combination with GLP-1RAs, GIPR antagonists reduced food intake and fat mass in animal models (87). This paradoxical finding reveals a unique therapeutic opportunity, as both activation and inhibition of GIPR signaling lead to weight reduction, though they operate through fundamentally different mechanisms. These opposing effects can be explained by their actions on distinct neuronal populations. GIPR agonists exert anorectic effects by activating GABAergic neurons in the hypothalamus and hindbrain, suppressing food intake (76). In contrast, GIPR antagonists may act by silencing these inhibitory GABAergic circuits, thereby unmasking adjacent glutamatergic neurons involved in satiety signaling, or enhancing GLP-1R–mediated pathways (88). In preclinical studies, GIPR antagonists such as AT-7687 reduced weight gain in high-fat–fed non-human primates and potentiated the weight-lowering effects of GLP-1RAs like liraglutide (89).

The hypothesis that GIPR agonism leads to desensitization and, eventually, functional antagonism has been proposed based on the concept of receptor down-regulation, but lacks robust *in vivo* support (90,91). While chronic agonist exposure can desensitize the GIPR in pancreatic islets (92), this mechanism appears limited and apparently does not extend to central appetite regulation (93).

This duality has informed the development of two contrasting therapeutic strategies; tirzepatide, a dual GLP-1R/GIPR co-agonist, achieves robust glycemic and weight-lowering effects through complementary actions on both receptors (13), and AMG133 (maridebart cafraglutide), combining GLP-1R agonism with GIPR antagonism, further enhances weight loss and improves metabolic parameters, likely by unmasking GLP-1–mediated satiety pathways (16). These complementary approaches highlight the complex and multifaceted role of GIP signaling in metabolic regulation and offer promising avenues for the treatment of obesity and related metabolic disorders (94). This paradox, where both GIPR agonism and antagonism can lead to weight loss, along with its relevance to tirzepatide's mechanism of action, is summarized in **Table 1.**

(3) Glucagon

Glucagon, physiologically secreted by pancreatic α-cells, is primarily known for its role in glucose homeostasis, particularly during fasting and in case of hypoglycaemia, when elevated plasma concentrations stimulate hepatic glycogenolysis and gluconeogenesis (95,96). Recently, additional functions of glucagon have been described: (a) insulinotropic actions within the endocrine islet, e.g. in response to exposure to amino acids (protein-rich meals), when it might, indeed, contribute to reducing plasma glucose concentrations, and (b) its physiological influence

on weight regulation. In humans, glucagon appears to decrease food intake by inducing satiety, potentially via the liver–vagus–hypothalamus axis (97-99). Additionally, glucagon may contribute to increases in resting energy expenditure under hypoinsulinaemic conditions, as its thermogenic effect depends on low insulin levels and can be inhibited by insulin (100-102). This dual role of glucagon, characterized by its ability to induce hyperglycemia and to promote weight loss, underscores its potential in metabolic disease management (103). A challenge with glucagon remains substantial induction of GI discomfort (104), probably related to its potent interference with gut smooth muscle contraction and peristalsis (105,106).

Beyond glucose regulation, glucagon influences lipid metabolism by promoting hepatic β-oxidation and inhibiting lipogenesis, effectively reducing hepatic fat accumulation (107). It also plays a crucial role in amino acid metabolism, facilitating ureagenesis and reducing circulating amino acid levels through enhanced hepatic uptake—a process central to the liver–α-cell axis, which maintains amino acid balance (98,108,109). Glucagon also contributes to energy homeostasis by increasing resting energy expenditure and inducing satiety via hepatic vagal afferent signaling (103,110).

These effects highlight glucagon's emerging significance as a metabolic hormone with both therapeutic challenges and opportunities, leading to active investigation. Glucagon receptor antagonists improve glycemic control in diabetes, but are often associated with adverse effects such as hepatic steatosis and hyperlipidemia (103). Conversely, co-agonists targeting both glucagon and GLP-1 receptors represent a promising approach for obesity and T2D treatment (111). These agents synergize glucagon's capacity to enhance energy expenditure with GLP-1's effects on glycemic control and appetite suppression, offering a novel therapeutic strategy for managing metabolic diseases (112).

(4) Amylin

Amylin, also known as islet amyloid polypeptide (IAPP), is a peptide hormone co-secreted with insulin by pancreatic β-cells. It plays a role in regulating postprandial satiety and glucose metabolism. By acting on amylin receptors (AMYRs), which are heterodimers of the calcitonin (CT) receptor (a class B1 G protein–coupled receptor) and one of three receptor activity-modifying proteins (RAMP1, RAMP2, or RAMP3), amylin suppresses appetite, delays gastric emptying, and inhibits glucagon secretion (113,114). These receptor subtypes include AMY1Rs (CTR-RAMP1), AMY2Rs (CTR-RAMP2), and AMY3Rs (CTR-RAMP3). Additionally, amylin interacts with calcitonin gene-related peptide (CGRP) receptors in the brainstem, contributing to its effects on appetite and gastrointestinal function (115,116). Unlike other peptides that attenuate appetite, amylin's effects do not induce a compensatory reduction in energy expenditure, likely due to its activation of the sympathetic nervous system (115,117,118).

The therapeutic potential of amylin has led to the development of synthetic analogues. Pramlintide, the first US FDA-approved amylin analogue, has demonstrated weight loss of up to 7.9% over 12 months when combined with lifestyle modifications (119). Cagrilintide, a long-acting analogue, has shown superior dose-dependent weight loss, ranging from 6% to 10.8% in phase 2 trials, outperforming liraglutide 3 mg and placebo (120). Notably, cagrilintide is being evaluated in combination with semaglutide to enhance long-term efficacy and leverage complementary mechanisms for obesity management (120).

Emerging innovations include dual-acting amylin and calcitonin receptor agonists, such as davalintide, KBP-042, and KBP-088, which have demonstrated significant weight loss in preclinical models (121-123). Early-phase clinical trials are also advancing amylin receptor

agonists like AZD6234 and ZPB8396, while oral dual GLP-1 and amylin agonists, including amycretin (NNC0487-0111), represent a new frontier in combination therapies.

Thus, amylin-based therapies, particularly in combination with other agents, represent a promising approach for obesity treatment (124). Ongoing research is expected to expand their clinical applications and optimize their therapeutic potential.

(5) Peptide YY (PYY)

Peptide YY (PYY) is co-secreted with GLP-1 by intestinal L cells in response to nutrient intake. It is converted from its inactive form, $PYY_{1-36,}$ to its active form, PYY_{3-36}, via DPP-4. PYY_{3-36} acts through Y2 receptors (Y2R) in the nervous system, particularly in the hypothalamus, where it inhibits neuropeptide Y (NPY) neurons and indirectly activates pro-opiomelanocortin (POMC) neurons to suppress appetite (125,126).

Several PYY_{3-36} analogues have been developed for obesity treatment. Long-acting receptor agonists, such as NN9748 and NNC0165-1875, are currently undergoing clinical trials. In a phase 1 trial, a PYY analogue (Y14 peptide) demonstrated a weight loss of 2.9–3.6 kg over 31 days, reducing food intake by 38–55% compared to placebo (127). While intravenous administration of PYY has consistently reduced food intake (128), subcutaneous delivery of long-acting PYY receptor agonists appears more practical for clinical use. Combining these agents with GLP-1RAs holds promise for achieving synergistic effects in obesity management (126).

PYY has been known as a classical weight loss-mediator (125) and its role has been investigated to explain the metabolic benefits after metabolic surgery (129). Postprandial PYY levels are significantly lower in people with obesity before bariatric surgery confirming its

negative correlation with BMI (128). In association with a significant reduction in body weight after metabolic surgery, a substantial increase in circulatory PYY levels was noted (130). Moreover, it was reported that suppression of PYY resulted in increased food intake in people with obesity (131).

Thus, PYY is a key effector of the early recovery of impairment of glucose-mediated insulin and glucagon secretion in people who received bariatric surgery (130). An animal study using Goto-Kakizaki diabetic rats suggested that the remission of diabetes after Roux-en-Y gastric bypass was mediated by PYY, suggesting that drugs promoting PYY release or action can restore pancreatic islet function in people with T2D (129). Ongoing research is focused on optimizing PYY-based therapies for obesity and T2D, with particular attention to improving delivery methods and efficacy in combination treatments.

3. Evolution of Novel GLP-1 Based Medicines for Type 2 Diabetes and Obesity

Building on the beneficial clinical effects of GLP-1 treatments, the concept of nutrient-stimulated hormone-based therapeutics has emerged, combining GLP-1 with other gut hormones such as GIP, glucagon, and PYY. These innovative approaches underscore the expanding role of GLP-1-based therapies in managing these chronic conditions. Novel agents targeting multiple receptors aim to enhance therapeutic outcomes by leveraging complementary mechanisms.

Fig. 2 provides an overview of novel GLP-1–based compounds currently in various stages of clinical development. **Fig. 3** illustrates the molecular structures and key modifications that enable prolonged action and receptor specificity in these therapeutic agents.

3.1. Innovation in Oral GLP-1 Receptor Agonists: Small-Molecule Agents

Recent advancements in GLP-1RA therapies have led to the development of oral formulations, notably oral semaglutide, which requires the use of the absorption enhancer SNAC (sodium N-(8-[2-hydroxybenzoyl] amino) caprylate) to achieve sufficient absorption (132). Oral administration offers significant advantages in terms of convenience and adherence, compared to injectable formulations. However, oral delivery faces challenges such as physical barriers in the GI tract, the acidic microenvironment of the stomach, inefficient absorption, protease degradation, and hepatic first-pass metabolism. Oral semaglutide addresses these limitations by using SNAC to enhance absorption through the GI mucosa. This is achieved by increasing lipophilicity, converting semaglutide into a more permeable monomeric form, locally elevating pH, and inhibiting pepsin activity (133,134). However, oral semaglutide still has modest absolute bioavailability (~1%) and requires strict dosing conditions (fasting and water, with no food for 30 minutes) to ensure absorption. High-dose oral semaglutide (25 mg and 50 mg daily) is currently under investigation for obesity treatment, as higher doses may achieve weight loss comparable to injectable semaglutide 2.4 mg weekly. The progress with oral semaglutide underscores both the possibilities and challenges of oral peptide therapy.

Beyond oral formulations, recent clinical investigations have explored higher-dose injectable semaglutide to enhance weight loss efficacy. In the STEP UP trial, once-weekly semaglutide 7.2 mg produced greater weight loss than the standard 2.4 mg dose (20.7% vs. 17.5% at 72 weeks), with a higher proportion achieving ≥25% reduction (33.2% vs. 16.7%). Safety profiles were similar, with GI events most common (135).

A groundbreaking advance has been the development of non-peptide, small-molecule GLP-1RAs that can be given orally without any absorption enhancer. Two leading candidates are

danuglipron (PF-06882961) and orforglipron (LY3502970) (136,137). Unlike large peptides, these synthetic molecules are chemically stable in the acidic, enzyme-rich gastrointestinal environment and readily absorbed. They bind to the GLP-1R at an allosteric site that accommodates small molecules, activating the receptor's signaling in a manner analogous to native GLP-1. Structural studies, including X-ray crystallography, have confirmed that such small-molecule agonists induce the active receptor conformation and trigger canonical downstream signaling via $G\alpha_s$ coupling and cyclic AMP elevation (137). Notably, a conserved tryptophan residue at position 33 in the receptor's N-terminal extracellular domain is critical for their activity, and these agonists engage it similarly to GLP-1 (136,137).

This innovation represents a significant advancement in oral incretin-based pharmacotherapy, effectively overcoming the longstanding barriers associated with peptide delivery. Small-molecule GLP-1RAs offer advantages in stability, dosing, and scalable manufacturing, broadening treatment accessibility and supporting patient-centered care (**Table 2**).

Danuglipron

Danuglipron, a small-molecule oral GLP-1RA, is being investigated as an adjunct to diet and exercise for improving glycemic control in T2D (**Table 2**) (138). Preclinical studies in humanized mouse models demonstrated that danuglipron stimulated glucose-dependent insulin secretion and suppressed food intake with efficacy comparable to injectable GLP-1RAs (138).

In a phase 1 study, 16 weeks of danuglipron treatment in adults with T2D who were taking metformin resulted in reduced glycemic indices and body weight, with favorable safety and pharmacokinetic profiles (138). Subsequently, a phase 2b study assessed the efficacy, safety, and tolerability of danuglipron over 16 weeks in 411 adults with T2D (**Table 3**) (139). Participants in

the 120 mg twice-daily group achieved reductions in HbA1c and fasting glucose levels of –1.16% (90% CI, –1.47% to –0.86%) and –33.24 mg/dL (90% CI, –45.63 to –20.84 mg/dL), respectively, compared to placebo. Body weight reductions were also observed: –2.04 kg (90% CI, –3.01 to –1.07 kg) in the 80 mg group and –4.17 kg (90% CI, –5.15 to –3.18 kg) in the 120 mg group (139). A meta-analysis of four trials published between 2021 and 2023 confirmed that danuglipron is effective in glycemic control and weight reduction in patients with T2D (140). However, clinical development was halted in April 2025 due to hepatotoxicity (141).

Orforglipron

A phase 1a trial evaluated the safety, pharmacokinetics, and pharmacodynamics of single and multiple doses of orforglipron in 92 healthy adults aged 18–65 years (HbA1c <6.5%, BMI 20–40 kg/m²) (142). Weight loss occurred in all patients completing 28 days of treatment, with dose-dependent reductions, and all but the lowest dose group achieved statistically significant weight loss compared to placebo.

In a phase 2 trial, orforglipron demonstrated significant efficacy in reducing blood sugar and body weight (143). At 36 weeks, weight reductions ranged from –9.4% to –14.7%, compared to –2.3% in the placebo group. A separate study assessing orforglipron (45 mg/day) in T2D patients reported a 1.67% reduction in HbA1c and a 7.4% decrease in body weight (144). Orforglipron (≥12 mg/day) outperformed dulaglutide (1.5 mg/week) in both blood glucose control and weight loss. However, higher doses of orforglipron were associated with a greater incidence of GI-related adverse events, such as nausea (25% vs. 18%) and vomiting (22% vs. 8%), compared to dulaglutide.

In a phase 3 ACHIEVE-1 trial, once-daily orforglipron (3-36 mg) treatment for 40 weeks

significantly reduced HbA1c by –1.24 to –1.48% points versus -0.41 with placebo in adults with T2D (145). Body weight decreased by –4.5% to –7.6% across doses versus –1.7% with placebo. Gastrointestinal adverse events were most common but generally mild-to-moderate, with discontinuation rates of 4.4-7.8% for orforglipron versus 1.4% for placebo (145).

Orforglipron is currently being evaluated in the phase 3 ACHIEVE-4 trial (NCT05803421), which focuses on patients with T2D and obesity or overweight who are at high risk for CV complications, including those with chronic kidney disease (CKD). The trial compares orforglipron with insulin glargine, with results expected to further elucidate its efficacy and safety.

Orforglipron addresses several limitations of oral semaglutide, including food-drug interactions and low oral bioavailability. However, as a non-peptide molecule, orforglipron simplifies both usage and manufacturing processes, potentially reducing costs and broadening access to GLP-1RA therapies. These attributes make orforglipron a compelling candidate in the ongoing evolution of GLP-1RA-based therapies, albeit that any off target effects, especially in the brain will need to be excluded.

The pursuit of non-injectable oral GLP-1RAs reflects significant advancements in the field, addressing patient preferences for convenience and adherence. The emergence of high-dose oral semaglutide, orforglipron, and danuglipron highlights both the potential but also the risks of orally absorbable peptides and non-peptide agents to transform the treatment of obesity and metabolic diseases.

3.2. Dual Agonists for the Treatment of Obesity

(1) GLP-1/ GIP Receptor Co-agonists

Tirzepatide, a dual agonist targeting both GLP-1 and GIP receptors, has already demonstrated remarkable efficacy in the management of diabetes (146) and obesity (147). Beyond tirzepatide, a pipeline of innovative dual GIP and GLP-1 receptor agonists is being developed to enhance metabolic outcomes: SCO-094 (JapicCTI-205323), VK2735 (NCT06068946), and CT-388 (NCT06525935).

One such agent, DR10627, is a chemically synthesized linear peptide consisting of 39 amino acids (4457.96 Da) (148). The N-terminal sequence (1–29) is derived from GLP-1, with specific mutations to enhance GIP activity. Its C-terminal sequence incorporates ten amino acids from exenatide, forming a "tryptophan cage" to improve metabolic stability. Additionally, the C-terminus is amidated, and a palmitoyl group is conjugated via a γ-glutamyl-linker at the Lys position, extending its half-life.

Preclinical studies of DR10627 demonstrated significant improvements in glucose control in both Sprague-Dawley rats and *db/db* mice (148). At doses of 10 and 30 nmol/kg, DR10627 outperformed liraglutide (80 nmol/kg) in potentiating weight loss, lowering lipid levels, and enhancing overall metabolic health (148). Currently, DR10627 is undergoing phase 1 trials for the treatment of obesity and diabetes, representing a promising addition to dual-incretin-based therapeutics.

(2) Unimolecular GLP-1 Receptor Agonists/ GIP Receptor Antagonists

Interestingly, GIPR antagonism, as well as agonism, has emerged as a viable strategy for managing obesity and T2D. When combined with GLP-1R agonism, GIPR antagonism further

enhances glycemic control and weight loss outcomes in pre-clinical models of obesity and diabetes mellitus (84,149).

***Maridebart cafraglutide* (MariTide)**

Maridebart cafraglutide (AMG 133), a bispecific molecule combining a GIPR antagonist with GLP-1RA peptides, exemplifies this novel therapeutic approach (**Table 2**) (16,87,150). It is engineered by conjugating a fully human anti-GIPR monoclonal antibody to GLP-1 analogue peptides, thereby leveraging the complementary mechanisms of GIPR antagonism and GLP-1R agonism to achieve substantial weight reduction and metabolic improvements.

GIPR antagonism has been shown to suppress adipogenesis and enhance energy expenditure (149). Genetic studies and preclinical models indicate that GIPR knockout animals are resistant to diet-induced obesity, and pharmacological GIPR blockade reduces body weight and improves glucose homeostasis (66). By inhibiting cAMP signaling in adipocytes, GIPR antagonism mitigates the obesogenic effects of GIP, including fat deposition and lipid storage (87).

Clinical trials of maridebart cafraglutide have demonstrated promising results. When administered every four weeks, the treatment resulted in a 15% reduction in body weight after four doses over 85 days in people with obesity with a mean BMI of 33.8 kg/m^2 (16). Adverse effects were mild to moderate, but highly prevalent (70–100%). In a subsequent 52-week, phase 2 trial of 592 adults with obesity (with or without T2D), once-monthly maridebart cafraglutide induced –12% to –16% weight loss in those without diabetes and –8% to –12% in those with diabetes, compared with minimal changes in the placebo group. Among participants with T2D, HbA1c reductions of –1.2 to –1.6% were observed. DXA analyses showed preferential fat mass reduction compared with lean mass loss. Gastrointestinal adverse events remained prominent,

with some mitigation with slower dose-escalation (151). However, these obvious tolerability problems remain a challenge and need to be addressed by more effective dose escalation regimens.

Another GIPR antagonist, AT-7687, has shown impressive results in combination with liraglutide in preclinical studies. In cynomolgus monkeys, this combination therapy achieved a 16.3% weight reduction, along with significant improvements in metabolic profiles, including a 30% decrease in glucose levels, a 52% reduction in insulin levels, and reductions in triglycerides (39%) and LDL-cholesterol (48%) (89). These findings highlight the potential of combining GIPR antagonists with GLP-1RAs for comprehensive metabolic management.

(3) Glucagon/GLP-1 Receptor Co-Agonists: Survodutide and Mazdutide

Recent advances in peptide engineering have enabled the development of single peptides capable of targeting multiple receptors simultaneously, mimicking combination therapy.

Survodutide

Survodutide (BI 456906) is a dual glucagon and GLP-1 receptor agonist with a prolonged half-life of 100 hours in humans (152), with a structure modified from glucagon to achieve full activation of GLP-1 receptors and partial activation of glucagon receptors, thereby demonstrating GLP-1R-biased activity (**Table 2**) (152). Additionally, survodutide incorporates a C_{18} fatty acid for extended half-life and utilizes structural modifications, including C-terminal amidation and substitution at the second amino acid, to resist DPP-4-mediated degradation (152).

In phase 1 studies involving healthy volunteers and individuals with a BMI >27 kg/m^2, survodutide achieved a maximum placebo-corrected weight loss of 13.8% by week 16 (153).

Higher doses were associated with increased GI-related adverse events. Phase 2 data revealed that doses exceeding 1.2 mg twice weekly resulted in more than 50% of participants with T2D achieving over 5% body weight reduction, while over 25% experienced weight loss exceeding 10% (154). Interestingly, HbA1c was remarkably improved despite glucagon agonism of the molecule in the subjects with T2D (154).

Currently, three phase 3 trials are underway. SYNCHRONIZE-1 (NCT06066515) includes 726 participants with obesity (BMI ≥30 kg/m² or ≥27 kg/m² with at least one obesity-related complication) without T2D and SYNCHRONIZE-2 (NCT06066528) involves 755 participants with BMI ≥27 kg/m² and T2D, and SYNCHRONIZE-CVOT (NCT06077864) involving 4,935 participants with BMI ≥27 kg/m² and CVD (155). Participants in both studies receive weekly subcutaneous survodutide injections (uptitrated to 3.6 or 6.0 mg) alongside lifestyle interventions.

Additionally, survodutide demonstrated significant improvements in metabolic dysfunction-associated steatohepatitis (MASH) without fibrosis progression in 47–62% of participants, compared to 14% in the placebo group (156). Liver fat content was reduced more than 30% in 57–67% of participants across various dosage groups (156).

Mazdutide

Mazdutide (IBI362 or LY3305677), a once-weekly GLP-1 and glucagon receptor dual agonist, has demonstrated significant efficacy in reducing body weight and HbA1c across multiple clinical trials. In China, a 20-week phase 2 trial in patients with T2D, mazdutide up to 6 mg reduced HbA1c (–1.41% to –1.67%) and body weight (–7.1%) significantly more than placebo, with common adverse events including mild gastrointestinal symptoms and hypoglycemia (157).

In a 24-week trial in Chinese adults with overweight or obesity, mazdutide reduced body weight by –6.7%, –10.4% and –11.3% across doses of 3.0, 4.5 and 6.0 mg respectively compared to 1.0% with placebo (all $p < 0.0001$), with good tolerability (158). A meta-analysis further confirmed its efficacy in weight loss (mean difference: –6.22%), with greater effects in participants without diabetes (–8.44%) and longer treatment durations (–10.47% at 24 weeks) (159). The phase 3 GLORY-1 trial (NCT05607680) assessed the efficacy and safety of mazdutide in 610 Chinese adults with overweight or obesity. At week 32, mazdutide significantly reduced body weight, with mean reductions of –10.1% (4 mg) and –12.6% (6 mg) compared to a 0.5% increase with placebo. Additionally, 73.9% and 82.0% of participants on 4 mg and 6 mg, respectively, achieved ≥5% weight loss compared to 10.5% with placebo. Mazdutide also improved cardiometabolic risk factors and was well tolerated, with mild to moderate gastrointestinal symptoms being the most common adverse events (157).

(4) Amylin/GLP-1 Receptor Agonist: Fixed-Dose Combinations or Dual Agonists

CagriSema

CagriSema is a once-weekly fixed-ratio combination of the long-acting GLP-1RA semaglutide (2.4 mg) and the amylin analogue cagrilintide (2.4 mg) (**Table 2)**. Building on the mechanisms described earlier in Section 2.4, amylin complements GLP-1 by enhancing satiety and slowing gastric emptying, supporting their combined use (160).

In a phase 2 trial, cagrilintide alone resulted in a 10% body weight reduction over 26 weeks in participants with BMI >27 kg/m^2 and associated comorbidities, compared to 3% with placebo (120). A phase 1b study combining cagrilintide (up to 4.5 mg) with semaglutide (2.4 mg) achieved a mean weight loss of 17%, outperforming semaglutide alone (10%) over 20 weeks

(161). This combination therapy leverages complementary mechanisms, enhancing therapeutic efficacy (162).

In a phase 2 trial involving individuals with T2D (BMI ≥27 kg/m^2), weekly CagriSema administration achieved a 2.18% reduction in HbA1c and a 15.6% weight loss (17). Another phase 2 trial with 706 participants showed weight loss rates of 6.0–10.8% in the CagriSema-treated group versus 3.0% in the placebo group.

The recently completed REDEFINE 1 trial evaluated the efficacy of subcutaneous CagriSema over 68 weeks in 3,417 participants with BMI ≥27 kg/m^2 and obesity related complications. CagriSema achieved a mean weight loss of 22.7%, compared to 11.8% with cagrilintide, 16.1% with semaglutide, and 2.3% with placebo. Furthermore, 40.4% of CagriSema-treated participants experienced ≥25% weight loss, compared to 6.0% with cagrilintide, 16.2% with semaglutide, and 0.9% with placebo. Gastrointestinal adverse events were the most common but were generally mild to moderate and diminished over time (163). The REDEFINE 2, a 68-week efficacy and safety trial investigating once-weekly subcutaneous CagriSema, included 1,206 people with BMI ≥27 kg/m^2 and T2D. The people treated with CagriSema achieved a superior weight loss of 15.7% after 68 weeks compared to 3.1% with placebo. Weight loss of 5% or more after 68 weeks was achieved by 89.7% of patients on CagriSema, compared to 30.3% by placebo (164).

Amycretin

Amycretin is a single molecule that operates as a GLP-1RA and amylin receptor agonist. It can be delivered orally. A first-in-human trial investigated the safety, tolerability, and efficacy of oral amycretin in adults with BMI ≥27 kg/m^2 without diabetes. Over 12 weeks, amycretin

demonstrated significant, dose-dependent reductions in body weight, with mean changes of –10.4% and –13.1% for 50 mg and 2×50 mg daily doses, respectively, compared to –1.1% with placebo. Adverse events were predominantly gastrointestinal, mild to moderate in severity, and dose dependent (165). These agents target multiple metabolic pathways to achieve greater efficacy in weight loss and metabolic control (166). In a phase 1b/2a randomized, placebo-controlled and double-blinded study, amycretin was reported to body weight loss of 9.7% on 1.25 mg (20 weeks), 16.2% on 5 mg (28 weeks) and 22.0% on 20 mg (36 weeks) in people living with BMI ≥27 kg/m^2 (167).

3.3. Triple Peptide Receptor Agonists for the Treatment of Obesity and Type 2 Diabetes

(1) GIP/GLP-1/Glucagon Receptor Co-Agonists: Retatrutide

Retatrutide, a triple-agonist peptide targeting GIP, GLP-1, glucagon receptors, is engineered with a fatty diacid moiety that enhances its pharmacokinetics, enabling a half-life of approximately six days and facilitating weekly dosing (**Table 2**) (168,169). Compared to endogenous ligands, retatrutide demonstrates a higher affinity for the GIP receptor than for glucagon and GLP-1 receptors, leveraging complementary mechanisms: GLP-1 and GIP inhibit glucagon-induced gluconeogenesis, while glucagon augments energy expenditure synergistically with GLP-1/GIP-induced appetite suppression (168).

In a phase 2 trial involving participants with BMI ≥30 kg/m^2 without obesity related complications or BMI ≥27 kg/m^2 with obesity related complications, retatrutide delivered dose-dependent weight reductions after 24 weeks: –7.2% for 1 mg, –12.9% for 4 mg, –17.3% for 8 mg, and –17.5% for 12 mg, compared to –1.6% with placebo (170). By 48 weeks, weight reductions of ≥5%, ≥10%, and ≥15% were achieved by 92%, 75%, and 60% of participants in

the 4 mg group, increasing to 100%, 91%, and 75% in the 8 mg group, and 100%, 93%, and 83% in the 12 mg group, compared to only 27%, 9%, and 2% in the placebo group (170).

In a phase 2 study of adults with T2D, retatrutide similarly achieved dose-dependent weight reductions over 36 weeks: 3.2% with 0.5 mg, 7.9% and 10.4% with 4 mg (with and without escalation), and 16.8%, 16.3%, and 16.9% with 8 mg (slow and fast escalation) and 12 mg doses, respectively (104). The most common side effects were gastrointestinal symptoms, which were dose-dependent and generally mild to moderate. A transient, dose-dependent increase in heart rate, peaking at 24 weeks and attributed to glucagon-mediated sympathetic nervous system activation, was also observed (170).

To further evaluate retatrutide, multiple phase 3 trials are ongoing. The TRANSCEND-1 trial (NCT06354660) is an 11-month study investigating retatrutide's glycemic control in adults with uncontrolled T2D, while TRANSCEND-2 (NCT06297603) is a 52-week study comparing retatrutide with semaglutide in adults with T2D inadequately controlled on metformin with or without SGLT2 inhibitors. Additionally, the TRIUMPH outcomes trial is a 5-year study examining retatrutide's impact on CV and kidney outcomes in individuals with obesity and established atherosclerotic CVD or CKD. This trial focuses on composite endpoints, including major adverse CV events (MACE), heart failure-related hospitalizations, and renal function decline (NCT06383390).

4. Kidney protection effect with novel GLP-1-based medications

In several large-scale clinical studies targeting CVD, established GLP-1RAs, such as liraglutide in LEADER (171,172), semaglutide 1.0 mg in SUSTAIN-6 (173), and dulaglutide in REWIND (174), showed beneficial renal outcomes, mainly driven by reductions in albuminuria or its

progression (175) and by reducing the decline in eGFR over time (172,176,177).

Of note, in the FLOW trial, the first, multicenter, randomized controlled study with kidney outcome, semaglutide 1.0 mg therapy reduced the risk of major kidney disease events in 3,533 patients with T2D and CKD (≥50% eGFR decline, or kidney/cardiovascular death) by 24% and all-cause mortality by 20% over 3.4 years (177). In a prespecified exploratory analysis of the SURPASS-4 trial, tirzepatide reduced the risk of a composite kidney endpoint by 42% compared with insulin glargine over 85 weeks (178). These findings suggest that semaglutide and tirzepatide may provide substantial kidney protection in people with T2D at high cardiovascular risk. A recent meta-analysis reported that long-acting GLP-1RA, including both once-weekly semaglutide injection and oral semaglutide, reduced incidence of MACE, composite renal events, and all-cause mortality in patients with T2D (179).

5. Sarcopenia and muscle health considerations with novel GLP-1-based medications

Although GLP-1-based medications have transformed obesity management, concerns exist regarding clinically meaningful sarcopenia, characterized by diminished muscle mass and strength, which in other circumstances correlates with poor health outcomes and increased mortality (180,181).

Clinical trials of GLP-1RAs consistently demonstrate reductions in lean body mass. In the STEP 1 trial, semaglutide treatment resulted in lean mass loss comprising 45.5% of overall weight reduction (182), whereas tirzepatide in SURMOUNT-1 accounted for 34.3% of weight loss from lean tissue (74). Magnetic resonance imaging data from the SURPASS-3 substudy demonstrated that tirzepatide therapy produced decreases in muscle volume (−0.44 to −0.76 L), concurrent with decreased muscle fat infiltration (−0.23 to −0.44% points) (183), raising the

possibility of reduced muscle mass, but improved muscle quality.

Evidence supports combining resistance training with adequate protein intake (>1.2 g/kg/day) to preserve fat-free mass, with benefits persisting up to a year after treatment cessation (184) Pharmacological strategies include inhibitors of the myostatin/activin pathway such as bimagrumab, which increased lean mass by 3.6% and reduced fat mass by 20.5% (185), and is under study in combination with GLP-1RAs (NCT05616013, NCT06643728). Emerging agents—trevogrumab, garetosmab, urocortin-2 peptides (186-188), and selective androgen receptor modulators like enobosarm (NCT06282458)—target muscle catabolism to preserve or augment lean mass. Importantly, assessing muscle strength and function will be critical to optimize GLP-1–based regimens and mitigate sarcopenia risk during long-term therapy.

6. Summary and Conclusion

Recent developments have provided novel medications, all based on stimulating GLP-1 plus other receptors, which can – on average – lead to more than 20% body weight reductions. The effect sizes are highly variable between individuals, and there is a lack of predictive markers or criteria for early detection of non or low responders. In the end, the therapeutic goal is not just to induce weight loss, but to improve symptoms and consequences of obesity-associated complications like progression of prediabetes to manifest T2D (189), advances stages of MASLD (with fibrosis/cirrhosis) (190,191), obesity-associated heart failure with preserved ejection fraction (191-193), obstructive sleep apnoea syndrome (194), and osteoarthritis (195).

Diabetes and obesity are escalating global health challenges, with lifestyle interventions and behavioral modifications currently forming the foundation of prevention and management. However, medications serve as essential adjuncts, promoting additional weight loss and aiding

weight maintenance. Semaglutide and tirzepatide, two widely used GLP-1-based agents, have set new standards in the management of these conditions.

Emerging therapies, including dual and triple agonists targeting combinations of GLP-1, GIP, glucagon, and amylin, are poised to achieve even greater efficacy. These agents, with expected weight loss reductions exceeding 20%, exemplify the potential of advanced pharmacological strategies. The challenge will be how to improve the tolerability of these medications to facilitate the long-term treatment required to address obesity related complications.

Recent identification of peptides such as irisin, adropin, and spexin has revealed new regulatory pathways in metabolic regulation (196-198). Irisin, a hormone-like peptide cleaved from the transmembrane precursor FNDC5 in skeletal muscle and adipose tissue, promotes the browning of white adipose tissue by enhancing mitochondrial activity and UCP1 expression (199). Beyond its role in energy expenditure, irisin augments insulin biosynthesis and supports the expansion of β-cell functional mass (200). An especially innovative strategy involves combining N-methyl-D-aspartate receptor antagonism with GLP-1R agonism; for example, the bimodal GLP-1–MK-801 conjugate demonstrated enhanced weight loss efficacy while mitigating adverse effects through targeted brain delivery (201). Together, these advances underscore the therapeutic promise of newly discovered peptides.

The combination of GLP-1-based treatments with the actions of other gastro-entero-pancreatic peptide hormones with therapeutic potential promises a future with more effective management of obesity and its associated co-morbidities. Multi-agonists that simultaneously activate multiple hormone receptors hold the potential to redefine obesity pharmacotherapy, addressing the multifactorial nature of the disease and improving outcomes for patients

worldwide.

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References

1. N. C. D. Risk Factor Collaboration. Worldwide trends in diabetes prevalence and treatment from 1990 to 2022: a pooled analysis of 1108 population-representative studies with 141 million participants. *Lancet*. 2024;404(10467):2077-2093.
2. Ahmad E, Lim S, Lamptey R, Webb DR, Davies MJ. Type 2 diabetes. *Lancet*. 2022;400(10365):1803-1820.
3. N. C. D. Risk Factor Collaboration. Worldwide trends in underweight and obesity from 1990 to 2022: a pooled analysis of 3663 population-representative studies with 222 million children, adolescents, and adults. *Lancet*. 2024;403(10431):1027-1050.
4. Elmaleh-Sachs A, Schwartz JL, Bramante CT, Nicklas JM, Gudzune KA, Jay M. Obesity Management in Adults: A Review. *JAMA*. 2023;330(20):2000-2015.
5. Hales CM, Carroll MD, Fryar CD, Ogden CL. Prevalence of Obesity and Severe Obesity Among Adults: United States, 2017-2018. *NCHS Data Brief*. 2020(360):1-8.
6. Ward ZJ, Bleich SN, Long MW, Gortmaker SL. Association of body mass index with health care expenditures in the United States by age and sex. *PLoS One*. 2021;16(3):e0247307.
7. Neeland IJ, Lim S, Tchernof A, Gastaldelli A, Rangaswami J, Ndumele CE, Powell-Wiley TM, Despres JP. Metabolic syndrome. *Nat Rev Dis Primers*. 2024;10(1):77.

8. Rubino F, Cummings DE, Eckel RH, Cohen RV, Wilding JPH, Brown WA, Stanford FC, Batterham RL, Farooqi IS, Farpour-Lambert NJ, le Roux CW, Sattar N, Baur LA, Morrison KM, Misra A, Kadowaki T, Tham KW, Sumithran P, Garvey WT, Kirwan JP, Fernandez-Real JM, Corkey BE, Toplak H, Kokkinos A, Kushner RF, Branca F, Valabhji J, Bluher M, Bornstein SR, Grill HJ, Ravussin E, Gregg E, Al Busaidi NB, Alfaris NF, Al Ozairi E, Carlsson LMS, Clement K, Despres JP, Dixon JB, Galea G, Kaplan LM, Laferrere B, Laville M, Lim S, Luna Fuentes JR, Mooney VM, Nadglowski J, Jr., Urudinachi A, Olszanecka-Glinianowicz M, Pan A, Pattou F, Schauer PR, Tschop MH, van der Merwe MT, Vettor R, Mingrone G. Definition and diagnostic criteria of clinical obesity. *Lancet Diabetes Endocrinol*. 2025;13(3):221-262.

9. Loos RJF, Yeo GSH. The genetics of obesity: from discovery to biology. *Nat Rev Genet*. 2022;23(2):120-133.

10. Farooqi SI. Genetic, molecular and physiological mechanisms involved in human obesity: Society for Endocrinology Medal Lecture 2012. *Clin Endocrinol (Oxf)*. 2015;82(1):23-28.

11. Moiz A, Filion KB, Toutounchi H, Tsoukas MA, Yu OHY, Peters TM, Eisenberg MJ. Efficacy and Safety of Glucagon-Like Peptide-1 Receptor Agonists for Weight Loss Among Adults Without Diabetes : A Systematic Review of Randomized Controlled Trials. *Ann Intern Med*. 2025;178(2):199-217.

12. Cleto AS, Schirlo JM, Beltrame M, Gomes VHO, Acras IH, Neiverth GS, Silva BB, Juliatto BMS, Machozeki J, Martins CM. Semaglutide effects on safety and cardiovascular outcomes in patients with overweight or obesity: a systematic review and meta-analysis. *Int J Obes (Lond)*. 2025;49(1):21-30.

13. Rabbani SA, El-Tanani M, Matalka, II, Rangraze IR, Aljabali AAA, Khan MA, Tambuwala MM. Tirzepatide: unveiling a new dawn in dual-targeted diabetes and obesity management. *Expert Rev Endocrinol Metab*. 2024;19(6):487-505.
14. Alruwaili H, Dehestani B, le Roux CW. Clinical Impact of Liraglutide as a Treatment of Obesity. *Clin Pharmacol*. 2021;13:53-60.
15. Frias JP, De Block C, Brown K, Wang H, Thomas MK, Zeytinoglu M, Maldonado JM. Tirzepatide Improved Markers of Islet Cell Function and Insulin Sensitivity in People With T2D (SURPASS-2). *J Clin Endocrinol Metab*. 2024;109(7):1745-1753.
16. Veniant MM, Lu SC, Atangan L, Komorowski R, Stanislaus S, Cheng Y, Wu B, Falsey JR, Hager T, Thomas VA, Ambhaikar M, Sharpsten L, Zhu Y, Kurra V, Jeswani R, Oberoi RK, Parnes JR, Honarpour N, Neutel J, Strande JL. A GIPR antagonist conjugated to GLP-1 analogues promotes weight loss with improved metabolic parameters in preclinical and phase 1 settings. *Nat Metab*. 2024;6(2):290-303.
17. Frias JP, Deenadayalan S, Erichsen L, Knop FK, Lingvay I, Macura S, Mathieu C, Pedersen SD, Davies M. Efficacy and safety of co-administered once-weekly cagrilintide 2.4 mg with once-weekly semaglutide 2.4 mg in type 2 diabetes: a multicentre, randomised, double-blind, active-controlled, phase 2 trial. *Lancet*. 2023;402(10403):720-730.
18. Samms RJ, Coghlan MP, Sloop KW. How May GIP Enhance the Therapeutic Efficacy of GLP-1? *Trends Endocrinol Metab*. 2020;31(6):410-421.
19. Drucker DJ. Efficacy and Safety of GLP-1 Medicines for Type 2 Diabetes and Obesity. *Diabetes Care*. 2024.
20. Jastreboff AM, Kushner RF. New Frontiers in Obesity Treatment: GLP-1 and Nascent

Nutrient-Stimulated Hormone-Based Therapeutics. *Annu Rev Med*. 2023;74:125-139.

21. Nauck MA, Heimesaat MM, Orskov C, Holst JJ, Ebert R, Creutzfeldt W. Preserved incretin activity of glucagon-like peptide 1 [7-36 amide] but not of synthetic human gastric inhibitory polypeptide in patients with type-2 diabetes mellitus. *J Clin Invest*. 1993;91(1):301-307.

22. Nauck MA, Kleine N, Orskov C, Holst JJ, Willms B, Creutzfeldt W. Normalization of fasting hyperglycaemia by exogenous glucagon-like peptide 1 (7-36 amide) in type 2 (non-insulin-dependent) diabetic patients. *Diabetologia*. 1993;36(8):741-744.

23. Willms B, Werner J, Holst JJ, Orskov C, Creutzfeldt W, Nauck MA. Gastric emptying, glucose responses, and insulin secretion after a liquid test meal: effects of exogenous glucagon-like peptide-1 (GLP-1)-(7-36) amide in type 2 (noninsulin-dependent) diabetic patients. *J Clin Endocrinol Metab*. 1996;81(1):327-332.

24. Drucker DJ, Nauck MA. The incretin system: glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors in type 2 diabetes. *Lancet*. 2006;368(9548):1696-1705.

25. Ussher JR, Drucker DJ. Glucagon-like peptide 1 receptor agonists: cardiovascular benefits and mechanisms of action. *Nat Rev Cardiol*. 2023;20(7):463-474.

26. Muller TD, Finan B, Bloom SR, D'Alessio D, Drucker DJ, Flatt PR, Fritsche A, Gribble F, Grill HJ, Habener JF, Holst JJ, Langhans W, Meier JJ, Nauck MA, Perez-Tilve D, Pocai A, Reimann F, Sandoval DA, Schwartz TW, Seeley RJ, Stemmer K, Tang-Christensen M, Woods SC, DiMarchi RD, Tschop MH. Glucagon-like peptide 1 (GLP-1). *Mol Metab*. 2019;30:72-130.

27. Nauck MA, Muller TD. Incretin hormones and type 2 diabetes. *Diabetologia*.

2023;66(10):1780-1795.

28. Flint A, Raben A, Astrup A, Holst JJ. Glucagon-like peptide 1 promotes satiety and suppresses energy intake in humans. *J Clin Invest*. 1998;101(3):515-520.

29. Zander M, Madsbad S, Madsen JL, Holst JJ. Effect of 6-week course of glucagon-like peptide 1 on glycaemic control, insulin sensitivity, and beta-cell function in type 2 diabetes: a parallel-group study. *Lancet*. 2002;359(9309):824-830.

30. Drucker DJ. Mechanisms of Action and Therapeutic Application of Glucagon-like Peptide-1. *Cell Metab*. 2018;27(4):740-756.

31. Bettge K, Kahle M, Abd El Aziz MS, Meier JJ, Nauck MA. Occurrence of nausea, vomiting and diarrhoea reported as adverse events in clinical trials studying glucagon-like peptide-1 receptor agonists: A systematic analysis of published clinical trials. *Diabetes Obes Metab*. 2017;19(3):336-347.

32. McLean BA, Wong CK, Campbell JE, Hodson DJ, Trapp S, Drucker DJ. Revisiting the Complexity of GLP-1 Action from Sites of Synthesis to Receptor Activation. *Endocr Rev*. 2021;42(2):101-132.

33. Turton MD, O'Shea D, Gunn I, Beak SA, Edwards CM, Meeran K, Choi SJ, Taylor GM, Heath MM, Lambert PD, Wilding JP, Smith DM, Ghatei MA, Herbert J, Bloom SR. A role for glucagon-like peptide-1 in the central regulation of feeding. *Nature*. 1996;379(6560):69-72.

34. Song Y, Koehler JA, Baggio LL, Powers AC, Sandoval DA, Drucker DJ. Gut-Proglucagon-Derived Peptides Are Essential for Regulating Glucose Homeostasis in Mice. *Cell Metab*. 2019;30(5):976-986 e973.

35. Holt MK, Richards JE, Cook DR, Brierley DI, Williams DL, Reimann F, Gribble FM,

Trapp S. Preproglucagon Neurons in the Nucleus of the Solitary Tract Are the Main Source of Brain GLP-1, Mediate Stress-Induced Hypophagia, and Limit Unusually Large Intakes of Food. *Diabetes*. 2019;68(1):21-33.

36. He Z, Gao Y, Lieu L, Afrin S, Cao J, Michael NJ, Dong Y, Sun J, Guo H, Williams KW. Direct and indirect effects of liraglutide on hypothalamic POMC and NPY/AgRP neurons - Implications for energy balance and glucose control. *Mol Metab*. 2019;28:120-134.

37. Washington MC, Raboin SJ, Thompson W, Larsen CJ, Sayegh AI. Exenatide reduces food intake and activates the enteric nervous system of the gastrointestinal tract and the dorsal vagal complex of the hindbrain in the rat by a GLP-1 receptor. *Brain Res*. 2010;1344:124-133.

38. Dossat AM, Lilly N, Kay K, Williams DL. Glucagon-like peptide 1 receptors in nucleus accumbens affect food intake. *J Neurosci*. 2011;31(41):14453-14457.

39. Richard JE, Farkas I, Anesten F, Anderberg RH, Dickson SL, Gribble FM, Reimann F, Jansson JO, Liposits Z, Skibicka KP. GLP-1 receptor stimulation of the lateral parabrachial nucleus reduces food intake: neuroanatomical, electrophysiological, and behavioral evidence. *Endocrinology*. 2014;155(11):4356-4367.

40. Hsu TM, Hahn JD, Konanur VR, Lam A, Kanoski SE. Hippocampal GLP-1 receptors influence food intake, meal size, and effort-based responding for food through volume transmission. *Neuropsychopharmacology*. 2015;40(2):327-337.

41. Terrill SJ, Jackson CM, Greene HE, Lilly N, Maske CB, Vallejo S, Williams DL. Role of lateral septum glucagon-like peptide 1 receptors in food intake. *Am J Physiol Regul Integr Comp Physiol*. 2016;311(1):R124-132.

42. Adams JM, Pei H, Sandoval DA, Seeley RJ, Chang RB, Liberles SD, Olson DP.

Liraglutide Modulates Appetite and Body Weight Through Glucagon-Like Peptide 1 Receptor-Expressing Glutamatergic Neurons. *Diabetes*. 2018;67(8):1538-1548.

43. Scrocchi LA, Brown TJ, MaClusky N, Brubaker PL, Auerbach AB, Joyner AL, Drucker DJ. Glucose intolerance but normal satiety in mice with a null mutation in the glucagon-like peptide 1 receptor gene. *Nat Med*. 1996;2(11):1254-1258.

44. Hansotia T, Maida A, Flock G, Yamada Y, Tsukiyama K, Seino Y, Drucker DJ. Extrapancreatic incretin receptors modulate glucose homeostasis, body weight, and energy expenditure. *J Clin Invest*. 2007;117(1):143-152.

45. Scrocchi LA, Marshall BA, Cook SM, Brubaker PL, Drucker DJ. Identification of glucagon-like peptide 1 (GLP-1) actions essential for glucose homeostasis in mice with disruption of GLP-1 receptor signaling. *Diabetes*. 1998;47(4):632-639.

46. Lopez-Ferreras L, Richard JE, Noble EE, Eerola K, Anderberg RH, Olandersson K, Taing L, Kanoski SE, Hayes MR, Skibicka KP. Lateral hypothalamic GLP-1 receptors are critical for the control of food reinforcement, ingestive behavior and body weight. *Mol Psychiatry*. 2018;23(5):1157-1168.

47. Lee SJ, Sanchez-Watts G, Krieger JP, Pignalosa A, Norell PN, Cortella A, Pettersen KG, Vrdoljak D, Hayes MR, Kanoski SE, Langhans W, Watts AG. Loss of dorsomedial hypothalamic GLP-1 signaling reduces BAT thermogenesis and increases adiposity. *Mol Metab*. 2018;11:33-46.

48. Bailey CJ, Flatt PR, Conlon JM. Multifunctional incretin peptides in therapies for type 2 diabetes, obesity and associated co-morbidities. *Peptides*. 2025;187:171380.

49. Psaltis JP, Marathe JA, Nguyen MT, Le R, Bursill CA, Marathe CS, Nelson AJ, Psaltis PJ. Incretin-based therapies for the management of cardiometabolic disease in the clinic:

Past, present, and future. *Med Res Rev*. 2025;45(1):29-65.

50. Noyan-Ashraf MH, Shikatani EA, Schuiki I, Mukovozov I, Wu J, Li RK, Volchuk A, Robinson LA, Billia F, Drucker DJ, Husain M. A glucagon-like peptide-1 analog reverses the molecular pathology and cardiac dysfunction of a mouse model of obesity. *Circulation*. 2013;127(1):74-85.

51. Shiraishi D, Fujiwara Y, Komohara Y, Mizuta H, Takeya M. Glucagon-like peptide-1 (GLP-1) induces M2 polarization of human macrophages via STAT3 activation. *Biochem Biophys Res Commun*. 2012;425(2):304-308.

52. DeFronzo RA, Okerson T, Viswanathan P, Guan X, Holcombe JH, MacConell L. Effects of exenatide versus sitagliptin on postprandial glucose, insulin and glucagon secretion, gastric emptying, and caloric intake: a randomized, cross-over study. *Curr Med Res Opin*. 2008;24(10):2943-2952.

53. Rizzo M, Rizvi AA, Patti AM, Nikolic D, Giglio RV, Castellino G, Li Volti G, Caprio M, Montalto G, Provenzano V, Genovese S, Ceriello A. Liraglutide improves metabolic parameters and carotid intima-media thickness in diabetic patients with the metabolic syndrome: an 18-month prospective study. *Cardiovasc Diabetol*. 2016;15(1):162.

54. Nystrom T, Gutniak MK, Zhang Q, Zhang F, Holst JJ, Ahren B, Sjoholm A. Effects of glucagon-like peptide-1 on endothelial function in type 2 diabetes patients with stable coronary artery disease. *Am J Physiol Endocrinol Metab*. 2004;287(6):E1209-1215.

55. Ban K, Noyan-Ashraf MH, Hoefer J, Bolz SS, Drucker DJ, Husain M. Cardioprotective and vasodilatory actions of glucagon-like peptide 1 receptor are mediated through both glucagon-like peptide 1 receptor-dependent and -independent pathways. *Circulation*. 2008;117(18):2340-2350.

56. Salehi M, Aulinger BA, D'Alessio DA. Targeting beta-cell mass in type 2 diabetes: promise and limitations of new drugs based on incretins. *Endocr Rev*. 2008;29(3):367-379.
57. Yusta B, Baggio LL, Estall JL, Koehler JA, Holland DP, Li H, Pipeleers D, Ling Z, Drucker DJ. GLP-1 receptor activation improves beta cell function and survival following induction of endoplasmic reticulum stress. *Cell Metab*. 2006;4(5):391-406.
58. Nauck MA, Quast DR, Wefers J, Meier JJ. GLP-1 receptor agonists in the treatment of type 2 diabetes - state-of-the-art. *Mol Metab*. 2021;46:101102.
59. Alhomoud IS, Talasaz AH, Chandrasekaran P, Brown R, Mehta A, Dixon DL. Incretin hormone agonists: Current and emerging pharmacotherapy for obesity management. *Pharmacotherapy*. 2024;44(9):738-752.
60. Drucker DJ. Efficacy and Safety of GLP-1 Medicines for Type 2 Diabetes and Obesity. *Diabetes Care*. 2024;47(11):1873-1888.
61. Kang YM, Punov V, Lim S, Nauck MA. Comparative efficacy and tolerability of currently approved incretin mimetics: A systematic analysis of placebo-controlled clinical trials. *Diabetes Obes Metab*. 2025;27(7):3736-3746.
62. Monami M, Nreu B, Scatena A, Cresci B, Andreozzi F, Sesti G, Mannucci E. Safety issues with glucagon-like peptide-1 receptor agonists (pancreatitis, pancreatic cancer and cholelithiasis): Data from randomized controlled trials. *Diabetes Obes Metab*. 2017;19(9):1233-1241.
63. Nreu B, Dicembrini I, Tinti F, Mannucci E, Monami M. Pancreatitis and pancreatic cancer in patients with type 2 diabetes treated with glucagon-like peptide-1 receptor agonists: an updated meta-analysis of randomized controlled trials. *Minerva Endocrinol*

(Torino). 2023;48(2):206-213.

64. Douros JD, Novikoff A, DuBois B, Rohlfs R, Mokrosinski J, Hogendorf WFJ, Augustin R, Merkestein M, Egaa Martini LB, Linderoth L, Gerrard E, Kodra JT, Norlin J, Roed NK, Oldenburger A, Mowery SA, Waldhoer M, Perez-Tilve D, Finan B, Reedtz-Runge S, Muller TD, Knerr PJ. A GLP-1 analogue optimized for cAMP-biased signaling improves weight loss in obese mice. *Mol Metab*. 2025:102124.

65. Cary BP, Hager MV, Mariam Z, Morris RK, Belousoff MJ, Deganutti G, Sexton PM, Wootten D, Gellman SH. Prolonged signaling of backbone-modified glucagon-like peptide-1 analogues with diverse receptor trafficking. *Proc Natl Acad Sci USA*. 2025;122(14):e2407574122.

66. Zhang Q, Delessa CT, Augustin R, Bakhti M, Collden G, Drucker DJ, Feuchtinger A, Caceres CG, Grandl G, Harger A, Herzig S, Hofmann S, Holleman CL, Jastroch M, Keipert S, Kleinert M, Knerr PJ, Kulaj K, Legutko B, Lickert H, Liu X, Luippold G, Lutter D, Malogajski E, Medina MT, Mowery SA, Blutke A, Perez-Tilve D, Salinno C, Sehrer L, DiMarchi RD, Tschop MH, Stemmer K, Finan B, Wolfrum C, Muller TD. The glucose-dependent insulinotropic polypeptide (GIP) regulates body weight and food intake via CNS-GIPR signaling. *Cell Metab*. 2021;33(4):833-844 e835.

67. Christensen MB, Calanna S, Holst JJ, Vilsboll T, Knop FK. Glucose-dependent insulinotropic polypeptide: blood glucose stabilizing effects in patients with type 2 diabetes. *J Clin Endocrinol Metab*. 2014;99(3):E418-426.

68. Christensen MB, Gasbjerg LS, Heimburger SM, Stensen S, Vilsboll T, Knop FK. GIP's involvement in the pathophysiology of type 2 diabetes. *Peptides*. 2020;125:170178.

69. Campbell JE, Beaudry JL, Svendsen B, Baggio LL, Gordon AN, Ussher JR, Wong CK,

Gribble FM, D'Alessio DA, Reimann F, Drucker DJ. GIPR Is Predominantly Localized to Nonadipocyte Cell Types Within White Adipose Tissue. *Diabetes*. 2022;71(5):1115-1127.

70. Kim SJ, Nian C, McIntosh CH. Resistin is a key mediator of glucose-dependent insulinotropic polypeptide (GIP) stimulation of lipoprotein lipase (LPL) activity in adipocytes. *J Biol Chem*. 2007;282(47):34139-34147.

71. Asmar M, Asmar A, Simonsen L, Gasbjerg LS, Sparre-Ulrich AH, Rosenkilde MM, Hartmann B, Dela F, Holst JJ, Bulow J. The Gluco- and Liporegulatory and Vasodilatory Effects of Glucose-Dependent Insulinotropic Polypeptide (GIP) Are Abolished by an Antagonist of the Human GIP Receptor. *Diabetes*. 2017;66(9):2363-2371.

72. Daousi C, Wilding JP, Aditya S, Durham BH, Cleator J, Pinkney JH, Ranganath LR. Effects of peripheral administration of synthetic human glucose-dependent insulinotropic peptide (GIP) on energy expenditure and subjective appetite sensations in healthy normal weight subjects and obese patients with type 2 diabetes. *Clin Endocrinol (Oxf)*. 2009;71(2):195-201.

73. Bergmann NC, Lund A, Gasbjerg LS, Meessen ECE, Andersen MM, Bergmann S, Hartmann B, Holst JJ, Jessen L, Christensen MB, Vilsboll T, Knop FK. Effects of combined GIP and GLP-1 infusion on energy intake, appetite and energy expenditure in overweight/obese individuals: a randomised, crossover study. *Diabetologia*. 2019;62(4):665-675.

74. Jastreboff AM, Aronne LJ, Ahmad NN, Wharton S, Connery L, Alves B, Kiyosue A, Zhang S, Liu B, Bunck MC, Stefanski A, Investigators S-. Tirzepatide Once Weekly for the Treatment of Obesity. *N Engl J Med*. 2022;387(3):205-216.

75. Muller TD, Adriaenssens A, Ahren B, Bluher M, Birkenfeld AL, Campbell JE, Coghlan

MP, D'Alessio D, Deacon CF, DelPrato S, Douros JD, Drucker DJ, Figueredo Burgos NS, Flatt PR, Finan B, Gimeno RE, Gribble FM, Hayes MR, Holscher C, Holst JJ, Knerr PJ, Knop FK, Kusminski CM, Liskiewicz A, Mabilleau G, Mowery SA, Nauck MA, Novikoff A, Reimann F, Roberts AG, Rosenkilde MM, Samms RJ, Scherer PE, Seeley RJ, Sloop KW, Wolfrum C, Wootten D, DiMarchi RD, Tschop MH. Glucose-dependent insulinotropic polypeptide (GIP). *Mol Metab*. 2025;95:102118.

76. Liskiewicz A, Muller TD. Regulation of energy metabolism through central GIPR signaling. *Peptides*. 2024;176:171198.

77. Borner T, Geisler CE, Fortin SM, Cosgrove R, Alsina-Fernandez J, Dogra M, Doebley S, Sanchez-Navarro MJ, Leon RM, Gaisinsky J, White A, Bamezai A, Ghidewon MY, Grill HJ, Crist RC, Reiner BC, Ai M, Samms RJ, De Jonghe BC, Hayes MR. GIP Receptor Agonism Attenuates GLP-1 Receptor Agonist-Induced Nausea and Emesis in Preclinical Models. *Diabetes*. 2021;70(11):2545-2553.

78. Geisler CE, Antonellis MP, Trumbauer W, Martin JA, Coskun T, Samms RJ, Hayes MR. Tirzepatide suppresses palatable food intake by selectively reducing preference for fat in rodents. *Diabetes Obes Metab*. 2023;25(1):56-67.

79. Bergmann NC, Gasbjerg LS, Heimburger SM, Krogh LSL, Dela F, Hartmann B, Holst JJ, Jessen L, Christensen MB, Vilsboll T, Lund A, Knop FK. No Acute Effects of Exogenous Glucose-Dependent Insulinotropic Polypeptide on Energy Intake, Appetite, or Energy Expenditure When Added to Treatment With a Long-Acting Glucagon-Like Peptide 1 Receptor Agonist in Men With Type 2 Diabetes. *Diabetes Care*. 2020;43(3):588-596.

80. Heise T, DeVries JH, Urva S, Li J, Pratt EJ, Thomas MK, Mather KJ, Karanikas CA, Dunn J, Haupt A, Milicevic Z, Coskun T. Tirzepatide Reduces Appetite, Energy Intake,

and Fat Mass in People With Type 2 Diabetes. *Diabetes Care*. 2023;46(5):998-1004.

81. Kim SJ, Nian C, McIntosh CH. Activation of lipoprotein lipase by glucose-dependent insulinotropic polypeptide in adipocytes. A role for a protein kinase B, LKB1, and AMP-activated protein kinase cascade. *J Biol Chem*. 2007;282(12):8557-8567.

82. Kim SJ, Nian C, McIntosh CH. GIP increases human adipocyte LPL expression through CREB and TORC2-mediated trans-activation of the LPL gene. *J Lipid Res*. 2010;51(11):3145-3157.

83. Regmi A, Aihara E, Christe ME, Varga G, Beyer TP, Ruan X, Beebe E, O'Farrell LS, Bellinger MA, Austin AK, Lin Y, Hu H, Konkol DL, Wojnicki S, Holland AK, Friedrich JL, Brown RA, Estelle AS, Badger HS, Gaidosh GS, Kooijman S, Rensen PCN, Coskun T, Thomas MK, Roell W. Tirzepatide modulates the regulation of adipocyte nutrient metabolism through long-acting activation of the GIP receptor. *Cell Metab*. 2024;36(7):1534-1549 e1537.

84. Killion EA, Chen M, Falsey JR, Sivits G, Hager T, Atangan L, Helmering J, Lee J, Li H, Wu B, Cheng Y, Veniant MM, Lloyd DJ. Chronic glucose-dependent insulinotropic polypeptide receptor (GIPR) agonism desensitizes adipocyte GIPR activity mimicking functional GIPR antagonism. *Nat Commun*. 2020;11(1):4981.

85. Samms RJ, Christe ME, Collins KA, Pirro V, Droz BA, Holland AK, Friedrich JL, Wojnicki S, Konkol DL, Cosgrove R, Furber EPC, Ruan X, O'Farrell LS, Long AM, Dogra M, Willency JA, Lin Y, Ding L, Cheng CC, Cabrera O, Briere DA, Alsina-Fernandez J, Gimeno RE, Moyers JS, Coskun T, Coghlan MP, Sloop KW, Roell WC. GIPR agonism mediates weight-independent insulin sensitization by tirzepatide in obese mice. *J Clin Invest*. 2021;131(12).

86. Yu X, Chen S, Funcke JB, Straub LG, Pirro V, Emont MP, Droz BA, Collins KA, Joung C, Pearson MJ, James CM, Babu GJ, Efthymiou V, Vernon A, Patti ME, An YA, Rosen ED, Coghlan MP, Samms RJ, Scherer PE, Kusminski CM. The GIP receptor activates futile calcium cycling in white adipose tissue to increase energy expenditure and drive weight loss in mice. *Cell Metab*. 2025;37(1):187-204 e187.

87. Lu SC, Chen M, Atangan L, Killion EA, Komorowski R, Cheng Y, Netirojjanakul C, Falsey JR, Stolina M, Dwyer D, Hale C, Stanislaus S, Hager T, Thomas VA, Harrold JM, Lloyd DJ, Veniant MM. GIPR antagonist antibodies conjugated to GLP-1 peptide are bispecific molecules that decrease weight in obese mice and monkeys. *Cell Rep Med*. 2021;2(5):100263.

88. Wean J, Kowalsky AH, Laker R, Will S, Drucker DJ, Rhodes CJ, Seeley RJ. Specific loss of GIPR signaling in GABAergic neurons enhances GLP-1R agonist-induced body weight loss. *Mol Metab*. 2025;95:102074.

89. Jensen MH, Sanni SJ, Riber D, Holst JJ, Rosenkilde MM, Sparre-Ulrich AH. AT-7687, a novel GIPR peptide antagonist, combined with a GLP-1 agonist, leads to enhanced weight loss and metabolic improvements in cynomolgus monkeys. *Mol Metab*. 2024;88:102006.

90. Campbell JE. Targeting the GIPR for obesity: To agonize or antagonize? Potential mechanisms. *Mol Metab*. 2021;46:101139.

91. Douros JD, Mowery SA, Knerr PJ. The Premise of the Paradox: Examining the Evidence That Motivated GIPR Agonist and Antagonist Drug Development Programs. *J Clin Med*. 2025;14(11).

92. Davies I, Adriaenssens AE, Scott WR, Carling D, Murphy KG, Minnion JS, Bloom SR,

Jones B, Tan TM. Chronic GIPR agonism results in pancreatic islet GIPR functional desensitisation. *Mol Metab*. 2025;92:102094.

93. Fukuda M. The Role of GIP Receptor in the CNS for the Pathogenesis of Obesity. *Diabetes*. 2021;70(9):1929-1937.

94. Wolfe MM, Boylan MO, Chin WW. Glucose-Dependent Insulinotropic Polypeptide in Incretin Physiology: Role in Health and Disease. Endocr Rev 2025. Accessed Feb 14

95. Habegger KM, Heppner KM, Geary N, Bartness TJ, DiMarchi R, Tschop MH. The metabolic actions of glucagon revisited. *Nat Rev Endocrinol*. 2010;6(12):689-697.

96. Jiang G, Zhang BB. Glucagon and regulation of glucose metabolism. *Am J Physiol Endocrinol Metab*. 2003;284(4):E671-678.

97. Geary N, Kissileff HR, Pi-Sunyer FX, Hinton V. Individual, but not simultaneous, glucagon and cholecystokinin infusions inhibit feeding in men. *Am J Physiol*. 1992;262(6 Pt 2):R975-980.

98. Muller TD, Finan B, Clemmensen C, DiMarchi RD, Tschop MH. The New Biology and Pharmacology of Glucagon. *Physiol Rev*. 2017;97(2):721-766.

99. Al-Massadi O, Ferno J, Dieguez C, Nogueiras R, Quinones M. Glucagon Control on Food Intake and Energy Balance. *Int J Mol Sci*. 2019;20(16).

100. Calles-Escandon J. Insulin dissociates hepatic glucose cycling and glucagon-induced thermogenesis in man. *Metabolism*. 1994;43(8):1000-1005.

101. Nair KS. Hyperglucagonemia increases resting metabolic rate in man during insulin deficiency. *J Clin Endocrinol Metab*. 1987;64(5):896-901.

102. Wewer Albrechtsen NJ, Holst JJ, Cherrington AD, Finan B, Gluud LL, Dean ED, Campbell JE, Bloom SR, Tan TM, Knop FK, Muller TD. 100 years of glucagon and 100

more. *Diabetologia*. 2023;66(8):1378-1394.

103. Haedersdal S, Andersen A, Knop FK, Vilsboll T. Revisiting the role of glucagon in health, diabetes mellitus and other metabolic diseases. *Nat Rev Endocrinol*. 2023;19(6):321-335.

104. Rosenstock J, Frias J, Jastreboff AM, Du Y, Lou J, Gurbuz S, Thomas MK, Hartman ML, Haupt A, Milicevic Z, Coskun T. Retatrutide, a GIP, GLP-1 and glucagon receptor agonist, for people with type 2 diabetes: a randomised, double-blind, placebo and active-controlled, parallel-group, phase 2 trial conducted in the USA. *Lancet*. 2023;402(10401):529-544.

105. Dotevall G, Kock NG. The effect of glucagon on intestinal motility in man. *Gastroenterology*. 1963;45:364-367.

106. Lahoti S, Catalano MF, Geenen JE, Hogan WJ. A prospective, double-blind trial of L-hyoscyamine versus glucagon for the inhibition of small intestinal motility during ERCP. *Gastrointest Endosc*. 1997;46(2):139-142.

107. Galsgaard KD, Pedersen J, Knop FK, Holst JJ, Wewer Albrechtsen NJ. Glucagon Receptor Signaling and Lipid Metabolism. *Front Physiol*. 2019;10:413.

108. Couet C, Fukagawa NK, Matthews DE, Bier DM, Young VR. Plasma amino acid kinetics during acute states of glucagon deficiency and excess in healthy adults. *Am J Physiol*. 1990;258(1 Pt 1):E78-85.

109. El K, Capozzi ME, Campbell JE. Repositioning the Alpha Cell in Postprandial Metabolism. *Endocrinology*. 2020;161(11).

110. Heppner KM, Habegger KM, Day J, Pfluger PT, Perez-Tilve D, Ward B, Gelfanov V, Woods SC, DiMarchi R, Tschop M. Glucagon regulation of energy metabolism. *Physiol*

Behav. 2010;100(5):545-548.

111. Kusminski CM, Perez-Tilve D, Muller TD, DiMarchi RD, Tschop MH, Scherer PE. Transforming obesity: The advancement of multi-receptor drugs. *Cell*. 2024;187(15):3829-3853.

112. Hope DCD, Vincent ML, Tan TMM. Striking the Balance: GLP-1/Glucagon Co-Agonism as a Treatment Strategy for Obesity. *Front Endocrinol (Lausanne)*. 2021;12:735019.

113. Christopoulos G, Perry KJ, Morfis M, Tilakaratne N, Gao Y, Fraser NJ, Main MJ, Foord SM, Sexton PM. Multiple amylin receptors arise from receptor activity-modifying protein interaction with the calcitonin receptor gene product. *Mol Pharmacol*. 1999;56(1):235-242.

114. Cao J, Belousoff MJ, Liang YL, Johnson RM, Josephs TM, Fletcher MM, Christopoulos A, Hay DL, Danev R, Wootten D, Sexton PM. A structural basis for amylin receptor phenotype. *Science*. 2022;375(6587):eabm9609.

115. Boccia L, Gamakharia S, Coester B, Whiting L, Lutz TA, Le Foll C. Amylin brain circuitry. *Peptides*. 2020;132:170366.

116. Hay DL, Chen S, Lutz TA, Parkes DG, Roth JD. Amylin: Pharmacology, Physiology, and Clinical Potential. *Pharmacol Rev*. 2015;67(3):564-600.

117. Lutz TA. Control of food intake and energy expenditure by amylin-therapeutic implications. *Int J Obes (Lond)*. 2009;33 Suppl 1:S24-27.

118. Dehestani B, Stratford NR, le Roux CW. Amylin as a Future Obesity Treatment. *J Obes Metab Syndr*. 2021;30(4):320-325.

119. Smith SR, Aronne LJ, Burns CM, Kesty NC, Halseth AE, Weyer C. Sustained weight loss following 12-month pramlintide treatment as an adjunct to lifestyle intervention in

obesity. *Diabetes Care*. 2008;31(9):1816-1823.

120. Lau DCW, Erichsen L, Francisco AM, Satylganova A, le Roux CW, McGowan B, Pedersen SD, Pietilainen KH, Rubino D, Batterham RL. Once-weekly cagrilintide for weight management in people with overweight and obesity: a multicentre, randomised, double-blind, placebo-controlled and active-controlled, dose-finding phase 2 trial. *Lancet*. 2021;398(10317):2160-2172.

121. Mack CM, Soares CJ, Wilson JK, Athanacio JR, Turek VF, Trevaskis JL, Roth JD, Smith PA, Gedulin B, Jodka CM, Roland BL, Adams SH, Lwin A, Herich J, Laugero KD, Vu C, Pittner R, Paterniti JR, Jr., Hanley M, Ghosh S, Parkes DG. Davalintide (AC2307), a novel amylin-mimetic peptide: enhanced pharmacological properties over native amylin to reduce food intake and body weight. *Int J Obes (Lond)*. 2010;34(2):385-395.

122. Hjuler ST, Andreassen KV, Gydesen S, Karsdal MA, Henriksen K. KBP-042 improves bodyweight and glucose homeostasis with indices of increased insulin sensitivity irrespective of route of administration. *Eur J Pharmacol*. 2015;762:229-238.

123. Gydesen S, Andreassen KV, Hjuler ST, Christensen JM, Karsdal MA, Henriksen K. KBP-088, a novel DACRA with prolonged receptor activation, is superior to davalintide in terms of efficacy on body weight. *Am J Physiol Endocrinol Metab*. 2016;310(10):E821-827.

124. Boyle CN, Zheng Y, Lutz TA. Mediators of Amylin Action in Metabolic Control. *J Clin Med*. 2022;11(8).

125. Batterham RL, Cowley MA, Small CJ, Herzog H, Cohen MA, Dakin CL, Wren AM, Brynes AE, Low MJ, Ghatei MA, Cone RD, Bloom SR. Gut hormone PYY(3-36) physiologically inhibits food intake. *Nature*. 2002;418(6898):650-654.

126. Neary NM, Small CJ, Druce MR, Park AJ, Ellis SM, Semjonous NM, Dakin CL, Filipsson K, Wang F, Kent AS, Frost GS, Ghatei MA, Bloom SR. Peptide YY3-36 and glucagon-like peptide-17-36 inhibit food intake additively. *Endocrinology*. 2005;146(12):5120-5127.

127. Tan TM, Minnion J, Khoo B, Ball LJ, Malviya R, Day E, Fiorentino F, Brindley C, Bush J, Bloom SR. Safety and efficacy of an extended-release peptide YY analogue for obesity: A randomized, placebo-controlled, phase 1 trial. *Diabetes Obes Metab*. 2021;23(7):1471-1483.

128. Batterham RL, Cohen MA, Ellis SM, Le Roux CW, Withers DJ, Frost GS, Ghatei MA, Bloom SR. Inhibition of food intake in obese subjects by peptide YY3-36. *N Engl J Med*. 2003;349(10):941-948.

129. Ramracheya RD, McCulloch LJ, Clark A, Wiggins D, Johannessen H, Olsen MK, Cai X, Zhao CM, Chen D, Rorsman P. PYY-Dependent Restoration of Impaired Insulin and Glucagon Secretion in Type 2 Diabetes following Roux-En-Y Gastric Bypass Surgery. *Cell Rep*. 2016;15(5):944-950.

130. Guida C, Stephen SD, Watson M, Dempster N, Larraufie P, Marjot T, Cargill T, Rickers L, Pavlides M, Tomlinson J, Cobbold JFL, Zhao CM, Chen D, Gribble F, Reimann F, Gillies R, Sgromo B, Rorsman P, Ryan JD, Ramracheya RD. PYY plays a key role in the resolution of diabetes following bariatric surgery in humans. *EBioMedicine*. 2019;40:67-76.

131. le Roux CW, Batterham RL, Aylwin SJ, Patterson M, Borg CM, Wynne KJ, Kent A, Vincent RP, Gardiner J, Ghatei MA, Bloom SR. Attenuated peptide YY release in obese subjects is associated with reduced satiety. *Endocrinology*. 2006;147(1):3-8.

132. Bucheit JD, Pamulapati LG, Carter N, Malloy K, Dixon DL, Sisson EM. Oral Semaglutide: A Review of the First Oral Glucagon-Like Peptide 1 Receptor Agonist. *Diabetes Technol Ther*. 2020;22(1):10-18.

133. Buckley ST, Baekdal TA, Vegge A, Maarbjerg SJ, Pyke C, Ahnfelt-Ronne J, Madsen KG, Scheele SG, Alanentalo T, Kirk RK, Pedersen BL, Skyggebjerg RB, Benie AJ, Strauss HM, Wahlund PO, Bjerregaard S, Farkas E, Fekete C, Sondergaard FL, Borregaard J, Hartoft-Nielsen ML, Knudsen LB. Transcellular stomach absorption of a derivatized glucagon-like peptide-1 receptor agonist. *Sci Transl Med*. 2018;10(467).

134. Meier JJ. Efficacy of Semaglutide in a Subcutaneous and an Oral Formulation. *Front Endocrinol (Lausanne)*. 2021;12:645617.

135. Novo Nordick Global. Novo Nordisk A/S: Semaglutide 7.2 mg s.c. achieved 20.7% weight loss in the STEP UP obesity trial, and 18.7% regardless of treatment adherence. 2025.

136. Choe HJ, Cho YM. Peptidyl and Non-Peptidyl Oral Glucagon-Like Peptide-1 Receptor Agonists. *Endocrinol Metab (Seoul)*. 2021;36(1):22-29.

137. Kawai T, Sun B, Yoshino H, Feng D, Suzuki Y, Fukazawa M, Nagao S, Wainscott DB, Showalter AD, Droz BA, Kobilka TS, Coghlan MP, Willard FS, Kawabe Y, Kobilka BK, Sloop KW. Structural basis for GLP-1 receptor activation by LY3502970, an orally active nonpeptide agonist. *Proc Natl Acad Sci USA*. 2020;117(47):29959-29967.

138. Griffith DA, Edmonds DJ, Fortin JP, Kalgutkar AS, Kuzmiski JB, Loria PM, Saxena AR, Bagley SW, Buckeridge C, Curto JM, Derksen DR, Dias JM, Griffor MC, Han S, Jackson VM, Landis MS, Lettiere D, Limberakis C, Liu Y, Mathiowetz AM, Patel JC, Piotrowski DW, Price DA, Ruggeri RB, Tess DA. A Small-Molecule Oral Agonist of the Human

Glucagon-like Peptide-1 Receptor. *J Med Chem*. 2022;65(12):8208-8226.

139. Saxena AR, Frias JP, Brown LS, Gorman DN, Vasas S, Tsamandouras N, Birnbaum MJ. Efficacy and Safety of Oral Small Molecule Glucagon-Like Peptide 1 Receptor Agonist Danuglipron for Glycemic Control Among Patients With Type 2 Diabetes: A Randomized Clinical Trial. *JAMA Netw Open*. 2023;6(5):e2314493.

140. Fatima H, Rangwala HS, Mustafa MS, Shafique MA, Abbas SR, Rizwan A, Fadlalla Ahmed TK, Arshad A. Evaluating Glycemic Control Efficacy and Safety of the Oral Small Molecule Glucagon-Like Peptide 1 Receptor Agonist Danuglipron in Type 2 Diabetes Patients: A Systemic Review and Meta-Analysis. *Diabetes Metab Syndr Obes*. 2023;16:3567-3578.

141. Pfizer. Pfizer Provides Update on Oral GLP-1 Receptor Agonist Danuglipron. 2025.

142. Pratt E, Ma X, Liu R, Robins D, Haupt A, Coskun T, Sloop KW, Benson C. Orforglipron (LY3502970), a novel, oral non-peptide glucagon-like peptide-1 receptor agonist: A Phase 1a, blinded, placebo-controlled, randomized, single- and multiple-ascending-dose study in healthy participants. *Diabetes Obes Metab*. 2023;25(9):2634-2641.

143. Wharton S, Blevins T, Connery L, Rosenstock J, Raha S, Liu R, Ma X, Mather KJ, Haupt A, Robins D, Pratt E, Kazda C, Konig M, Investigators G. Daily Oral GLP-1 Receptor Agonist Orforglipron for Adults with Obesity. *N Engl J Med*. 2023;389(10):877-888.

144. Frias JP, Hsia S, Eyde S, Liu R, Ma X, Konig M, Kazda C, Mather KJ, Haupt A, Pratt E, Robins D. Efficacy and safety of oral orforglipron in patients with type 2 diabetes: a multicentre, randomised, dose-response, phase 2 study. *Lancet*. 2023;402(10400):472-483.

145. Rosenstock J, Hsia S, Nevarez Ruiz L, Eyde S, Cox D, Wu WS, Liu R, Li J, Fernandez

Lando L, Denning M, Ludwig L, Chen Y, Investigators A-T. Orforglipron, an Oral Small-Molecule GLP-1 Receptor Agonist, in Early Type 2 Diabetes. *N Engl J Med*. 2025.

146. Naseralallah L, Aboujabal B. Profile of tirzepatide in the management of type 2 diabetes mellitus: design, development, and place in therapy. *Expert Opin Pharmacother*. 2023;24(4):407-418.

147. de Mesquita YLL, Pera Calvi I, Reis Marques I, Almeida Cruz S, Padrao EMH, Carvalho PEP, da Silva CHA, Cardoso R, Moura FA, Rafalskiy VV. Efficacy and safety of the dual GIP and GLP-1 receptor agonist tirzepatide for weight loss: a meta-analysis of randomized controlled trials. *Int J Obes (Lond)*. 2023;47(10):883-892.

148. Shao Y, Chen Y, Zhu M, Liu Y, Fang C, Wang M, Sun P, Fu W, Huang J, Sheng S, Huang Y. DR10627, a Novel Dual Glucagon-like Peptide-1 and Gastric Inhibitory Polypeptide Receptor Agonist for the Treatment of Obesity and Type 2 Diabetes Mellitus. *Diabetes Metab Syndr Obes*. 2024;17:1563-1573.

149. Killion EA, Lu SC, Fort M, Yamada Y, Veniant MM, Lloyd DJ. Glucose-Dependent Insulinotropic Polypeptide Receptor Therapies for the Treatment of Obesity, Do Agonists = Antagonists? *Endocr Rev*. 2020;41(1).

150. Holst JJ. What combines best with GLP-1 for obesity treatment: GIP receptor agonists or antagonists? *Cell Rep Med*. 2021;2(5):100284.

151. Jastreboff AM, Ryan DH, Bays HE, Ebeling PR, Mackowski MG, Philipose N, Ross L, Liu Y, Burns CE, Abbasi SA, Pannacciulli N, MariTide Phase 2 Obesity Trial I. Once-Monthly Maridebart Cafraglutide for the Treatment of Obesity - A Phase 2 Trial. *N Engl J Med*. 2025.

152. Zimmermann T, Thomas L, Baader-Pagler T, Haebel P, Simon E, Reindl W, Bajrami B,

Rist W, Uphues I, Drucker DJ, Klein H, Santhanam R, Hamprecht D, Neubauer H, Augustin R. BI 456906: Discovery and preclinical pharmacology of a novel GCGR/GLP-1R dual agonist with robust anti-obesity efficacy. *Mol Metab*. 2022;66:101633.

153. Jungnik A, Arrubla Martinez J, Plum-Morschel L, Kapitza C, Lamers D, Thamer C, Scholch C, Desch M, Hennige AM. Phase I studies of the safety, tolerability, pharmacokinetics and pharmacodynamics of the dual glucagon receptor/glucagon-like peptide-1 receptor agonist BI 456906. *Diabetes Obes Metab*. 2023;25(4):1011-1023.

154. Bluher M, Rosenstock J, Hoefler J, Manuel R, Hennige AM. Dose-response effects on HbA(1c) and bodyweight reduction of survodutide, a dual glucagon/GLP-1 receptor agonist, compared with placebo and open-label semaglutide in people with type 2 diabetes: a randomised clinical trial. *Diabetologia*. 2024;67(3):470-482.

155. Kosiborod MN, Platz E, Wharton S, le Roux CW, Brueckmann M, Ajaz Hussain S, Unseld A, Startseva E, Kaplan LM, Committees S-CT, Investigators. Survodutide for the Treatment of Obesity: Rationale and Design of the SYNCHRONIZE Cardiovascular Outcomes Trial. *JACC Heart failure*. 2024;12(12):2101-2109.

156. Sanyal AJ, Bedossa P, Fraessdorf M, Neff GW, Lawitz E, Bugianesi E, Anstee QM, Hussain SA, Newsome PN, Ratziu V, Hosseini-Tabatabaei A, Schattenberg JM, Noureddin M, Alkhouri N, Younes R, Trial I. A Phase 2 Randomized Trial of Survodutide in MASH and Fibrosis. *N Engl J Med*. 2024;391(4):311-319.

157. Zhang B, Cheng Z, Chen J, Zhang X, Liu D, Jiang H, Ma G, Wang X, Gan S, Sun J, Jin P, Yi J, Shi B, Ma J, Ye S, Wang G, Ji L, Gu X, Yu T, An P, Deng H, Li H, Li L, Ma Q, Qian L, Yang W. Efficacy and Safety of Mazdutide in Chinese Patients With Type 2 Diabetes: A Randomized, Double-Blind, Placebo-Controlled Phase 2 Trial. *Diabetes*

Care. 2024;47(1):160-168.

158. Ji L, Jiang H, Cheng Z, Qiu W, Liao L, Zhang Y, Li X, Pang S, Zhang L, Chen L, Yang T, Li Y, Qu S, Wen J, Gu J, Deng H, Wang Y, Li L, Han-Zhang H, Ma Q, Qian L. A phase 2 randomised controlled trial of mazdutide in Chinese overweight adults or adults with obesity. *Nat Commun*. 2023;14(1):8289.

159. Nalisa DL, Cuboia N, Dyab E, Jackson IL, Felix HJ, Shoki P, Mubiana M, Oyedeji-Amusa M, Azevedo L, Jiang H. Efficacy and safety of Mazdutide on weight loss among diabetic and non-diabetic patients: a systematic review and meta-analysis of randomized controlled trials. *Front Endocrinol (Lausanne)*. 2024;15:1309118.

160. Mathiesen DS, Bagger JI, Knop FK. Long-acting amylin analogues for the management of obesity. *Curr Opin Endocrinol Diabetes Obes*. 2022;29(2):183-190.

161. Enebo LB, Berthelsen KK, Kankam M, Lund MT, Rubino DM, Satylganova A, Lau DCW. Safety, tolerability, pharmacokinetics, and pharmacodynamics of concomitant administration of multiple doses of cagrilintide with semaglutide 2.4 mg for weight management: a randomised, controlled, phase 1b trial. *Lancet*. 2021;397(10286):1736-1748.

162. Becerril S, Fruhbeck G. Cagrilintide plus semaglutide for obesity management. *Lancet*. 2021;397(10286):1687-1689.

163. Garvey WT, Bluher M, Osorto Contreras CK, Davies MJ, Winning Lehmann E, Pietilainen KH, Rubino D, Sbraccia P, Wadden T, Zeuthen N, Wilding JPH, Group RS. Coadministered Cagrilintide and Semaglutide in Adults with Overweight or Obesity. *N Engl J Med*. 2025;393(7):635-647.

164. Davies MJ, Bajaj HS, Broholm C, Eliasen A, Garvey WT, le Roux CW, Lingvay I,

Lyndgaard CB, Rosenstock J, Pedersen SD, Group RS. Cagrilintide-Semaglutide in Adults with Overweight or Obesity and Type 2 Diabetes. *N Engl J Med*. 2025;393(7):648-659.

165. Gasiorek A, Heydorn A, Gabery S, Hjerpsted JB, Kirkeby K, Kruse T, Petersen SB, Toubro S, Vegge A, Key C. Safety, tolerability, pharmacokinetics, and pharmacodynamics of the first-in-class GLP-1 and amylin receptor agonist, amycretin: a first-in-human, phase 1, double-blind, randomised, placebo-controlled trial. *Lancet*. 2025;406(10499):135-148.

166. Melson E, Ashraf U, Papamargaritis D, Davies MJ. What is the pipeline for future medications for obesity? *Int J Obes (Lond)*. 2025;49(3):433-451.

167. Dahl K, Toubro S, Dey S, Duque do Vale R, Flint A, Gasiorek A, Heydorn A, Jastreboff AM, Key C, Petersen SB, Vegge A, Adelborg K. Amycretin, a novel, unimolecular GLP-1 and amylin receptor agonist administered subcutaneously: results from a phase 1b/2a randomised controlled study. *Lancet*. 2025;406(10499):149-162.

168. Coskun T, Urva S, Roell WC, Qu H, Loghin C, Moyers JS, O'Farrell LS, Briere DA, Sloop KW, Thomas MK, Pirro V, Wainscott DB, Willard FS, Abernathy M, Morford L, Du Y, Benson C, Gimeno RE, Haupt A, Milicevic Z. LY3437943, a novel triple glucagon, GIP, and GLP-1 receptor agonist for glycemic control and weight loss: From discovery to clinical proof of concept. *Cell Metab*. 2022;34(9):1234-1247 e1239.

169. Urva S, Coskun T, Loh MT, Du Y, Thomas MK, Gurbuz S, Haupt A, Benson CT, Hernandez-Illas M, D'Alessio DA, Milicevic Z. LY3437943, a novel triple GIP, GLP-1, and glucagon receptor agonist in people with type 2 diabetes: a phase 1b, multicentre, double-blind, placebo-controlled, randomised, multiple-ascending dose trial. *Lancet*.

2022;400(10366):1869-1881.

170. Jastreboff AM, Kaplan LM, Frias JP, Wu Q, Du Y, Gurbuz S, Coskun T, Haupt A, Milicevic Z, Hartman ML, Retatrutide Phase 2 Obesity Trial I. Triple-Hormone-Receptor Agonist Retatrutide for Obesity - A Phase 2 Trial. *N Engl J Med*. 2023;389(6):514-526.

171. Marso SP, Daniels GH, Brown-Frandsen K, Kristensen P, Mann JF, Nauck MA, Nissen SE, Pocock S, Poulter NR, Ravn LS, Steinberg WM, Stockner M, Zinman B, Bergenstal RM, Buse JB, Committee LS, Investigators LT. Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes. *N Engl J Med*. 2016;375(4):311-322.

172. Mann JFE, Orsted DD, Brown-Frandsen K, Marso SP, Poulter NR, Rasmussen S, Tornoe K, Zinman B, Buse JB, Committee LS, Investigators. Liraglutide and Renal Outcomes in Type 2 Diabetes. *N Engl J Med*. 2017;377(9):839-848.

173. Marso SP, Bain SC, Consoli A, Eliaschewitz FG, Jodar E, Leiter LA, Lingvay I, Rosenstock J, Seufert J, Warren ML, Woo V, Hansen O, Holst AG, Pettersson J, Vilsboll T, Investigators S-. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med*. 2016;375(19):1834-1844.

174. Gerstein HC, Colhoun HM, Dagenais GR, Diaz R, Lakshmanan M, Pais P, Probstfield J, Riesmeyer JS, Riddle MC, Ryden L, Xavier D, Atisso CM, Dyal L, Hall S, Rao-Melacini P, Wong G, Avezum A, Basile J, Chung N, Conget I, Cushman WC, Franek E, Hancu N, Hanefeld M, Holt S, Jansky P, Keltai M, Lanas F, Leiter LA, Lopez-Jaramillo P, Cardona Munoz EG, Pirags V, Pogosova N, Raubenheimer PJ, Shaw JE, Sheu WH, Temelkova-Kurktschiev T, Investigators R. Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomised placebo-controlled trial. *Lancet*. 2019;394(10193):121-130.

175. Sattar N, Lee MMY, Kristensen SL, Branch KRH, Del Prato S, Khurmi NS, Lam CSP, Lopes RD, McMurray JJV, Pratley RE, Rosenstock J, Gerstein HC. Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of randomised trials. *Lancet Diabetes Endocrinol*. 2021;9(10):653-662.

176. Tuttle KR, Lakshmanan MC, Rayner B, Busch RS, Zimmermann AG, Woodward DB, Botros FT. Dulaglutide versus insulin glargine in patients with type 2 diabetes and moderate-to-severe chronic kidney disease (AWARD-7): a multicentre, open-label, randomised trial. *Lancet Diabetes Endocrinol*. 2018;6(8):605-617.

177. Perkovic V, Tuttle KR, Rossing P, Mahaffey KW, Mann JFE, Bakris G, Baeres FMM, Idorn T, Bosch-Traberg H, Lausvig NL, Pratley R, Committees FT, Investigators. Effects of Semaglutide on Chronic Kidney Disease in Patients with Type 2 Diabetes. *N Engl J Med*. 2024;391(2):109-121.

178. Heerspink HJL, Friedman AN, Bjornstad P, van Raalte DH, Cherney D, Cao D, Garcia-Perez LE, Stefanski A, Turfanda I, Bunck MC, Benabbad I, Griffin R, Piras de Oliveira C. Kidney Parameters with Tirzepatide in Obesity with or without Type 2 Diabetes. *J Am Soc Nephrol*. 2025.

179. Lee MMY, Sattar N, Pop-Busui R, Deanfield J, Emerson SS, Inzucchi SE, Mann JFE, Marx N, Mulvagh SL, Poulter NR, Badve SV, Pratley RE, Perkovic V, Buse JB, McGuire DK, Investigators ST. Cardiovascular and Kidney Outcomes and Mortality With Long-Acting Injectable and Oral Glucagon-Like Peptide 1 Receptor Agonists in Individuals With Type 2 Diabetes: A Systematic Review and Meta-analysis of Randomized Trials. *Diabetes Care*. 2025;48(5):846-859.

180. Benz E, Pinel A, Guillet C, Capel F, Pereira B, De Antonio M, Pouget M, Cruz-Jentoft AJ, Eglseer D, Topinkova E, Barazzoni R, Rivadeneira F, Ikram MA, Steur M, Voortman T, Schoufour JD, Weijs PJM, Boirie Y. Sarcopenia and Sarcopenic Obesity and Mortality Among Older People. *JAMA Netw Open*. 2024;7(3):e243604.

181. Damluji AA, Alfaraidhy M, AlHajri N, Rohant NN, Kumar M, Al Malouf C, Bahrainy S, Ji Kwak M, Batchelor WB, Forman DE, Rich MW, Kirkpatrick J, Krishnaswami A, Alexander KP, Gerstenblith G, Cawthon P, deFilippi CR, Goyal P. Sarcopenia and Cardiovascular Diseases. *Circulation*. 2023;147(20):1534-1553.

182. Wilding JPH, Batterham RL, Calanna S, Davies M, Van Gaal LF, Lingvay I, McGowan BM, Rosenstock J, Tran MTD, Wadden TA, Wharton S, Yokote K, Zeuthen N, Kushner RF, Group SS. Once-Weekly Semaglutide in Adults with Overweight or Obesity. *N Engl J Med*. 2021;384(11):989-1002.

183. Linge J, Birkenfeld AL, Neeland IJ. Muscle Mass and Glucagon-Like Peptide-1 Receptor Agonists: Adaptive or Maladaptive Response to Weight Loss? *Circulation*. 2024;150(16):1288-1298.

184. Jensen SBK, Blond MB, Sandsdal RM, Olsen LM, Juhl CR, Lundgren JR, Janus C, Stallknecht BM, Holst JJ, Madsbad S, Torekov SS. Healthy weight loss maintenance with exercise, GLP-1 receptor agonist, or both combined followed by one year without treatment: a post-treatment analysis of a randomised placebo-controlled trial. *EClinicalMedicine*. 2024;69:102475.

185. Heymsfield SB, Coleman LA, Miller R, Rooks DS, Laurent D, Petricoul O, Praestgaard J, Swan T, Wade T, Perry RG, Goodpaster BH, Roubenoff R. Effect of Bimagrumab vs Placebo on Body Fat Mass Among Adults With Type 2 Diabetes and Obesity: A Phase 2

Randomized Clinical Trial. *JAMA Netw Open*. 2021;4(1):e2033457.

186. Latres E, Pangilinan J, Miloscio L, Bauerlein R, Na E, Potocky TB, Huang Y, Eckersdorff M, Rafique A, Mastaitis J, Lin C, Murphy AJ, Yancopoulos GD, Gromada J, Stitt T. Myostatin blockade with a fully human monoclonal antibody induces muscle hypertrophy and reverses muscle atrophy in young and aged mice. *Skelet Muscle*. 2015;5:34.

187. Latres E, Mastaitis J, Fury W, Miloscio L, Trejos J, Pangilinan J, Okamoto H, Cavino K, Na E, Papatheodorou A, Willer T, Bai Y, Hae Kim J, Rafique A, Jaspers S, Stitt T, Murphy AJ, Yancopoulos GD, Gromada J. Activin A more prominently regulates muscle mass in primates than does GDF8. *Nat Commun*. 2017;8:15153.

188. Borg ML, Massart J, De Castro Barbosa T, Archilla-Ortega A, Smith JAB, Lanner JT, Alsina-Fernandez J, Yaden B, Culver AE, Karlsson HKR, Brozinick JT, Zierath JR. Modified UCN2 peptide treatment improves skeletal muscle mass and function in mouse models of obesity-induced insulin resistance. *J Cachexia Sarcopenia Muscle*. 2021;12(5):1232-1248.

189. Jastreboff AM, le Roux CW, Stefanski A, Aronne LJ, Halpern B, Wharton S, Wilding JPH, Perreault L, Zhang S, Battula R, Bunck MC, Ahmad NN, Jouravskaya I, Investigators S-. Tirzepatide for Obesity Treatment and Diabetes Prevention. *N Engl J Med*. 2025;392(10):958-971.

190. Newsome PN, Buchholtz K, Cusi K, Linder M, Okanoue T, Ratziu V, Sanyal AJ, Sejling AS, Harrison SA, Investigators NN. A Placebo-Controlled Trial of Subcutaneous Semaglutide in Nonalcoholic Steatohepatitis. *N Engl J Med*. 2021;384(12):1113-1124.

191. Loomba R, Hartman ML, Lawitz EJ, Vuppalanchi R, Boursier J, Bugianesi E, Yoneda M, Behling C, Cummings OW, Tang Y, Brouwers B, Robins DA, Nikooie A, Bunck MC,

Haupt A, Sanyal AJ, Investigators S-N. Tirzepatide for Metabolic Dysfunction-Associated Steatohepatitis with Liver Fibrosis. *N Engl J Med*. 2024;391(4):299-310.

192. Kosiborod MN, Abildstrom SZ, Borlaug BA, Butler J, Rasmussen S, Davies M, Hovingh GK, Kitzman DW, Lindegaard ML, Moller DV, Shah SJ, Treppendahl MB, Verma S, Abhayaratna W, Ahmed FZ, Chopra V, Ezekowitz J, Fu M, Ito H, Lelonek M, Melenovsky V, Merkely B, Nunez J, Perna E, Schou M, Senni M, Sharma K, Van der Meer P, von Lewinski D, Wolf D, Petrie MC, Committees ST-HT, Investigators. Semaglutide in Patients with Heart Failure with Preserved Ejection Fraction and Obesity. *N Engl J Med*. 2023;389(12):1069-1084.

193. Kosiborod MN, Petrie MC, Borlaug BA, Butler J, Davies MJ, Hovingh GK, Kitzman DW, Moller DV, Treppendahl MB, Verma S, Jensen TJ, Liisberg K, Lindegaard ML, Abhayaratna W, Ahmed FZ, Ben-Gal T, Chopra V, Ezekowitz JA, Fu M, Ito H, Lelonek M, Melenovsky V, Merkely B, Nunez J, Perna E, Schou M, Senni M, Sharma K, van der Meer P, Von Lewinski D, Wolf D, Shah SJ, Committees ST-HDT, Investigators. Semaglutide in Patients with Obesity-Related Heart Failure and Type 2 Diabetes. *N Engl J Med*. 2024;390(15):1394-1407.

194. Malhotra A, Grunstein RR, Fietze I, Weaver TE, Redline S, Azarbarzin A, Sands SA, Schwab RJ, Dunn JP, Chakladar S, Bunck MC, Bednarik J, Investigators S-O. Tirzepatide for the Treatment of Obstructive Sleep Apnea and Obesity. *N Engl J Med*. 2024;391(13):1193-1205.

195. Bliddal H, Bays H, Czernichow S, Udden Hemmingsson J, Hjelmesaeth J, Hoffmann Morville T, Koroleva A, Skov Neergaard J, Velez Sanchez P, Wharton S, Wizert A, Kristensen LE, Group SS. Once-Weekly Semaglutide in Persons with Obesity and Knee

Osteoarthritis. *N Engl J Med*. 2024;391(17):1573-1583.

196. Hasanpour-Segherlou Z, Butler AA, Candelario-Jalil E, Hoh BL. Role of the Unique Secreted Peptide Adropin in Various Physiological and Disease States. *Biomolecules*. 2024;14(12).

197. Sun X, Yu Z, Xu Y, Pu S, Gao X. The role of spexin in energy metabolism. *Peptides*. 2023;164:170991.

198. Kolodziejski PA, Pruszynska-Oszmalek E, Wojciechowicz T, Sassek M, Leciejewska N, Jasaszwili M, Billert M, Malek E, Szczepankiewicz D, Misiewicz-Mielnik M, Hertig I, Nogowski L, Nowak KW, Strowski MZ, Skrzypski M. The Role of Peptide Hormones Discovered in the 21st Century in the Regulation of Adipose Tissue Functions. *Genes (Basel)*. 2021;12(5).

199. Gizaw M, Anandakumar P, Debela T. A Review on the Role of Irisin in Insulin Resistance and Type 2 Diabetes Mellitus. *J Pharmacopuncture*. 2017;20(4):235-242.

200. Marrano N, Biondi G, Borrelli A, Cignarelli A, Perrini S, Laviola L, Giorgino F, Natalicchio A. Irisin and Incretin Hormones: Similarities, Differences, and Implications in Type 2 Diabetes and Obesity. *Biomolecules*. 2021;11(2).

201. Petersen J, Ludwig MQ, Juozaityte V, Ranea-Robles P, Svendsen C, Hwang E, Kristensen AW, Fadahunsi N, Lund J, Breum AW, Mathiesen CV, Sachs L, Moreno-Justicia R, Rohlfs R, Ford JC, Douros JD, Finan B, Portillo B, Grose K, Petersen JE, Trauelsen M, Feuchtinger A, DiMarchi RD, Schwartz TW, Deshmukh AS, Thomsen MB, Kohlmeier KA, Williams KW, Pers TH, Frolund B, Stromgaard K, Klein AB, Clemmensen C. GLP-1-directed NMDA receptor antagonism for obesity treatment. *Nature*. 2024;629(8014):1133-1141.

202. Knop FK, Urva S, Rettiganti M, Benson C, Roell W, Mather KJ, Haupt A, Pratt EJ. 56-OR: A Long-Acting Glucose-Dependent Insulinotropic Polypeptide Receptor Agonist Shows Weight Loss without Nausea or Vomiting. *Diabetes*. 2023;72(Supplement_1):56-OR.

203. Frias JP, Davies MJ, Rosenstock J, Perez Manghi FC, Fernandez Lando L, Bergman BK, Liu B, Cui X, Brown K, Investigators S-. Tirzepatide versus Semaglutide Once Weekly in Patients with Type 2 Diabetes. *N Engl J Med*. 2021;385(6):503-515.

204. Heise T, Mari A, DeVries JH, Urva S, Li J, Pratt EJ, Coskun T, Thomas MK, Mather KJ, Haupt A, Milicevic Z. Effects of subcutaneous tirzepatide versus placebo or semaglutide on pancreatic islet function and insulin sensitivity in adults with type 2 diabetes: a multicentre, randomised, double-blind, parallel-arm, phase 1 clinical trial. *Lancet Diabetes Endocrinol*. 2022;10(6):418-429.

205. Adriaenssens AE, Biggs EK, Darwish T, Tadross J, Sukthankar T, Girish M, Polex-Wolf J, Lam BY, Zvetkova I, Pan W, Chiarugi D, Yeo GSH, Blouet C, Gribble FM, Reimann F. Glucose-Dependent Insulinotropic Polypeptide Receptor-Expressing Cells in the Hypothalamus Regulate Food Intake. *Cell Metab*. 2019;30(5):987-996 e986.

206. Miyawaki K, Yamada Y, Ban N, Ihara Y, Tsukiyama K, Zhou H, Fujimoto S, Oku A, Tsuda K, Toyokuni S, Hiai H, Mizunoya W, Fushiki T, Holst JJ, Makino M, Tashita A, Kobara Y, Tsubamoto Y, Jinnouchi T, Jomori T, Seino Y. Inhibition of gastric inhibitory polypeptide signaling prevents obesity. *Nat Med*. 2002;8(7):738-742.

207. Kizilkaya HS, Sorensen KV, Kibsgaard CJ, Gasbjerg LS, Hauser AS, Sparre-Ulrich AH, Grarup N, Rosenkilde MM. Loss of function glucose-dependent insulinotropic polypeptide receptor variants are associated with alterations in BMI, bone strength and

cardiovascular outcomes. *Front Cell Dev Biol*. 2021;9:749607.

208. Mather KJ, Mari A, Weerakkody G, Heise T, DeVries JH, Urva S, Coskun T, Milicevic Z, Haupt A, Thomas MK. Greater improvement in insulin sensitivity per unit weight loss associated with tirzepatide versus semaglutide: An exploratory analysis. *Diabetes Obes Metab*. 2025;27(3):1507-1514.

209. Mentis N, Vardarli I, Kothe LD, Holst JJ, Deacon CF, Theodorakis M, Meier JJ, Nauck MA. GIP does not potentiate the antidiabetic effects of GLP-1 in hyperglycemic patients with type 2 diabetes. *Diabetes*. 2011;60(4):1270-1276.

210. Hojberg PV, Vilsboll T, Rabol R, Knop FK, Bache M, Krarup T, Holst JJ, Madsbad S. Four weeks of near-normalisation of blood glucose improves the insulin response to glucagon-like peptide-1 and glucose-dependent insulinotropic polypeptide in patients with type 2 diabetes. *Diabetologia*. 2009;52(2):199-207.

211. Willard FS, Douros JD, Gabe MB, Showalter AD, Wainscott DB, Suter TM, Capozzi ME, van der Velden WJ, Stutsman C, Cardona GR, Urva S, Emmerson PJ, Holst JJ, D'Alessio DA, Coghlan MP, Rosenkilde MM, Campbell JE, Sloop KW. Tirzepatide is an imbalanced and biased dual GIP and GLP-1 receptor agonist. *JCI Insight*. 2020;5(17).

212. Pratt E, Ma X, Liu R, Robins D, Coskun T, Sloop KW, Haupt A, Benson C. Orforglipron (LY3502970), a novel, oral non-peptide glucagon-like peptide-1 receptor agonist: A Phase 1b, multicentre, blinded, placebo-controlled, randomized, multiple-ascending-dose study in people with type 2 diabetes. *Diabetes Obes Metab*. 2023;25(9):2642-2649.

213. Ono R, Furihata K, Ichikawa Y, Nakazuru Y, Bergman A, Gorman DN, Saxena AR. A phase 1 study to evaluate the safety, tolerability, pharmacokinetics and pharmacodynamics of danuglipron (PF-06882961), an oral small-molecule glucagon-like

peptide-1 receptor agonist, in Japanese adults with type 2 diabetes mellitus. *Diabetes Obes Metab*. 2023;25(3):805-814.

214. Frias JP, Nauck MA, Van J, Kutner ME, Cui X, Benson C, Urva S, Gimeno RE, Milicevic Z, Robins D, Haupt A. Efficacy and safety of LY3298176, a novel dual GIP and GLP-1 receptor agonist, in patients with type 2 diabetes: a randomised, placebo-controlled and active comparator-controlled phase 2 trial. *Lancet*. 2018;392(10160):2180-2193.

215. Kruse T, Hansen JL, Dahl K, Schaffer L, Sensfuss U, Poulsen C, Schlein M, Hansen AMK, Jeppesen CB, Dornonville de la Cour C, Clausen TR, Johansson E, Fulle S, Skyggebjerg RB, Raun K. Development of Cagrilintide, a Long-Acting Amylin Analogue. *J Med Chem*. 2021;64(15):11183-11194.

216. Thomas L, Martel E, Rist W, Uphues I, Hamprecht D, Neubauer H, Augustin R. The dual GCGR/GLP-1R agonist survodutide: Biomarkers and pharmacological profiling for clinical candidate selection. *Diabetes Obes Metab*. 2024;26(6):2368-2378.

217. Ji L, Gao L, Jiang H, Yang J, Yu L, Wen J, Cai C, Deng H, Feng L, Song B, Ma Q, Qian L. Safety and efficacy of a GLP-1 and glucagon receptor dual agonist mazdutide (IBI362) 9 mg and 10 mg in Chinese adults with overweight or obesity: A randomised, placebo-controlled, multiple-ascending-dose phase 1b trial. *EClinicalMedicine*. 2022;54:101691.

218. Jiang H, Pang S, Zhang Y, Yu T, Liu M, Deng H, Li L, Feng L, Song B, Han-Zhang H, Ma Q, Qian L, Yang W. A phase 1b randomised controlled trial of a glucagon-like peptide-1 and glucagon receptor dual agonist IBI362 (LY3305677) in Chinese patients with type 2 diabetes. *Nat Commun*. 2022;13(1):3613.

219. Abdul-Rahman T, Roy P, Ahmed FK, Mueller-Gomez JL, Sarkar S, Garg N, Femi-Lawal VO, Wireko AA, Thaalibi HI, Hashmi MU, Dzebu AS, Banimusa SB, Sood A. The power

of three: Retatrutide's role in modern obesity and diabetes therapy. *Eur J Pharmacol*. 2024;985:177095.

220. le Roux CW, Steen O, Lucas KJ, Startseva E, Unseld A, Hennige AM. Glucagon and GLP-1 receptor dual agonist survodutide for obesity: a randomised, double-blind, placebo-controlled, dose-finding phase 2 trial. *Lancet Diabetes Endocrinol*. 2024;12(3):162-173.

Table 1. GIP receptor agonism and its effects on body weight in general, and as part of the mode-of-action of the dual GIP/GLP-1 receptor agonist tirzepatide in the treatment of type 2 diabetes and obesity in particular.

A	What suggests an anorexigenic role for GIP receptor agonism?	What suggest an orexigenic (obesogenic) role for GIP receptor agonism	Commentary
	• In rodents, long-acting GIP receptor agonists (administered intracerebroventricularly or peripherally) reduce food intake and body weight (66) • In human subjects, long-acting GIP receptor agonists lead to some weight loss (-2-3 kg) (202). However, a mechanism has not been delineated. • In rodents (66) and in human subjects with type 2 diabetes (203,204), dual GIP/GLP-1 receptor agonists (administered) reduce food intake and body weight more than selective GLP-1 receptor agonists alone • In mice, GIP receptor-expressing hypothalamic neurons, when stimulated, cause reductions in food (energy) intake (205).	• Global GIP receptor knock-out mice are resistant to high-energy overfeeding (206) • Within the human population, individuals with loss-of-function mutations of the GIP receptor have lower body-mass-indices (207) • GIP receptor antagonists can lead to body weight reduction in rodents (149) and in human subjects (16), especially when combined with GLP-1 receptor agonism.	The finding, that GIP receptor agonism and antagonism can both lead to weight loss, is a paradox. It cannot be resolved, if one assumes that the same receptors on the same cells (neurons) are responsible. For rodents, recently, hypothalamic neurons expressing GIP receptors have been found responsible for the body weight reduction in response to stimulating GIP receptors (66), and brains stem neurons expressing GIP receptors, when knocked out specifically in these cells, sensitize to weight-loss actions of GLP-1 receptor agonism (88), indicating that agonism and antagonism at the GIP receptor address different brain areas and specific neurons triggering differing biological responses.
B	**What speaks in favour of GIP receptor agonism playing a role in the superior body-weight reducing effect of tirzepatide over selective GLP-1 receptor agonists?**	**What speaks against of a role of GIP receptor agonism mediating the superior body-weight reducing effect of tirzepatide over selective GLP-1 receptor agonists?**	**Commentary**
	• Tirzepatide leads to more body weight reduction than the selective GLP-1 receptor agonist semaglutide in people with type 2 diabetes (203	• Exogenous (intravenous) GIP does not lead to a reduction in *ad libitum* food (energy) intake in healthy human subjects (73) or in individual	The neurobiology of GIP receptor-agonism-induced weight loss has only been delineated in rodents. The lack of effect of exogenous GIP on

	); the difference could be pointing to a role of GIP receptor agonism • Long-acting GIP receptor agonists lead to some moderate body weigh t reduction in healthy human volun teers and subjects with T2D (202).	s with type 2 diabetes being treated with GLP-1 receptor agonists (79). Rather, it impairs GLP-1's ability t o reduce *ad libitum* food (energy) i ntake in healthy human subjects (7 3). • Tirzepatide did not reduce *ad libitu m* food (energy) intake more than d id semaglutide in T2D (80), althou gh tirzepatide led to greater weight reduction .	appetite, and *ad libitum* food (energy) intake, in human clinical studies points to a potential species difference. Similar experiments with exogenous GLP-1 have robustly shown a reduction in appetite and ad libitum food (energy) intake compatible with long-term body weight reduction (28,73).
C	**What speaks in favour of GIP receptor agonism playing a role in the superior glycaemic control of tirzepatide vs. selective GLP-1 receptor agonists?**	**What speaks against of a role of GIP receptor agonism mediating superior glycaemic control vs. selective GLP-1 receptor agonists?**	**Commentary**
	• Tirzepatide reduces fasting plasma glucose and HbA_{1c} more than dose the most efficacious selective GLP -1 receptor agonists, semaglutide (203). The difference may be the co nsequence of GIP receptor agonis m. • Tirzepatide treatment improves ins ulin sensitivity (204), perhaps mor e than just by reducing body weigh t (208). • Tirzepatide increases early and late phase insulin secretion in response to hyperglycaemia (in T2D) (204), however, under conditions, when p articipants were exposed to effecti ve concentrations of tirzepatide, pr oviding stimulation of GIP and GL P-1 receptors.	• In individuals with T2D, exogenou s GIP has a greatly reduced insulin otropic potency (21) and does not a cutely reduce plasma glucose in ca se of hyperglycaemia (209). • Tirzepatide is characterized by GL P-1 receptor agonism biased towar ds cAMP formations and against ß -arrestin expression (211), which p otentially may lead to GLP-1 recep tor internalization, and a depletion of the GLP-1 receptor pool on the cell surface of ß-cells, and, thus, de sensitization.	Prominent effect of GIP receptor agonism in T2D contrast to the universal finding of a substantial loss of insulinotropic potency of GIP in T2D. Improved glycaemic control may improve the insulinotropic function of GIP receptor agonism in T2D, but attempts with intensified insulin regimens have not normalized the insulinotropic potency of exogenous GIP, but rather only partially rescued effects on insulin secretory responses. It can only be hypothesized, that glucose-lowering through GLP-1 receptor agonism will elicit a similar phenomenon. Tirzepatide may just be a very potent GLP-1 receptor agonist.

- The impaired insulinotropic action (21) and glucose-lowering activity (209) of GIP (or IP receptor agonism provided by, e.g., tirzepatide) may be improved due to the initial glucose-lowering activitiy of GLP-1 receptor agonism provided by tirzepatide (analogous to the effect of intensified insulin regimens (210).

Table 2. Pharmacological features of novel GLP-1 based agents targeting obesity and diabetes

Name	Molar mass	Feature	Dose	Bioavailability	Half-life	Ref.
Semaglutide (NN9535)*	4113.64 g/mol	GLP-1RA	0.25, 0.5, 1.0, 1.7, 2.4 mg	89%	145-165 hours	(182)
Danuglipron (PF-06882961)	555.61 g/mol	Oral, non-peptide, small molecule, GLP-1RA	2.5, 10, 40, 80, or 120 mg	NA	5.3 ± 0.81 hours in 120 mg	(138)
Orfoglipron (LY-3502970)	882.97 g/mol	Oral, non-peptide, small molecule, GLP-1RA	9, 15, 27, or 45 mg	20-40%	25–68 hours	(137,212,213)
Tirzepatide (LY-3298176)*	4813.53 g/mol	GLP-1 and GIP receptor dual agonist	5, 10, or 15 mg	80%	5 days	(214)
Maridebart cafraglutide (MariTide) (AMG 133)	4600.70 g/mol	Agonist of GLP-1R and antagonist of GIPR (monoclonal antibody)	21 to 840 mg	NA	16.5–23.8 days	(16)
Cagrilintide/semaglutide (Cagrisema) (NN-9388)	31,200 g/mol + 4113.64 g/mol	Amylin and GLP-1 receptors dual agonist	Cagrilintide 2.4 mg/ semaglutide 2.4 mg	Cagrilintide 30% (215)/ semaglutide 89%	Cagrilintide 159–195 hours /semaglutide 145-165 hours	(161)
Survodutide (BI 456906)	4231.69 g/mol	Glucagon/GLP-1 receptors dual agonist	0.45, 1.8, 2.4, 3.0, or 4.8 mg	93%(216)	100 hours	(152)
Mazdutide (IBI362 or LY3305677)	4476.06 g/mol	Glucagon/GLP-1 receptors dual agonist	3.0, 4.5, or 6.0 or 9.0 mg	NA	7.3–44.8 days	(217,218)
Retatrutide (LY-3437943)	4845.44 g/mol	GLP-1, GIP, and Glucagon receptors triple agonist	1, 3, 8, or 12 mg	NA	6 days	(168,219)

*Semaglutide and tirzepatide are presented for comparison. RA, receptor agonist; Ref., reference; NA, not available.

Table 3. Major clinical study data of novel GLP-1 based agents targeting obesity

Name	Dose	Duration (weeks)	Study population	Age / female%†	Baseline weight and BMI†	Baseline WC†	Body weight reduction†	WC reduction†	Study name (References)
Semaglutide (NN9535)*	0.25, 0.5, 1.0, 1.7, 2.4 mg	68	PWO without diabetes	46 ± 13 years / 73.1%	105.4±22.1 kg/ 37.8±6.7 kg/m^2	5.7±0.3%	-12.4% (-14.9% vs. -2.4%)	-0.34% point (-0.52% vs. -0.17%)	STEP 1 (182)
Danuglipron (PF-06882961)	80, 120, 200 mg bid (Cohort 3)	32	PWO without diabetes	18-44 years (38.9%), 45-64 years (52.8%), ≥65 years (8.3%)/61.1%	NA	NA	-13.05% (-11.65% vs. 1.40%)	-11.62cm (-11.43cm vs. 0.19cm)	NCT04707313 (phase 2b)
Orfoglipron (LY-3502970)	12, 24, 36, or 45 mg	36	PWO without diabetes	50.9±12.6 years / 53%	110.9±28.1 kg/ 38.7±7.6 kg/m^2	117.7±14.8 cm	-12.4% (-14.7% vs. -2.3%)	-9.6 cm (-13.6 cm vs. -4.0 cm)	GZGI: NCT05051579 (phase 2) (143)
Tirzepatide (LY-3298176)*	5, 10, 15 mg	72	PWO without diabetes	44.9±12.3 years / 67.8%	105.6±22.92 kg/ 38.1±6.69 kg/m^2	114.4±15.59 cm	-17.8% (-20.9% vs. -3.1%)	-14.5 cm (-18.5 cm vs. -4.0 cm)	SURMOUNT-1 (74)
Maridebart cafraglutide (AMG 133)	140, 280, 420 mg (multiple ascending doses)	30	PWO without diabetes	51.6±12.8 years / 87.5%	90.5±10.3 kg/ 32.5±2.6 kg/m^2	102.4±10.8 cm	-10.81% (-11.23% vs.-0.42%)	-8.37 cm (-8.17 cm vs. 0.3 cm)	NCT04478708 (phase 1) (16)
Cagrilintide/ semaglutide	2.4 mg (Semaglutid	20	PWO without	37.0±9.7 years / 27.0%	98.0±17.3 kg/ 33.0±4.2	NA	-7.4% (-15.4% vs. -8.0% in	NA	NCT04982575 (phase 1b) (161)

(Cagrisema)	e) + 0.16, 0.3, 0.6, 1.2, 2.4, 4.5 mg (Cagrilintide)		diabetes		kg/m^2		placebo plus semaglutide 2.4 mg)		
Survodutide (BI 456906)	0.6, 2.4, 3.6, 4.8 mg	46	PWO without diabetes	47.6 ± 13.5 years / 70.0%	105.9±17.4 kg/ 37.6±6.0 kg/m^2	112.8±13.0 cm	-12.1% (-14.9% vs. -2.8%)	-12.1 cm (-16.0 cm vs. -4.0 cm)	NCT0466737 (phase 2) (220)
Mazdutide (IBI362 or LY3305677)	3.0, 4.5 or 6.0 mg	24	PWO without diabetes	35.8 ± 9.2 years / 44.3%	88.5±15.3 kg/ 31.7±4.0 kg/m^2	103.9±11.4 cm	-12.3% (-11.3% vs. 1.0%)	-7.6 cm (-8.8 cm vs. -1.1 cm)	NCT04904913 (phase 2) (158)
Retatrutide (LY-3437943)	1, 4, 8, 12 mg	48	PWO without diabetes	45.8 ± 12.2 years / 48.0%	108.0±21.7 kg/ 37.4±6.0 kg/m^2	116.5±16.4 cm	-15.8% (-17.5% vs. -1.6%)	-17.0 cm (-19.6 cm vs. -2.6 cm)	NCT04881760 (phase 2) (170)

[*]Semaglutide and tirzepatide are presented for comparison. [†]Data in the high dose group. PWO, people with obesity. NA, not available

Figure 1. Development of novel pharmacotherapy approaches based on incretin for obesity and diabetes. CNS, central nervous system; PYY, peptide YY

Figure 2. Novel GLP-1 based medications undergoing development or clincial trials for diabetes and obesity NN, Novo Nordisk

Key: P1 = Phase 1; P2 = Phase 2; P3 = Phase 3

Figure 3. Amino acid structure of incretin-based medications

RA, receptor agonist; GCG, glucagon; Ant, antagonist

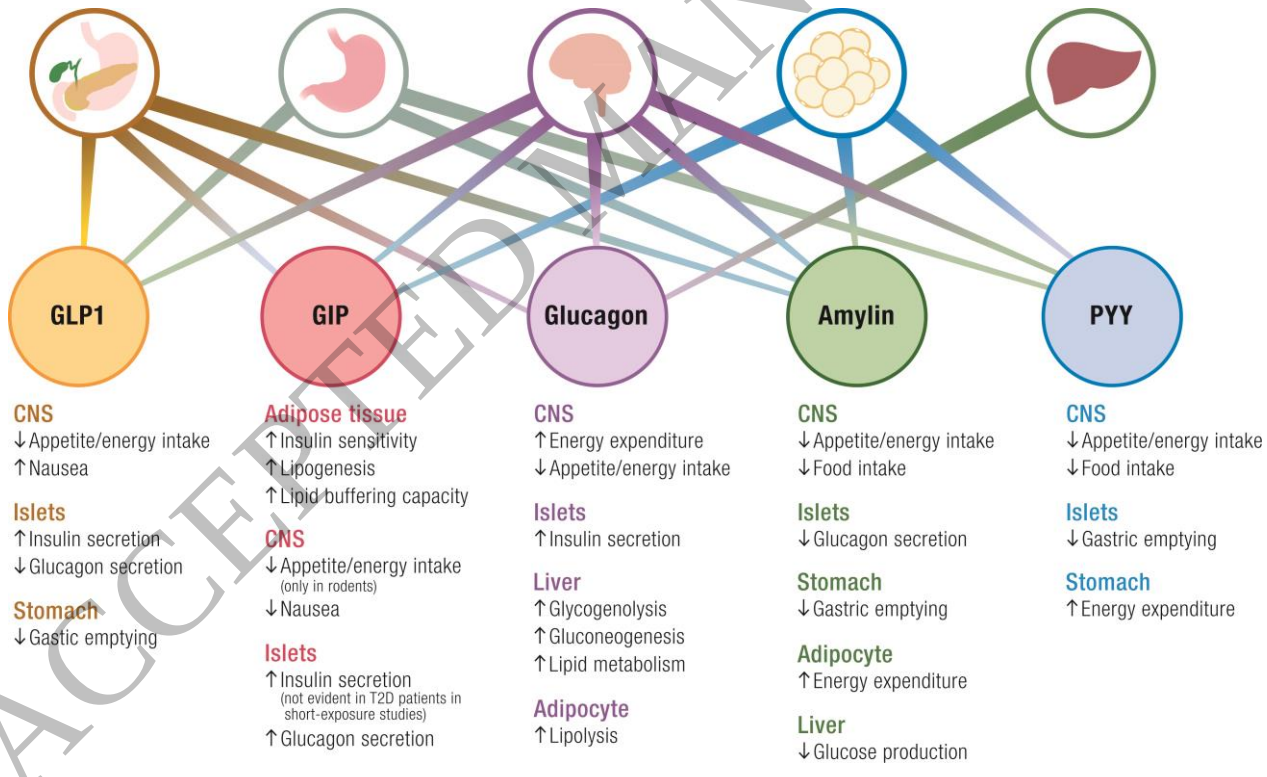

Figure 1
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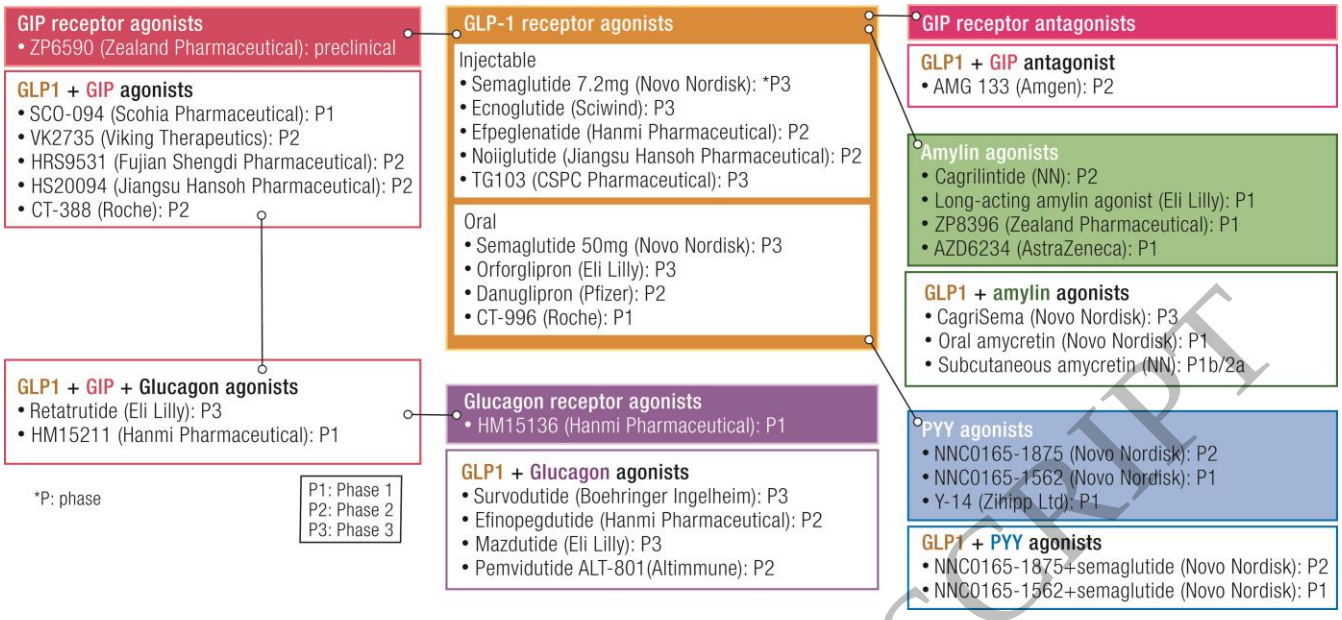

Figure 2
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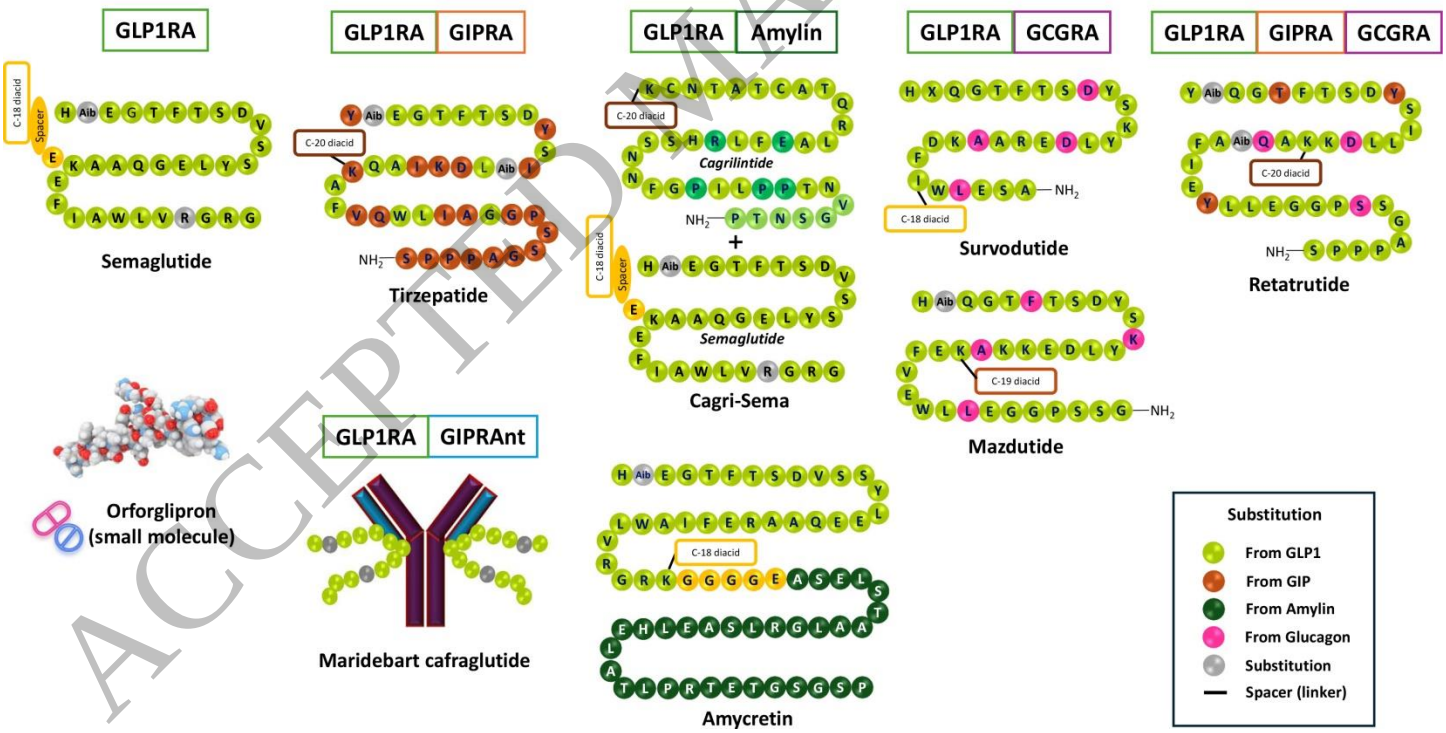

Figure 3
272x138 mm (DPI)

Essential Points

- GLP-1 receptor agonists (GLP-1RAs) have revolutionized treatment paradigms for type 2 diabetes and obesity, and next-generation agents are building on this foundation with enhanced potency and multi-receptor targeting.
- Novel multi-agonist therapies such as tirzepatide, retatrutide, and maridebart cafraglutide combine GLP-1 activity with GIP, glucagon, or amylin signaling to amplify weight loss and metabolic outcomes.
- The paradoxical efficacy of both GIP receptor agonism and antagonism in combination with GLP-1RA highlights the complex and therapeutically exploitable biology of gut hormones.
- Co-agonists involving glucagon receptor signaling expand the therapeutic mechanism by increasing energy expenditure alongside appetite suppression.
- Amylin-based agents further augment GLP-1 therapies by delaying gastric emptying, enhancing satiety, and improving metabolic control.
- The emergence of orally bioavailable GLP-1 receptor agonists, including peptide and small-molecule compounds, represents a transformative advance in patient-centered obesity and diabetes care.