Recent achievements and future directions of anti-obesity medications

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Summary

Pharmacological management of obesity long suffered from a reputation of a 'Mission Impossible,' with inefficient weight loss and/or unacceptable tolerability. However, the tide has turned with recent progress in biochemical engineering and the development of long-acting agonists at the receptor for glucagon-like peptide-1 (GLP-1), and with unimolecular peptides that simultaneously possess activity at the receptors for GLP-1, the glucose-dependent insulinotropic polypeptide (GIP) and glucagon. Some of these novel therapeutics not only improve body weight and glycemic control in individuals with obesity and type 2 diabetes with hitherto unmet efficacy and tolerable safety, but also exhibit potential therapeutic value in diverse areas such as neurodegenerative diseases, fatty liver disease, dyslipidemia, atherosclerosis, and cardiovascular diseases. In this review, we highlight recent advances in incretin-based therapies and discuss their pharmacological potential within and beyond the treatment of obesity and diabetes, as well as their limitations in use, side effects, and underlying molecular mechanisms.

Keywords: **Obesity; Anti-obesity medication (AOM); GLP-1; GIP; Diabetes**

Introduction

The guideline-based management of obesity is one of the greatest medical challenges of our society. In Europe, more than half of adults and one-third of children and adolescents are living with overweight or obesity, making obesity a leading risk factor for disability and a major contributor to mortality in the region.[1] Excess body fat at the population-level places enormous burdens on our health care systems due to its association with cardiometabolic conditions, of which type 2 diabetes (T2D), chronic kidney disease (CKD), cardiovascular diseases (CVD), metabolic dysfunction-associated steatohepatitis (MASH) and several types of cancer are the most devastating.[2] The incidence of T2D among European youth is rising, with over 80% of adolescents living with overweight or obesity at the time of diagnosis.[3] Reflecting the importance of reducing excess body fat for managing T2D, bariatric surgery is recommended for the treatment of T2D in specific (mostly extreme) patient groups, which not only highlights the success of such interventions, but also the limited effectiveness of previous pharmacological options in similar patient populations. While progress in drug development has led to effective therapeutics for managing obesity-linked co-morbidities such as hypertension, T2D, and hypercholesterolemia, treating common (polygenic) obesity itself remains challenging, with employed drugs often falling behind in efficacy and/or safety when translated from preclinical to clinical studies.[2] The decades-long challenge behind developing effective anti-obesity pharmacotherapies is multifactorial, including the body's natural inclination to protect against body weight loss. Typically, body weight loss heightens intrinsic sensitivity to factors that stimulate food intake and promote weight regain. While this drive to maintain body weight represents an evolutionary advantage for survival, it presents a significant challenge to achieving sustained weight loss as evidenced by the high likelihood of weight rebound after discontinuation of lifestyle intervention.[2] Nonetheless, bariatric surgery, considered the benchmark for sustained weight loss, can achieve a 25–30% reduction in body weight in a significant number of individuals.[2] Despite being highly effective, surgical intervention does however not represent an ultimate solution to the obesity pandemic, since such treatment is often available to only extreme patient populations. In addition, it lacks the scalability to meet broader medical needs, making pharmacotherapy an invaluable treatment option for most individuals who require medical aid to reduce excess body fat.

Another challenge in pharmacological obesity management is the paramount importance of drug safety. Many previous anti-obesity medications (AOMs) have suffered from clinically important adverse CV effects

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that went unrecognized in preclinical studies.[2] It is a sober realization that rodents, while being invaluable for studying drug effects on body weight and glucose control, exhibit very limited ability to assess drug effects on the CV and renal system. Most obesity-associated deaths are, however, due to CVD,[4] and CKD and heart failure are frequently observed co-morbidities of T2D.[5,6] The lack of animal models capable of accurately predicting drug effects on conditions such as pulmonary arterial hypertension (PPH) and valvopathy in humans, highlights a critical gap in preclinical testing. This gap is emphasized by the clinical discontinuation of fenfluramine and dexfenfluramine in 1997, and of sibutramine in 2010, due to unexpected adverse CV effects.[2] Rodent studies on obesity are further typically performed in homogeneous cohorts of inbred mice, whereas patient populations in need for obesity management are highly heterogeneous, with a significant number of elderly patients, which are often at risk for CVD and CKD.[2] Collectively, the intrinsic mechanisms that defend body weight, and the absence of preclinical models to predict CV safety, have impeded the development of effective therapeutics and have led to series of drug withdrawals.[2]

Nonetheless, recent years have witnessed true progress not only with long-acting agonists targeting the glucagon-like peptide-1 (GLP-1) receptor, but also with the development of therapeutics that combine the metabolic action of GLP-1 with that of several other key metabolic hormones.[2] In this context, profound therapeutic value has been demonstrated by unimolecular peptides that simultaneously act at the receptors for GLP-1, the glucose-dependent insulinotropic polypeptide (GIP) and/or glucagon. Additionally, co-therapies of GLP-1R agonists (GLP-1RAs) with amylin or its long-acting analogue cagrilintide, have shown promise.[2] Although variations in efficacy exist across different molecules and patient populations (AOMs are typically less efficacious in subjects living with T2D) (Fig. 1), these new AOMs can decrease body weight by at least 10% in most individuals, and unprecedentedly, in a significant number of individuals beyond 15% and 20%, while retaining commendable safety profiles.[2] These incretin-based therapies, which act broadly in both the brain and periphery, show promise for treating not only metabolic disorders, but also MASH, hypercholesterolemia, atherosclerosis, and CV diseases, and potentially also neurodegenerative diseases. In this review, we highlight recent advances in incretin-based pharmacology, discuss drug effects in selected patient cohorts with various chronic diseases, and summarize their limitations, along with potential future directions and open questions surrounding their use and molecular mechanisms.

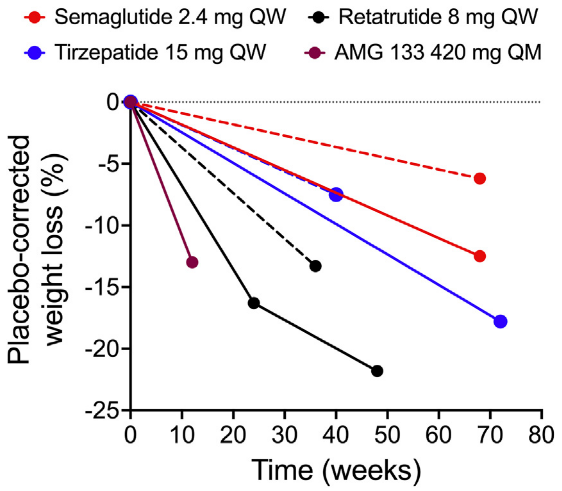

Fig. 1: **Weight loss efficacy of selected AOMs in clinical studies.** Placebo-corrected weight loss (% to baseline) of semaglutide 2.4 mg QW (red), tirzepatide 15 mg QW (blue), retatrutide 8 mg QW (black), and AMG133 420 mg QM (red) were selected from Ref.[7–14] Effects in individuals with overweight/obesity without T2D are indicated as solid lines, whereas effects in subjects with overweight/obesity with T2D are indicated as dashed lines. QW: once-weekly; QM: once-monthly.

The biological action of GLP-1

Produced primarily from enteroendocrine L-cells in the large intestine, and to a lower extend from pancreatic alpha-cells, GLP-1 is cleaved from proglucagon by the action of the prohormone convertase 1/3 (PC1/3).[15] The main active forms of GLP-1 in circulation are GLP-1 (7–36)NH_2, which is predominant, and GLP-1 (7–37), present in smaller amounts. Less prevalent forms include GLP-1 (1–37) and GLP-1 (1–36)NH_2, which have much lower ability to promote insulin secretion.[15] In humans, plasma levels of total GLP-1 are in the range of 5–10 pmol/L during fasting, and up to 40 pmol/L postprandially, while levels of active GLP-1 are typically below 2 pmol/L at baseline and between 5 and 10 pmol/L postprandially.[16–18] Albeit best known for its insulinotropic action, GLP-1 also promotes insulin synthesis,[19] suppresses glucagon secretion,[20,21] and delays intestinal glucose entry by slowing gastric emptying.[22] As demonstrated using clamp studies in patients with T2D, the insulinotropic and glucagonostatic effects of GLP-1 (7–36)NH_2 contribute equally to lower blood glucose,[21] and consistent with this, the glucose lowering effect of GLP-1 is partially preserved in patients with T1D.[20,23] GLP-1 and its analogs further stimulate β-cell proliferation in rodents and reduce β-cell apoptosis and inflammation in both murine and human β-cell lines, and in isolated human islets.[15] Consequently, GLP-1R agonism acutely improves glycemia through its insulinotropic, glucagonostatic, and gastric inhibitory actions. Over the long term, GLP-1R agonism may also provide anti-inflammatory and anti-apoptotic benefits, contributing to the preservation of islet mass. However, these effects vary by age and species, as β-cell proliferation is generally greater in mice than humans and declines with age in both species.[15] Therapeutic potential of GLP-1R agonism notably goes beyond just regulation of glucose metabolism and includes potent central regulation of food intake for body weight reduction. It has also been implicated in enhancing CV function, protecting against ischemic injury or myocardial infarction, reducing inflammation and apoptosis in the brain and the periphery, and further potentially offering neuroprotective effects for patients with neurodegenerative diseases.

Biochemically optimized GLP-1R agonists for management of T2D

The ability of GLP-1 to improve glycemic control via its insulinotropic and glucagonostatic action at the pancreas has spurred great interest in its pharmacological use for managing T2D. However, native GLP-1 has a half-life of just 2–3 min, which is primarily owed to its rapid enzymatic degradation and swift renal elimination.[15] As a result, only 10–15% of active GLP-1 is presumed to reach the general circulation, and much less to relevant brain areas that control appetite and body weight.[24] A variety of chemically and structurally refined GLP-1RAs have been developed to overcome these limitations. They have not only transformed the landscape of how T2D can be managed pharmacologically, but also impressively demonstrate implication towards the management of other diseases, most notably obesity. Reflecting the rapid progress that has been made in this field, GLP-1RAs have developed from a native peptide with a half-life of just 2–3 min to long-acting formulations suitable for application twice daily (exenatide BID), once daily (liraglutide, lixisenatide), and even once weekly (exenatide ER, albiglutide, dulaglutide, semaglutide) (Fig. 2). Also, the development of orally administered GLP-1RAs, most notably Rybelsus® (Novo Nordisk), which was approved for the treatment of T2D by the U.S. Food and Drug Administration (FDA) in 2019 and by the European Medicines Agency (EMA) in 2020, underline the significant progress that has been in this area. The strategies employed to extend GLP-1RA half-life include biochemical modifications to protect them from enzymatic degradation (as has been applied for exenatide, lixisenatide, albiglutide, dulaglutide, and semaglutide), and/or to hinder renal elimination by increasing their molecular size (albiglutide, dulaglutide), or prolong diffusion into circulation (Exenatide extended-release (ER), liraglutide, semaglutide). These differences in bioavailability and duration of action translate to notable differences in their pharmacodynamics. Short-acting GLP-1RAs (exenatide BID, lixisenatide) show significant fluctuations in plasma levels due to their daily application. Consequentially, they mainly reduce postprandial blood glucose by acutely inhibiting gastric emptying.[25] Long-acting GLP-1R agonists (albiglutide, dulaglutide, exenatide ER, semaglutide) maintain more stable plasma concentrations due their weekly application, with less inhibition of gastric emptying and greater reduction in blood glucose through their insulinotropic and glucagonostatic effects in the pancreas.[25] Ozempic (semaglutide 1 mg once weekly (QW)) is the most recently registered GLP-1R monoagonist for the management of T2D, and was approved by the EMA in 2018, and by the FDA in 2017 (Fig. 2). In the SUSTAIN trials, Ozempic was well tolerated (Tables 1 and 2), and at its highest approved dose, improved glucose control in subjects with T2D with superiority over placebo,[26,27] sitagliptin,[28] exenatide ER,[29] and insulin glargine,[30] with reductions in HbA1c of −1.5% to −1.8% after 30–56 weeks of treatment (Tables 1 and 2).

While long-acting GLP-1RAs are now established as invaluable treatment options for managing T2D, they suffer from the dose-dependent appearance of adverse effects, which are mostly transient and of gastrointestinal nature. The most frequently observed adverse effects associated with the use of GLP1RAs are constipation, diarrhea, nausea and emesis, which, with minor variations across the different molecules and study populations, may occur in >50% of patients at treatment initiation[7,31–33] (Tables 1 and 2). Less frequent, but potentially more harmful, adverse effects include gallstones (occurring in >3% of individuals) and acute kidney injury (<1%), with no clear indication of an enhanced risk for pancreatitis or pancreatic, colorectal, or thyroid carcinoma.[34] Although adverse GI-effects associated with the use of GLP-1RAs are mostly transient and often resolve after 1–2 months without the necessity of treatment discontinuation,[7,31–33] the importance of medical counseling and the requirement of careful personalized dose-escalation in the initial phase of treatment is emphasized.

Biochemically optimized GLP-1R agonists for managing obesity

Based on their body weight lowering effects,[15] GLP-1RAs are also attractive candidates for managing obesity. However, since treatment of obesity generally requires (∽2-fold) greater doses relative to treatment of T2D, the dose-dependent occurrence of adverse GI-effects may limit the use of doses potentially required to optimize weight loss. Nonetheless, liraglutide 3 mg (Saxenda®, Novo Nordisk) has been established in the European Union for the treatment of obesity in adults in 2015 (following FDA approval in 2014), and in 2021 for managing obesity in adolescents (following FDA approval in 2020)[2] (Fig. 2). In adult subjects living with obesity without T2D, treatment with Saxenda led to a mean placebo-corrected weight loss of ∼5% after 32–56 weeks of treatment,[35–37] with around one-third of individuals achieving more than 10% weight loss.[35–37] Appreciably, weight loss induced by Saxenda was

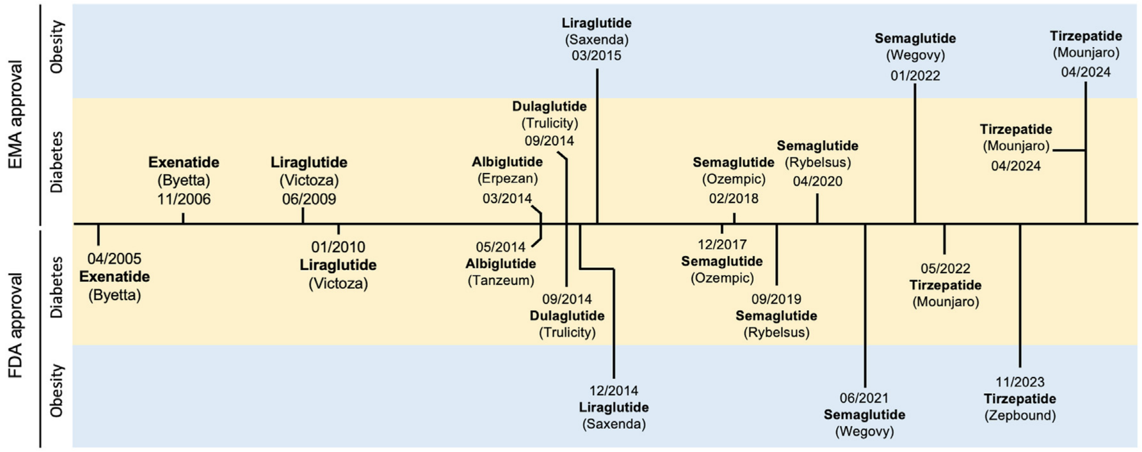

Fig. 2: **Schematic time-line on the approval of incretin-based drugs for treatment of T2D and obesity by the FDA and EMA.**

paralleled by improved glucose control, a placebo-corrected reduction in systolic and diastolic blood pressure of –2.8 and –0.9 mmHg, and improvement in lipid and cholesterol metabolism, but with a notable increase in heart rate of +2.4 bpm relative to individuals receiving placebo.[37] In 2022, the European Union has expanded its portfolio of GLP-1RAs for management of obesity in adults with the approval of semaglutide 2.4 mg (Wegovy®, Novo Nordisk). In the multicenter STEP trials, Wegovy decreased at its highest approved dose of 2.4 mg QW body weight in individuals living with obesity without T2D by a placebo-corrected –10.3 to –13.9% after 68–104 weeks of treatment[7,38–41] (Tables 1 and 2), and with an appreciable –7.5% greater weight loss relative to treatment with Saxenda.[40] Although the weight-lowering efficacy of semaglutide 2.4 mg is dampened by approximately 50% within concomitant T2D[8] (Fig. 1), weight loss of more than 10% overall is still achieved in as much as 50–80% of individuals across the STEP trials (Tables 1 and 2).[7,8,38–41]

The biological action of GIP

Anchored on the observation that mice deficient for the GIP receptor (GIPR) are protected from diet-induced obesity (DIO), and the demonstration that the insulinotropic action of the peptide is largely diminished in patients with T2D, there is ongoing debate whether GIPR should be activated or inhibited to achieve metabolic benefits.[42] In humans, GIP increases blood flow to the adipose tissue, and under hyperinsulinemic conditions, decreases circulating lipids by promoting their storage into white adipose tissue.[43] When used in combination with GLP-1RAs, GIPR antagonists decrease body weight and food intake, or at least prevent weight gain, in DIO mice and non-human primates, which spurred interest in the development of unimolecular approaches combining both GIPR antagonism and GLP-1R agonism for the treatment of obesity.[43] However, under conditions where insulin action is limited, such as during normo-/hypoinsulinemia or insulin resistance, GIP is lipolytic and decreases fat mass in DIO mice[42] and humans.[44] Long-acting GIPR agonists further act in the brain to decrease body weight via inhibition of food intake, and these effects vanish in mice with either neuronal loss of GIPR,[45] or in which GIPR has been specifically deleted in GIPR positive GABAergic neurons.[46] Consistent with this are chemogenetic studies which show that targeted activation of GIPR neurons in the hypothalamus or the hindbrain decreases food intake[47] and that decreased food intake induced via chemogenetic induction of K-cell GIP hypersecretion is blocked by central antagonization of GIPR.[48] Despite persistent uncertainties related to whether the GIP receptor should be activated or inhibited for the treatment of obesity,[42] there is preclinical evidence indicating that GIPR agonism decreases apoptosis and inflammation, has neuroprotective effects in the brain,[49] and preserves bone mass by promoting bone formation and inhibiting bone resorption.[50] The latter has been verified in clinical studies, showing that GIP inhibits bone resorption in healthy humans,[51] postmenopausal women,[52] and in individuals with type 1 diabetes.[53]

Unimolecular agonists targeting the receptors for GLP-1 and GIP

Another successfully employed strategy in the development of AOMs include the generation of single molecules with activity at several key metabolic hormones. The concept was introduced by the groups of Matthias Tschöp and Richard DiMarchi as unimolecular peptides with activity at the receptors for GLP-1 and glucagon in 2009,[54] and with activity at the receptors for GLP-1 and GIP in 2013.[55] Several such unimolecular co-agonists have subsequently progressed to clinical development. The most advanced is the GIPR:GLP-1R co-agonist

	SUSTAIN-1 (40 weeks)			SUSTAIN-2 (56 weeks)			SUSTAIN-3 (56 weeks)		SUSTAIN-4 (30 weeks)			SUSTAIN-5 (30 weeks)			SUSTAIN-6 (104 weeks)			SUSTAIN-7 (40 weeks)	
Participants Background Med. Comparator	Obesity with T2D No OAMs Placebo			Obesity with T2D Met Sitagliptin 100 mg			Obesity with T2D OAMs Exenatide ER 2 mg		Obesity with T2D Met ± SU Insulin Glargine			Obesity with T2D Ins ± Met Placebo			Obesity with T2D ± OAM Placebo			Obesity with T2D Met Dulaglutide 1.5 mg	
Participant race (%)	AS (21); White (64); Black or Afr. Am. (8); Other (7)			AS (25); White (68); Black or Afr. Am. (5); Other (2)			AS (2); White (84); Black or Afr. Am. (7); Other (7)		AS (11); AI/AN (<1); White (77); Black or Afr. Am. (9)			AS (17); White (78); Black or Afr. Am. (5); Other (<1)			AS (8); White (83); Black or Afr. Am. (7); Other (2)			AS (16); AI/AN (77); White (36); Black or Afr. Am. (6); Other (<1)	
Trial locations	CA, ITLY, MX, RUS, SA, UK, USA			AF (1); AS (4); EU (11); NAR (1); SOAM (1)			EU (10); NAR (3); SOAM (1)		AF (1); AS (1); EU (9); NAR (3); SOAM (1)			DE, JPN, PR, RS, SK			AF (1); AS (4); EU (9); ME (1); NAR (3); OC (1); SOAM (2)			AS (2); EU (13); NAR (2)	
Main drug effects after study completion																			
Doses (mg QW)	**0.5**	**1**	**Pl.**	**0.5**	**1.0**	**Sita.**	**1.0**	**Exen.**	**0.5**	**1.0**	**Ins**	**0.5**	**1.0**	**Pl.**	**0.5**	**1.0**	**Pl.**	**1.0**	**Dula**
HbA1c (Δ% unit)	−1.5	−1.6	0.0	−1.3	−1.6	−0.5	−1.5	−0.9	−1.2	−1.6	−0.8	−1.4	−1.8	−0.1	−1.1	−1.4	−0.4	−1.8	−1.4
BW (Δ%)	−4.1	−4.9	−1.1	−4.8	−6.8	−2.1	−5.6	−2.0	−3.7	−5.5	1.2	−4.0	−7.0	−1.5	−3.9	−5.3	−0.7	−7.1	−3.3
SBP (Δ mmHg)	−2.6	−2.7	−1.7	−5.1	−5.6	−2.3	−4.6	−2.2	−4.7	−5.2	−1.7	−4.3	−7.3	−1	−3.4	−5.4	−2.5	−4.9	−2.9
DBP (Δ mmHg)	−0.5	0.2	0.4	−2	−1.9	−1.1	−1	−0.1	−1.4	−1.0	−1.4	−1.8	−1.5	−2.2	−1.4	−1.6	−1.6	−2	<-0.1
Pulse rate (Δ bpm)	2.4	2.4	−0.5	1.6	1.3	0.6	2.1	1.1	2.3	3.1	−0.1	0.8	4	−0.8	2.1	2.4	0.0	4	2.4
BW ≥ 10% (%)	8	13	2	13	24	3	21	4	8	16	2	9	26	3	n/a	n/a	n/a	27	8
Adverse effects observed in ≥ 5% of subjects																			
Nausea (%)	20	31	8	18	18	7	22	12	21	22	4	11	17	5	17	22	8	21	20
Vomiting (%)	4	7	2	8	10	3	7	6	7	10	3	6	12	3	11	15	5	10	10
Diarrhea (%)	16	14	3	13	13	7	11	8	16	19	4	5	7	2	18	18	11	14	18
Dyspepsia (%)	5	4	2	6	5	2	7	5	3	7	1	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Headache (%)	12	7	6	6	7	4	9	10	5	6	6	n/a	n/a	n/a	n/a	n/a	n/a	7	6
Constipation (%)	6	4	<1	4	6	2	6	5	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	5	5
Nasopharyngitis (%)	5	5	5	12	7	10	10	9	12	8	12	n/a	n/a	n/a	n/a	n/a	n/a	5	7
Lipase Increase (%)	6	4	4	8	8	7	10	12	10	8	4	n/a	n/a	n/a	n/a	n/a	n/a	6	6

Treatment: OAM: Oral Anti-Diabetic Medication; Met: Metformin; SGLT-2i: SGLT-2 inhibitor; SU: Sulfonylurea; TZD: Thiazolidinediones; Ins: Insulin; Exen: Exenatide ER; Dula: Dulaglutide; PL: Placebo. **Race:** Afr. Am.: African American; AS: Asian; AI/AN: American Indian and Alaska Native; EU: Europe(an); HS: Hispanic; NHPI: Native Hawaiian and Pacific Islander. **Geography:** AF: Africa; AS: Asia; EU: Europe; ME: Middle East; NAR: North American Region; OC: Oceania; SOAM: South America; ARG: Argentina; AUS: Australia; BR: Brazil; CA: Canada. CN: China; ES: Spain; DE: Germany; HK: Hong Kong; HU: Hungary; IN: India; ISRL: Isreal; ITLY: Italy; JPN: Japan; KOR: South Korea; MX: Mexico; PR: Puerto Rico; RS: Serbia; RUS: Russia; SA: South Africa; SK: Slovakia; USA: United States of America; UK: United Kingdom. **Endpoints:** WL: weight loss; Li: Lifestyle intervention; SBP: systolic blood pressure; DBP: diastolic blood pressure; BW: body weight; ^{E} Efficacy Estimand.

Table 1: **Summary of composition and metabolic outcome of the SUSTAIN (A) trials.**

	STEP-1 (68 weeks)		STEP-2 (68 weeks)			STEP-3 (68 weeks)		STEP-4 (20 + 48 weeks)		STEP-5 (104 weeks)		STEP-6 (68 weeks)			STEP-7 (44 weeks)	
Participants Background Med. Comparator	Obesity without T2D No OAMs Placebo		Obesity with T2D OAMs Placebo			Obesity without T2D No OAMs Placebo with Li		Obesity without T2D No OAMs Placebo		Obesity without T2D No OAMs Placebo		Obesity with at least one comorbidity OAMs Placebo			Obesity without T2D OAMs Placebo	
Participant race (%)	AS (13); White (75); Black or Afr. Am. (6); Other (6)		AS (26); White (62); Black or Afr. Am. (8); HIS: (13); Other (4)			AS (2); White (76); Black or Afr. Am. (20); Other (2)		AS (2); White (84); Black or Afr. Am. (13); Other (1)		AI/AN (<1); AS (<1); White (95); Black or Afr. Am. (4); Other (6)		AS (100)			AS (91); White (8); Black or Afr. Am. (1)	
Trial locations	AS (3); EU (9); NAR (4); SOAM (1)		AF (1); AS (2); EU (5); ME (1); NAR (3); SOAM (1)			USA		AF (1); EU (7); ME (1); NAR (1)		CA, ES, HU, ITLY, USA		JPN, KOR			BR, CN, HK, KOR	
Main drug effects after study completion																
Doses (mg QW)	**2.4**	**Pl.**	**1**	**2.4**	**Pl.**	**2.4**	**Pl.**	**2.4**	**Pl.**	**2.4**	**Pl.**	**1.7**	**2.4**	**Pl.**	**2.4**	**Pl.**
HbA1c (Δ% unit)	−0.5	−0.2	−1.5	−1.6	−0.4	−0.5	−0.3	−0.1	0.1	−0.4	−0.1	−0.9	−0.9	−0.0	−0.8	−0.1
BW (Δ%)	−14.9	−2.4	−7.0	−9.6	−3.4	−16	−5.7	−7.9	6.9	−15.2	−2.6	−9.6	−13.2	−2.1	−12.1	−3.6
SBP (Δ mmHg)	−6.2	−1.1	−2.9	−3.9	−0.5	−5.6	−1.6	0.5	4.4	−5.7	−1.6	−10.8	−10.8	−5.3	−6.1	−2.6
DBP (Δ mmHg)	−2.8	−0.4	−0.6	−1.6	−0.9	−3	0.8	0.3	0.9	−4.4	−0.8	−4.6	−5.3	−2.2	−4.3	−0.7
Pulse rate (Δ bpm)	3.5	−0.7	1.5	2.5	−0.2	3.1	2.1	n/a	n/a	3.3	−0.8	6	4	2	–	–
BW ≥ 10% (%)	69.1	12	28.7	45.6	8.2	75.3	27	n/a	n/a	61.8	13.3	42	61	5	85	31
Adverse effects observed in ≥ 5% of subjects																
Nausea (%)	44	17	32	34	9	58	22	14	5	53	22	18	18	4	24	7
Vomiting (%)	24	7	13	22	3	27	11	10	3	30	5	10	9	2	8	0
Diarrhea (%)	31	16	22	21	12	36	22	14	7	35	24	22	16	6	26	10
Dyspepsia (%)	10	4	n/a	n/a	n/a	n/a	n/a	n/a	n/a	13	5	n/a	n/a	n/a	6	0
Headache (%)	15	12	n/a	n/a	n/a	19	10	8	4	11	11	n/a	n/a	n/a	n/a	n/a
Constipation (%)	23	10	13	17	6	37	25	12	6	31	11	19	26	3	12	6
Nasopharyngitis (%)	22	20	12	17	15	22	24	11	15	16	15	24	27	18	n/a	n/a
Abdominal pain (%)	10	6	n/a	n/a	n/a	13	5	n/a	n/a	13	3	11	6	1	5	2

Treatment: OAM: Oral Anti-Diabetic Medication; Met: Metformin; SGLT-2i: SGLT-2 inhibitor; SU: Sulfonylurea; TZD: Thiazolidinediones; Ins: Insulin; Exen: Exenatide ER; Dula: Dulaglutide; PL: Placebo. **Race:** Afr. Am.: African American; AS: Asian; AI/AN: American Indian and Alaska Native; EU: Europe(an); HS: Hispanic; NHPI: Native Hawaiian and Pacific Islander. **Geography:** AF: Africa; AS: Asia; EU: Europe; ME: Middle East; NAR: North American Region; OC: Oceania; SOAM: South America; ARG: Argentina; AUS: Australia; BR: Brazil; CA: Canada. CN: China; ES: Spain; DE: Germany; HK: Hong Kong; HU: Hungary; IN: India; ISRL: Isreal; ITLY: Italy; JPN: Japan; KOR: South Korea; MX: Mexico; PR: Puerto Rico; RS: Serbia; RUS: Russia; SA: South Africa; SK: Slovakia; USA: United States of America; UK: United Kingdom. **Endpoints:** WL: weight loss; Li: Lifestyle intervention; SBP: systolic blood pressure; DBP: diastolic blood pressure; BW: body weight; ^{E} Efficacy Estimand.

Table 2: **Summary of composition and metabolic outcome of the STEP (B) trials.**

tirzepatide, which was developed by Eli Lilly, and approved by the EMA in 2024 for the treatment of uncontrolled T2D in adults (Mounjara®), and for treatment of adult obesity (Zepbound®) in the same year. While the metabolic action of GIP is controversial and subject of ongoing investigation, preclinical[56] and clinical[57] studies using long-acting GIPR agonists demonstrated that they act centrally to ameliorate the emetic effect of GLP-1RAs and to decrease body weight via inhibition of food intake.[45,46] In the SURPASS trials, tirzepatide dose-dependently decreased HbA1c between −1.9 and 2.6% after 40–52 weeks of treatment,[9,58–62] with superiority to semaglutide 1 mg,[58] insulin degludec,[59] insulin glargine,[60,61] and insulin lispro[62] (Tables 3 and 4). In the SURMOUNT-1 trial, performed in individuals with obesity without T2D, tirzepatide decreased body weight up to 20.9% after 72 weeks of treatment, relative to −3.1% in individuals receiving placebo.[10] Remarkably, 63% of individuals treated with tirzepatide lost more than 20% body weight, with as much as 40% of individuals losing more than 25%.[10] Until recently, such magnitude of weight loss was observed only in subjects that underwent bariatric surgery. Although with minor variations (Tables 3 and 4), tirzepatide performed equally well across the SURPASS and SURMOUNT trials,[9,58–68] establishing GLP-1R:GIPR co-agonism as a highly effective treatment for the management of obesity and diabetes. Gastrointestinal adverse effects, and a slight increase in heart rate of 1–3 bpm, remain the most frequently reported side effects associated with the use of tirzepatide, with a prevalence comparable to semaglutide in the SUSTAIN and STEP trials (Tables 1 and 2).[9,58–68] However, as demonstrated in SURMOUNT-4, discontinuation of drug treatment results in progressive body weight regain, and while treatment with tirzepatide led to a placebo-corrected weight loss of −20.9% after 36 weeks of treatment, as much as 14% of the lost body weight was regained in individuals that were switched to receive placebo for an additional 52 weeks.[68] Again, this emphasizes the bodies intrinsic attempt to defend the initial (higher) body weight, and further urges awareness that even best-in-class AOMs do not represent a cure for the disease.

The biological action of glucagon

Glucagon is proteolytically cleaved from proglucagon by the action of the prohormone convertase 2 in the pancreatic alpha-cells, and to a lesser extend in the gastric and duodenal α-cells.[69,70] Secreted primarily under conditions of hypoglycemia, glucagon acts on the liver to increase blood glucose via stimulation of glycogen breakdown and de novo glucose production.[69,70] However, glucagon is pleiotropic, with a series of beneficial effects outside of the liver that include decreases in body weight by inhibition of food intake and stimulation of energy expenditure, and the decrease of fat mass by stimulation of lipolysis and inhibition of lipid synthesis.[69] Glucagon further increases insulin secretion, renal glomerular filtration and autophagy, but with unfavorable effects on the CV system characterized by elevation in heart rate and blood pressure.[69] Glucagon may further be proteolytic and decrease lean tissue mass via signaling through the TOR pathway.[71,72] Early observations indicating that postprandial hyperglucagonemia might be causally linked to the development of T2D has spurred interest to pharmacologically silence the glucagon receptor (GCGR) for the treatment of T2D.[69] Although a series of GCGR antagonists exhibited in clinical studies meaningful reduction of HbA1c and fasting glucose levels, some studies raised concerns about their potential to elevate total and LDL cholesterol.[69]

New AOMs on the horizon

While GCGR antagonists have nowadays largely fallen from favor as a pharmacological strategy to manage T2D, engagement of glucagon receptor (GCGR) agonism to decrease body weight and food intake are increasingly appreciated when used in unimolecular formulations with GLP-1RAs to treat T2D, obesity and MASH[2,73–76] (Table 5). Co-agonism at the receptors for GLP-1 and glucagon is also achieved by the gut-derived peptide hormone oxyntomodulin (OXM), which is cleaved from proglucagon by the action of the prohormone convertase 1/3 simultaneously to GLP-1.[69] But despite being a natural GLP-1R:GCGR co-agonist, OXM shows 10- to 100-fold lower potency relative to native GLP-1 and glucagon at its designated receptors[77,78] and consequentially, decreases food intake exclusively via GLP-1R.[79] Nonetheless, following the first preclinical reports on the use of bioengineered highly potent GLP-1R:GCGR co-agonism[54] and GIPR:GLP-1R:GCGR tri-agonism[80] for management of T2D obesity in rodents, a series of co- and tri-agonists progressed to clinical development.[42] Most notable is Mazdutide (LY3305677, Eli Lilly), which in a Phase 2 study in Chinese individuals with overweight or obesity, showed good tolerability and a placebo-corrected weight loss of −12.6% at the highest tested dose (6 mg QW) after 24 weeks of treatment.[81] Appreciably, treatment with Mazdutide further decreased HbA1c, fasting glucose, serum lipids and alanine aminotransferase (ALT) relative to treatment with placebo.[81] The molecule recently progressed to Phase 3, where it is in the DREAM and GLORY trials investigated for the treatment of obesity (NCT05607680) and T2D (NCT05606913). The GLP-1R:GCGR co-agonist servodutide (Boehringer Ingelheim and Zealand Pharma) showed a dose-dependent and placebo-corrected decrease in body weight of up to −12,1% after 48 weeks of treatment in a recent Phase 2 study in individuals living with overweight/obesity

	SURPASS-1 (40 weeks)				SURPASS-2 (40 weeks)			SURPASS-3 (52 weeks)			SURPASS-4 (52 weeks)				SURPASS-5 (40 weeks)				SURPASS-6 (52 weeks)		
Participants Background Med. Comparator	Obesity with T2D No OAMs Placebo				Obesity with T2D + Met Semaglutide 1 mg			Obesity with T2D + Met ± SGLT-2i Insulin Degludec			Obesity with T2D Met ± SGLT-2i ± SU Insulin Glargine				Obesity with T2D Ins. Glargine ± Met Placebo				Obesity with T2D Basal Ins. Insulin Lispro		
Participant race (%)	AS (35); AI/AN (25); White (36); Black or Afr. Am. (5)				AS (1); White (82); HS (70); Non-HS (30); Black or Afr. Am. (4)			AS (5); White (91); Black or Afr. Am. (3); Other (1)			AS (4); White (82); Black or Afr. Am. (4)				AS (18); Black or Afr. Am. (1); AI/AN (1); White (80)				AS (<1); Black or Afr. Am. (4); AI/AN (<1); Multiple (1); White (94)		
Trial locations	USA, IN, JPN, MX, PR				USA, ARG, AUS, BR, CA, ISRL, MX, UK, PR			AS (2); EU (8); NAM (2); SOAM (1)			AS (1); EU (6); ME (1); OC (1); NAR (4); SOAM (2)				AS (1); EU (5); NAR (2)				EU (11); NAR (3); SOAR (2)		
Main drug effects after study completion																					
Doses (mg QW)	**5**	**10**	**15**	**Pl.**	**5**	**10**	**15 Sema**	**5**	**10 15**	**Ins**	**5**	**10**	**15**	**Ins**	**5**	**10**	**15**	**Pl.**	**5**	**10 15**	**Ins**
HbA1c (Δ% unit)	−1.9	−1.9	−2.1	0.0	−2.0	−2.2	−2.3–1.9	−1.9	−2.2–2.4	−1.3	−2.2	−2.4	−2.6	−1.4	−2.1	−2.4	−2.3	−0.9	−1.9	−2.2–2.3	−1.1
BW (Δ%)	−8	−9.1	−8.3	−0.8	−8.2	−9.8	−11.9–6.1	−7.9	−11.3–13.6	2.4	−7.9	−11	−13	2.1	−5.6	−7.9	−9.2	1.7	−7.3	−10.3–12.1	3.5
SBP (Δ mmHg)	−4.7	−5.2	−4.7	−2	−4.8	−5.3	−6.5–3.6	−4.9	−6.6–5.5	0.5	−0.6	−6	−3.2	3.6	−6.1	−8.3	−12.6	−1.7	−7.4	−9–5.9	−0.4
DBP (Δ mmHg)	−2.9	−3.1	−3.4	−1.4	−1.9	−2.5	−2.9–1	−2	−2.5–1.9	0.4	−1	−1.4	−1.2	1	−2	−3.3	−4.5	−2.1	−2.3	−3.3–1	−0.4
Pulse rate (Δ bpm)	0.8	2.2	1.3	1.2	2.3	2.2	2.6 2.5	0.9	0.7 2.7	0.6	2.4	4	4.8	0.4	1.3	3.5	5.6	−0.8	2.6	1.4 1.4	1
BW ≥ 10% (%)	31	40	47	1	36	53	65 25	37	56 69	3	36	53	66	2	20.7	41.6	40.7	0.8	32	49 57	5
Adverse effects observed in ≥ 5% of subjects																					
Nausea (%)	12	13	18	6	17	19	22 18	12	23 24	2	12	16	23	2	13	18	18	3	14	21 26	1
Vomiting (%)	3	2	6	2	6	9	10 8	6	9 10	1	5	8	9	2	7	8	13	3	5	9 13	1
Diarrhea (%)	12	14	12	8	13	16	14 12	15	17 16	4	13	20	22	4	12	13	21	10	12	15 11	2
Dyspepsia (%)	9	7	6	3	7	6	9 7	4	9 5	0	6	8	8	1	7	8	5	2	11	11 6	1
Constipation (%)	6	5	7	1	7	5	5 6	n/a	n/a n/a	n/a	5	4	4	<1	6	7	7	2	3	3 6	1
Nasopharyngitis (%)	6	7	7	9	n/a	n/a	n/a n/a	3	4 4	6	3	5	5	7	16	7	13	19	n/a	n/a n/a	n/a
Abdominal pain (%)	n/a	n/a	n/a	n/a	3	5	5 5	2	5 6	1	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a n/a	n/a
Lipase Increase (%)	5	0	2	0	n/a	n/a	n/a n/a	6	4 6	2	3	4	6	2	3	2	8	2	n/a	n/a n/a	n/a

Treatment: OAM: Oral Anti-Diabetic Medication; Met: Metformin; SGLT-2i: SGLT-2 inhibitor; SU: Sulfonylurea; TZD: Thiazolidinediones; Ins: Insulin; Exen: Exenatide ER; Dula: Dulaglutide; PL: Placebo. **Race:** Afr. Am.: African American; AS: Asian; AI/AN: American Indian and Alaska Native; EU: Europe(an); HS: Hispanic; NHPI: Native Hawaiian and Pacific Islander. **Geography:** AF: Africa; AS: Asia; EU: Europe; ME: Middle East; NAR: North American Region; OC: Oceania; SOAM: South America; ARG: Argentina; AUS: Australia. BR: Brazil; CA: Canada; CN: China; ES: Spain; DE: Germany; HK: Hong Kong; HU: Hungary; IN: India; ISRL: Isreal; ITLY: Italy; JPN: Japan; KOR: South Korea; MX: Mexico; PR: Puerto Rico; RS: Serbia; RUS: Russia; SA: South Africa; SK: Slovakia; USA: United States of America; UK: United Kingdom. **Endpoints:** WL: weight loss; Li: Lifestyle intervention; SBP: systolic blood pressure; DBP: diastolic blood pressure; BW: body weight; ^{E} Efficacy Estimand.

***Table 3:* Summary of composition and metabolic outcome of the SURPASS (A) trials.**

	SURMOUNT-1 (72 weeks)			SURMOUNT-2 (72 weeks)			SURMOUNT-3 (72 weeks)		SURMOUNT-4 (36 + 52 weeks)^E		
Participants Background Med. Comparator	Obesity without T2D No OAMs Placebo			Obesity with T2D OAMs Placebo			Obesity with at least one comorbidity (excl. T2D) No OAMs Placebo after ≥5 WL after Li		Obesity without T2D No OAMs Placebo		
Participant race (%)	AS (11); Black or Afr. Am. (8); AI/AN (9); White (71)			AS (13); Black or Afr. Am. (8); NHPI (<1); White (76)			AS (1); Black or Afr. Am. (11); NHPI (1); White (86)		AS (7); Black or Afr. Am. (11); NHPI (<1); White (82)		
Trial Locations	AS (4); EU (1); NAR (3); SOAM (2)			AS (3); EU (1); NAR (2); SOAM (2)			NAR (2); SOAM (2)		AS (1); NAR (2); SOAM (2)		
Main drug effects after study completion											
Doses (mg QW)	**10**	**15**	**Pl.**	**10**	**15**	**Pl.**	**10 or 15**	**PL**	**for 36 weeks**	**10 or 15 (Δ week 36 to 88)**	**Pl. (Δ week 36 to 88)**
HbA1c (Δ% unit)	−0.5	−0.5	−0.1	−2.1	−2.1	−0.5	−0.5	0	−0.5	−0.1	0.3
BW (Δ%)	−19.5	−20.9	−3.1	−12.8	−14.7	−3.2	−18.4	2.5	−20.9	−6.7	14.8
SBP (Δ mmHg)	−7.2	−7.2	−1	−5.9	−7.7	−1.2	−5.1	4.1	−5.1	−0.4	3.2
DBP (Δ mmHg)	−4.8	−4.8	−0.8	−2.1	−2.9	−0.3	−3.2	2.3	n/a	n/a	n/a
Pulse rate (Δ bpm)	2.3	2.6	0.1	0.6	1	−0.5	2.7	0.9	n/a	n/a	n/a
BW ≥ 10% (%)	78.1	83.5	18.8	61	65	9	76.7	8.9	n/a	n/a	n/a
Adverse effects observed in ≥ 5% of subjects											
Nausea (%)	33	31	10	20	22	6	40	14	n/a	8,1	2,7
Vomiting (%)	11	12	2	11	13	3	18	1	n/a	5,7	1,2
Diarrhea (%)	21	23	7	20	22	9	31	9	n/a	10,7	4,8
Dyspepsia (%)	10	11	4	7	7	3	9	3	n/a	n/a	n/a
Headache (%)	7	7	7	5	5	3	9	8	n/a	n/a	n/a
Constipation (%)	17	12	6	8	9	4	23	7	n/a	n/a	n/a
Nasopharyngitis (%)	n/a	n/a	n/a	3	5	5	2	6	n/a	n/a	n/a
Abdominal pain (%)	5	5	3	4	7	2	11	2	n/a	n/a	n/a

Treatment: OAM: Oral Anti-Diabetic Medication; Met: Metformin; SGLT-2i: SGLT-2 inhibitor; SU: Sulfonylurea; TZD: Thiazolidinediones; Ins: Insulin; Exen: Exenatide ER; Dula: Dulaglutide; PL: Placebo. **Race:** Afr. Am.: African American; AS: Asian; AI/AN: American Indian and Alaska Native; EU: Europe(an); HS: Hispanic; NHPI: Native Hawaiian and Pacific Islander. **Geography:** AF: Africa; AS: Asia; EU: Europe; ME: Middle East; NAR: North American Region; OC: Oceania; SOAM: South America; ARG: Argentina; AUS: Australia. BR: Brazil; CA: Canada; CN: China; ES: Spain; DE: Germany; HK: Hong Kong; HU: Hungary; IN: India; ISRL: Isreal; ITLY: Italy; JPN: Japan; KOR: South Korea; MX: Mexico; PR: Puerto Rico; RS: Serbia; RUS: Russia; SA: South Africa; SK: Slovakia; USA: United States of America; UK: United Kingdom. **Endpoints:** WL: weight loss; Li: Lifestyle intervention; SBP: systolic blood pressure; DBP: diastolic blood pressure; BW: body weight; ^{E} Efficacy Estimand.

Table 4: **Summary of composition and metabolic outcome of the SURMOUNT (B) trials.**

without T2D.[75] In individuals with overweight/obesity and T2D, servodutide decreased body weight with superiority over semaglutide 1 mg QW (−8.7% vs −5.3%) and with a decrease of HbA1c of up to −1.71% and −1.47%, respectively after 16 weeks of treatment.[74] Similar to GLP-1RAs, gastrointestinal side effects remained the most frequently reported, with the appearance of severe adverse effects being comparable to semaglutide.[74] Efinopegdutide is a GLP-1R:GCGR co-agonist jointly developed by Merck and Hanmi Pharmaceuticals, and which showed in Phase 2a superiority over semaglutide 1 mg QW to reduce liver fat in individuals with obesity after 24 weeks of treatment (−72.7% vs −42.3%), although with largely similar ability to decrease body weight (−8,5% vs −7.1%)[82] (Table 5).

Retatrutide is a GIPR:GLP-1R:GCGR triagonist that demonstrated superiority to tirzepatide in body weight loss and glucose control within obese rodents.[83] In a Phase 1 clinical trial, retatrutide exhibited comparable safety relative to dulaglutide, with treatment-emergent adverse events being primarily gastrointestinal and occurring in 63%, 60%, and 54% of subjects treated with retatrutide, dulaglutide, and placebo, respectively.[84] In Phase 2, retatrutide decreased placebo-corrected body weight by 22.1% after 48 weeks of treatment in patients with overweight/obesity without T2D, with 26% of patients achieving over 30% weight loss, at the highest tested dosage of 12 mg QW.[11] Retatrutide notably increased heart rate by +7 bpm at week 24, and by +5.7 bpm at week 48,[11] which is slightly greater relative to semaglutide which increased heart rate in the range of +1 to +4 bpm in the SUSTAIN and STEP trials (Tables 1 and 2). Weight loss associated with the use of retatrutide was paralleled by remarkable reductions in hepatosteatosis, with as much as 86% of the subjects suffering from established MASH exhibiting normalized levels of hepatic fat content after 48 weeks of treatment.[85] In individuals living with overweight/obesity and T2D, retatrutide further lowered HbA1c with superiority over treatment with dulaglutide, with reductions of −2.02% vs −1.41% after 24 weeks of treatment, and with a dose-dependent decrease in body weight of up to −16.9% relative to −3.0% and −2.02% in patients receiving placebo or dulaglutide, respectively.[12]

Agent	Company	Development stage	Indication	ClinicalTrials.gov ID
GLP1/glucagon dual agonists				
BI 456906 (Survodutide)	Boehringer Ingelheim	Phase III	Obesity, T2D	NCT06066515, NCT06066528
LY3305677 (Mazdutide)	Eli Lilly	Phase II/III	Obesity, MASH	NCT06124807, NCT04944992 NCT05607680, NCT05606913
Efinopegdutide (MK-6024)	Hanmi Pharmaceutical	Phase II	Obesity, MASH	NCT06482112
GIP/GLP1 dual agonists				
AMG 133 (maridebart cafraglutide)	Amgen	Phase II	Obesity, T2D	NCT05669599
VK2735	Viking Therapeutics	Phase I	Obesity, MASH	NCT05203237
GIP/GLP1/glucagon tri-agonists				
HM15275 (LA-GLP/GIP/GCG)	Hanmi Pharmaceutical	Phase I	Obesity, T2D	NCT06481098
HM15211 (LAPSTriple Agonist)	Hanmi Pharmaceutical	Phase II	Obesity, MASH	NCT04505436, NCT03374241
LY3437943 (Retatrutide)	Eli Lilly	Phase III	Obesity T2D	NCT04881760
GIPR agonists				
LY3532226	Eli Lilly	Phase I	T1D	NCT05887999
GLP1R agonists				
Efpeglenatide (LAPSExd4 Analog)	Hanmi Pharmaceutical	Terminated	T2D	NCT03496298
HM11260C	Hanmi Pharmaceutical	Phase III	Obesity, T2D	NCT06174779
Danuglipron (PF-06882961)	Pfizer	Phase II	Obesity, T2D	NCT04707313
LY3502970 (Orforglipron)	Eli Lilly	Phase III	Obesity, T2D	NCT06109311, NCT05872620
PF-07081532	Pfizer	Terminated	Obesity, T2D	NCT05579977
GLP2 agonist				
HM15912	Zealand Pharma	Phase II	Obesity	NCT04775706
GLP1R/GLP2R dual agonist				
Dapiglutide	Zealand Pharma	Phase II	Obesity	NCT05788601
ZP7570	Zealand Pharma	Phase I	Obesity	NCT06000891
Glucagon analogues				
Efpegerglucagon	Hanmi Pharmaceutical	Phase II	Obesity	NCT04732416
Amylin analogues				
CagriSema (Cagrilintide + Semaglutide)	Novo Nordisk	Phase III	Obesity, T2D	NCT06388187, NCT06403761
Amycretin	Novo Nordisk	Phase I	Obesity	NCT06049329
ZP8396 (Petrelintide)	Zealand Pharma	Phase I	Obesity	NCT05613387
LY3841136 (Eloralintide)	Eli Lilly	Phase II	Obesity	NCT06230523

Table 5: **Summary of selected incretin-based drugs in clinical development for the treatment of T2D, obesity and MASH.**

Collectively, these data encourage its further development in Phase 3 trials (Table 5).

AMG133 (maridebart cafraglutide, maritide), a monoclonal anti-GIPR antagonist coupled to two GLP-1R agonists, is in Phase 2 clinical development for the treatment of T2D and obesity. The molecule demonstrates superiority to the individual targeting of each receptor for greater yield on body weight loss and glucose handling improvements in obese mice and non-human primates relative to dulaglutide.[86] The molecule passed Phase 1 with good tolerability, and once-monthly treatment over three months yielded more than 10% weight loss in healthy human subjects[13] (Table 5).

Another new promising AOM is the co-therapy of GLP-1RAs with amylin, a pancreas-derived hormone that increases satiety and slows gastric emptying. In a recent Phase 2 trial in subjects with overweight/obesity and T2D, the co-therapy of semaglutide 2.4 mg and the amylin analog cagrilintide (CagriSema) decreased body weight by ∽16%, with superiority over semaglutide (–5%) and cagrilintide (–8%) alone after 32 weeks of treatment.[14] Weight loss induced by the cagrisema co-therapy was paralleled by a reduction in HbA1c of –2.2%, relative to –1.8% and –0.9% after treatment with semaglutide and cagrilintide, respectively.[14] The molecule was well tolerated with a safety profile comparable to other GLP-1RAs or tirzepatide,[14] which has encouraged further development in Phase 3 trials for the treatment of obesity (NCT05567796) (Table 5).

Treatment failures associated with the use GLP-1RAs and polyagonists

While average weight loss associated with the use of best-in-class GLP-1RAs or polyagonists is well beyond 10–15% in most individuals, a certain number of subjects achieve only weight loss <5%. In the STEP trials, weight loss <5% was after treatment with semaglutide 2.4 mg QW observed in ∽12% of individuals with overweight/obesity without T2D and in ∽21% of individuals with T2D.[8,38–41,87–89] In SURMOUNT/SURPASS, weight loss <5% was after treatment with tirzepatide 15 mg QW observed in ∽6% of individuals with overweight/obesity without T2D and in ∽18% of individuals with T2D.[10,12,58–62,66–68] Weight loss >5% is hence achieved in a greater number of individuals after treatment with tirzepatide 15 mg QW relative to semaglutide 2.4 mg QW, and in a greater number of individuals without T2D relative to subjects with T2D. Impressively, in individuals living with overweight/obesity and at least one weight-related condition, the GIPR:GLP-1R:GCGR triagonist retatrutide decreased body weight >5%, >10%, >20% and >30% in 100%, 93%, 63% and 26% of individuals, respectively at the highest tested dose of 12 mg QW.[11] While it warrants clarification why a certain number of individuals respond rather poorly to the treatment with GLP-1R agonists, these data impressively underline that polypharmacological approaches are capable to overcome the limited weight loss that is observed in certain patient cohorts by GLP-1RA alone.

The therapeutic implication of incretin-based therapeutics expands beyond managing T2D and obesity

MASH

Appreciably, the therapeutic value of incretin-based therapeutics expands well beyond the management of T2D and obesity. In a recent phase 2 study in individuals with biopsy-confirmed MASH and moderate or severe fibrosis, resolution of MASH without worsening of fibrosis was observed in up to 62% of individuals treated with tirzepatide, relative to 10% of subjects receiving placebo. Further, up to 51% of people treated with tirzepatide exhibited improvement of at least one fibrosis stage, relative to 30% of subjects receiving placebo.[90] The GLP-1R:GCGR co-agonist servodutide (Boehringer Ingelheim and Zealand Pharma) showed a placebo-corrected decrease in liver fat of up to −53% in individuals, while improvement of fibrosis of at least one stage was observed in up to 36% of individuals treated with servodutide relative to 22% in placebo controls in a recent Phase 2 study in individuals with biopsy-confirmed MASH and fibrosis stage 1–3 after 46 weeks of treatment.[76] Similar improvements in MASH are reported using semaglutide, which after 72 weeks of treatment at a dose of 0.4 mg QW resulted in resolution of MASH in 59% of individuals relative to 17% receiving placebo.[91] Although not reaching significance over placebo, improvement of at least one fibrosis stage was observed in 43% and 33% of individuals, respectively.[91]

CVD and CKD

The clinical safety of GLP-1RAs has been studied in cardiovascular outcome trials for lixisenatide (ELIXA),[92] liraglutide (LEADER),[93,94] dulaglutide (REWIND),[95] semaglutide 1 mg (SUSTAIN-6),[96] extended-release exenatide (EXSCEL),[97] albiglutide (HARMONY),[98] oral semaglutide (PIONEER-6),[99] and more recently semaglutide 2.4 mg (SELECT-CVOT).[100] After follow-up for 2–4 years, the respective studies show either an unchanged[92,97] or a reduced risk[93–95,98–100] for a major adverse CV event (MACE) in patients living with T2D and a high CV risk. In the LEADER trial, liraglutide 1.8 mg QW reduced overall mortality and the risk for non-fatal myocardial infarction, non-fatal stroke, and hospitalization for heart failure,[93,94] and although with minor variations, similar effects were observed in the REWIND,[95] HARMONY,[98] SUSTAIN-6[96] and SELECT-CVOT[100] trials. An increase in heart rate of 1–3 bpm, and a moderate reduction in blood pressure, was observed after treatment with albiglutide,[98] lixisenatide,[92] dulaglutide,[95] exenatide ER[97] liraglutide,[96] and semaglutide,[96,99,100] and this was also confirmed in a meta-analysis comprising 4 weight-loss trials using Saxenda.[101] In the STEP-HFpEF and STEP-HFpEF DM trials, which comprised individuals with T2D and obesity-related heart failure with preserved ejection fraction, semaglutide 2.4 mg reduced heart failure-related symptoms and physical limitations relative to placebo after 52 weeks of treatment, as assessed by treatment-induced changes in the Kansas City Cardiomyopathy Questionnaire clinical summary score (KCCQ-CSS).[102–104]

In a recent analysis of the SELECT trial, treatment with semaglutide 2.4 mg further led to a 22% reduction in the main 5-component kidney composite endpoint, which comprised death from CKD, initiation of chronic kidney replacement therapy, onset of persistent estimated glomerular filtration rate (eGFR) < 15 mlmin^{-1} 1.73 m^{-2}, persistent ≥50% reduction in eGFR, or onset of persistent macroalbuminuria.[105] These data align with the FLOW trial, in which semaglutide 1 mg QW let after 48 weeks of treatment to a 24% reduced the risk of the primary outcome, defined as a composite of kidney failure, ≥50% reduction in the estimated glomerular filtration rate, kidney death or CV death.[106] Collectively, available cardiovascular and renal outcome trials support the safety and tolerability of GLP-1RAs in individuals living with obesity and T2D, and in subjects at risk for CVD and CKD. If and to what extent GIPR agonism contributes to these effects, warrants clarification. Although the CV outcome trials for tirzepatide are still ongoing,[107] a decreased hazard ratio for composite MACE-3, MACE-4 and all-cause death has been reported in a meta-analysis comprising seven studies of the SURPASS trials.[108] Further, a long-acting GIPRA was recently shown to decrease LDL cholesterol in male but not female DIO mice, an effect further accelerated by treatment with the GIPR:GLP-1R co-agonist MAR709.[109] Treatment of ApoE deficient mice with GIP(1–42) prevents development of atherosclerotic lesions[110] and attenuates cardiac hypertrophy and cardiac fibrosis induced by Angiotensin II.[111] Ventricular injury following myocardial infarction is nonetheless reduced in GIPR deficient mice, and this coincides with enhanced survival and increased myocardial triglyceride stores.[112] The CV effects of GIP hence seem to depend on the pathological condition, with GIPR agonism improving atherosclerosis under conditions of obesity, while GIPR antagonism has beneficial effects in the ischemic heart.

Alzheimer's, Parkinson's, and substance abuse

Both incretins further exhibited anti-apoptotic, anti-inflammatory, neurotrophic, and neuroprotective properties in preclinical models of neurodegenerative diseases,[49] suggesting that GLP-1RAs and GIPR:GLP-1R co-agonists may hold promising for also treatment of neurodegenerative diseases such as Alzheimer's and Parkinson's Disease. Within this context, the loss of GLP-1R in rodents has been shown to amplify the consequences of neurodegenerative and neuroinflammatory events in rodents.[113] Post-hoc analysis of a phase 2 clinical trial assessing the efficacy of exenatide (2 mg) in Parkinson's Disease has found some capacity to improve outcome measures evaluating motor severity, nonmotor symptoms, cognition, and quality of life.[114] Further, a sequential trial emulation with Swedish national registers has suggested GLP-1RAs to be associated with a lower risk of dementia relative to other anti-glycemic non-GLP-1RA treatments.[115] However, exercising caution is required in interpreting the protective effects of GLP-1R agonists against Parkinson's Disease, dementia, and Alzheimer's Disease, as beneficial effects of GLP-1RAs on neurodegenerative diseases are not confirmed in all preclinical studies,[116] and clinical trials assessing these as primary endpoints are currently ongoing (NCT02953665, NCT01469351, NCT03659682).

Other broad, mechanistically undefined phenomenons of GLP-1RA treatment is the reduction or discontinuation of potentially addictive hedonistic activities. In an Initial real-world social media-based study examining self-reported cravings and bouts of alcohol intake, both semaglutide and tirzepatide have been softly suggested to reduce alcohol consumption.[117] Further, preliminary evidence indicates potential of GLP-1RA in treating cannabis use disorder,[118] and nicotine use disorder.[119] However, conflicting evidence on the efficacy of GLP-1RA on non-appetitive hedonistic behaviors indicates the strong need for controlled clinical trials to accurately assess and provide conclusions on their benefit.

Effects on lean body mass

Weight loss, irrespective of whether it was achieved by diet, pharmacology or bariatric surgery, is mediated by a loss in both fat mass and fat free mass (FFM).[34,120] Although large variations exist across different studies,[34,120] loss of FFM has been reported to account for as much as ∽35–45% of total body mass loss after treatment with semaglutide in the STEP-1 and SUSTAIN-8 trials,[7,89,121] and ∽26% after treatment with tirzepatide in SURMOUNT-1.[10] These observations have raised the question whether the observed decline is disproportionate and may lead to physical impairment and sarcopenia. Such concerns are not trivial since many patients in need for weight loss intervention are elderly, and muscle size and strength declines by 10–15% every decade after the age of 50 years.[122] Nonetheless, it is important to note that a loss of FFM (often referred to as lean mass) is not equivalent to muscle mass. Depending on the used methodology, FFM is typically comprised of large mass quantities of muscle, organ, bone and body fluids, and even ∽15% of fat mass is made up of fat-free mass.[120,123,124] As a rule of thumb, weight loss follows roughly a ¼ equation, meaning that FFM accounts for at least a quarter of the lost body mass.[120,123,124] And while the loss of FFM induced by treatment with semaglutide or tirzepatide in STEP-1, SUSTAIN-8 and SURMOUNT-1 were reported to make up for as much as 26–45% of the total weight that was lost, the changes in skeletal muscle mass was not assessed in these studies. Furthermore, a linear regression analysis comparing changes in lean and total body mass due to diet, pharmacology (semaglutide and tirzepatide), and bariatric surgery reveals that these changes largely all fall on the same regression line. This indicates that the degree of FFM loss that is achieved by AOMs is not disproportional and is expected based on the observed degree of total body weight loss.[120] In elderly subjects with obesity and T2D, semaglutide did further not decrease skeletal muscle mass after 26 weeks of treatment,[125] and the use of GLP-1RAs is not associated with an increased risk of fracture in people living with T2D.[126] Similarly, GIP is well-known for its ability to preserve or even enhance bone mass and formation.[50] Collectively, current data do not support that AOMs induce sarcopenia or physical impairment.[34,120,127] Moreover, weight regain after discontinuation of a weight loss intervention is not found to negatively affect body composition and does not favor the disproportionate gain of fat over lean body mass.[128]

Conclusion and open questions

Incretin-based polypharmacology is transforming the treatment landscape, effectively addressing not only

Search strategy and selection criteria

References for this Review were identified through searches of PubMed with the search terms "Diabetes", "obesity", "GLP-1", "GIP", "anti-obesity medication", "co-agonist", "MASH"and "dementia" from 1995 until August 2024. Articles were also identified through searches of the authors' own files. Only papers published in English were reviewed. The final reference list was generated on the basis of originality and relevance to the broad scope of this Review.

diabetes and obesity, but also extending its benefits to related conditions like MASH, CV, CKD, and neurodegeneration. Strategic pharmacological approaches to successfully treating or co-treating these morbidities are expected to continue evolving, with further approvals by the FDA and EMA likely in the future. With these seemingly profound improvement in pharmacology efficacy, a question arises: Have we finally succeeded in tackling the obesity epidemic? Future considerations of what these unparalleled pharmacological efficacies mean, and the potential next steps, are discussed in a separate forward-thinking Viewpoint article[129] in this issue.

Contributors

The manuscript was written by TDM with help of GG, AN and XL. The Figures and Tables were made by GG, AN and XL. All authors have read and approved the final document.

Declaration of interests

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