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REVIEW ARTICLE

The role of incretin receptor agonists in the treatment of obesity

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Abstract

Introdroduction: Obesity and its associated metabolic conditions have become a significant global health problem in recent years, with many people living with obesity fulfilling criteria for pharmacological treatment. The development of the glucagon-like peptide-1 receptor agonists for chronic weight management has triggered new interest in the incretins and other hormones as targets for obesity, and investigations into dual and triple co-agonists.

Methods: The objective of this narrative review was to summarize the available data on approved and emerging incretin-based agents for the treatment of obesity.

Results: In clinical trials of currently available agents in people with overweight or obesity, weight loss of between 6% and 21% of baseline body weight has been observed, with between 23% and 94% of participants achieving 10% or higher weight loss, depending on the study and the agent used. Favourable outcomes have also been seen with regard to cardiovascular risk and outcomes, diabetes prevention, metabolic dysfunction-associated steatotic liver disease/steatohepatitis and prevention of weight regain after metabolic surgery. Limitations associated with these agents include high costs, the potential for weight regain once treatment is stopped, the potential loss of lean body mass and gastrointestinal adverse events; potential issues with respect to gallbladder and biliary diseases require further investigation.

Conclusions: Many dual and triple co-agonists are still in development, and more data are needed to assess the efficacy, safety and tolerability of these emerging therapies versus the established incretin-based therapies; however, data are promising, and further results are eagerly awaited.

KEYWORDS
dual co-agonists, incretins, obesity, semaglutide, tirzepatide

1 | BACKGROUND

Excess adiposity is becoming the most common worldwide health condition. The number of people living with overweight (body mass index [BMI] of 25 to < 30 kg/m^2 in Western populations,[1] 23 to < 25 kg/m^2 in Asian populations[2,3]) may increase to 4 billion or higher by 2035, affecting more than 50% of the global population.[4] The prevalence of obesity (BMI ≥ 30 kg/m^2 in Western populations[1] and ≥ 25 kg/m^2 in Asian populations[5,6]) is expected to affect ~2 billion people by 2035.[4] Younger individuals are not spared: in 2022, more than 390 million children and adolescents aged 5-19 years globally were overweight or obese,[1] and the prevalence of overweight and obesity in this age group is also expected to increase substantially over time.[4]

Obesity is associated with multiple metabolic complications, including insulin resistance, diabetes, dyslipidaemia, hypertension, metabolic dysfunction-associated steatotic liver disease (MASLD; previously non-alcoholic fatty liver disease [or NAFLD])/metabolic dysfunction-associated steatohepatitis (MASH; previously non-alcoholic steatohepatitis [NASH]), cardiovascular complications and heart failure.[7–13] Management of patients with obesity relies on lifestyle interventions, pharmacological therapy and bariatric/metabolic surgery.[14–17]

Pharmacological therapy included orlistat, phentermine/topiramate (United States only), naltrexone/bupropion and the glucagon-like peptide-1 (GLP-1) receptor agonist liraglutide at a dose of 3 mg once-daily (QD),[15,17] until 2021, when the GLP-1 receptor agonist semaglutide at a dose of 2.4 mg once-weekly (QW) was approved, initially by the US Food and Drug Administration (FDA)[18] and then by the European Medicines Agency (EMA),[19] for chronic weight management in adults with a BMI of 30 kg/m^2 or higher or 27 kg/m^2 or higher with co-morbidities. Both semaglutide 1.0 mg QW and liraglutide 1.2 mg QD were approved previously for glycaemic control of type 2 diabetes (T2D).[20,21] More recently, the dual GLP-1-GIP (glucose-dependent insulinotropic polypeptide) receptor agonist, tirzepatide, first approved for T2D in 2022,[22] has been approved for treatment of obesity by the FDA, the EMA and the UK regulatory agency.[23–25] The approval of high-dose semaglutide and tirzepatide for obesity has renewed interest in the potential of incretin-based medications for obesity management. The objective of this narrative review is to summarize the available data on approved and emerging incretin-based agents for the treatment of obesity. For each of the currently approved agents, papers reporting data from the main clinical trials were sourced, and other information was obtained using targeted topic-specific keywords in PubMed as well as via the authors, who recommended supporting references according to their areas of expertise.

2 | THE ROLE OF INCRETINS AND OTHER HORMONES IN OBESITY

The incretins, GLP-1 and GIP, are peptide hormones secreted by enteroendocrine cells in the intestine following food intake.[26] They bind to receptors on pancreatic beta cells and potentiate insulin secretion in a glucose-dependent manner,[26] accounting for 60% or more of total secreted insulin in response to food ingestion.[27] GLP-1 and GIP receptors are present on many other tissues where they can exert several biological actions relevant to obesity, including enhanced satiety, regulation of gastric emptying (GLP-1), lowering of adipose tissue inflammation (GIP) and increasing postprandial lipid clearance via stimulation of lipoprotein lipase activity (GIP) (Table 1).[26,28]

Mechanistic studies in animals have shown that GLP-1 receptor agonists reduce food intake, increase fatty acid oxidation and induce weight loss after being transported into the brain.[29] In addition to directly entering the brain, gut-derived GLP-1 can activate intestinal vagal afferents, leading to activation of GLP-1–producing neurons that project into several areas of the brain responsible for regulation of food ingestion.[30] Brain-derived GLP-1 synthesized in neurons can also project into GLP-1 receptor-expressing brain regions, including the hindbrain and hypothalamus.[31] Glycaemic changes can modulate entry of GLP-1 receptor agonists into the brain,[32] although obesity and/or high fat feeding can blunt such an effect.[32]

GIP is also present in the brain, and brain-derived GIP has been shown to regulate body weight and food intake, an effect mediated by GIP receptor signalling in inhibitory GABAergic neurons.[33,34] GIP analogues have been shown to augment weight loss, reduce food intake and prevent fat mass accumulation when co-administered with GLP-1 receptor agonists.[35] GIP receptor agonism has been shown to attenuate GLP-1 receptor agonist-related nausea and vomiting.[36] These features of GIP provide a rationale for dual GLP-1/GIP receptor agonism.

Glucagon is a pancreatic peptide hormone whose receptors are mostly expressed in the liver where it exerts a hyperglycaemic effect by increasing glycogenolysis and gluconeogenesis (Table 1).[35] Glucagon also regulates amino acid metabolism, stimulates beta oxidation of fatty acids and increases energy expenditure.[35,37] Under discussion remains its ability to generate a satiety signal and reduce food intake,[35] as suggested by studies in animals.[38] Increased glucagon secretion has been observed in obesity, T2D and MASH.[35] Glucagon has a peptide sequence related to that of GLP-1 and GIP, making it possible to create agonists for more than one receptor, such as GLP-1/GIP, GLP-1/glucagon or GLP-1/GIP/glucagon.[35]

In addition to GLP-1 and GIP, and glucagon, other potential therapeutic targets in obesity include the peptide hormones oxyntomodulin, amylin, secretin, peptide tyrosine tyrosine (PYY), neuropeptide Y (NPY) and fibroblast growth factor (FGF) 21 (Table 1).[35,39,40] Oxyntomodulin is a dual agonist of the GLP-1 and glucagon receptors that is secreted from the gut in response to food intake.[40] Amylin is co-secreted with insulin, and acts to suppress appetite, decrease glucagon secretion and delay gastric emptying.[39,41] The addition of calcitonin to amylin in dual amylin/calcitonin agonists results in enhanced potency at the amylin receptor versus amylin analogues alone.[39] Secretin inhibits gastric emptying and food intake.[39] FGF21-based therapies have been shown to lower circulating triglyceride levels and improve MASH-related fibrosis,[42] and animal studies have suggested roles in energy expenditure and regulation of food intake.[39] PYY and NPY have roles in gastric emptying and appetite, respectively.[43,44]

TABLE 1 The main biological actions of incretins and other hormones in obesity[26,28,35,39–44,149].

	Pancreas	CNS	GI tract	Liver	Subcutaneous adipose tissue
GLP-1	• Insulin ↑ • Postprandial glucagon ↓	• Satiety ↑ • Nausea/ vomiting ↑ • Body weight ↓	• Gastric emptying ↓		
GIP	• Insulin ↑ • Glucagon ↑ (in case of low glucose)	• Satiety ↑ • Anti-emetic / nausea ↓ • Body weight ↓			• Blood flow ↑ • Insulin sensitivity ↑ • Lipid storage capacity ↑ • Triglyceride storage capacity ↑ • Adipo-inflammation ↓
Glucagon				• Glycogenolysis ↑ • Gluconeogenesis ↑ • Beta oxidation of fatty acids ↑ • Regulates amino acid metabolism	• Energy expenditure ↑
Oxyntomodulin			• Secreted in response to food intake • Dual agonist of GLP-1 and glucagon receptors		
Amylin	• Glucagon secretion ↓	• Appetite ↓	• Gastric emptying ↓		
Secretin			• Gastric emptying ↓ • Food intake ↓		
FGF21			• Food intake[a]	• MASH fibrosis ↓	• Triglyceride levels ↓ • Energy expenditure[a]
PYY			• Gastric emptying		
NPY			• Appetite		

Abbreviations: CNS, central nervous system; FGF, fibroblast growth factor; GI, gastrointestinal; GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide-1; MASH, metabolic dysfunction-associated steatohepatitis; NPY, neuropeptide Y; PYY, peptide YY.
[a]Animal studies only.[39]

3 | INCRETIN-BASED TREATMENTS FOR OBESITY

3.1 | GLP-1 receptor agonists

3.1.1 | Liraglutide

The impact of liraglutide on weight loss and metabolic characteristics in people living with obesity has been investigated in several clinical trials. In most trials, the dose used was higher than that approved in T2D (3.0 vs. 1.8 mg/d). In one study, adults with obesity had significantly decreased body weight after 56 weeks of liraglutide 3.0-mg treatment (−8.4 kg, −8.0% vs. baseline) compared with placebo (Table 2).[45] Liraglutide also improved glycaemic control and decreased the prevalence of prediabetes. Similar results were seen in studies of adults with overweight/obesity and prediabetes, with liraglutide 3.0- or 1.8-mg recipients losing significantly more weight than placebo recipients (Table 2), along with significant improvements in glycaemic control, systolic blood pressure,[46,47] triglycerides[46] and high sensitivity C-reactive protein.[47] Over a 3-year treatment period, liraglutide 3.0 mg delayed the onset of diabetes,[47] and 52 weeks of liraglutide 1.8-mg treatment was associated with improvements in glucose tolerance, fasting plasma glucose (FPG), HbA1c and body weight, and a significant reduction in the prevalence of prediabetes in women with prior gestational diabetes.[48] In adolescents with obesity with or without T2D, body weight reduction was superior with liraglutide 3.0 mg versus placebo (Table 2), although this was not associated with differences in glycaemic and cardiometabolic parameters.[49] Weight loss (Table 2), as well as improvements in glycaemic control and a decreased need for glucose-lowering therapies, has been documented in overweight/obese subjects with T2D treated with liraglutide 3.0 or 1.8 mg.[50,51]

Liraglutide 3.0-mg treatment has been shown to maintain and even promote additional weight loss when started after low-calorie-diet–induced weight loss.[52,53] Liraglutide can also be effective for

TABLE 2 Weight-related outcomes from the clinical trials of liraglutide.

Study (study length)	Study design	Population	Treatment (*n*)	Weight-related endpoints
Without T2D				
SCALE obesity and prediabetes (56 wk)[45]	Phase 3, randomized, double-blind, placebo-controlled, international	Patients with a BMI of ≥ 30 or ≥ 27 kg/m^2 with dyslipidaemia or hypertension	LIRA 3.0 mg (2487) PL (1244)	LIRA vs. PL Change in BW: −8.4 vs. −2.8 kg (P < .001) ≥ 5% loss of BW: 63.2% vs. 27.1% (P < .001) ≥ 10% loss of BW: 33.1% vs. 10.6% (P < .001)
SCALE Obesity and Prediabetes (160 wk)[47]	Phase 3, randomized, double-blind, placebo-controlled, international extension	Patients with a BMI of ≥ 30 or ≥ 27 kg/m^2 with dyslipidaemia or hypertension with prediabetes at screening (HbA1c 5.7%-6·4% and/or FPG 5.6-6.9 mmol/L and/or 2-h postchallenge plasma glucose 7.8-11.0 mmol/L)	LIRA 3.0 (1505) PL (749)	LIRA vs. PL Change in BW: −6.1 vs. −1.9 kg (P < .0001) ≥ 5% loss of BW: 49.6% vs. 23.7% (P < .0001) ≥ 10% loss of BW: 24.8% vs. 9.9% (P < .0001)
Kim et al. 2013 (14 wk)[46]	Phase 3, randomized, double-blind, placebo-controlled, United States only	Patients with a BMI of 27-40 kg/m^2 with prediabetes (FPG 5.6-6.9 mmol/L or 2-h glucose 7.8-11.0 mmol/L after a 75-g oral glucose challenge)	LIRA 1.8 mg (24) PL (27)	LIRA vs. PL Change in BW: −6.8 vs. −3.3 kg (P < .001) ≥ 5% loss of BW: 88% vs. 22% (P < .001) ≥ 10% loss of BW: 17% vs. 0% (P < .04)
With T2D				
SCALE Diabetes (56 wk)[50]	Phase 3, randomized, double-blind, placebo-controlled, international	Patients with a BMI of ≥ 27 kg/m^2 with T2D (HbA1c 7%-10%) treated with diet ±1-3 oral glucose-lowering agents and a	LIRA 3.0 mg (423) LIRA 1.8 mg (211) PL (212)	LIRA 3.0 and 1.8 vs. PL Change in BW: −6.0% and − 4.7% vs. −2.0% (P < .001, all LIRA vs. PL) ≥ 5% loss of BW: 54.3% and 40.4% vs. 21.4% (P < .001, all LIRA vs. PL) > 10% loss of BW: 25.2% and 15.9% vs. 6.7% (P < .01, all LIRA vs. PL)
SCALE Insulin (56 wk)[51]	Phase 3, randomized, double-blind, placebo-controlled, international	Patients with a BMI of ≥ 27 kg/m^2 with T2D (HbA1c 6%-10%) treated with basal insulin and ≤ 2 oral glucose-lowering agents	LIRA 3.0 mg plus intensive behavioural therapy (198) PL plus intensive behavioural therapy (198)	LIRA vs. PL Change in BW: −5.8% vs. −1.5% (P < .0001) ≥ 5% loss of BW: 51.8% vs. 24.0% (P < .0001) > 10% loss of BW: 22.8% vs. 6.6% (P < .0001)
With or without T2D				
Kelly et al. 2020 (56 wk)[49]	Phase 3, randomized, double-blind, placebo-controlled, international	Adolescents aged 12-17 y with a BMI ≥ 30 kg/m^2 or within the 95th or higher percentile for age and sex, and a poor response to lifestyle therapy alone	LIRA 3.0 mg (125) PL (126)	LIRA vs. PL Change in BW: −2.3 vs. 2.3 kg ≥ 5% reduction in BMI: 43.3% vs. 18.7% ≥ 10% reduction in BMI: 26.1% vs. 8.1%

Abbreviations: BMI, body mass index; BW, body weight; FPG, fasting plasma glucose; LIRA, liraglutide; PL, placebo; SCALE, Satiety and Clinical Adiposity — Liraglutide Evidence in non-diabetic and diabetic individuals; T2D, type 2 diabetes.

lowering body weight after metabolic/bariatric surgery, as shown in the BARI-OPTIMIZE (3.0 mg)[54] and GRAVITAS (1.8 mg)[55] studies.

In overweight patients with MASH, 48 weeks of treatment with liraglutide 1.8 mg resulted in a greater proportion of patients having resolution of definite MASH than placebo (39% vs. 9%; $P = .019$) and fewer patients having progression of fibrosis (9% vs. 36%; $P = .03$).[56]

In people with T2D, liraglutide 1.8 mg has been proven to reduce the risk of death from cardiovascular causes, non-fatal myocardial infarction or non-fatal stroke (13.0% vs. 14.9%; $P < .001$ for non-inferiority, $P = .01$ for superiority).[57] No cardiovascular outcomes trials have been performed in non-diabetic obese subjects, but a post hoc analysis of the Satiety and Clinical Adiposity—Liraglutide Evidence in non-diabetic and diabetic individuals (SCALE) trials found that liraglutide 3.0 mg was not associated with excess cardiovascular risk in patients with overweight/obesity without T2D.[58]

3.1.2 | Subcutaneous semaglutide

The effect of subcutaneous semaglutide on weight, metabolic and other outcomes has been extensively investigated in the Semaglutide Treatment Effect in People with obesity (STEP) programme. Again, in most studies, higher doses of subcutaneous semaglutide compared with the doses approved for use in T2D were studied (2.4 vs. 1.0 mg QW). Adults with overweight/obesity without T2D were included in STEP 1, STEP 3 and STEP 8. In STEP 1 and STEP 3, subcutaneous semaglutide 2.4 mg plus lifestyle interventions or intensive behavioural therapy, respectively, resulted in significantly greater weight loss than placebo over 68 weeks (Table 3).[59,60] In STEP 8, subcutaneous semaglutide 2.4-mg treatment was associated with significantly greater weight loss than liraglutide over 68 weeks (Table 3), and significantly greater odds of achieving 10% or higher, 15% or higher, or 20% or higher weight loss.[61] In STEP TEENS, adolescents aged 12-17 years with overweight or obesity were enrolled and received subcutaneous semaglutide 2.4 mg or placebo for 68 weeks, as well as lifestyle intervention.[62] Results were similar to those seen with adults, with semaglutide treatment inducing greater body weight reductions (Table 3) and improvement in cardiometabolic risk factors versus placebo.

STEP 2 investigated subcutaneous semaglutide 2.4 or 1.0 mg versus placebo in adults with T2D and obesity; the weight loss achieved with semaglutide 2.4 mg was superior to that achieved with placebo (estimated treatment difference [ETD] for semaglutide 2.4 mg vs. placebo: −6.2 percentage points, 95% confidence interval [CI] −7.3 to −5.2; $P < .0001$) (Table 3).[63] Superior and clinically meaningful weight loss with subcutaneous semaglutide 2.4 mg versus placebo was also found in adult Asian patients with or without T2D enrolled in STEP 6 (ETD for semaglutide 2.4 mg vs. placebo: −11.1 percentage points [95% CI −12.9 to −9.2]; $P < .0001$) (Table 3).[64] The loss of body weight was associated with reduction in abdominal visceral fat (semaglutide 2.4 mg vs. placebo: 40% vs. 6.9%; ETD −33.2% [95% CI −42.1 to −24.2]).[64]

In patients experiencing weight regain or insufficient weight loss following metabolic surgery, subcutaneous semaglutide has been shown to induce weight loss.[65–67] In one study, 6 months of subcutaneous semaglutide 1.0 mg resulted in a body weight loss corresponding to 67.4% of the postsurgery weight regain,[65] and in another, subcutaneous semaglutide (titrated from 0.25 to 1.0 mg QW according to tolerability) resulted in sustained weight loss over 12 months postsurgery.[66] The weight loss seen with subcutaneous semaglutide 1.0 mg in a group of patients with postsurgery weight gain was superior to that seen with liraglutide.[67]

Data on subcutaneous semaglutide for the treatment of MASH show modest results,[28,68,69] with some studies showing MASH resolution with no worsening of fibrosis, but no difference between groups in terms of improvement during the fibrosis stage,[69] and others showing no statistically significant improvement of fibrosis or achievement of MASH resolution.[68]

Analyses of data from STEP 1 and STEP 4 showed that, in general, there were greater improvements in blood pressure, lipids and FPG with subcutaneous semaglutide 2.4 mg versus placebo, and patients receiving semaglutide had a net reduction in use of antihypertensive and lipid-lowering medications versus placebo.[70] Data from patients with prediabetes in STEP 1, STEP 3 and STEP 4 showed that, compared with placebo, subcutaneous semaglutide 2.4-mg treatment was associated with a higher likelihood of normoglycaemia, and significant improvements in HbA1c, FPG and insulin resistance.[71] Of note, the STEP 1 extension study and STEP 1 and STEP 4 analyses of the impact of subcutaneous semaglutide 2.4 mg on cardiometabolic risk factors showed a loss of cardiometabolic treatment benefits after semaglutide discontinuation.[70,72]

In the SELECT trial, a total of 17 604 patients with overweight or obesity and established cardiovascular disease were randomized to subcutaneous semaglutide 2.4 mg QW or placebo. Over a mean follow-up of 39.8 months, a 20% relative risk reduction versus placebo (hazard ratio, 0.80; 95% CI 0.72 to 0.90; $P < .001$) in the primary cardiovascular endpoint (a composite of death from cardiovascular causes, non-fatal myocardial infarction or non-fatal stroke) occurred in the semaglutide group.[73]

Adult patients with obesity and heart failure with preserved ejection fraction (HFpEF) were enrolled into STEP HFpEF.[74,75] A prespecified analysis of the STEP HFpEF trial by obesity class and degree of body weight reduction found that subcutaneous semaglutide improved outcomes across obesity classes, with the magnitude of benefit directly related to the degree of weight loss.[74]

3.1.3 | Oral GLP-1 receptor agonists

Oral semaglutide is a co-formulation of semaglutide and the permeation enhancer sodium N-(8-[2-hydroxybenzoyl]amino)caprylate (SNAC).[76] SNAC increases gastric pH to protect semaglutide from enzymatic degradation, promotes monomerization of semaglutide and fluidizes the lipid membrane of the gastric epithelium, all of which enhances the absorption of semaglutide.[76] Oral semaglutide has been

TABLE 3 Weight-related outcomes from the clinical trials of semaglutide.

Study (study length)	Study design	Population	Treatment (*n*)	Weight-related endpoints
Without T2D				
STEP 1 (68 wk)[60]	Phase 3, randomized, double-blind, placebo-controlled, international	Patients with ≥ 1 self-reported unsuccessful diet attempt and a BMI of ≥ 30 kg/m^2 or ≥ 27 kg/m^2 with ≥ 1 weight-related co-morbidity	SEMA 2.4 mg (1306) PL (655)	SEMA vs. PL Change in BW: −14.9% vs. −2.4% (P < .001) ≥ 5% loss of BW: 86.4% vs. 31.5% (P < .001) ≥ 10% loss of BW: 69.1% vs. 12.0% (P < .001)
STEP 3 (68 wk)[59]	Phase 3a, randomized, double-blind, placebo controlled, United States only	Patients with ≥ 1 self-reported unsuccessful diet and a BMI of ≥ 30 kg/m^2 or ≥ 27 kg/m^2 with ≥ 1 weight-related co-morbidity	SEMA 2.4 mg (407) PL (204)	SEMA vs. PL Change in BW: −16.0% vs. −5.7% (P < .001) ≥ 5% loss of BW: 86.6% vs. 47.6% (P < .001) ≥ 10% loss of BW: 75.3% vs. 27.0% (P < .001)
STEP 4 (48 wk after a 20-wk SEMA lead-in period)[150]	Phase 3, randomized, double-blind, placebo-controlled, international	Patients with ≥ 1 self-reported unsuccessful diet attempt and a BMI of ≥ 30 kg/m^2 or ≥ 27 kg/m^2 with ≥ 1 weight-related co-morbidity	SEMA 2.4 mg (535) PL (268)	68 wk of SEMA vs. 20 wk of SEMA and 48 wk of PL (weeks 0-68) Change in BW: −17.4% vs. −5.0% (weeks 20-68: −7.9% vs. 6.9%; P < .001) ≥ 5% loss of BW: 88.7% vs. 47.6% ≥ 10% loss of BW: 79.0% vs. 20.4%
STEP 5 (104 wk)[151]	Phase 3, randomized, double-blind, placebo-controlled, international	Patients with ≥ 1 self-reported unsuccessful diet attempt and a BMI of ≥ 30 kg/m^2 or ≥ 27 kg/m^2 with ≥ 1 weight-related co-morbidity	SEMA 2.4 mg (152) PL (152)	SEMA vs. PL Change in BW: −15.2% vs. −2.6% (P < .0001) ≥ 5% loss of BW: 77.1% vs. 34.4% (P < .0001) ≥ 10% loss of BW: 61.8% vs. 13.3% (P < .0001)
STEP 8 (68 wk)[61]	Phase 3, randomized, open-label, active- and placebo-controlled, United States only	Patients with ≥ 1 self-reported unsuccessful diet attempt and a BMI of ≥ 30 kg/m^2 or ≥ 27 kg/m^2 with ≥ 1 weight-related co-morbidity	SEMA 2.4 mg (126) LIRA 3.0 mg (127) PL (85)	SEMA vs. LIRA Change in BW: −15.8% vs. −6.4% (P < .001) ≥ 5% loss of BW: 87.2% vs. 58.1% ≥ 10% loss of BW: 70.9% vs. 25.6% (P < .001)
With T2D				
STEP 2 (68 wk)[63]	Phase 3, randomized, double-blind, double-dummy placebo-controlled, international	Patients with a BMI of ≥ 27 kg/m^2 with T2D (HbA1c 7%-10%)	SEMA 2.4 mg (404) SEMA 1.0 mg (403) PL (403)	SEMA 2.4 and 1.0 vs. PL Change in BW: −9.6% and − 7.0% vs. −3.4% (P < .0001 SEMA 2.4 vs. SEMA 1.0 and PL) ≥ 5% loss of BW: 68.8% and 57.1% vs. 28.5% (P < .0001, SEMA 2.4 vs. PL) ≥ 10% loss of BW: 45.6% and 28.7% vs. 8.2% (P < .0001, SEMA 2.4 vs. PL)

TABLE 3 (Continued)

Study (study length)	Study design	Population	Treatment (*n*)	Weight-related endpoints
With or without T2D				
STEP 6 (68 wk)[64]	Phase 3a, randomized, double-blind, double-dummy, placebo-controlled, Japan and South Korea only	Patients with a BMI of ≥ 27 kg/m^2 with ≥ 2 weight-related co-morbidities or ≥ 35 kg/m^2 with ≥ 1 weight-related co-morbidities (at least one being hypertension, dyslipidaemia or T2D [Japan only]) and ≥ 1 self-reported unsuccessful diet attempt	SEMA 2.4 mg (199) SEMA 1.7 mg (101) PL (101)	SEMA 2.4 and 1.7 vs. PL Change in BW: −13.2% and 9.6% vs. −2.1% (*P* < .0001, all SEMA vs. PL) ≥ 5% loss of BW: 83% and 72% vs. 21% (*P* < .0001, all SEMA vs. PL) ≥ 10% loss of BW: 61% and 42% vs. 5% (*P* < .0001, all SEMA vs. PL)
STEP TEENS (68 wk)[62]	Phase 3a, randomized, double-blind, placebo-controlled, international	Adolescents aged 12-17 y with a BMI within the 95th or higher percentile for age and sex, or in the 85th percentile or higher with ≥ 1 weight-related co-morbidity, ≥ 1 self-reported unsuccessful diet attempt	SEMA 2.4 mg (134) PL (67)	SEMA vs. PL Change in BW: −15.3 vs. 2.4 kg ≥ 5% loss of BW: 73% vs. 18% ≥ 10% loss of BW: 62% vs. 8%

Abbreviations: BMI, body mass index; BW, body weight; LIRA, liraglutide; PL, placebo; SEMA, semaglutide; STEP, Semaglutide Treatment Effect in People with obesity; T2D, type 2 diabetes.

investigated in people living with T2D in the PIONEER studies (reviewed by Singh and colleagues[77]). Compared with placebo, oral semaglutide recipients had significantly greater improvements in HbA1c and body weight, and weight loss with oral semaglutide was greater than with dulaglutide and liraglutide in the active-controlled PIONEER studies.[77] In the OASIS 1 study, 68 weeks of oral semaglutide 50 mg QD in adults with overweight or obesity led to a mean body weight change from baseline of −15.1% versus −2.4% for placebo (*P* < .0001), and significantly more participants losing 5% or more of baseline body weight (85% vs. 26%; *P* < .0001); these weight changes with oral semaglutide were superior and clinically meaningful versus placebo.[78]

Orforglipron is an oral, once-daily non-peptide GLP-1 receptor agonist in phase 2 clinical development for obesity and type 2 diabetes.[79,80] In contrast to oral semaglutide, which has complex administration requirements with respect to food, water and other medications, and limited bioavailability (0.4%-1.0%),[81] orforglipron has no food or water restrictions and a bioavailability of 20%-40%.[80] In patients with obesity or overweight without diabetes, 26 weeks of orforglipron treatment at doses of 12, 24, 36 or 45 mg resulted in a mean weight change from baseline of −8.6% to −12.6% versus −2.0% with placebo; after 36 weeks, the mean weight change was −9.4% to −14.7% with orforglipron versus −2.3% with placebo.[79] At week 36, a body weight reduction of 10% or higher was seen in 46%-75% of orforglipron recipients compared with 9% of placebo recipients.[79] In patients with T2D, 26 weeks of orforglipron (3, 12, 24, 36 or 45 mg) resulted in a mean weight loss of up to −10.1 versus −2.2 and −3.9 kg in the placebo and dulaglutide groups, respectively.[80] In addition, orforglipron treatment resulted in improvement on HbA1c in patients with T2D (mean change in HbA1c at week 26: up to −2.1% vs. −0.4% and −1.1% for placebo and dulaglutide, respectively),[80] and improvements in cardiometabolic risk in obese/overweight individuals without T2D.[79] The phase 3 ATTAIN-1 study (NCT05869903), which is investigating orforglipron in adults with overweight or obesity, is currently ongoing.

With initial results now obtained with orforglipron, more non-peptide GLP-1 receptor agonists are expected to enter clinical development.[82]

3.2 | Dual co-agonists

3.2.1 | GIP/GLP-1 receptor agonists

The efficacy and safety of tirzepatide is being assessed in the SURMOUNT programme, which was designed to specifically investigate tirzepatide at the same doses as those approved for T2D (up to 15 mg QW) in people with overweight/obesity (Table 4). In SURMOUNT-1, 72 weeks of tirzepatide treatment (5, 10 or 15 mg) provided substantial and significantly greater weight reduction than placebo in patients with overweight/obesity without T2D (up to 21% vs. 3% for placebo; *P* < .001), with more than 90% and more than 80% of tirzepatide 15-mg recipients achieving greater than 5% and greater than 10% weight loss from baseline, respectively.[83] In SURMOUNT-3, adults with obesity/overweight who achieved a 5.0% or higher weight reduction after a 12-week intensive lifestyle intervention received tirzepatide 10 or 15 mg, or placebo for 72 weeks.[84] After 72 weeks of treatment, tirzepatide recipients had additional weight loss that was substantially greater than that seen with placebo, and a greater proportion of participants losing 5.0% or higher, or 10.0% or higher body

TABLE 4 Weight-related outcomes from the clinical trials of tirzepatide in patients with overweight/obesity.

Study (study length)	Study design	Population	Treatment (n)	Weight-related endpoints
Without T2D				
SURMOUNT-1 (72 wk)[83]	Phase 3, randomized, double-blind, placebo-controlled, international	Patients with ≥ 1 self-reported unsuccessful diet attempt and a BMI of ≥ 30 or ≥ 27 kg/m^2 with ≥ 1 weight-related co-morbidity	TIRZ 15 mg (630)	TIRZ 15, 10, 5 vs. PL Change in BW:
			TIRZ 10 mg (636)	−20.9%, −19.5%, −15.0% vs. −3.1% (P < .001)
			TIRZ 5 mg (630)	≥ 5% loss of BW: 90.9%, 88.9%, 85.1% vs. 34.5% (P < .001)
			PL (643)	≥ 10% loss of BW: 83.5%, 78.1%, 68.5% vs. 18.8% (P < .001)
SURMOUNT-3 (72 wk after a 12-wk intensive lifestyle lead-in period)[84]	Phase 3, randomized, double-blind, placebo-controlled, international	Patients with obesity or overweight with weight-related co-morbidities	TIRZ 10 or 15 mg (287)	Change in BW TIRZ: Additional −21.1% loss from randomization (P < .001 vs. PL)
			PL (292)	PL: A regain of 3.3% ≥ 5% loss of BW: TIRZ: 94.4% PL: 10.7% (P < .001) ≥ 10% loss of BW: TIRZ: 88.0% PL: 4.8% (P < .001)
SURMOUNT-4 (52 wk following a 36-wk TIRZ lead-in period)[85]	Phase 3, randomized, double-blind, placebo-controlled, international	Patients with obesity or overweight with weight-related co-morbidities	TIRZ 10 or 15 mg (335)	Change in BW TIRZ: Additional −6.7% loss from randomization
			PL (335)	PL: A regain of 14.8% (P < .001) ≥ 5% loss of BW: TIRZ: 98.5% PL: 69.0% (P < .001) ≥ 10% loss of BW: TIRZ: 94.0% PL: 44.4% (P < .001)
With T2D				
SURMOUNT-2 (72 wk)[86]	Phase 3, randomized, double-blind, placebo-controlled, international	Patients with T2D with HbA1c 7%-10% and BMI ≥ 27 kg/m^2, on diet and exercise alone or oral glucose-lowering therapy	TIRZ 15 mg (311)	TIRZ 15 and 10 vs. PL Change in BW:
			TIRZ 10 mg (312)	−14.7% and − 12.8% vs. −3.2% (P < .0001)
			PL (315)	≥ 5% loss of BW: 83% and 79% vs. 32% (P < .0001) ≥ 10% loss of BW: 65% and 61% vs. 9% (P < .0001)

Abbreviations: BMI, body mass index; BW, body weight; PL, placebo; T2D, type 2 diabetes; TIRZ, tirzepatide.

weight (Table 4). In SURMOUNT-4, participants were randomized to 52 weeks of tirzepatide or placebo after a 36-week, open-label tirzepatide lead-in period.[85] Similar to SURMOUNT-3, after 52 weeks, the tirzepatide group had substantially greater weight loss compared with the placebo group (Table 4).

The body weight-lowering efficacy of tirzepatide has been confirmed in SURMOUNT-2, which included people with obesity and T2D (Table 4).[86] After 72 weeks of treatment with tirzepatide 10 or 15 mg, change in body weight from baseline and the proportion of participants losing 5%, 10%, or more was significantly greater with

tirzepatide versus placebo. HbA1c levels were also significantly lower with tirzepatide than with placebo, and a greater proportion of participants receiving tirzepatide were able to decrease their glucose-lowering medications. An impact on progression to T2D has also been reported for tirzepatide, with a post hoc analysis of SURMOUNT-1 reporting a reduction of the 10-year predicted risk of T2D development in people receiving tirzepatide of up to 69% at week 72, with significantly greater risk reductions with tirzepatide versus placebo, irrespective of the baseline glycaemic status.[87]

Of note, the SURMOUNT studies also reported improvements in patient-reported outcomes, with participants reporting improvements in physical functioning with tirzepatide versus placebo,[83–86] as well as improvements in emotional and mental health scores.[85]

Underway is the SURMOUNT-MMO study (NCT05556512), which is investigating the impact of tirzepatide on the reduction of morbidity and mortality in adults with obesity with an established or increased risk of cardiovascular disease.

Table 5 summarizes the weight-related endpoints across the SURPASS clinical trial programme in individuals with T2D. Tirzepatide treatment resulted in significant body weight reduction versus placebo in patients with T2D naïve to injectable glucose-lowering therapy[88] and those inadequately controlled on insulin glargine.[89] In Japanese patients receiving tirzepatide as an add-on to oral glucose-lowering therapy, body weight reduction occurred regardless of the type of background oral therapy.[90] In the active-controlled SURPASS trials, tirzepatide was found to be superior to semaglutide 1.0 mg,[91] insulin degludec,[92] insulin glargine[93] and dulaglutide[94] for reduction in body weight.

Some real-world data are available for tirzepatide versus semaglutide, in a United States-based study utilizing electronic health records in individuals with or without T2D receiving tirzepatide or semaglutide as per the T2D labels ($n = 41\,223$ total; semaglutide 0.5 mg: 32 030; tirzepatide 5 mg: 9193). Those receiving tirzepatide had greater weight loss from baseline than semaglutide recipients at 3, 6 and 12 months, and were significantly more probable to achieve weight loss of 5%, 10% and 15% of baseline.[95]

Post hoc analyses of the SURPASS trials indicate that tirzepatide can decrease liver fat content and the volume of visceral adipose tissue and abdominal subcutaneous adipose tissue.[96] Preliminary results from patients with MASH enrolled in the phase 2 SYNERGY-NASH study show that a greater proportion of patients receiving tirzepatide than those receiving placebo achieved resolution of MASH without worsening of fibrosis after 52 weeks of treatment (74% vs. 13%).[97] In patients with T2D, higher doses of tirzepatide (10 or 15 mg) significantly decreased MASH-related biomarkers such as alanine and aspartate aminotransferase, keratin-18, procollagen III and adiponectin.[98]

Tirzepatide treatment has also been associated with lower blood pressure and improved lipid profile in SURMOUNT-1, −2 and −3,[83,84,86] and with proven cardiovascular safety, as indicated by results from SURPASS-4 in subjects with T2D and increased cardiovascular risk, and a recent meta-analysis.[93,99] A cardiovascular outcomes trial in patients with T2D and increased cardiovascular risk, SURPASS-CVOT (NCT04255433), is currently underway, investigating the effect of tirzepatide versus dulaglutide on major cardiovascular events.

Tirzepatide is probable to be followed soon by other dual GIP/GLP-1 receptor agonists such as NNC0090-2746.[100] In patients with T2D, NNC0090-2746 significantly improved glycaemic control and reduced body weight versus placebo.[100]

3.2.2 | Glucagon/GLP-1 receptor agonists

The rationale for the first dual glucagon/GLP-1 receptor agonist[101] originated from the observation that chronic infusion of a water-soluble glucagon improves body weight and glycaemic control in diet-induced obese mice.[102] Soon after, another GLP-1/glucagon co-agonist was developed based on the structure of oxyntomodulin,[103] a molecule with natural activity at both target receptors. In healthy volunteers, oxyntomodulin suppressed appetite and reduced food intake[104]; similarly, in a study of people with overweight/obesity, energy intake was decreased in those receiving oxyntomodulin, and there was corresponding weight loss and altered levels of adipose hormones consistent with adipose tissue loss.[105] Currently, the following dual glucagon/GLP-1 receptor agonists are under investigation.

Mazdutide (IBI362, LY3305677) is a long-acting analogue of oxyntomodulin that is currently in phase 2 development in China (Table 6).[106–108] In Chinese people with overweight or obesity, mazdutide was associated with greater weight loss and reductions in BMI than placebo.[106,107] In Chinese people with T2D, mazdutide was associated with clinically meaningful improvements in glycaemic variables (HbA1c, FPG, postprandial glucose, insulin resistance) and weight.[108,109]

Cotadutide (MEDI0382) is a glucagon analogue that has been modified to have dual glucagon and GLP-1 receptor activity[110] and was under development for MASH, T2D and obesity.[111,112] However, the manufacturer has terminated the clinical programme for once-daily cotadutide in favour of AZD9550, a once-weekly injectable GLP-1 receptor/glucagon agonist.[113]

Efinopegdutide (MK-6024, HM12525A, JNJ-64565111) is a synthetic oxyntomodulin conjugated to the constant region of human immunoglobulin G4[114] that has been investigated in obesity with and without T2D and MASLD. In patients with obesity, efinopegdutide treatment resulted in a significant dose-dependent reduction in body weight versus placebo, irrespective of diabetes status (Table 6).[115,116] Efinopegdutide treatment was also shown to result in a significant reduction of liver fat content versus semaglutide in patients with MASLD at 24 weeks (least-squares mean relative reduction from baseline: 72.7% vs. 42.3%; $P < .001$).[114]

Survodutide (BI 456906) is an acylated peptide containing a C18 fatty acid to extend its half-life that acts via increasing energy expenditure and reducing food intake.[117] In early-stage trials of healthy volunteers and individuals with overweight/obesity, BI 456096 decreased body weight by ~6%-14% after 16 weeks (placebo corrected).[118,119] Results from the phase 2 dose-finding study of

TABLE 5 Weight-related outcomes from the clinical trials of tirzepatide in patients with T2D.

Study (study length)	Study design	Population	Treatment (*n*)	Weight-related endpoints
SURPASS-1 (40 wk)[88]	Phase 3, randomized, double-blind, placebo-controlled, international	Patients with T2D inadequately controlled by diet and exercise and naïve to injectable therapies	TIRZ 15 mg (121)	TIRZ 15, 10, 5 vs. PL Change in BW:
			TIRZ 10 mg (121)	−9.5, −7.8, −7.0 vs. −0.7 kg (*P* < .0001, all TIRZ vs. PL)
			TIRZ 5 mg (121)	≥ 5% loss of BW: 77%, 78%, 67% vs. 14% (*P* < .0001, all TIRZ vs. PL)
			PL (115)	≥ 10% loss of BW: 47%, 40%, 31% vs. 1% (*P* < .0001, all TIRZ vs. PL)
SURPASS-2 (40 wk)[91]	Phase 3, randomized, open-label, active-controlled, international	Patients with T2D inadequately controlled by metformin ≥ 1500 mg/d, HbA1c 7%-10.5% and BMI ≥ 25 kg/m^2	TIRZ 15 mg (470)	TIRZ 15, 10, 5 vs. SEMA Change in BW:
			TIRZ 10 mg (469)	−11.2, −9.3, −7.6 vs. −5.7 kg (*P* < .001, all TIRZ vs. SEMA)
			TIRZ 5 mg (470)	≥ 5% loss of BW: 80%, 76%, 65% vs. 54%
			SEMA (469)	≥ 10% loss of BW: 57%, 47%, 34% vs. 24%
SURPASS-3 (52 wk)[92]	Phase 3, randomized, open-label, placebo-controlled, international	Patients with T2D with HbA1c 7%-10.5% and BMI ≥ 25 kg/m^2 who were insulin-naïve and treated with metformin ± an SGLT2 inhibitor	TIRZ 15 mg (359)	TIRZ 15, 10, 5 vs. INS DG Change in BW:
			TIRZ 10 mg (360)	−12.9, −10.7, −7.5 vs. 2.3 kg (*P* < .0001, all TIRZ vs. INS DG)
			TIRZ 5 mg (358)	≥ 5% loss of BW: 88%, 84%, 66% vs. 6% (*P* < .0001, all TIRZ vs. INS DG)
			INS DG (360)	≥ 10% loss of BW: 69%, 56%, 37% vs. 3% (*P* < .0001, all TIRZ vs. INS DG)
SURPASS-4 (52 wk)[93]	Phase 3, randomized, open-label, active-controlled, international	Patients with T2D treated with metformin, sulphonylurea, or SGLT2 inhibitor, HbA1c of 7.5%-10.5%, BMI ≥ 25 kg/m^2 and established CVD or a high risk of CV events	TIRZ 15 mg (338)	TIRZ 15, 10, 5 vs. INS GL Change in BW:
			TIRZ 10 mg (328)	−11.7, −9.5, −7.1 vs. 1.9 kg (*P* < .0001, all TIRZ vs. INS GL)
			TIRZ 5 mg (329)	≥ 5% loss of BW: 85%, 78%, 63% vs. 8% (*P* < .0001, all TIRZ vs. INS GL)
			INS GL (1000)	≥ 10% loss of BW: 66%, 53%, 36% vs. 2% (*P* < .0001, all TIRZ vs. INS GL)
SURPASS J-mono (52 wk)[94]	Phase 3, randomized, double-blind, active-controlled, Japan only	Patients with T2D who had discontinued oral glucose-lowering therapy or who were treatment-naïve, HbA1c of 7%-10%, BMI ≥ 2 kg/m^2	TIRZ 15 mg (160)	TIRZ 15, 10, 5 vs. DULA Change in BW:
			TIRZ 10 mg (158)	−10.7, −8.5, −5.8 vs. −0.5 kg (*P* < .0001, all TIRZ vs. DULA)
			TIRZ 5 mg (159)	≥ 5% loss of BW:
			DULA 0.75 mg (159)	89%, 82%, 61% vs. 11% ≥ 10% loss of BW: 67%, 50%, 34% vs. 3%
SURPASS J-combo (52 wk)[90]	Phase 3, randomized, open-label, Japan only	Patients with inadequately controlled T2D (HbA1c 7% to < 11%) receiving oral glucose-lowering therapy	TIRZ 15 mg (148)	TIRZ 15, 10, 5 Change in BW:
			TIRZ 10 mg (147)	−10.2, −7.5, −3.8 kg ≥ 5% loss of BW:
			TIRZ 5 mg (148)	84%, 71%, 44% ≥ 10% loss of BW: 64%, 48%, 20%

Abbreviations: BMI, body mass index; BW, body weight; CV, cardiovascular; CVD, cardiovascular disease; DULA, dulaglutide; INS DG, insulin degludec; INS GL, insulin glargine, PL, placebo; SEMA, semaglutide; SGLT2, sodium-glucose co-transporter-2; T2D, type 2 diabetes; TIRZ, tirzepatide.

TABLE 6 Weight-related outcomes from the clinical trials of other incretin agents in patients with overweight/obesity.

Study (study length)	Study design	Population	Treatment (*n*)	Weight-related endpoints
Mazdutide				
Without T2D				
Ji et al. 2021 (12 wk)[107]	Phase 1b, randomized, placebo-controlled, multiple ascending dose, China only	Patients with overweight (BMI ≥ 24 kg/m^2) and hyperphagia and/or ≥ 1 weight-related co-morbidity, or obesity (BMI ≥ 28 kg/m^2)	MAZ 6.0 mg (8) MAZ 4.5 mg (8) MAZ 3.0 mg (8) PL (12)	MAZ 6.0, 4.5, 3.0 vs. PL Change in BW: −5.1, −5.8, −3.8 vs. 0.4 kg (P < .0001)
Ji et al. 2022 (12-16 wk)[106]	Phase 1b, randomized, placebo-controlled, multiple ascending dose, China only	Patients with overweight (BMI ≥ 24 kg/m^2) and hyperphagia and/or ≥ 1 weight-related co-morbidity, or obesity (BMI ≥ 28 kg/m^2)	MAZ 10 mg (8) MAZ 9 mg (8) PL (8)	MAZ 10 vs. PL at week 16 Change in BW: −7.6 vs. −2.9 kg (P = .033) MAZ 9 vs. PL at week 12 Change in BW: −9.2 vs. −1.6 kg (P = .0003)
With T2D				
Jiang et al. 2022 (12 wk)[108]	Phase 1b, randomized, active- and placebo-controlled, multiple ascending dose, China only	Patients with T2D inadequately controlled with diet and exercise alone or with stable metformin therapy (HbA1c 7.5%-11.0%) and a BMI of 20-35 kg/m^2	MAZ 6.0 mg (8 MAZ 4.5 mg (8) MAZ 3.0 mg (8) DULA 1.5 mg (6) PL (12)	Change in BW: MAZ 6.0 mg: −5.4% (P < .01) MAZ 4.5 mg: −5.0% (P = .02) MAZ 3.0 mg: −0.9% DULA 1.5 mg: −0.9% PL: −1.1%
Zhang et al. 2024 (20 wk)[109]	Phase 2, randomized, double-blind placebo-controlled, China only	Patients with T2D inadequately controlled with diet and exercise alone or with stable metformin therapy (HbA1c 7.0%-10.5%) and a BMI of 20 to < 40 kg/m^2	MAZ 6.0 mg (49) MAZ 4.5 mg (49) MAZ 3.0 mg (51) DULA 1.5 mg (50) PL (51)	Change in BW: MAZ 6.0 mg: −7.1% (P < .0001 vs. PL and DULA) MAZ 4.5 mg: −5.3% (P < .0001 vs. PL P < .01 vs. DULA) MAZ 3.0 mg: −4.1% (P < .01 vs. PL) DULA 1.5 mg: −2.7% PL: −1.4%
Efinopegdutide				
Without T2D				
Alba et al. 2021 (26 wk)[115]	Phase 2 randomized, double-blind, open-label, active- and placebo-controlled, United States only	Patients with a BMI of 35-50 kg/m^2	EFIN 10.0 mg (118) EFIN 7.4 mg (118) EFIN 5.0 mg (59) LIRA 3.0 mg (119) PL (60)	EFIN 10.0, 7.4, 5.0 vs. LIRA and PL Change in BW: −11.8%, −9.8%, −8.5% vs. −7.5% and − 1.8% (P < .001 all EFIN and LIRA vs. PL) ≥ 5% loss of BW: 53.4%, 80.3%, 57.6% vs. 51.4% and 13.3% (P < .001 all EFIN and LIRA vs. PL) ≥ 10% loss of BW: 39.7%, 37.1%, 39.0% vs. 24.8% and 3.3% (P < .001 all EFIN and LIRA vs. PL)

(Continues)

TABLE 6 (Continued)

Study (study length)	Study design	Population	Treatment (*n*)	Weight-related endpoints
With T2D				
Di Prospero et al. 2021 (12 wk)[116]	Phase 2 randomized, double-blind, placebo-controlled, United States only	Patients with T2D (HbA1c 6.5%-9.5%), BMI of 35-50 kg/m^2	EFIN 10.0 mg (49)	EFIN 10.0, 7.4, 5.0 vs. PL
			EFIN 7.4 mg (49)	Change in BW: −7.9%, −6.5%, −5.3%, vs. −0.7% (P < .001 all EFIN vs. PL)
			EFIN 5.0 mg (48)	≥ 5% loss of BW: 62.5%, 41.7%, 42.6% vs. 2.0% (P < .001 all EFIN vs. PL)
			PL (49)	≥ 10% loss of BW: 20.8%, 12.5%, 4.3% vs. 0%

Abbreviations: BMI, body mass index; BW, body weight; DULA, dulaglutide; EFIN, efinopegdutide; LIRA, liraglutide; MAZ, mazdutide; PL, placebo; T2D, type 2 diabetes.

survodutide in people with overweight/obesity showed body weight loss ranging from −6.2% to −14.9% with survodutide versus −2.8% with placebo after 46 weeks of treatment.[120] Of note, in this study, more than 90% of patients receiving survodutide experienced adverse events, and 24.6% stopped treatment during the study compared with 75% and 3.9% of placebo recipients, respectively.[120] In people with MASH, preliminary data from a phase 2 trial showed a significantly greater proportion of participants receiving survodutide versus placebo had an improvement in MASH after 48 weeks (83.0% vs. 18.2%; P < .0001); liver fibrosis was also improved with survodutide versus placebo.[121]

SAR425899 is another glucagon/GLP-1 receptor agonist in early-stage trials. In a trial of individuals with overweight/obesity, participants were randomized to a calorie-reduced diet and either escalating doses of SAR425899 or placebo.[122] Weight loss was seen with SAR425899 and placebo (−4.83 and −3.68 kg, respectively; P < .05), but recipients of SAR425899 lost more fat mass and fat free mass compareed to placebo (P < .05). SAR425899 treatment led to a significantly smaller reduction than placebo in body composition-adjusted sleeping metabolic rate (P = .002) and greater increases in fat oxidation and ketogenesis (P < .05).

3.2.3 | Other dual hormone agonists under investigation

Currently, dual calcitonin/amylin, GLP-1/amylin, GLP-1/secretin, GLP-1/FGF21, GLP-1/PYY and GLP-1/NPY agonists are under investigation for use in obesity or T2D.[39,43,44] Of these, more data are available for the combination of cagrilintide, a long-acting amylin analogue that has shown clinically significant weight loss that was significantly greater than placebo in clinical trials of people with overweight or obesity,[123] and semaglutide. When co-administered, GLP-1 receptor/amylin agonism in individuals with T2D yielded a mean body weight change greater than the use of semaglutide 2.4 mg (P < .0001) or cagrilintide 2.4 mg (P < .0001) alone (cagrilintide/semaglutide: −15.6%; semaglutide: −5.1%; cagrilintide: −8·1%).[124] The REDEFINE clinical programme currently underway is investigating the use of cagrilintide/semaglutide in individuals with overweight or obesity (REDEFINE 1; NCT05567796), individuals with overweight or obesity and T2D (REDEFINE 2; NCT05394519) and individuals with established cardiovascular disease (REDEFINE 3; NCT05669755).

Animal studies of the dual calcitonin/amylin receptor agonist KBP-089 combined with liraglutide have shown a complementary action on body weight, food intake and glucose tolerance.[125,126]

3.3 | Triple co-agonists

3.3.1 | Glucagon/GIP/GLP-1 receptor agonists

Retatrutide (LY3437943) is a fatty acid acylated peptide with agonist activity for the glucagon, GIP and GLP-1 receptors.[127] In phase 2 trials, retatrutide treatment resulted in substantial body weight reductions, regardless of T2D status. The percentage body weight reduction was dose dependent in both trials (obesity without T2D: −8.7% to −24.2% for 1-12 mg doses vs. −2.1% for placebo; obesity with T2D: −3.2% to −16.9% for 0.5-12 mg doses vs. 3.0% and 2.0% for dulaglutide).[128,129] In people with obesity, treatment with retatrutide for 48 weeks resulted in substantial weight loss, with 100% of patients who received the 8 and 12 mg doses having weight loss of 5% or higher, and more than 90% of patients receiving these doses having a weight loss of 10% or higher.[128] In a substudy of this trial, the change in liver fat from baseline at week 24 ranged from −42.9% with retatrutide 1 mg to −82.4% with retatrutide 12 mg, versus +0.3% with placebo, and more than 85% of participants receiving the two highest retatrutide doses (8 and 12 mg) achieved resolution of steatosis (< 5% total liver fat content).[130] These liver fat reductions were significantly

related to reductions in body weight and abdominal adipose tissue and improvements in markers of insulin sensitivity and lipid metabolism.[130] Other evidence suggests that adding glucagon agonism may provide additional liver-related benefits that are independent of weight loss.[131]

SAR441255 is another glucagon/GIP/GLP-1 agonist that has been investigated in animal models and healthy subjects.[132] In a phase 1 study of lean to overweight healthy subjects, SAR441255 improved glycaemic control during a mixed meal tolerance test.[132]

Efocipegtrutide (HM15211) is a triple agonist being investigated in patients with MASH in a study currently in progress.[133]

3.3.2 | Other triple co-agonists under investigation

GLP-1/glucagon/leptin co-agonism is also a potentially promising option to explore, with GLP-1/glucagon administration able to restore the benefits of leptin on food intake, body weight and glycaemic control in a hypercaloric environment.[39]

4 | LIMITATIONS AND TOLERABILITY OF INCRETIN-BASED TREATMENTS FOR OBESITY

Incretin-based therapies come with some limitations, including high cost and potential loss of lean body mass.[134–136] The disadvantages of loss of muscle mass during weight loss are being recognized,[137] and work is underway on ways to preserve muscle mass while losing fat, with animal studies suggesting antibody blockade of activin type II receptors may preserve lean mass and increase fat loss during treatment with GLP-1 receptor agonists.[138] Although the percentage of patients achieving weight loss of 5% or more in clinical trials is substantial, particularly for semaglutide and tirzepatide (Tables 3–5), no clinical trial reports 100% of patients achieving this weight loss goal, suggesting that a subset of patients do not respond to treatment with these agents. There is also the issue of weight regain once treatment is stopped,[84,85] suggesting that lifelong treatment with these medications may be required for many people, which may lead to safety issues for some. Although generally well tolerated, the gastrointestinal adverse events associated with incretin-based therapies are well known.[139–141] For individuals undergoing endoscopy, the slowing of gastric motility in people treated with GLP-1 receptor agonists can result in gastric residue, retention of solids and an increased risk of aspiration while sedated during the procedure.[142]

Potential issues with self-harm, pancreatitis, malignancies and gallbladder and biliary diseases with incretin therapies have also been investigated. In a study of self-harm and depression in patients initiating incretin-based therapies for T2D, no increased risk of depression or self-harm was found, although patients with a prior history of depression, self-harm or serious psychiatric conditions were excluded.[143] Of note, the FDA is conducting an ongoing evaluation of reports of suicidal thoughts or actions in people receiving GLP-1 receptor agonists; currently the preliminary evaluation does not suggest a causal link, but as an increased risk cannot be definitively ruled out, the evaluation is continuing.[144]

In meta-analyses, no increased risk of malignancies was found,[145,146] and an increased risk of pancreatitis was associated with dipeptidyl peptidase-4 inhibitors, but not GLP-1 receptor agonists;[145] however, individuals with medullary thyroid cancers and pancreatitis were excluded from clinical trials. Other meta-analyses have found an increased risk of gallbladder or biliary diseases[147] and an increased risk of worsening diabetic retinopathy with GLP-1 receptor agonists.[148] The clinical trial of retatrutide reported cardiac arrythmia and parasthesia.[128] Long-term safety data for the newer incretin-based therapies for obesity are needed.

5 | SUMMARY AND FUTURE DIRECTIONS

Obesity and its associated complications are increasing in prevalence and have become a significant problem. While lifestyle modifications are generally the initial step, obesity is a chronic disease and most patients fulfil criteria for the use of pharmacotherapy; however, the recommended duration for and long-term effect of pharmacotherapy for obesity is currently unknown.

There are few drugs approved for obesity, but the recent approval of the GLP-1 receptor agonist semaglutide (high dose) and the dual GIP/GLP-1 agonist tirzepatide have put renewed focus on incretin-based therapies for the treatment of obesity. With the introduction of these incretin-based therapies, weight-lowering effects between 6% and 21% have been observed. The proportion of people achieving 10% or higher weight loss varies between 23% and 33% with liraglutide 3.0 mg, 46%-79% with semaglutide 2.4 mg and 61%-94% with tirzepatide 10 or 15 mg. Preliminary data for the triple co-agonists seem to surpass these effects, and approach effects seen with bariatric/metabolic surgery. In addition to the weight-lowering effects, beneficial effects on cardiovascular risk factors and outcomes have been seen, a significant advantage for agents used to treat obesity and T2D. Research is also broadening to include other patient populations, including adolescents, those experiencing weight regain following metabolic surgery, those with sleep apnoea and patients with MASLD/MASH, and to date favourable outcomes in these patients have been observed; in patients with MASLD/MASH, preliminary data suggest dual and triple co-agonism may lead to greater benefits than single agonism. Prevention of diabetes in those with prediabetes has also been reported. Therefore, these newer pharmacological agents can be considered in some people (e.g. in those with a high cardiovascular risk profile, or where anaesthesia and extubation might become problematic) as an alternative to bariatric surgery. In people with severe obesity, surgery is hampered by an enlarged liver, and incretin-based therapy could be a bridge to surgery in this scenario.

While the gastrointestinal effects associated with incretin therapies are well known and generally mild and tolerable, we recommend that therapy should be stopped in patients who develop intolerable

gastrointestinal side effects, and in people who develop pancreatitis, because people with a history of pancreatitis were excluded from participation in clinical trials. In addition, people with medullary thyroid carcinoma, multiple endocrine neoplasia type 2A or depression were also excluded from participation in clinical trials, and while the risk of malignancy or suicidal ideation/attempts appears low, uncertainty remains. Furthermore, no data in pregnancy are available.

Many of the dual and triple co-agonists are still in development, and further head-to-head data are needed to assess the efficacy of these emerging dual and triple agonists versus the established incretin therapies. Other current research gaps of interest include the prevention of excessive loss of lean mass in patients receiving these therapies, as well as the optimal maintenance regimen for patients who have reached their weight loss goal, including if the dose or dosing frequency can be reduced without the weight regain seen when treatment is fully withdrawn. Further data are needed in broader populations to those in clinical trials, including older people, for whom data are currently scarce. The cardiorenal benefits and effects on heart failure of incretin therapies requires further investigation, as does the use of these agents following the failure of bariatric surgery. However, despite these gaps, the available data to date are promising, and further results are eagerly awaited.

AUTHOR CONTRIBUTIONS

TF was involved in the conception of the manuscript, acquisition and interpretation of the data included in the manuscript and drafting and critical revision of the manuscript for important intellectual content. CDB was involved in the conception of the manuscript, interpretation of the data included in the manuscript and critical revision of the manuscript for important intellectual content. SDP was involved in analysis and interpretation of the data included in the manuscript and critical revision of the manuscript for important intellectual content. SA was involved in the conception and design of the manuscript, the acquisition, analysis and interpretation of the data included in the manuscript and drafting and critical revision of the manuscript for important intellectual content. JF was involved in the interpretation of the data included in the manuscript and critical revision of the manuscript for important intellectual content. AL was involved in the conception of the manuscript, the acquisition of the data included in the manuscript and critical revision of the manuscript for important intellectual content. BL was involved in the conception and design of the manuscript, the acquisition, analysis and interpretation of the data included in the manuscript and drafting and critical revision of the manuscript for important intellectual content. MM was involved in the conception of the manuscript and critical revision of the manuscript for important intellectual content. CM was involved in interpretation of the data included in the manuscript and critical revision of the manuscript for important intellectual content. TDM was involved in critical revision of the manuscript for important intellectual content. OS was involved in the conception and design of the manuscript, the interpretation of the data included in the manuscript and drafting the manuscript. All authors read and approved the final manuscript.

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CONFLICT OF INTEREST STATEMENT

TF is an employee of CRS Clinical Research Services GmbH, Germany, and has contributed to speaker panels for Amarin, AstraZeneca, Boehringer Ingelheim, Berlin Chemie, Cipla, Daiichi-Sankyo, Eli Lilly and Company, Fortbildungskolleg, MSD, Novartis, Novo Nordisk, Sanofi and Santis; and contributed to advisory panels for AstraZeneca, Atrogi, Bayer, Cipla, Diabetes Akademie Bad Mergentheim, Eli Lilly and Company, Eysense, Fortbildungskolleg, Novo Nordisk, Pfizer, Sanofi, Remynd and Roche. CDB has contributed to advisory board panels for AstraZeneca, Abbott Diagnostics, Boehringer-Ingelheim, Eli Lilly and Company, Indigo Diabetes, Insulet, Medtronic, Novo Nordisk and Sanofi. He is on the speaker panel for Abbott Diagnostics, Eli Lilly and Company, Insulet, Medtronic and Novo Nordisk. SDP consulted for Abbott, Amarin Corporation, Applied Therapeutics, AstraZeneca, Eli Lilly and Company, Eva Pharma, Menarini International, Novo Nordisk, Sanofi and Sun Pharmaceuticals, and received funding for these consulting services; received grant support from AstraZeneca and Boehringer Ingelheim; and received speaker fees from Abbott, AstraZeneca, Boehringer Ingelheim, Eli Lilly and Company, Laboratori Guidotti, Menarini International, MSD, Novartis Pharmaceuticals, Novo Nordisk and Sanofi. SA is an employee of CRS Clinical Research Services GmbH, Germany. JF reports research support from Akero, Altimmune, Boehringer Ingelheim, 89bio, Eli Lilly and Company, Janssen, Madrigal, Merck, Novartis, Novo Nordisk, Pfizer and Sanofi; advisory boards and consulting for Akero, Altimmune, Boehringer Ingelheim, Carmot Therapeutics, Echosens, 89bio, Eli Lilly and Company, Merck, Novo Nordisk, Pfizer and Sanofi; lectures and speaker bureau for Eli Lilly and Company, Novo Nordisk, Sanofi; and employee and stockholder: Biomea Fusion, Inc. BL received honoraria for advisory panels and lectures as well as study fees from AstraZeneca, Bayer, Boehringer Ingelheim, Eli Lilly and Company, Novo Nordisk and Sanofi. AL reports research support from AstraZeneca and received honoraria as a consultant and speaker from Novo Nordisk, Eli Lilly and Company, Boehringer Ingelheim and AstraZeneca. BL reports research support from Amgen, Astra Zeneca, Bayer, Boehringer Ingelheim, Eli Lilly and Company, Madrigal, MSD, Novo Nordisk and Sanofi, and received honoraria as a consultant and speaker from Amgen, Astra Zeneca, Boehringer Ingelheim, Eli Lilly and Novo Nordisk. MM is an employee of Clinical Research Services GmbH, Germany. CM serves or has served on the advisory panel for Novo Nordisk, Sanofi, Merck Sharp and Dohme Ltd, Eli Lilly and Company, Novartis, AstraZeneca, Boehringer Ingelheim, Roche, Medtronic, ActoBio Therapeutics, Pfizer, Imcyse, Insulet, Zealand Pharma, Avotres, Mannkind, Sandoz and

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DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no datasets were generated or analysed.

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