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REVIEW

The promise of glucagon-like peptide 1 receptor agonists (GLP-1RA) for the treatment of obesity: a look at phase 2 and 3 pipelines

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ABSTRACT

Introduction: GLP-1-based therapies have changed the treatment of overweight/obesity. Liraglutide 3.0 mg daily, the first GLP-1 RA approved for treatment of overweight, induced a weight loss of 6–8%, Semaglutide 2.4 mg once weekly improved weight loss to about 12–15%, while the dual GIP/GLP-1 receptor agonist tirzepatide once weekly has induced a weight loss of about 20% in obese people without diabetes.

Areas covered: This review describes results obtained with GLP-1 mono-agonists, GLP-1/GIP dual agonists, GLP-1/glucagon co-agonists, and the triple agonist retatrutide (GIP/GLP-1/glucagon), which have shown beneficial effect both on body weight and steatotic liver disease. A combination of semaglutide (a GLP-1 agonist) and cagrilintide (a long-acting amylin analogue) for weekly administration is currently in phase III development, and so is oral semaglutide and several non-peptide small molecule GLP-1 agonists for oral administration. The adverse events with the GLP-1-based therapies are primarily gastrointestinal and include nausea, vomiting, obstipation, or diarrhea, which often can be mitigated by slow up titration.

Expert opinion: The GLP-1-based therapies will change the treatment of obesity and its comorbidities including steatotic liver disease in the future. Outstanding question is maintenance of the weight loss, possibly pharmacological treatment needs to be life-long.

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1. Overview

Obesity is a chronic and relapsing disease, and the obesity rates have been increasing during the last decades [1,2]. Obesity is associated with an increased risk of the metabolic syndrome, type 2 diabetes, cardiovascular diseases, skeletal and muscle pains, liver diseases and cancer as well as psychiatric diseases [3]. Obesity is very difficult to threat. Lifestyle intervention may induce weight losses of about 5–10 kg, but most people will regain weight after 6–12 months follow-up, resulting in only small and unsatisfactory weight losses [4,5].

The body´s intrinsic system for regulation of appetite and energy expenditure promotes weight regain after a weight loss [6]. The intrinsic system is regulated by the brain, adipose tissue, and the gut-brain axis, and includes several hormones including glucagon-like peptide-1 (GLP-1) glucose-dependent insulinotropic polypeptide (GIP), cholecystokinin (CCK), peptide YY (PYY), and glucagon acting in concert with adipose tissue-derived hormones, leptin, and adiponectin as well as the liver-secreted fibroblast growth factor 21 [6,7]. The Gut hormones have pleiotropic metabolic effects as illustrated in Figure 1 [7].

Until recently, the weight loss with anti-obesity drugs (AOD) has been moderate, in the range of 3–8 kg, which is not sufficient for remission of most obesity associated comorbidities, and does not comply with the expectations about weight loss treatment among obese people [8,9].

1.1. GLP-1 physiology

The GLP-1 agonists were primarily developed for the treatment of people with type 2 diabetes [10,11]. GLP-1 RAs mimic the effects of native GLP-1, which increases insulin secretion, inhibits glucagon secretion, increases satiety, and slows gastric emptying [10,11]. The effect on gastric emptying is pronounced with the short acting GLP-1 agonists, since tachyphylaxis for this effect develops after few days' treatment with the long acting GLP-1 agonists [10,12]. GLP-1 agonists increase pulse rate and reduce postprandial triglyceride concentrations and blood pressure [13].

The mechanism by which GLP-1 exerts its anorectic effects involves both peripheral and brain GLP-1 receptors [14,15].

1.2. Areas covered in this review

The present narrative review focuses on GLP-1-based anti-obesity drugs (AOD). The phase 3 studies with liraglutide 3.0 mg once daily, semaglutide 2.4 mg once weekly and with Tirzepatide in people with and without type 2 diabetes will initially be reviewed to put the newer AOD in development into perspective. Emphasis will be on co-agonists of GLP-1RAs in combination with GIP, glucagon, amylin, and FGF-21; also, triple agonists will be discussed. We and others have previously in details discussed non-GLP-1-based AOD [9,16].

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Article highlights

- Understanding of the gut-brain axis on appetite regulation has stimulated to developing of new pharmacotherapies, which has completely changed the treatment of type 2 diabetes and obesity.
- A mean weight loss of about 16% –18% and 20% to 24% is possible with the GLP-1 agonist semaglutide 2.4 mg and the dual GLP-1/GIP agonist tirzepatide 10–15 mg, respectively, approaching the weight loss achieved with bariatric surgery.
- GLP-1 agonists like semaglutide protect against cardiovascular disease in people with obesity and against progression of kidney disease in people with type 2 diabetes.
- The effect on cardiovascular disease of the dual and triple agonists in phase 3 development is unknown but has demonstrated impressive results in people with fat liver disease.
- The obesity pharmacotherapies with different mechanisms of action will allow an individual treatment based on the comorbidities of the obese person. Long-term results in relation to safety is still missing, yet the longest placebo-controlled trial with a GLP-1 agonist is about 4 years .Limitations associated with GLP-1-based therapy include high cost, loss of lean body mass, gastrointestinal adverse events and weight regain after stop of therapy.

2. Search methodology

A systematic literature review was performed to identify all relevant published articles concerning treatment with a GLP-1 receptor agonist (GLP-1RA)-based therapy. We also search the reference lists of original articles, reviews, and meta-analysis focusing on treatment of obesity and type 2 diabetes. Specific search was performed on each GLP-1 RA-based therapy discussed in the present review. We reviewed the abstract programs for European Association of the Study of Diabetes (EASD) and American Diabetes Association (ADA) during the last 5 years for relevant presentations and press releases from relevant pharmaceutical companies for inspiration for search strategies. Focus was on randomized-controlled trials. Only publications written in English were included in the review.

3. Single GLP-1 RAs

3.1. Liraglutide

Liraglutide 3.0 mg once daily (OD) is approved for treatment of overweight and obesity. In the SCALE-1 Obesity and Prediabetes study with a duration of initially 56 weeks, 3731 subjects were included, 2285 of whom had prediabetes [17]. The prediabetes group was followed for 160 weeks to assess the ability of liraglutide to delay the onset of progression to type 2 diabetes. After 56 weeks, the weight loss was – 8% in the liraglutide group compared with – 2.6% in the placebo group, while 9.9% and 3.8% withdrew due to adverse events in the liraglutide and placebo groups. Liraglutide was associated with a reduced progression to prediabetes (7.2% vs. 20.7%) and increased reversal of prediabetes (69.2% vs. 32.7%) to normal glucose tolerance [17].

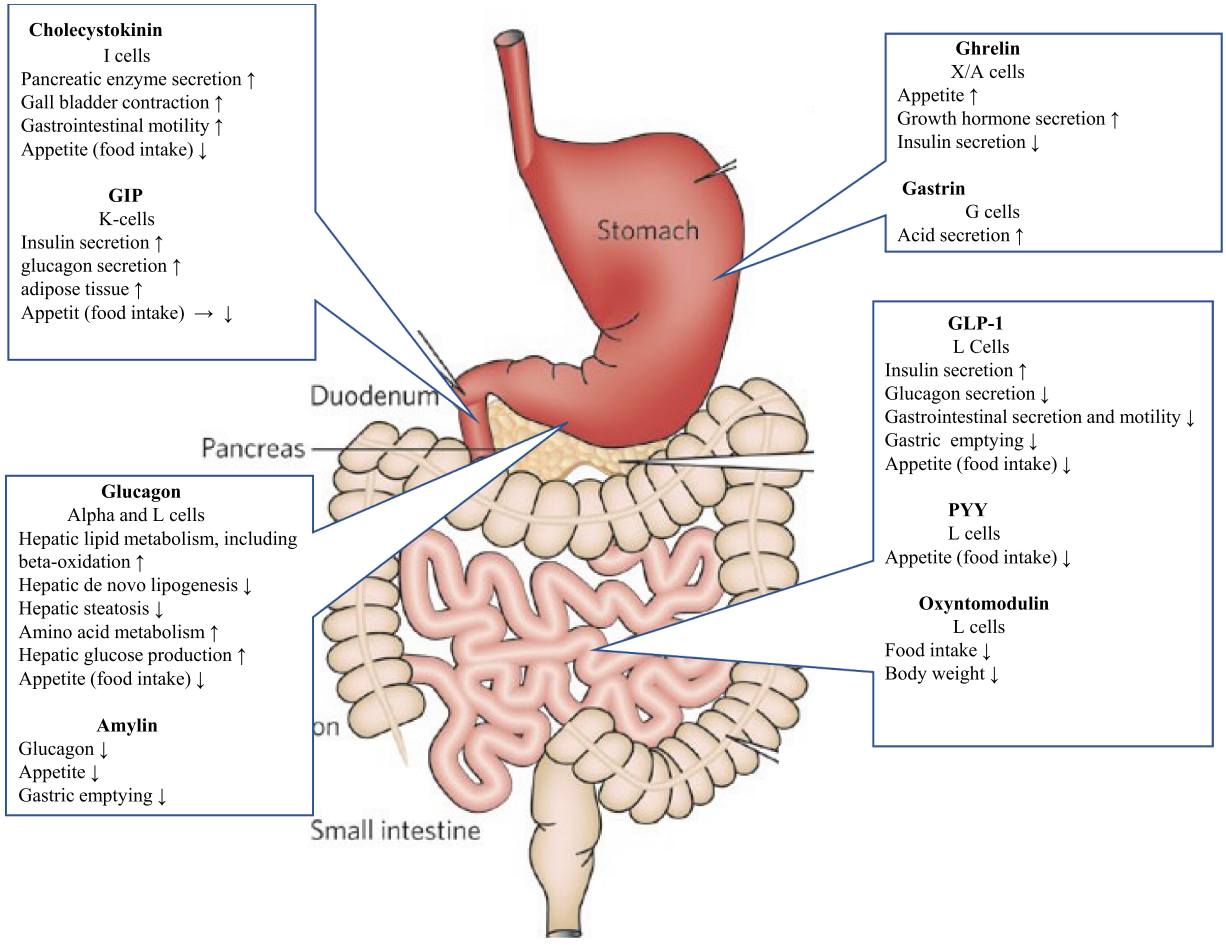

Figure 1. Secretion and main action of gut hormones used in anti-obesity drugs.

After 160 weeks, 2% in the liraglutide group compared with 6% in the placebo group were diagnosed with diabetes while on treatment. Weight loss was greater with liraglutide (−6.1% vs −1.9%) than with placebo. In a post-hoc analysis for individuals who lost > 5% body weight after 16 weeks of treatment the weight loss was − 12% after 1 year and − 8.6% at week 160. Thus, early responders achieved greater long-term weight loss than non-responders [18].

In the SCALE-Diabetes study, 846 patients with type 2 diabetes were randomized to liraglutide 3.0 mg, 1.8 mg or placebo and followed for 56 weeks [19]. The weight loss was − 6.4%, − 4.7% and − 2.0%. The reduction in HbA1c (baseline HbA1c 7.9% (63 mmol/mol)) was −1.3% (14.2 mmol/mol), −1.1% (12.0 mmol/mol) and −0.3% (3.3 mmol/mol), respectively.

In the SCALE Maintenance trial, overweight subjects were treated with a 1200–1400 kcal/day diet and entered the trial if they managed to lose > 5% in body weight after 12 weeks before randomization to liraglutide or placebo for 52 weeks [20]. The mean weight loss at randomization was − 6%. After 1 year, − 6.2% additional weight loss was obtained with liraglutide as opposed to placebo (−0.2%).

In a randomized study, liraglutide induced a significant reduction in obstructive sleep apnea compared with placebo after a weight loss of −5.7% vs −1.6% [21].

In adolescents with obesity the study comprised a 56-week treatment period and enrolled 251 participants age 12–18 years assigned 1:1 to liraglutide or placebo, in addition to life style therapy [22]. Mean age was 14.5 years and body weight about 100 kg corresponding to a BMI of 35.5 kg/m^2. The use of liraglutide led to a greater reduction in body weight with a treatment difference of − 5.1% after 52 weeks of treatment.

The results from the SCALE development program are summarized in Table 1.

In the SCALE studies, small reductions in LDL, VLDL, triglycerides, systolic and diastolic blood pressure were reported.

Liraglutide 1.8 mg or 3.0 mg can also lower body weight after insufficient weight loss after bariatric surgery [23,24].

In these studies, the adverse events to liraglutide 3.0 mg were primarily the usual gastrointestinal events associated with GLP-1 RA treatment including nausea, diarrhea, constipation and vomiting. Nausea peaked after 4 weeks of treatment and subsided thereafter. Gallbladder related complications including cholelithiasis and cholecystitis were more common in the liraglutide arms.

Liraglutide 3.0 mg has demonstrated superior weight loss compared with orlistat and less when compared with semaglutide 2.4 mg once weekly (OW) in STEP 8 trial as discussed below (Table 2).

3.1.1. Semaglutide 2.4 mg once weekly

Semaglutide was developed based on the experience with liraglutide, but for weekly administration and preserved effects on insulin secretion and food intake [25]. In the phase 3 program with 1 mg of semaglutide in people with type 2 diabetes, the mean weight loss was about − 5% to − 6% and reduction in HbA1c was about 1.6% (18 mmol/mol) [26]. In a later trial comparing semaglutide 1 mg versus 2 mg in people with type 2 diabetes, the weight loss were − 6.2% vs − 7.2% and the reduction in HbA1c were − 1.95% (21.3 mmol/mol) and − 2.1% (23 mmol/mol), respectively [27].

Semaglutide 2.4 mg OW was evaluated in the Semaglutide Treatment effect in People with obesity (STEP) studies in relation to treatment of obesity and in the STEP 2 also in the treatment of type 2 diabetes [28–32]. In 2021, semaglutide 2.4 mg weekly was approved for treatment of overweight/obesity based on the STEP 1–5 trials [28–32].

In total, 4988 overweight or obese people were included in the trials. Up-titration of semaglutide over a 16-week dose escalation period included 0.25, 05, 1.0, 1.7, and 2.4 mg each for 4 weeks. The treatment periods varied from 68 weeks (STEP 1–3), 48 week for STEP 4, and 104 weeks for STEP 5 (Table 2) [28–32].

In Steps 1–3 and 5, the weight loss was − 15% to −17% and − 9.6% in people with type 2 diabetes (STEP 2) (Table 2). In the studies, an improvement in CVD risk factors was reported.

In STEP 8, semaglutide 2.4 mg OW was compared with liraglutide 3.0 mg or placebo daily for 68 weeks [33]. The mean weight losses were −15.8%, −6.4% and −1.9%, respectively. The proportion of participants discontinuing treatment

Table 1. The SCALE phase 3 studies with liraglutide 3.0 mg OD. In the SCALE maintenance trial, overweight subjects were treated with a 1200–1400 kcal/day diet and entered the trial if they managed to lose > 5% in body weight after 12 weeks before randomization to liraglutide or placebo for 52 weeks. Numbers in parentheses referred to the number in reference list. Converting HbA1c in percentage to mmol/mol= % x 10.93 = mmol/mol.

Trial	Drug	N	Participants	Duration (wk)	Baseline weight (kg)	Comparator	Change in BW (%)	Change in HbA1c (%)
SCALE Obesity and prediabetes [17]	Liraglutide 3.0 mg SC OD	3731	BMI ≥30 or ≥27 kg/m^2 with comorbidity	56	106	Liraglutide 3 mg Placebo	−8.0 −2.6	N/A
SCALE Obesity and prediabetes [18]	Liraglutide 1.8 and 3.0 mg SC OD	2254	BMI ≥30 or ≥27 kg/m^2 with comorbidity	160	108	Liraglutide 3 mg Placebo	−6.1 −1.9	N/A
SCALE Diabetes [19]	Liraglutide 3.0 mg SC OD	846	T2D	56	106	Liragkutide 3.0 Liraglutide 1.8 Placebo	−6.4 −4.7 −2.0	−1.3 −1.1 −0.3
SCALE Maintenance [20]	Liraglutide 3.0 mg SC OD	422	BMI ≥30 or ≥27 kg/m ^{2}with comorbidity	12 + 56	99	Run-in weight loss Liraglutide 3 mg Placebo	−6.0 −6.2 −0.2	N/A
SCALE Sleep apnea [21]	Liraglutide 3.0 mg SC OD	359	BMI ≥30 kg/m^2 with sleep apnea	32	117	Liraglutide 3 mg Placebo	−5.7 −1.6	N/A
SCALE Adolescens [22]	Liraglutide 3.0 mg SC OD	251	Mean BMI 35.6 kg/m^2	56	100	Liraglutide 3 mg Placebo	−2.7 + 2.4	N/A

Abbreviations: T2D: type 2 diabetes, SC: subcutaneous, OD: once daily. BW: body weight, N/A: none applicable.

Table 2. Summarizes the phase 3 studies with semaglutide. Numbers in parentheses referred to the number in reference list. Converting HbA1c in percentage to mmol/mol= % x 10.93 = mmol/mol.

Trial	Drug	N	Participants	Duration (wk)	Baseline weight (kg)	Comparator	Change in BW (%)	Change in HbA1c (%)
STEP 1 [30]	Semaglutide 2.4 mg SC OW	1961	BMI ≥30 or ≥27 kg/m^2 with at least one comorbidity	68	105	Semaglutide 2.4 mg Placebo	−14.9 −2.4	N/A
STEP 2 [28]	Semaglutide 2.4 mg SC OW	1210	T2D	68	99	Semaglutide 2.4 mg Semaglutide 1.0 mg Placebo	− 9.6 − 7.0 − 3.4	−1.6 −1.5 −0.4
STEP 3 [29]	Semaglutide 2.4 mg SC OW	611	BMI ≥30 or ≥27 kg/m^2 with at least one comorbidity	68	105	Semaglutide 2.4 mg placebo	−16.0 −5.7	N/A
STEP 4 [31]	Semaglutide 2.4 mg SC OW	803	BMI ≥30 or ≥27 kg/m^2 with at least one comorbidity	20 + 48	107	20-week run-in 48-week follow-up (change from week 20): Semaglutide 2.4 mg Placebo	-10.6 - 7.9 + 6.9	N/A
STEP 5 [32]	Semaglutide 2.4 mg SC OW	304	BMI ≥30 or ≥27 kg/m^2 with at least one comorbidity	104	106	Semaglutide 2.4 mg Placebo	−15.2 −2.6	N/A
STEP 6 [36]	Semaglutide 2.4 mg SC OW Semaglutide 1.7 mg SC OW	401	East Asia BMI ≥27·0 kg/m^2 with two or more comorbidities or a BMI ≥35.0 kg/m^{2}with at least one comorbidity	68	87	Semaglutide 2.4 mg Semaglutide 1.7 mg Placebo	−13.2 −9.6 −2.1	N/A
STEP 7 [35]	Semaglutide 2.4 mg SC OW	375	Asia BMI ≥27 kg/m^2 with at least one comorbidity or BMI ≥30 kg/m^2	44	96	Semaglutide 2.4 mg Placebo	−12.1 −3.6	N/A
STEP 8 [33]	Semaglutide 2.4 mg SC OW Liraglutide 3.0 mg SC OD	338	US BMI ≥27 kg/m^2 with at least one comorbidity or BMI ≥30 kg/m^2	68	105	Semaglutide 2.4 mg Liraglutide 3.0 mg Placebo	−15.8 −6.4 −1.9	N/A
STEP 10 [37]	Semaglutide 2.4 mg SC OW	138	≥30 kg/m^2 Prediabetes	52	112	Semaglutide 2.4 mg Placebo	−13.9 −2.7	−0.4 +0.1
STEP TEENS [38]	Semaglutide 2.4 mg SC OW	201	Overweight Obesity	68	108	Semaglutide 2.4 mg Placeebo	−13.9 −2.7	N/A
STEP Up [39]	Semaglutide 7.2 mg Semaglutide 2.4 mg Placebo SC OW	1407	BMI ≥30 kg/m^2	72	113	Semaglutide 7.2 mg Semaglutide 2.4 mg Placebo	−18.7 −15.6 −3.9	N/A
SELECT [44]	Semaglutide2.4 mg SC OW	17604	BMI ≥27 kg/m^2 CVD	159	97	Semaglutide 2.4 mg Placebo	−9.4 −0.9	N/A
STEP-HFpEF [46]	Semaglutide 2.4 mg SC OW	529	BMI ≥30 kg/m^2 Heart failure	52	105	Semaglutide 2.4 mg placebo	−13.3 −2.6	N/A
STEP-HFpEF DM [49]	Semaglutide 2.4 mg SC OW	616	BMI ≥30 kg/m^2 Heart failure T2D	52	103	Semaglutide 2.4 mg placebo	−9.8 −3.4	N/A
FLOW Trial [51]	Semaglutide 2.4 mg SC OW	3533	T2D kidney disease	159	90	Semaglutide 2.4 mg placebo	−5.6 −1.5	−0.87 −0.06
NASH Trial [42]	Semaglutide0.1, 0.2, 04 mg SC OD	320	NAFLD with liver fibrosis	72	98	Semaglutide 0.1 mg Semaglutide 0.2 mg Semaglutide 0.4 mg Placebo	−5.0 −9.0 −13.0 −1.0	N/A
Knee Arthritis Trial [52]	Semaglutide 2.4 mg SC OW	407	Knee arthritis BMI ≥30 kg/m^2	68	108	Semaglutide 2.4 Placebo	−13.7 −3.2	N/A
OASIS 1 [54]	Oral Semaglutide 50 mg OD	667	BMI ≥30 kg/m^2 or ≥27 kg/m^2 with at least one comorbidity	68	105	Semaglutide 50 mg Placebo	−15.1 −2.4	N/A
PIONEER PLUS [55]	Oral Semaglutide 14, 25, 50 mg OD	1606	T2D BMI ≥25 kg/m2	52	96	Semaglutide 14 mg Semaglutide 25 mg Semaglutide 50 mg	−4.4 −6.7 −8.0	−1.5 −1.8 −2.0

Abbreviations: T2D: type 2 diabetes, SC: subcutaneous, OD: once daily, OW: once weekly, N/A not applicable, NAFLD: nonalcoholic fatty liver disease.

for any reason were 13.5% with semaglutide and 27.6% with liraglutide. Gastrointestinal adverse effects did not differ between semaglutide and liraglutide.

In STEP 1 trial, which resulted in a mean weight loss of − 14.9% semaglutide 2.4 OW and − 2.4% with placebo after 68 weeks, an extension period of 52 weeks without treatment was included. During this period, there was a weight gain of + 11.6% and + 1.9%, respectively, and a deterioration of CVD risk factors illustrating that obesity is a chronical relapsing disease [34].

Semaglutide 2.4 mg has been investigated in two phase 3 studies in Asian populations with overweight or obesity (STEP 6 and 7) resulting in significantly greater weight loss compared with placebo and liraglutide 3.0 mg OD (Table 2) [35,36].

In STEP 10, people ($n = 138$) with obesity and prediabetes were randomized to semaglutide 2.4 mg or placebo for 52 weeks [37]. Reduction in body weight was −13.9% and −2.7%, respectively. More with semaglutide reverted to normoglycaemia compared with placebo (81% vs 14%).

Semaglutide once weekly was also assessed in adolescent (STEP TEENS) (12–18 years of age). After 68 weeks the reduction in BMI was −13.9% with semaglutide 2.4 mg and −2.7% with placebo [38]. The incidence of gastrointestinal events was greater with semaglutide compared with placebo (62% vs. 42%).

Recently, the results from the phase 3b study STEP UP were presented. A high dose of semaglutide 7.2 mg once weekly (OW) was tested in people with a BMI ≥30 kg/m^2. After 72 weeks, the weight loss was −18.7% with semaglutide 7.2 mg, −15.6% with semaglutide 2.4 mg and −3.9% with placebo (Table 2) [39]. STEP UP T2D testing semaglutide in people with T2D ($n = 512$) is ongoing and results are expected in 2025.

In patients experiencing weight regain after bariatric surgery, semaglutide induces a significant weight loss [40,41].

In these trials, the safety profile was consistent with the known profile of GLP-1 agonists with nausea and vomiting being the most frequent, but the events were often transient. No difference in occurrence of pancreatitis between semaglutide and placebo was observed, while there was a higher rate of gall bladder diseases.

In a placebo-controlled phase 2 trial, the effect of semaglutide 0.1, 0.2 and 0.4 mg OD over 72 weeks was investigated in participant with biopsy verified metabolic dysfunction-associated steatotic liver disease (MASLD) [42]. MASLD resolution with no worsening in fibrosis was observed in 40%, 36%, and 59%, respectively, compared with 17% in the placebo group. An improvement in fibrosis stage occurred in 43% in the 2.4 mg group and in 33% in the placebo group. The mean weight loss was −13% in the 0.4 mg group and −1% with placebo.

The phase 3 ESSENCE trial (press release Novo Nordisk A/S) is a 240-week double-blinded trial in 1200 adult with MASLD with fibrosis. In an interim analysis of the first 800 randomized people at 72 weeks, semaglutide 2.4 mg demonstrated superior improvement in liver fibrosis (37.0% vs 22.5%) as well as resolution of steatohepatitis (62.9% vs 34.1%) compared with placebo. Weight reduction was −10.5% with semaglutide compared with −2% in the placebo group [43].

The safety and effects of semaglutide 2.4 mg were evaluated in the SELECT study including 17,600 obese people without diabetes but with cardiovascular disease [44]. After 3.8 years follow-up, the occurrence of Major Advance Cardiovascular Events (MACE, including death of cardiovascular diseases, non-fatal myocardial infarction, and non-fatal stroke) was reduced by 20%. Semaglutide was also superior to placebo in reducing the incidence of death of cardiovascular diseases, non-fatal myocardial infarction, and non-fatal stroke. The weight loss with semaglutide without lifestyle intervention in SELECT study was about − 9.4% compared with − 1% in the placebo groups. Adverse events leading to discontinuation of the trial occurred in 16.6% with semaglutide and 8.2% with placebo. In the SELECT trial, Semaglutide reduced the proportion developing diabetes (1.5% versus 6.9%) compared with the placebo group at week 156 [45].

Patients with heart failure are classified with reduced ejection fraction when it is below 40% and as preserved when the ejection fraction is > 50%; heart failure with an injection fraction of 40% to 50% is midrange. The effect of semaglutide on heart failure with preserved ejection fraction (84% of participants had > 50%) was assessed in a trial including 529 participants with a median BMI of 37 kg/m^2 [46,47]. After 52 weeks treatment, the reduction in body weight with semaglutide was − 13.3% compared with − 2.6% in the placebo group. Semaglutide improved the symptoms and physical function (evaluated by Kansas City Cardiomyopathy Questionnaire Clinical Summery Score) and walking distance. The magnitude of benefit in relation to symptoms and physical limitations was directly related the extent of weight loss [48]. In another trial in people with obesity, heart failure with preserved ejection fraction and type 2 diabetes, semaglutide 2.4 mg or placebo for 52-weeks improved heart-failure-related symptoms and physical limitations [49]. Weight loss after 52 weeks was − 9.8% with semaglutide and − 3.4% with placebo. Accordingly, in a prespecified analyses of the SELECT trial, the composite heart failure outcome (cardiovascular death, or hospitalization or urgent hospital visit) improves with semaglutide 2.4 mg both the group with reduced injection rate (HR 0.79) and with preserved ejection fraction (HR 0.75) compared with placebo [50].

In the phase 3 FLOW study in people ($n = 3533$) with type 2 diabetes and chronic kidney disease, (Table 2) the weight loss was −5.6% and −1.5% with semaglutide 2.4 mg and placebo, respectively, and semaglutide reduced the risk of clinical important kidney outcome and cardiovascular death compared with placebo [51].

In patients with obesity and knee osteoarthritis ($n = 4079$, BMI 40.3 kg/m^2), semaglutide 2.4 mg OW reduced body weight with −13.7% and −3.2% with placebo, which resulted in significantly greater pain relief related to knee osteoarthritis compared with placebo [52].

The phase 3 studies with Semaglutide 2.4 mg OW are summarized in Table 2.

3.1.2. Oral semaglutide

Oral incretin-based therapy has the potential to increase acceptance of treatment. In the PIONEER trails, 14 mg daily led to a weight reduction of − 3.4 kg to −4.4 kg after 26 weeks of treatment among patients with type 2 diabetes [53].

In a phase 3 study in adults with overweight or obesity, the efficacy and safety of 50 mg of oral semaglutide was evaluated [54]. The participants were randomized to oral semaglutide escalating to 50 mg daily or placebo for 68 weeks. Oral semaglutide was initiated at 3 mg, escalating to 7, 14, 25 and 50 mg at week 16. The mean body weight reduction after 68 weeks was −15.1% vs −2.4% with oral semaglutide and placebo, respectively, and 34% vs 3%, respectively, lost more than 20% body weight. The adverse events were the usual well-known associated with GLP-1 RAs treatment. The greater body weight reduction with oral semaglutide resulted in a significant improvement in patient reported outcomes (quality of life) and in physical function score. The gastrointestinal adverse events were most frequent during dose escalation. In total, 19 vs 7 participants stopped treatment with oral semaglutide and placebo because of gastrointestinal problems. Gall-bladder-related disorders were reported in 13 vs 4 participants. Altered skin sensation was reported by 42 vs. 4 participants, and the pulse rate increase was 4.1 bpm vs 0.4 bpm. Most participants completed treatment with oral semaglutide 50 mg (86%) and placebo (78%), and 80% was on 50 mg dose at week 68. New adverse events with oral semaglutide included altered skin sensations and more benign neoplasm, which was not observed in the PIONEER program with doses of oral semaglutide up to 14 mg daily.

In the PIONEER PLUS trial in adults with type 2 diabetes (mean HbA1c 9.0% (74.4 mmol/mol), mean BMI 33.8 kg/m2) the efficacy and safety of oral semaglutide 14 mg, 25 mg, and 50 mg once daily were compared [55]. After 52 weeks of treatment weight loss was −4.4 kg, −7.0 kg, and − 8.0 kg, and the reduction in HbA1c were −1.5% (- 16.2 mmol/mol), −1.8% (- 19.4 mmol/mol), and −2.0% (- 22.0 mmol/mol), respectively. Treatment was completed in 83%, 79%, and 81%, respectively, of participants.

3.2. Oral small molecule GLP-1RAs

3.2.1. Oral danuglipron

Danuglipron is an oral, non-peptide G-protein GLP-1 agonist for twice daily administration, which elicits the cellular effects of GLP-1 receptor activation via the cAMP pathway as well as the beta-arrestin pathway of the GLP-1 receptor (i.e. it is a balanced agonist) [56]. In a randomized phase 2 trial, the efficacy and safety of danuglipron was studied over 16 weeks in people with type 2 diabetes [57]. Of 411 participants randomized, 316 completed treatment with 2.5, 10, 40, 80, or 120 mg twice daily. HbA1c was dose dependently reduced up to −1.18% (12.7 mmol/mol) with the 120 mg dose. Fasting plasma glucose was reduced with − 1.8 mmol/l (33.2 mg/dl). Body weight was significantly reduced compared with placebo for the 80 mg twice daily (− 2.04 kg) and −4.17 kg in the 120 mg twice daily group (Table 4). Most subjects reported adverse events were nausea, diarrhea, and vomiting.

In a phase 2 study in obese people with type 2 diabetes involving doses of 80 to 200 mg twice daily, the weight loss after 12 weeks was up to − 5.4% compared with − 0.4% in the placebo group (Table 4) [58]. In a phase 2b study in obese subjects involving doses of 40 to 200 mg twice daily, weight loss after 32 weeks was up to −13% compared with −1.4% in the placebo group [59]. Discontinuation rates, greater than 50%, were observed across all doses compared with up to 40% with placebo. Pfizer has announced the advancement of a once-daily extended formulation of danuglipron for further development, while twice daily danuglipron will not advance into phase 3 studies.

3.2.2. Oral orforglipron

Orforglipron is a potent non-peptide partial agonist of the GLP-1 receptor that has a greater effect on cyclic AMP (cAMP) signaling than on β-arrestin recruitment (i.e. it is a biased agonist) – a pharmacologic profile that may offer lower receptor desensitization than full GLP-1 receptor agonists [60]. The pharmacokinetic profile of orforglipron, with a half-life of 29 to 49 h, supports once daily oral administration. In a phase 2 study as a once daily therapy for 36 weeks in 272 people with obesity (mean BMI 37.9 (108.7 kg)) [61]. At week 36, the mean change in bodyweight dose-dependently ranged from −9.4% to − 14.7% and −2.3% with placebo (Table 4). Furthermore, the weight loss had not plateaued at week 36, which suggest additional weight loss in longer studies. The reduction in systolic blood pressure was up to −10.5 mm Hg compared with −3.6 mm Hg with placebo. Orforglipron treatment also had a beneficial effect on lipids, and there was a change in pulse rate from + 3.2 to +7.4 bpm and −1.8 bpm in the placebo group. One case of pancreatitis was reported. The most common adverse events were the well-known during treatment with GLP-1 RAs and led to discontinuation of orforglipron in 10% to 17% across dose cohorts.

In patients with type 2 diabetes, 26 weeks of treatment with orforglipron induced a weight loss of − 10.1% versus −2.2% and −3.9% with placebo and dulaglutide (Table 4) [62]. The reductions in HbA1c were −2.1% (22.9 mmol/mol), −0.4% (4.4 mmol/mol), and −1.1% (12.0 mmol/mol), respectively. Orforglipron is in phase 3 development.

3.2.3. CT-996

CT-996 is another small molecule, orally active-biased GLP-1 RA, which after 4 weeks treatment in a phase 1 study induced a mean weight loss of −7.3% compared with −1.2% with placebo and mostly mild-to-moderate gastrointestinal-related adverse events [63]. Pharmacokinetics support one daily dosing for treatment of both obesity and type 2 diabetes. Blood levels of CT-996 were unaffected by fasting or meal intake. CT-996 is designed to activate cAMP signaling with minimal to no beta-arrestin recruitment [63].

4. Amylin analogue

4.1. Cagrilintide

Cagrilintide is a long-acting amylin analogue. Amylin is secreted from the beta-cells in the pancreas and functions as a satiety signal, slows gastric emptying, and suppresses postprandial glucagon response to a meal (although probably by slowing gastric emptying) [64]. In a 26 weeks dose finding

phase 2 trial, participants (mean BMI 37.8 kg/m2) without diabetes were included [65]. Participants were randomized to once weekly subcutaneous injection of cagrilintide in doses of 0.3, 0.6, 1.2, 2.4, and 4.5 mg, once daily liraglutide 3.0 mg or placebo. About 10% discontinued treatment, similarly across groups. The weight loss was − 10.8% with 4.5 mg cagrilintide compared with − 9% with liraglutide 3.0 mg and − 3% with placebo (Table 4). Weight loss did not appear to have reached a plateau at week 26 for the highest doses of cagrilintide. No change in HbA1c and fasting glucose was observed with caligrilintide. Approximately 40–63% had gastrointestinal side effect with cagrilintide compared with 32% with placebo and 60% with liraglutide. Gastrointestinal adverse effects were dose-dependent. Systolic and diastolic blood pressure were reduced with cagrilintide but did not differ from placebo. Heart rate did not differ from placebo. Cagrilintide has been further explored in combination with semaglutide 2.4 mg (CagriSema) [66].

5. Dual GLP-1/amylin agonist

5.1. CagriSema

A phase 1b dose-finding study in people with overweight and or obesity showed a body weight reduction of − 17.1% with cagrilintide 2.4 mg and semaglutide 2.4 mg after 20 weeks versus − 9.5% with semaglutide 2.4 mg alone [67]. In the phase 2 and 3 cagrisema studies, semaglutide 2.4 mg weekly is combined with the long-acting amylin analogue cagrilintide 2.4 mg weekly [66]. The efficacy and safety were assessed in 92 participants with type 2 diabetes and mean HbA1c 8.4% (69 mmol/mol, BMI 35.5 kg/m2, mean diabetes duration 9 years) treated with metformin with or without an SGLT2 inhibitor over 32 weeks [66]. The participants received separate subcutaneous injection of semaglutide 2.4 and cagrilintide 2.4 mg, or semaglutide 2.4 mg, or cagrilintide 2.4 mg. Treatment doses were escalated every 4 weeks from 0.25, to 0.5 mg, 1.0 mg, 1.7 mg, and 2.4 mg until the maximal doses of 2.4 mg was reached after 16 weeks. The mean change in HbA1c from baseline to week 32 was with cagrisema −2.2% (24 mmol/mol), − 1.8% (20 mmol/mol) with semaglutide, and −0.9% (10 mmol/mol) with cagrilintide, which was greater with cagrisema compared with cagrilintide (Table 4). The corresponding mean changes in body weight was −15.6%, −5.1%, and -8.1%, respectively, and the change was greater with cagrisema compared with both semaglutide and cagrilintide. Mild and moderate gastrointestinal adverse events were most common and occurred in 58% with CagriSema, 32% with semaglutide and 33% with cagrilintide, and majority of events occurred during the uptitration phase. Mean changes in systolic blood pressure were −13 mm Hg, − 1 mg Hg, and −3 mm Hg, and mean change in pulse rate was + 3, +7, and −1 with cagrisema, semaglutide, and cagrilintide, respectively. No level 2 or 3 hypoglycemia events were reported. Cagrisema is in phase 3 development (REDEFINE program, NCT05567796, NCT05394519, NCT05813925) and in a press release Novo Nordisk A/S announced the results from REDEFINE 1 (n = 3417 participants, body weight 106.9 kg). After 68 weeks follow-up, the weight loss was − 22.7% with cagrisema 2.4 mg compared with − 16.1% for semaglutide 2.4 mg og − 11.8% with cagrilintide 2.4 mg and − 2.3% with placebo [68]. At week 68% with cagrisema, 70% with semaglutide and 83% with cagrilintide were on highest dose.

Amycretin, a single molecule with both GLP-1 and amylin activity, is also in development for both SC and oral administration.

6. Dual GLP-1/GIP agonists

6.1. Tirzepatide

The unimolecular GLP-1/GIP dual agonist, tirzepatide, has been approved for treatment of type 2 diabetes and in 2023 also for treatment of overweight and obesity. The binding to the GIP receptor is comparable to that of native GIP, while the binding affinity for the GLP-1 receptor is five times lower than that of the native hormone [69]. The mechanism of actions of tirzepatide on body weight and improvement in glycemic control is not fully clarified, but it has been suggested that GLP-1 receptor activation with tirzepatide is biased with preference for the cAMP pathway compared to the beta-arrestin pathway, which is responsible for the receptor internalization and termination of activity, resulting in prolonged GLP-1 activity [70]. In addition, animal experiments have suggested that inclusion of GIP activity mitigates the gastrointestinal side effects of GLP-1 and, therefore, higher doses of the GLP-1-GIP co-agonist can be administered [71]. GIP agonism has been ineffective in studies of appetite sensations and food intake in humans [72]. The insulinotropic effect of GIP in people with type 2 diabetes is minimal or absent but can be partly reestablished if normoglycaemia is obtained [73]. A thorough review on GIP physiology was recently published [72].

In the clinical SURPASS 1–5 trials for tirzepatide registration (Table 3), participants with type 2 diabetes (n = 6263) were randomized to once-weekly tirzepatide (5, 10 or 15 mg) or placebo, or daily basal insulin, and in SURPASS 2, semaglutide once weekly [74]. The mean weight loss ranged from 6.2 to 14.9 kg dependent of the dose of trizepatide, and was significantly greater than with semaglutide 1 mg [75]. The reduction in HbA1c ranged from 1.7% (19 mmol/mol) to 2.6% (28 mmol/mol) [75]. Gastrointestinal adverse events were nausea, diarrhea, and vomiting, and as with other GLP-1-based therapies the side effects were transient, mild to moderate and more common during up titration and at higher doses [74,75].

In the SURPASS −3 trial, the changes in liver fat by MRI-proton density fat fraction in response to tirzepatide were compared with insulin degludec treatment after 52 weeks [76]. The reduction in liver fat was about 50% with tirzepatide compared with approximately 20% with insulin degludec.

In SURPASS-6, Tirzepatide was compared with insulin lispro added to basal insulin in type 2 diabetes (Table 3) [77]. After 52 weeks, the mean change in weight with 15 mg was −11.0 kg vs + 3.2 with lispro and the reduction in HbA1c −2.1% (23 mmol/mol) and −1.1% (12 mmol/mol) from baseline HbA1c of 8.8% (73 mmol/mol), respectively.

In predominately Chinese people with type 2 diabetes, tirzepatide also demonstrated superior reduction in body

weight and HbA1c compared with insulin glargine when added as second-line or third-line therapy and was generally well tolerated (Table 3) [78].

Two studies performed in treatment naive or on single oral anti-hyperglycemic medication Japanese patients with type 2 diabetes show reduction in weight and HbA1c as well as in safety profile comparable to previous SURPASS studies (Table 3) [79,80].

In the SURMOUNT obesity development program, the efficacy and safety of tirzepatide was evaluated in four published phase 3 studies in adults with BMI >27 kg/m2 [81]. The studies were double-blinded and participants had a mean age of 44.9 to 54.2 years and 50.7% to 69.7% were females; mean BMI ranged from 36.1 kg/m^2 to 38.9 kg/m2 (Table 3) [81].

In SURMOUNT 1, 2539 participants were randomized to tirzepatide 5, 10, 15 mg once weekly for 72 weeks, including a 20-week dose escalating period [82]. The mean percentage reduction in body weight at week 72 was − 15.0% with 5 mg, − 19.5% with 10 mg and − 20.9% with 15 mg versus − 3.1% with placebo. The adverse events were primarily gastrointestinal, occurring during dose escalation. Adverse events causing discontinuation of treatment were 4.3%, 7.1%, and 6.2% compared with 2.6% in the placebo group (Table 3).

In SURMOUNT 2, 938 participants with type 2 diabetes were randomly assigned to tirzepatide 10 mg ($n = 312$), tirzepatide 15 mg ($n = 311$), or placebo ($n = 315$) [83]. Baseline mean HbA_{1c} was 8.02% (64 mmol/mol). Mean change in body weight at week 72 with tirzepatide 10 mg and 15 mg was −12·8% and −14·7%, respectively, and −3·2% (0·5) with placebo (Table 3).

In SURMOUNT 3, participants with Type 2 diabetes who achieved ≥ 5.0% weight reduction after a 12-week intensive lifestyle intervention were randomized to tirzepatide and to highest tolerated dose of 10 or 15 mg or placebo once weekly for 72 weeks [84]. The additional mean weight change from randomization to week 72 was −18.4% with tirzepatide and + 2.5% with placebo. The change in body weight from start of intensive lifestyle intervention was − 24.3% with tirzepatide (Table 3).

In surmount 4, participants enrolled in an open-label lead-in period received once-weekly subcutaneous maximum tolerated dose (10 or 15 mg) of tirzepatide for 36 weeks [85]. At week 36, participants were randomized [1] to continue receiving tirzepatide ($n = 335$) or switch to placebo ($n = 335$) for 52 weeks. Participants who completed the 36-week lead-in period experienced a mean weight reduction of 20.9%. The mean percent weight change from week 36 to week 88 was −5.5% with tirzepatide vs + 14.0% with placebo. The overall mean weight reduction from week 0 to 88 was − 25.3% for tirzepatide and − 9.9% for placebo (Table 3). Thus, withdrawing tirzepatide led to substantial regain of lost weight, whereas continued treatment maintained and augmented initial weight reduction.

The results from the SURMOUNT-5 trial were recently announced in a press release from E Lilly. Participants ($n =$ 751) obese people were randomized to tirzepatide 10–15 mg or semaglutide 1.7–2.4 mg for 72 weeks (body weight about 110 kg) [86]. Weight loss was −20.2% and −13.7% with tirzepatide and semaglutide, respectively.

Tirzepatide was approved for treatment of weight management by the US Food and Drug administration (FDA) and the European Medicines Agency (EMA) in 2023.

The efficacy and safety of tirzepatide in people with biopsy-confirmed metabolic dysfunction-associated steatohepatitis (MASH) were investigated among 190 participants for 52 weeks (SYNERGY-NASH) [87]. Resolution of MASH without worsening of fibrosis was 10% in the placebo group and, 44%, 56%, and 62% in the 5 mg, 10 mg, and 15 mg dose of tirzepatide, respectively, Improvement in fibrosis stage was 30% with placebo compared with 55%, 51%, and 51% and in the 5,10, and 15 mg groups, respectively. The mean reduction in body weight was −10.7%, −13.3%, −15.6% in the 5 mg, 10 mg, and 15 mg groups, respectively, compared with −0.8% in the placebo group (Table 3).

In the SURMOUNT-OSA, which comprises of two back-to-back trials, the effect of tirzepatide on moderate to severe obstructive sleep apnea and obesity (BMI >30 kg/m2) was investigated over 52 weeks [88]. Mean BMI was 39 kg/m^2 and participants were randomized to 10 or 15 mg of tirzepatide or placebo. Weight loss was − 17.7% to − 19.6% with tirzepatide versus − 1.6% to − 2.3% with placebo, resulting in about 58% reduction from baseline in the number of apneas and hypopneas with tirzepatide compared with 3% reduction with placebo (Table 3). Tirzepatide also significantly improved sleep-related patient reported outcome and reduced systolic blood pressure.

In the SUMMIT-HFpEF trial, 731 patients with heart failure and an ejection fraction of at least 50% and a BMI >30 kg/m^2 were randomized to tirzepatide up to 15 mg or placebo (Table 3) [89]. After 52 week, the weight loss was −13.9%with tirzepatide and −2.2% with placebo and lead to a lower risk of a composite of death from cardiovascular causes or worsening of heart failure than placebo and improved health status (Table 3).

The placebo-controlled, double-blinded SURMOUNT-Morbidity and Mortality in Obesity trial is ongoing (SURMOUNT- MMO, NCT05556512). The goal is to randomize 15,374 participants without diabetes and with a body mass >27 kg/m^2 and with CVD or CVD risk factors to treatment with tirzepatide or placebo. This study will investigate the effect of tirzepatide on morbidity and mortality, including all-cause mortality, non-fatal myocardial infarction, non-fatal stroke, and heart failure in adults and will provide additional evidence for the potential clinical benefits of tirzepatide in obese people. The trial dates are 11 October 2022 - Oct 2027. Currently, tirzepatide is being investigated in obese people with kidney disease (TREASURE CKD). Other studies are investigating the regions in the brain involved in regulating food intake during treatment with tirzepatide (NCT04311411).

6.2. NNC0090

NNC0090–2746 study, a unimolecular dual GLP-1/GIP agonist, was investigated in a 12-week randomized, placebo-controlled double blind phase 2 trial [90]. In total, 108 participants with 8 years duration of diabetes and a mean body weight of 90.9 kg (BMI 33.0 kg/m2) were randomized to 1.8 mg of GLP-1/GIP agonist, liraglutide 1.8 mg or

Table 3. Summarizes the phase 3 trials and one phase 2 trial with tirzepatide OW. Numbers in parentheses referred to the number in reference list. In SURMOUNT-3 trial participants who achieved ≥ 5% in weight loss after 12 weeks of intensive life-style intervention were randomized to tirzepatide or placebo. In SURMOUNT-4 trial, a 36-week open-label tirzepatide lead-in period was included. At week 36, the participants were randomized to tirzepatide or placebo for 52 weeks. Converting HbA1c in percentage to mmol/mol= % x 10.93 = mmol/mol.

Trial Company	Drug	N	Participants	Duration (wk)	Baseline weight (kg)	Comparator	Change in BW (%)	Change in HbA1c (%)
SURPASS −1 [75]	Tirzepatide SC OW	478	T2D	40	86	Tirzepatide 5	−7.0	−1.9
						Tirzepatide 10	−7.8	−1.9
						Tirzepatide 15	−9.5	−2.1
						Placebo	−0.8	0.0
SURPASS − 2 [75]	Tirzepatide SC OW	1879	T2D BMI ≥25 kg/m^2	40	94	Tirzepatide 5	−7.6	−2.0
						Tirzepatide 10	−9.3	−2.1
						Tirzepatide 15	−11.2	−2.3
						Semaglutide 1	−5.7	−1.9
SURPASS − 3 [76]	Tirzepatide SC OW	1444	T2D BMI ≥25 kg/m^2	52	94	Tirzepatide 5	−7.1	−1.9
						Tirzepatide 10	−10.7	−2.2
						Tirzepatide 15	−12.9	−2.4
						Insulin Degludec	+2.3	−1.3
SURPASS − 4 [75]	Tirzepatide SC OW	2002	T2D BMI ≥25 kg/m^2	52	90	Tirzepatide 5	−7.1	−2.2
						Tirzepatide 10	−9.5	−2.4
						Tirzepatide 15	−11.7	−2.6
						Insulin Glargine	+1.9	−1.4
SURPASS − 5 [75]	Tirzepatide SC OW	475	T2D Treated with Insulin Glargine	40	95	Tirzepatide 5	−5.4	−2.1
						Tirzepatide 10	−7.4	−2.4
						Tirzepatide 15	−8.8	−2.3
						Placebo	+1.6	−0.9
SURPASS − 6 [77]	Tirzepatide SC OW	1428	T2D Insulin treated	52	91	Tirzepatide 5	−6.7	−1.9
						Tirzepatide 10	−9.2	−2.1
						Tirzepatide 15	−11.0	−2.3
						Insulin Lispro	+3.2	−1.1
SURPASS J-mono [79]	Tirzepatide SC cOW	821	Japan T2D Treatment Naive	52	78	Tirzepatide 5	−7.8	−2.4
						Tirzepatide 10	−11.0	−2.6
						Tirzepatide 15	−13.9	−2.8
						Dulaglutide 0.75	−0.7	−1.3
SURPASS J-combo [80]	Tirzepatide SC OW	443	Japan T2D on one oral anti-diabetica BMI ≥23 kg/m2	52	77	Tirzepatide 5	−5.1	−2.5
						Tirzepatide 10	−10.1	−3.0
						Tirzepatide 15	−13.2	−3.0
SURPAS -AP-combo [78]	Tirzepatide SC OW	917	ASIA T2D on one or two anti-diabetica	40	76	Tirzepatide 5	−6.5	−2.2
						Tirzepatide 10	−9.3	−2.4
						Tirzepatide 15	−9.4	−2.5
						Insulin Glargine	+2.1	−1.0
SURMOUNT − 1 [82]	Tirzepatide SC OW	2539	BMI ≥30 or ≥27 kg/m^2 with at least one comorbidity	72	105	Tirzepatide 5	−15.0	NA
						Tirzepatide 10	−19.5	
						Tirzepatide 15	−20.9	
						Placebo	−3.1	
SURMOUNT − 2 [83]	Tirzepatide SC OW	938	T2D BMI ≥27 kg/m2	72	101	Tirzepatide 10	−12.8	−2.1
						Tirzepatide 15	−14.7	−2.1
						Placebo	−3.2	−0.5
SURMOUNT − 3 [84]	Tirzepatide SC OW	579	BMI ≥30 or ≥27 kg/m^2 with at least one comorbidity	12 + 72	110	12-week lead in with intensive lifestyle	−6.9	N/A
						Tirzepatide 15		
						Placebo	- 18.4 +2.5	
SURMOUNT − 4 [85]	Tirzepatide SC OW	783	BMI ≥30 or ≥27 kg/m^2 with at least one comorbidity	36 + 52	107	0–36 week treated med tirzepatide 10 or 15 mg	−20.9	N/A
						Tirzepatide 15		
						Placebo	- 5.5 + 14.0	
SUMMIT-HFpEF [89]	Tirzepatide SC OW	731	Heart failure (EF > 50%) BMI ≥30 kg/m^2	52	103	Tirzepatide 15	−13.9	N/A
						Placebo	−2.2	
Obstructive Sleep apnea [88]	Tirzepatide SC OW Two 'back to back' studies	469	obstructive sleep apnea BMI ≥30 kg/m^2	52	116	Tirzepatide	−18.1 and −20.1	N/A
						Placebo	−1.3 and −2.3	
Phase 2 Trial with Tirzepatide								
SYNERGY-NASH Phase 2 [87]	Tirzepatide SC OW	190	NASH	104	100	Tirzepatide 5	−10.7	N/A
						Tirzepatide 10	−13.3	
						Tirzepatide 15	−15.6	
						Placebo	−0.8	

Abbreviations: T2D: type 2 diabetes, SC: subcutaneous, OW: once weekly, N/A not applicable, NASH: nonalcoholic steatohepatitis.

Table 4. Illustrates the results from phase 2 trials. Numbers in parentheses referred to the number in reference list. Converting HbA1c in percentage to mmol/mol= % x 10.93 = mmol/mol.

Trial Company	Agent	N	Participants	Duration (wk)	Baseline weight (kg)	Comparator	Change in BW (%)	Change in HbA1c (%)
Phizer [57] Phase 2	Danuglipron Oral non-peptide GLP-1 agonist Twice daily	411	T2D	16	91	Danuglipron 2.5 mg	+0.02	−0.49
						Danuglipron 10 mg	−0.06	−0.91
						Danuglipron 40 mg	−1.16	−1.03
						Danuglipron 80 mg	−2.48	−0.96
						Danuglipron 120 mg	−4.60	−1.18
						Placebo	−0.43	−0.02
Phizer [58] Phase 2	Danuglipron Oral non-peptide GLP-1 agonist Twice daily	123	T2D BMI ≥27 kg/m^2	12	95	Danuglipron 80 mg	−3.64	−1.07
						Danuglipron 120 mg	−5.38	−1.56
						Danugliptron 200 mg	−5.37	−1.57
						Placebo	−0.42	−0.32
E Lilly [61] Phase 2	Orforglipron Oral non-peptide GLP-1 agonist OD	272	BMI ≥30 or ≥27 kg/m^2 with at least one comorbidity	36	109	Orforglipron 12 mg	−9.4	N/A
						Orforglipron 24 mg	−12.5	
						Orforglipron 36 mg	−13.5	
						Orforglipron 45 mg	−14.7	
						Placebo	−2.3	
E Lilly [62] Phase 2	Orforglipron Oral non-peptide GLP-1 agonist OD	383	T2D with and without metformin treatment	26	100	Orforglipron 3 mg	−3.7	−1.2
						Orforglipron 12 mg	−6.5	−1.7
						Orforglipron 24 mg	−9.7	−1.8
						Orforglipron 36 mg	−9.5	−2.0
						Orforglipron 45 mg	−10.1	−2.1
						Dulaglutide 1.5 mg	−3.9	−1.1
						Placebo	−2.2	−0.4
Novo Nordisk [65] Phase 2	Cagrilintide Amylin analogue SC OW	706	BMI ≥30 or ≥27 kg/m^2 with at least one comorbidity	26	107	Cagrilintide 0.3 mg	−6.0	N/A
						Cagrilintide 0.6 mg	−6.8	
						Cagrilintide 1.2 mg	−9.1	
						Cagrilintide 2.4 mg	−9.7	
						Cagrilintide 4.5 mg	−10.8	
						Liraglutide 3.0 mg	−9.0	
						Placebo	−3.0	
Novo Nordisk [66] Phase 2	Cagrisema SC OW	92	T2D treated with metformin and ± SGLT2i BMI ≥27 kg/m^2	32	106	Cagrisema 2.4 mg	−15.6	−2.2
						Cagrilintide 2.4 mg	−8.1	−0.9
						Semaglutide 2.4 mg	−5.1	−1.8
Novo Nordisk [90] Phase 2	GLP-1/GIP agonist SC OD	108	T2D	12	91	GLP-1/GIP 1.8 mg	−2.86	−0.99
						Placebo	−1.19	0.0
Viking Therapeutics [92]	GLP-1/GIP agonist SC OW	174	BMI ≥30 or ≥27 kg/m^2 with at least one comorbidity	13	102	VK2735 2.5 mg	−9.2	N/A
						VK2735 5.0 mg	−10.7	
						VK2735 10 mg	−13.3	
						VK2735 15 mg	−14.6	
						Placebo	−1.8	
AstraZeneca [103]	GLP-1/glucagon agonist SC OD	834	T2M treated with metformin	54	100	Cotadutide 100 mg	−3.7	−1.03
						Cotadutide 200 mg	−3.2	−1.16
						Cotadutide 300 mg	−5.0	−1.19
						Liraglutide 1.8 mg	−3.3	−1.17
						Placebo	−0.7	−0.45
Altimmune [105]	GLP-1/glucagon agonist SC OW	160	BMI ≥30 or ≥27 kg/m^2 with at least one comorbidity	24	100	Pemvidutide 1.2 mg	−7.3	
						Pemvidutide 1.8 mg	−9.4	
						Pemvidutide 2.4 mg	−10.7	
						Placebo	−1.0	
Boehringer Ingelheim [108]	GLP-1/glucagon agonist SC OW	387	BMI ≥27 kg/m^2	46	106	Survodutide 0.6 mg	−6.2	N/A
						Survodutide 2.4 mg	−12.5	
						Survodutide 3.6 mg	−13.2	
						Survodutide 4.8 mg	−14.9	
						Placebo	−2.8	
Boehringer Ingelheim [109]	GLP-1/glucagon agonist SC OW or twice weekly	413	T2D BMI 25–50 kg/m^2	16	97	Survodutide 0.3 mg OW	N/A	−0.91
						Survodutide 0.9 mg OW	N/A	−1.46
						Survotutide 1.8 mg OW	N/A	−1.71
						Survodutide 1.2 mg BIW	N/A	−1.63
						Survodutide 1.8 mg BIW	N/A	−1.68
						Semaglutide 1 mg OW	−8.7	−1.46
						Placebo	−5.3	−0.15
							−0.9	
Boehringer Ingelheim [110]	GLP-1/glucagon agonist SC OW	293	MASH	48	101	Survodutide 2.4 mg	−10.4	N/A
						Survodutide 4.8 mg	−12.9	
						Survodutide 6.0 mg	−13.1	
						Placebo	−0.6	
E Lilly [112]	GLP-1/glucagon agonist SC OW	248	BMI ≥28 or BMI ≥24 kg/m^2 and hyperphagia	24	90	Mazdutide 3 mg	−6.7	N/A
						Mazdutide 4.5 mg	−10.4	
						Masdutide 6 mg	−11.3	
						Placebo	+1.0	

(*Continued*)

Table 4. (Continued).

Trial Company	Agent	N	Participants	Duration (wk)	Baseline weight (kg)	Comparator	Change in BW (%)	Change in HbA1c (%)
E Lilly [113]	GLP-1/glucagon agonist SC OW	252	T2D ±metformin BMI ≥20 kg/m^2 and <40 kg/m^2	20	75	Mazdutide 3 mg	−4.1	−1.4
						Mazdutide 4.5 mg	−5.1	−1.67
						Masdutide 6 mg	−7.1	−1.55
						Dulaglutide 1.5 mg	−2.7	−1.35
						Placebo	−1.4	+0.03
Jansen Research and Development [114]	GLP-1/Glucagon agonist JNJ-64565111 SC OW	195	T2D BMI ≥35 kg/m^2 and <50 kg/m^2	12	113	JNJ-64565111 5.0 mg	−5.3	−0.0
						JNJ-64565111 7.4 mg	−6.5	−0.0
						JNJ-64565111 10.0 mg	−7.9	−0.1
						Placebo	−0.7	−0.1
Jansen Research and Development [115]	GLP-1/Glucagon agonist JNJ-64565111 SC OW	474	BMI ≥35 kg/m^2 and <50 kg/m^2	26	113	JNJ-64565111 5.0 mg	−8.5	N/A
						JNJ-64565111 7.4 mg	−9.8	
						JNJ-64565111 10.0 mg	−11.8	
						Liraglutide 3.0 mg	−7.5	
						Placebo	−1.8	
Merck Sharp Dohme [116]	GLP-1/glucagon agonist Efinopegdutide SC OW	145	NAFLD	24	97	Efinopegdutide 10 mg	−8.5	N/A
						Semaglutide 1 mg	−7.1	
Novo Nordisk [119]	Semaglutid SC OW, Cilofexor and Firsocostat SC OD	108	MASLD	24	96	Semaglutide 2.4 mg + Cilofexor 30 mg	−8.6	N/A
							−9.6	
						Semaglutide 2.4 mg + cilofexor 100 mg	−7.6	
							−7.0	
						Semaglutide 2.4 mg + fircostat 20 mg	−7.6	
						Semaglutide 2.4 mg + ciloxexor 30 mg + fircostat 20 mg		
						Semaglutide 2.4 mg		
E Lilly [123]	GIP/GLP-1/glucagon agonist Retatrutide SC OW	338	BMI ≥30 kg/m^2 or ≥27 kg/m^2 with at least one comorbidity	48	108	Retatrutide 1 mg	− 8.7	N/A
						Retatrutide 4 mg	−17.1	
						Retatrutide 8 mg retatrutide 12 mg	−22.8	
							−24.2	
						Placebo	−2.1	
E Lilly [125]	GIP/GLP-1/glucagon agonist Retatrutide SC OW	281	T2D BMI 25–50 kg/m^2 ±metformin	36	98	Retatrutide 1 mg	−3.2	−0.54
						Retatrutide 4 mg	−10.3	−1.50
						Retatrutide 8 mg retatrutide 12 mg	−16.3	−2.13
							−16.9	−2.16
						Dulaglutide 1.5 mg	−2.0	−1.36
						Placebo	−3.0	−0.30

Abbreviations: T2D: type 2 diabetes, OD: once daily, OW: once weekly. SC: subcutaneous, N/A: not available, NAFLD. nonalcoholic fatty liver disease, MASLD: metabolic dysfunction-associated steatotic liver disease, MASH: metabolic dysfunction-associated steatohepatitis.

placebo administered once daily (Table 4). Body weight reduction was −2.86% with the GLP-1/GIP analogue, −1.67% with liraglutide and −1.19% with placebo. The reduction in body weight did not differ between GLP-1/GIP agonist and Liraglutide.

6.3. VK2735

VK2735 is a once weekly GLP1/GIP agonist from Viking Therapeutics. In a phase 1 study of 28 days duration, the weight loss was up to − 7.8% with concomitant reduction in liver fat and plasma lipids compared to placebo [91].

In the 13-week phase 2 VENTURE trial in 176 adults with obesity, up to −13.1% placebo adjusted weight loss was observed and with no plateau at 13 weeks [92]. About 13% of subjects terminated treatment with the agonist as well as with placebo (Table 4). The side events were mild or moderate and gastrointestinal in nature (95%). A phase 1 trial of a daily oral formulation of VK2735 has been carried out in people with a BMI >30 kg/m2, and demonstrated a mean weight loss relative to placebo of − 6.8% after 28 days of dosing with the highest 100 mg dose [93].

6.4. CT-388

CT-388 is a unimolecular GLP-1/GIP agonist for once weekly administration developed by Carmot Therapeutics, which is currently in phase 2 development for treatment of type 2 diabetes and obesity in a collaboration between Roche and Carmot Therapeutics. In a Phase 1 clinical trial of CT-388 once weekly in overweight and obese otherwise healthy participants, there was more than − 8% (7.7 kg) weight loss in 4 weeks [94]. Most common adverse events (AEs) were gastrointestinal related, consistent with the GLP-1 class. In a phase 1b 24 week study in people with obesity the mean placebo adjusted weight loss was − 18.8% with mild-to-moderate gastrointestinal-related adverse events [95].

6.5. MariTide (AMG133)

Is a GIP receptor antagonist conjugated to GLP-1 analogue developed by Amgen for once monthly injection. After 3 months, AMG133 induced weight losses of −14% to −15% compared with −1.5% with placebo [96], and is now in phase 2 development. The fact that MariTide is an antagonist of the GIP receptor while Tirzepatide is an agonist for the GIP

receptor, both inducing major weight loss, makes it difficult to understand the mechanisms of action of GIP in relation to weight regulation as discussed in [72]. A possible mechanism is that the potential desensitization of the GIP receptor induced by GIP agonist exposure is lifted by GIP antagonists [72,97]. In a 52 week phase 2 study ($n = 592$) mariTide demonstrated up to −20% weight loss without a weight loss plateau in people with obesity or overweight and −17% in people with type 2 diabetes and lowered HbA1c with − 2.2% (24 mmol/mol) [98]. The most common adverse events were gastrointestinal-related. A phase 3 program is initiated.

7. GLP-1/glucagon receptor agonists

This combination is of interest because here the GLP-1 effects are combined with the effects of glucagon in the liver with stimulation of beta-oxidation of lipids and inhibition of de novo lipogenesis in the liver [99,100]. Glucagon also reduces food intake possibly via activation of receptors in the hypothalamus and brainstem [99,100]. The effect of glucagon on energy expenditure in humans is unclear, but it has been suggested that glucagon enhances energy expenditure [99,100]. Glucagon increases glycemia by stimulation of hepatic glucose production, which make the balance between the GLP-1 receptor agonist and the glucagon receptor agonism of importance for the effect on glucose tolerance [99,100]. Oxyntomodulin, secreted from the L-cell, is a hormone with natural activity of both the GLP-1 and glucagon receptors, but only with about 1/100 of the potency of the cognate ligands. Oxyntomodulin also inhibits appetite and food intake [101]. Several long acting GLP-1/glucagon analogues are in clinical development for treatment of obesity, MASLD and MASH and have shown varying efficacies and adverse events, which may be explained by different ratios between GLP-1 and glucagon activities of the co-agonist [102].

7.1. Cotadutide

The dual agonist Cotadutide was in development for treatment of nonalcoholic steatohepatitis and type 2 diabetes. In a phase 2b study including 834 adults with type 2 diabetes and treated with metformin, it was administered as a once daily injection [103]. Participants was randomized to cotadutide 100 ug, 200 ug, 300 ug, placebo or liraglutide 1.8 mg. After 54 weeks, no difference in reduction of HbA1c was reported between cotadutide dose groups and liraglutide, but a significantly greater decrease in body weight was observed with cotadutide 300 ug compared with liraglutide (- 5.02 kg vs − 3.33 kg) (Table 4). Cotadutide 300 ug improves lipid profile, AST and ALT and fibrosis-4 index, but not more than liraglutide [103]. In a 26-week phase 2b study, patients with type 2 diabetes and diabetic kidney disease were randomized to cotadutide 100, 200, 300, 600 ug once daily or placebo for 32 days [104]. Urinary albumin creatinine ratio decreased by 51% and weight loss was −3.4 kg compared with placebo. Currently, AstraZeneca has terminated the development program of cotadutide.

7.2. Pemvidutide (ALT 801)

In a phase 2 trial (MOMENTUM) of pemvidutide, another GLP-1/glucagon dual agonist, with a claimed 1:1 potency ratio for activation of the GLP-1 and glucagon receptor, a prespecified interim analyses of 160 participants, who have completed 24 weeks follow-up, was reported [105]. Participants with a mean BMI of 36 kg/m2 (100 kg) were randomized 1:1:1:1 to pemvidutide 1.2, 1.8, 2.4 mg or placebo. The 1.2 and 1.8 mg doses were administered without dose titration. A short 4-week titration period was included with the 2.4 mg dose. Weight loss was − 7.3%, − 9.4% and − 10.7% vs −1.0% with placebo (Table 4). About 50% achieved > 10%, and 20% achieved > 15% in weight loss at the 1.8 and 2.4 mg doses, respectively. A significant improvement or trends were observed with respect to cardiometabolic risk factors, including LDL cholesterol (−5.5%, −10.3%, − 12.7% and −1.1%, respectively), triglycerides (−25.2%, −14.4%, −25% vs −3.3%, respectively) and systolic blood pressure. No significant changes in fasting glucose, HbA1c were observed at any doses. Adverse events were the well-known during treatment with a GLP-1 receptor agonist. Adverse events discontinuation was observed in 7.5%, 10%, 26.8% and 2.6% for the three doses of pemvidutide and placebo, respectively.

In a phase 2 obesity trial, mean weight loss was − 13.4% (placebo adjusted) after 48 weeks with the 2.4 mg dose 20% of participants discontinued mostly due to nausea and vomiting [106]. In another phase 2 study in people with MASLD, 24 weeks of pemvidutide treatment reduced liver fat by 76% compared with 14% with placebo [107].

7.3. Survodutide (BI 456,906)

Compared with other GLP-1/glucagon dual agonists, the phase 2 results with survodutide in people living with overweight/obesity are of interest [108]. Participants were randomized to 0.6, 2.4, 3.6, 4.8 mg or placebo for 46 weeks, with a 20-week escalation period with increasing doses every second week, followed by a 26-week maintenance period. Overall, 387 participants with a BMI of 37.1 kg/m2, body weight 105.7 kg, were randomized. At week 46, the greatest weight loss was reported with 4.8 mg (−14.9%) (Table 4) together with a −6.2 mm Hg reduction in systolic blood pressure and a −2.9 mmHg for diastolic blood pressure [108].

In a 16 weeks phase 2 study in people with type 2 diabetes ($n = 413$, HbA1c 8.1% (64.7 mmol/mol)) treated with metformin, participants were randomized to survodutide 0.3, 0.9, 1,8, 2.7 mg once weekly or 1.2 or 1.8 mg twice weekly or placebo or semaglutide up to 1 mg once weekly [109]. The reduction in HbA1c was about − 1.5% (16.4 mmol/mol) to − 1.7% (18.4 mmol/mol) for 1.8 and 2.7 mg weekly as well as for 1.2 and 1.8 mg twice weekly, compared with − 1.5% (16.1 mmol/mol) with semaglutide (Table 4). Reduction in body weight was dose-dependent up to − 8.7%, which was greater than with semaglutide (−5.3%). Gastrointestinal adverse events were reported in 77.8% of survodutide treated participants and in 52.0% and in 52.5% of semaglutide and placebo-treated participants but can probably be mitigated with slower dose escalation.

In a 48 weeks phase 2 trial with survodutide in 393 participants with biopsy-confirmed MASH and fibrosis stage 1 through 3, improvement in MASH with no worsening of fibrosis was observed in 47% with 2.4-mg group, and 62% in in the 4.8 -mg group compared with 14% in the placebo group [110]. Improvement in fibrosis by at least one stage occurred in 34%, 36%, 34%, and 22%, respectively. Changes in body weight are presented in Table 4.

7.4. Mazdutide

Known as IBI362 or LY3305677 is an once-weekly analog of oxyntomodulin and is developed by Eli Lilly [111]. In a phase 2 randomized trial with 248 participants (BMI 31.8 kg/m2, 90 kg), the weight loss after 24 weeks with 3 mg was − 6.7%, with 4.5 mg −10.4%, with 6 mg −11.3%, and + 1% with placebo (Table 4) [112]. Reduction in HbA1c, fasting glucose and HOMA-IR, lipids and blood pressure was observed for all doses of mazdutide. The adverse events were the usual known from treatment with GLP-1 agonists. The increase in heart rate with 6 mg was 9 beat per minut(bpm). For comparison in the STEP 7 trial with semaglutide 2.4 mg, also performed in predominantly east Asian population, the weight loss after 44 weeks was − 12.1% compared with − 3.6% with placebo [35].

In another phase 2 trial in Chinese people with type 2 diabetes (HbA1c 8.0% (65 mmol/mol), BMI 27.5 kg/m2) were randomized to mazdutide 3 mg, 4.5 mg, 6 mg, and 1.5 mg dulaglutide, or placebo for 20 weeks [113]. Reductions in HbA1c ranged from −1.41% (15.4 mmol/mol) to −1.67% (18.3 mmol/mol) with mazdutide compared with −1.35% (14.7 mmol/mol) with dulaglutide and + 0.03% (o.3 mmol/mol) with placebo. Weight loss with mazdutide was up to −7.1% without reaching a plateau, −2.7% with dulaglutide and −1.4% with placebo (Table 4). The most common adverse events were diarrhea 36%, nausea 23%, vomiting 14%, hypoglycemia 10% (8% with placebo). Mazdutide also reduced lipids, blood pressure and increased heart rate compared with placebo. In a recent meta-analysis, the seven RCTs with mazdutide are compared [111].

Mazdutide is at present in phase 3 development in Chinese people with obesity or type 2 diabetes in collaboration with Eli Lilly (NCT05607680, NCT05606913).

7.5. Efinopegdutide (JNJ-6456111)

This GLP-1/glucagon agonist was investigated in a phase 2 study in people with obesity and type 2 diabetes randomized to placebo or 5.0 mg, 7.5 mg or 10 mg of efinopegdutide [114]. After 12 weeks, the placebo subtracted weight loss was −4.6%, − 5.9% and −7.2% with no change in HbA1c (Table 4). Adverse events were nausea and vomiting. In people with obesity without diabetes, the placebo subtracted weight loss was after 26 weeks − 6.8%, − 8.1% and −10.0% with 5.0 mg, 7.5 mg and 10 mg and −5.8% for liraglutide 3.0 mg (Table 4) [115]. In patients with MASLD, the reduction in liver fat at week 24 with 10 mg efenopegtudie was 72.7% compared with 42.3% with semaglutide 1 mg [116]. The mean reduction in body weight was − 8.5% and − 7.1%, respectively, with a higher incidence of adverse events with efinopegdutide than placebo, primarily related to gastrointestinal events.

7.6. SAR425899

Is also a GLP-1/glucagon dual agonist. It was evaluated in two studies of 21 or 28 days, inducing a weight loss of − 5.3% to − 5.5% in healthy overweight without or with type 2 diabetes and reduced fasting glucose and HbA1c in participants with type 2 diabetes [117].

7.7. NN9277/NN6177

A GLP-1/glucagon dual agonist Developed by Novo Nordisk for treatment of obesity and showed a weight loss of about −13% after 12 weeks, but was closed down because of adverse events including increases in heart rate [118].

8. GLP-1RA+ FXR agonist and firsocostat

Semaglutide up to 2.4 mg weekly, alone or in combination with daily doses of the farnesoid X receptor agonist cilofexor and/or the acetyl-coenzyme A carboxylase inhibitor firsocostat was studied in patients with NASH for 24 weeks [119]. Cilofexor inhibits lipogenesis, gluconeogenesis and bile acid synthesis, while firsocostat reduces de novo liver lipogenesis. The combination therapy resulted in a greater improvement in liver steatosis and in fibrosis as well as liver biochemistry and noninvasive test of fibrosis compared with semaglutide alone. The weight loss in the groups was about − 7% to −10% (Table 4). This combination of drugs is being evaluated in people with cirrhosis (NCT04971785).

9. GLP-1/FGF-21 receptor agonist

Fibroblast growth factor 21 (FGF21) regulates lipid and glucose metabolism and energy expenditure [120]. The long-acting FGF-21 analogue pegozafermin was shown in a phase 2b trial to improve fibrosis and MASH resolution (reduction in liver fat by up to 48% compared with −5% with placebo) after 24 weeks treatment [121]. In two phase 2 trial efruxifermin, a long acting FGF21 agonist, was tested for the treatment of MASH. A combination of semaglutide and a FGF21 analogue has been tested in people with NASH, but no results are available (NNC0194–0499)

10. Other GLP-1-based dual agonists

PYY is co-secreted from the L-cells. GLP-1/PYY dual agonists (NNC0165–1875) have been studied in people with obesity, but no results have been presented. Other studies have also looked at the combination of GLP-1/PYY, i.e (LY3457263) and (BI 1,820,237). Lastly, a GLP-1/GLP-2 unimolar compound for once weekly dosing induced a weight loss of − 4.5% after 4 weeks (ADA 2022, 335-or).

11. GLP-1-based triple agonists

12.1. A monomolecular triple GLP-1/GIP/glucagon agonist (retatrutide) is currently in development for treatment of type 2 diabetes and obesity. Compared with the endogenous receptor ligands, retatrutide is less potent at the glucagon and

GLP-1 receptor, 0.3 and 0.4 fold, respectively, but more potent at the GIP receptor by a factor 8.9 [122]. The half-life is approximately 6 days, consistent with weekly administration. In a 12-week proof-of-concept phase 1b study 72 people with type 2 diabetes were randomized to ascending dose of retatrutide compared with dulaglutide and placebo [122]. 29 participants discontinued the study prematurely. The reduction in body weight was dose dependent and up to − 8.96 kg and reduction in HbA1c was up to − 1.6% (17 mmol/mol) [122].

In a phase 2 study, double-blinded, randomized, placebo-controlled, participants received retatrutide 1 mg, 4 mg (initial dose 2 mg), 4 mg (initial dose 4 mg), 8 mg (initial dose 2 mg), 8 mg (initial dose 4 mg), or 12 mg (initial dose 2 mg) or placebo once weekly for 48 weeks. Overall, 338 adults with a mean BMI of 37.3 kg/m2 (107.7 kg) were enrolled [123]. In total, 36% had prediabetes. After 48 weeks follow-up, the body weight reduction was up to − 24.2% in the 12 mg group as compared to −2.1% in the placebo group, 83% had lost more than 15% in weight, and 26% had lost more than 30% (Table 4). A greater percentage body weight reduction was attained among participants with a BMI of 35 or more than in those with a BMI less than 35 (for 12 mg: 26.5% vs 22.1%) and among female than among male participants (28.5% vs 21.9%). The weight reduction curves indicated that a plateau had not yet been reached at week 48. The most common adverse events were gastrointestinal and were dose related, and were mostly mild to moderate in severity, and were partly mitigated with a lower starting dose. About 6–16% of the participants discontinued treatment with retatrutide because of adverse events compared with none in the placebo group. Increases in amylase and lipase levels and one case of acute pancreatitis were reported. The heart rate increased in a dose-dependent manner up to 24 weeks and declined thereafter. No cases of hypoglycemia were reported. Cutaneous hyperesthesia and increased skin sensitivity were reported in 7% of the participants who received retatrutide. Retatrutide was associated with improvement in blood pressure, fasting glucose and lipids. Among participants with prediabetes, 72% have returned to normoglycemia (HbA1c < 5.7% (38 mmol/mol)). In total, 74% to 88% completed the trial across the retatrutide groups compared with 71% in the placebo group.

In a sub-study of this trial, 98 participants, who met the inclusion criterion of 10% or greater liver fat content by magnetic resonance imaging were included [124]. Mean BMI was 38.4 kg/m2. Most of the reduction in liver fat occurred within the first 24 weeks, where the reduction in liver fat was −42.9%, −57.0%, −81.4% and −82.4% for the 1, 4, 8, and 12 mg doses, respectively, compared with + 0.3% changes in the placebo group. At 48 weeks the reductions were −51.3%, −59,0%, −81.7%, and −86.0% compared with −4.6% with placebo. A total liver fat content of less than 5% was obtained in 89% and 93% in the groups treated with 8 mg and 12 mg, respectively. The reduction in liver fat was strongly correlated with percent changes in body weight and nearly maximal reduction in liver fat appeared to coincide with approximately 20% reduction in body weight.

In a 24-week phase 2 trial with retatrutide, people with type 2 diabetes treated with lifestyle alone or a stable dose of metformin were randomized to placebo, dulaglutide 1.5 mg or retatrutide 0.5 mg, 4 mg, 8 mg or 12 mg weekly [125]. Two starting doses (2 mg vs 4 mg) were explored for doses greater than 0.5 mg. Reductions in HbA1c were − 0.01% (0.12 mmol/mol) with placebo, −1.41% (15.4 mmol/mol) with dulaglutide and − 2.0% (22.1 mmol/mol) with 12 mg retatrutide, and HbA1c < 6.5% (48 mmol/mol) was reported in 77% and HbA1c < 5.7% (38 mmol/mol) in 27%. The corresponding reduction in body weight was −3.0%, −2.0% and − 16.9% (Table 4). Lipids (NON-HDL-cholesterol: −3.9%, − 0.7% − 19.6%, triglycerides: −9.9%, −4.3%,- 34.4%), and blood pressure (systolic pressure: 1.5 mmHg,-1.5 mm Hg, −8.8 mm Hg) also decreased more with retatrutide compared with placebo and dulaglutide. Mild-to-moderate gastrointestinal related adverse events, including nausea, diarrhea, vomiting, and constipation were reported in 13–50% of retatrutide treated participants, 13% with placebo and 35% with dulaglutide, primarily during dose escalating and were mitigated by lowering starting dose (2 mg vs 4 mg). There were no reports of clinically meaningful or severe hypoglycemia. A dose-dependent increase in pulse rate of up to 4.3 bpm was observed with retatrutide vs −3.2 bpm with placebo and 1.8 bpm with dulaglutide. It remains to be seen whether retatrutide improves glycemic control as well as tirzepatide.

A cardiovascular safety study is ongoing in individuals with obesity and established CVD (NCT05882045)

11.1. Other triple agonists

11.1.1. Eficopegtrutide

Is a GLP-1/GIP/glucagon triple agonist, which has demonstrated up to 81% reduction in liver fat after 12 weeks in patients with MASLD and is at present investigated in a 52 week phase 2 study [126].

11.1.2. SAR441255

Is another triple agonist which has been shown to improve glycemic control during a mixed meal, no long-term results have been published [127].

11.1.3. HM5211

Is a third triple agonist in clinical development with focus on obesity-related liver disease.

12. Expert opinion

The gut is an organ involved in the regulation of body weight and food intake, and during the last 15–20 years the successful development of therapeutics based on GLP-1 RA (and GIP) has completely changed the treatment of type 2 diabetes and obesity [6,7]. GLP-1 RAs reduce the rates of Major Cardiovascular Events (MACE), heart failure, and elicit significant improvements of MASLD, kidney disease and reduce low grade inflammation [13,44]. Limitations associated with GLP-1-based therapy include high cost, loss of lean body mass, gastrointestinal adverse events and weight regain after stop of therapy.

Most of the new anti-obesity drugs (AOD) are based on a GLP-1 receptor agonist alone or in combination with GIP,

amylin, or glucagon. The modification of liraglutide to semaglutide 2.4 mg resulted in a weight loss of about 15% [30], although in the SELECT study with 17.600 participants the weight loss was about 9–10% during a 3.8 years follow-up, resulting in a significant reduction in MACE of 20% [44]. Tirzepatide, a dual GLP-1/GIP agonist has resulted in weight losses of 18% – 23% and is also approved for treatment of obesity [82]. The exact mechanism of action of tirzepatide is incompletely understood, but the incorporation of GIP may change its GLP-1 activity (biased agonism), but may also attenuate the GLP-1 induced adverse effects [8,69,70] allowing higher doses to be used.

Metabolic dysfunction-associated steatotic liver disease (MASLD) is frequent in obesity, including those with type 2 diabetes, and is a risk factor for the development of cardiovascular diseases, cirrhosis and liver cancer [128]. Glucagon reduces hepatic liver fat content and may increase energy expenditure and reduce food intake, which is the background for the development of the dual GLP-1/glucagon co-agonists [99]. The potency of the different GLP-1/glucagon co-agonists differ and some has been stopped in the development phase, while others are still in development, e.g. servodutide generating a weight loss of about −15% after 46 weeks [108,110]. Since both GLP-1 and glucagon therapies are associated with nausea and vomiting, the adverse events profile is of major interest, but seems to be acceptable and comparable to the well described during treatment with a GLP-1 RA. The potential of cardiovascular adverse effects of glucagon needs to be evaluated in larger and probably dedicated studies.

Several trials in MASLD using GLP-1-based therapy have been reported. The greatest reduction in liver fat has been reported with the triple agonists retatrutide, GIP/GLP-1/glucagon agonists and with FGF21 analogs [116,121,129]. The reduction in liver fat was about 47% after 52 weeks with tirzepatide, and approximately 50% with semaglutide after 52 weeks [42,76,130]. In relation to metabolic dysfunction-associated steatohepatitis MASH, larger and longer trials are of interest for further assessment of the efficacy and safety and to determine whether treatment will lead to a reduction of the risk of major adverse liver outcomes. For comparison, the reduction in fibrosis after bariatric surgery in patients with MASH was greater after 5 years follow-up compared with one year after surgery [131]. Semaglutide 2.4 mg weekly is currently being studied in a 5-year phase 3 study (ESSENCE) with inclusion of about 1200 individuals with MASH (NCT04822181). In an interim analysis of the first 800 randomized people at 72 weeks semaglutide 2.4 mg demonstrated superior improvement in liver fibrosis (37.0% vs 22.5%) as well as resolution of steatohepatitis (62.9% vs 34.1%) compared with placebo [43].

And interesting dual agonist is the combination of semaglutide with the long-acting amylin analoque cagrilintide (CagriSema), which in phase 2 trials has shown excellent reductions in body weight and in people with type 2 diabetes [66]. CagriSema is currently in a phase 3 development program and the first results from REDEFINE-1 reported a weight loss of – 22.7% with cagrisema 2.4 mg compared with – 16.1% for semaglutide 2.4 mg and – 11.8% with cagrilintide compared with −2.3% with placebo.

It has been observed in most studies that the weight loss in people with type 2 diabetes is less than that obtained in obese people without diabetes. There is currently no explanation for this difference, but in some cases treatment with other antidiabetic drugs, e.g. insulin and sulfonylurea, which are associated with risk of increased body weight, may contribute.

The adverse events with the GLP-1-based AOD are primarily the well-known, nausea, vomiting, diarrhea or constipation and abdominal pain, which necessitate a careful and slow uptitration to safely obtain the maximal dose. Other adverse effects are gall bladder disease with risk of gall stone pancreatitis. A new adverse event with the GLP-1 based AOD is altered skin sensations such as dysesthesia, hyperesthesia, skin pain, paresthesia and alopecia with oral (50 mg) and subcutaneous semaglutide [54]. Also with the triple agonist retatrutide more skin events were described [123]. The percentage of participants who had stopped the treatment in the discussed phase 2 and 3 studies is up to 30% and even higher in some studies.

In most studies about 2/3 of the weight loss has been explained by loss of fat tissue and about 1/3 in lean body mass (muscles). To minimize the loss of muscle mass, it is very important to include physical activity in the weight loss program, also because physical activities have multiple other health benefits [132].

GLP-1 agonists have been used in the treatment of type 2 diabetes since 2005 and in the treatment of obesity and overweight since 2021 (semaglutide 2.4 mg) in high doses. Tirzepatide has only been approval since 2023 for treatment of obesity and overweight. The information of the adverse effects of future GLP-1/glucagon agonists and GIP/GLP-1/glucagon triple agonists are primarily from short-term phase 2 studies with few participants. It is crucial to assess benefits and adverse events of these new pharmacotherapies to fully understand the long-term impact of major weight loss on i.e. type 2 diabetes, liver disease, cardiovascular disease, risk of cancers, retinal disease, sarcopeni, osteoporose, malnutrition and psychological problems and tolerability. Today, the longest randomized study is about 4 years including 17,600 participants.

The individual variability in response to obesity treatment is substantial [133]. At present we cannot predict the weight loss in the individual participants, and we do not know why a given subgroup did not respond with the expected weight loss. Current recommendation is that AOD should be discontinued if loss of at least 5% in body weight has not occurred after 12 weeks of use.

A very important point is how to maintain the weight loss. Studies with semaglutide and tirzepatide have demonstrated rapid weight regain when treatment is stopped [34]. Does this mean that pharmacological treatment needs to be life-long? Probably yes, but hopefully the weight loss can be maintained with lower doses of AOD when combined with a more healthy lifestyle [134]. Adherence to treatment is another problem, and one year treatment discontinuation rates in real -world studies are high, probably also because of high out of pocket cost, lack of long-term studies and safety concerns.

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Declaration of interest

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Throughout the development of GLP-1RAs, JJ Holst has had numerous contacts with the pharmaceutical industry and has been a member of advisory boards and given paid lectures. Most contacts have been with Merck and Novo Nordisk. Currently, they are a member of advisory boards for Novo Nordisk and gives occasional paid lectures for this and other companies. JJ Holst is a cofounder and a member of the board of Antag Therapeutics.

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