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Emerging Pharmacotherapies for Obesity: A Systematic Review

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Abbreviations:

AMPK, adenine monophosphate–activated protein kinase; BMI, body mass index; CI, confidence interval; COVID-19, Coronavirus Disease 2019; FDA, Food and Drug Administration; $GABA_A$, γ-Aminobutyric acid sub-type A; GIP, glucose-dependent insulinotropic peptide; GLP-1, glucagon-like peptide 1; GLP-2, glucagon-like peptide-2; ID, initial dose; MASH, metabolic dysfunction-associated steatohepatitis; MASLD, metabolic dysfunction-associated steatotic liver disease; MeSh, Medical Subject Headings; MetAP2, methionine aminopeptidase 2; OR, odds ratio; OXM, oxyntomodulin; PRIME, Priority

Medicine; RAs, receptor agonists; RCT, randomized controlled trial; SD, standard deviation; SE, standard error; SGLT, sodium-glucose cotransporter.

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Abstract

The history of anti-obesity pharmacotherapies is marked by disappointments, often entangled with societal pressure promoting weight loss and the prevailing conviction that excess body weight signifies a lack of willpower. However, categories of emerging pharmacotherapies generate hope to reduce obesity rates. This systematic review of phase 2 and phase 3 trials in adults with overweight/obesity investigates the effect of novel weight loss pharmacotherapies, compared to placebo/control or Food and Drug Administration-approved weight loss medication, through searching Medline, Embase, and ClinicalTrials.gov (2012-2024). We identified 53 phase 3 and phase 2 trials, with 36 emerging anti-obesity drugs or combinations thereof and four withdrawn or terminated trials. Oral semaglutide 50 mg is the only medication that has completed a phase 3 trial. There are 14 ongoing phase 3 trials on glucagon-like peptide-1 (GLP-1) receptor agonists (RAs) (ecnoglutide, orforglipron, TG103), GLP-1 RA/amylin agonist (CagriSema), GLP-1/glucagon RAs (mazdutide, survodutide), GLP-1/glucose-dependent insulinotropic polypeptide and glucagon RA (retatrutide), dapagliflozin, and the combination sibutramine/topiramate. Completed phase 2 trials on incretin-based therapies showed a mean percent weight loss of 7.4–24.2%. Almost half of the drugs undergoing phase 2 trials were incretin analogs. The obesity drug pipeline is expanding rapidly, with the most promising results reported with incretin analogs. Data on mortality and obesity-related complications, such as cardio-renal-metabolic events, are needed. Moreover, long-term follow-up data on the safety and efficacy of weight maintenance with novel obesity pharmacotherapies, along with studies focused on under-represented populations, cost-effectiveness assessments, and drug availability, are needed to bridge the care gap for patients with obesity.

Significance Statement

Obesity is the epidemic of the 21st century. Except for the newer injectable medications, drugs with suboptimal efficacy have been available in the clinician's armamentarium. However, emerging alternatives of novel agents and combinations populate the obesity therapeutic pipeline. This systematic review identifies the state and mechanism of action of emerging pharmacotherapies undergoing or having completed phase 2 and phase 3 clinical trials. The information provided herein furthers the understanding of obesity management, implying direct clinical implications and stimulating research initiatives.

1. Introduction

Obesity is the global epidemic of the 21st century (Blüher, 2019; Chakhtoura et al., 2023a; Chakhtoura & Mantzoros, 2023; Koliaki et al., 2023; Upadhyay et al., 2018). Obesity rates are alarmingly increasing, with an almost three-fold expansion worldwide since 1975 (Blüher, 2019; Koliaki et al., 2023; Lingvay et al., 2024). According to the World Health Organization, over 66% of the adult population in the United States has either overweight or obesity, with a projected further increase by 2030 (Kokkorakis et al., 2023a; Ward et al., 2019). Besides, the prevalence of various cardiometabolic diseases increased alongside the rapid growth of obesity rates, leading to higher morbidity and mortality (Boutari & Mantzoros, 2022; Kokkorakis et al., 2023b; Kokkorakis et al., 2024b).

The three most common components of lifestyle interventions for treating obesity include the prescription of a healthy, moderately reduced-calorie diet, a program of increased physical activity, and the implementation of behavioral strategies to support adherence to diet and physical activity recommendations (American College of Cardiology/American Heart Association Task Force on Practice Guidelines, 2014; Jensen et al., 2014; Wadden et al., 2020). In comprehensive lifestyle interventions, individuals with overweight or obesity are generally advised to follow a diet that creates an energy deficit of at least 500 kcal/day. This is typically achieved by recommending a daily intake of 1200 to 1500 kcal for women, and 1500 to 1800 kcal for men (Jensen et al., 2014; Liu et al., 2022). It is also recommended to increase aerobic physical activity, such as brisk walking, to at least 150 minutes per week (equivalent to 30 minutes per day on most days) (Jensen et al., 2014). To maintain weight loss or minimize weight regain over the long term (beyond one year), higher levels of physical activity, around 200 to 300 minutes per week, are advised (Jensen et al., 2014). Additionally, a structured behavior change program should incorporate regular self-monitoring of food intake, physical activity, and body

weight monitoring on a weekly basis or more frequently (Jensen et al., 2014). Compared to baseline, a high-intensity lifestyle program allows mean reductions of 5-8% of total body weight, along with improvement in cardio-renal-metabolic comorbidities (Boutari et al., 2023; Wadden et al., 2020). Despite their potential benefits, such interventions tend to yield only temporary changes that are difficult to sustain over time or are frequently insufficient to achieve a modest weight loss of 5–10%, necessary for a significant reduction in comorbidities and improvement in the quality of life (Ryan & Yockey, 2017; Williamson, 2017). Consequently, medical, endoscopic, and surgical interventions are recommended to enhance weight outcomes (Apovian et al., 2015; Garvey et al., 2016; Glass et al., 2019; Jensen et al., 2014; Kokkorakis et al., 2023a; Williamson, 2017). Pharmacotherapy is indicated when body mass index (BMI) is ≥30 kg/m^2 or ≥27 kg/m^2 in the presence of comorbidities (Grunvald et al., 2022); (Apovian et al., 2015; Garvey et al., 2016). The indications for surgical interventions were recently revised, and bariatric surgery is now recommended when BMI is ≥35 kg/m^2 and should be considered for those with a BMI of ≥30 kg/m^2 in the presence of comorbidities (Eisenberg et al., 2022, 2023). Achieving and sustaining a healthy weight is the primary aim of treating obesity, which in turn is expected to prevent and improve obesity-related complications, including type 2 diabetes, metabolic syndrome, cardiovascular disease, and metabolic dysfunction-associated steatotic liver disease (MASLD), and to positively impact quality of life (Garvey et al., 2016; Kokkorakis et al., 2024b).

The currently available medications for weight reduction either decrease appetite or modify the absorption of calories. The Food and Drug Administration (FDA) has approved six agents for chronic weight management, including orlistat 120 mg three times daily, phentermine-topiramate 15 mg/92 mg daily, naltrexone-bupropion 32 mg/360 mg total daily dose, liraglutide

3.0 mg daily, semaglutide 2.4 mg weekly, and recently tirzepatide 15 mg weekly (Chakhtoura et al., 2023a; Müller et al., 2018; ZEPBOUND, 2023). Even though obesity has been officially recognized as a chronic disease by the American Medical Association since 2013, and the Centers for Disease Control and Prevention reports that the prevalence of adult obesity in the United States is 41.9% (2017-March 2020), it is estimated that only 2% of patients with overweight or obesity in the United States were ever prescribed medications for weight loss (CDC, 2023; Kyle et al., 2016; Semla et al., 2017). This is mainly due to avoiding the discussion of obesity as a medical problem during clinic visits or stigmatization associated with the topic (Kanj & Levine, 2020). Additionally, some anti-obesity medications currently come with potential adverse effects, and several previously FDA-approved anti-obesity agents have been withdrawn due to serious adverse effects (Kanj & Levine, 2020). In addition, the newest potent approved medications are administered as injections, which may constitute a barrier to some patients (Chao et al., 2022). Lastly, a lack of insurance coverage for chronic weight loss agents, along with a scarcity of board-certified obesity medicine physicians or trained specialists, appear to contribute to the under-treatment of obesity (Gomez & Stanford, 2018). While there is an apparent worldwide shortage due to high global demand for injectables and a worldwide underproduction, additional formulations that can satisfy the market/patients' needs are worth receiving increased attention (Bailey et al., 2023). Nonetheless, there is a continuous effort to overcome some of the aforementioned problems, and hence, multiple drugs are currently being developed for medical weight management, with some already in phase 3 clinical trials and others still at earlier stages of development. Not only single agents are being explored, but also combinations, including dual and triple agonists, most likely driven by successful results on

glycemic control in patients with type 2 diabetes or inspired by the gut hormonal changes that occur following bariatric surgery (Ji et al., 2022).

Although several reviews have described the available pharmacotherapy options for chronic weight management, to the best of our knowledge, there is no previous systematic review covering all drugs in the pipeline for managing obesity (Alkhezi et al., 2023; Melson et al., 2024; Ryan, 2021, 2022; Srivastava & Apovian, 2018; Yanovski & Yanovski, 2021). Our primary objective is to describe the emerging pharmacotherapies for the management of adult patients with obesity. Our secondary objectives are to map the main geographic locations and funders of emerging drug trials and to explore the reasons for the withdrawal or suspension of drugs during their development.

2. Materials and methods

This systematic review is registered on PROSPERO (CRD42023428157) (Chakhtoura et al., 2023b).

2.1. Eligibility criteria

We included phase 2 or 3 trials conducted in adult participants (≥18 years) with obesity (BMI ≥30 kg/m^2 or ≥27 kg/m^2, or their equivalent cutoffs in Asian populations, with at least one obesity-related comorbidity, in whom there is an indication to treat with drug therapy,), investigating a new pharmacologic intervention, compared to placebo or an FDA-approved weight-reducing medication (orlistat, phentermine-topiramate, naltrexone-bupropion, semaglutide, liraglutide, and tirzepatide), with weight or BMI being a primary outcome. Exclusion criteria were pregnant women, children, and adolescents, trials exclusively enrolling patients with certain comorbidities that can potentially affect weight or BMI or can affect the response to weight-reducing medications (i.e., studies exclusively enrolling patients with type 2

diabetes and/or pre-existent cardiovascular disease, patients who had undergone bariatric surgery, patients with psychiatric diseases, polycystic ovary syndrome, or common orthopedic disorders, patients with lipodystrophy, or human immunodeficiency virus, and patients on chronic use of glucocorticoids). Besides, trials were excluded when the intervention was an FDA-approved medication for chronic weight management, surgery, supplements (including herbal), behavioral intervention, diet, or device, as well as trials with BMI/weight as a secondary or tertiary outcome and phase 1 studies.

Although we excluded trials on patients with specific comorbidities, we briefly describe pivotal cardiovascular outcomes trials investigating drugs in the pipeline of obesity pharmacotherapy to highlight the multisystem beneficial effects of future cardiometabolic agents.

2.2. Search strategy

We conducted a thorough systematic search in Medline and Embase from January 1st, 2012, to May 16th, 2024 (Appendix 1) (CRD42023428157). The search included Medical Subject Headings (MeSh) terms and Keywords relevant to obesity, body mass index, clinical trials, and investigational drugs (Appendix 1). Our search was limited to the period following 2012, in line with the new FDA-issued guidance on obesity pharmacotherapy (Kaul, 2012). We searched ClinicalTrials.gov from January 1st, 2012, to May 24th, 2024, using the following criteria: interventional phase 2 and phase 3 trials enrolling adults and older adults with obesity (or overweight and at least one cardiometabolic risk factor), without restricting to specific drugs. In addition, we manually screened previous reviews on obesity pharmacotherapy to identify potential studies (Alkhezi et al., 2023; Chakhtoura et al., 2023a; Ryan, 2021, 2022; Srivastava & Apovian, 2018; Yanovski & Yanovski, 2021).

2.3. Screening process

Pairs of two researchers (MK, CR, JAR, MG) reviewed the title and abstract of the retrieved citations from Medline and Embase, in duplicate and independently, using an a priori prepared screening form based on the population, intervention/comparator, and outcome of interest. Similarly, groups of five researchers (MK, CR, JAR, MG, LVV) screened the retrieved clinical trials from ClinicalTrials.gov. We included citations kept by at least one reviewer for the full-text screening. The full-text screening followed the same process. We reported the reasons for exclusion (Appendix 2). In case of discrepancy, the reviewers sought advice from a content expert (MC or CSM). For each step, the reviewers conducted a calibration exercise on a sample of abstracts, full-text articles, and registered trial records until the discrepancy between them fell below 5%; this was done to ensure standardization in the screening process. Group discussions were conducted to resolve disagreements between authors during the screening of articles for inclusion.

2.4. Data extraction

We conducted data extraction in duplicate and independently.

For completed and published studies, we abstracted data on population characteristics (age, gender, BMI), sample size, intervention and comparator (with dose, administration mode, and duration, when applicable), mechanism of action, results on the outcome of interest (weight or BMI), adverse events, name of the pharmaceutical company producing the intervention, and the trial registration number on ClinicalTrials.gov.

For ongoing studies and for completed studies without published results, we abstracted data on population characteristics (age, gender, BMI), sample size, intervention, comparator (with dose, administration mode, and duration, when applicable), mechanism of action, primary

outcomes(s), expected completion date, location, name of the pharmaceutical company producing the intervention, registration number on ClinicalTrials.gov.

2.5. Risk of bias assessment

We assessed the risk of bias of the included studies using the Cochrane risk of bias assessment tool 2019, in duplicate and independently (https://methods.cochrane.org/bias/resources/rob-2-revised-cochrane-risk-bias-tool-randomized-trials).

3. Results

Figure 1 outlines the flow diagram of our systematic review. Our search strategy yielded a total number of 3,187 citations from Medline and Embase, after removing duplicates, and 1,470 records from ClinicalTrials.gov. In total, we included the following: 15 phase 3 trials on 10 drugs, one of which is completed (Table 1), and 14 ongoing trials on nine drugs (Table 2); 38 phase 2 trials on 32 drugs or combinations thereof: 24 completed trials, 16 with available published results (Table 1), 8 without results (Table 3), and 14 ongoing trials (Table 4). We also identified three terminated studies and one suspended study. Figure 2 demonstrates a schematic overview of all anti-obesity drugs (total of 36) under development in phase 2 and phase 3 clinical trials (ongoing and completed). The completed phase 2 and phase 3 trials showed that >50% of enrolled participants were women, except for one trial on retatrutide, where >50% were men. The range of mean age was 34–57 years, and the range of mean baseline BMI was 31–32 kg/m^2 for trials in China and 35–40 kg/m^2 for studies from the USA, Europe, and Australia (Table 1).

3.1. Drugs in phase 3 trials

Nine drugs for the management of obesity are currently in phase 3 trials (a total of 14 ongoing trials), and one drug (oral semaglutide) has completed a phase 3 trial with published results (Tables 1 and 2). The ongoing phase 3 trials are on the following drugs (alphabetical order): CagriSema, dapagliflozin, ecnoglutide, mazdutide, orforglipron, retatrutide, sibutramine/topiramate XR, survodutide, and TG103. All these trials are placebo-controlled, except two trials on CagriSema, comparing it to semaglutide or tirzepatide. The main site of action of each pharmacologic agent currently in phase 3 is described in Figure 3. The majority of agents that progressed to phase 3 are acting on glucagon-like peptide 1 (GLP-1) receptors either i) alone as an oral preparation (orforglipron, semaglutide) or subcutaneous preparation (ecnoglutide, TG103) or ii) in combination with other molecules (i.e., GLP-1 receptor agonist (RA) and amylin [CagriSema], dual agonists [GLP-1 and glucagon RAs (mazdutide, survodutide)], or triple agonist [GLP-1, glucose-dependent insulinotropic peptide (GIP), and glucagon RA (retatrutide)]). GLP-1 and GIP, via their respective pancreatic islet β-cell receptors, induce the "incretin effect", enhancing insulin release in response to nutrient/carbohydrate ingestion, with a higher secretion with oral compared to intravenously administered glucose (Nauck et al., 1986a). In healthy individuals, GIP seems to contribute more than GLP-1 to this phenomenon (Gasbjerg et al., 2020). Patients with type 2 diabetes demonstrate an impaired incretin effect, showing a loss of pancreatic β-cell responsiveness to GIP (Nauck et al., 1986b). Patients with obesity have impaired incretin secretion (Højberg et al., 2009). Dapagliflozin is a sodium-glucose cotransporter (SGLT) 2 inhibitor that promotes renal excretion of glucose (Kasichayanula et al., 2014). Sibutramine/Topiramate XR primarily acts centrally on norepinephrine, serotonin, dopamine reuptake inhibition, and γ-aminobutyric acid sub-type A ($GABA_A$) receptor stimulation (Halpern et al., 2010; Pearl et al., 2023). Only 29% of all ongoing

phase 3 trials reported lifestyle modifications (i.e., dietary and exercise education) for all participants on ClinicalTrials.gov (Table 2). However, it is possible that lifestyle interventions were not reported on ClinicalTrials.gov despite being part of the trials. Specifically, one randomized controlled trial (RCT) includes a run-in period before randomization to drug therapy initiating lifestyle interventions (physical activity, nutrition counseling, and behavior modification counseling) (NCT06000462). Two ongoing phase 3 RCTs list regular diet and exercise as part of their inclusion criteria (NCT05813795; NCT05997576), and another RCT offers counseling to all participants to make changes to their diet and exercise regularly (NCT06066515).

3.1.1. Drug with completed and published phase 3 trial

Semaglutide (oral)

Semaglutide, a GLP-1 RA, has been approved for chronic weight management as a subcutaneous injection. GLP-1 is an incretin hormone that is secreted from the L cells of the lower intestine, i.e., the distal ileum and colon. GLP-1 delays gastric emptying. However, this effect seems to be transient (Fig. 3) (Kokkorakis et al., 2023a; van Bloemendaal et al., 2014). Additionally, GLP-1 RAs reduce gastric and small bowel motility through mechanisms dependent on the central nervous system and myenteric neurons in mice, though these effects can be subject to tachyphylaxis (Baggio & Drucker, 2014). GLP-1 activity in the brain activates various circuits associated with stress responses, aversion, anorexia, hypothalamic-pituitary function, neuroinflammation, and neuroprotection (Baggio & Drucker, 2014). Numerous GLP-1 receptor neurons are dispersed throughout at least ten different regions in the central nervous system of mice and rats, including the hypothalamus and hindbrain, which translate pharmacological signals from GLP-1 RAs into the behavioral outcome of reduced food intake

(Baggio & Drucker, 2014). Reflecting these results, selectively targeting GLP-1 receptor neurons in the hypothalamus or hindbrain does not fully diminish the weight-loss effects of GLP-1 RAs in rodents (Baggio & Drucker, 2014). Consequently, other regions like the parietal cortex, dorsal medial nucleus of the hypothalamus, arcuate nucleus, and the nucleus of the solitary tract are also involved (Fig. 2, Fig. 3) (Baggio & Drucker, 2014).

In the OASIS 1 phase 3 RCT, 667 participants (mean age 49 years, mean BMI 37.5 kg/m²) were randomly assigned to once daily oral semaglutide 50 mg (n=334) or placebo (n=333) (Table 1) (Knop et al., 2023; NCT05035095). From baseline to week 68, the estimated mean body weight change was -15.1% (standard error [SE] 0.5) with oral semaglutide 50 mg versus -2.4% (SE 0.5) with placebo (Fig. 4) (coprimary endpoint; estimated treatment difference -12.7%, 95% confidence interval [CI] -14.2 to -11.3, $p<0.0001$) (Knop et al., 2023). With oral semaglutide 50 mg once daily, compared to placebo, at week 68, more participants reached body weight reductions of ≥5% (odds ratio [OR] 12.6, 95% CI 8.5–18.7), 10% (OR 14.7, 95% CI 9.6–22.6), 15% (OR 17.9, 95% CI 10.4–30.7), and 20% (OR 18.5, 95% CI 8.8–38.9) (Knop et al., 2023). Adverse events occurred in 307 (92%) of 334 participants on oral semaglutide 50 mg and 285 (86%) of 333 participants on placebo. The most common adverse events were related to the gastrointestinal tract (including nausea, constipation, diarrhea, and vomiting) and were more common with semaglutide. Additionally, altered skin sensation was experienced by 13% of subjects receiving oral semaglutide 50 mg, and only 1% of participants on placebo (Appendix 3) (Knop et al., 2023). Coronavirus Disease 2019 (COVID-19) infection occurred in one-third of participants in both arms (Appendix 3) (Knop et al., 2023).

3.1.2. Drugs currently investigated in phase 3 trials

GLP-1 RAs

We identified three GLP-1 RAs that are now being investigated in phase 3 trials: orforglipron, ecnoglutide, and TG103 (Table 2).

Orforglipron

Orforglipron, also known as LY3502970, is a potent oral non-peptide partial GLP-1 RA with a more pronounced impact on cyclic adenosine monophosphate signaling compared to its influence on β-arrestin recruitment, potentially leading to reduced receptor desensitization when compared to complete GLP-1 RA agonists (Fig. 2, Fig. 3) (Pratt et al., 2023). The mean half-life of orforglipron ranges from 28.7 to 49.3 h across all doses (Pratt et al., 2023). Orforglipron is administered as a once daily oral agent (Pratt et al., 2023). Since it is a small molecule, it does not have specific requirements for administration, simplifying its use, as it can be taken without food or water restrictions (Pratt et al., 2023).

In a multicenter phase 2 trial, 272 participants (mean age 54.2 years, mean BMI 37.9 kg/m^2) were randomly assigned to one of four doses of oral orforglipron (12, 24, 36, or 45 mg) once daily or placebo, for 36 weeks (Wharton et al., 2023). At 26 weeks, the mean percentage change from baseline in body weight was -8.6 (95% CI -10.2 to -6.9), -11.2 (95% CI -12.8 to -9.6), -12.3 (95% CI -13.8 to -10.7), and -12.6 (95% CI -14.1 to -11.1) with the following daily doses, respectively, 12 mg, 24 mg, 36 mg, and 45 mg, compared to -2.0 (95% CI -3.6 to -0.4) with placebo (Wharton et al., 2023). At 36 weeks, the mean percentage change from baseline in body weight ranged from -9.4 (95% CI -11.5 to -7.4) to -14.7 (95% CI -16.5 to -12.8) with orforglipron and was -2.3 (95% CI -4.3 to -0.4) with placebo (Wharton et al., 2023), with a trend for a smaller effect with the lowest dose of 12 mg compared to the three other doses (Table 1,

Fig. 4). The most commonly described adverse events with orforglipron were gastrointestinal events, which occurred more frequently than with placebo, but were mild to moderate in severity, and occurred primarily during dose escalation; discontinuation rate due to adverse events was reported in 10–17% of participants (Wharton et al., 2023). The safety profile of orforglipron was consistent with other GLP-1 RAs (Appendix 3) (Wharton et al., 2023).

Currently, an ongoing phase 3 trial of orforglipron (ATTAIN-1), plans to recruit 3,000 participants with obesity or overweight (along with at least one treated or untreated weight-related comorbidity) from the United States, Europe, and Asia, who will be receiving undisclosed oral doses of the drug or placebo for 72 weeks and is expected to be completed in September 2027 (Table 2) (NCT05869903). ATTAIN-1 aims to investigate the mean percent change from baseline in body weight to week 72 as a primary outcome (NCT05869903). Another ongoing phase 3 trial (ATTAIN-J) administers undisclosed doses of oral orforglipron, (NCT05931380), targeting exclusively Japanese individuals, and aims to include 236 participants with a BMI of 27−35 kg/m² and at least two obesity-related comorbidities (treated or untreated) or a BMI ≥35 kg/m² and at least one obesity-related comorbidity (treated or untreated) (Table 2). In this RCT, participants must have reported at least one unsuccessful dietary effort to lose body weight (NCT05931380). ATTAIN-J aims to investigate as primary outcomes the mean percent change in body weight and percentage of participants achieving ≥5% body weight loss from baseline to week 72 (NCT05931380).

Ecnoglutide

Ecnoglutide, also known as XW003, is an engineered GLP-1 analog, administered as a weekly subcutaneous injection, that is currently under investigation (Fig. 2) (Guo et al., 2023). The phase 2 trial enrolled 206 participants from Australia and compared 3 doses of 1.2 mg, 1.8,

and 2.4 mg weekly to liraglutide 3 mg daily for 26 weeks (Table 3) (NCT05111912). The trial was completed in 2022, but the results have not yet been published. Ecnoglutide is currently in a phase 3 RCT aiming to include 664 Chinese individuals with a BMI >24 kg/m^2 and <28 kg/m^2 with at least one comorbidity, expected to be completed in January 2025 (Table 2) (NCT05813795). This trial will investigate the percent change in body weight as well as the percentage of patients with ≥5% weight reduction as primary outcomes (Table 2) (NCT05813795).

TG103

TG103 is a novel GLP-1/Fc fusion protein, similar to the GLP-1 RA dulaglutide, administered as a weekly subcutaneous injection (Fig. 2). The phase 2 trial is currently marked as ongoing on ClinicalTrials.gov in China, comparing 2 doses of TG103 15 mg and 22.5 mg subcutaneously weekly, to placebo on 195 participants with overweight or obesity (Table 4) (NCT05299697). The phase 3 trial is also currently ongoing in China, administering TG103 7.5 mg increasing to 22.5 mg subcutaneously once weekly, compared to placebo, for 40 weeks in adult participants with obesity or overweight (accompanied by one cardiometabolic comorbidity), expected to be completed in April 2025 (Table 2) (NCT05997576). This trial investigates the relative change in body weight as well as the percentage of patients with ≥5% weight reduction as primary outcomes (Table 2) (NCT05997576).

GLP-1 RA and amylin analog

CagriSema

CagriSema refers to the co-administration of cagrilintide, a long-acting amylin analog with a half-life of 168–192 h that reduces food intake and body weight in a dose-dependent manner, and semaglutide, a GLP-1 RA with a half-life of 145–165 h (Fig. 2, Fig. 3). Amylin, a

hormone produced by pancreatic β cells, is released alongside insulin after food intake. This hormone plays a role in signaling feelings of fullness, impacting both the body's energy balance mechanisms and pleasure-related brain regions centrally, while peripherally, it delays gastric emptying and reduces the glucagon response after meals (Boyle et al., 2018; Zakariassen et al., 2020). Amylin's influence on appetite and satiety occurs in specific brain regions, particularly the area postrema and nucleus of the solitary tract in the hindbrain (Fig. 3). Additionally, it is believed that amylin affects food choices through receptors present in the hypothalamus, ventral tegmental area, and latero-dorsal tegmental nucleus (Boyle et al., 2018). Evidence shows that the combination CagriSema appears to have a synergistic effect compared to cagrilintide monotherapy and/or semaglutide monotherapy. In a phase 1b trial, cagrilintide, at various doses, was compared to placebo, while all the trial participants received semaglutide (Enebo et al., 2021). There was a significant difference in weight loss of 6-7% in the arms receiving cagrilintide at doses of 1.2, 2.4, and 4.5 mg, with concomitant semaglutide, compared to semaglutide alone (Enebo et al., 2021). A multicenter phase 2 RCT (NCT04982575) in patients with type 2 diabetes mellitus showed that treatment with CagriSema resulted in significantly greater weight loss of 15.6% compared to 8.1% with cagrilintide alone ($p<0.0001$) and 5.1% with semaglutide alone ($p<0.0001$) at 32 weeks (Frias et al., 2023). In the same RCT, CagriSema treatment resulted in a 2.2 percentage point reduction in HbA1c, which was greater than the 0.9 percentage point reduction with cagrilintide alone ($p<0.0001$) but not significantly different from the 1.8 percentage point reduction with semaglutide alone ($p=0.075$) (Frias et al., 2023). However, CagriSema showed a greater improvement in other glycemic parameters, such as fasting plasma glucose (-3.3 mmol/L) compared to cagrilintide (-1.7 mmol/L), and time in the target glucose range of 3.9–10 mmol/L (88.9% vs 71.7% for cagrilintide) (Frias et al., 2023).

These potential synergistic effects of CagriSema on weight loss and glycemic control suggest that the combination of cagrilintide and semaglutide may have complementary mechanisms of action compared to the individual components.

We identified four ongoing phase 3 trials on CagriSema (Table 2). The REDEFINE 1 trial enrolls 3,400 participants with overweight or obesity (BMI ≥30 kg/m^2 or ≥27 kg/m^2 with comorbidities) from United States or Europe, who will receive once weekly subcutaneous CagriSema 2.4 mg/2.4 mg (cagrilintide 2.4 mg, semaglutide 2.4 mg), or cagrilintide 2.4 mg alone, or semaglutide 2.4 mg or a matched placebo for 68 weeks, and is expected to be completed in October 2026 (Table 2) (NCT05567796). The primary outcomes of this trial are the relative change in body weight and the proportion of participants achieving ≥5% weight reduction from baseline to week 68 (NCT05567796). Two other similar trials are currently ongoing and investigate the effect of CagriSema 2.4 mg/2.4 mg compared to placebo/semaglutide 2.4 mg in adults with overweight or obesity in an Asian population, China (n=300) or Japan/Taiwan (n=330), expected completion in 2025 (Table 2) (NCT05813925; NCT05996848). One ongoing trial compares CagriSema to tirzepatide in adults with obesity from the United States over 72 weeks and investigates the percent change in body weight as a primary outcome, also expected to be completed in 2025 (Table 2) (NCT06131437).

Another phase 3 RCT (REDEFINE 3; (NCT05669755)) is currently ongoing with the aim to recruit 7,000 participants and investigate the effects of CagriSema 2.4 mg/2.4 mg on cardiovascular events (i.e., cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke).

GLP-1 and glucagon RAs

We identified two dual GLP-1 and glucagon RAs currently undergoing phase 3 trials: mazdutide and survodutide. These molecules mimic, albeit with different glucagon receptor and GLP-1 receptor activity balance, the action of oxyntomodulin (OXM), an anorectic gut proglucagon-derived peptide co-secreted with peptide YY, that serves as a dual agonist for both glucagon receptor and GLP-1 receptor (Table 2) (Holst et al., 2018; Klein et al., 2024). OXM activates the glucagon receptor and GLP-1 receptor and promotes weight loss through elevated energy expenditure and decreased energy intake in humans (Wynne et al., 2006; Wynne et al., 2005). Glucagon is a peptide hormone secreted from the alpha cells of the pancreatic islets of Langerhans (Rix et al., 2000). Glucagon release is stimulated by hypoglycemia, amino acids, and GIP, whereas hyperglycemia and GLP-1, as well as other factors such as somatostatin, insulin, zinc, and potentially amylin, inhibit glucagon release (Rix et al., 2000). Glucagon regulates plasma glucose concentrations during fasting, exercise, and hypoglycemia through an increased hepatic glucose output to the circulation (Rix et al., 2000). Specifically, glucagon promotes glycogenolysis, stimulates gluconeogenesis, and inhibits glucose glycolysis and glycogenesis (Rix et al., 2000). The role of the glucagon-glucagon receptor axis has been extensively studied in maintaining euglycemia in response to an overnight fast (Conceição-Furber et al., 2022). Besides, small-scale studies support the ability of glucagon receptor activation to increase metabolic rate in both fed and fasted conditions, making the glucagon-glucagon receptor axis an attractive therapeutic approach to combine with anti-obesity medications that work by reducing caloric intake (Nair, 1987; Salem et al., 2016; Stahel et al., 2019; Tan et al., 2013). In the liver, glucose metabolism is mainly regulated by, among other hormones, insulin and glucagon, as well as by substrate availability (Scoditti et al., 2024). Consequently, hepatic glucagon resistance is expected to have an important role in the pathophysiology of metabolic dysfunction-associated

steatohepatitis (MASH) (Suppli et al., 2016), and therefore, glucagon receptor agonism may exert direct hepatic benefits, independent of weight reduction, which are additive to incretin therapy (Brouwers et al., 2024). In preclinical studies, cotadutide, a GLP-1/glucagon receptor co-agonist, reduced liver fat, de novo lipogenesis, and induced MASH resolution (Boland et al., 2020). In a phase 2a trial investigating the efficacy and safety of the GLP-1/glucagon receptor co-agonist efinopegdutide in patients with non-alcoholic fatty liver disease, glucagon receptor agonism appeared to potentially reduce liver fat content by acting on the liver directly to stimulate fatty acid oxidation and reduce lipogenesis (Romero-Gómez et al., 2023). Further evidence from experimental physiological studies suggests that GLP-1 and glucagon exhibit a dose-dependent synergistic effect, resulting in a greater reduction in food intake and an increase in resting energy expenditure than when each hormone is administered individually (Hope et al., 2021). Furthermore, this combination allows the use of lower doses of individual hormones, therefore widening the therapeutic window and avoiding toxicity. So far, GLP-1 and glucagon RAs have overall demonstrated favorable cardio-metabolic outcomes by achieving a significant weight loss and reduction in HbA1c lipid parameters (Hope et al., 2021; Ji et al., 2022; Melson et al., 2024). However, current evidence is limited regarding the potential drawbacks of combining glucagon with GLP-1, which has a glucagonostatic action accounting for 50% of its blood glucose lowering ability, which may lead to opposing effects on blood glucose levels (Finan et al., 2015; Hare, 2010). Additionally, activation of the glucagon receptor leads to the direct degradation of proteins and amino acids, resulting in the loss of lean mass, which significantly impacts muscle strength, as demonstrated in preclinical models (Hope et al., 2022; Hope et al., 2021). Clinical research on GLP-1/glucagon receptor co-agonists also reveals clear decreases in amino acid levels (Parker et al., 2020; Simonsen et al., 2022).

Mazdutide

Mazdutide, also known as IBI362 or LY3305677, is a synthetic dual agonist peptide hormone, analog of mammalian OXM, with a fatty-acyl group to extend its half-life. After T_{max} (the time at which the maximum concentration is observed), mazdutide concentrations declined gradually in the span of several weeks with a half-life ranging from 150.9 h to 403.5 h (Ji et al., 2021), and it is administered as a subcutaneous once weekly injection (Fig. 2, Fig. 3).

There is one ongoing phase 2 trial in the United States, enrolling 165 participants with overweight and at least one comorbidity or obesity comparing percentage weight loss of mazdutide at different doses with placebo with expected completion in May 2025 (NCT06124807). Another phase 2 trial of mazdutide in 248 participants was completed in January 2024, and its results have been published showing mean percentage changes from baseline to week 24 in body weight of -6.7% (SE 0.7) with mazdutide 3 mg, -10.4% (SE 0.7) with 4.5 mg, -11.3% (SE 0.7) with 6 mg and 1.0% (SE 0.7) with placebo (NCT04904913) (Ji et al., 2023) (Table 4). Initial data was published through a press release for a phase 2 trial of mazdutide 9 mg versus placebo for 24 weeks in 80 participants, showing a treatment difference of the mean percent change in body weight from baseline of -15.4%（95% CI: -18.8 to -11.9%) with mazdutide compared to placebo (https://www.prnewswire.com/news-releases/innovent-announces-phase-2-clinical-study-of-higher-dose-9-mg-mazdutide-ibi362-in-chinese-adults-with-obesity-achieved-the-24-week-primary-endpoint-301821038.html).

Currently, two ongoing phase 3 trials in China assess the weight-lowering effect of mazdutide in individuals with obesity or overweight (Table 2) (NCT05607680; NCT06164873). In one trial, 600 participants with overweight and obesity (BMI ≥28 kg/m², or ≥24 kg/m² and at least one concomitant cardiometabolic comorbidity) will receive a weekly subcutaneous dose of 2 mg for four weeks and thereafter 4 mg for 44 weeks or 2 mg for four weeks, followed by 4 mg

for four weeks, followed by 6 mg for 40 weeks (NCT05607680). This RCT examines the relative change in body weight and the achievement of ≥5% weight loss as primary outcomes, expected to be completed in April 2024 (NCT05607680). Another similar ongoing trial targets 450 participants with a BMI ≥30 kg/m^2 with at least one unsuccessful dietary effort to lose weight and investigates the percentage change in body weight and the proportion of participants who lose ≥5% of their baseline weight, expected to be completed in September 2025 (NCT06164873).

Survodutide

Survodutide, also known as BI 456906, is another glucagon/GLP-1 receptor dual RA with a half-life of ≥100 h in humans (Fig. 2, Fig. 3).

A phase 2 trial on survodutide (four doses of 0.6, 2.4, 3.6, and 4.8 mg) (NCT04667377) compared to placebo in 387 adults with BMI ≥27 kg/m^2 and showed mean (95% CI) changes in body weight from baseline to week 46 of -6.2% (-8.3 to -4.1; with the 0.6 mg); -12.5% (-14.5 to -10.5; with the 2.4 mg); -13.2% (-15.3 to -11.2; with the 3.6 mg); -14.9% (-16.9 to -13.0; with the 4.8 mg); -2.8% (-4.9 to -0.7; with placebo) (le Roux et al., 2024) (Table 3). A phase 3 RCT was recently launched, aiming to enroll 600 individuals with overweight or obesity, expected to be completed in January 2026 (Fig. 2) (Table 2) (NCT06066515). The intervention arms consist of survodutide 3.6 or 6 mg once weekly as subcutaneous injections or placebo injections for 76 weeks (Table 2) (NCT06066515). As primary outcomes, this trial investigates the relative change in body weight as well as the achievement of ≥5% weight loss (Table 2) (NCT06066515).

Survodutide has also completed a phase 2 trial, evaluating the percentage of patients with histological improvement of MASH, and received an FDA Fast Track Designation 2021,

followed by the EMA granting access for survodutide to the Priority Medicine (PRIME) Scheme for MASH with fibrosis (F1-F3) in November 2023 (NCT04771273) (https://www.boehringer-ingelheim.com/human-health/metabolic-diseases/survodutide-top-line-results-mash-fibrosis). Another ongoing phase 3 RCT of survodutide "SYNCHRONIZE-CVOT" is investigating the effects of survodutide effects on cardiovascular death, non-fatal stroke, non-fatal myocardial infarction, ischemia related coronary revascularization, or heart failure events, in participants with obesity and established cardiovascular or kidney disease, expected to be completed in April 2026 (NCT06077864).

GLP-1, GIP, and glucagon RAs

Retatrutide

Although both GLP-1 and GIP enhance the release of insulin and reduce glucagon secretion, they possess distinct additional functions; GLP-1 and glucagon effects have been described in sections 3.1.1. and 3.1.2. above. GIP is an incretin hormone involved in nutrient and energy metabolism (Fisman & Tenenbaum, 2021), secreted from K cells of the upper intestine, i.e., the duodenum and jejunum, when food is ingested (Fig. 2). Regarding its central mode of action, a limited amount of evidence supports that GIP receptors are expressed throughout the brain, mainly in areas involved in energy balance regulation (i.e., hypothalamus), and GIP is believed to be capable of crossing the blood-brain barrier (Fig. 3) (Samms et al., 2020). GIP has also anti-emetic effects, reducing GLP-1-induced nausea (Hayes et al., 2021). Peripherally, GIP receptor expression is detected in cultured human adipocyte-like cells ex vivo and beyond the pancreas (Fig. 3) (Hammoud & Drucker, 2023). Activating both GLP-1 and GIP receptors leverages their distinct yet synergistic actions: GLP-1 enhances insulin release and reduces appetite, while GIP improves lipid handling and white adipose tissue function (Samms et al.,

2020). GIP receptor activation in white adipose tissue aids in lipid storage and reduces lipid spillover, contributing to better metabolic control (DeFronzo, 2010; Rudovich et al., 2007). Additionally, GIP may enhance GLP-1's effectiveness by either decreasing its nausea-inducing side effects and/or expanding its access to appetite-regulating neuronal populations, e.g., in the mediobasal hypothalamus, potentially reducing caloric intake and mitigating nausea associated with GLP-1 RAs (Samms et al., 2020). Clinical evidence shows that this dual agonism approach provides superior glucose-lowering and weight-reducing effects compared to GLP-1 RAs alone, as exemplified by tirzepatide – the first dual GIP and GLP-1 RA approved for chronic weight management and type 2 diabetes (Jastreboff et al., 2022). Given the benefits of the GIP and GLP-1 co-agonism and GLP-1 and glucagon co-agonism, a triple agonist has the potential to provide a superior therapeutic approach with improved glycemic control and higher weight loss compared to single or dual RAs (Coskun et al., 2022; Rizvi & Rizzo, 2022). So far, in preclinical models, the combination of all these three receptor activities reversed diet-induced obesity and prevented diabetes progression in rodent models to a greater extent than reciprocal co-agonism at the individual receptors (Finan et al., 2015). In this study, triple co-agonism exceeded dual incretin co-agonism, i.e., GLP-1/GIP, regarding improvements in body weight and composition, an effect partially attributed to the addition of glucagon pharmacology and its subsequent potential contribution to enhancing energy expenditure and hepatic lipid metabolism (Finan et al., 2015). Additionally, it was observed in diabetic *db/db* mice that the GLP-1 and GIP counterbalanced the potential diabetogenic effect of excessive glucagon receptor agonism, which appeared more fragile when relying solely on GLP-1 to counteract glucagon action (Finan et al., 2015).

Retatrutide, also known as LY3437943, is a triple agonist of GLP-1, GIP, and glucagon receptors with a half-life of approximately six days, allowing its subcutaneous weekly administration. Retatrutide in humans is more potent at the GIP receptors and less potent at the glucagon and GLP-1 receptors (Fig. 2, Fig. 3) (Coskun et al., 2022; Jastreboff et al., 2023). In a multicenter phase 2 trial, 338 participants (mean age 48.2 years, mean BMI 37.3 kg/m^2) were randomly assigned to subcutaneous retatrutide at a dose of 1 mg, 4 mg with an initial dose (ID) of 2 mg, 4 mg with an ID of 4 mg, 8 mg with an ID of 2 mg, 8 mg with an ID of 4 mg, or 12 mg with an ID of 2 mg, or to placebo for 48 weeks (Jastreboff et al., 2023). At 48 weeks, the least-squares mean percentage change from baseline in body weight was -8.7 (95% CI -10.5 to -6.8) in the 1 mg group, -16.3 (95% CI -19.4 to -13.2) in the 4 mg with an ID of 2 mg group, -17.8 (95% CI -20.8 to -14.8) in the 4 mg with an ID of 4 mg group, -21.7 (95% CI -24.5 to -19.0) in the 8 mg with an ID of 2 mg group, -23.9 (95% CI -26.8 to -20.9) in the 8 mg with an ID of 4 mg group, -24.2 (95% CI -26.6 to -21.8) in the 12 mg with an ID of 2 mg group as compared with -2.1 (95% CI -3.5 to -0.7) in the placebo group. Therefore, the response was dose-dependent; weight loss was the same regardless of the start-up dose, and the 8 mg and 12 mg doses overlapped in terms of efficacy (Jastreboff et al., 2023) (Table 1, Fig. 4). Prespecified analyses of this study revealed that participants with a BMI of ≥35 kg/m^2 experienced greater percentage reductions in weight with retatrutide compared to those with a BMI <35 kg/m^2, and female participants experienced greater reductions than male participants (Jastreboff et al., 2023). The study drug discontinuation due to adverse events occurred in 6–16% of the individuals receiving retatrutide, while none of the participants receiving placebo discontinued the treatment. The most commonly described adverse events in the retatrutide groups were gastrointestinal; these were

dose-related, mostly mild to moderate in severity, and partially mitigated with a lower starting dose (2 mg vs 4 mg) (Jastreboff et al., 2023) (Appendix 3).

We identified one ongoing phase 3 trial on retatrutide (Table 2). TRIUMPH-1 aims to include 2,100 participants with obesity or overweight (plus at least one weight-related comorbidity), who will receive undisclosed doses of retatrutide or placebo subcutaneously once weekly for approximately 89 weeks (NCT05929066). The trial is expected to be completed in May 2026 (Table 2). This study's primary outcome is the percentage change from baseline in body weight (NCT05929066). Another phase 3 RCT on retatrutide (TRIUMPH-3; (NCT05882045)) is currently ongoing to investigate the percent change from baseline in body weight as a primary outcome in individuals with obesity and established cardiovascular disease (i.e., prior myocardial infarction, prior ischemic or hemorrhagic stroke, or symptomatic peripheral arterial disease) and is expected to be completed in February 2026.

SGLT-2 inhibitor

Dapagliflozin is an SGLT-2 inhibitor with a mean plasma half-life of approximately 12.9 h (after a single oral dose of 10 mg) and is approved for the treatment of type 2 diabetes and, more recently, chronic kidney disease and heart failure (Lv et al., 2023). SGLT-2 inhibitors in the kidney involve the inhibition of the coupled reabsorption of sodium and glucose from the proximal tubules, leading to increased renal excretion of glucose and sodium (Kasichayanula et al., 2014). Besides, it has been postulated that dapagliflozin can reduce body weight by calorie loss through glycosuria and by reducing subcutaneous and visceral abdominal adipose tissue (Pereira & Eriksson, 2019; Zheng et al., 2021).

Currently, dapagliflozin is undergoing an ongoing phase 3 RCT estimated to enroll 150 adults from Oman with a BMI >30 kg/m^2 and <35 kg/m^2, with a stable body weight, who will

receive dapagliflozin 10 mg orally once daily, metformin 1000 mg or placebo, and is expected to be completed in December 2025 (Table 2) (NCT06000462). This trial investigates the percentage of patients with ≥5% weight reduction as a primary outcome (Table 2) (NCT06000462).

Norepinephrine, serotonin, and dopamine reuptake inhibition & $GABA_A$ receptor stimulation

Sibutramine/Topiramate XR

Sibutramine is a serotonin-noradrenaline reuptake inhibitor with a half-life of approximately one hour that has been used to achieve short- and long-term modest weight loss. Sibutramine was initially approved in 1997 by the FDA at daily doses of 5, 10, and 15 mg but was withdrawn from the market in the United States and most other countries in 2010 due to increased risk of cardiovascular events ("Sibutramine," 2012). Even though sibutramine is banned in the United States and most other countries, in October 2011, the National Health Surveillance Agency in Brazil reassessed and approved the continued use of sibutramine as an anti-obesity drug, mentioning that its benefit was greater than the risk, provided that it is prescribed for the appropriate patient profile (https://www.gov.br/anvisa/pt-br/assuntos/noticias-anvisa/2018/sibutramina-e-remedios-para-emagrecer-entenda). Peripherally, sibutramine stimulates β3-adrenergic receptors to promote satiety; however, it also raises systolic and diastolic blood pressure as well as heart rate (Araújo & Martel, 2012).

Topiramate XR, an extended-release formulation of topiramate with a half-life of 55.7 h under fasting conditions and 72.5 h in the fed state, is a weak inhibitor of carbonic anhydrase. It is an FDA-approved treatment for epilepsy and the prevention of migraines (Butsch, 2015; Chung, 2015). Although the exact mechanism for its weight loss effect remains unclear, it may be associated with a decrease in compulsive or addictive food cravings by blocking α-amino-3-

hydroxy-5-methyl-4-isoxazolepropionic acid receptors and kainate receptors, reduced lipogenesis, alteration of food taste through inhibition of carbonic anhydrase isoenzymes, and possibly by enhancing energy expenditure through the activation of γ-aminobutyric acid receptors (Verrotti et al., 2011).

An ongoing phase 3 RCT, named "UNLIMITED", is currently taking place in Brazil, aiming to recruit 1855 participants with a BMI ≥27 kg/m^2 and <45 kg/m^2 (individuals with a BMI ≥27 kg/m^2 and <30 kg/m^2 must have at least one concomitant weight-related comorbidity) who will receive for 58 weeks once daily capsules of sibutramine IR 15 mg with topiramate XR 75 mg, or sibutramine IR 15 mg with topiramate XR 100 mg, or only sibutramine 15 mg, or placebo (Table 2) (Fig. 2, Fig. 3) (NCT05209984). As a primary outcome, this study aims to investigate the difference in mean percent body weight loss between study arms (NCT05209984). UNLIMITED is expected to be completed in May 2027 (NCT05209984).

3.2. Drugs in phase 2 trials

3.2.1. Drugs with completed and published phase 2 trials

We identified 16 trials exploring different drugs (Table 1). Four drugs (orforglipron [oral GLP-1 RA], retatrutide [GLP-1, GIP, and glucagon RA], mazdutide and survodutide [GLP-1 and glucagon RAs]) have progressed to phase 3 and have been described in Section 3.1. above. The remaining drugs are described in detail below (Fig. 2). Nine of the included phase 2 trials described recommendations for lifestyle changes to all participants, which include, yet are not limited to, dietary and physical education.

Amylin analog

Cagrilintide

Cagrilintide is a long-acting amylin analog with a half-life of 168–192 h that reduces food intake and body weight, as mentioned above in the phase 3 trials section, in combination with semaglutide. In a multicenter phase 2 trial, 706 participants (mean age 52.3 years, mean BMI 37.8 kg/m^2) were randomized to subcutaneous injections of once-weekly cagrilintide (0.3, 0.6, 1.2, 2.4, or 4.5 mg), once daily liraglutide 3.0 mg, or placebo for 26 weeks (Lau et al., 2021). At the end of the study, the mean percentage weight reductions from baseline were greater with all doses of cagrilintide (0.3–4.5 mg, -6.0 to -10.8%) versus placebo (-3.0%; estimated treatment difference range 3.0–7.8%; $p<0.001$) (Fig. 4) (Lau et al., 2021). Weight reductions were also greater with cagrilintide 4.5 mg versus liraglutide 3.0 mg (-10.8% vs -9.0%; estimated treatment difference 1.8%, $p=0.03$) (Lau et al., 2021). The most frequently reported adverse events with cagrilintide 0.3–4.5 mg were gastrointestinal disorders, that were more common than in the placebo arm (41–63% vs 32%), primarily nausea (20–47% vs 18%) (Appendix 3) (Lau et al., 2021).

GLP-1 RAs

In addition to orforglipron, described in Section 3.1., we identified efpeglenatide, a long-acting GLP-1 RA administered once weekly subcutaneously, and noiiglutide, a GLP-1 RA administered once daily subcutaneously. In a multicenter phase 2 trial, 295 participants (mean age 43.4 years, mean BMI 35.4 kg/m^2) were randomized to efpeglenatide (4 mg once weekly, 6 mg once weekly, 6 mg once every two weeks, or 8 mg once every two weeks) or placebo for 20 weeks (Pratley et al., 2019). At the end of the study, the least square mean percentage change from baseline in body weight with placebo was 0.1 (SE 0.6). All doses of efpeglenatide

significantly reduced body weight compared to placebo, with the least squares mean changes from baseline being -6.8% (95.1% CI -8.4 to -5.1) for 4 mg once weekly, -7.4% (95.1% CI -9.1 to -5.7) for 6 mg once weekly, -6.7% (95.1% CI -8.4 to -5.1) for 6 mg once every two weeks, and -7.5% (95.1% CI -9.2 to -5.8) for 8 mg once every two weeks ($p<0.0001$ for all doses compared to placebo) (Fig. 4) (Pratley et al., 2019). Additionally, efpeglenatide was associated with significantly improved glycemic variables and lipid profiles versus placebo (Pratley et al., 2019). The most frequently reported side effects were gastrointestinal side effects, which occurred in 64.4−83.1% of participants in the efpeglenatide groups and 46.7% of participants in the placebo group (Pratley et al., 2019). We did not identify any ongoing study of efpeglenatide in individuals with obesity. In another multicenter phase 2 trial, participants were randomized to noiiglutide 0.12 mg, 0.24 mg, 0.36 mg, and placebo for 24 weeks (Li et al., 2024). At the end of the study, the least square mean percentage change in weight from baseline was -3.97 (95% CI -5.39 to -2.56) with placebo, -9.80 (95% CI -11.18 to -8.43) with noiiglutide 0.12 mg, -9.01 (95% CI -10.40 to -7.62) with noiiglutide 0.24 mg, -9.39 (95% CI-10.80 to -7.97) with noiiglutide 0.36 mg, all p-values <0.0001 (Li et al., 2024). Gastrointestinal adverse events, such as nausea, diarrhea, and vomiting, were more common in all noiiglutide groups (15.4–30.2%, 18.8–22.2%, 15.6–18.5%) than in the placebo group (8.1%, 6.5%, 0%) (Appendix 3).

GLP-1 and glucagon RAs

We identified two GLP-1/glucagon RAs. Survodutide, which has advanced to phase 3, as described above in section 3.1., and efinopegdutide, also known as JNJ-64565111.

Efinopegdutide is a dual agonist of GLP-1 and glucagon receptors. In a multicenter phase 2 trial, 474 participants (mean age 46.3 years, mean BMI 40.5 kg/m^2) were randomized to efinopegdutide (5.0, 7.4, or 10.0 mg, each with no dose escalation, weekly subcutaneous

administration) or open-label subcutaneous liraglutide 3.0 mg, or placebo for 26 weeks (Alba et al., 2021). At the end of the study, all 3 doses of efinopegdutide significantly reduced body weight from baseline in a dose-dependent manner compared with placebo ($p<0.001$) (Alba et al., 2021). The least square mean percentage change from baseline in body weight was -1.8 (SE 0.7) with placebo, -8.5 (SE 0.8) with 5 mg efinopegdutide, -9.8 (SE 0.6) with 7.4 mg efinopegdutide, -11.8 (SE 0.6) with 10 mg efinopegdutide, -7.5 (SE 0.5) with liraglutide 3 mg (Fig. 4) (Alba et al., 2021). All doses of efinopegdutide exhibited greater weight loss compared to liraglutide 3 mg, this difference was statistically significant for the 7.4 mg and the 10 mg doses only. The most frequently described adverse events with efinopegdutide were gastrointestinal, ranging from 71.2% up to 83.9% at higher doses compared to 28.3% with placebo and 59.7% with liraglutide (Alba et al., 2021). We did not identify on clinicaltrials.gov any ongoing phase 3 trial on efinopegdutide for obesity treatment. For now, significant ongoing research and investment remain on MASH as the primary outcome rather than weight loss.

SGLT-2 inhibitors

We identified three completed trials on SGLT-2 inhibitors (canagliflozin and licogliflozin) (Fig 2.).

Canagliflozin is FDA-approved for the treatment of type 2 diabetes at doses of 100 to 300 mg once daily. In a phase 2 trial from the United States and Puerto Rico, 376 participants (mean age 44.8 years, mean BMI 37.0 kg/m^2) were randomized to oral canagliflozin 50, 100, and 300 mg daily or placebo for 12 weeks (Bays et al., 2014). At the end of the study, the mean change in weight (kg) was -1.1 (standard deviation [SD] 2.5) with placebo (Table 1). Subjects in the canagliflozin 50, 100, and 300 mg and placebo groups experienced percent body weight least squares mean changes of -2.2, -2.9, -2.7, and -1.3, respectively, with placebo-subtracted percent

values of -0.9 (p=0.031), -1.6 (p<0.001), and -1.4 (p<0.001) (Fig. 4) (Bays et al., 2014). Overall adverse event rates were similar across groups (Bays et al., 2014). Canagliflozin was associated with higher rates of genital mycotic infections in women (Appendix 3) (Bays et al., 2014).

Licogliflozin is a dual SGLT-1/SGLT-2 inhibitor that is not yet FDA-approved for treating type 2 diabetes. In a phase 2 trial from the United States, 88 participants (mean age 40.2 years, mean BMI 40.17 kg/m^2) were randomized to oral licogliflozin 150 mg daily or placebo for 12 weeks. At the end of the study, treatment with licogliflozin significantly reduced body weight, compared with placebo (-5.7% [80% CI -6.5 to -4.9%]; p<0.001; -6.4 kg with licogliflozin [80% CI -7.1 to -5.7] vs 0.2 kg with placebo [80% CI -0.5 to 0.9]; p<0.0001) (He et al., 2019). The most commonly reported side effects with licogliflozin were diarrhea (90.9% versus 25.0% with placebo) and flatulence (43.2% versus 9.1% with placebo) (Appendix 3). We identified another multicenter phase 2 trial on oral licogliflozin, comparing several doses (2.5–150 mg daily or twice daily) to placebo in 460 adults (median age 53 years, mean BMI 37.9 kg/m^2) for 24 weeks. At the end of the trial, a statistically significant dose-response weight loss was demonstrated for both once daily and twice daily licogliflozin regimens versus placebo (p<0.0001%), the percentage change in body weight from baseline was -1.2 (95% CI -2.5 to -0.4) with licogliflozin 2.5 mg once daily, -2.0 (95% CI -3.4 to -0.9) with licogliflozin 10 mg once daily, -3.5 (95% CI -4.6 to -1.9) with licogliflozin 50 mg once daily, -4.4 (95% CI -5.4 to -3.4) with licogliflozin 150 mg once daily, -1.7 (95% CI -2.6 to -0.23) with licogliflozin 2.5 mg twice daily, -2.5 (95% CI -3.9 to -1.3) with licogliflozin 5 mg twice daily, -4.1 (95% CI -5.5 to -2.9) with licogliflozin 25 mg twice daily, -4.5 (95% CI -5.5 to -3.) with licogliflozin 50 mg twice daily and -0.6 (95% CI -1.6 to 0.4) with placebo (Bays et al., 2020). The most frequently reported adverse events were gastrointestinal disorders (33−68%): diarrhea (15.8−68.8%) and flatulence (13.2−36.8%), which

appeared to be dose-related across both regimens, occurring more frequently at higher doses (Appendix 3).

SGLT-2 inhibitors in combination with other drugs

We identified two completed phase 2 trials on the combination of drugs with SGLT-2 inhibitors: canagliflozin/phentermine and dapagliflozin/exenatide (Fig. 2).

Phentermine is an anorectic sympathomimetic amine that stimulates satiety centers in the brain by upregulating dopamine, noradrenaline, and serotonin and is indicated for short-term weight management (Apovian et al., 2015). The combination canagliflozin/phentermine was investigated in a multicenter phase 2 trial, 335 individuals (mean age 45.7 years, mean BMI 37.3 kg/m^2) randomized to canagliflozin 300 mg orally daily, phentermine 15 mg orally daily, and canagliflozin/phentermine 300/15 mg or placebo orally daily for 26 weeks (Hollander et al., 2017). The least-square means percent changes in body weight were -1.9 (SE 0.6) with canagliflozin, -4.1 (SE 0.6) with phentermine, and -7.5 (SE 0.6) with canagliflozin/phentermine, and -0.6 (SE 0.6) with placebo (Fig. 4) (Hollander et al., 2017). Canagliflozin/Phentermine had statistically superior percent weight loss versus placebo (difference of -6.9%; $p<0.001$) (Hollander et al., 2017). Canagliflozin/Phentermine was generally well tolerated, with a safety profile consistent with that of each drug alone (Appendix 3) (Hollander et al., 2017).

Exenatide was the first GLP-1 RA approved for treating type 2 diabetes (BYETTA, 2005). Dapagliflozin and exenatide are current treatments for type 2 diabetes associated with weight loss. In a phase 2 trial from Sweden, 50 adults with obesity (mean age 52 years, mean body weight 104.6 kg) were randomized to receive a combination of oral dapagliflozin 10 mg daily and subcutaneous exenatide 2 mg once weekly (mean age 53.5 years, mean BMI 35.8 kg/m^2) or placebo (oral and subcutaneous) (mean age 50 years, mean BMI 35 kg/m^2) for 24

weeks. At the end of the study, combination therapy resulted in an adjusted (for treatment, week, treatment-by-week, sex, and baseline value) mean percentage change in body weight of -4.5 (95% CI -6.0 to -2.9) compared to -0.3 (95% CI -1.9 to 1.4) with placebo ($p<0.001$) (Fig. 4) (Lundkvist et al., 2017). The most frequently reported side effects were gastrointestinal (64% with the combination vs 40% with placebo) and injection-site reactions (44% with the combination vs 32% with placebo) (Appendix 3) (Lundkvist et al., 2017). Only two and three participants, respectively, discontinued because of adverse events (Lundkvist et al., 2017).

Others

We identified three additional drugs with completed phase 2 trials: beloranib, the combination leucine/sildenafil/metformin, and the combination orlistat/acarbose (Fig. 2).

Beloranib

Beloranib is a selective and potent methionine aminopeptidase 2 (MetAP2) inhibitor. MetAP2 inhibition reduces fat biosynthesis and stimulates fat oxidation and lipolysis (Rupnick et al., 2002). In a phase 2 trial from Australia, 147 participants with obesity (mean age 48.4 years, mean BMI 37.6 kg/m^2) were randomized to beloranib suspension (0.6, 1.2, and 2.4 mg) twice weekly or placebo for 12 weeks (Kim et al., 2015). At the end of the study, the absolute change in weight (kg) was -0.4 (SE 0.4) with placebo, -5.5 (SE 0.5) with 0.6 mg beloranib, -6.9 (SE 0.6) with 1.2 mg beloranib, and -10.9 (SE 1.1) with 2.4 mg beloranib ($p<0.001$ for all doses of beloranib compared to placebo) (Kim et al., 2015). The most frequently reported side effects with beloranib were gastrointestinal disorders (13.5% and up to 31.4% at higher doses) compared to 15.8% with placebo (Kim et al., 2015) (Appendix 3). Beloranib did not progress to phase 3 trials due to significant safety concerns from phase 3 trials for Prader-Willi syndrome after two patients' deaths. The FDA placed a clinical hold on trials involving beloranib for

potential cardiovascular risks (https://www.fiercebiotech.com/biotech/fda-hits-zafgen-s-beloranib-successor-clinical-hold).

Leucine/Sildenafil/Metformin

Leucine is a branched-chain amino acid, and its metabolites have been shown to increase the activity of a fuel-sensing enzyme, the adenine monophosphate–activated protein kinase (AMPK), and thus serves as a partial mimetic of an energy-depleted state (Bruckbauer & Zemel, 2014). Metformin increases hepatic insulin sensitivity, and rodent models suggest that its action may be mediated by AMPK (Rena et al., 2017). Sildenafil is an endothelial nitric oxide synthase activator that, similar to leucine and metformin, enhances AMPK activity (Das et al., 2015). A combination of leucine, metformin, and sildenafil, also known as NS-0200, has been shown to act in synergy to increase fat oxidation (Bruckbauer et al., 2016). In a multicenter phase 2 trial, 267 participants (mean age 41.1 years, mean BMI 36.9 kg/m^2) were randomized to 1 of 5 treatment groups: placebo, 1.1 g leucine and 1.0 mg sildenafil (NS-0300, Leu/Sil 1.0), 1.1 g leucine and 4.0 mg sildenafil (NS-0300, Leu/Sil 4.0), 1.1 g leucine and 1.0 mg sildenafil and 500 mg metformin (NS-0200, Leu/Met/Sil 1.0), or 1.1 g leucine and 4.0 mg sildenafil and 500 mg metformin (NS-0200, Leu/Met/Sil 4.0). Participants received the mentioned doses orally twice daily for 24 weeks. At the end of the study, the least square mean percent body weight change from baseline as per the intent to treat analysis was 1.2 (SE 0.5) with placebo, 0.5 (SE 0.5) with Leu/Sil 1.0 (p=0.3722 compared to placebo), -0.3 (SE 0.5) with Leu/Sil 4.0 (p=0.0298 compared to placebo), -0.6 (SE 0.5) with Leu/Met/Sil 1.0 (p=0.0090 compared to placebo), and -0.25 (SE 0.48) with Leu/Met/Sil 4.0 (p=0.0389 compared with placebo) (Fig. 4) (Rebello et al., 2021). All the combinations except 1.1 g Leucine and 1 mg sildenafil achieved weight loss that was

significantly greater than placebo. The most common side effects were gastrointestinal related to metformin (diarrhea 19% pooled effect in the treatment group) (Appendix 3).

Orlistat/Acarbose

The combination orlistat/acarbose, also known as EMP16, is a novel oral modified release formulation of the lipase inhibitor orlistat approved for chronic weight management and the glucosidase/amylase inhibitor acarbose approved for the treatment of type 2 diabetes and postprandial hyperinsulinemic hypoglycemia following gastric bypass surgery (Holmbäck et al., 2020; McIver et al., 2023). In a phase 2 trial from Sweden, 175 participants were randomized to the combination orlistat/acarbose twice (first and last day) or thrice daily at 120/40 mg (mean age 49.4 years, mean BMI 35.1 kg/m^2) or 150/50 mg (mean age 50.7 years, mean BMI 34.6 kg/m^2), or placebo (mean age 49.5 years, mean BMI 36.2 kg/m^2) for 26 weeks (Holmbäck et al., 2022). The absolute weight change (kg) at week 26 from baseline was -6.0 (SD 5.3) with the 120/40 mg and -6.4 (SD 4.8) with the dose 150/50 mg, compared to -0.8 (SD 3.9) with placebo ($p<0.001$ for both active treatment groups compared to placebo) (Fig. 4) (Holmbäck et al., 2022). The most frequently reported side effects were gastrointestinal, reaching 31% with the high dose formulation compared to 10% with placebo, along with infections and infestations (mostly nasopharyngitis and COVID-19), reaching 33% with the high dose formulation but also 38% in the placebo arm (Appendix 3) (Holmbäck et al., 2022). Orlistat/Acarbose is currently being investigated in another phase 2 trial in Sweden, with two different doses compared to orlistat alone or placebo, with expected completion in March 2024 (Table 4).

3.2.2. Drugs with completed phase 2 trials but not published yet

We identified eight completed phase 2 trials but without published results online (Fig. 2, Table 3). One drug, ecnoglutide (GLP-1 RA), has already progressed to phase 3, as described in

section 3.1 (Tables 2 and 3). In addition, despite the lack of officially published results, primary findings for danuglipron (GLP-1 RA) and pemvidutide (GLP-1/glucagon RA) were disseminated through press releases.

GLP-1 RAs

In addition to ecnoglutide, which is currently in phase 3, danuglipron, a GLP-1 RA, also known as PF-06882961, recently completed a phase 2 trial with a sample size of 630 participants grouped in three cohorts of different treatment durations and planned visits (NCT04707313) (Table 3). Based on a Pfizer press release in 2023, danuglipron, at doses of 40-200 mg twice per day, showed mean placebo-adjusted weight reductions between -8% and -13% at 32 weeks (https://www.pfizer.com/news/press-release/press-release-detail/pfizer-announces-topline-phase-2b-results-oral-glp-1r). To note, future development of danuglipron will focus on a once daily formulation to improve tolerability and streamline trial design and execution, with no further investigation into the twice daily formulation in phase 3 due to the high discontinuation rate of more than 50% compared to placebo (https://www.pfizer.com/news/press-release/press-release-detail/pfizer-announces-topline-phase-2b-results-oral-glp-1r).

GLP-1 and glucagon RA

Pemvidutide, a GLP-1/glucagon RA, also known as ALT-801, recently completed a phase 2 trial of 320 participants and an intervention duration of 48 weeks (Table 3) (NCT05295875). Results of the MOMENTUM 48-week phase 2 obesity trial, shared during the Altimmune press release in 2024, showed that participants achieved a mean weight loss of 15.6% with a 2.4 mg dose of pemvidutide, and nearly 30% of them lost 20% or more of their body weight (https://ir.altimmune.com/news-releases/news-release-details/altimmune-announces-positive-lean-mass-preservation-data). Those with increased baseline lipids experienced

significant decreases in triglycerides (55.8%), total cholesterol (20.0%), and low-density lipoprotein cholesterol (17.4%) at the 2.4 mg dosage. Additionally, nearly 78.6% of individuals experienced a reduction in liver fat content. Furthermore, the treatment resulted in improvements in blood pressure without adverse cardiac events (https://ir.altimmune.com/news-releases/news-release-details/altimmune-announces-positive-lean-mass-preservation-data).

GLP-1 RA in combination with a neuropeptide Y receptor type 2 agonist

Semaglutide, in combination with NNC0165-1875, a neuropeptide Y receptor type 2 agonist, compared to semaglutide and placebo, completed a phase 2 trial with a sample size of 120 participants and an intervention duration of 48 weeks (Table 3) (NCT04969939).

Others

Setmelanotide, a selective agonist of the melanocortin 4 receptor, has completed two phase 2 trials, one trial with a sample size of 99 participants and an intervention duration of 12 weeks (NCT02041195) and a second trial with a sample size of 74 participants and an intervention duration of 909 days (NCT01749137). Both trials enrolled adults with a BMI between 30 kg/m^2 and 40 kg/m^2 and assessed the effect of setmelanotide as a treatment for common obesity. It should be noted, however, that setmelanotide is currently approved for the treatment of obesity caused by genetic disorders, such as deficiencies in leptin receptor, proprotein convertase subtilisin/kexin type 1, or proopiomelanocortin (Table 3) (Hussain & Farzam, 2024; Kokkorakis et al., 2023a).

Two other drugs that have also completed phase 2 trials are oral denatonium acetate and MBL949. Oral denatonium acetate, also known as ARD-101, which targets bitter taste receptors, was investigated in a trial on 20 participants and for an intervention duration of 28 days (Table 3)

(NCT05121441). MBL949, a growth/differentiation factor 15 agonist, was evaluated in 126 participants and an intervention duration of 16 weeks (Table 3) (NCT05199090).

3.2.3 Drugs currently investigated in phase 2 trials

We identified 14 ongoing phase 2 trials (Table 4), one trial on TG103, a GLP-1 RA now also being investigated in a phase 3 trial (Table 1), and one trial on mazdutide, a GLP-1 and glucagon RA that also already progressed to phase 3 (see section 3.2), and the remaining 12 trials investigate new drugs, almost half of them being incretin-based, GLP-1 RA, GLP-1 and GIP RA, or dual GLP-1 and glucagon-like peptide-2 (GLP-2) RA, while the others have distinct mechanisms of action (Fig. 2, Table 4).

GLP-1 RA

TG103, a GLP-1 RA, is currently assessed in a phase 3 RCT. The phase 2 trial aims to investigate changes in body weight among obese adults with a BMI of >30 kg/m^2. Two doses, 15 mg and 22.5 mg, are administered subcutaneously and compared to a placebo. The sample size is 195, and the trial, with unknown status, was expected to be completed in September 2023.

GLP-1 RA and GIP receptor antagonist

AMG 133, also known as maridebart cafraglutide or MariTide, a GLP-1 RA and GIP receptor antagonist (NCT05669599), is currently investigating the percentage change in body weight among adults with BMI ≥30 kg/m^2 taking three different doses, as compared to placebo. The expected completion of this phase 2 trial is in January 2026, following the phase 1 trial that assessed the safety and tolerability of AMG 133 (NCT04478708). The latter study revealed that participants, with an average age ranging from 40.3 to 53.8 years and a BMI of 32.5–34.8 kg/m² with no history of diabetes, had a substantial weight loss of -8.2% at day 92 for the maximum

single dose of 840 mg of AMG 133 compared to placebo (1.7%). The discussed latter demonstrates a sustained weight-reducing impact following a single dose of AMG 133, with noteworthy evidence of manageable safety profiles (Véniant et al., 2024).

GLP-1 and GIP RAs

Three new GLP-1/GIP RAs are currently being investigated in phase 2, VK2735 (NCT06068946), HS-20094 (NCT06118021), and HRS9531 (NCT05881837; NCT06054698) (Table 4). All of the trials enroll individuals with a BMI ≥30 kg/m^2 or ≥27 kg/m^2, or the equivalent cutoffs in Asian countries, and at least one comorbidity. The sample sizes range from 60 to 249 at the highest. The major goal of these trials is to examine the primary outcome of change in body weight, with the trials expected to be completed in 2024.

Dual GLP-1 and GLP-2 RA

We identified one GLP-1 and GLP-2 RA, dapiglutide (NCT05788601) (Table 4). This trial enrolls adult participants with a BMI >30 kg/m^2 to investigate weight change as a primary outcome. The sample size is 54 for dapiglutide and is expected to be completed by August 2024.

GLP-1 and glucagon RA

There is one ongoing phase 2 trial in the United States enrolling 165 participants, with overweight and at least one comorbidity or obesity, comparing the percentage weight loss achieved by mazdutide at different doses compared to placebo with expected completion in May 2025 (NCT06124807) (Table 4).

Others

Six drugs currently in phase 2 trials have various mechanisms of action. These trials enroll adults with a BMI of ≥30 kg/m² or ≥ 27 kg/m² with at least one weight-related ailment.

The sample size varies between 54 and 624 participants. Vutiglabridin (HSG4112), a synthetic structural analog of glabridin (NCT05197556), is being investigated in different oral doses of 200 mg, 400 mg, or 600 mg compared to placebo. Glabridin works by preventing the oxidation of low-density lipoprotein either by directly attaching to the low-density lipoprotein particle or by preserving paraoxonase activity (Fuhrman et al., 1997). Additionally, it decreases low-density lipoprotein oxidation and the expression of adhesion molecules by inhibiting the release of reactive oxygen species and inflammatory mediators from macrophages and dendritic cells (Zhang et al., 2023).

Bimagrumab, a human monoclonal antibody to the activin receptor type II, alone or in combination with semaglutide (NCT05616013) is currently under investigation in different dosing regimens of bimagrumab and semaglutide compared to placebo. In addition, trevogrumab, a myostatin inhibitor, garetosmab, an antibody that binds to activin A, blocking its activity, and semaglutide, alone or in different combinations with each other, are currently being investigated (NCT06299098). Specifically, activins, in conjunction with myostatin, help regulate normal muscle growth, and follistatin binds to activins and neutralizes them, thereby reducing their activity and conserving energy during times of energy deficiency (Angelidi et al., 2024; Perakakis et al., 2018).

The combination K-757 and K-833 nutrient receptor stimulants (NCT06019559) are currently investigated in different doses of K-757 alone and in combination with K-833. K-757 and K-833 function by boosting metabolic signals to stimulate the release of appetite-suppressing satiety hormones GLP-1 and peptide YY. S-309309 inactivates monoacylglycerol acyltransferase-2, an enzyme implicated in the process of absorbing and re-synthesizing triglycerides in small intestinal epithelial cells, and is another molecule under investigation with

three dose levels and a placebo group (NCT05925114) (https://www.shionogi.com/content/dam/shionogi/global/investors/ir-library/presentation/2023/2q/20231107_FY2023%202Q%20Script.pdf). Finally, the combination orlistat/acarbose is also under investigation (NCT05934110). This latter has already completed another phase 2 trial, as described in Section 3.2.1. The primary outcome of the above trials is the percentage change in body weight and the majority are expected to be completed in 2024 (Table 4).

3.3. Terminated and suspended studies

We identified three terminated and one suspended trial on ClinicalTrials.gov. One trial compared metformin to orlistat, topiramate, and placebo, and was terminated because of insufficient funding (NCT01351753). One trial on HPP404, a histamine H3 receptor antagonist, was terminated without an identifiable reason (NCT01540864). A recently terminated trial aimed to investigate the placebo-adjusted percentage change from baseline in body weight after 32-week-long treatment with different dosages of the GLP-1 RA, lotiglipron, also known as PF-07081532, in participants with obesity (NCT05579977). The reason for this trial's termination was the increase in transaminases in phase 1 studies, as well as a phase 2 study. Finally, a trial investigating a fixed-dose combination of fluoxetin and metformin was suspended in 2017 due to a business decision (NCT03051451).

3.4. Trials' geographic location and funders

The world map delineates the global distribution of completed and ongoing phase 2 and phase 3 trials on weight-reducing medications, along with the drugs' mechanism of action (Fig. 5). The majority of trials are taking place in the United States (n=31), followed by Asia (China, Japan, Korea, Taiwan and Hong Kong, n=35), and several in Europe (mostly Poland, the United

Kingdom, and Sweden), Canada, in addition to one trial in Oman. The United States, driven by diverse pharmaceutical companies' interests, has the most diverse range of trials, targeting almost all mechanisms of action, followed by China, which primarily focuses on GLP-1 RAs alone or in combination with other molecules. In Canada, there is an equal focus on both GLP-1 RAs and GLP-1/glucagon RAs (n=3 trials each) in addition to targeting various mechanisms of action. Out of eight trials in Japan, 50% investigated primarily GLP-1 RAs.

It is worth noting that 21.3% of all trials investigated GLP-1 RAs, followed by GLP-1 RA/amylin analog (16.2%) and GLP-1/glucagon RAs (16.2%) (Fig. 5). However, while there are more GLP-1/glucagon RAs under development as distinct drugs, the concentration of trials for the only GLP-1/amylin analog, CagriSema, reflects the extensive clinical program for this particular molecule.

Many pharmaceutical companies are funding weight loss drug trials. Eli Lilly and Company showcases a strong pipeline with a well-distributed number of studies across all phases (phase 3 and phase 2, n=6), while Novo Nordisk A/S exhibits significant activity, particularly in phase 3 studies (n=7). Other companies have one to three drugs being investigated in phase 2 or phase 3 (Fig. 6).

4. Risk of bias assessment

The risk of bias assessment of published trials in phase 2 and phase 3 showed a low risk of bias in the majority of studies. A few studies only have some concerns related to limitations in the randomization process (three studies), deviation from the intended interventions (two studies), missing outcome data (three studies), or measurement of the outcome (one study) (Appendix 4). Almost all these trials were funded by pharmaceutical companies.

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5. Discussion

The worldwide incidence and prevalence of obesity are alarmingly high, implying an increased and unmet need for available, safe, and effective therapies. GLP-1 RAs and dual or triple agonists (GLP-1 RA/amylin analog, GLP-1/GIP RAs, GLP-1/glucagon RAs, GLP-1/GIP/glucagon RAs) are populating the therapeutic pipeline of obesity, as subcutaneous injections, or oral preparations. These new drugs showed a weight loss of more than 10% (10.8 to 24.2%, except for efpeglenatide and noiiglutide) (Fig. 4). Importantly, the majority of completed phase 2 trials have spanned over three to 12 months and for some drugs weight had not reached a plateau at the time of the study completion, implying a potential further weight loss with longer treatment duration (Jastreboff et al., 2023; Wharton et al., 2023). Other drugs also showed significant weight loss, such as beloranib, which resulted in a weight loss of 10.9 kg with the highest dose. SGLT-2 inhibitors are being investigated alone or in combination with GLP-1 RAs or phentermine, with a modest weight loss range of 4.5–7.5% (Fig. 4).

The safety profile of the drugs currently investigated for weight management seems favorable, with a low rate of dropout due to adverse events (Appendix 3). Gastrointestinal side effects are the most common with incretin-based therapies; they are dose-dependent and tend to decrease with time. The risk can be reduced by slow dose up-titration, and in case they happen, dietary changes are advised (Wharton et al., 2022). The rate of serious adverse events was relatively low across different drugs (Appendix 3).

Interestingly, within the GLP-1 RA class, drugs are evolving, and the newer ones (second-generation) are more potent than the initially approved liraglutide for weight management (Garvey, 2022). In the head-to-head “STEP 8” trial, semaglutide was compared to liraglutide and showed a larger weight loss at 68 weeks (-15.8% with semaglutide vs -6.4% with liraglutide, $p<0.001$) (Rubino et al., 2022). A weight loss similar to what was reported with

subcutaneous semaglutide 2.4 mg once weekly was reproduced with oral semaglutide in the recently published "OASIS 1" phase 3 RCT, an achievement that is anticipated to revolutionize chronic weight management (Knop et al., 2023), directly addressing the injection barrier with the currently approved potent weight loss medications (WEGOVY, 2017; ZEPBOUND, 2023). Nonetheless, limitations associated with oral semaglutide are that the drug should be taken on an empty stomach, away from any other food, liquid, or drug for at least 30 min, and with a maximum of 120 ml of water (Knop et al., 2023). Orforglipron, another oral GLP-1 RA, showed a weight-reducing effect in a phase 2 trial that is similar to other molecules in this category. In addition, being a small molecule, orforglipron does not require food or water restriction, and it appears to have the potential to meet the clinical need for effective and possibly easier-to-produce oral alternatives to the current subcutaneous formulations (Fig. 4) (Wharton et al., 2023). Therefore, oral GLP-1 RAs are expected to have a substantial role in weight management, as they may provide higher acceptability and better adherence, compared to injectable GLP-1 RAs. Indeed, oral medications have historically offered a preferred and easy way of administration due to patient comfort and convenience and may be better applicable for patients seen in primary care clinics (Gallwitz & Giorgino, 2021; Kokkorakis et al., 2023a; Quante et al., 2012).

Currently, being the only triple hormone RA, retatrutide presents a promising drug, as it yielded the highest reported mean weight loss (-17.9%) compared to all published results from the emerging pharmacotherapies (Fig. 4). Body weight reduction involves multiple pathways, and, thus, the combination of medications that target more than one pathway is expected to result in greater weight loss than what each of these molecules achieve when used separately. Such an approach is similar to the common practice for other metabolic diseases, such as type 2 diabetes

("Summary of Revisions: Standards of Care in Diabetes-2024," 2024), hypertension, dyslipidemia (Garvey et al., 2016), and MASLD (Kokkorakis et al., 2024a; Kokkorakis et al., 2023b; Kokkorakis et al., 2024b). Indeed, such remarkable results of ≥15% weight loss are expected to concurrently reduce cardiometabolic comorbidities and improve long-term outcomes, i.e., cardiovascular disease and potentially mortality (Gregg et al., 2016).

Some of the new anti-obesity drugs exert direct and weight-independent actions on ectopic fat of specific organs, paving the way for a new era of tailored treatment choices based on patient's comorbidities. For instance, efinopegdutide 10 mg, a GLP-1/glucagon RA, achieved higher reductions in liver fat content in a phase IIa RCT individuals with MASLD compared to semaglutide 1 mg alone, despite similar weight loss results, potentially due to the fact that glucagon receptor agonism may have a direct effect on the liver, to stimulate fatty acid oxidation and reduce lipogenesis (Melson et al., 2024; Romero-Gómez et al., 2023). Therefore, individuals with predominant MASLD or MASH may be directed towards combinations that include glucagon to benefit from the liver-targeted effects. Additionally, GLP-1 RAs can significantly decrease epicardial adipose tissue, and there is evidence that semaglutide 2.4 mg improves heart failure with preserved ejection fraction in individuals without diabetes by a potentially direct or indirect effect on epicardial adipose tissue (Kosiborod et al., 2023; Myasoedova et al., 2023). Therefore, exploring the full potential of all molecules and combinations to enhance metabolic and mechanical cardiometabolic complications will aid in developing successful personalized pharmacotherapy options.

More than a quarter of all the identified phase 2 and phase 3 trials recommended lifestyle modifications on ClinicalTrials.gov for all participants in the investigational and control arms, highlighting the importance of a healthy lifestyle to optimize weight loss, while most likely all

the remaining RCTs may recommend lifestyle modifications without reporting this on ClinicalTrials.gov (Acosta et al., 2017; Apovian et al., 2015; Cornier, 2022; Durrer Schutz et al., 2019; Garvey et al., 2016; Wharton et al., 2020). Notably, lifestyle modifications lacked recommendations for behavioral interventions for chronic weight management, which should receive more attention since it is a key component of the primary intervention strategies (Kelley et al., 2016; Olateju et al., 2021; Teixeira et al., 2015).

Despite such promising results, understanding the causes of clinical trial suspensions, withdrawals, and terminations, i.e., due to funding reasons, for weight-reducing medications is imperative, given the low success rate of these medications in progressing to phase 3 and completing it. Indeed, several completed phase 2 trials are not yet available online, which could be, among others, secondary to negative findings or adverse events.

Finally, while obesity is a global pandemic, the main centers of most trials on investigational drugs for weight loss are clustered in the United States and Asia, with a smaller proportion emerging in Europe and other regions. Data from the Arab countries, known to have alarming rates of obesity, is inexistent, and this invites pharmaceutical companies to invest in the populations that are so far under-represented in landmark weight loss trials (Okati-Aliabad et al., 2022).

6. Future directions

Recent results from RCTs and cohort studies have clearly demonstrated that we should treat overweight and obesity as a disease, even in the absence of type 2 diabetes, as excessive weight profoundly increases cardiometabolic and cancer risk, along with increased mortality (Larsson et al., 2022; Lincoff et al., 2023; Nichols et al., 2017; Powell-Wiley et al., 2021; Tan et al., 2023). Even though there is a lack of consensus regarding treatment duration beyond the trial

period of anti-obesity drugs, it was demonstrated that individuals with obesity and overweight substantially regained the lost weight after stopping weight-reducing drugs, such as semaglutide and tirzepatide, while ongoing therapy sustained and enhanced the initial decrease in weight (Aronne et al., 2023; Wilding et al., 2022). These results confirm obesity's nature as a cardiometabolic condition, potentially needing lifelong treatment unless yet to be fully elucidated mechanisms, such as hypothalamic inflammation, which has been proposed to promote long-term weight maintenance, are also improved over a period of time, allowing thus discontinuation of therapies.

The future of obesity pharmacotherapy is bright, and the availability of various anti-obesity medications with diverse mechanisms of action in various tissues and organs and different degrees of efficacy and side effects will allow personalized choices of medications based on the underlying metabolic profile, patient preference, and the expected response to treatment. Regarding the rapid emergence of novel agents, there should be an appropriate balance between efficacy and cost-effectiveness, and there is an imminent need for more production facilities of existing companies, in addition to new entries by more companies. Semaglutide, which is an expensive drug (Wegovy® has a list price of $1,349.02/month without insurance in the United States (NovoCare®, 2021)), recently demonstrated a sustained weight loss (mean reduction of 10.2%) over four years in 17,604 adults with preexisting cardiovascular disease, obesity, and without type 2 diabetes, along with a 20% reduction in major adverse cardiovascular events and is thus expected to be added to our armamentarium for cardiometabolic outcomes (Ryan et al., 2024). Of note, considering the prevalence of overweight, obesity, and cardiovascular disease, the healthcare budgets are likely going to be expanded. A recent economic evaluation study conducted from September 1, 2022, to May 31,

2023, using a Markov cohort model analysis, assuming a United States health care system's perspective, demonstrated that endoscopic sleeve gastroplasty, a globally adopted minimally invasive endoscopic bariatric procedure, is a cost-effective strategy, providing greater weight loss and cost savings compared to semaglutide among individuals with class II obesity (BMI of 35–39.9 kg/m^2) over five years (Haseeb et al., 2024). Specifically, it was concluded that the annual cost of semaglutide would need to be decreased three-fold to be a cost-competitive alternative, implying the need to reduce the prices of anti-obesity medications and meet willingness-to-pay thresholds per quality-adjusted life-year to compete with minimally invasive endoscopic gastroplasty for subjects with stage II obesity (Haseeb et al., 2024). Nonetheless, endoscopic sleeve gastroplasty is not a scalable option, and it should be noted that the price of semaglutide or other anti-obesity drugs varies significantly between countries (https://www.healthsystemtracker.org/brief/prices-of-drugs-for-weight-loss-in-the-us-and-peer-nations/).

When choosing between novel oral (i.e., oral semaglutide, orforglipron) and injectable forms (i.e., retatrutide) in the future, we envision that oral agents might be better placed in the primary care setting for individuals needing modest weight loss, with low drug doses. Injectable drugs (i.e., tirzepatide) or higher doses of oral agents (i.e., oral semaglutide 50 mg) may be reserved for individuals requiring higher weight loss. Consequently, policymakers must carefully assess the trade-offs they are prepared to make to attain equal access to such innovative pharmaceutical advancements long-term, support weight maintenance, and identify cost-effective strategies to achieve this. While the number of potential weight loss medications continuously increases, several future challenges exist. It is essential to understand the long-term safety and efficacy of the new pharmacotherapies for the management of obesity (including long-term

cardiovascular safety, which so far has been proven only for semaglutide 2.4 mg once weekly). Besides, there is a need to optimize bone or muscle mass loss by investigating the potential risk of macronutrient and micronutrient deficiencies following treatment with the agents under development, reaching a weight loss of >25%, as is observed after bariatric surgery (Ansari et al., 2024). With more significant weight loss conveyed by newer weight loss agents, it remains to be assessed whether concomitant muscle or bone mass loss will also be significant (Conte et al., 2024). In this case, co-administration with medications that may preserve or augment muscle and/or bone mass would be advisable and may be a future direction. In this regard, several compounds currently in phase 2 and 3 RCTs, mainly leveraging the activin-myostatin-follistatin axis, are in development and may be used alone or in combination with other agents. Additionally, data from under-represented populations, cost-effectiveness studies, and drug availability are still needed to close the care gap for patients with obesity. Lastly, demonstrating the effect of each treatment on other obesity-related complications, including the direct effect on various tissues, is crucial. Therefore, it is necessary to investigate whether new treatments will demonstrate similar benefits. Specifically, preferential effects of certain anti-obesity medications on liver health or neurocognition, or other cardio-renal-metabolic effects, in addition to weight loss, may be critical factors that will determine the prioritization of certain medications in the context of personalized medicine in the future.

Authors contributions

M.C. and C.S.M. participated in the research design of the study. M.K., C.R., J.A.R., M.G., and L.V.V. performed data analysis, including screening citations retrieved from the search and abstracting data. M.K., J.A.R., and L.V.V. also contributed to designing the tables,

while M.K. and J.A.R. designed the figures. M.K., M.C., J.A.R., and C.S.M. wrote or contributed to the writing of the manuscript.

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Data availability statement

The authors declare that all the data supporting the findings of this study are contained within the manuscript and supplement.

Declaration of interests

C.S.M. has been a shareholder of and reports grants through his institution from Merck, grants through his Institution and personal consulting fees from Coherus Inc. and AltrixBio, he reports grants through his institution and personal consulting fees from Novo Nordisk, reports personal consulting fees and support with research reagents from Ansh Inc., reports personal consulting fees from Genfit, Lumos, Amgen, Corcept, Intercept, Astra Zeneca, 89bio and Regeneron, reports support (educational activity meals at and through his institution) from Amarin, Novo Nordisk and travel support and fees from TMIOA, Elsevier, the California Walnut Commission, College Internationale Researche Servier and the Cardio Metabolic Health Conference. None is related to the work presented herein. All other authors declare no conflict of interest.

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Figure legends

Figure 1. Flow diagram of the identified trials on Medline and Embase as well as ClinicalTrials.gov.

[1] Database search on Medline and Embase was first conducted on May 16th, 2023, and was updated on May 20th, 2024
[2] ClinicalTrials.gov search done on April 6th, 2023, and updated on December 12th, 2023. It was then re-updated on May 24th, 2024.
[3] Special population includes: heart failure, hypogonadotropic hypogonadism, nonobstructive hypertrophic cardiomyopathy, men with testosterone deficiency
Abbreviations: NASH, nonalcoholic steatohepatitis; BMI, body mass index; RCT, randomized controlled trial.

Figure 2. Overview of agents under development for chronic weight loss as of May 2024, per study phase grouped by mechanism of action.

Abbreviations: GLP-1, Glucagon-like peptide-1; RA, receptor agonist; SGLT-2, sodium/glucose cotransporter 2; $GABA_AR$, γ-Aminobutyric acid sub-type A receptors; GIP, glucose-dependent insulinotropic peptide. [1]Indicates oral Semaglutide; [2]There are two trials of canagliflozin, one as monotherapy and one in combination with phentermine. Created with BioRender.com.

Figure 3. The sites of action of drugs in phase 3 randomized controlled trials (ongoing or completed) for chronic weight management**.**

Data presented are based on animal and/or human studies. 1) Orbitofrontal cortex; 2) Parietal cortex; 3) Putamen; 4) Hypothalamus; 5) Insula; 6) Nucleus tractus solitarii; 7) Area postrema; 8) Stomach; 9) Pancreas; 10) White adipose tissue (indirect action of GLP-1 and GIP); 11) Glucagon receptors in the liver; 12) Intestines and intestines smooth muscles; 13) Proopiomelanocortin neuron; 14) Kidneys. Abbreviations: GLP-1, glucagon-like peptide-1; GLP-1R, glucagon-like peptide-1 receptor; GIP, glucose-dependent insulinotropic polypeptide; NPY, neuropeptide Y; AgRP, agouti-related peptide; POMC, proopiomelanocortin; $GABA_AR$, γ-Aminobutyric acid sub-type A receptor; SGLT-2, sodium/glucose cotransporter 2. [1]Indicates oral Semaglutide. Created with BioRender.com.

Figure 4. Summary of the highest percent weight change in completed phase 2 and phase 3 trials.

This figure does not include trials enrolling exclusively participants with diabetes mellitus. The percent weight change in the figure is placebo-subtracted.

[1] SGLT-2 Inhibitors alone or in combination with other medication
[2] Least square mean percent change
[3] Retatrutide 12 mg (initial dose 2 mg)
[4] Results published from a press release
[5] Weight absolute change in kg
[6] Administered twice daily
Abbreviations: GLP-1, glucagon-like peptide-1; RA, receptor agonist; GIP, glucose-dependent insulinotropic polypeptide; SGLT-2, sodium/glucose cotransporter 2.

Figure 5. Summary of the geographic distribution of completed and ongoing phase 2 and phase 3 randomized controlled trials on drugs for weight management, along with the mechanism of action of the anti-obesity drugs.

For multicenter trials, all participating countries reported on ClinicalTtrials.gov were included in this figure. The rectangles are color-coded to show the mechanism of action of the anti-obesity drug

investigated in each. Each small colored rectangle refers to one study conducted in each country. The length of each colored rectangle is proportional to the number of studies per drug category in a given country. The numbers in brackets next to the name of each country refer to the total number of completed or ongoing randomized controlled trials studying antiobesity drugs in each country. Created with BioRender.com.

Abbreviations: GLP-1, glucagon-like peptide-1; GLP-2, glucagon-like peptide-2; RA, receptor agonist; GIP, glucose-dependent insulinotropic polypeptide; SGLT-2, sodium/glucose cotransporter 2.

Figure 6. Bar chart of the number of phase 2 and phase 3 trials (completed or ongoing) by pharmaceutical companies

*Others include Aardvark Therapeutics, Inc., Altimmune, Amgen, CSPC Baike (Shandong) Biopharmaceutical Co., Ltd., Eurofarma Laboratorios S.A, Glaceum, Hangzhou Sciwind Biosciences Co., Ltd., Hanmi Pharmaceutical Company Limited, Jiangsu Hansoh Pharmaceutical Co., Ltd., Johnson & Johnson Pharmaceutical Research & Development, L.L.C., Kallyope Inc., NuSirt Biopharma, Oman Ministry of Health, Regeneron Pharmaceuticals, Sciwind Biosciences, Shionogi, Uppsala University, Versanis Bio, Viking Therapeutics, Inc., Zafgen, Inc., and Zealand Pharma

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Tables

Table 1. Summary of included completed and published phase 3 and phase 2 trials

Author, Year Countries (NCT)	Eligibility criteria	Intervention (s) and comparator Duration	Gender (% men/ arm)	Age mean ± SD or median (range)(years)	BMI mean ± SD or median (range)(kg/m^2)	N randomized / N discontinued	% Weight change mean ± SD or SE or 95% CI
Phase 3 Trial							
GLP-1 RA							
Knop, 2023 USA, Canada, Denmark, Finland, France, Germany, Japan, Poland, and Russian Federation (NCT05035095)	- ≥18 years (aged 20 years or older in Japan per Japanese regulatory requirements) - BMI >30 kg/m² or BMI >27 kg/m² with at least one comorbidity[1,2]	I1: Oral Semaglutide 50 mg (oral, QD) C: Placebo Duration: 68 weeks	I1: 26% C: 29%	I1: 49 ± 13 C: 50 ± 12	I1: 37.3 ± 6.3 C: 37.7 ± 6.8	I1: 334/ 14 C: 333/ 26	I1: –15.1 ± 0.5 C: –2.4 ± 0.5
Phase 2 Trials							
Amylin Analog							
Lau, 2021 USA, Canada, Denmark, Finland, Ireland, Japan, Poland, Serbia, South Africa, and UK (NCT03856047)	- ≥18 years - BMI >30 kg/m², or BMI >27 kg/m² with at least one comorbidity[1] - No DM	Cagrilintide (SC, QW) I1: 0.3 mg I2: 0.6 mg I3: 1.2 mg I4: 2.4 mg I5: 4.5 mg I6: Liraglutide 3 mg (SC, QD) C: Placebo Duration: 32 weeks	I1: 45% I2: 38% I3: 38% I4: 26% I5: 45% I6: 34% C: 42%	I1: 53.5 ± 10.3 I2: 53.2 ± 11 I3: 52.1 ± 8.7 I4: 52.7 ± 9.8 I5: 51.5 ± 12.7 I6: 51.5 ± 9.3 C: 51.4 ± 11.9	I1: 38.4 ± 7.5 I2: 37.2 ± 6.9 I3: 37.1 ± 6.2 I4: 37.9 ± 7.6 I5: 38.4 ± 7.7 I6: 38.4 ± 7.4 C: 37.4 ± 5.7	I1: 101/ 4 I2: 100/ 5 I3: 102/ 10 I4: 102/ 8 I5: 101/ 4 I6: 99/ 10 C: 101/ 11	I1: −6.0 ± 0.6 I2: −6.8 ± 0.6 I3: −9.1 ± 0.7 I4: −9.7 ± 0.6 I5: −10.8 ± 0.6 I6: −9.0 ± 0.6 C: −3.0 ± 0.6
GLP-1 RA							

Author, Year Countries (NCT)	**Eligibility criteria**	**Intervention (s) and comparator Duration**	**Gender (% men/ arm)**	**Age mean ± SD or median (range)(years)**	**BMI mean ± SD or median (range)(kg/m^2)**	**N randomized / N discontinued**	**% Weight change mean ± SD or SE or 95% CI**
Pratley, 2019 USA (NCT02075281)	- ≥18 to <65 years - BMI ≥30 kg/m², or BMI ≥27 and <30 kg/m² with at least one comorbidity[1]	Efpeglenatide (SC) I1: 4 mg QW I2: 6 mg QW I3: 6 mg Q2W I4: 8 mg Q2W C: Placebo Duration: 20 weeks[3]	I1: 30.5% I2: 22% I3: 27.1% I4: 12.1% C: 26.7%	I1: 42.9 ± 12.1 I2: 43.0 ± 13.0 I3: 43.3 ± 12.5 I4: 43.9 ± 9.2 C: 43.7 ± 11.8	I1: 35.2 ± 4.5 I2: 36.3 ± 4.4 I3: 35.6 ± 4.8 I4: 35.2 ± 3.9 C: 34.9 ± 3.2	I1: 59/ 17 I2: 59/ 18 I3: 59/ 20 I4: 60/ 22 C: 60/ 13	Least square mean % change: I1: −6.7 ± 0.6 I2: −7.3 ± 0.6 I3: −6.7 ± 0.6 I4: −7.4 ± 0.6 C: 0.1 ± 0.6
Wharton, 2023 USA, Canada, Hungary, Puerto Rico (NCT05051579)	- ≥18 to 75 years - BMI >30 kg/m², or BMI >27 kg/m² with at least one comorbidity[1], stable body weight - No DM	Orforglipron (oral, QD)[4] I1: 12 mg I2: 24 mg I3: 36 mg Subcohort 1 I4: 36 mg Subcohort 2 I5: 45 mg Subcohort 1 I6: 45 mg Subcohort 2 C: Placebo Duration: 36 weeks	I1: 38% I2: 43% I3: 38% I4: 38% I5: 39% I6: 47% C: 42%	I1: 49.8 ± 10.5 I2: 57.0 ± 9.1 I3: 56.3 ± 11.8 I4: 55.4 ± 10.9 I5: 56.5 ± 10.7 I6: 50.9 ± 12.6 C: 54.0 ± 8.8	I1: 37.7 ± 7.7 I2: 38.1 ± 7.7 I3: 38.0 ± 6.4 I4: 38.0 ± 6.3 I5: 36.8 ± 5.5 I6: 38.7 ± 7.6 C: 37.8 ± 6.5	I1: 50/ 6 I2: 53/ 7 I3: 29/ 2 I4: 29/ 5 I5: 31/ 8 I6: 30/ 2 C: 50/ 7	I1: −9.4 (−11.5 to −7.4) I2: −12.5 (−14.5 to −10.5) I3-I4: −13.5 (−15.3 to −11.6) I5-I6: −14.7 (−16.5 to −12.8) C: −2.3 (−4.3 to −0.4) Results for I3 and I4, I5 and I6 are pooled
Li, 2023 China (NCT04799327)	- ≥18 to 65 years - BMI 28-40 kg/m² - No DM	Noiiglutide (SC, QD) I1:0.12 mg I2: 0.24 mg I3: 0.36 mg C: Placebo Duration: 24 weeks	I1: 45.3% I2: 46.2% I3: 44.4% C: 46.8%	I1: 35.3 ± 8.4 I2: 34.4 ± 8.7 I3: 36.3 ± 9.6 C: 35.7 ± 7.7	I1: 31.7 ± 2.7 I2: 32.3 ± 3.2 I3: 32.5 ± 3.6 C: 32.4 ± 3.4	I1: 64 / 4 I2: 65 / 8 I3: 63 / 12 C: 62 / 8	Least squares mean % change: I1: -9.80 (-11.18 to -8.43) I2: -9.01 (-10.40 to -7.62) I3: -9.39 (-10.80 to -7.97) C: -3.97 (-5.39 to -2.56)
GLP-1 / GIP / Glucagon RA							
Jastreboff, 2023 USA, Puerto Rico (NCT04881760)	- ≥18 to 75 years - BMI >30 and <50 kg/m² or BMI >27 and <30	Retatrutide (SC, QW) I1: 1 mg I2: 4 mg (initial dose 2 mg) I3: 4 mg (initial dose 4 mg)	I1: 52% I2: 52% I3: 53% I4: 51% I5: 51% I6: 52% C: 51%	I1: 50.6 ± 13.3 I2: 50.8 ± 11.9 I3: 46.8 ± 14.1 I4: 46.1 ± 13.5 I5: 48.7 ± 11.1 I6: 45.8 ± 12.2 C: 48.0 ± 12.5	I1: 37.5 ± 5.9 I2: 37.3 ± 5.9 I3: 37.4 ± 4.7 I4: 37.4 ± 6.0 I5: 37.0 ± 5.5 I6: 37.4 ± 6.0 C: 37.3 ± 5.9	I1: 69/ 9 I2: 33/ 7 I3: 34/ 8 I4: 35/ 5 I5: 35/ 6 I6: 62/ 8 C: 70/ 20	Least square mean % change: I1: −8.7 (−10.5 to −6.8) I2: −16.3 (−19.4 to −13.2) I3: −17.8 (−20.8 to −14.8) I4: −21.7 (−24.5 to −19.0) I5: −23.9 (−26.8 to −20.9)

Author, Year Countries (NCT)	Eligibility criteria	Intervention (s) and comparator Duration	Gender (% men/ arm)	Age mean ± SD or median (range)(years)	BMI mean ± SD or median (range)(kg/m^2)	N randomized / N discontinued	% Weight change mean ± SD or SE or 95% CI
	kg/m² with at least one comorbidity[1] - No DM	I4: 8 mg (initial dose 2 mg) I5: 8 mg (initial dose 4 mg) I6: 12 mg (initial dose 2mg) C: Placebo (QW, SC) Duration: 48 weeks[3]					I6: −24.2 (−26.6 to −21.8) C: −2.1 (−3.5 to −0.7)
GLP-1/ Glucagon RA							
Alba, 2020 USA, Belgium, Canada, Poland, Sweden, and UK (NCT03486392)	- ≥18 to 70 years - BMI >35 and <50 kg/m², stable body weight	Efinopegdutide (JNJ-64565111, QW, SC) I1: 5 mg I2: 7.4 mg I3: 10 mg I4: Liraglutide 3 mg (SC) C: Placebo Duration: 26 weeks	I1: 20.3% I2: 27.1% I3: 27.1% I4: 25.2% C: 20%	I1: 47.3 ± 11.2 I2: 46.2 ± 11.7 I3: 46.2 ± 12.2 I4: 45.6 ±11.7 C: 46.9 ± 11.8	I1: 40.3 ± 4.3 I2: 40.0 ± 4.0 I3: 40.5 ± 3.9 I4: 40.9 ± 4.3 C: 40.4 ± 4.1	I1: 59/ 16 I2: 118/ 37 I3: 118/ 46 I4: 119/ 24 C: 60 / 8	Least square mean % change: I1: −8.5 ± 0.8 I2: −9.8 ± 0.6 I3: −11.8 ± 0.6 I4: −7.5 ± 0.5 C: −1.8 ± 0.7
Le Roux, 2024 USA, Australia, Belgium, Canada, China, Germany, South Korea, Netherlands, New Zealand, Poland, Sweden, and UK (NCT04667377)	- ≥18 to < 75 years - BMI ≥27 kg/m², stable body weight[2] - No DM	Survodutide (BI 456906, SC, QW) I1: 0.6 mg I2: 2.4 mg I3: 3.6 mg I4: 4.8 mg C: Placebo Duration: 46 weeks	I1: 34% I2: 31% I3: 33% I4: 30% C: 31%	I1: 48.6 ± 12.6 I2: 49.0 ± 13.1 I3: 50.3 ± 11.8 I4: 47.6 ± 13.5 C: 50.0 ± 13.5	I1: 37.8 ± 6.3 I2: 37.6 ± 7.3 I3: 37.0 ± 5.7 I4: 37.6 ± 6.0 C: 35.8 ± 5.0	I1: 78 / 18 I2: 78 / 18 I3: 77 / 15 I4: 77 / 10 C: 77 / 18	I1: −6.2 (−8.3 to −4.1) I2: −12.5 (−14.5 to −10.5) I3: −13.2 (−15.3 to −11.2) I4: −14.9 (−16.9 to −13.0) C: −2.8 (−4.9 to −0.7)
Ji, 2023 China	- ≥18 to 75 years	Mazdutide (IBI362, SC,	I1: 43.5%	I1: 37.2 ± 10.7 I2: 33.6 ± 10.0	I1: 31.8 ± 3.9 I2: 31.8 ± 4.7	I1: 62 / 7 I2: 63 / 3	I1: −6.7 ± 0.7 I2: −10.4 ± 0.7

Author, Year Countries (NCT)	**Eligibility criteria**	**Intervention (s) and comparator Duration**	**Gender (% men/ arm)**	**Age mean ± SD or median (range)(years)**	**BMI mean ± SD or median (range)(kg/m^2)**	**N randomized / N discontinued**	**% Weight change mean ± SD or SE or 95% CI**
(NCT04904913)	- BMI ≥28 kg/m², or ≥24 kg/m² with at least one comorbidity[1]	QW) I1: 3 mg I2: 4.5 mg I3: 6 mg C: Placebo Duration: 24 weeks	I2: 41.3% I3: 55.7% C: 51.6%	I3: 35.8 ± 9.2 C: 35.5 ± 7.1	I3: 31.7 ± 4.0 C: 32.0 ± 4.2	I3: 61 / 5 C: 62 / 5	I3: −11.3 ± 0.7 C: 1.0 ± 0.7
SGLT-2 Inhibitors[5]							
Bays, 2013 USA, Puerto Rico (NCT00650806)	- ≥18 to 65 years - BMI ≥30 and <50 kg/m² if generally healthy or BMI ≥27 kg/m² with at least one comorbidity[1]	Canagliflozin (oral, QD) I1: 50 mg I2: 100 mg I3: 300 mg C: Placebo Duration: 12 weeks[3]	I1: 12% I2: 18% I3: 10% C: 16%	I1: 44.9 ± 11.8 I2: 45.8 ± 11.0 I3: 43.5 ± 11.0 C: 45.1 ± 11.9	C: 36.6 ± 5.5 I1: 36.6 ± 5.3 I2: 37.9 ± 5.1 I3: 36.9 ± 5.3	I1: 98/ 21 I2: 93/ 29 I3: 96/ 26 C: 89/ 18	Weight absolute change (kg) I1: −1.9 ± 2.9 I2: −2.8 ± 2.9 I3: −2.4 ± 2.9 C: −1.1 ± 2.5
Hollander, 2017 USA (NCT02243202)	- ≥18 years - BMI ≥30 and <50 kg/m², or BMI ≥27 and <50 kg/m² with at least one comorbidity[1] - No DM	I1: Canagliflozin 300 mg (oral, QD) I2: Phentermine 15 mg (oral, QD) I3: Canagliflozin 300 /Phentermine 15 mg (oral, QD) C: Placebo Duration: 26 weeks[3]	I1: 19% I2:18.8% I3: 16.9% C: 18.3%	I1: 45.2 ± 11.0 I2: 46.4 ± 11.1 I3: 46.3 ± 12.5 C: 44.8 ± 11.1	I1: 37.3 ± 4.7 I2: 37.0 ± 5.4 I3: 36.8 ± 5.4 C: 38.0 ± 5.2	I1: 84/ 31 I2: 85/ 25 I3: 83/ 22 C: 82/ 25	I1: –1.9 ± 0.6 I2: –4.1 ± 0.6 I3: –7.5 ± 0.6 C: –0.6 ± 0.6
Bays, 2020 USA, Austria, Canada,	- ≥18 years to 75 years - BMI ≥	Licogliflozin I1: 2.5 mg (oral, QD) I2: 10 mg (oral,	I1: 39.5% I2: 28.9%	I1: 51.3 ± 12.2 I2: 53.2 ± 10.1 I3: 52.9 ± 13.6 I4: 51.1 ± 12.9	I1: 39.3 ± 9.5 I2: 37.0 ± 5.9 I3: 38.6 ± 7.4 I4: 37.5 ± 7.3	I1: 38/ 3 I2: 38/ 7 I3: 38/ 9 I4: 77/ 14	I1: −1.2 (−2.5 to −0.5) I2: -2.0 (−3.4 to −0.9) I3: −3.5 (−4.6 to −1.9) I4: −4.4 (−5.4 to −3.4)

Author, Year Countries (NCT)	Eligibility criteria	Intervention (s) and comparator Duration	Gender (% men/ arm)	Age mean ± SD or median (range)(years)	BMI mean ± SD or median (range)(kg/m^2)	N randomized / N discontinued	% Weight change mean ± SD or SE or 95% CI
Czechia, Hungary, Slovakia, and UK (NCT03100058)	30 kg/m², or BMI≥ 27 kg/m² with at least one comorbidity[1]	QD) I3: 50 mg (oral, QD) I4: 150 mg (oral, QD) I5: 2.5 mg (oral, BID) I6: 5 mg (oral, BID) I7: 25 mg (oral, BID) I8: 50 mg (oral, BID) C: Placebo Duration: 24 weeks[3]	I3: 34.2% I4: 42.9% I5: 47.4% I6: 38.5% I7: 31.6% I8: 35.5% C: 42.3%	I5: 53.4 ± 12.4 I6: 49.8 ± 11.5 I7: 49.7 ± 11.9 I8: 52.9 ± 11.9 C: 51.1 ± 13.27	I5: 37.0 ± 5.4 I6: 37.8 ± 6.5 I7: 38.5 ± 6.8 I8: 36.9 ± 6.7 C: 38.7 ± 7.8	I5: 38/ 2 I6: 39/ 2 I7: 38/ 7 I8: 76/ 16 C: 78/ 5	I5: −1.7 (−2.6 to −0.3) I6: −2.5 (−3.9 to −1.3) I7: −4.1 (−5.5 to −2.9) I8: −4.5 (−5.5 to −3.0) C: −0.6 (−1.6 to 0.4)
He, 2019[6] USA (NCT02470403)	- ≥18 to 65 years - BMI >35 and <50 kg/m², stable body weight	I: Licogliflozin 150 mg (oral, QD) C: Placebo Duration: 12 weeks	43%-50%	40 to 56	30.2 to 40.2	I: 44/ 2 C: 44/ 1	Weight absolute change (kg) I: −6.4 (80% CI, −7.1 to −5.7) C: 0.2 (80% CI, −0.5 to 0.9)
Lundkvist, 2016 Sweden (NCT02313220)	- ≥ 18 to70 years - BMI >30 and <45 kg/m² - No DM	I: Dapagliflozin 10 mg (oral, QD) + Exenatide 2 SC (SC, QW) C: Placebo oral (QD) + Placebo (SC, QW) Duration: 24 weeks	I: 40% C: 37.5%	I: 53.5 ± 13.5 C: 50.0 ± 11.8	I: 35.8 ± 2.9 C: 35.0 ± 3.7	I: 25/ 2 C: 25/ 5	I: −4.47 (−6.04, −2.89) C: −0.27 (−1.92, 1.37)
Others[7]							
Kim, 2015 Australia (NCT01666691)	- ≥18 to 65 years - BMI >30 and <50 kg/m² [8]	Beloranib (BIW, SC) I1: 0.6 mg I2: 1.2 mg I3: 2.4 mg C: Placebo Duration: 12	I1: 8.1% I2:8.1% I3: 0% C: 10.5%	I1: 47.9 ± 14.2 I2: 47.7 ± 12.2 I3: 48.2 ± 10.4 C: 49.2 ± 10.5	I1: 37.7 ± 5.6 I2: 37.3 ± 4.5 I3: 38.3 ± 5.9 C: 37.6 ± 4.4	I1:37/ 4 I2:37/ 7 I3:35/ 20 C:38/ 4	Weight absolute change (kg) I1: −5.5 ± 0.5 I2: −6.9 ± 0.6 I3: −10.9 ± 1.1 C: −0.4 ± 0.4

Author, Year Countries (NCT)	**Eligibility criteria**	**Intervention (s) and comparator Duration**	**Gender (% men/ arm)**	**Age mean ± SD or median (range)(years)**	**BMI mean ± SD or median (range)(kg/m^2)**	**N randomized / N discontinued**	**% Weight change mean ± SD or SE or 95% CI**
		weeks					
Rebello, 2021 USA (NCT03364335)	- ≥18 to 65 years - BMI 30 and 45 kg/m², stable body weight	I1: Leucine 1.1 g + Sildenafil 1 mg (oral, BID) I2: Leucine 1.1 g + Sildenafil 4 mg (oral, BID) I3: Leucine 1.1 g + Sildenafil 1 mg + Metformin 500 mg (oral, BID) I4: Leucine 1.1 g + Sildenafil 4 mg + Metformin 500 mg (oral, BID) C: Placebo Duration: 24 weeks	I1: 43.1% I2: 39.6% I3: 22% I4: 32.7% C: 26.9%	I1: 41.3 ± 11.6 I2: 39.2 ± 11.1 I3: 42.1 ± 12.6 I4: 42.1 ± 10.4 C: 40.8 ± 11.0	I1: 37.1 ± 4.28 I2: 37.9 ± 4.19 I3: 36.4 ± 4.12 I4: 37.1 ± 4.23 C: 35.7 ± 3.3	I1: 54/ 14 I2: 54/ 11 I3: 52/ 11 I4: 54/ 11 C: 53/ 8	Least square mean % change: I1: 0.6 ± 0.5 I2: −0.3 ± 0.5 I3: −0.7 ± 0.5 I4: −0.3 ± 0.5 C: 1.2 ± 0.5
Holmbäck, 2022 Sweden (NCT04521751)	- ≥18 to 75 years - BMI >30 kg/m², or BMI >28 kg/m² with at least one comorbidity[1]	Orlistat/Acarbose (EMP16-02) (oral, TID) I1: 120 mg/40 mg I2: 150 mg /50 mg C: Placebo Duration: 26 weeks	I1: 27% I2: 31% C: 29%	I1: 49.4 ± 12.2 I2: 50.7 ± 13.6 C: 49.5 ± 12.8	I1: 35.1 ± 3.3 I2: 34.6 ± 3.6 C: 36.2 ± 4.5	I1: 52/ 8 I2: 52/ 7 C: 52/ 6	I1: −6.03 ± 5.3 I2: −6.40 ± 4.8 C: −0.82 ± 3.8

Abbreviation list: GLP-1 RA, Glucagon-Like Peptide-1 Receptor Agonists; GLP-1 / GIP / Glucagon RA, Glucagon-Like Peptide 1, Glucose-Dependent Insulinotropic Polypeptide and Glucagon Receptor; SGLT2 Inhibitor, Sodium-glucose Cotransporter-2 Inhibitor; SE, Standard error; SD, standard deviation; CI, confidence interval; C, control; I, intervention; DM, diabetes; QD, once daily; BID, twice daily; TID, three times daily; QW, once weekly; Q2W, biweekly; BIW, twice weekly; SC, subcutaneously. Numbers are rounded to one decimal place.

[1] Weight-related comorbidities include, but are not limited to, hypertension, dyslipidemia, obstructive sleep apnea, cardiovascular disease

[2] At least one unsuccessful dietary effort to lose weight

[3] Participants received a lifestyle counseling, i.e., dietary and exercise education

[4] The 36-mg and 45-mg dose cohorts were each divided into two sub-cohorts that had different starting doses and dose-escalation schemes

[5] SGLT-2 Inhibitors alone or in combination with other medication which include: Exenatide; GLP-1 RA, Phentermine; an indirect sympathomimetic agent norepinephrine, dopamine and serotonin; Licogliflozin; dual SGLT-1/2 inhibitor

[6] Patients characteristics are combined between two studies, with obesity and with type 2 diabetes

[7] Others include: Beloranib; MetAP2 Inhibitor, Leucine + Metformin; activate the AMP-activated protein kinase/ histone/protein deacetylase (AMPK/Sirt1) and Sildenafil activates Endothelial nitric oxide synthase (eNOs) and inhibits phosphodiesterase 5 (PDE5) resulting in concomitant activation of the cGMP-dependent protein kinases (PKGs), and Orlistat; gastric and pancreatic lipases inhibitor and Acarbose is a pancreatic alpha-amylase inhibitor

[8]All participants were surgically sterile, of non-childbearing potential, or agreed to use acceptable birth control during the study

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Table 2. Summary of included phase 3 ongoing trials

Drug (NCT)	Eligibility criteria	Sample size	Intervention and comparator Duration	Primary outcome	Expected completion date	Location	Company
GLP-1 RA							
Ecnoglutide XW003 (NCT05813795)	- ≥18 to 75 years - BMI >24 and <28 kg/m^2 with at least one comorbidity[1], stable body weight	664	Ecnoglutide (SC, QW)[2] I1: low dose I2: medium dose I3: high dose C: Placebo Duration: 48 weeks[3]	- % change in body weight - % of patients with ≥5% weight reduction	Jan 2025	China	Hangzhou Sciwind Biosciences Co., Ltd.
Orforglipron LY3502970 (NCT05931380)	- ≥18 years - BMI ≥27 kg/m² and <35 kg/m² with at least two comorbidities[1], or BMI ≥35 kg/m² with at least one comorbidity[1,4]	236	Orforglipron (oral, QD)[2] I1: dose 1 I2: dose 2 I3: dose 3 C: Placebo Duration: 72 weeks	- % change in body weight - % of patients with ≥5% weight reduction	July 2025	Japan	Eli Lilly and Company
Orforglipron LY3502970 (NCT05869903)	- ≥18 years - BMI ≥30 kg/m^2, or BMI ≥27 kg/m^2 with at least one comorbidity[1,4]	3000	Orforglipron (oral, QD)[2] I1: dose 1 I2: dose 2 I3: dose 3 C: Placebo Duration: 72 weeks	- % change in body weight	Sep 2027	USA/ Brazil / China/ India/ Japan / Republic of Korea/ Puerto Rico/ Slovakia/ Spain/ Taiwan	Eli Lilly and Company
TG103 (NCT05997576)	- ≥18 to ≤75 years - BMI ≥28 kg/m^2, or BMI <24 and ≤28 kg/m^2 with at least one comorbidity[1], stable body weight	675	I: TG103 22.5 mg (SC, QW) doses gradually increased from 7.5 mg to 22.5 mg C: Placebo (SC, QW) Duration: 40 weeks[3]	- % change in body weight - % of patients with ≥5% weight reduction	April 2025	China	CSPC Baike (Shandong) Biopharmaceutical Co., Ltd.
GLP-1/ Amylin Analog[5]							
CagriSema (NCT05567796)	- ≥18 years - BMI ≥30 kg/m², or ≥27 kg/m² with at least one comorbidity[1]	3400	I1: Cagrisema (SC, QW) 2.4 mg/ 2.4 mg I2: Cagrilintide (SC, QW) 2.4 mg I3: Semaglutide (SC, QW) 2.4 mg C: Placebo (SC, QW) Duration: 68 weeks	- Relative change in body weight - % of patients with ≥5% weight reduction	Oct 2026	USA/ Australia/ Belgium/ Bulgaria/ Canada/ Denmark/ Finland/ France/ Germany/ India/ Italy/ Japan / Republic of Korea/ Mexico/Netherland/ Poland /Serbia/ South	Novo Nordisk A/S

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Drug (NCT)	Eligibility criteria	Sample size	Intervention and comparator Duration	Primary outcome	Expected completion date	Location	Company
						Africa/ Spain/ Taiwan/ Turkey/ United Kingdom	
CagriSema (NCT06131437)	- ≥18 years - BMI >30 kg/m^2	800	I: CagriSema 2.4 mg/2.4 mg (SC, QW) C: Tirzeptaide 15 mg (SC, QW) Duration: 72 weeks	- % change in body weight	Oct 2025	USA	Novo Nordisk A/S
CagriSema (NCT05813925)	- ≥18 years - BMI ≥27 kg/m^2 with at least two comorbidities[1]	330	I: CagriSema 2.4 mg/2.4 mg (SC) with a dose escalation period of 16 weeks[6] C: Semaglutide 2.4 mg (SC, QW) dose escalation period of 16 weeks[7] Duration: 52 weeks	- % change in body weight	March 2025	Japan/ Taiwan	Novo Nordisk A/S
CagriSema (NCT05996848)	- ≥18 years - BMI >30 kg/m^2, or BMI >27 kg/m^2 with at least one comorbidity[1]	300	I: CagriSema 2.4 mg Cagrilintide /2.4 mg Semaglutide (SC, QW) C: Semaglutide 2.4 mg (SC, QW), Placebo (SC, QW) Duration: 44 weeks	- % change in body weight - % of patients with ≥5% weight reduction	April 2025	China	Novo Nordisk A/S
GLP-1/ GIP/ Glucagon RA							
Retatrutide LY3437943 (NCT05929066)	- ≥18 years - BMI≥30 kg/m², or ≥27 kg/m² with at least one comorbidity[1,4]	2100	Retatrutide (SC)[2] I1: dose 1 I2: dose 2 I3: dose 3 C: Placebo (SC) Duration: 80 weeks	- % change in body weight - Change from baseline in the WOMAC Score - Change from baseline in AHI Events Per Hour	May 2026	USA / Australia / Brazil/ Canada/ China/ Hungary/ India/ Korea/ Mexico/ Poland/ Puerto Rico/ Romania/ Spain/ Taiwan/ United Kingdom	Eli Lilly and Company
GLP-1/ Glucagon RA							
Mazdutide IBI362 or LY3305677 (NCT05607680)	- ≥18 years - BMI ≥28 kg/m², or ≥24 kg/m² with at least one comorbidity[1]	600	I1: IBI362 (SC, QW) 2 mg for 4 weeks, 4 mg for 44 weeks I2: IBI362 (SC, QW) 2 mg for 4 weeks, 4 mg for 4 weeks, 6 mg	- % change in body weight - % of patients with ≥5% weight reduction	April 2024	China	Innovent Biologics (Suzhou) Co. Ltd.

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Drug (NCT)	Eligibility criteria	Sample size	Intervention and comparator Duration	Primary outcome	Expected completion date	Location	Company
			for 40 weeks C: Placebo (SC, QW) for 48 weeks Duration: 48 weeks				
Mazdutide IBI362 or LY3305677 (NCT06164873)	- ≥18 years - BMI >30 kg/m^2 [4]	450	I: IBI362 (SC, QW)[2] C: Placebo (SC) Duration: 60 weeks	- % change in body weight - % of patients with ≥5% weight reduction	Sep 2025	China	Innovent Biologics (Suzhou) Co. Ltd.
Survodutide BI 456906 (NCT06066515)	- ≥18 years - BMI ≥30 kg/m^2, or BMI ≥27 kg/m^2 with at least one comorbidity[1,4]	725	BI 456906 (SC, QW) I1: 3.6 mg I2: 6.0 mg C: Placebo (SC, QW) Duration: 76 weeks[3]	- % change in body weight - % of patients with ≥5% weight reduction	Jan 2026	USA/ Canada/ New Zealand	Boehringer Ingelheim
SGLT-2 inhibitor							
Dapagliflozin (NCT06000462)	- ≥18 years - BMI >30 and <35 kg/m^2, stable body weight[4]	150	I1: Dapagliflozin 10 mg orally (QD) C: Metformin 1000 mg (QD), Placebo (QD) Duration: 32 weeks[3]	- % of patients with ≥5% weight reduction	Dec 2025	Oman	Oman Ministry of Health
Sibutramine inhibits norepinephrine, serotonin, and to a lesser extent, dopamine reuptake at the neuronal synapse, and Topiramate XR stimulates GABA-A receptor activity							
Sibutramine/ Topiramate XR (NCT05209984)	- ≥18 to 60 years - BMI ≥ 27 kg/m^2 with at least one comorbidity[1], or BMI ≥30 kg/m^2 and <45 kg/m^2	1855	I1: Sibutramine IR 15 mg / Topiramate XR 75 mg orally (QD) I2: Sibutramine IR 15 mg (Sibus®) Topiramate XR 100 mg orally (QD) C: Sibutramine 15 mg, Placebo Duration: 58 weeks	- Change in body weight	July 2027	Brazil	Eurofarma Laboratorios S.A.

Abbreviation list: GLP-1 RA, Glucagon-Like Peptide-1 Receptor Agonists; GLP-1 / GIP / Glucagon RA, Glucagon-Like Peptide 1, Glucose-Dependent Insulinotropic Polypeptide and Glucagon Receptor; SGLT2 Inhibitor, Sodium-glucose Cotransporter-2 Inhibitor; C, Control; I, Intervention; QD, Once daily; QW, Once weekly; SC, Subcutaneously; WOMAC, Western Ontario and McMaster Universities Arthritis Index; AHI, Apnea-Hypopnea Index. Numbers are rounded to one decimal place.

[1] Weight-related comorbidities include, but are not limited to, hypertension, dyslipidemia, obstructive sleep apnea, cardiovascular disease

[2] Dose or frequency not specified on clinicaltrials.gov

[3] Participants received a lifestyle counseling, i.e., dietary and exercise education

[4] At least one unsuccessful dietary effort to lose weight

[5] Cagrilintide is an amylin analog and semaglutide is a GLP-1 RA

[6] (0.25 mg of cagrilintide and 0.25 mg of semaglutide from weeks 0-4, 0.5 mg of cagrilintide and 0.5 mg of semaglutide from weeks 5-8, 1 mg of cagrilintide and 1 mg of semaglutide from weeks 9-12 and 1.7 mg of cagrilintide and 1.7 mg of semaglutide from weeks 13-16, 2.4 mg of cagrilintide and 2.4 mg of semaglutide thereafter)

[7] (0.25 mg for weeks 0-4, 0.5 mg for weeks 5-8, 1 mg for weeks 9-12 and 1.7 mg for weeks 13-16, 2.4 mg of semaglutide thereafter)

Table 3. Summary of included completed but not published phase 2 trials

Drug (NCT)	Eligibility criteria	Sample size	Intervention and comparator Duration	Primary Outcome	Expected completion date	Location	Company
GLP-1 RA							
Danuglipron [1] PF-06882961 (NCT04707313)	- ≥18 to 75 years - BMI ≥ 30 kg/m², stable body weight	630	I: PF-06882961 40 mg, 80 mg, 120 mg, 160 mg, 200 mg (BID) C: Placebo Duration: 32 weeks	- % change in body weight Press release: Mean placebo-adjusted weight reductions 8-13%	Oct 2023	USA/ Canada/ Japan/ Taiwan	Pfizer
Ecnoglutide XW003 (NCT05111912)	- ≥18 to 70 years - BMI ≥ 30 and ≤40 kg/m², stable body weight, HbA1c <6.5%	206	XW003 (SC, QW) I: 1.2 mg, 1.8 mg, or 2.4 mg C: Liraglutide 3 mg (SC) Duration: 26 weeks	- % change in body weight	Dec 2022	Australia	Sciwind Biosciences
GLP-1/ Glucagon RA							
Pemvidutide [6] ALT-801 (NCT05295875)	- ≥18 to 75 years - BMI ≥ 30 kg/m² or BMI ≥ 27 kg/m² with at least one comorbidity [2]	320	ALT-801 (SC)[3] I1: dose 1 I2: dose 2 I3: dose 3 C: Placebo Duration: 48 weeks[4]	- % change in body weight Press release: mean weight loss of 15.6% on 2.4 mg dose of pemvidutide at week 48, with weight loss continuing at the end of treatment	Sep 2023	USA	Altimmune
Growth/differentiation factor 15 agonist							
MBL949 (NCT05199090)	- ≥18 to 60 years - BMI ≥ 32 kg/m², stable body weight	126	I: MBL949 (SC)[3] C: Placebo Duration: 16 weeks	- Frequency and severity of adverse events - Change in body weight	May 2023	USA	Novartis
Selective agonist of the melanocortin 4 receptor							
Setmelanotide RM-493 (NCT02041195)	- ≥18 to 65 years - BMI >30 and <40 kg/m²	99	I: RM-493 (SC, QD) or RM-493 split dose one half in the morning and one half in the evening[3] C: Placebo (SC) Duration: 12 weeks[4, 5]	- % change in body weight - Assessment of adverse events and clinical laboratory evaluations	Dec 2014	USA	Rhythm Pharmaceuticals, Inc.
Setmelanotide	- ≥18 to 65	74	I: RM-493	- % change in body	Sep 2014	USA	Rhythm

Drug (NCT)	Eligibility criteria	Sample size	Intervention and comparator Duration	Primary Outcome	Expected completion date	Location	Company
RM-493 (NCT01749137)	years - BMI >30 and <40 kg/m²		1mg/24hrs (SC) C: Placebo (SC) Duration: 130 weeks[4]	weight			Pharmaceuticals, Inc.
Semaglutide is a GLP-1 RA and NNC01651875 is a neuropeptide Y receptor type 2 agonist							
Semaglutide NNC0165-1875 (NCT04969939)	- ≥18 years - BMI >30 and <45 kg/m²	120	I1: Semaglutide 2.4 mg and NNC0165-1875 2.0 mg I2: Semaglutide 2.4 mg and NNC0165-1875 1.0 mg C1: Semaglutide 2.4 mg and Placebo 2.0 mg C2: Semaglutide 2.4 mg and Placebo 1.0 mg Duration: 40 weeks	- Number adverse events - % change in body weight	Jan 2023	USA	Novo Nordisk A/S
Targets bitter taste receptors (TS2R)							
Oral Denatonium Acetate ARD-101 (NCT05121441)	- ≥18 to 65 years - BMI >30 and <40 kg/m²	20	I: 200 mg (BID) C: Placebo Duration: 4 weeks	- % change in body weight	Nov 2022	USA	Aardvark Therapeutic, Inc.

Abbreviation list: GLP-1 RA, Glucagon-Like Peptide-1 Receptor Agonists; C, Control; I, Intervention; QD, Once daily; BID, Twice daily; QW, Once weekly; SC, Subcutaneously. Numbers are rounded to one decimal place.

[1] Results published from press release

[2] Comorbidities include, but are not limited to, hypertension, dyslipidemia, obstructive sleep apnea, cardiovascular disease

[3] Doses not specified on clinicaltrials.gov

[4] Participants received a lifestyle counseling, i.e., dietary and exercise education

[5] Mode of administration and frequency not described on clinicaltrials.gov

Table 4. Summary of included ongoing phase 2 trials

Drug NCT	Population	Sample size	Intervention	Primary outcome	Expected Completion date	Location	Company
GLP-1 RA							
TG103 (NCT05299697)	- ≥18 years to 75 years - BMI ≥ 28 kg/m², or >24 and <28 kg/m², with at	195	TG103 (SC, QW) I1: 15 mg I2: 22.5 mg C: Placebo (SC) Duration: 24 weeks[1]	- Change in body weight	Sep 2023	China	CSPC Baike (Shandong) Biopharma

Drug NCT	Population	Sample size	Intervention	Primary outcome	Expected Completion date	Location	Company
	least one comorbidity[1], stable body weight						ceutical
GLP-1 RA/ GIP receptor antagonist							
Maridebart Cafraglutide AMG 133 (NCT05669599)	- ≥18 to 99 years - BMI ≥30 kg/m² or ≥27 kg/m² with at least one comorbidity[2]	592	AMG 133[3,4] I1: dose 1 I2: dose 2 I3: dose 3 C: Placebo Duration: 52 weeks	- % change in body weight	Jan 2026	USA/ Australia / Canada/ Czechia/ Germany / Hong Kong/ Hungary/ Japan/ Republic of Korea/ Poland/ Spain/ Taiwan	Amgen
GLP-1/GIP RA							
HRS9531 (NCT05881837)	-≥18 to 65 years -BMI ≥28 and ≤40 kg/m², stable body weight -Diet and exercise control for at least 3 months	249	HRS9531 (SC)[3] I1: dose 1 I2: dose 2 I3: dose 3 I4: dose 4 C: Placebo Duration: 24 weeks	- % change in body weight	Oct 2024	China	Fujian Shengdi Pharmaceutical Co., Ltd.
HRS9531 (NCT06054698)	- ≥18 to 65 years - BMI ≥28 and ≤40 kg/m², stable body weight - Diet and exercise control for at least 3 months	60	I: HRS9531 (SC, QW)[3] C: Placebo Duration: 36 weeks	- % change in body weight	Sep 2024	China	Fujian Shengdi Pharmaceutical Co., Ltd
HS-20094 (NCT06118021)	- ≥18 to 65 years - BMI ≥28 kg/m², or BMI ≥24 and <28 kg/m² with at least one comorbidity[2], stable body weight - Diet and	200	HS-20094 (SC, QW) I1: 5 mg I2: 10 mg I3: 15 mg I4: 20 mg C: Placebo Duration: 24 weeks	- % change in body weight	Oct 2024	China	Jiangsu Hansoh Pharmaceutical Co., Ltd.

Drug NCT	Population	Sample size	Intervention	Primary outcome	Expected Completion date	Location	Company
	exercise control for at least 3 months						
VK2735 (NCT06068946)	- ≥18 years - BMI ≥30 kg/m², or BMI ≥27 kg/m², with at least one comorbidity[2], and BMI <50 kg/m²	176	VK2735[3,4] I1: dose 1 I2: dose 2 I3: dose 3 I4: dose 4 C: Placebo Duration: 13 weeks	- % change in body weight - % of patients with ≥5% weight reduction	June 2024	USA	Viking Therapeutics, Inc.
GLP-1/GLP-2 RA							
Dapiglutide (NCT05788601)	- ≥18 to 75 years - BMI ≥ 30 kg/m² with at least one comorbidity[2]	54	Dapiglutide (SC, QW) I1: 4 mg I2: 6 mg C: Placebo Duration: 12 weeks	- % change in body weight	Aug 2024	Denmark	Zealand Pharma
GLP-1/ Glucagon RA							
Mazdutide IBI362 or LY3305677 (NCT06124807)	- ≥16 to 75 years - BMI ≥27 kg/m², with at least one comorbidity[2], stable body weight	165	LY3305677 (SC, QW)[3] I1: dose 1 I2: dose 2 I3: dose 3 C: Placebo Duration: 62 weeks	- % change in body weight	May 2025	USA	Eli Lilly and Company
Others[5]							
Vutiglabridin HSG4112 (NCT05197556)	- ≥19 to 70 years - BMI >30 and < 39.9 kg/m², with or without comorbidities[2], or BMI >27 and <29.9 kg/m² with at least one comorbidity[2]	81	HSG4112 (oral, QD) I1: 200 mg I2: 400 mg I3: 600 mg C: Placebo Duration: 12 weeks	- Change in body weight - Adverse event monitoring	April 2023	Republic of Korea	Glaceum
Bimagrumab +/- GLP-1 (NCT05616013)	- ≥18 to 80 years - BMI ≥ 30 kg/m², or BMI ≥ 27 kg/m² with at least one comorbidity[2], stable body weight	507	Bimagrumab (IV), Semaglutide(SC) I1: Bimagrumab 10 mg/kg (at baseline, week 4, 16, 28, and 40) to bimagrumab 30 mg/kg (at week 52 and 64) I2: Bimagrumab 10 mg/kg (at baseline, week 4, 16, 28, 40, 52 and 64) + semaglutide 1.0 mg (QW)	- Change in body weight	June 2025	USA/ Australia / New Zealand	Versanis Bio

Drug NCT	Population	Sample size	Intervention	Primary outcome	Expected Completion date	Location	Company
			I3: Bimagrumab 10 mg/kg (at baseline, week 4, 16, 28, 40, 52 and 64) + semaglutide 2.4 mg (QW) I4: Bimagrumab 30 mg/kg (at baseline, week 4, 16, 28, 40, 52 and 64) I5: Bimagrumab 30 mg/kg (at baseline, week 4, 16, 28, 40, 52 and 64) + semaglutide 1.0 mg (QW) I6: Bimagrumab 30 mg/kg (at baseline, week 4, 16, 28, 40, 52 and 64) + semaglutide 2.4 mg (QW) C: - Placebo (at baseline, week 4, 16, 28 and 40) to bimagrumab 30 mg/kg (at week 52 and 64) - Placebo (at baseline, week 4, 16, 28, 40, 52 and 64) + semaglutide 1.0 mg (QW) - Placebo (at baseline, week 4, 16, 28, 40, 52 and 64) + semaglutide 2.4 mg (QW) Duration: 48 weeks				
S-309309 (NCT05925114)	- ≥18 years - BMI ≥30 kg/m², stable body weight[6]	365	S-309309[3,4] I1: low dose I2: middle dose I3: high dose C: Placebo Duration: 24 weeks[1]	- % change in body weight	May 2024	USA	Shionogi
K-757 K-833 (NCT06019559)	- ≥18 to 70 years - BMI >30 and <40 kg/m², stable body weight[6]	150	I1: K-757 and K-833[3,4] I2: K-757 and matching placebo to K-833[3,4] I3: Matching placebo to K-757 and matching placebo to K-833	- % change in body weight	Feb 2024	USA	Kallyope Inc.

Drug NCT	Population	Sample size	Intervention	Primary outcome	Expected Completion date	Location	Company
			Duration: 13 weeks[1]				
Orlistat/ Acarbose EMP16 (NCT05934110)	- ≥18 years - BMI ≥30 kg/m², or BMI ≥27 kg/m² with at least one comorbidity[2], adequate renal and hepatic function	320	EMP16-120/40 / EMP16-60/20[4] I1: week 1-2: 60 mg orlistat/20 mg acarbose I2: week 3-4: 60 mg orlistat/20 mg acarbose I3: week 5-26: 60 mg orlistat/20 mg acarbose C: - Modified release orlistat 120 mg - Conventional orlistat - Placebo Duration: 26 weeks	- % change in body weight - % of patients with ≥5% weight reduction	March 2024	Sweden	Empros Pharma AB
Trevogrumab/ Garetosmab / Semaglutide REGN1033 GDF8 (NCT06299098)	Part A - ≥18 to ≤55 years - BMI ≥18 and ≤32 kg/m² Part B [6] - ≥18 to ≤80 years - BMI ≥30 kg/m²	624	Part A (IV or SC)[3] - Trevogrumab - Placebo Part B[3] A0: - Semaglutide (SC) - Matching Placebo-Trevogrumab (SC) - Matching Placebo-Garetosmab (IV) A1: - Trevogrumab (SC, high dose) - Semaglutide (SC) - Matching Placebo-Trevogrumab (SC) - Matching Placebo-Garetosmab (IV) B0: - Trevogrumab (SC, low dose) - Semaglutide (SC) - Matching Placebo-Trevogrumab (SC) - Matching Placebo-Garetosmab (IV) B1: - Trevogrumab (SC, low	- % change in body weight (Part B)	June 2026	USA	Regeneron Pharmaceuticals

Drug NCT	Population	Sample size	Intervention	Primary outcome	Expected Completion date	Location	Company
			followed by high dose) - Semaglutide (SC) - Matching Placebo-Garetosmab (IV) C0: - Trevogrumab (SC, high dose) - Semaglutide (SC) - Matching Placebo-Trevogrumab (SC) - Matching Placebo-Garetosmab (IV) C1: - Trevogrumab (SC, high dose) - Semaglutide (SC) - Matching Placebo-Garetosmab (IV) D0: - Trevogrumab (SC, high dose) - Garetosmab (IV) - Semaglutide (SC) - Matching Placebo-Trevogrumab (SC) D1: - Trevogrumab (SC, high dose) - Garetosmab (IV) - Semaglutide (SC) Duration: 26 weeks				

Abbreviation list: GLP-1 RA, Glucagon-Like Peptide-1 Receptor Agonists; GLP-1 / GIP, Glucagon-Like Peptide 1 / Glucose-Dependent Insulinotropic Polypeptide; GLP-2, Glucagon-Like Peptide-2; SGLT2 Inhibitor, Sodium-glucose Cotransporter-2 Inhibitor; C, Control; I, Intervention; QD, Once daily; QW, Once weekly; SC, Subcutaneously; IV, Intravenous. Numbers are rounded to one decimal place.

[1] Participants received a lifestyle counseling, i.e., dietary and exercise education

[2] Comorbidities include, but are not limited to, hypertension, dyslipidemia, obstructive sleep apnea, cardiovascular disease

[3] Dose or frequency not specified on clinicaltrials.gov

[4] Mode of administration not described on clinicaltrials.gov

[5] Others include: Vutiglabridin; glabridin analog, Bimagrumab; human monoclonal antibody to the activin receptor type II, S-309309; MGAT2 transferase inhibitor, K-757 and K-833; nutrient receptor stimulants and Orlistat/ Acarbose; Orlistat is a gastric and pancreatic lipases inhibitor and Acarbose is a pancreatic alpha-amylase inhibitor

[6] At least one unsuccessful dietary effort to lose weight

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Fig 1

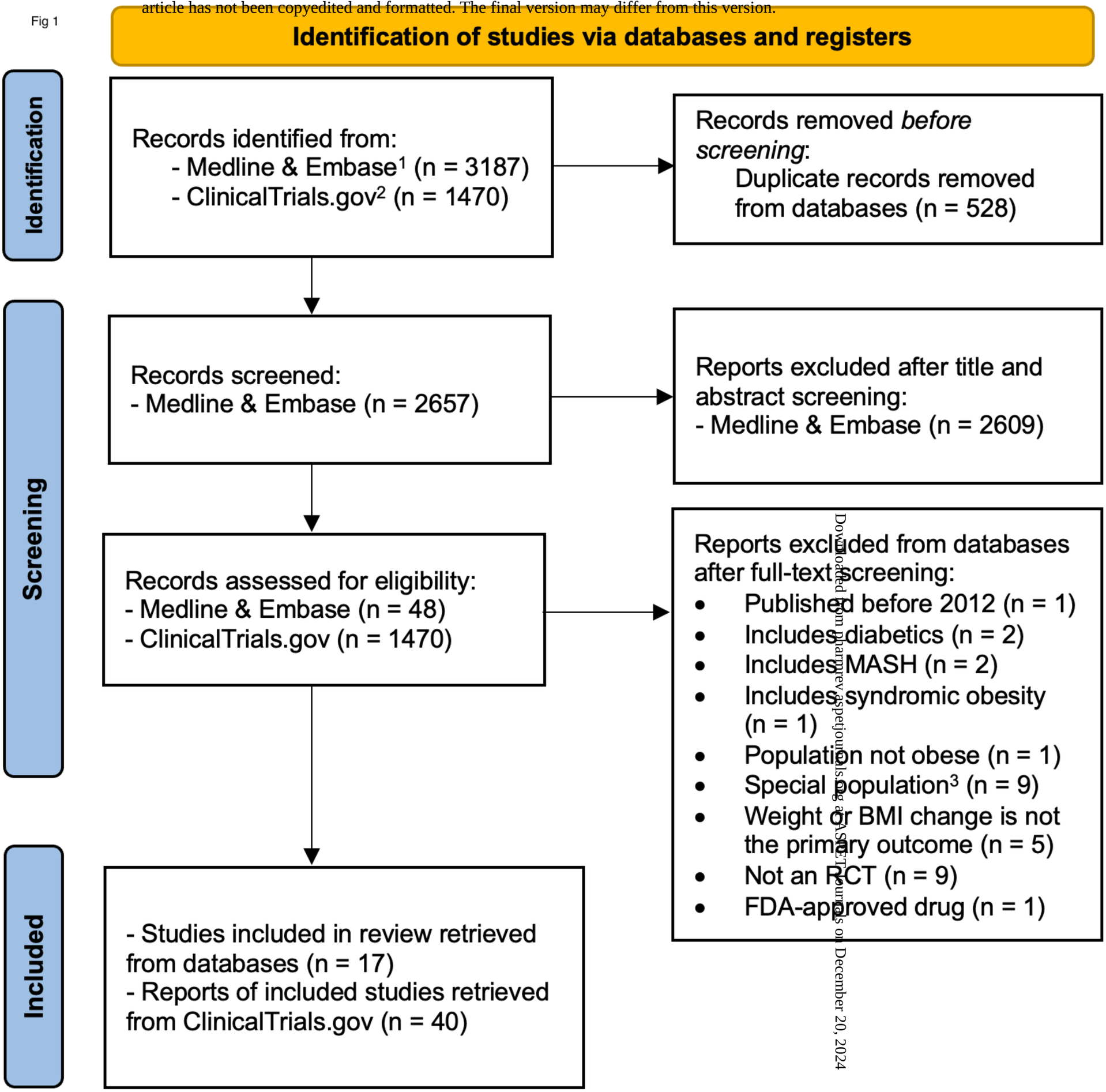
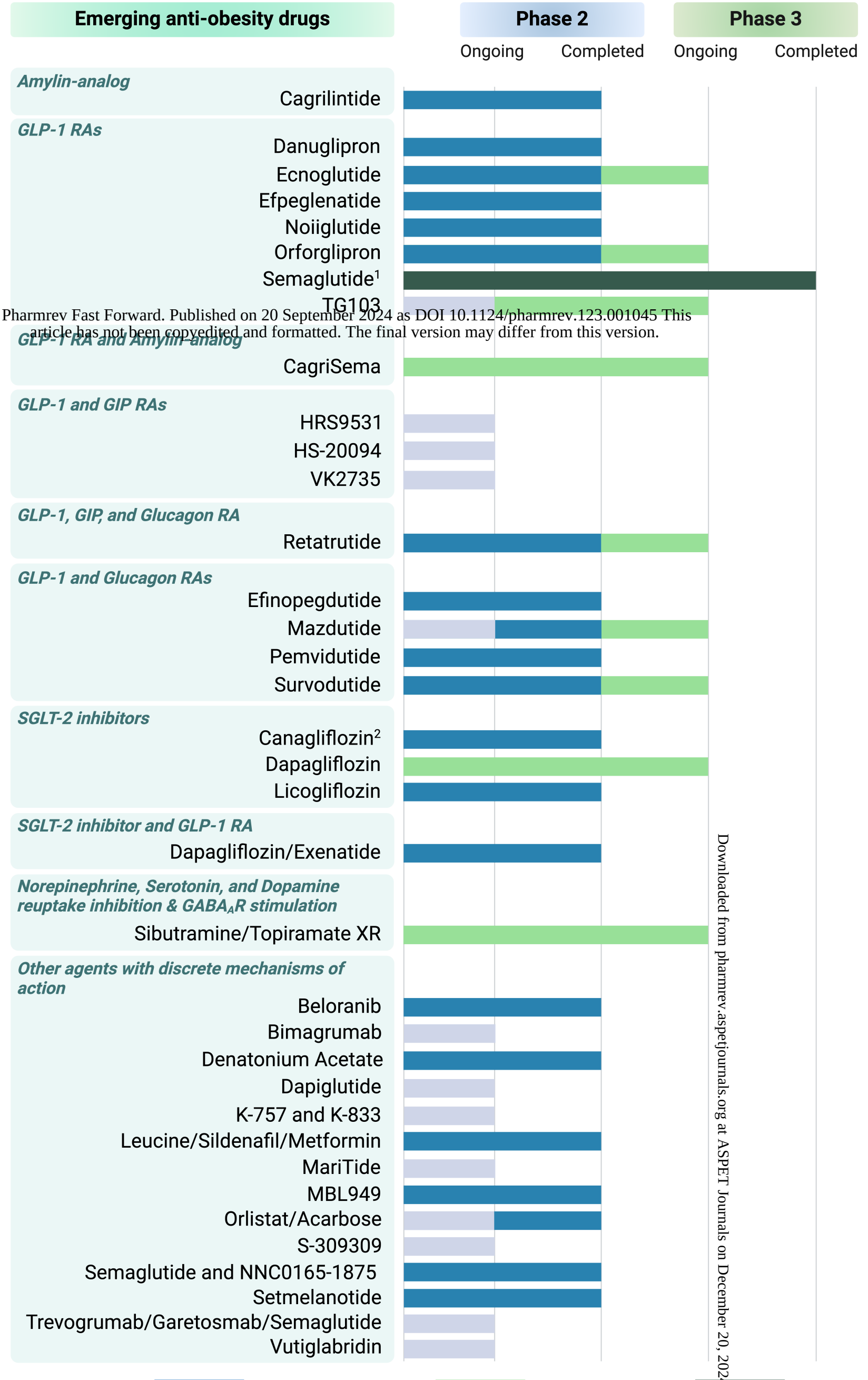


Fig 2



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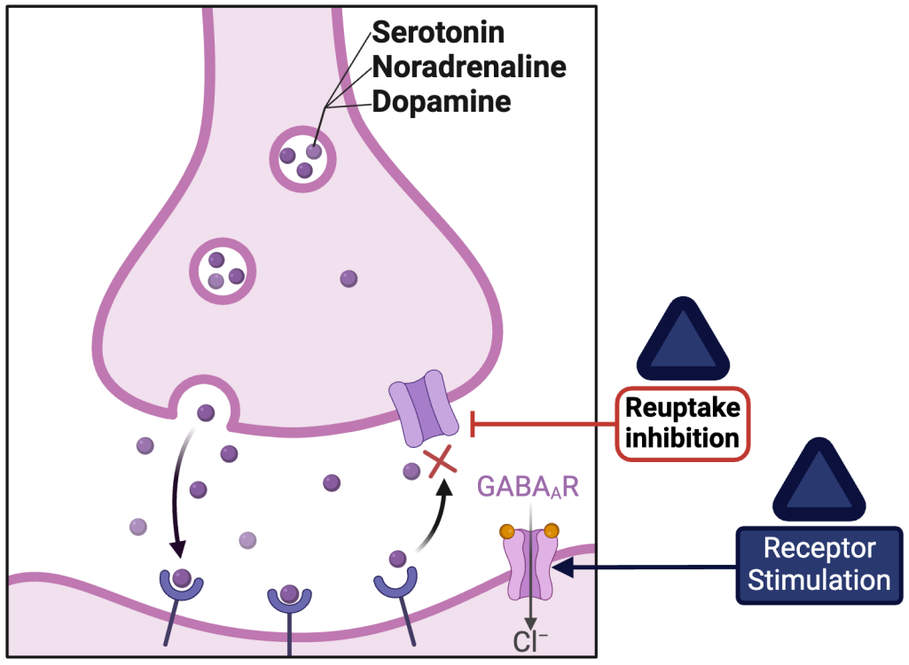
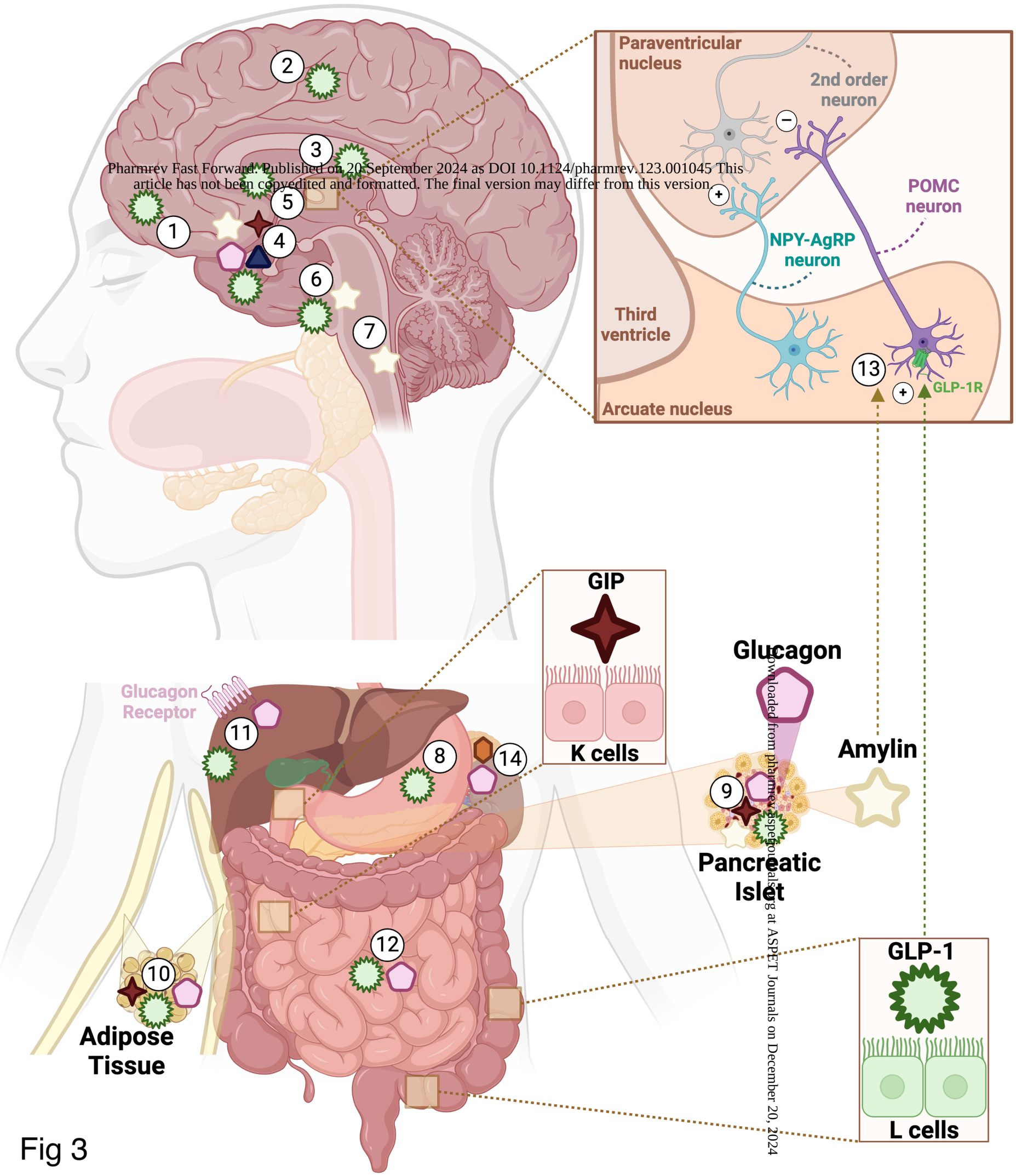




Completed & Ongoing Phase 3 Drugs

CagriSema

Amylin analog & GLP-1 receptor agonist

Dapagliflozin

SGLT-2 inhibitor

Mazdutide, Survodutide

Dual GLP-1 & Glucagon receptor agonist

Ecnoglutide, Orforglipron, Semaglutide[1], TG103

GLP-1 receptor agonist

Retatrutide

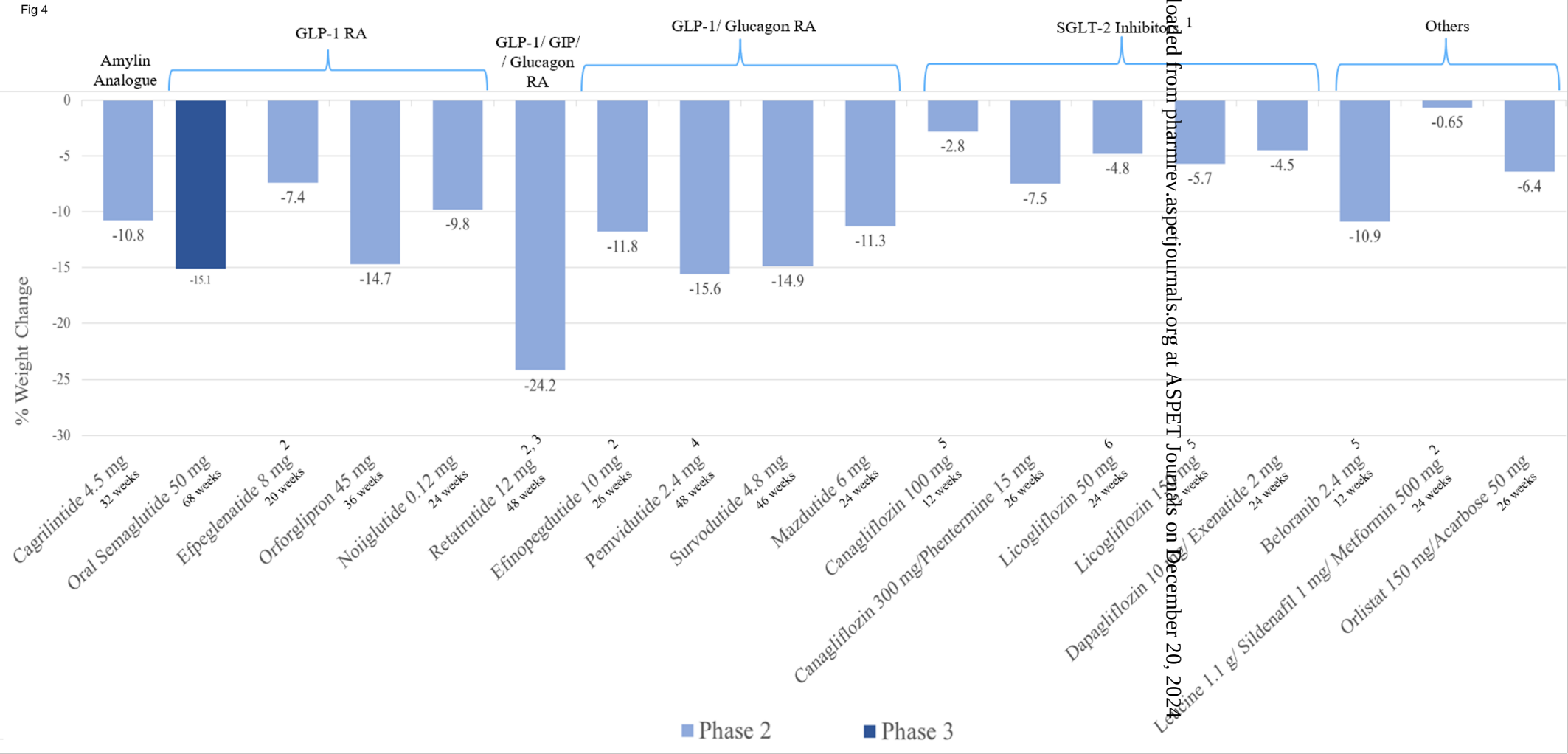
Triple GLP-1, GIP, and Glucagon receptor agonist

Sibutramine/ Topiramate XR

Norepinephrine, serotonin, and dopamine reuptake inhibition & GABA$_A$R stimulation

Fig 3

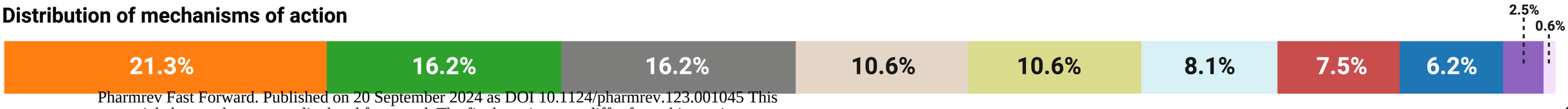
Fig 4



Mechanisms of action in development

- Amylin analog
- GLP-1 RA
- GLP-1 RA/Amylin analog
- GLP-1 RA/GIP receptor antagonist
- GLP-1/GIP RA
- GLP-1/GLP-2 RA
- GLP-1/GIP/Glucagon RA
- GLP-1/Glucagon RA
- SGLT-2 inhibitors
- Other mechanisms

Distribution of mechanisms of action



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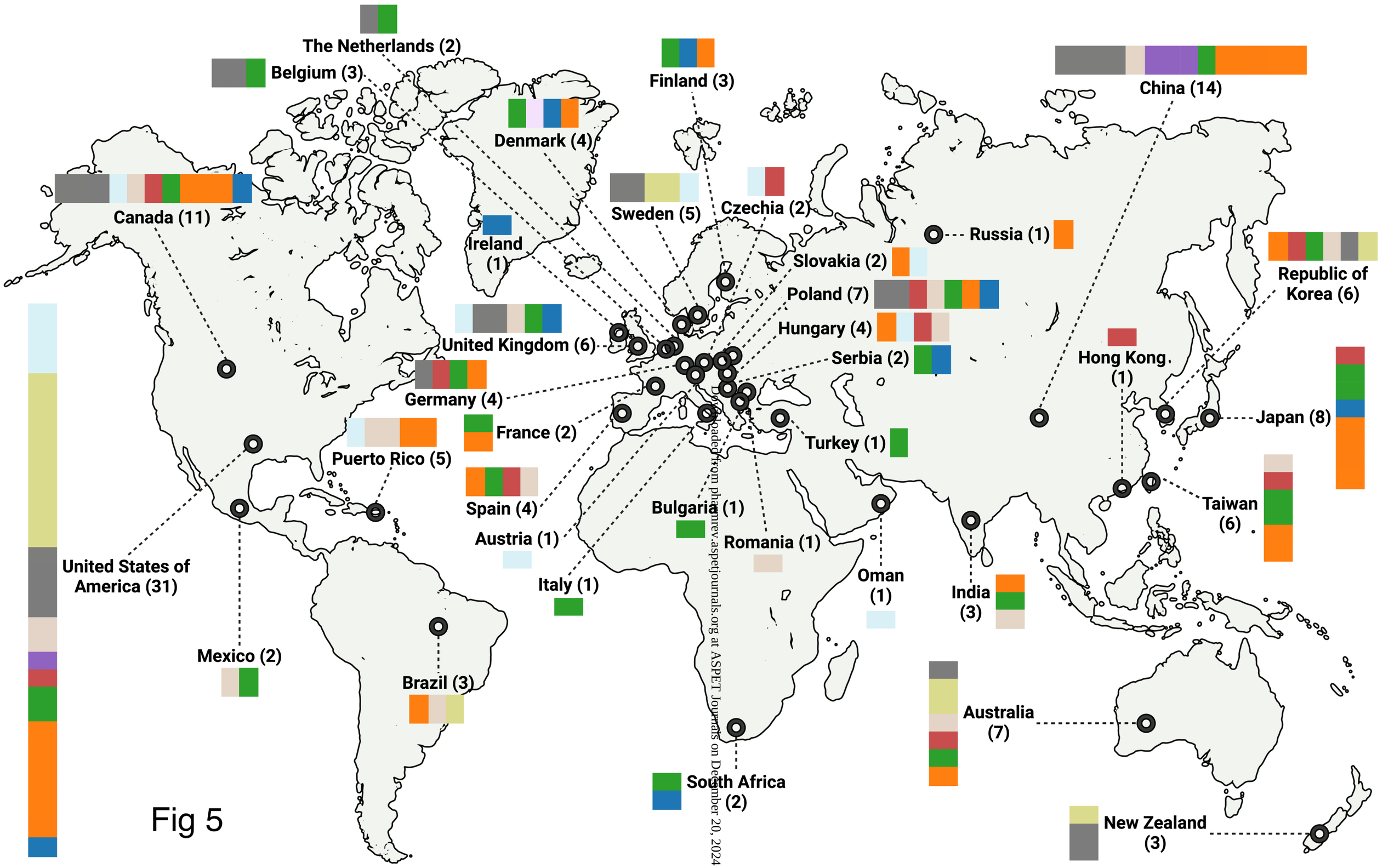

Fig 5

Fig 6