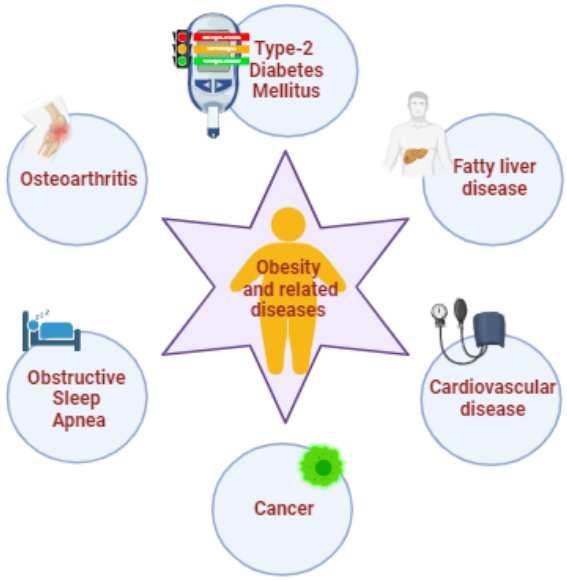
Therapeutic Concepts for Obesity and Related Diseases

According to the World Health Organisation (2016), more than 1.9 billion adults, 18 years and older, were overweight. Of these, over 650 million were obese. At current, most of the world's population live in countries where overweight and obesity kills more people than underweight. In view of these alarming figures, health programmes and drug developments have been initiated worldwide to promote healthy lifestyles and prevent the development of obesity and related diseases in all ages.



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Obesity together with physical inactivity, insulin resistance, and genetic predisposition are the leading causes of the *Metabolic Syndrome* that puts people at higher risk of cardiovascular diseases (coronary heart disease, heart failure, or stroke), type-2 diabetes mellitus (T2DM), and diseases related to fat accumulation in organs such as non-alcoholic fat liver disease/non-alcoholic steatohepatitis (NAFLD/NASH). Various innovative treatment strategies based on incretin mimetics such as glucagon like agonists on the peptide 1 receptor (GLP1R) or agonists on the glucose dependent insulinotropic peptide receptor (GIPR) are now in development as therapeutic options to treat obesity and related diseases.

The **Charité Research Organisation GmbH** has longstanding experience in the conduction of early phase projects for new medicines to improve metabolic diseases. We want to share our expertise in this special Whitepaper that comes in three parts.

In **Part 1**, new treatment approaches for *obesity with or without T2DM* will be presented and discussed based on current research and applicable guidelines. The management of T2DM patients has much improved since the introduction of GLP1R agonists and sodium-glucose cotransporter 2 inhibitors (SGLT2i). Their use as treatment intensification for T2DM patients with cardiovascular and/or renal disease and/or corresponding risk factor obesity will be described according to national guidelines.

In **Part 2**, the key drivers in the pathophysiology of NAFLD/NASH and the recommended diagnostic tools to be used in clinical trials will be discussed. The recently approved THR-ß agonist Resmetirom and other pharmacological approaches for the treatment of *NAFLD/NASH with or without obesity* will be presented. Most of these are targeting metabolic dysregulation and intrahepatic lipotoxicity or inflammation. Other strategies include modification of genetic risk factors or activation of inflammatory immune cells.

In **Part 3**, the diverse phenotypes of heart failure (HF) will be discussed with a special focus on the *cardiometabolic phenotype HF with preserved ejection fraction (HFpEF)*, in which chronic cardiometabolic stress resulting from T2DM and/or obesity are key drivers of HF pathophysiology. The new treatment options for the cardiometabolic HFpEF population will be described based on the recent focused update of the ESC Guideline in 2023.

Introduction

Human being is seemingly genius to circumvent its natural limits. Magnificent monuments like the Pyramids of Giza in Egypt or the Colosseum in Rome bear witness to his genius.

Since then the big *Industrial Revolutions*, *Scientific-Technical Revolution* and now the *Digital Evolution* have made even the unbelievable possible. Reaching out to the moon and the stars - Whatever it takes! Any challenge is welcome, no hurdle too high. If not in real - the virtual is fine. Quantum computing, virtual and augmented reality, nanotechnology, driverless technology, artificial intelligence, incredible fast internet, workplace automation, robotics, reusable rockets will soon be part of our everyday lives. Everything around us is already moving faster than we ever could. Every tool we use gets smaller, but we get fatter and fatter just moving our brains but almost no muscle.

What are the numbers we are talking about?

According to the World Health Organisation (WHO), obesity has nearly tripled since 1975. In 2016, more than 1.9 billion adults, 18 years and older, were overweight. Of these, over 650 million were obese. Most of the world's population lives in countries where overweight and obesity kills more people than underweight [WHO 2024]. In view of these alarming figures, health programmes have been initiated worldwide to promote healthy lifestyles and prevent the development of obesity in all age groups. Education on healthy eating and avoiding a sedentary lifestyle is a top priority. For example, it is important to avoid soft drinks with high-fructose corn syrup as a sweetener as those increase the consumption of dietary fructose and contribute to the manifestation of overweight and/or obesity. In addition, the consumption of high-fat red meat should be reduced.

But how is overweight/obesity actually defined and what health risks can be derived from it?

Overweight and obesity mean abnormal or excessive fat accumulation in the body that may impair health. The Body Mass Index (BMI) is a simple index of weight-for-height that is commonly used to classify overweight and obesity in adults. It is defined as a person's weight in kilograms divided by the square of his height in meters (kg/m^2). For adults, overweight is a BMI ≥ 25; and obesity is a BMI ≥ 30 (**Figure 1**).

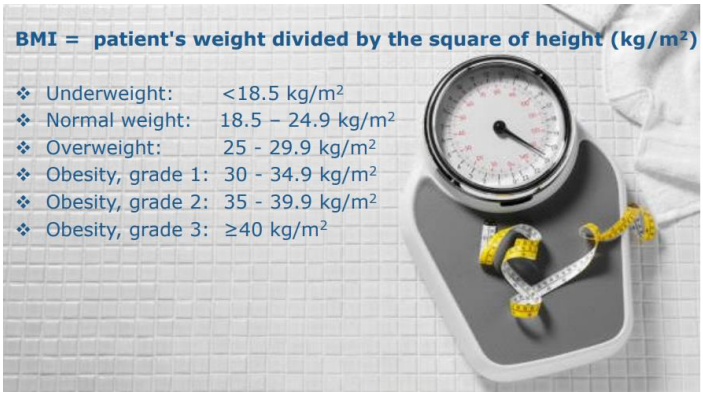

Figure 1: BMI Categories [WHO 2000]

Obesity together with physical inactivity, insulin resistance, and genetic predisposition are the leading causes of the *Metabolic Syndrome* [Hanefeld & Leonhardt 1981] [**Figure 2**]. Metabolic syndrome including obesity puts people at higher risk of cardiovascular diseases (coronary heart disease and heart failure, or stroke), type-2 diabetes mellitus (T2DM), and diseases related to fat accumulation in organs such as non-alcoholic fat liver disease (NAFLD). In addition, obesity may provoke musculoskeletal disorders (especially osteoarthritis) and some cancers (including endometrial, breast, ovarian, prostate, liver, gallbladder, kidney, and colon). It is estimated that 4–9% of all cancer diagnoses are attributable to obesity, and that obesity correlates with poorer prognosis for multiple malignant diseases (reviewed in Müller et al. 2022]. Obesity can consequently lead to serious diseases. Thus, it is of utmost importance to implement prevention programs stimulating life-style changes in the population and to develop drugs to treat obesity and related diseases.

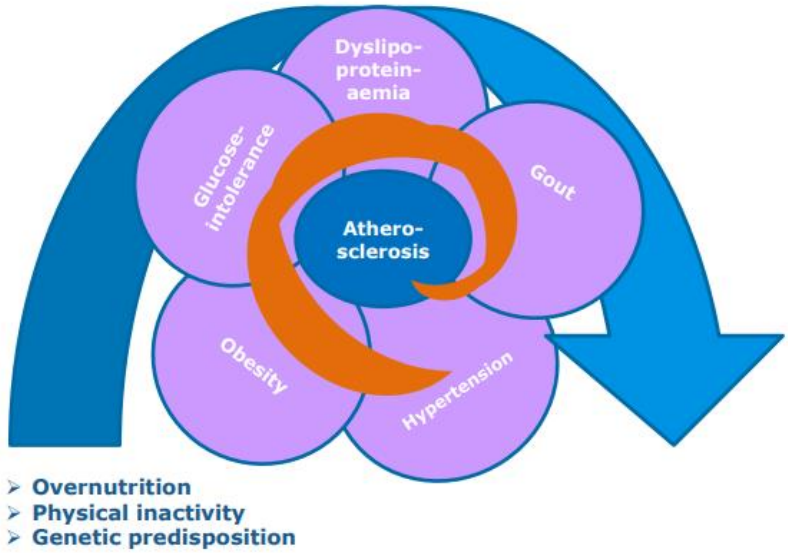

Figure 2: Metabolic Syndrome
Source: Adopted from Hanefeld & Leonhardt 1981

Various innovative treatment strategies based on incretin mimetics such as glucagon like agonists on the peptide 1 receptor (GLP1R) or agonists on the glucose dependent insulinotropic peptide receptor (GIPR) are now in development as therapeutic options to treat obesity and related diseases. The GLP1R agonists Liraglutide and Semaglutide have been already approved for weight reduction and/or improved control of hyperglycemia in T2DM patients. Dual incretin mimetics are in development and some of them such as Tirzepatide (GIPR/GLP1R agonist), which has been approved by the FDA in 2023, will probably soon be approved in Europe. And, triple incretin agonists are already on the horizon such as Retatrutide (GIPR/GLP1R + glucagon receptor (GCR) agonist).

In the following, we will give an overview of the current management of *Obesity (Body Weight Reduction)* based on current practice and applicable guidelines.

Obesity

In July 2020, obesity was recognized as an independent chronic disease with a high tendency to re-occur. This change in status is inextricably linked to the right to treatment [National Diabetes Strategy-2020] and serves also to destigmatize the common belief that obese people have insufficient self-discipline. The basic therapy for obesity consists of reduced-calorie diet, exercise and behavioral therapy. The treating physician should skillfully motivate a comprehensive change in lifestyle risk factors including self-management education, nutritional counselling (5:2 diet, Mediterranean diet), increasing physical activity, and psychosocial counselling (if indicated). As smoking is associated with an increased risk of diabetes, possibly through increased insulin resistance [Maddatu et al., 2017], smokers should give up tobacco consumption. The goal is to achieve a decrease of at least 5 % of the body weight for BMI 25-35 kg/m^2 and of more than 10 % of the body weight for BMI >35 kg/m^2 [German Interdisciplinary S3 Guideline, 2014]. As lifestyle changes are often not sufficient to achieve a significant and long-lasting weight loss, adding pharmacological and/or surgical interventions is often indicated. Bariatric surgery represents the most effective approach to weight loss, leading to decreased mortality from cardiovascular diseases or cancer by 30% and 23%, respectively [Carlsson et al. 2020].

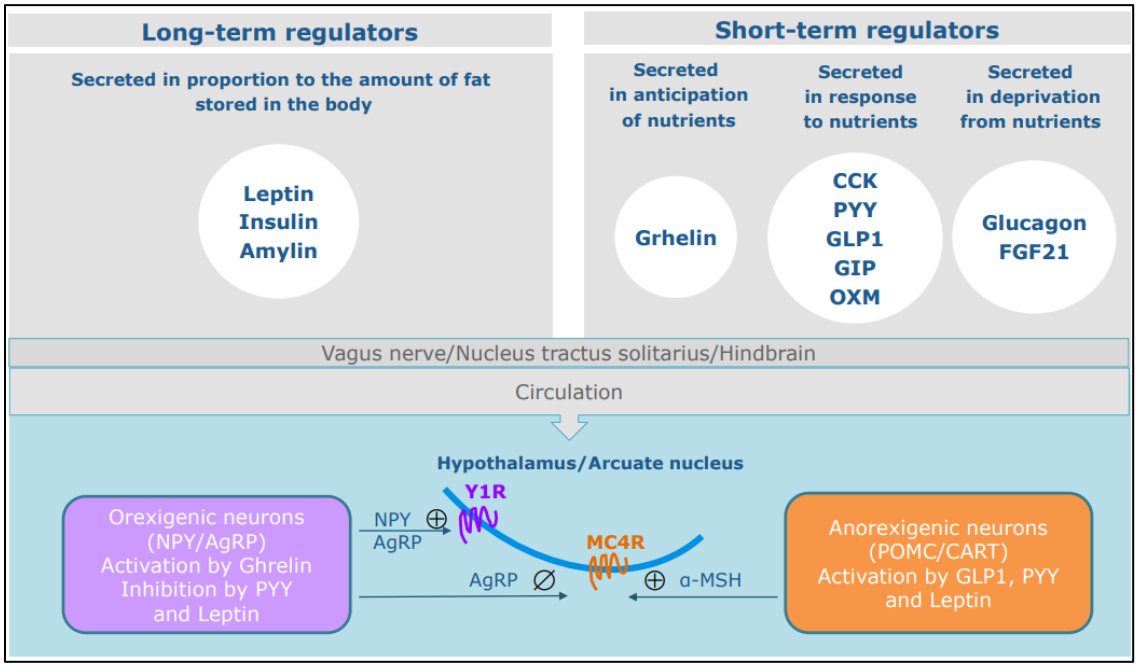

Figure 3: Regulators of food intake signaling to the brain
Figure based on review by Müller et al., 2022

In contrast, until recently it was a seemingly impossible task to achieve weight loss with sufficient tolerability and safety through long-term pharmacotherapy. Many drugs that were initially authorised had to be withdrawn due to cardiovascular adverse effects (Amfepramon), increased suicide risk (Rimonabant) or an increased likelihood of dependence and abuse (methamphetamine). In Germany, the lipase inhibitor Orlistat (generic) is still used to reduce triglyceride absorption; however, therapy is often

discontinued due to gastrointestinal side effects (fatty stools, flatulence) and impaired absorption of hormone preparations. In 2021, EMA approved the melanocortin-4 receptor analogue Setmelanotide as therapy for genetic obesity (confirmed biallelic proopiomelanocortin (POMC) or leptin receptor (LEPR) deficiency). Over the last two decades, our knowledge about the regulation of food intake has expanded enormously. We learned that various food intake-regulating hormones are involved in the central control of homeostatic and hedonistic eating behaviour [Müller et al., 2022] (**Figure 3**).

The gut-brain communication is driven by complex molecular communication between peripheral organs (gut, liver, and pancreas) and brain to avoid extreme situations such as starvation or overfeeding. The positive effects of the glucagon like peptide 1 (GLP1) on postprandial metabolism (improved glucose-dependent insulin secretion and insulin sensitivity of liver cells) led to the development of GLP1R agonists that are now integrate part of modern antidiabetic therapy. Weight loss however leads to a reactive influence on this complex gut-brain control system. Appetite and its hormonal mediators increase permanently. This is the biological reason for recurrent weight gain after dieting (*yo-yo effect*). If treatment is discontinued or reduced, a relapse inevitably occurs and long-term therapy seems unavoidable. The discovery that GLP1 receptor agonism in the arcuate nucleus (hypothalamus) causes an increased release of α-melanocyte stimulating hormone/activation of the melanocortin 4 receptor (MC4R) and a greater feeling of satiety, leading to weight loss has stimulated the development of new anti-obesity drugs such as Semaglutide (Wegovy®, NovoNordisk) that achieves clinical relevant and sustained weight loss without severe side effects [Müller et al., 2022; Rubino et al., 2021]. Similarly, the glucose dependent insulinotropic peptide (GIP) functions by improving insulin sensitivity in peripheral organs as well as in white adipose tissue and skeletal muscle [Samms et al., 2020]. The functional GIP-receptor (GIPR) is also expressed in human brain regions regulating food intake (such as hypothalamic nuclei and brainstem). As central or peripheral administration of GIPR agonists lowered weight by reducing caloric intake in animals, it is supposed that GIPR positive cells in the brain may enhance GLP1R signaling to anorexigenic neurons [Adriaenssens et al., 2019]. For these reasons, dual GLP1R/GIPR agonists have been developed such as Tirzepatide, which has been approved as Mounjaro™ by the FDA in 2023 (and which will probably approved by EMA in 2024).

Finally, triple incretin mimetics are already on the horizon such as Retatrutide (GIPR/GLP1R and glucagon receptor (GCR) agonist). GCR agonism is known to delay gastric emptying, and reduces body weight by increasing energy expenditure with additional positive effects on lipid metabolism (reduced serum triglycerides and cholesterol). Retatrutide has already shown positive phase 2 results in overweight or obese people which will be discussed in more detail in the next chapter.

Drug Pipeline: Obesity

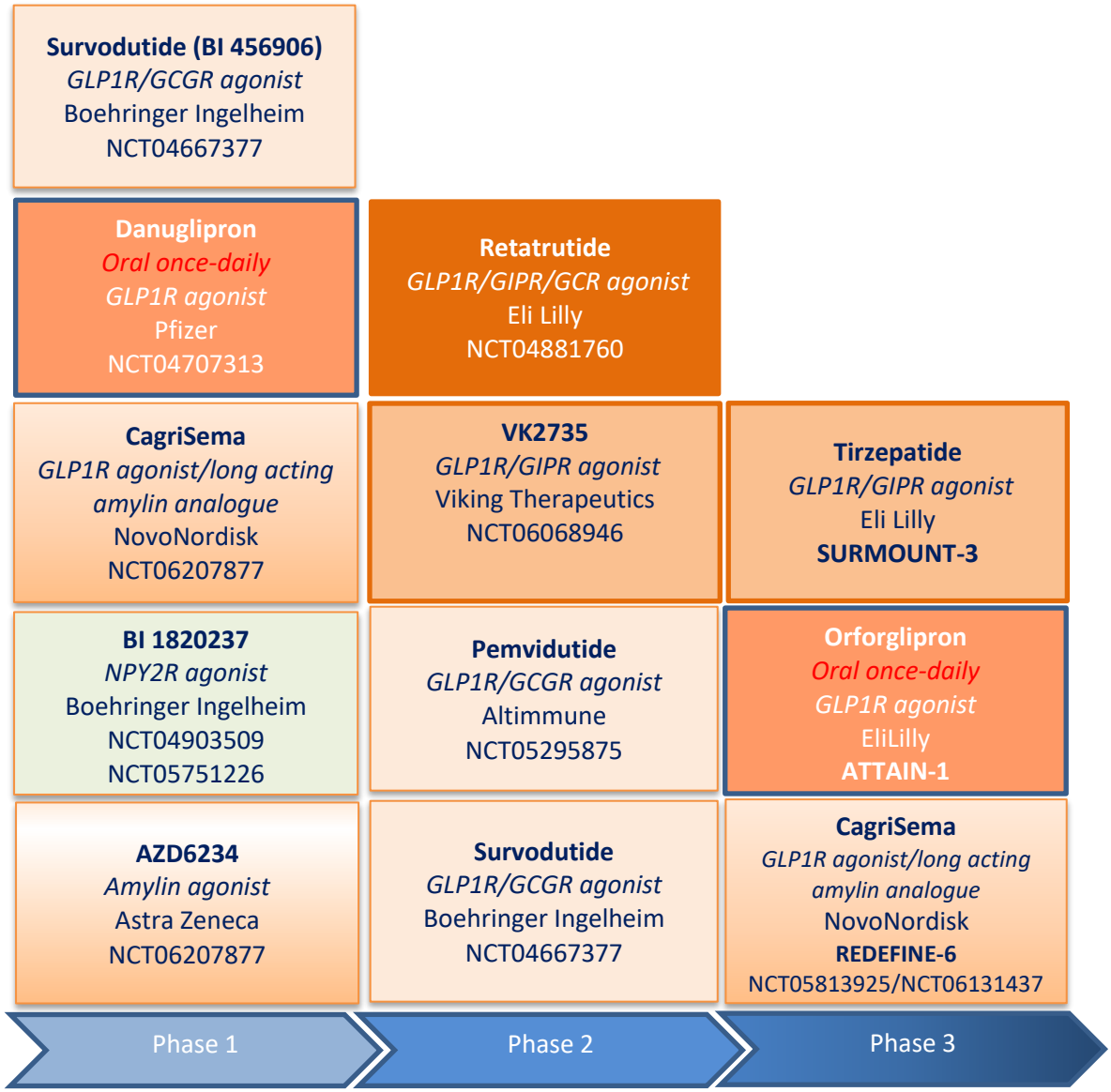

Figure 4. Current Drug Pipeline for Obesity

Abbreviations: GCR = glucagon receptor, GLP1R = glucagon like peptide 1 receptor, GIPR = glucose dependent insulinotropic peptide receptor; NPY2R = neuropeptide Y2 receptor

Note: Besides Danuglipron and Orforglipron, all drug candidates are to be administered by subcutaneous injections.

In the following, the **new drug candidates** for *Obesity (Body Weight Reduction)* that have entered the drug pipeline in 2023/2024, are presented and discussed according to their development phase. The following drug candidates were still in active development programs for *Obesity (Body Weight Reduction)* at time point of manuscript finalisation.

Phase 1

CagriSema (NovoNordisk) is a combination of Semaglutide (GLP1R agonist) and Cagrilintide (long acting amylin analogue). Amylin is an endogenous neuroendocrine peptide hormone that is co-secreted with insulin by pancreatic beta-cells in response to food intake. It is delaying gastric emptying and suppresses the post-prandial glucagon release. The peptide hormone is also involved in the central regulation of food intake and body weight in animals and humans. Amylin-binding sites have been identified in areas known to be involved in regulation of energy homeostasis and food intake [Lutz et al., 2013]. Therefore, Cagrilintide is expected to potentiate Semaglutide's weight loss effects. A reduced neural reactivity to food images in brain networks of reward and cognitive control, and elevated reactivity in regions of attentional control and visual processing were recently detected in obese people [Poghosyan et al., 2023] (**Figure 5**).

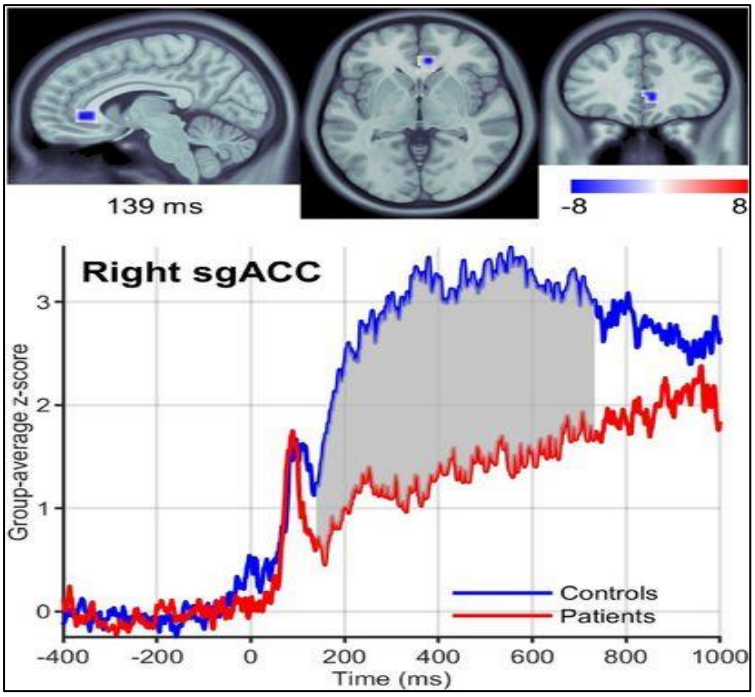

Figure 5. Right subgenual ACC response to high-calorie food images

(Upper row) Brain region showing the earliest significantly ($P < 0.05$) reduced response in the reward system in obese versus normal-weight individuals at 139 ms post-stimulus. (Lower row) Group-averaged activation time courses of the right subgenual ACC ROI. Gray shaded area indicates time period with significant difference between obese and normal-weight individuals. Abbreviations: ACC = Arcuate nucleus; ROI = Regions of Interest

Source: Poghosyan et al., 2023

A phase 1 trial NN9838-4944 (NCT06207877) will study the pharmacodynamic actions of CagriSema in specific brain areas and how CagriSema influences food intake, appetite and emptying of the stomach in people with excess body weight. Blood-oxygen-level-dependant (BOLD) functional magnetic resonance imaging (fMRI) during passive viewing of high-calorie foods, low-calorie foods, and non-food objects will be used for profiling of neural activity to food images in people with overweight or obesity. Longitudinal MRI assessments will be used to determine whether changes in activation of brain regions involved in reward processing mediate the effect of CagriSema on self-reported appetite. Study completion is expected in January 2025.

AZD6234 (Astra Zeneca) is an amylin agonist currently being studied in a phase 1 trial (NCT06207877) to assess the safety, tolerability, pharmacokinetics, and pharmacodynamics of subcutaneous AZD6234 after repeated dose administration in participants with overweight or obesity. Study completion is expected in October 2024.

BI 1820237 (Boehringer Ingelheim) is a peptidic neuropeptide Y2 receptor (NPY2R) agonist in clinical development for chronic weight management as an adjunct to a reduced-calorie diet and increased physical activity in overweight or obese people with one or more weight-related comorbidities. This NPY2R agonist has already demonstrated a good safety and tolerability profile in overweight men when given alone or in combination with Liraglutide (NCT04903509). The tolerability of different subcutaneous BI 1820237 doses is currently tested in a further phase 1 study (NCT05751226) in people with overweight or obesity when given alone or in combination with Semaglutide.

Survodutide (BI 456906) (Boehringer Ingelheim) is a dual GLP1R/GCGR agonist which is being developed for obesity (with or without T2DM) and NASH. A phase 1 study (NCT05896384) is now investigating a possible drug-drug interaction between Survodutide and oral contraceptives in overweight/obese women since this combination may be widely used in a clinical setting. A potential drug-drug interaction might result from BI 456906 induced delayed gastric emptying with impact on the absorption of oral contraceptives. Study completion is expected in October 2024.

Phase 2

Danuglipron (PF-06882961, Pfizer) is an oral GLP1R agonist in development for the treatment of obesity and T2DM with or without obesity. A phase 2b trial (NCT04707313) in adults with obesity without T2DM who received twice-daily dosing of Danuglipron showed statistically significant reductions from baseline in body weight for all doses. Placebo-adjusted reductions in mean body weight ranged from -8% to -13% at 32 weeks and -5% to -9.5% at 26 weeks. Depending on titration schedule, participants were at target dose levels for 6 to 24 weeks. To achieve a higher treatment compliance, Danuglipron will now be developed as once-daily oral treatment regimen.

Pemvidutide (ALT-801, Altimmune) is a dual GLP1R/GCGR agonist in development for the treatment of obesity and NASH. Pemvidutide has shown positive results in a phase 2 trial (MOMENTUM, NCT05295875): At Week 48, subjects receiving once-weekly subcutaneous Pemvidutide achieved mean weight losses of 15.6% at the (highest) 2.4 mg dose compared to 2.2% placebo. Over 50% of subjects achieved at least 15% weight loss and over 30% of subjects achieved at least 20% weight loss on the 2.4 mg dose. Pemvidutide resulted in robust reductions in serum lipids and improvements in blood pressure without imbalances in cardiac events. Glucose homeostasis was maintained, with no significant changes in fasting glucose or HbA1c [HTTPS://PIPELINEREVIEW.COM/ALTIMMUNE-ANNOUNCES-POSITIVE-TOPLINE-RESULTS-FROM-MOMENTUM-48-WEEK-PHASE-2-OBESITY-TRIAL-OF-PEMVIDUTIDE/].

Survodutide (BI 456906) (Boehringer Ingelheim) is a dual GLP1R/GCGR agonist which is being developed for obesity (with or without T2DM) and NASH. In a phase 2 dose-range study (NCT04667377), Survodutide treatment over 46 weeks was tested in people with overweight or obesity without T2DM. Body weight was significantly reduced at Week 46 for all BI 456906 treatment groups compared with placebo. The largest reduction in body weight from baseline was observed in the highest dose group of 4.8 mg Survodutide (-14.94 %), and the smallest weight reduction in the placebo group (-2.82%).

Retatrutide (EliLilly) is a triple GIPR/GLP1R/GCR agonist that has already shown positive phase 2 results in adults with obesity (NCT04881760). A total of 338 adults (51.8% of whom were men) were enrolled in this double-blind, randomized, placebo-controlled trial involving adults with a BMI of 30 and higher or with a BMI between 27 and 30 plus at least one weight-related condition. Participants were randomly assigned in a 2:1:1:1:1:2:2 ratio to receive subcutaneous Retatrutide (1mg, 4 mg [initial dose, 2 mg], 4 mg [initial dose, 4 mg], 8 mg [initial dose, 2 mg], 8 mg [initial dose, 4 mg], or 12 mg [initial dose, 2 mg]) or placebo once weekly for 48 weeks. At 48 weeks, the least-squares mean percentage change in body weight was -24.2% in the 12-mg Retatrutide group, as compared with -2.1% in the placebo group (**Figure 6A**). At 48 weeks, a weight reduction of 5% or more, 10% or more, and 15% or more had occurred in 100%, 93%, and 83% of those who received 12 mg; and 27%, 9%, and 2% of those who received placebo (**Figure 6B**).

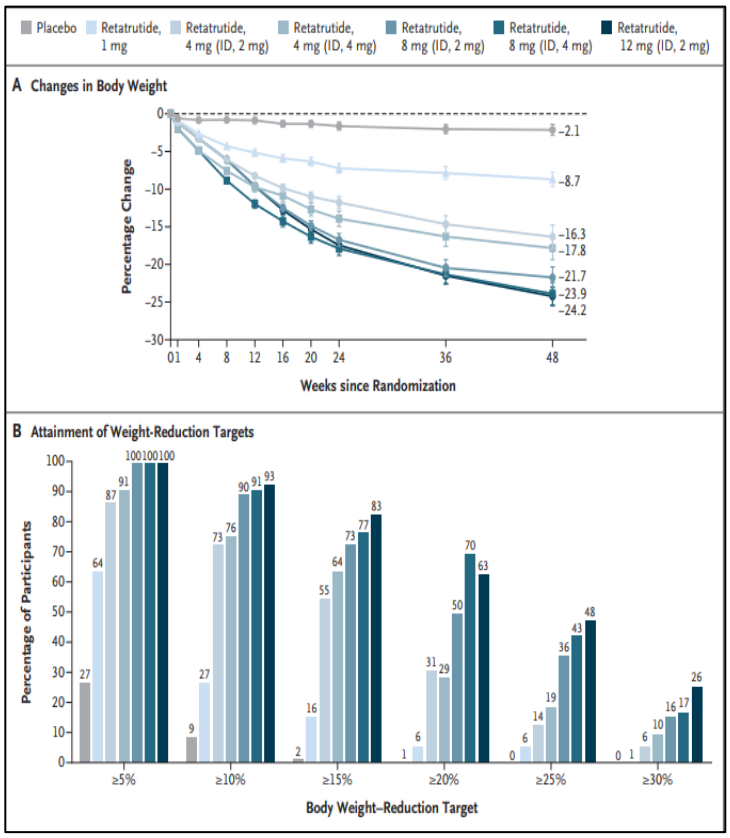

Figure 6. Changes in Body Weight with Retatrutide as Compared with Placebo.
Source: Jastreboff et al., 2023

The most common adverse events in the Retatrutide groups were gastrointestinal; these events 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].

VK2735 (Viking Therapeutics) is a dual GIPR/GLP1R agonist. It was tested in a phase 2 study (NCT06068946) in patients with obesity. According to Viking Therapeutics (press release on 27-February-2024), patients receiving weekly doses of VK2735 had clinical relevant reductions in mean body weight after 13 weeks of treatment, ranging up to 14.7 % from baseline in the highest dose group. Up to 88% of patients in VK2735 treatment groups achieved at least 10 % weight loss, compared with 4 % for placebo. Treatment with VK2735 was safe and well tolerated. Most TEAEs were observed in the gastrointestinal system; which were mild or moderate in intensity.

Phase 3

Tirzepatide (EliLilly) is a dual GIPR/GLP1R agonist that was tested in 579 adults with BMI ≥30 or ≥27 kg/m2 and at least one obesity-related complication (excluding diabetes), who achieved ≥5.0% weight reduction after a 12-week intensive lifestyle intervention, randomized (1:1) to Tirzepatide maximum tolerated dose (10 or 15 mg) or placebo once weekly for 72 weeks (SURMOUNT-3 trial, NCT04657016). Tirzepatide showed a strong and sustained weight loss (additional weight loss of 21.1% at week 72, which contributed to an average total weight loss of 26.6% from baseline after 84 weeks [Wadden et al., 2023] (**Figure 7**). The most common adverse events with Tirzepatide were gastrointestinal, with most being mild to moderate in severity. Based on these phase 3 data, Tirzepatide (Mounjaro™, EliLilly) has been approved by the US- FDA as anti-obesity drug in 2023, and EMA approval is expected in 2024.

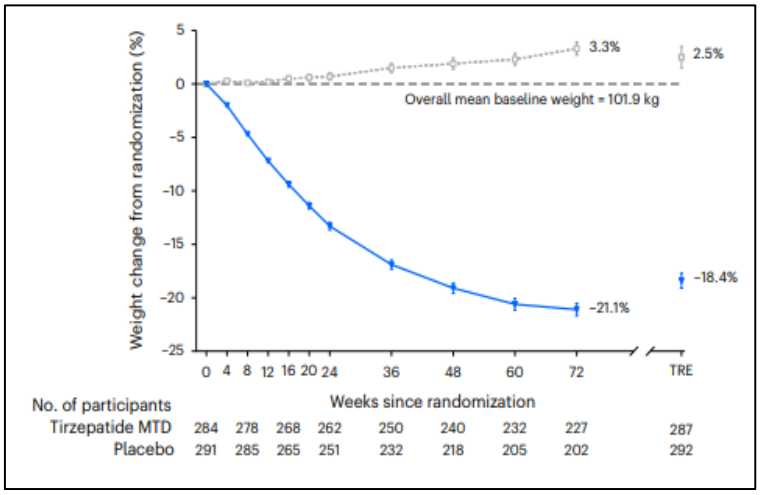

Figure 7. Changes in Body Weight with Tirzepatide as Compared with Placebo.
LSM (s.e.) per cent change in body weight over time from randomization to 72 weeks, derived from MMRM analysis for the efficacy estimand; week 72 estimates for the TRE are also shown.
Source: Wadden et al., 2023

CagriSema (NovoNordisk): Phase 1 and phase 2 clinical study results indicate that Cagrilintide in combination with Semaglutide subcutaneously has the potential to offer significantly greater weight loss and glycemic control in patients with T2DM than either monotherapy. In addition, CagriSema demonstrated a positive benefit-risk profile in people with obesity or overweight with comorbidities. Therefore, CagriSema is now entered in two phase 3 trials in Asia which investigate how well CagriSema helps people with excess body weight to lose weight (NCT05996848, NCT05813925). A phase 3 *head to head* study [NCT06131437] is currently being conducted in the USA to compare the efficacy of CagriSema (fixed dose combination of Semaglutide 2.4 mg and Cagrilintide 2.4 mg) with the maximum dose of Tirzepatide (15 mg) in patients with obesity. Study completion is expected in October 2025.

Orforglipron (LY3502970, Eli Lilly) is a novel once-daily oral non-peptide GLP1R agonist that achieved up to 14.7% mean weight reduction after 36 treatment weeks in adults with obesity or overweight in phase 2 [Wharton et al., 2023]. Weight reduction continued through week 36, with the placebo-corrected percentage change from baseline in body weight ranging from 7.1% to 12.3% [Dutta et al., 2024]. Daily oral Orforglipron related effects and safety profile appeared to be similar to the outcomes observed with injectable GLP1R agonists that have already been approved for weight management. A phase 3 trial (NCT05869903, ATTAIN-1) is ongoing to investigate the efficacy and safety of once daily oral Orforglipron in adult participants with obesity or overweight with weight-related comorbidities. The primary outcome measure is the body weight loss from baseline to week 72. Secondary outcome measures include the mean changes in blood pressure, blood lipids, Hemoglobin A1c (HbA1c) %, Fasting Glucose and Fasting Insulin and the change in quality of life determined by the SF-36 questionnaire. Study completion is expected in September 2027.

Obesity with Type 2 Diabetes Mellitus

Type 2 diabetes mellitus (T2DM) is not an isolated single disease, but part of a complex metabolic syndrome that includes obesity together with physical inactivity, insulin resistance, and genetic predisposition with ultimate stress on the cardiovascular system [Hanefeld & Leonhardt 1981]. The lifetime diabetes risk in adults increases from 7% to 70% (men) or from 12% to 74% (women) when BMI increases from less than 18.5 kg/m to more than 35 kg/m [Narayan et al., 2007]. Lack of physical activity, a low-fiber/high-fat diet as well as smoking increase the risk of diabetes, possibly due to increased insulin resistance [Maddatu et al., 2017]. Over time, the resulting chronically elevated blood sugar levels can lead to severe damage to the heart, blood vessels, eyes, kidneys and nerves. Therefore, screening for diabetes is indicated in all patients with obesity.

The first step of treatment begins with aggressive modification of lifestyle risk factors such as self-management education, nutritional counseling, increasing physical activity, psychosocial care (if required), and smoking cessation for smokers [Powers et al., 2020]. Timely, pure weight control/reduction - preferably as prophylaxis - through a balanced diet and physical activity already significantly loosens the circuit with overstimulation of metabolic processes. If you cannot resist the tasty temptations or cannot achieve the necessary level of calorific reduction through physical work or sport, then you often have to grab to medication.

In the last decade, new drugs such as the sodium glucose cotransporter 2 (SGLT2) inhibitors and GLP-1 receptor agonists have been approved due to their effectiveness to improve glycemic (HbA1c) profiles in T2DM patients. Meanwhile, it has been demonstrated that both drug classes also contribute to the reduction of calorific depots and weight loss. Their positive pleiotropic effects in diabetes patients may improve the prognosis of related cardiovascular diseases. Therefore, treatment intensification with GLP1R agonists or SGLT2 inhibitors in addition to metformin is of utmost importance for T2DM patients with cardiovascular and/or renal disease or should be considered if there are corresponding risk factors such as obesity.

More recently, hybrid ligands possessing agonist activity at both, glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 receptors, are being investigated for the treatment of T2DM. Activating both the GIP and GLP-1 receptors is attractive because the combination of these mechanisms is hypothesized to enhance glucose-dependent insulin secretion, decrease energy consumption, and both directly and indirectly improve white adipose tissue health and function and subsequently whole-body insulin sensitivity [Samms et al., 2020] (**Figure 8**).

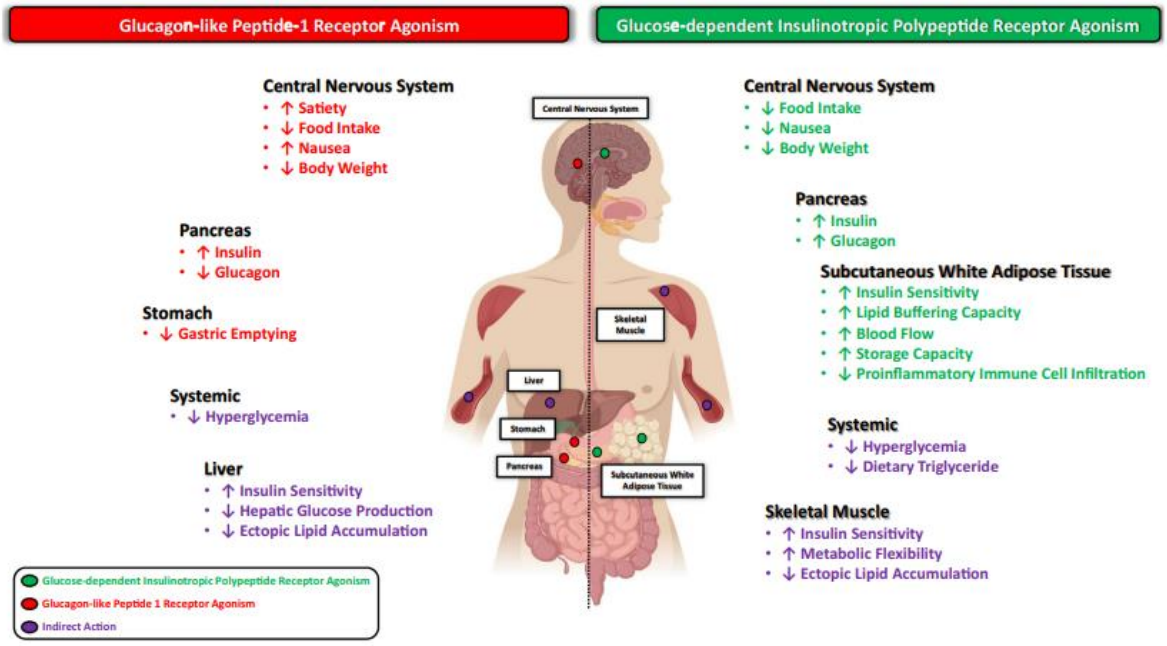

Figure 8: Schematic Depiction of the Pleiotropic Benefits of Dual Glucose-Dependent Insulinotropic Polypeptide (GIP)/Glucagon-Like Peptide-1(GLP-1) Receptor Agonist Therapy in T2DM.
Source: Samms et al., 2020

The current standard of care for the treatment of T2DM in Germany includes:
[National Health Care Guideline T2DM, 2023]

- Early diagnosis and treatment to avoid secondary diseases
- Choice of therapy and definition of therapy goals depending on the individual risk profile
- In patients with cardiovascular and/or renal diseases, therapy intensification with SGLT2 inhibitors or GLP1-RA in addition to metformin is mandatory according to guidelines and should be considered if there are corresponding risk factors (e.g. overweight/obesity).
- When starting injection therapy, therapy with GLP1-RA has "priority" over insulin therapy - this has not yet been sufficiently implemented in treatment reality.
- The indication for insulin therapy is given if the therapy goals are not achieved after the basic measures and oral antidiabetic agents including GLP-1-RA have been exhausted.
- Long-acting basal insulins are well suited for starting insulin therapy, as they cover the insulin requirement well due to their flat and stable action profile and longer duration of action and are also easy for patients to use

Comparison of treatment strategies based on GLP1R agonism:

A recent network meta-analysis compared the glucometabolic outcomes of innovative treatments based on GLP1R agonism (GLP1RA), among others Tirzepatide, GLP1RA plus basal insulin FRC, GLP1RA plus SGLT-2i combination and high-dose GLP1RA have been evaluated in 40 randomised controlled trials in 26 490 people with T2DM [Caruso et al., 2023]. Tirzepatide (10 mg or 15 mg - maximal tolerated dose) showed a better effect in terms of weight reduction (**Figure 9**) and lowering HbA1c levels compared to all other treatment strategies analysed.

In the subgroup analysis, on the other hand, a greater benefit was observed from treatment with fixed combinations of GLP1 analogues plus basal insulin in patients with a disease duration of more than ten years. This could possibly indicate the need for insulin replacement therapy in patients with a longer duration of disease. The authors concluded that *head to-head* trials are on demand to compare the safety and efficacy of new GLP1RA-based treatment options with or without combination of other glucose and/or weight lowering drugs in T2DM patients with short and longer disease duration. The results thereof will support a more tailored treatment to patients' needs.

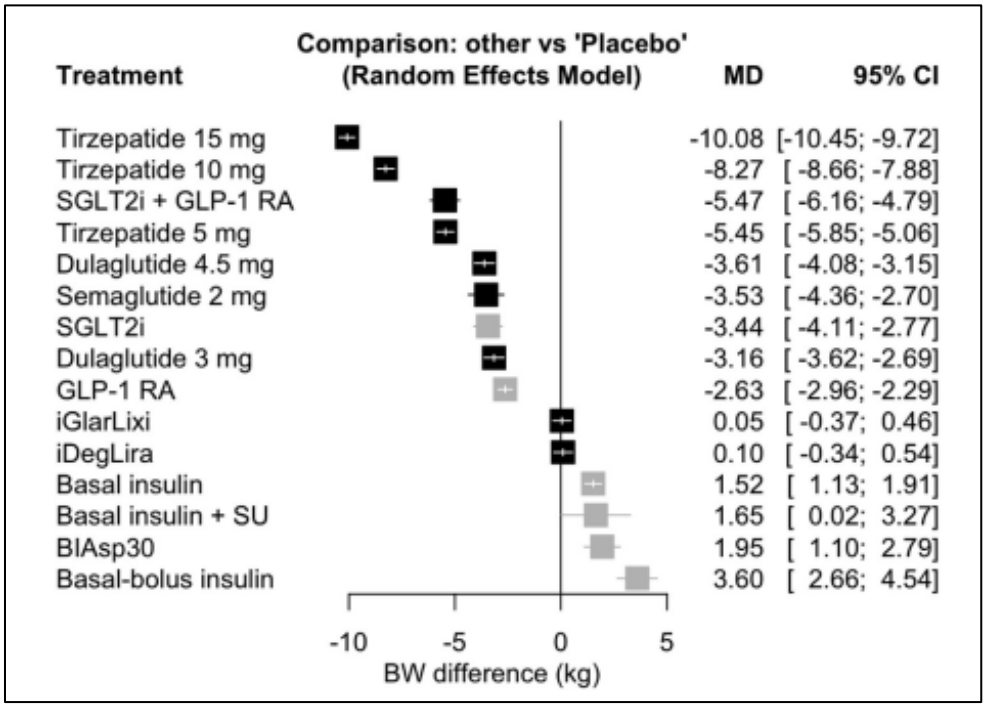

Figure 9: Network meta-analysis results for change from baseline in bodyweight compared with placebo
Treatments are presented according to their effect estimate compared with placebo. Effect sizes are presented as mean difference (MD) and 95% confidence intervals (CI). New GLP-1RA-based treatments are highlighted in black, other treatments in grey. Abbreviations: BIAsp30, biphasic insulin aspart 30/70; GLP-1 RA, glucagon like peptide-1 receptor agonists; SGLT-2i, sodium glucose cotransporter-2 inhibitors; SU, sulfonylurea
Source: Caruso et al., 2023

Drug Pipeline: Obesity with Diabetes Mellitus

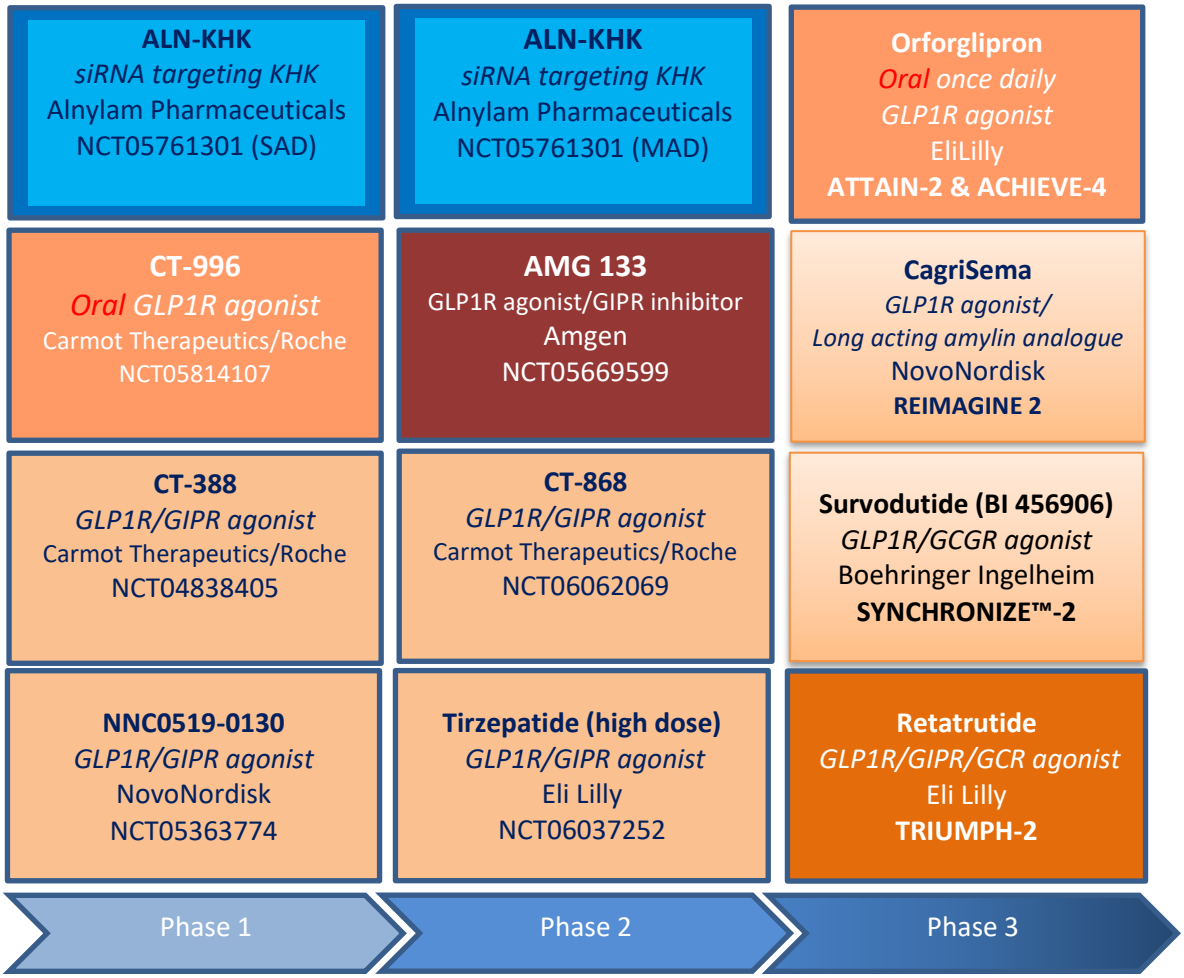

Figure 10. Current Drug Pipeline T2DM with Obesity
Abbreviations: GCR = glucagon receptor; GLP1R = glucagon like peptide 1 receptor; GIPR = glucose dependent insulinotropic peptide receptor; KHK = ketohexokinase
Note: Besides CT-996 and Orforglipron, all drug candidates are to be administered by subcutaneous injections

In the following, **new drug candidates** for *obesity with or without T2DM* that have entered the drug pipeline in 2023/2024, will be presented and discussed according to their development phase. The following drug candidates were still in active development programs for *obesity with or without T2DM* at time point of manuscript finalisation.

Phase 1

ALN-KHK (Alnylam Pharmaceuticals) is a small interference RNA (siRNA) therapeutic targeting ketohexokinase (KHK), the first enzyme in the pathway of fructose metabolism. Silencing the messenger RNA of KHK is expected to reduce fatty acid synthesis and to improve glycemic control in patients with T2DM. The use of high-fructose corn syrup as a sweetener of modern soft drinks increased consumption of dietary fructose and possibly contributes to the growing pandemic of obesity. Obesity is a significant risk factor for both T2DM and fatty liver disease. ALN-KHK will be tested in Part B of a Phase 1/2 trial (NCT05761301) investigating the safety, tolerability, efficacy, pharmacokinetics, and pharmacodynamics of multiple subcutaneous doses of ALN-KHK in obese patients with T2DM. Study completion is expected in July 2025.

CT-388 (Carmot Therapeutics/Roche) is a dual GLP1/GIP receptor agonist that is currently tested in a phase 1 study (NCT04838405) with otherwise healthy overweight and obese adult participants and in obese patients with T2DM. It is injected subcutaneously once a week. Study completion was expected for October 2023.

CT-996 (Carmot Therapeutics/Roche) is a novel *oral* GLP-1 receptor agonist for the treatment of obesity in patients with and without T2DM. The *first-time-in-human* trial (NCT05814107) is currently assessing the safety and tolerability, PK and PD of CT-996 when administered as single and multiple-ascending doses in overweight/obese participants and as multiple doses in patients with T2DM. CT-996 (capsule) is taken orally once daily. Study completion is expected in November 2024.

NNC0519-0130 (NovoNordisk) is a dual GLP1R/GIPR agonist in development for T2DM and weight management. A *first time in human* trial (NCT05363774) is currently investigating the safety, tolerability, pharmacokinetics and pharmacodynamics of single subcutaneous doses of NNC0519-0130 in healthy participants and multiple subcutaneous and oral doses of NNC0519-0130 in participants with overweight or obesity and participants with T2DM. Study completion is expected in March 2024. A further phase 1 study is investigating the effect of impaired renal function on the pharmacokinetics of subcutaneously administered NNC0519-0130 in participants with various degrees of renal function. (EU CT number: 2023-506381-32).

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Phase 2

AMG 133 (Amgen) is a is a bispecific GLP1R agonist and GIPR inhibitor molecule that was designed based on preclinical and human genetic data that strongly suggest GIPR inhibition as a strategy for weight loss, especially in combination with GLP-1 agonism. Phase 1 results with once-monthly dosing of subcutaneous AMG 133 were encouraging: The MAD cohorts showed mean percent changes in body weight, ranging from -7.2% at the lowest dose (140mg Q4W), to -14.5% at the highest dose (420mg Q4W) by day 85. A substantial degree of weight loss was maintained beyond the treatment period. Most treatment emergent adverse events (TEAEs) were mild and transient. The majority of the TEAEs were GI-related with the most common being nausea and vomiting, most events resolved within 48 hours. Based on these data, a Phase 2 trial (NCT05669599) was initiated in 2023 to further study the attributes of this molecule. Study completion is expected in 2026.

CT-868 (Carmot Therapeutics/Roche) is a GLP-1/GIP receptor agonist that is being tested in a phase 2 trial (NCT06062069) for the treatment of type 1 diabetes patients who are overweight or obese. CT868 is to be administered subcutaneously once daily for 16 weeks. Study completion is expected in October 2024.

Investigational Tirzepatide Doses (Eli Lilly and Company) are high subcutaneous Tirzepatide doses, which have not been approved so far for the treatment of T2DM and/or obesity. A phase 2 trial (NCT06037252) will now assess the efficacy (reductions in weight and HbA1c) and safety of two high Investigational Tirzepatide Doses in participants with T2DM and obesity who are already taking metformin. Study completion is expected in October 2025.

Phase 3

CagriSema (NovoNordisk) is a combination of Semaglutide (GLP1R agonist) and Cagrilintide (long acting amylin analogue with a half-life of about one week). Amylin is an endogenous neuroendocrine peptide hormone that is co-secreted with insulin by pancreatic beta-cells in response to food intake. It delays gastric emptying and suppresses the post-prandial glucagon release. The peptide hormone is also involved in the central regulation of food intake and body weight in animals and humans. Amylin-binding sites have been identified in areas known to be involved in regulation of energy homeostasis and food intake [Lutz et al., 2013].

In monkeys, a combination of the amylin agonist salmon calcitonin (sCT) and the GLP1 agonist exendin-4 (Ex-4) resulted in stronger decreases in eating than either peptide alone [Bello et al., 2010] (**Figure 11A**). The combined treatment of sCT and Ex-4 attenuated the rebound effect that was observed in pair-fed monkeys on the cessation of the intervention (**Figure 11B**). These results suggest that the repeated combinational dose of Ex-4 sCT did not produce tolerance to the anorectic potency, but persistently suppressed feeding.

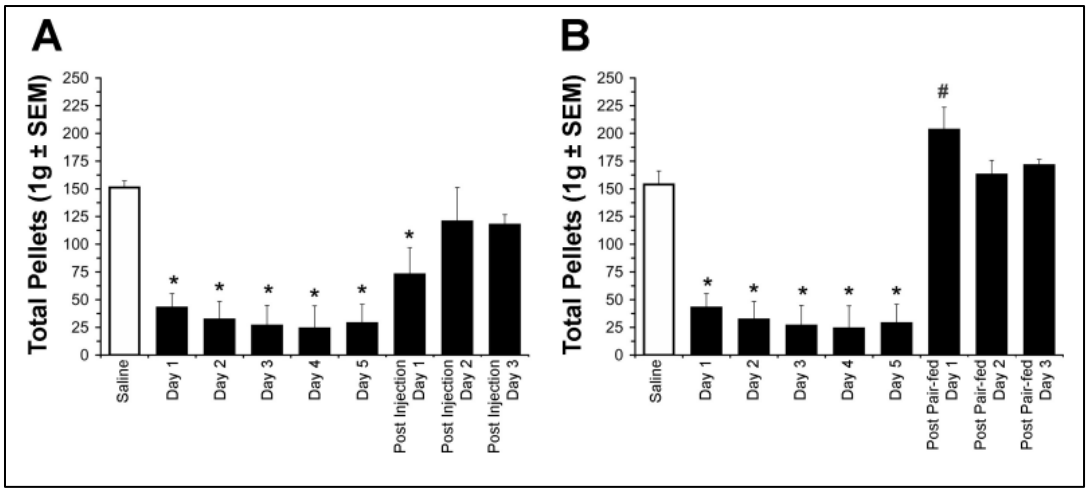

Figure 11. Effects of repeated 5-day administration of 0.56 µg/kg Ex-4 + 0.32 µg/kg sCT on food intake in rhesus monkeys consuming 1-g pellets.
A: daily intakes (means ± SE) were reduced from saline baseline on injection days 1 through 5 (*P < 0.001). Daily intakes also remained reduced from saline baseline on post-injection day 1 (*P < 0.001). B: pair-feeding for 5 days (i.e., food intakes matched to their intakes during the experimental combinational doses of Ex-4 + sCT) produced a similar reduction in food intake, but a significant rebound in daily food intake on post-pair-fed day 1 (#P < 0.05).
Source: Bello et al. 2010

The results of the Phase 1 and Phase 2 clinical trials showed a positive benefit-risk profile of subcutaneous Cagrilintide, leading to weight loss and improved glycaemic control in people who were overweight or obese with comorbidities and T2DM.

CagriSema is currently investigated in a phase 3 trial (NCT06065540; REIMAGINE 2) to see how well CagriSema compared to Semaglutide, Cagrilintide and Placebo lowers blood sugar and body weight in people with T2DM treated with Metformin with or without an SGLT2 Inhibitor. Study completion is expected in January 2026.

Orforglipron (LY3502970, Eli Lilly) is a novel *oral* non-peptide GLP1R agonist. It is being studied for the treatment of T2DM with or without obesity. A phase 3 study (NCT05872620, ATTAIN-2) is now investigating the safety and efficacy of once-daily oral Orforglipron compared with placebo on body weight in adult participants with obesity or overweight and T2DM. Study completion is expected in June 2025. A further phase 3 trial (NCT05803421, ACHIEVE-4) is ongoing to determine the safety and efficacy of once-daily oral Orforglipron compared with Insulin glargine in participants with T2DM and obesity or overweight at increased cardiovascular risk. Study completion is expected in December 2025.

Retatrutide (LY3437943) (Eli Lilly) is a triple GLP1R/GIPR/GCR agonist which is currently tested in a phase 3 trial (NCT05929079) in patients with T2DM who have obesity or overweight (TRIUMPH-2). Study completion expected in May 2026.

Survodutide (BI 456906) (Boehringer Ingelheim) is a dual GLP1R/GCGR agonist which is being developed for obesity (with or without T2DM) and NASH. Based on positive phase 2 study results in people with overweight or obesity (NCT04667377), Survodutide is currently studied for body weight reduction in patients with overweight or obesity who also have T2DM (NCT06066528; SYNCHRONIZE™-2). Study completion is expected in January 2026.

Concluding remarks

It took millions of years to optimize the human body for survival on earth. But over the last 200 years, we have developed technologies that ensure our survival and increase our prosperity, but increasingly bind us to a sedentary lifestyle. Today, most of the world's population lives in countries where overweight and obesity kills more people than underweight.

For many years we tried to treat obesity and related diseases by correcting single findings or metabolic deficiencies. Obese people were stigmatized due to the common belief that obese people have insufficient self-discipline:

- If you have overweight – „Lose weight! Eat half!“
- If you have type-2 diabetes - “Eat less but regularly! Substitute insulin!”
- If you have heart failure - „Reduce salt intake! Take medication!“

With increasing knowledge, a modern concept of obesity and its adequate treatment has been elaborated that includes the following:

- Obesity is not an isolated symptom but part of a complex *metabolic syndrome* that puts people at higher risk for cardiovascular diseases (coronary heart disease and heart failure, or stroke), T2DM, and diseases related to fat accumulation in organs such as non-alcoholic fat liver disease.
- Obesity is now recognized as an independent chronic disease with a high tendency to re-occur. This change in status is inextricably linked to the right to treatment.
- Obesity treatment consists of a comprehensive change in lifestyle risk factors including self-management education, nutritional counselling, increasing physical activity, and psychosocial counselling (if indicated). As lifestyle changes are often not sufficient to achieve a significant and long-lasting weight loss, adding pharmacological and/or surgical interventions is often indicated.
- Various innovative treatment strategies based on incretin mimetics such as glucagon like agonists on the peptide 1 receptor (GLP1R) or agonists on the glucose dependent insulinotropic peptide receptor (GIPR) are now in development as therapeutic options to treat obesity and its related diseases.
- As obesity is considered a risk factor for cardiovascular and/or renal diseases, therapy intensification with sodium-glucose cotransporter 2 inhibitors (SGLT2) inhibitors or GLP1R agonists in addition to metformin should be considered.

And, we need to learn from our ancestries that still there are things we do not know.

„…Through spirit-power and spirit-speech, -
And thus the bitter task forego –
Of saying the things I do not know,-
That I may detect the inmost force –
Which binds the world, and guides its course;…“
(Johann Wolfgang von Goethe, 1808)

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The **Charité Research Organisation GmbH** is excited to watch, participate and contribute in a new era of medical science and clinical development. Stay tuned!

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