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SEMAGLUTIDE: A GLUCAGON–LIKE PEPTIDE–1 RECEPTOR AGONIST AS ANTI-OBESITY DRUG

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ABSTRACT
The Semaglutide Treatment Effect in People With Obesity (STEP) trials have shown the efficacy of semaglutide for the treatment of obesity. In large RCTs, patients receiving semaglutide, 2.4 mg, lost a mean of 6% of their weight by week 12 and 12% of their weight by week. Semaglutide is a glucagon–like peptide–1 (GLP–1) receptor agonist. This medicine is also used together with diet and exercise to help lose weight and keep the weight off in patients with obesity caused by certain conditions. This medicine is available only with your doctor's prescription. Type 1 diabetes—Should not be used in patients with these conditions. Insulin is needed to control these conditions. Continuation of semaglutide (Rybelsus/Novo Nordisk) after 20 weeks of initial therapy leads to significant continued weight loss, according to a new study, but stopping the therapy causes patients to regain much of the weight they initially lost. Research has found that when people stop using semaglutide, weight rebound occurs. Experts say this is because the drug is not a cure and it does not prevent the metabolic adaptation that occurs during weight loss. Long–term changes in diet and activity are an important part of maintaining weight loss. But not everyone is eligible for treatment with semaglutide. Doctors can prescribe it for adults who have obesity, with a body mass index (BMI) of greater than 30; or overweight, with a BMI greater than 27 accompanied by weight–related medical problems such as high blood pressure, type 2 diabetes, or high cholesterol. Once–Weekly Semaglutide Is an Effective Adjunct for Weight Loss in Adults without Diabetes Who Are Overweight or Obese. Since the medication semaglutide was first developed for the treatment of type 2 Diabetes, many insurances still will not cover the prescription, brand name or generic, for weight loss. Semaglutide is a weight loss medication that has been shown to help increase your metabolism. This means that it will help you burn more calories and fat faster than usual. This can lead to weight loss, even if you don't change any other aspects of your diet or lifestyle. Semaglutide also decreased energy intake by 35%, reduced hunger, and increased fullness and satiety (all P < . 02) compared with placebo at 20 weeks. Once–weekly semaglutide decreases appetite, food cravings, energy intake, and body weight and increases control of eating at 20 weeks compared with placebo.

KEYWORDS: GLP-1 receptor agonist, obesity, semaglutide, weight loss, T2DM, BMI, DPP-4, HbA1c.

Overview: Semaglutide [CAS: 910463–68–2; MW: 4113.64g, $C_{187}H_{291}N_{45}O_{59}$], sold under the brand names Ozempic, Wegovy and Rybelsus, is an antidiabetic medication used for the treatment of type 2 diabetes and as anti–obesity medication for long–term weight management, developed by Novo Nordisk in 2012. Semaglutide is a glucagon–like peptide 1 (GLP–1) analog used to manage type 2 diabetes along with lifestyle changes, such as dietary restrictions and increased physical activity. Other members of this drug class include Exenatide and Liraglutide. Semaglutide was developed by Novo Nordisk and approved by the FDA for subcutaneous injection in December 2017. The tablet formulation was approved for oral administration in September 2019. Semaglutide works by binding to and activating the GLP–1 receptor, thereby stimulating insulin secretion and reducing blood glucose.[1]

The subcutaneous injection is administered once weekly and the tablet is administered once a day. Semaglutide offers a competitive advantage over other drugs used to manage diabetes, which may require several daily doses. Clinical trials have determined that this drug reduces glycosylated hemoglobin (HbA1c) levels and reduces body weight, proving to be effective for patients with type 2 diabetes. In June 2021, semaglutide was approved by the FDA for chronic weight management in adults with general obesity or overweight who have at least one

weight–related condition, marking semaglutide as the first approved drug for such use since 2014. The use of semaglutide in weight management is also approved by Health Canada 20 and the EMA. Semaglutide is a GLP–1 receptor agonist, meaning that it mimics the action of the human incretin glucagon–like peptide–1 (GLP–1), thereby increasing insulin secretion and increasing blood sugar disposal and improving glycemic control.[2]

Figure-1: Jesper Lau Hansen [Inventor of Semaglutide].

Side effects include nausea, vomiting, diarrhea, abdominal pain, and constipation. In December 2017, the injectable version named Ozempic was approved, in September 2019, a version which can be taken by mouth (Rybelsus) was approved, and in June 2021, a higher–dose injection sold under the brand name Wegovy for long–term weight management in adults was approved by the US Food and Drug Administration (FDA). In 2020, semaglutide was the 129th most commonly prescribed medication in the United States, with more than 4 million prescriptions. **Jesper Lau Hansen**, Vice President of Diabetes Protein and Peptide Chemistry at Novo Nordisk, Denmark is credited with the invention and development of Semaglutide in 2012.[3]

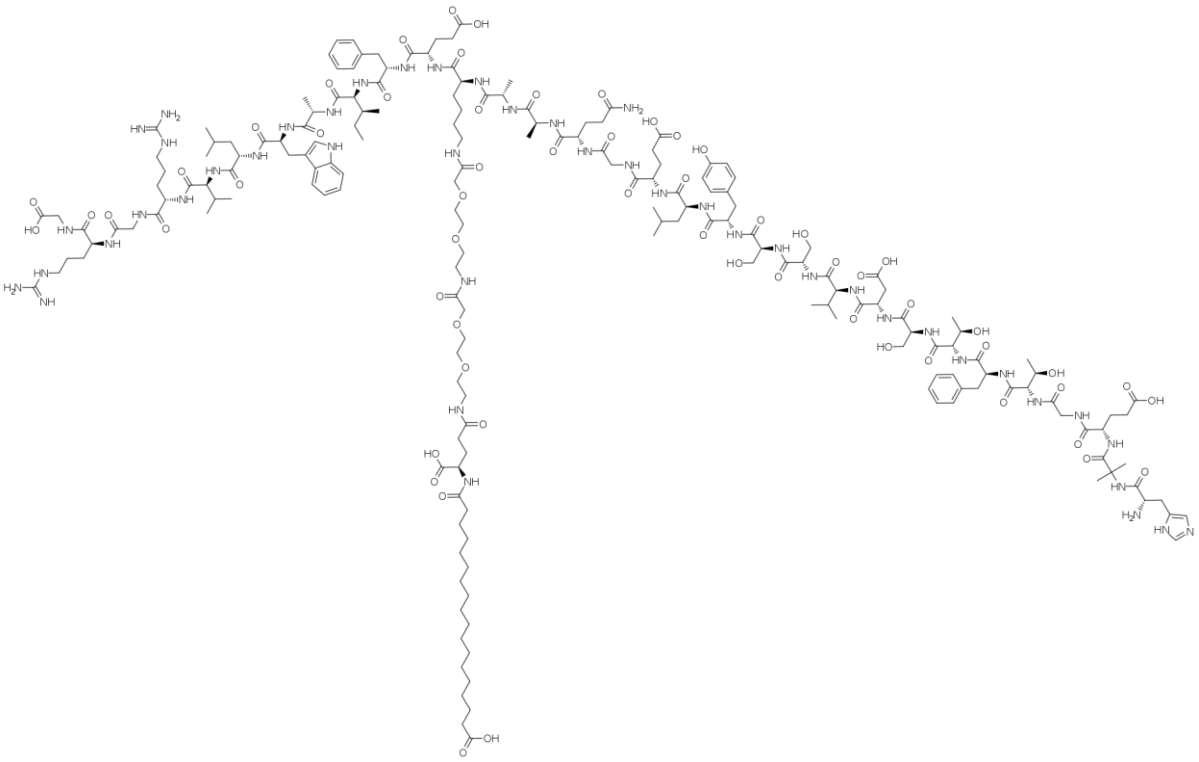

Figure-2: Semaglutide structure.

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{[(1S)–1–{[(1S)–4–carbamimi–damido–1–[({[(1S)–4–carbamimidamido–1–[(carboxymethyl)carbamoyl] butyl]carbamoyl}methyl)carbamoyl]butyl]carbamoyl}–2–methylpropyl]carbamoyl}–3–methylbutyl] carbamoyl}–2–(1H–indol–3–yl)ethyl]carbamoyl}ethyl]carbamoyl}–2–methylbutyl]carbamoyl}–2–phenylethyl]carbamoyl}–3–carboxypropyl]–carbamoyl}pentyl]carbamoyl} methoxy)ethoxy] ethyl}carbamoyl)methoxy]ethoxy}ethyl)carbamoyl]–1–propyl] carbamoyl}heptadecanoic acid.

Properties: logP= –18, pKa (Strongest Acidic)= 2.74, pKa (Strongest Basic)= 12.26, Physiological Charge= –4, Hydrogen Acceptor Count= 67, Hydrogen Donor Count= 57, Polar Surface Area= 1646.18 $Å^2$, Rotatable Bond Count= 149, Refractivity= 1048.56 $m^3 \cdot mol^{-1}$, Polarizability= 427.61 $Å^3$

The US Food and Drug Administration has approved semaglutide 2.4 mg (Wegovy), a once–weekly subcutaneous injection, for the additional indication of treating obesity in adolescents aged 12 years and older. This is defined as those with an initial BMI at or above the 95th percentile for age and sex (based on CDC growth charts). Semaglutide must be administered along with lifestyle intervention of a reduced calorie meal plan and increased physical activity.[4]

When Wegovy was approved for use in adults with obesity in June 2021, it was labeled a "game changer." The new approval is based on the results of the STEP TEENS phase 3 trial of once–weekly 2.4 mg of semaglutide in adolescents 12– to <18 years old with obesity, the drug's manufacturer, Novo Nordisk, announced in a press release. In STEP TEENS, reported at Obesity Week 2022 in November, and simultaneously published in the New England Journal of Medicine, adolescents with obesity treated with semaglutide for 68 weeks had a 16.1% reduction in BMI compared with a 0.6% increase in BMI in those receiving placebo. Both groups also received lifestyle intervention. Mean weight loss was 15.3 kg (33.7 lb) among teens on semaglutide, while those on placebo gained 2.4 kg (5.3 lb).[5]

Figure-3: Semaglutide formulation.

Pharmacology: Semaglutide is indicated to improve glycemic control in adults diagnosed with type 2 diabetes mellitus, and is used as an adjunct to diet and exercise. However, semaglutide is not a suitable first–line drug for diabetes that has not been controlled by diet and exercise. In addition, it has not been studied in patients with pancreatitis. Semaglutide is not intended for use in patients with type 1 diabetes or to treat diabetic ketoacidosis. Semaglutide is indicated for chronic weight management in adults with obesity or overweight with at least one weight–related condition (such as high blood pressure, type 2 diabetes, or high cholesterol), for use in addition to a reduced–calorie diet and increased physical activity. BMI >27 kg/m^2. Semaglutide is chemically similar to human GLP–1, with 94% similarity. The only differences are two amino–acid substitutions at positions 8 and 34, where alanine and lysine are replaced by 2–aminoisobutyric acid and arginine, respectively. Amino–acid substitution at position 8 prevents chemical breakdown by dipeptidyl peptidase–4. In addition, the lysine at position 26 is in its derivative form (acylated with stearic diacid). Acylation with a spacer and C–18 fatty diacid chain increases the drug's binding to blood protein (albumin), which enables longer presence in the blood circulation. Its half–life in the blood is about seven days (165–184 hours). It can be administered by subcutaneous injection once weekly or once–daily by mouth. No significant difference in the decrease from baseline body weight was observed between groups taking it orally (20 mg and 40–mg) or subcutaneously.[6]

Pharmacodynamics: Semaglutide reduces HbA1c, systolic blood pressure, and body weight. After 12 weeks of treatment, semaglutide decreased fasting and

postprandial glucose by increasing insulin production and decreasing glucagon secretion (which is normally associated with increases in blood sugar). Semaglutide also lowers fasting triglycerides and VLDL cholesterol, exerting beneficial effects on cardiovascular health. Semaglutide has been shown to cause medullary thyroid cell carcinoma in rodents. While its clinical relevance to humans is unknown, the FDA advises not to administer this drug in those with a personal or family history of medullary thyroid carcinoma. Semaglutide also poses a risk of pancreatitis and dehydration. Patients must be adequately hydrated while on semaglutide and are advised to seek medical attention immediately in cases of abdominal pain radiating to the back. Because this drug delays gastric emptying, it is important to monitor for the efficacy or adverse effects of other drugs that are administered orally.[7]

Mechanism of action in glycemic control: GLP–1 [Glucagon Like Peptide] is a physiological hormone that promotes glycemic control via several different mechanisms, including insulin secretion, slowing gastric emptying, and reducing postprandial glucagon secretion. The homeostasis of glucose is dependent on hormones such as insulin and amylin, which are secreted by the beta cells of the pancreas. Semaglutide is 94% similar to human GLP–1. Analogs of this hormone such as semaglutide stimulate the synthesis of insulin3 by stimulating pancreatic islet cells and reducing glucagon secretion. They directly bind with selectivity to the GLP–1 receptor, causing various beneficial downstream effects that reduce blood glucose in a glucose–dependent fashion.[8]

Mechanism of cardiovascular benefit and weight loss: In hypercholesterolemia, semaglutide is believed to reduce the progression of atherosclerosis via decreased gut permeability and decreased inflammation. Weight loss is believed to occur via the reduction of appetite and food cravings after semaglutide administration. Semaglutide is a glucagon–like peptide–1 receptor agonist. By mimicking the action of the incretin GLP–1, it increases the production of insulin, the hormone which lowers the blood sugar level. It appears to enhance growth of pancreatic beta cells, which are responsible for insulin production and release. It also inhibits the production of glucagon, the hormone that increases glycogenolysis (release of stored carbohydrate from the liver) and gluconeogenesis (synthesis of new glucose). It reduces food intake by lowering appetite and slowing down digestion in the stomach, helping to reduce body fat. It reduces hunger, food craving and body fat.[9]

Absorption: The C_{max} of semaglutide was 10.9 nmol/L, with AUC of 3123.4 nmol h/L and a T_{max} of 56 h in one clinical trial, achieved within 1–3 days. The absolute bioavailability is 89%.15 Steady–state concentration of the oral tablet is achieved in 4–5 weeks. Average steady state concentrations of semaglutide a subcutaneous injection is administered once weekly and the tablet is administered once a day. Semaglutide offers a competitive advantage over other drugs used to manage diabetes, which may require several daily doses. Clinical trials have determined that this drug reduces glycosylated hemoglobin (HbA1c) levels and reduces body weight, proving to be effective for patients with type 2 diabetes. In June 2021, semaglutide was approved by the FDA for chronic weight management in adults with general obesity or overweight who have at least one weight–related condition, marking semaglutide as the first approved drug for such use since 2014. The use of semaglutide in weight management is also approved by Health Canada 20 and the EMA. Semaglutide is a GLP–1 receptor agonist, meaning that it mimics the action of the human incretin glucagon–like peptide–1 (GLP–1), thereby increasing insulin secretion and increasing blood sugar disposal and improving glycemic control. The subcutaneous injection is administered once weekly and the tablet is administered once a day. Semaglutide offers a competitive advantage over other drugs used to manage diabetes, which may require several daily doses. Clinical trials have determined that this drug reduces glycosylated hemoglobin (HbA1c) levels and reduces body weight, proving to be effective for patients with type 2 diabetes. In June 2021, semaglutide was approved by the FDA for chronic weight management in adults with general obesity or overweight who have at least one weight–related condition, marking semaglutide as the first approved drug for such use since 2014. The use of semaglutide in weight management is also approved by Health Canada 20 and the EMA. Semaglutide is a GLP–1 receptor agonist, meaning that it mimics the action of the human incretin glucagon–like peptide–1 (GLP–1), thereby increasing insulin secretion and increasing blood sugar disposal and improving glycemic control. re the mean steady state concentrations after dosing at 0.5mg to 1mg range from 16 nmol/L to 30 nmol/L.[10]

Volume of distribution: The volume of distribution of semaglutide is 8L to 9.4L. It crosses the placenta in rats.

Protein binding: Semaglutide binds with high affinity to plasma albumin, promoting high levels of drug stability. It is more than 99% bound to albumin.[11]

Metabolism: Semaglutide is cleaved at the peptide backbone, followed by β-oxidation of the fatty acid chain. Naturally occurring GLP-1 is quickly metabolized by dipeptidyl peptidase-4 (DPP-4) and other enzymes, which is ubiquitous in human tissues. Chemical structure modifications render semaglutide less susceptible to enzymatic degradation by gastrointestinal DPP-4 enzymes. It is slowly and extensively metabolized, with about 83% of the administered dose measured in the plasma as unchanged drug. Neural endopeptidase (NEP) is another enzyme that metabolizes this drug. DPP–4 inactivates semaglutide, truncating the N–terminal segment while NEP hydrolyzes peptide bondsSix different metabolites of semaglutide have been identified

in human plasma. The major metabolite, named P3, accounts for about 7.7% of an ingested dose.[12]

Route of elimination: This drug is mainly cleared by the kidneys, and is found excreted in both the urine and feces. The main elimination route is the urine by corresponding to 53% of an ingested radiolabeled dose, with 18.6% found in the feces. A smaller amount of 3.2% was found to be exhaled.4 Hepatic impairment does not appear to affect the clearance of this drug and dose adjustments are not required in patients with decreased liver function.[13]

Half–life: One of the major properties of semaglutide is its long half–life of 168 h. The long half–life is attributed to its albumin binding. This lowers the renal clearance and protects semaglutide from metabolic breakdown.[14]

Clearance: The clearance rate of semaglutide is 0.039 L/h according to one clinical study. On the FDA label, semaglutide clearance is reported to be about 0.05 L/h in patients with type 2 diabetes mellitus.[15]

Toxicity: Overdoses of up to 4 mg in one ingestion have been reported, with nausea being the most commonly reported symptom. All patients in clinical trials who experienced an overdose recovered fully. Appropriate supportive care should be given according and dictated by the patient's condition. Prolonged observation and treatment may be required, as the half–life of this drug is about one week. There is no antidote to an overdose with semaglutide. Nausea, vomiting, abdominal pain, loss of appetite, diarrhea, or constipation may occur. Nausea usually lessens as you continue to take semaglutide. If any of these effects last or get worse, tell your doctor or pharmacist promptly. Remember that this medication has been prescribed because your doctor has judged that the benefit to you is greater than the risk of side effects. Many people using this medication do not have serious side effects. Tell your doctor right away if you have any serious side effects, including: signs of kidney problems (such as change in the amount of urine), vision changes (such as decreased/blurred vision). Get medical help right away if you have any very serious side effects, including: signs of pancreas or gallbladder disease (such as nausea/vomiting that doesn't stop, severe stomach/abdominal pain).[16]

Drug Interactions: Drug interactions may change how your medications work or increase your risk for serious side effects. This document does not contain all possible drug interactions. Keep a list of all the products you use (including prescription/nonprescription drugs and herbal products) and share it with your doctor and pharmacist. Do not start, stop, or change the dosage of any medicines without your doctor's approval. Beta-blocker medications (such as metoprolol, propranolol, glaucoma eye drops such as timolol) may prevent the fast/pounding heartbeat you would usually feel when your blood sugar falls too low (hypoglycemia). Other symptoms of low blood sugar, such as dizziness, hunger, or sweating, are not affected by these drugs. Many drugs can affect your blood sugar, making it harder to control. Before you start, stop, or change any medication, talk with your doctor or pharmacist about how the medication may affect your blood sugar. Check your blood sugar regularly as directed and share the results with your doctor. Tell your doctor right away if you have symptoms of high or low blood sugar. Your doctor may need to adjust your diabetes medication, exercise program, or diet.[17]

Food Interactions: Take on an empty stomach. For oral use of semaglutide, take 30 minutes before the first meal of the day. Take with plain water. For oral use of semaglutide, do not exceed 4 ounces of water (1/2 cup). Side effects include nausea, vomiting, diarrhea, abdominal pain, and constipation. In people with heart problems, it can cause damage to the retina of the eye (retinopathy). Other, less common side effects include kidney problems, allergic reactions, low blood sugar, and pancreatitis. Due to data from rodents studies of GLP–1–mediated thyroid C–cell hyperplasia, the use is contraindicated in people with a personal or family history of medullary thyroid carcinoma and in patients with multiple endocrine neoplasia syndrome type 2.[18]

Medication: Take this medication with a sip of plain water (no more than 4 ounces or 120 milliliters) as directed by your doctor, usually once daily. Do not take it with any other beverage. Swallow the tablet whole. Do not split, chew or crush the tablet. Wait at least 30 minutes after taking semaglutide before you eat or drink anything other than plain water and before taking any other medication by mouth. For the best effect, you should eat 30 to 60 minutes after taking semaglutide. It is important to take this medication the same way with every dose. The dosage is based on your medical condition and response to treatment. To reduce your risk of side effects, your doctor may direct you to start this medication at a low dose and gradually increase your dose. Follow your doctor's instructions carefully. Use this medication regularly to get the most benefit from it. To help you remember, take it at the same time each day. Do not increase your dose or use this drug more often or for longer than prescribed. Your condition will not improve any faster, and your risk of side effects will increase. Tell your doctor if your condition does not get better or if it gets worse (your blood sugar is too high or too low). Although semaglutide by itself usually does not cause low blood sugar (hypoglycemia), low blood sugar may occur if this drug is prescribed with other diabetes medications. Talk with your doctor or pharmacist about whether the dose(s) of your other diabetes medication(s) needs to be lowered. Drinking large quantities of alcohol, not getting enough calories from food, or doing unusually heavy exercise may also lead to low blood sugar. Symptoms may include sudden sweating, shaking, fast heartbeat, hunger, blurred vision, dizziness, or tingling hands/feet. It is a good habit to carry glucose

tablets or gel to treat low blood sugar. If you don't have these reliable forms of glucose, rapidly raise your blood sugar by eating a quick source of sugar such as table sugar, honey, candy, or drink fruit juice or non-diet soda. Check with your doctor or pharmacist to find out what you should do if you miss a meal. Symptoms of high blood sugar (hyperglycemia) include increased thirst/urination. If these symptoms occur, tell your doctor right away. Your dosage may need to be increased. A very serious allergic reaction to this drug is rare. However, get medical help right away if you notice any symptoms of a serious allergic reaction, including: rash, itching/swelling (especially of the face/tongue/throat), severe dizziness, trouble breathing.[19]

Precautions: Before taking semaglutide, tell your doctor or pharmacist if you are allergic to it; or if you have any other allergies. This product may contain inactive ingredients, which can cause allergic reactions or other problems. Talk to your pharmacist for more details. Before using this medication, tell your doctor or pharmacist your medical history, especially of: a certain eye problem (diabetic retinopathy), a disease of the pancreas (pancreatitis), gallbladder disease, kidney problems, stomach/intestinal disorders (such as gastroparesis, digestion problems). You may experience blurred vision, dizziness, or drowsiness due to extremely low or high blood sugar. Do not drive, use machinery, or do any activity that requires alertness or clear vision until you are sure you can perform such activities safely.[20]

Limit alcohol while using this medication because it can increase your risk of developing low blood sugar. It may be harder to control your blood sugar when your body is stressed (such as due to fever, infection, injury, or surgery). Consult your doctor because this may require a change in your treatment plan, medications, or blood sugar testing. Before having surgery, tell your doctor or dentist about all the products you use (including prescription drugs, nonprescription drugs, and herbal products). During pregnancy, this medication should be used only when clearly needed. If you are planning pregnancy, become pregnant, or think you may be pregnant, discuss with your doctor right away the benefits and risks of using this medication during pregnancy.[21]

The manufacturer recommends stopping use of this medication 2 months before a planned pregnancy. Pregnancy may cause or worsen diabetes. Discuss a plan with your doctor for managing your blood sugar while pregnant. Your doctor may change your diabetes treatment during your pregnancy (such as diet and medications including insulin). It is unknown if this medication passes into breast milk. Consult your doctor before breast-feeding. Consult your pharmacist or physician.[22-24]

CONCLUSION

Semaglutide is a recombinant DNA produced polypeptide analogue of human glucagon-like peptide-1 (GLP-1) which is used in combination with diet and exercise in the therapy of type 2 diabetes, either alone or in combination with other antidiabetic agents. There have been no published reports of hepatotoxicity attributed to semaglutide therapy. Semaglutide is a polypeptide that contains a linear sequence of 31 amino acids joined together by peptide linkages. It is an agonist of glucagon-like peptide-1 receptors (GLP-1 AR) and used for the treatment of type 2 diabetes. It has a role as a hypoglycemic agent, a glucagon-like peptide-1 receptor agonist, an anti-obesity agent, a neuroprotective agent and an appetite depressant. It is a polypeptide and a lipopeptide. Semaglutide was recently evaluated as an antiobesity drug in a phase II dose-finding trial, which demonstrated superior weight loss efficacy of once daily sc semaglutide compared with both placebo and once daily 3.0 mg liraglutide in patients with obesity but without T2DM. Semaglutide is a glucagon-like peptide-1 receptor agonist (GLP-1 RA) with a long elimination half-life, allowing subcutaneous (sc) administration once per week. Both the European Medicines Agency (EMA) and the Food and Drug Administration (FDA) recently approved once-weekly subcutaneously semaglutide for the treatment of type 2 diabetes mellitus (T2DM). The weight loss efficacy of once-weekly subcutaneously semaglutide appears to be superior compared with the other once-weekly GLP-1 RAs in patients with T2DM. Semaglutide was recently evaluated as an antiobesity drug in a phase II dose-finding trial, which demonstrated superior weight loss efficacy of once daily sc semaglutide compared with both placebo and once daily 3.0 mg liraglutide in patients with obesity but without T2DM. The magnitude of semaglutide-induced weight loss in this study exceeded the criteria of both the EMA and FDA for antiobesity drugs, and there were no safety concerns, indicating the eligibility of once daily sc semaglutide as a future antiobesity drug.

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