Review Article

Semaglutide: An expedition on last approved glucagon-like peptide-1 analog of past decade

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ABSTRACT

Semaglutide (Ozempic once in a week sub-cutaneous injection; Rybelsus: Oral tablet) is a glucagon-like peptide 1 receptor agonist indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM). It was the last United States Food and Drug Administration (FDA) approved drug, developed by Novo Nordisk, of the past decade for the treatment of type 2 diabetes. The current expedition on semaglutide will update the clinician and researchers about the different aspects of the newer drug including FDA approval and market authorization, description of structural class, mechanism, pharmacokinetics, pre-clinical studies, clinical studies, dosages, adverse effects, and interactions.

Keywords: Glucagon-like peptide 1, oral anti-diabetic, semaglutide, type 2 diabetes mellitus

INTRODUCTION

Semaglutide, a newer Glucagon-like peptide 1 (GLP-1) receptor agonist, developed by Novo Nordisk for the treatment of type 2 diabetes. The drug got approval from the United States Food and Drug Administration (FDA) for subcutaneous injection (Ozempic) on December 5, 2017, and for oral tablets (Rybelsus) in September 2019 as an adjunct to diet and exercise to improve glycemia control. Semaglutide has been developed as a once-a-week subcutaneous injection and is currently also being developed for daily oral administration. It is structurally similar to liraglutide but it is more enzymatically stable in turn less susceptible to degradation by enzyme protease dipeptidyl peptidase-4 (DPP-4).[1] The drug has been evaluated *via* some large-scale long-term randomized trials; however, a comprehension is still needed on the evaluation of its efficacy and safety.[2,3]

GLP-1, an incretin hormone, is a glucose-lowering hormone in response to food intake in a glucose-dependent manner [Figure 1]. It glucose-dependently stimulates insulin secretion by membrane depolarization and insulin storage granule exocytosis. GLP-1 can also facilitate insulin gene transcription and biosynthesis to keep insulin stores and secretory capacity in pancreatic β-cell. In addition, GLP-1 leads to the inhibition on glucagon release and the decreased gastric emptying [Figure 2]. However, native GLP-1 will be degraded rapidly by DPP-4 enzyme, which results in the very short plasma half-life. Accordingly, GLP-1 analogs are developed and modified to resist inactivation by DPP-4 enzyme.[4]

The development of GLP-1 analogs signifies a great breakthrough for the treatment of type 2 diabetes. GLP-1 analogs are attractive benefiting from their advantages, including weight reduction, low risk of hypoglycemia and improved β-cell function. However, it is important to note that not all GLP-1 analogs are equal, with each possessing its own distinct pharmacokinetic and pharmacodynamic characteristics. Each of them has diverse effects on body weight, blood pressure and adverse effects, despite no much difference in glycosylated hemoglobin (HbA_{1c}). In general, they are classified as short-acting and long-acting GLP-1 analogs. For short-acting GLP-1 analogues (e.g., exenatide immediate release, liraglutide, and lixisenatide), they need to be administrated once or twice a day, and long acting GLP-1 analogs (exenatide extended-release, albiglutide, and dulaglutide) can be injected once-weekly. Given the long-term treatment of diabetes, once-weekly administration of antidiabetic agents potentially provides greater convenience, better compliance

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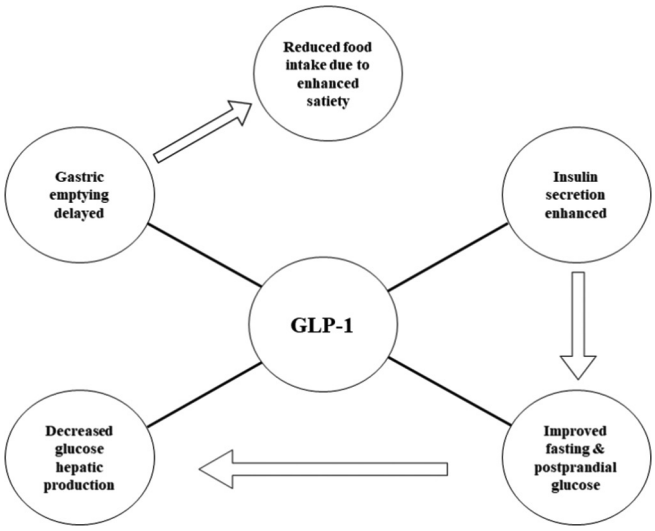

Figure 1: Consequences of GLP-1

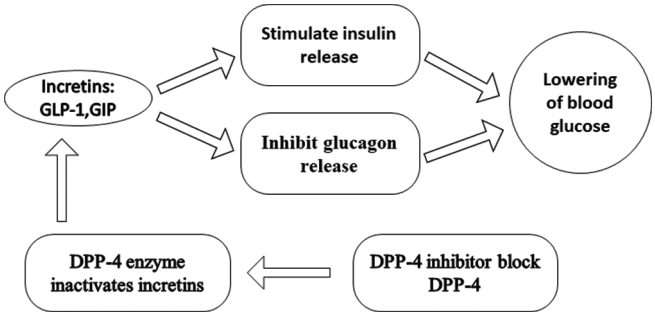

Figure 2: Effect of GLP 1 in control of blood glucose

and better treatment outcomes in comparison to short-acting GLP-1 analogs.[4,5]

The purpose of this article is to provide a review of all available data regarding semaglutide including its pharmacodynamics, pharmacokinetics, clinical efficacy, and safety profiles. We search the PubMed, Google scholar, and MEDLINE databases with the titles "semaglutide," "NN9934," "NN9535," "NN9936," and to identify all clinical events evaluating semaglutide treatment in type 2 diabetics.

FDA APPROVAL AND MARKET AUTHORIZATION

Semaglutide (Ozempic) has been developed using Novo Nordisk's proprietary protein-acylation technology, and is administered using an injection device. Semaglutide lowers blood glucose by stimulating the release of insulin and also lowers body weight. Once weekly subcutaneous semaglutide has recently been approved in the US, Puerto Rico and Canada and has received a positive opinion in the EU for the treatment of patients with type 2 diabetes. In December 2017, semaglutide also received a positive opinion from the EU Committee for Medicinal Products for Human Use for the treatment of type 2 diabetes. It is indicated for use in adults with insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise.[5] The approval of semaglutide was based on results from the SUSTAIN clinical trial program. It is recommended that semaglutide be initiated at 0.25 mg once weekly and after 4 weeks, the dosage should be increased to 0.5 mg once weekly.[4] If additional glycemic control is needed after at least 4 weeks, the dosage may be increased to 1 mg (maximum dose) once weekly. Semaglutide can be used as monotherapy when metformin is considered inappropriate (due to intolerance or contraindications) or in combination with other medicinal products for the treatment of diabetes.[5] Health Canada in January 2018 approved semaglutide as an adjunct to diet and exercise in adults with type 2 diabetes, when metformin is not tolerated or contraindicated.[6]

DESCRIPTION OF STRUCTURAL CLASS

Semaglutide, a fatty-acylated GLP-1 analog [Figure 3], (molecular formula: $C_{187}H_{291}N_{45}O_{59}$, molecular weight: 4113.67 g/mmol) is 94% structurally analogous to native human GLP-1 [Figure 4]. Three minor modifications contribute to semaglutide suitable for once-weekly clinical use: amino acid substitutions at position 8 (alanine to alpha-aminoisobutyric acid, a synthetic amino acid) and position 34 (lysine to arginine), and acylation of the lysine at position 26 with a spacer and C-18 fatty di-acid chain. This fatty acid conjugation shows long duration of action *via* strong binding to albumin and thus decreases their renal clearance. The amino acid substitution at position 8 makes semaglutide less susceptible to be degraded by DPP-4. The reported half-life of semaglutide is 165–184 h (*i.e.*, suitable for once-weekly administration).[7,8] It has a stearic-diacid at lysine position 20, linked *via* a di-aminoethoxy, γ-glutamic acid spacer, and an amino-isobutyric residue at position 2 to provide protection from DPP-IV degradation. Semaglutide has a half-life of 165 h in humans, due in part to noncovalent association with human serum albumin.

MECHANISM OF GLP-1 ANALOGUE

GLP-1 potently stimulates insulin secretion in a strictly glucose-dependent manner. Binding of GLP-1 to the GLP-1 receptor of β-cells causes activation *via* a stimulatory G protein of adenylate cyclase, resulting in the formation of cAMP. Subsequent activation of protein kinase A and the cAMP-regulated guanine nucleotide exchange factor II (also known as Epac2) leads to a plethora of events including altered ion channel activity, intracellular calcium handling, and enhanced exocytosis of insulin-containing granules [Figure 5]. The clinical implication of the dependence on blood glucose concentrations at or above normal fasting glucose levels is that GLP-1 is incapable of causing profound hypoglycemia.

GLP-1 stimulates all steps of insulin biosynthesis, as well as insulin gene transcription, thereby providing continued and augmented supplies of insulin for secretion. The activation of PDX-1, a key regulator of islet growth and insulin gene transcription, might be involved. In addition, GLP-1 upregulates genes for the cellular machinery involved in insulin secretion, such as glucokinase and glucose transporter-2 genes.[9,10] GLP-1 also strongly inhibits glucagon secretion. In patients with T2DM, there is fasting hyperglucagonemia as well as exaggerated glucagon responses

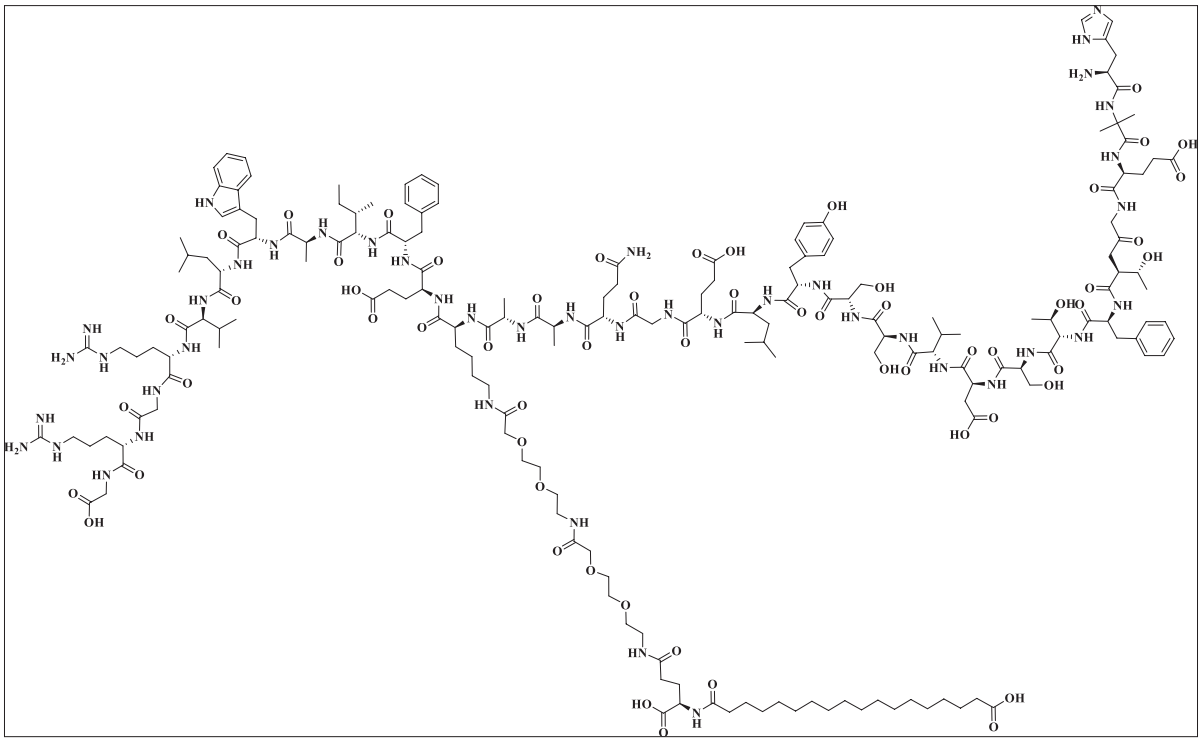

Figure 3: Chemical structure of Semaglutide

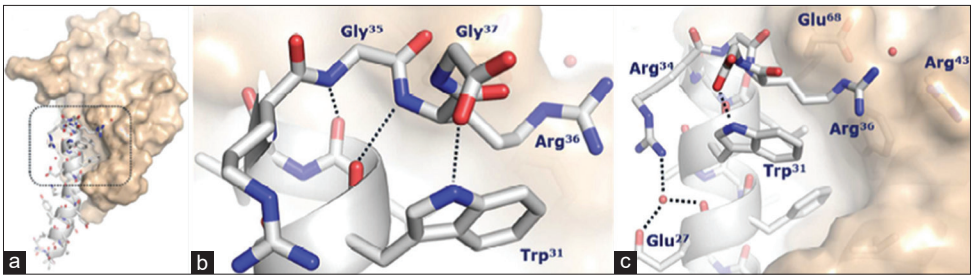

Figure 4: (a-c) Crystal structure of the semaglutide peptide backbone (grey) in complex with the GLP-1 receptor extracellular domain (golden surface)

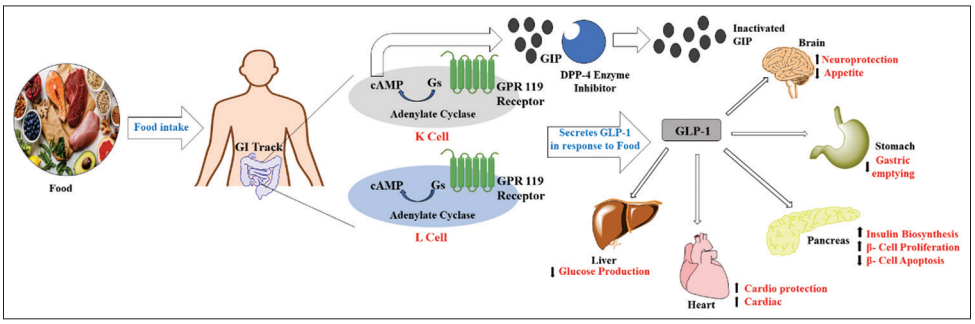

Figure 5: Mechanism of action of GLP-1 analogues

to meal ingestion; therefore, it is likely that the hyperglucagonemia contributes to the hyperglycemia of the patients. This effect could be as important as the insulinotropic effects. Further important effects of GLP-1 include inhibition of gastrointestinal (GI) secretion and motility, notably gastric emptying. This effect is desirable in patients with diabetes because the slower gastric emptying rate reduces postprandial glucose excursions; the clinical importance of this is evident from the use of another potent gastric inhibitor, amylin, for diabetes treatment.[11]

PHARMACOKINETICS

The pharmacokinetic studies have confirmed that the parameters for semaglutide are suitable for once-weekly administration, which gives it an advantage over the GPR-1A that have to be used daily, *e.g.*, liraglutide and lixisenatide. Thus, in mini-pigs, after iv administration, the $t_{1/2}$ was much longer with semaglutide (46.1 h) than with liraglutide (12.4 h). Clearance was lower with semaglutide

than with liraglutide, probably due to the greater albumin binding with semaglutide. After sc administration, the t_{max}, and MRT (mean residence time) were longer for semaglutide than liraglutide, and the bioavailability was greater with semaglutide (94%). In the db/db mouse, a hyperglycemic, hyperinsulinemic, and obese model of type 2 diabetes, over 50 h, semaglutide was more effective than liraglutide at reducing blood glucose.[8,10]

After the sc administration of a single dose of 0.5 mg radioactive [3H]-semaglutide to seven healthy males, t_{max} was 56 h, $t_{1/2}$ was 168 h, and area under the curve $(AUC)_{0\text{-infinity}}$ was 3123 nmol/h/L. Apparent clearance, CL/F was 0.039 L/h and volume of distribution, Vz/F, was 9.4L. Semaglutide was the main component in the plasma (83%) but seven metabolites were also identified in plasma. Most of the radioactivity (97%) was excreted in the urine, and this radioactivity was mainly metabolites, as semaglutide only accounted for 3%.[11] It has increased affinity to albumin thereby has a half-life of approximately 1 week, rendering it appropriate for once-weekly subcutaneous administration.[2,3]The comparison of pharmacokinetic properties of Ozempic and Rybelsus are depicted in Table 1.

PRECLINICAL STUDIES

Preclinical safety studies demonstrated no indication of pancreatitis or pancreatic inflammation in cynomolgus monkeys. Semaglutide has advanced to registration phase clinical trials. In patients with type 2 diabetes, semaglutide is reported to improve glycemic control dose-dependently, decreasing HbA_{1c} levels by 1.7% (18.7 mmol/mol) versus 0.5% (5.5 mmol/mol) with placebo and 4.8 kg of weight loss versus 1.2 kg with placebo, relative to baseline. The magnitude of these effects was greater than those with open-label liraglutide in the same study. In addition, in a cardiovascular outcome study involving patients with type 2 diabetes, of whom more than 80% had a history of cardiovascular disease, semaglutide treatment lowered the rates of 3-point MACE (myocardial infarction, stroke, and cardiovascular death).[12]

CLINICAL STUDY

The glucose-lowering efficacy of semaglutide once-weekly administration as monotherapy, or add-on therapy to oral anti-diabetes agents in patients inadequately controlled type 2 diabetes was investigated in several randomized, double-blind, multinational trials, but the results of most trials were still unavailable. A 12-week, randomized, double-blind, parallel-group trial (ClinicalTrials.gov Identifier: NCT00696657) was performed to investigate the dose-response relationship of semaglutide versus placebo and liraglutide in subjects with type 2 diabetes.The changes from baseline in HbA_{1c} were set as the primary outcome measures after 12 weeks of treatment. Secondary outcome measures included changes from baseline in fasting plasma glucose (FPG), postprandial plasma glucose, AUC, and other glycemic control parameters (e.g., insulin, C-peptide, and glucagon). In addition, safety assessments included percentage of subjects with adverse events and hypoglycemic episode, change from baseline in electrocardiogram, vital signs (pluse and blood pressure), and standard safety laboratory parameters (hematology, biochemistry, urinalysis, calcitonin and semaglutide antibodies). In this trial, a total of 415 enrolled subjects were randomized to receive once-weekly semaglutide (0.1, 0.2, 0.4, or 0.8 mg), once-weekly semaglutide with dose escalation (0.8 or 1.6 mg), placebo or once-daily liraglutide (1.2 or 1.8 mg). Compared with placebo, six treatments of semaglutide all achieved significant reduction in HbA_{1c} ($P < 0.05$) and showed dose-dependent efficacy. Subcutaneous administration of 0.8 and 1.6 mg semaglutide achieved greater reduction from baseline in HbA_{1c} in comparison to placebo (−1.2% [−1.6, −0.8], $P < 0.0001$). At week 12, up to 81% patients achieved target HbA_{1c} <7.0% with semaglutide (0.1–1.6 mg) in comparison to 57% with 1.8 mg liraglutide and 15% with placebo. Up to 63% patients reached target HbA_{1c} ≤6.5% with semaglutide (0.1–1.6 mg) in comparison to 36% with 1.8 mg liraglutide and 4% with placebo. FPG levels reduced with semaglutide 0.1–1.6 mg in a dose dependent manner. The reduction in FPG levels was significantly greater in subjects receiving semaglutide 0.4–1.6 mg than those receiving placebo ($P < 0.01$), and was greater with semaglutide 0.8–1.6 mg in comparison to liraglutide 1.2 mg.The reduction in body weight was also observed in subjects receiving semaglutide 0.1–1.6 mg at week 12. Compared with placebo, body weight was significantly reduced in subjects receiving semaglutide 0.8–1.6 mg (range −3.4–−4.8 kg; $P < 0.001$). In addition, the mean reduction from baseline in body weight was greater in subjects receiving semaglutide 0.8 and 1.6 mg than those receiving liraglutide 1.2 mg.[4]

Table 1: Comparison of pharmacokinetic properties of ozempic and rybelsus

Property	Ozempic	Rybelsus
IC_{50}	0.38 nM	752 µM
$t_{1/2}$	1 week	1 week
Bioavailability	89%	0.4%-1%
Protein Binding	>99% (bound to plasma albumin)	>99%
Excretion	3.1%	3%
Dosage	0.25 mg, 0.5 mg, 1 mg	3 mg, 7 mg, 14 mg

DOSAGE

Semaglutide 0.5 or 1.0 mg once weekly monotherapy significantly improved glycemic control and reduced bodyweight in treatment-naive patients with type 2 diabetes, according to results from the 30-week, phase 3a, placebo-controlled SUSTAIN 1 study (NCT02054897). At week 30, HbA_{1c} levels (primary endpoint) were significantly ($P < 0.0001$) reduced with semaglutide 0.5 or 1.0 mg compared with placebo (mean change from baseline – 1.45 and −1.55 versus −0.02; baseline 8.05%). Mean bodyweight (confirmatory secondary endpoint) was also significantly (*P*\0.0001) reduced with semaglutide 0.5 or 1.0 mg relative to placebo (mean change from baseline −3.73 and –4.53 versus −0.98 kg, respectively; baseline 91.93 kg).[2,6]

Efficacy was assessed as secondary outcomes, with safety the primary outcome of the study. Other secondary outcomes were also significantly (*P*\0.0001) improved with semaglutide 0.5 and 1.0 mg relative to sitagliptin, including the proportion of patients achieving HbA_{1c} targets of B6.5% (71 and 87 vs. 16%) and\7% (84

and 95 vs. 35%), and the mean change from baseline in BMI and WC. This randomized, open-label, multicenter study included patients aged C20 years who were treated with diet and exercise plus oral antidiabetic drug (OAD) monotherapy if their HbA_{1c} levels were 6.5–9.5%, or those treated with diet and exercise only if their HbA_{1c} levels were 7.0–10.5% for 30 days before screening; the mean disease duration was 8.0 years.[6,12]

ADVERSE EFFECTS

The most common adverse events were GI, which were mostly mild to moderate in severity with oral semaglutide [Table 2]. The proportion of patients reporting GI events was higher with oral semaglutide (31–77%; 255 of 490 patients) and subcutaneous semaglutide (54%; 37 of 69 patients) than with placebo (28%; 20 of 71 patients). Fewer nausea events were reported when patients started on a lower dose (e.g., 2.5 mg vs. 5 mg).[13]

Subcutaneous semaglutide 0.5 and 1.0 mg once weekly was generally well tolerated in clinical trials in patients with type 2 diabetes. The most common adverse reactions with semaglutide 0.5 and 1.0 mg (n = 260 and 261) compared with placebo (n = 262) were nausea (15.8 and 20.3 vs. 6.1%), vomiting (5.0 and 9.2 vs. 2.3%), diarrhea (8.5 and 8.8 vs. 1.9%), abdominal pain (7.3 and 5.7 vs. 4.6%), and constipation (5.0 and 3.1 vs. 1.5%). GI adverse reactions, overall, occurred approximately twice as frequently with semaglutide 0.5 and 1.0 mg than placebo (32.7 and 36.4 vs. 15.3%); the proportion of patients discontinuing treatment because of GI adverse reactions was also higher in the semaglutide groups than the placebo group (3.1 and 3.8 vs. 0.4%).[11]

Table 2: Adverse reactions from long-term controlled Phase IIIa trials

Organ	Very common	Common	Uncommon	Rare
Cardiac disorders	-		Increased heart rate	
General disorders and administration site conditions	-	Fatigue	Injection site reactions	
GI disorders	Nausea Diarrhea	Vomiting Abdominal pain Abdominal Distension Constipation Dyspepsia Gastritis Gastroesophageal Reflux disease Eructation Flatulence	Acute pancreatitis	
Hepatobiliary disorders	-	Cholelithiasis		
Immune system disorders	-			Anaphylactic reaction
Metabolism and nutrition disorders	Hypoglycemia when used with insulin or sulfonylurea	Hypoglycemia when used with other OADs Decreased appetite		
Nervous system disorders		Dizziness	Dysgeusia	
Investigation	-	Increased lipase Increased amylase Weight decreased		

OAD: Oral antidiabetic drug, GI: Gastrointestinal

DRUG INTERACTIONS

Drug-drug interaction studies are needed to identify exposure, safety and tolerability issues related to the concomitant use of typically prescribed oral medications. In these studies, the absorption pharmacokinetics of four separately administered oral drugs was assessed before and with semaglutide treatment, to evaluate the potential for semaglutide to affect the absorption of co-administered oral drugs. For all of the concomitant medications evaluated in this study, the ratio for total exposure (AUC) was within the pre-specified limits (0.80–1.25), suggesting that there is no drug–drug interactions between semaglutide and the co-administered drugs.[15,16]

Semaglutide did not reduce the bioavailability of ethinyl-estradiol or levonorgestrel. The prespecified bioequivalence criterion was met for ethinyl-estradiol but not for levonorgestrel; mean exposure was 20% higher at semaglutide steady-state. In this study, drug-drug interactions were performed at steady state for both semaglutide (at the highest intended clinical dose level) and the oral contraceptive, according to EMA and FDA guidelines.[14]

Semaglutide has very low potential to induce or inhibit CYP enzymes or to inhibit drug transporters, according to *in vitro* studies.[4] As semaglutide causes a delay of gastric emptying, there is a potential for it to impact the absorption of oral medications administered concomitantly.[4] However, no clinically relevant drug-drug interactions were seen when semaglutide was Coad ministered with metformin, warfarin, digoxin or atorvastatin, as well as with the oral contraceptives ethinyl-estradiol or levonorgestrel. Nevertheless, caution is advised when Coad ministering semaglutide with oral medications.[11]

CONCLUSION

Semaglutide, administered subcutaneously once weekly, provided superior glycemic control and body weight reductions compared with placebo in patients with T2D receiving basal insulin therapy. No unexpected safety issues were identified. Semaglutide was well tolerated, with a safety profile similar to that of other GLP-1 receptor agonist. Semaglutide treatment was well tolerated in Japanese participants with type 2 diabetes. Adverse events were more frequently reported with both doses of semaglutide than with 1 additional OAD, primarily driven by GI AEs; the proportion of participants reporting SAEs was similar across treatment groups. No new safety issues were identified and the safety profile of semaglutide was similar to that of other GLP-1 receptor agonists. In addition, semaglutide treatment significantly reduced HbA_{1c} and body weight, and improved lipids and systolic blood pressure.

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