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REVIEW

Clinical potential of treatment with semaglutide in type 2 diabetes patients

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Abstract

Glucagon-like receptor agonists (GLP-1RAs) are included in current national and international guidelines as second-line treatment especially in patients with type 2 diabetes and concomitant cardiovascular disease (CVD). First-generation GLP-1RAs were two- or once-daily injectables, but longer-acting GLP-1RAs have now been developed for once-weekly administration – e.g., exenatide ER, dulaglutide and semaglutide. With semaglutide, the same prolongation principle as designed in liraglutide is used (spacer and fatty acid chain). However, the similarity to endogenous human GLP-1 is well preserved, sharing 94% homology. It is administered with a simple device and without resuspension before use. The efficacy and safety of semaglutide have been investigated in an extensive clinical development program including more than 9,000 patients with type 2 diabetes. Semaglutide has been compared head-to-head with a dipeptidyl peptidase-4 (DPP4)-inhibitor, GLP-1RAs and basal insulin. Further head-to-head studies are awaiting that compare semaglutide against a sodium-dependent-glucose transporter-2 (SGLT2)-inhibitor. In these studies, semaglutide was found to provide significant and clinically relevant reductions in HbA1c, fasting plasma glucose (FPG), glucose excursions, body weight and blood pressure. The reduction in glycaemic parameters was more pronounced than that in the comparator GLP-1RAs. The rate of hypoglycemia is very low during treatment with semaglutide if not combined with sulphonylureas or insulin. A cardiovascular outcome trial (CVOT) was performed before the approval of semaglutide, at the request of legal authorities. Not only non-inferiority was confirmed, but also superiority compared with placebo used in a population of patients with type 2 diabetes and CVD treated with oral antihyperglycaemic drugs (OADs) and/or insulin with regard to the primary composite endpoint: death from cardiovascular (CV) causes, nonfatal myocardial infarction or nonfatal stroke. The safety of treatment with semaglutide in patients with type 2 diabetes has been extensively investigated. Overall, gastrointestinal side effects dominate, as observed with other GLP-1RAs, and was observed in the same range as for comparator GLP-1RAs. As observed with other GLP-1RAs, side effects such as nausea and vomiting diminished over time during continuous treatment. Regarding microvascular complications, an unexpected increase in diabetes-related retinopathy was observed in the CVOT; Semaglutide Unabated Sustainability in Treatment of Type 2 diabetes' [SUSTAIN 6]), but not in other studies. The reason for this increase is not finally elucidated, but may be due to a nonspecific effect of a rapid decrease in glycaemic parameters in patients with preexisting retinopathy with high HbA1c at the start of the treatment. There is currently a warning in the Summary of Product Characteristics (SmPC) for semaglutide concerning treatment in patients with preexisting retinopathy. Further studies are needed to clarify this.

Keywords: cardiovascular disease, GLP-1, semaglutide, SUSTAIN, type 2 diabetes.

Citation

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Introduction

Type 2 diabetes is a heterogenous disease characterized by insulin resistance and dysfunction of the insulin-producing pancreatic beta-cells.[1] The pathogenesis and nature of disease progression is complex, involving not only the pancreas but also organs and tissues such as the liver, muscles, fat tissue, kidneys and brain. A progressive loss of beta-cell function occurs after years of disease persistence.[2] Type 2 diabetes is associated with the development of microvascular complications such as retinopathy, nephropathy and neuropathy, and an increased risk of cardiovascular disease (CVD). CVD is the main reason for a considerable increase in mortality and morbidity among people with type 2 diabetes.[3]

Modern pharmacologic treatment of type 2 diabetes is targeted against the different organs involved in glucose metabolism, in which a combination of different pharmacologic treatment modalities are needed when disease progression takes place. Treatment to avoid hyperglycaemic symptoms is necessary in some cases. However, most importantly, treatment is necessary to avoid or minimize the risk of microvascular complications and CVD. Furthermore, it is deemed necessary to minimize side effects such as hypoglycaemia, potential weight gain and interactions of multipharmacologic therapy. The recent class of GLP-1RAs share many of these beneficial properties.[4] The very recent guidelines from the American and European Diabetes Associations recommend GLP-1RA or sodium–glucose transport cotransporter 2 inhibitor therapy as a second-line treatment after metformin if the patient has an established CVD.[5,6]

Semaglutide is a new second-generation long-acting GLP-1RA for once-weekly subcutaneous use, and was recently approved by the U.S. Food and Drug Administration (FDA) in December 2017 and by the European Medicines Agency (EMA) in February 2018 as an adjunct to diet and exercise in patients with insufficiently controlled type 2 diabetes.[7] The aim of this review is to give an overview and discuss the current evidence of semaglutide: the molecule, pharmacokinetic profile, mode of action and clinical data on the effects and safety of semaglutide in the treatment of patients with type 2 diabetes. To review the published literature, an English language MEDLINE search through August 2019 was performed using the search terms 'semaglutide' and 'type 2 diabetes'.

Molecular structure and pharmacokinetics

The endogenous incretin hormone GLP-1, derived from the gut has a very short half-life of 1–2 minutes in the circulation, subsequently degraded by the enzymes dipeptidyl peptidase-4 (DPP-4) and neutral endopeptidase (NEP).[8] Earlier, GLP-1RAs such as liraglutide and exenatide were designed to have a reduced susceptibility to enzymatic degradation, and would therefore be suitable for once- or twice-daily administration while exerting their antihyperglycaemic effect. More recently, GLP-1RAs such as albiglutide and dulaglutide with longer half-lives have been developed allowing once-weekly administration.

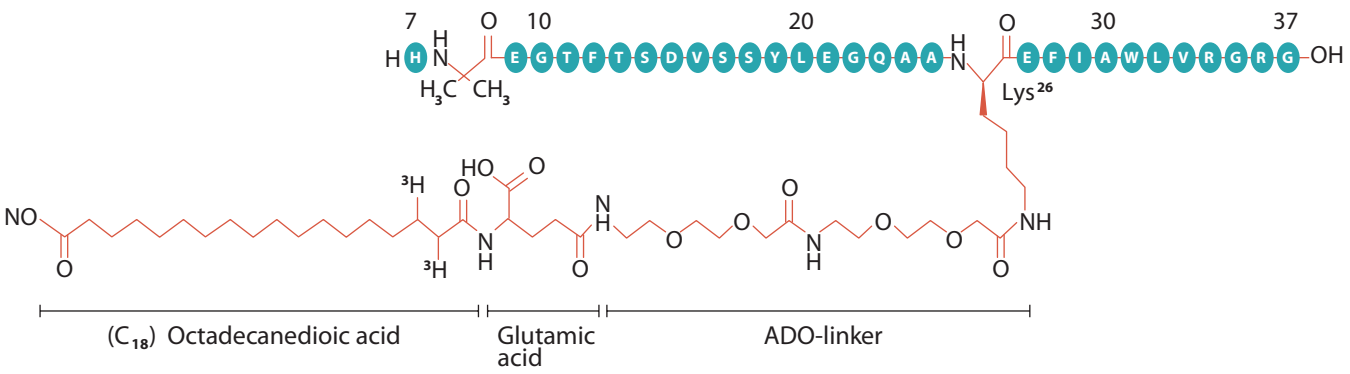
The aim of development of semaglutide was to further optimize the half-life to allow once-weekly dosing without compromising the clinical efficacy in type 2 diabetes patients. Thus, semaglutide shares 94% homology in structure with endogenous GLP-1. There are however three major modifications: substitutions at position 8 (alanine to alpha-aminoisobutyric acid) and at position 34 (lysine to arginine), and acylation of the lysine in position 26 with a spacer consisting of two 8-amino-3,6-dioxaoctanoic acid (ADO) moieties, a glutamic acid moiety and C-18 fatty di-acid side chain.[9] The fatty di-acid side chain and spacer mediate strong binding with albumin, whereas the amino-acid substitution at position 34 limits the options for acylation to the one remaining lysine in the sequence. The substitution at position 8 reduces the susceptibility of semaglutide to degradation by DPP-4 (Figure 1).

These modifications taken together result in a prolonged elimination half-life of semaglutide of approximately 168 hours in humans. After subcutaneous administration (0.5 mg), the maximal concentration of semaglutide in the circulation (T_{max}) was observed after 56 hours, and the absolute bioavailability was found to be 89%. Semaglutide is extensively metabolized and excreted as metabolites mainly via the urine (approximately two-thirds) and to a minor degree via faeces (approximately one-third).[10] Exposure of semaglutide is however not significantly affected by mild, moderate or severe renal impairment, or by impaired hepatic function.[11]

Mode of action

As a GLP-1RA, semaglutide has been shown to act similarly to the naturally occurring GLP-1. GLP-1 acts through the

Figure 1. Molecular structure of the GLP-1RA semaglutide.



Adapted from Jensen et al.[10]

glucagon-like peptide-1 receptors (GLP-1R), which belongs to the superfamily of G protein-coupled receptors. This receptor has been shown to be expressed widely in different tissues both in humans and other primates. Thus, GLP-1R seems to be distributed in the pancreas, gastrointestinal tract, kidneys, lungs, heart, brain and blood vessels of several organs.[12] The potentiation of glucose-stimulated insulin secretion is thought to be the primary mode of action for semaglutide, like GLP-1, in glucose homeostasis. However, semaglutide also regulates glycaemia by insulin-independent mechanisms. At the same time of potentiation of insulin secretion from the pancreatic beta-cells, semaglutide suppresses glucagon secretion from the pancreatic alpha-cells and inhibits gastric emptying rate. The combined effect results in reduced (hyper)glycaemia by enhanced glucose disposal in peripheral tissues, reduced hepatic glucose production and a reduction in postprandial glucose (PPG) excursions.[13,14] Mediated by the central nervous system, semaglutide induces increasing satiety and reduced food intake resulting in weight loss.[15] Thus, the induced weight loss by semaglutide seems to be mediated by several factors such as reduced appetite, improved control of eating with less food cravings and a diminished preference for fatty, energy-dense foods.[14]

Clinical efficacy

Dose-finding study and other phase II studies

To establish the optimal dose regimen to be used in the phase III clinical study program, a 12-week phase II study was performed.[16] In this trial, 415 patients with type 2 diabetes were randomized to once-weekly subcutaneous injections of semaglutide with stable doses of 0.1, 0.2, 0.4 and 0.8 mg or with dose escalation from 0.4 to 1.6 mg *versus* liraglutide (1.2 or 1.8 mg daily) *versus* placebo. The trial showed after 12 weeks of treatment with semaglutide, a dose-dependent clinically relevant reduction in HbA1c levels and weight. As with other GLP-1RAs, transient dose-related gastrointestinal side effects were observed. The incidence of side effects, primarily gastrointestinal adverse events such as nausea, vomiting and diarrhoea, with 1.6 mg of semaglutide was however considered unacceptably high. Thus, based on the results from this trial, weekly subcutaneous doses of semaglutide of 0.5 and 1.0 mg were selected for the phase III development program.

Two phase II or IIIa studies in Japanese subjects were also performed. A study with 601 patients with type 2 diabetes randomized to either semaglutide 0.5 mg or 1.0 mg once-weekly *versus* additional oral antihyperglycaemic drugs (OADs) showing a significantly greater reduction in HbA1c with the two semaglutide doses after 56 weeks of treatment (secondary endpoint).[17] The second Japanese study randomized 308 patients with type 2 diabetes to either semaglutide 0.5 mg or 1.0 mg once-weekly *versus* sitagliptin 100 mg once-daily. This study found also a significant higher reduction in HbA1c with semaglutide (20.8 and 24.1 mmol/mol, respectively) *versus* sitagliptin (7.7 mmol/mol) after 30 weeks of treatment.[18]

Phase III study program

The clinical development program of semaglutide, termed the 'Semaglutide Unabated Sustainability in Treatment of Type 2 diabetes' (SUSTAIN), consisted of six trials wherein the primary endpoint was change in HbA1c from baseline to the end the of trial (EOT; 30–56 weeks). Furthermore, a CVOT was performed. In total, 8416 patients with type 2 diabetes were studied. An overview of clinical trials is depicted in Table 1. Semaglutide was investigated in different populations with type 2 diabetes, drug-naïve, as well as patients treated with and in combination with metformin, thiazolidinediones, sulphonylureas, other OADs and with insulin. All studies were designed as randomized controlled trials (RCTs) studying the efficacy of semaglutide *versus* placebo, DPP-4inhibitor (DPP4i), other GLP-1RAs and long-acting insulin analogues.

Glycaemic control

Change in glycaemic control, defined as change in HbA1c from the start of the treatment to the EOT, was evaluated as the primary efficacy endpoint in the SUSTAIN 1–5 and 7 trials. An overview of the HbA1c results from these trials is shown in Figure 2. Further prespecified secondary endpoints were changed in FPG and seven-point self-measured blood-glucose profile (SMBG).

In the SUSTAIN 1 trial, semaglutide 0.5 mg and 1.0 mg once-weekly were tested against placebo injections in patients with type 2 diabetes treated with diet and exercise only for 30 weeks.[19] The mean HbA1c at baseline was 64.5±9.3 mmol/mol (8.05±0.85%) (±SD). The patients had a mean diabetes duration for 4.2 years and a mean body mass index (BMI) of 32.9 kg/m^2. After 30 weeks, HbA1c was decreased by 16.0 mmol/mol with semaglutide 0.5 mg and by 17.1 mmol/mol with semaglutide 1.0 mg. In both groups the HbA1c reduction was significantly greater than that in the placebo group, wherein a small reduction of 0.2 mmol/mol was observed. As expected, significantly more patients achieved an HbA1c<53 mmol/mol with semaglutide 0.5 mg (74%) and semaglutide 1.0 mg (72%) *versus* placebo (25%), $p<0.0001$.

The SUSTAIN 2 trial had a different study population and design. In that study, semaglutide 0.5 mg and 1.0 mg once-weekly were tested against the DPP4-inhibitor, sitagliptin, 100 mg once-daily for 56 weeks.[20] The background therapy in this population of type 2 diabetes patients was mainly metformin (99–100%), thiazolidinediones (5–6%) or both (4–5%). The patients were moderately dysregulated with a mean baseline HbA1c of 64.1–65.8 mmol/mol. The mean diabetes duration was 6.4–6.7 years and most patients were obese with a mean BMI of 32.5 kg/m^2. After 56 weeks of treatment, HbA1c fell significantly more with semaglutide 0.5 mg (14.4 mmol/mol)

Table 1. Semaglutide clinical development program.

Study name	Study population	Randomized patients	Study duration	Semaglutide dose	Comparator medication	Primary endpoint
SUSTAIN 1	T2DM, drug-näive, HbA1c 53–86 mmol/mol	n=388 RCT 1:1:1	30 weeks	0.5 mg and 1.0 mg once-weekly	Placebo	HbA1c, change from baseline to EOT
SUSTAIN 2	T2DM, on metformin, thiazolidione or both, HbA1c 53–91 mmol/mol	n=1231 RCT 1:1:1	56 weeks	0.5 mg and 1.0 mg once-weekly	Sitagliptin 100 mg once-daily	HbA1c, change from baseline to EOT
SUSTAIN 3	T2DM, on one or two OADs, HbA1c 47–98 mmol/mol	n=813 RCT 1:1	56 weeks	1.0 mg once-weekly	Exenatide extended release 2.0 mg once-weekly	HbA1c, change from baseline to EOT
SUSTAIN 4	T2DM, on metformin or metformin and SU, HbA1c 53–86 mmol/mol	n=1089 RCT 1:1:1	30 weeks	0.5 mg or 1.0 mg once-weekly	Insulin glargine, starting at 10 IE once-daily, titrated to FPG 4.0–5.5 mM	HbA1c, change from baseline to EOT
SUSTAIN 5	T2DM, on basal insulin with or without metformin, HbA1c 53–86 mmol/mol	n=397 RCT 1:1:1	30 weeks	0.5 mg or 1.0 mg once-weekly	Placebo	HbA1c, change from baseline to EOT
SUSTAIN 6	T2DM, on 0–2 OADs and/or basal insulin or premix insulin, HbA1c > 53 mmol/mol	n=3297 RCT 1:1:1	104 weeks	0.5 or 1.0 mg once-weekly	Placebo	Composite: CV death, nonfatal myocardial infarction, nonfatal stroke
SUSTAIN 7	T2DM, on metformin, HbA1c 53–91 mmol/mol	n=1201 RCT 1:1:1:1	40 weeks	0.5 mg or 1.0 mg once-weekly	Dulaglutide 0.75 mg or 1.5 mg once-weekly	HbA1c, change from baseline to EOT

EOT, end of trial; OAD, oral antidiabetic drugs; SU, sulphonylureas; T2DM, type 2 diabetes mellitus.

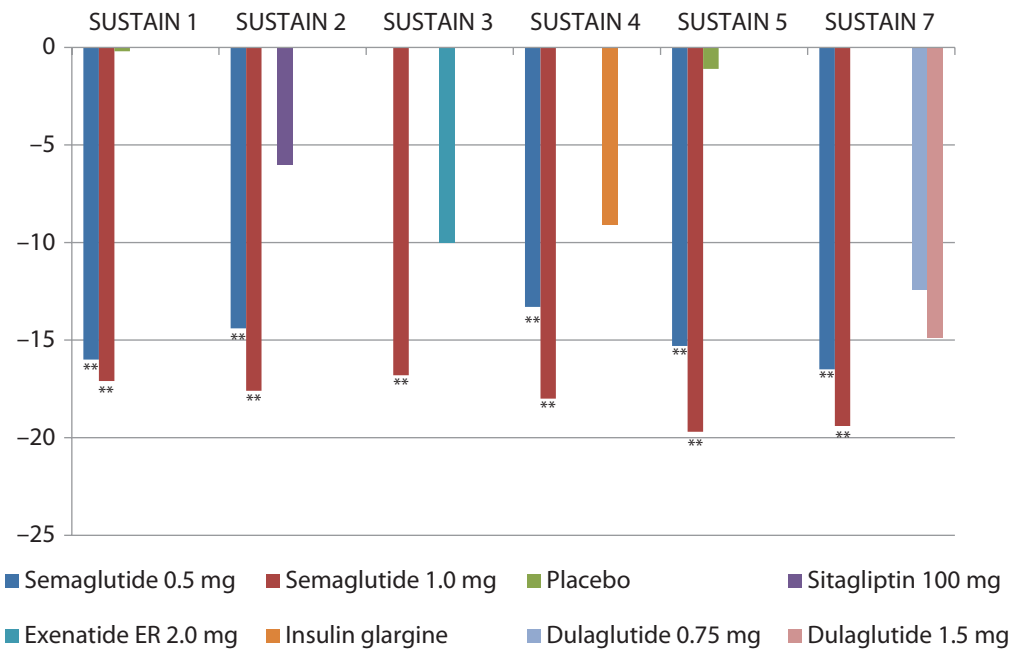
and semaglutide 1.0 mg (17.6 mmol/mol) *versus* sitagliptin 100 mg (6.0 mmol/mol), $p<0.0001$.

The SUSTAIN 3 trial was the first trial studying semaglutide against another GLP-1RA. In the trial, only one dose of semaglutide (1.0 mg once-weekly) was studied against exenatide extended release (exenatide ER) 2.0 mg once-weekly for 56 weeks in addition to the background therapy.[21] The patients were treated with a stable dose of one or two OADs, mainly metformin (96.3–96.8%), sulphonylureas (44.8–51.4%) and thiazolidinediones (1.5–3.2%). The patients had a mean diabetes duration of 9.2 years and as in the other SUSTAIN trials were moderately obese with a mean BMI of 33.8 kg/m^2. After 56 weeks of treatment, HbA1c fell by 16.8±0.68 mmol/mol (±SD) in the semaglutide group *versus* 10.0±0.70 mmol/mol in the exenatide ER group, $p<0.0001$.

In the SUSTAIN 4 trial, semaglutide was investigated against a long-acting insulin analogue, insulin glargine. Patients treated with a stable dose of metformin and/or sulphonylureas were randomized to semaglutide 0.5 mg or 1.0 mg once-weekly or a starting dose of 10 IU insulin glargine, which was titrated according to pre-breakfast plasma glucose target of 4.0–5.5 mmol/l.[22] All patients were insulin-naïve at baseline, had a mean duration of diabetes of 8.6±6.3 year (±SD) and were obese with a mean BMI of 33.0±6.5 kg/m^2. The mean baseline HbA1c was 8.2±0.89 mmol/mmol. After 30 weeks of treatment, HbA1c fell with all three treatments: 13.2 mmol/mol with semaglutide 0.5 mg *versus* 17.9 mmol/mol with semaglutide 1.0 mg *versus* 9.1 mmol/mol with insulin glargine, both semaglutide doses were significantly better than insulin glargine, $p<0.001$. The mean dose of insulin glargine EOT was 29.2±16.0 IU/day and the mean pre-breakfast plasma glucose was 7.1 mmol/l.

Semaglutide was investigated as an add-on to basal insulin therapy in the SUSTAIN 5 study. All patients were at baseline treated with a stable dose of either neutral protamine Hagedorn insulin (NPH insulin), insulin glargine, insulin detemir or insulin degludec alone or in combination with

Figure 2. Change in glycated hemoglobin (HbA1c) (mmol/mol) across the SUSTAIN 1–5 and 7 clinical trials. ** $p<0.001$ *versus* comparator.



metformin.[23] Patients were randomized to either 0.5 or 1.0 mg of semaglutide once-weekly, or placebo. The mean diabetes duration was 13.3 years prior to the study start. Basal insulin doses were 36.6–39.3 IU/day among the three groups at baseline. Insulin dose was reduced by 20% at the study start if HbA1c was ≤63.9 mmol/mol to avoid increase in hypoglycaemia risk. Uptitration was allowed between weeks 10 and 16 in these patients. The mean HbA1c was 67.9±9.0 mmol/mol at baseline. After 30 weeks of treatment, HbA1c fell significantly more with semaglutide 0.5 mg and 1.0 mg once-weekly: 15.8 (1.4%) and 20.2 (1.8%) mmol/mol, respectively, *versus* placebo: 1.0 mmol/mol (0.1%), $p<0.0001$. Insulin doses decreased from baseline to the EOT: in the semaglutide 0.5 mg once-weekly group from 39.3 to 35.4 IU/day, in the semaglutide 1.0 mg once-weekly group from 37.4 to 31.5 IE/day and in the placebo group from 36.6 to 35.2 IU/day.

The second trial wherein semaglutide was studied against another GLP-1RA was the SUSTAIN 7 trial. In this trial, semaglutide was compared head-to-head with dulaglutide. Patients were randomized to once-weekly treatments of semaglutide 0.5 mg or 1.0 mg, or dulaglutide 0.75 mg or 1.5 mg.[24] At baseline, the mean HbA1c was 66.1–67.2 mmol/mol among the four treatment groups. The mean diabetes duration was 7.0–7.7 years and mean BMI was 33.1–33.7 kg/m^2, and all patients at baseline were treated with a stable dose of metformin monotherapy of minimum 1500 mg/day. The follow-up period was 40 weeks. At EOT, HbA1c was significantly reduced in all four groups, however, significantly more with semaglutide *versus* dulaglutide: 16.5 mmol/mol (1.5%) with semaglutide 0.5 mg *versus* 12.1 mmol/mol (1.1%) with dulaglutide 0.75 mg, $p<0.0001$, and 19.4 mmol/mol (1.8%) with semaglutide 1.0 mg *versus* 14.9 mmol/mol (1.4%) with dulaglutide 1.5 mg, $p<0.0001$.

In the SUSTAIN 6 trial (CVOT – see later), the change in glycaemic control after 104 weeks of treatment was also measured. Thus, it can be regarded as long-term data on glycaemic control for treatment with semaglutide. In this study, HbA1c changed from 71.6 to 59.6 (–12.0) mmol/mol after 104 weeks of treatment with 0.5 mg semaglutide once-weekly, and from 71.6 to 56.3 (–15.3) mmol/mol with 1.0 mg semaglutide. This was significantly higher than that in the placebo group (71.6–67.2 (–4.4) mmol/mol), $p<0.001$, despite additional antihyperglycaemic treatment being initiated in this group more often and insulin treatment being initiated more than twice as often as in the semaglutide groups.[25]

The mean FPG and PPG excursions were significantly reduced in some trials with semaglutide 0.5 mg once-weekly *versus* comparators,[19,20,23] whereas these parameters were significantly reduced across all trials with semaglutide 1.0 mg once-weekly.

Beta-cell function and glucagon

As with other GLP-1RAs, semaglutide was associated with increased beta-cell function measured as fasting C-peptide levels and decreased levels of glucagon. Homoeostatic model assessment of beta-cell function (HOMA-B) and insulin resistance (HOMA-IR) were calculated in some studies. HOMA-B was found to be increased and HOMA-IR was found to be decreased with semaglutide in SUSTAIN 1–3.[19–21] HOMA-IR was also significantly decreased compared with exenatide ER.[21]

Fasting proinsulin-to-insulin ratio, which is elevated in most patients with type 2 diabetes and the magnitude of elevation is associated with decreased insulin secretory capacity.[26] This parameter was calculated and found to be significantly reduced with semaglutide in SUSTAIN 1–3, thus supporting an improvement in beta-cell function in these subjects.[19–21]

Body weight and weight control

The effect of semaglutide on change in body weight was evaluated as a secondary confirmatory endpoint in the SUSTAIN 1–5 and 7 trials.[19–24] The results are summarized in Figure 3.

Both doses of semaglutide (0.5 mg and 1.0 mg once-weekly) showed consistently significant and clinical meaningful reductions in body weight after 30–56 weeks of treatment. Thus, treatment with 0.5 mg semaglutide produced a weight reduction of 3.5 to 4.6 kg across the trials, which corresponded to 3.7–4.8% weight loss from the baseline body weight. Treatment with 1.0 mg semaglutide resulted in weight reductions of 4.5 to 6.5 kg corresponding to weight losses of 4.7–7.0% of initial body weights across trials. Weight reductions with semaglutide 0.5 mg and 1.0 mg were significantly greater than those observed with placebo and sitagliptin 100 mg/day.[20] Semaglutide 1.0 mg also resulted in significantly greater weight reductions than with the other GLP-1RAs: exenatide ER 2.0 mg once-weekly and dulaglutide 1.5 mg once-weekly.[21,24] As expected, in the trial comparing semaglutide with insulin glargine, a minor weight gain was observed with insulin and a weight reduction with semaglutide.[22] However, interestingly, a significant weight loss was also obtained with semaglutide as add-on to ongoing basal insulin therapy, which is generally associated with weight gain.[23,27]

Long-term data (104 weeks) as observed in the SUSTAIN 6 trial showed a weight reduction with 0.5 mg semaglutide of 3.6 kg (3.9%) and with 1.0 mg semaglutide of 4.9 kg (5.3%), $p<0.001$ *versus* placebo. This weight reduction was sustained throughout the treatment follow-up period.[25]

Blood pressure, CV risk markers and pulse rate

Both doses of semaglutide (0.5 and 1.0 mg) were associated with reductions in systolic blood pressure which was clinically meaningful across the trials. The effect of semaglutide was significantly greater than the comparators in all trials, except SUSTAIN 1[19] (drug-naïve subjects with short diabetes duration) and SUSTAIN 7[24] (*versus* the GLP-1RA dulaglutide). The systolic blood pressure reduction amounted from 2.4 to 5.1 mm Hg with semaglutide 0.5 mg and from 2.7 to 6.3 mm Hg with semaglutide 1.0 mg. The overview of change in systolic blood pressure is shown in Figure 4. Diastolic blood pressure was also reduced with semaglutide, although to a lesser extent, and generally not significantly different from comparators, except in SUSTAIN 7 wherein the reduction was significantly greater with semaglutide *versus* dulaglutide.[24]

High-dose (1.0 mg) semaglutide was associated with improvements in lipid parameters, which was significant in some, but not all studies. Thus, a significant reduction in the total cholesterol and low-density lipoprotein (LDL) was observed in SUSTAIN 1 and 4,[19,22] reductions in free fatty acids in SUSTAIN 1 and 3[19–21] and that in triglycerides in SUSTAIN 3 and 4.[20–22] Furthermore, a significant increase in high-density lipoprotein (HDL) and a significant reduction in very low-density lipoprotein (VLDL) were observed in SUSTAIN 2.[20]

Figure 3. Change in body weight (kg) across the SUSTAIN 1–5 and 7 clinical trials. ** $p<0.05$ *versus* comparator.

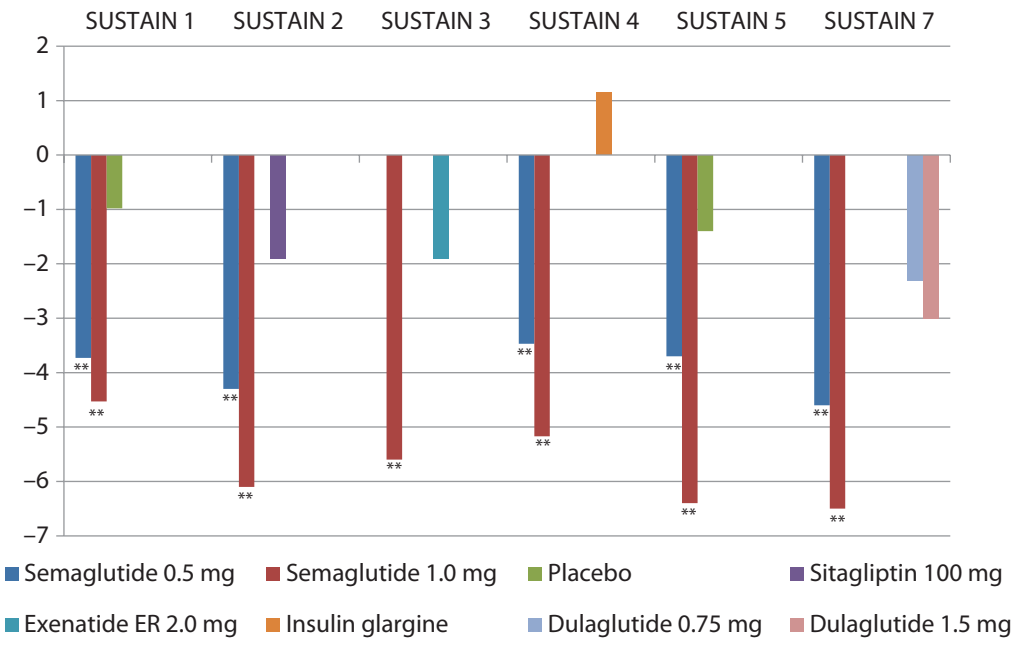
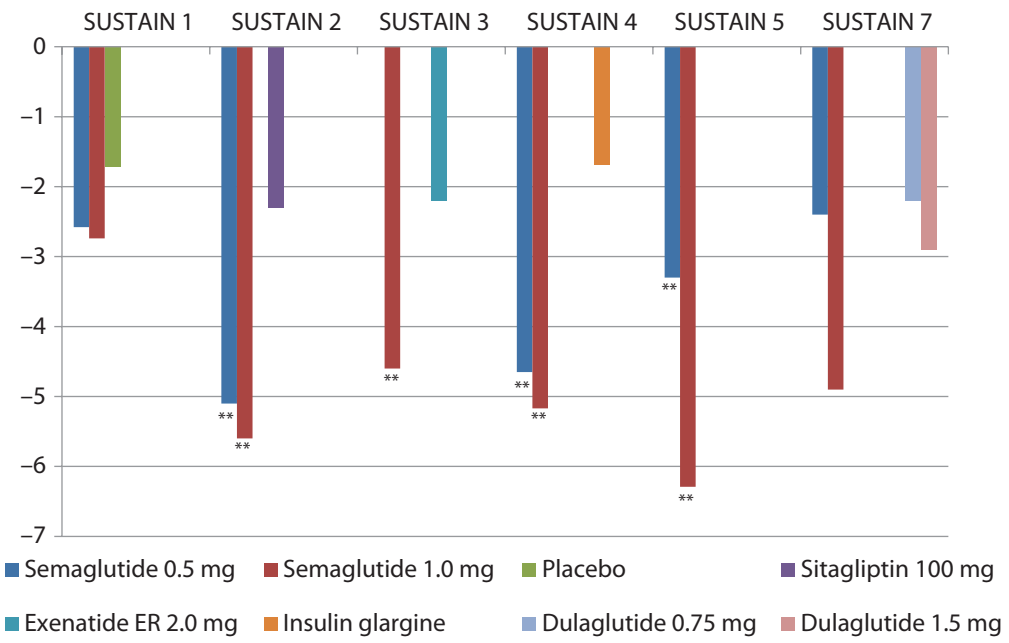


Figure 4. Change in systolic blood pressure (mm Hg) across the SUSTAIN 1–5 and 7 clinical trials. ** $p<0.05$ *versus* comparator.



C-reactive protein, regarded as a biomarker for atherosclerosis and cardiovascular risk,[28] was investigated in SUSTAIN 2 and 4 and was found significantly reduced by semaglutide (0.5 and 1.0 mg) *versus* comparators.[20,22]

Across all studies, semaglutide was associated with a small but consistent increase in pulse rate of 1–4 beats per minute. This phenomenon has been consistently observed with other GLP-1RAs[4], and was found similarly in the comparator studies with semaglutide *versus* other GLP-1RAs, except SUSTAIN 7 wherein a significant higher increase in pulse rate was observed with semaglutide 1.0 mg *versus* dulaglutide 1.5 mg once-weekly (change of 4.0 *versus* 2.4 beats per min).[24]

CV outcomes

Both the U.S. FDA and the EMA have made it mandatory that the pharmaceutical industry should conduct independent CVOTs to specifically assess CV safety of a new antihyperglycaemic drug during its development. Semaglutide was evaluated in the CVOT: Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Type 2 diabetes patients (SUSTAIN 6).[25] This trial was a pre-approved randomized, double-blind, placebo-controlled, multicenter study conducted from 2013 to 2016. In this CVOT, patients were randomized to two doses of semaglutide, 0.5 mg and 1.0 mg once-weekly, or placebo, in addition to the standard therapy. The patient inclusion criteria in this trial were very similar to the LEADER CVOT evaluating liraglutide.[29] Thus, the patients enrolled were ≥50 years type 2 diabetes and established CVD patients, either coronary heart disease, CVD, peripheral vascular disease, chronic kidney disease (stage 3 or higher), or chronic heart failure of New York Heart Association classes II–III. Patients >60 years of age with at least one CV risk factor were also included. Major exclusion criteria in the trial were recent treatment with DPP-4 inhibitors, other GLP-1RAs or fast-acting insulin, a history of an acute coronary or cerebrovascular event within 90 days before screening, or long-term dialysis treatment. The primary composite CV outcome was death from CV causes, nonfatal myocardial infarction or nonfatal stroke. The patients in the four groups were well balanced at baseline. The follow-up time was 25 months. During the treatment period semaglutide 0.5 mg and 1.0 mg significantly reduced HbA1c levels by 7.7 (1.1%) and 11.1 (1.4%) mmol/mol, respectively. The primary endpoint occurred in significantly fewer patients in the semaglutide combined group *versus* that in the placebo group (6.6% *versus* 8.9%), HR 0.74 (95% CI 0.58 – 0.95); (p=0.02 for superiority). For the different entities in the composite endpoint no significant differences were found, except for nonfatal stroke which occurred in 1.6% of the patients in the semaglutide group *versus* 2.7% in the placebo group, HR 0.61 (95% CI 0.38 – 0.99). The hospitalization rate for heart failure was similar in the two groups: 3.6% *versus* 3.3% (semaglutide *versus* placebo). Despite the fact that the number of patients in the SUSTAIN 6 trial were fewer and the follow-up time was shorter than for liraglutide in the LEADER trial, SUSTAIN 6 shows that treatment with semaglutide significantly reduced CV events in a population of high-risk patients with type 2 diabetes.

Clinical safety

As depicted in Table 1, more than 8,400 patients with type 2 diabetes were included in the clinical development program in which safety parameters were assessed (8 clinical trials).

The rate of discontinuations due to adverse events (AEs) were generally low (5–13%) in the SUSTAIN 1-5 and 7. A somewhat higher discontinuation rate was observed in SUSTAIN 6 (approximately 20%), but the duration of this trial was longer (see Table 1). The discontinuation rate was higher with semaglutide *versus* placebo, sitagliptin and insulin glargine (SUSTAIN 2, 4 and 5), but was comparable with exenatide ER and dulaglutide (SUSTAIN 3 and 7). The predominant AE with semaglutide which resulted in discontinuation from the trials were gastrointestinal AEs.[19–24,29] Thus, nausea (reported by 11–24% of the patients), diarrhoea (reported by 5–19% of the patients) and vomiting (reported by 4–14% of the patients) were the most frequent AEs in subjects treated with semaglutide. This was as expected and consistent with the gastrointestinal safety profile of other GLP-1RAs.[30] Compared with the GLP-1RA head-to-head comparators, semaglutide was associated with similar or slightly higher rates of gastrointestinal AEs, but diminished over time.[21,24]

To avoid or diminish gastrointestinal AEs, a titration regimen is recommended in the SmPC starting with 0.25 mg semaglutide once-weekly for 4 weeks. Thereafter, the dose is increased to 0.5 mg once-weekly for another 4 weeks and then to 1.0 mg once-weekly depending on tolerability and glycaemic effect.

Frequencies of severe hypoglycaemia or blood-glucose confirmed hypoglycaemia (plasma glucose<3.1 mmol/l) were generally very low in trials wherein semaglutide was not combined with insulin or sulphonylurea treatment and comparable with the other GLP-1RAs (1–2%).[19,20,24] In studies wherein semaglutide was administrated in addition to sulphonylureas or insulin, hypoglycaemia rates were higher (4–10%). [21–23] In SUSTAIN 5 wherein semaglutide was added to the basal insulin-treated subjects, hypoglycaemia rates were higher with semaglutide (8.3–10.7%) than placebo (5.3%).[23]

Calcitonin levels had special attention in the trials, as GLP-1 activation has been associated with increased levels potentially leading to the development of thyroid C-cell carcinomas in rodents.[31] In the SUSTAIN trials, neither elevated calcitonin levels were observed nor cases of medullary thyroid carcinoma. An even distribution of other benign or malignant neoplasms was observed in the semaglutide groups *versus* comparator groups.[19–25]

Amylase and lipase levels increased significantly during semaglutide treatment across all studies; however, the incidence of pancreatitis was low with semaglutide (<1%) and similar to comparator treatments.

With regard to microvascular complications, opposing results were observed in the long-term trial, SUSTAIN 6. After 104 weeks of treatment, a significantly decreased rate of new or worsening of existing diabetic nephropathy was seen with semaglutide *versus* placebo (3.8% *versus* 6.1%, hazard ratio (HR) 0.64, $p<0.01$). Conversely, an increased rate of diabetic retinopathy was observed with semaglutide *versus* placebo (3.0% *versus* 1.8%, HR 1.76, $p=0.02$).[25] However, in the SUSTAIN 1–5 and 7 trials diabetic retinopathy was not observed to increase. The reason for this finding is not finally elucidated. Post hoc analyses of the data from SUSTAIN 6 and the other SUSTAIN trials found that the majority of this effect could be explained by the magnitude of HbA1c elevation at baseline and the rapidity of reduction of HbA1c during the first 16 weeks of treatment in subjects with preexisting retinopathy.[32] Worsening of preexisting retinopathy associated with rapid and marked decrease in HbA1c have been observed earlier in patients treated with intensive insulin therapy, bariatric surgery and pregnant women.[33–35]

Recent studies and future aspects

Semaglutide in its current formulation as an injectable medication has recently been investigated in other patient populations as well as being evaluated against other comparators. Thus, the SUSTAIN 8–10 trials were recently finalized. In SUSTAIN 8, semaglutide 1.0 mg once-weekly was evaluated *versus* canagliflozin 300 mg once-daily in patients with type 2 diabetes ($n=788$) not sufficiently controlled on metformin treatment. The results from this trial, which were published very recently, showed that semaglutide was superior to canagliflozin in reducing HbA1c with an estimated treatment difference of −5.34 mmol/mol (−0.49%).[36] In SUSTAIN 9, the patient population studied was type 2 diabetes patients inadequately controlled on treatment with an SGLT2-inhibitor, with or without metformin or sulphonylurea treatment. Patients were randomized ($n=302$) to either semaglutide 1.0 mg once-weekly or placebo. The results from this trial was also published very recently.[37] Patients treated with semaglutide as an add-on to SGLT2-inhibitor therapy reduced HbA1c by 15.5 mmol/mol (1.42%) compared with placebo. In SUSTAIN 10, semaglutide was investigated *versus* liraglutide in patients with type 2 diabetes treated with up to three different OADs. In total, 577 patients not sufficiently controlled on OADs were randomized to either semaglutide 1.0 mg once-weekly or liraglutide 1.2 mg once-daily. The results from this comparative trial showed a significant reduction in HbA1c with semaglutide *versus* liraglutide with an estimated treatment difference of –7.5 mmol/mol (–0.69%).[38]

A new tablet formulation for oral administration of semaglutide has been developed.[39] Once-daily oral semaglutide has been investigated and the pharmacokinetic profile has been established.[40] A dose-finding study is finalized.[41] Oral semaglutide 7 and 14 mg once-daily has recently been extensively studied against different comparator drugs including injectable GLP-1RA (liraglutide) in the PIONEER trial program. Results from these studies are now available and published.[42–45] A large-scale CVOT ($n=3,183$ patients with type 2 diabetes) is also completed and recently published.[46,47]

On the basis of the evaluation of the results from these studies, oral semaglutide was approved by the U.S. FDA on September 20, 2019, for the treatment of patients with type 2 diabetes as the first oral formulation of a GLP-1RA.

Conclusion

Semaglutide is approved for the treatment of adults with insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise, either as monotherapy when metformin is not appropriate or not tolerated, or in addition to other antihyperglycaemic drugs. The approval was granted by the U.S. FDA in 2017 and the EMA in 2018. Semaglutide is a new, promising and efficient GLP-1RA with an excellent CV profile. Semaglutide also shows potential in reducing microvascular complications such as diabetic nephropathy, although the observation concerning a potential worsening of diabetic retinopathy in some individuals needs to be further clarified. Injectable semaglutide is administered once-weekly and may be combined with other OADs in the treatment of type 2 diabetes. However, in the near future, the first GLP-1RA, semaglutide, for oral administration will be available, which will potentially increase the number of patients who could benefit from this drug.

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