



Queensland University of Technology
Brisbane Australia

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[Doggrell, Sheila](#)
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Sgemaglutide in type 2 diabetes - is it the best glucagon-like peptide 1 receptor agonist (GLP-1R agonist)?

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Semaglutide in type 2 diabetes – is it the best glucagon-like peptide 1 receptor agonist (GLP-1R agonist)?

Abstract

Introduction: Glucagon-like peptide-1 (GLP-1) is produced by the gut, and in a glucose-dependent manner stimulates insulin secretion while inhibiting glucagon secretion, reduces appetite and energy intake, and delays gastric emptying. The GLP-1R agonist semaglutide has recently been registered to treat type 2 diabetes.

Area covered: This review is of semaglutide in type 2 diabetes, and considers which properties of this GLP-1R agonist, may be responsible for its clinical outcome benefits.

Expert opinion: The pharmacokinetics of semaglutide make it ideal for once-weekly dosing. SUSTAIN 6 (Trial to Evaluate Cardiovascular and Other Long-term Outcomes With Semaglutide in Subjects With Type 2 Diabetes) showed that semaglutide 0.5 or 1 mg subcutaneously once-weekly reduced cardiovascular outcomes in subjects with type 2 diabetes and cardiovascular disease or risk, mean age 65 years, baseline HbA1c 8.7% and mean body weight of 92 kg. Although, semaglutide may be a useful drug in this population, it increased retinopathy to a small extent and this needs further investigation. Also, it is not known whether semaglutide will improve cardiovascular outcomes in other populations including those with lower ages, HbA1c values, and body weights similar to those included in the unsuccessful clinical outcome trials with the GLP-1R agonists, lixisenatide and exenatide.

Keywords cardiovascular outcomes, exenatide, glucagon-like peptide 1 receptor agonists, liraglutide, lixisenatide, once-weekly dosing, semaglutide

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1. Introduction

In the USA, the prevalence of type 2 diabetes has increased from 8.8% in 1999/2000 to 11.7% in 2013/4 with the increase being limited to individuals with abdominal obesity and those aged ≥ 45 years [1]. Despite the treatments available for type 2 diabetes, about two thirds of the subjects die from heart disease or stroke. Diabetes is also a leading cause of blindness, end-stage kidney failure, and lower limb amputations [2]. Clearly, there is a need for improved treatments for type 2 diabetes, and any new medicines that reduce cardiovascular outcomes will have a huge market.

In subjects with type 2 diabetes, when lifestyle changes have failed to manage the diabetes, medications are used. Metformin is the medication of first choice in subjects with type 2 diabetes. When lifestyle changes and the highest tolerated dose of metformin fail to control the diabetes, other oral anti-hyperglycemic drugs are added and these used to be either a sulfonylurea (e.g. glimepiride) or a thiazolidinedione (e.g. pioglitazone). Recently two other groups of drugs have become available as add-on oral anti-hyperglycaemic drugs and these are the sodium-glucose cotransporter-2 (SGLT2s) inhibitors, or drugs that stimulate the glucagon-like peptide 1 (GLP-1) receptor directly (e.g. the glucagons) or indirectly by prolonging the actions of the endogenous GLP-1 at its receptors i.e. the gliptins. These two groups of drugs are still undergoing extensive development and comparison for their use in the treatment of type 2 diabetes. Finally, when oral medication does not control type 2 diabetes, injectable insulin is added. Despite these medicines, type 2 diabetes is often progressive, with subjects unable to maintain long-term glycaemic control [3]. Also, some of these diabetic medicines (notably insulin and the sulfonylureas) increase body weight, which contributes to the diabetes.

GLP-1 is produced by the gut, and in a glucose-dependent manner stimulates insulin secretion while inhibiting glucagon secretion, reduces appetite and energy intake, and delays gastric emptying. Exenatide was the first GLP-1R agonist to be approved by the FDA for use in the treatment of type 2 diabetes. Although exenatide was approved in 2005, it wasn't until 2017 that the clinical outcomes study was published with this agent showing it had no benefit on cardiovascular outcomes in subjects with type 2 diabetes [4]. In this interval other GLP-1R agonists had been developed, and two (liraglutide [5] and semaglutide [6]) have been shown to have cardiovascular benefits, and one (lixisenatide [7]) has not. This review is of semaglutide in type 2 diabetes, and considers which properties of this GLP-1R agonist, may be responsible for its clinical outcome benefits in this condition.

2. Chemistry

Semaglutide is being developed by Novo Nordisk A/S, Denmark, the company also responsible for the development of liraglutide. Liraglutide has a half-life of 13-15 hours, which makes it suitable for once-daily subcutaneous administration. As exenatide is available in a once-weekly administration, which is an advantage over liraglutide, the company tried to modify liraglutide to make a GLP-1R agonist that was suitable for one-weekly use. However, when the side-chain of liraglutide was modified to increase the affinity for serum albumin, with the intention of increasing the slow release properties from albumin and hence the half-life, there was a loss of affinity for the GLP-1R. Thus, in their discovery of semaglutide, the chemists at Novo Nordisk A/S went back to the structure of GLP-1, and increased the length of the fatty acid moiety which increased the affinity for serum albumin. In the same molecule, two amino acid substitutions of the GLP-1 decreased the affinity of

semaglutide for the GLP-1R three-fold, compared to liraglutide, but semaglutide remained potent at the receptor with an EC_{50} value of 6.2 pM. Importantly, the second N-terminal amino acid substitution reduced the susceptibility to degradation by dipeptidyl peptidase-4 (DPP-4) making a longer acting molecule [8].

3. Pharmacokinetic studies

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, hyperinsulinaemic and obese model of type 2 diabetes, over 50 hours, semaglutide was more effective than liraglutide at reducing blood glucose [8].

After the sc administration of a single dose of 0.5 mg radioactive [^3H]-semaglutide to seven healthy males, t_{max} was 56 hours, $t_{1/2}$ was 168 hours, and $AUC_{0-infinity}$ was 3123 nmol/h/L. Apparent clearance, CL/F was 0.039 L/h and volume of distribution, V_z/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% [9].

Kidney dysfunction is common in subjects with type 2 diabetes, and may increase the $t_{1/2}$ and C_{max} of some drugs, and lead to hypoglycaemia if the drug is being used to treat diabetes. A single 0.5 mg subcutaneous dose of semaglutide was injected into the thigh (Nordipen[®]) of 56 subjects with varying degrees of renal impairment; 14 with normal creatinine clearance ($CL_{CR} > 80$ mL/min), and 10 subjects in each of the following groups; mild ($CL_{CR} > 50$ and ≤ 80 mL/min), moderate ($CL_{CR} > 30$ and ≤ 50 mL/min), severe ($CL_{CR} \leq 30$ mL/min), and end-stage renal failure requiring haemodialysis. In the subjects with normal kidney function, t_{max} was at 24 hours with plasma concentrations of semaglutide of ~ 8 nmol/L, $t_{1/2}$ was at 183 hours with plasma concentrations of ~ 6 nmol/L, and $AUC_{0-infinity}$ was 2600 nmol/h/L, and these parameters were not significantly altered in kidney impairment. However, two major episodes of hypoglycaemia did occur in one subject without type 2 diabetes who had severe kidney impairment [10].

In another study, 43 postmenopausal women with type 2 diabetes received subcutaneously once-weekly semaglutide at 0.25 mg for 4 weeks, 0.5 mg for 4 weeks, and finally 1.0 mg for 5 weeks. At steady state after the 1 mg dose in postmenopausal women with diabetes, the $AUC_{0-168 h}$, C_{max} , $t_{1/2}$, and t_{max} were 4602 nmol/L, 33.8 nmol/L, 165 hours and 36 hours, respectively. Plasma concentrations of semaglutide remained above 5 nmol/L for 500 hours after steady state had been reached with 1 mg semaglutide. By delaying the rate of gastric emptying, the GLP-1R agonists have the potential to delay the absorption of concomitantly administered medications. For the oral contraceptives, this could lead to unwanted pregnancies. Although, semaglutide did increase the t_{max} for ethinylestradiol, it did not alter the other pharmacokinetic properties (AUC , C_{max} , C_{trough} , $t_{1/2}$, apparent clearance or apparent volume of distribution) of this oral contraceptive agents or levonorgestrel [11].

No serious adverse effects were reported with semaglutide in the postmenopausal women. However, gastrointestinal adverse effects were common with nausea occurring in about a third of women during the 0.5 mg dosing, but then declining as tolerance seemed to have developed by the 1.0 mg dosing of semaglutide. Diarrhoea occurred in 14% of subjects, and vomiting in 9% of the postmenopausal women. There were no injection-site reactions, no effects on calcitonin levels and no antibodies to semaglutide. No cases of severe hypoglycaemia were reported over the 13 weeks, but one subject each had symptomatic and asymptomatic hypoglycaemia. Four of the postmenopausal women had elevations in alanine and aspartate aminotransferase [11].

When a similar protocol to that used to give steady state after 1 mg semaglutide in postmenopausal women was used, in 54 healthy subjects with HbA1c < 6.5%, there were similar pharmacokinetic data; C_{max} 43-49 nmol/L, t_{max} 36 h, $t_{1/2}$ 156-160 h. Semaglutide may have had a minor effect of the absorption but there were no significant effect on the pharmacokinetics of the following drugs; metformin, warfarin, atorvastatin or digoxin. In addition, semaglutide did not alter the anticoagulant activity of warfarin. The most common adverse effect to semaglutide was nausea. No severe hypoglycaemic was reported, but three subjects had symptomatic and one asymptomatic hypoglycaemia [12].

4. Pharmacodynamics, clinical efficacy, and safety

4.1 Phase 1 and 2

The phase I clinical trial of semaglutide in the 43 postmenopausal women with type 2 diabetes, who received escalating doses of semaglutide once-weekly over 13 week, was the first to report the effects on pharmacodynamics. Thus, at the end of treatment, the HbA1c had been reduced 1.1% from a baseline of 7.3%, fasting plasma glucose from 8.4 mmol/L to 6.5 mmol/L, and body weight by 4.3 kg [10]. In subjects with type 2 diabetes, semaglutide escalated to 1 mg sc, had improved beta cell function at 12 weeks [13].

In a phase II clinical trial, once-weekly semaglutide without dose escalation (0.1-0.8 mg) or with dose escalation (0.4 mg steps to 0.6 or 1.6 mg over 1-2 weeks), was compared to open-label liraglutide or placebo in 415 subjects with type 2 diabetes inadequately controlled with diet and exercise, over 12 weeks. The subjects had a mean age of ~55 years and HbA1c of ~8.1%. After a standardized breakfast, the post-prandial rate of gastric emptying was delayed within the first hour by semaglutide, compared to placebo, but there was no overall effect on gastric emptying. By week 12, there was a dose-dependent reduction in HbA1c with semaglutide, compared to placebo, of 0.4, 0.6, 1.0, and 1.2%, with 0.2, 0.4, 0.8 and 1.6 mg, respectively. Body weight was reduced by 0.8, ~2.5 and 3.6 kg, with 0.4, 0.8 and 1.6 mg of semaglutide, respectively. The beneficial effects of semaglutide 0.4 mg were similar to those of liraglutide (1.2 or 1.8 mg), while those of semaglutide 0.8 and 1.6 mg were greater than of liraglutide [14].

As usual, in this phase II clinical trial, gastrointestinal adverse effects were the most common adverse effects with semaglutide, and led to the withdrawal of 40 of the 415 subjects. Nausea, as an adverse effect, increased dose-dependently to occur in 12, 27, 60, 40 and 57% of subjects taking 0.2, 0.4, 0.8 without escalation, 0.8 mg with escalation, and 1.6 mg of semaglutide, compared to 4% with placebo and ~32% with liraglutide. There was no severe hypoglycaemia, but there were eight subjects who had minor hypoglycaemia (< 3.1 mmol/L of plasma glucose) and 11 who reported symptoms-only hypoglycaemia. There were 2 cases of injection-site reactions with semaglutide, and

one subject who developed antibodies to semaglutide. Semaglutide had no effect on blood pressure, but did increase pulse rate by about 4 bpm, which was not significant, and a similar effect to with liraglutide. From these findings the authors concluded that the nausea with 1.6 mg of semaglutide was too high for general use of this dose [14].

4.2 Phase 3

SUSTAIN is a series of phase 3 clinical trials conducted by Novo Nordisk A/S with semaglutide, and the results are given in Table 1. In SUSTAIN 1 (Efficacy and Safety of Semaglutide Once-weekly Versus Placebo in Drug-naïve Subjects With Type 2 Diabetes), subjects who had type 2 diabetes but were not being treated with drugs, were randomised to semaglutide 0.5 or 1 mg and compared to placebo. At week 30, HbA1c was decreased by 1.4 and 1.6%, and body weight was decreased by 2.8 and 3.6 kg by semaglutide at 0.5 and 1 mg, respectively, compared to placebo. There was no severe or blood-glucose-confirmed hypoglycaemia with semaglutide. Small reductions in LDL-cholesterol were observed with the higher dose of semaglutide without effects on HDL-cholesterol or triglycerides. Semaglutide had no effect on blood pressure, but did increase pulse rate. As previously, nausea was the most common adverse effect with semaglutide [16].

SUSTAIN 2 (Efficacy and Safety of Semaglutide Once-weekly Versus Sitagliptin Once-daily as add-on to Metformin and/or TZD in Subjects With Type 2 Diabetes) compared once weekly semaglutide to sitagliptin, as an add-on to metformin, in subjects with poorly controlled type 2 diabetes. The mean HbA1c was reduced by 1.3 and 1.6% by semaglutide at 0.5 and 1 mg, respectively, over 52 weeks, which was significant more than the 0.5% by sitagliptin. Baseline body was reduced 4.3 and 6.1 kg by semaglutide at 0.5 and 1 mg, respectively, and 1.9 kg by sitagliptin. In contrast to previous studies, there was a small decrease in systolic blood pressure from baseline, with little effect on pulse rate, with semaglutide in SUSTAIN 2. Nausea occurred in more subjects with semaglutide than sitagliptin (Table 1; [16]).

SUSTAIN 3 (Efficacy and Safety of Semaglutide Once-weekly Versus Exenatide ER 2.0 mg Once-weekly as add-on to 1-2 Oral Antidiabetic Drugs (OADs) in Subjects with Type 2 Diabetes), study compared semaglutide 1 mg to once-weekly exenatide extended release. HbA1c and body weight was reduced to a greater extent by semaglutide than exenatide (Table 1; [17]). SUSTAIN 4 (Efficacy and Safety of Semaglutide Once Weekly Versus Insulin Glargine Once Daily as add-on to Metformin With or Without Sulphonylurea in Insulin-naïve Subjects With Type 2 Diabetes) compared once-weekly semaglutide to daily insulin glargine as add-on to metformin monotherapy or metformin plus a sulphonylurea in insulin naïve- subjects. HbA1c was reduced to a greater extent by semaglutide than insulin glargine. Severe or blood glucose-confirmed hypoglycaemia occurred in fewer subjects on semaglutide than insulin glargine. Body weight was reduced by semaglutide, while being increased by the insulin glargine. In SUSTAIN 4, diastolic blood pressure was unaffected, but systolic blood pressure was decreased and pulse rate was increases by semaglutide, while being unaffected by the insulin glargine. Nausea occurred more commonly with semaglutide than with insulin glargine (Table 1; [18]).

SUSTAIN 5 (Efficacy and Safety of Semaglutide Once-weekly Versus Placebo as add-on to Basal Insulin Alone or Basal Insulin in Combination with Metformin in Subjects With Type 2 Diabetes) has only been published as an abstract, and was a study of semaglutide as add-on to basal insulin alone

or in combination with metformin in subjects with prolonged diabetes. Once again, this study demonstrated the ability of semaglutide to reduce HbA1c and body weight (Table 1; [19]).

The most important SUSTAIN trial was 6, as this has clinical outcomes. SUSTAIN 6 (Trial to Evaluate Cardiovascular and Other Long-term Outcomes With Semaglutide in Subjects With Type 2 Diabetes) enrolled 3297 subjects with type 2 diabetes and ≥ 50 years old with established cardiovascular disease, chronic heart failure, or chronic kidney disease or an age of ≥ 60 years old with at least one cardiovascular risk factor. Consistent with previous findings, in SUSTAIN 6, semaglutide reduced HbA1c and body weight and increased nausea (Table 1). The primary composite outcome was the first occurrence of death from cardiovascular causes, nonfatal myocardial infarction or nonfatal stroke, and after a median time of 2.1 years, this occurred significantly less with the combined doses of semaglutide (108/1648, 6.6%) than with placebo (146/1649, 8.9%). This reduction was due to a significant reduction in nonfatal stroke (1.6 vs 2.7%), a non-significant reduction in nonfatal myocardial (2.9 vs 3.9%), with no change in cardiovascular deaths (2.7 vs 2.8%). Analysis showed similar findings for a wide range of subgroups: <65 vs ≥ 65 years, BMI ≤ 30 vs > 30 kg/m², baseline HbA1c ≤ 8.5 vs $> 8.5\%$, baseline insulin treatment or not, eGFR < 30 ml/min/1.73m² or not, and for the two doses of semaglutide [7].

For secondary outcomes, semaglutide had no effect of hospitalizations either for unstable angina or heart failure, but did significantly reduce revascularizations (5.0 vs 7.6% in the placebo group). Semaglutide significantly reduced and new or worsening nephropathy (persistent macroalbuminuria, persistent doubling of serum creatinine levels and a creatinine clearance of < 45 mL/min/1.73m²; 3.8 vs 6.1%) but increases retinopathy complications (vitreous haemorrhage, onset of diabetes-related blindness, and the need for treatment with an intravitreal agent or retinal photocoagulation; 3.0 vs 1.8%) [7].

5. Expert Opinion

5.1 Semaglutide successfully registered

Liraglutide was successfully developed for clinical use by Novo Nordisk A/S, but has the disadvantage of having to be used daily. It is impressive that Novo Nordisk A/S has subsequently run a program to develop a GLP-1R agonist that can be used once weekly, and that when they were unable to do this using liraglutide as their lead compound, they went back to first principles to develop an agonist with suitable pharmacokinetic properties to be used weekly. This development led to semaglutide which has recently culminated in Ozempic (semaglutide) 0.5 and 1mg injection being approved for weekly subcutaneous use in type 2 diabetes by the US FDA on 5th December, 2017 [20].

5.2 SUSTAIN 6

The evidence that lead to this registration of semaglutide probably gave great importance to SUSTAIN 6; the study showing that semaglutide reduces cardiovascular outcomes [7]. As in most of the other SUSTAIN trials, 2 doses of semaglutide were used in SUSTAIN 6, 0.5 and 1 mg sc/weekly. In the main body of SUSTAIN 6, the results for the 0.5 and 1 mg doses of semaglutide are combined, which contrasts with the other SUSTAIN trials, in which the results are presented separately. The results for the individual doses are given in the supplementary appendix to SUSTAIN 6 [7]. The graphs for the individual doses show differences in the Kaplan-Meier plots of the control/placebo lines/values for the two doses. In addition, sometimes e.g. in the graph of subjects with non-fatal

myocardial infarction, the difference between the two control/placebo lines is greater than the differences between the control/placebo line and the semaglutide 0.5 mg. Given that the FDA has approved both the 0.5 and 1 mg doses of semaglutide, it seems to me that the data for both doses should be published separately in the body of a journal article with full discussion of significance and differences.

5.3 Variation in clinical efficacy of GLP-1R agonists

Approval of the first glucagon-like peptide-1 receptor (GLP-1R) agonist, exenatide, by the FDA in 2005 generated an expectation that the clinical outcomes in type 2 diabetes would be improved by this agent, but when the Exenatide Study of Cardiovascular Even Lowering (EXSCEL) trial was eventually published in 2017, it did not support this, merely showing non-inferiority to placebo [4]. Another GLP-1R agonist lixisenatide also does not reduce clinical outcomes in subjects with type 2 diabetes and acute coronary syndromes in the Evaluation of Lixisenatide in Acute Coronary Syndrome (ELIXA) trial [5]. In contrast, the GLP-1R agonist liraglutide, which like exenatide was approved and used for 10 years without clinical outcome data [21], has eventually been shown in LEADER (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcomes Results) to reduce cardiovascular deaths and microvascular events [6]. Like liraglutide, semaglutide has been shown to reduce cardiovascular outcomes in subjects with type 2 diabetes (SUSTAIN 6, [7]). Thus, it seems to me that the GLP-1R agonists with positive clinical outcome trials (i.e. liraglutide and semaglutide) should be preferred to those without (exenatide and lixisenatide) in the treatment of type 2 diabetes.

5.4 Given that GLP-1R agonists with given cardiovascular benefits are available, should others be in use?

There are other GLP-1R agonists available for use, which have not had clinical outcomes data published including dulaglutide (Trulicity, Eli Lilly). Dulaglutide was registered by the FDA in September, 2014, and is widely used in the USA. A preliminary report of a head-to-head clinical trial (SUSTAIN 7 [22]) has shown that semaglutide has greater effects in reducing HbA1c and body weight than dulaglutide [23]. A cardiovascular outcomes trial with dulaglutide is underway, REWIND (Researching cardiovascular events with a weekly incretin in diabetes), but is not due for completion to July 2018 [24]. It seems to me that semaglutide should be preferred to dulaglutide presently, and in the future unless/until dulaglutide is shown to have a better beneficial/detrimental cardiovascular outcomes profile than semaglutide.

5.5 Why do some GLP-1R agonists reduce cardiovascular outcomes and others not?

In the absence of comparisons trials of GLP-1R- agonists on cardiovascular outcomes in the same populations, it is only possible to speculate why some of these agents reduce cardiovascular outcomes and others do not. In the trials showing that lixisenatide and exenatide did not reduce cardiovascular outcomes, there were only small reductions in HbA1c and body weight by these agents, compared to the placebo group (Table 2), and these reductions may not have been sufficient to lead to cardiovascular benefits. Liraglutide, which does reduce cardiovascular outcomes, also only had a small ability to reduce HbA1c, but did reduce body weight to a greater extent than lixisenatide or exenatide, compared to placebo (Table 2), and this ability to reduce body weight may have added to the possibility of observing cardiovascular benefit. SUSTAIN 6 enrolled fewer subjects

(3297) than the cardiovascular outcome trials with lixisenatide, liraglutide or exenatide, and this may have contributed to the differences between the trials. Semaglutide caused bigger reductions in HbA1c and body weight, compared to placebo (Table 1) than the other agents involved in cardiovascular outcomes trials (Table 2) and this may have contributed to cardiovascular benefit with this agent. However, by comparing, the data in Tables 1 and 2, it is apparent that the subjects had higher HbA1c values, body weight and were older in the studies with liraglutide and semaglutide, than with lixisenatide or exenatide and to speculate that this may have contributed to the effectiveness of these agents.

Although both liraglutide and semaglutide decreased the composite of cardiovascular outcomes, there were differences between them. Thus, there is only statistical evidence, to date, that liraglutide decreased cardiovascular deaths (liraglutide, 4.7%; placebo, 6.0% [6]; semaglutide, 2.7%; placebo, 2.8% [7]). Both liraglutide and semaglutide significantly reduced non-fatal stroke, but had no significant difference on the rates of non-fatal myocardial infarction [6,7]. Also there were differences between liraglutide and semaglutide with regard to retinal complications with these increasing with semaglutide (section 4.2 [6]), but not with liraglutide (Table 2 [7]). At present, the reason for the increased retinal complications with semaglutide is unknown, and thus, further trials are needed to establish the retinal safety and mechanism of semaglutide.

6. Conclusions

The question posed by the title of this review is “Is semaglutide the best GLP-1R agonist for type 2 diabetes?”. There is not a clear-cut answer to this. At present, in considering the choice of GLP-1R agonist for type 2 diabetes, the ones that have shown clinical benefit (liraglutide and semaglutide) probably should be preferred to those that have not (exenatide and lixisenatide) and to those for which cardiovascular benefit studies are yet to be reported (e.g. dulaglutide). Semaglutide has the advantage of once-weekly dosing, whereas liraglutide has to be administered daily.

It should be remembered that clinical trials are only valid for their population/conditions. SUSTAIN 6 enrolled subjects with type 2 diabetes and cardiovascular disease or risk, mean age 65 years, baseline HbA1c 8.7% and mean body weight of 92 kg, and in this population, semaglutide reduced some of the cardiovascular outcomes. However, semaglutide increased retinopathy to a small extent, and this raises an important question about the safety of semaglutide, which require further investigation. As there is no evidence that liraglutide increases retinopathy, perhaps liraglutide should be preferred to semaglutide in subjects with any signs of retinopathy.

In subgroup analysis undertaken in SUSTAIN 6, it was shown that the findings with semaglutide was consistent between subgroups [7]. However, the subgroups analysed (e.g. HbA1c; $\leq 8.5\%$ vs $> 8.5\%$; age; < 65 years vs ≥ 65 years), were not equivalent to the populations used in the clinical trials with lixisenatide or exenatide; thus it remains unknown as to whether semaglutide would have shown cardiovascular benefit in these populations/conditions. Thus, semaglutide requires further testing in other populations of subjects with type 2 diabetes.

Drug summary box

Drug name Semaglutide (Ozempic)

Phase 3

Indication Type 2 diabetes

Pharmacology description/mechanism of action Glucagon-like peptide 1 receptor agonist

Route of administration Subcutaneous Once-weekly

Chemical structure

Pivotal trial SUSTAIN 6 (Trial to Evaluate Cardiovascular and Other Long-term Outcomes With Semaglutide in Subjects With Type 2 Diabetes); Marso SP, Bain SC, Consoli A et al. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med 2016;375:1834-44

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Table 1. The SUSTAIN phase 3 clinical trials of semaglutide in subjects with type 2 diabetes

Trial	Groups	Population	HbA1c	Body weight	Cardiovascular changes	Adverse effects with semaglutide
SUSTAIN 1 30 weeks [15]	a) Control group b) Semaglutide 0.5 mg sc/ once weekly c) Semaglutide 1.0 mg sc/once weekly	388 subjects not taking drugs for diabetes. Mean age 54 years HbA1c 8.1% Body weight 92 kg	a) Decreased by 0.02% b) Decreased by 1.45% c) Decreased by 1.55%	a) Reduced by 0.98 kg b) Reduced by 3.73 kg c) Reduced by 4.53 kg	No effect on blood pressure Pulse rate; a) Reduced by 0.54 bpm b) Increased by 2.35 bpm c) Increased by 2.43 bpm	Most common = nausea (20 and 24% with semaglutide 0.5 and 1 mg; control, 8%) No severe or blood-glucose confirmed hypoglycaemia
SUSTAIN 2 – 56 weeks [16]	All taking metformin a) Semaglutide 0.5 mg sc/ once weekly b) Semaglutide 1.0 mg sc/once weekly c) Sitagliptin 100 mg	1225 subjects with poorly controlled diabetes Mean age ~55 years HbA1c ~8.1% Body weight 89 kg	a) Decreased by 1.3% b) Decreased by 1.6% c) Decreased by 0.5%	a) Reduced by 4.3 kg b) Reduced by 6.1 kg c) Decreased by 1.9 kg	Small decrease in systolic blood pressure ~3 mmHg but no effect on pulse rate with both doses of semaglutide	Nausea in 18% of subjects taking both doses of semaglutide and 7% with sitagliptin Blood-glucose confirmed hypoglycaemia was ≤ 2% of subjects
SUSTAIN 3 – 56 weeks [17]	Taking one or two oral antidiabetic drugs a) Semaglutide 1.0 mg sc/once weekly b) Exenatide 2.0 mg once weekly	813 subjects with inadequately controlled diabetes Mean age ~57 years HbA1c 8.3% Body weight ~96kg	a) Decreased by 1.5% b) Decreased by 0.9%	a) Reduced by 5.6 kg b) Reduced by 1.9 kg	Pulse rate increased by 2.3 beats/min with semaglutide and 3.3 beats/min by exenatide	Gastrointestinal side effects in 42% with semaglutide and 33% with exenatide Injection-site reactions were lower with semaglutide (1.2%) than exenatide (22.0%)
SUSTAIN 4 30 weeks [18]	Metformin monotherapy or plus a sulfonylurea a) Semaglutide 0.5 mg sc/once weekly b) Semaglutide 1.0 mg sc/once weekly c) Insulin glargine starting at 10 IU	1089 insulin-naïve subjects Mean age ~65 years HbA1c ~8.7% Body weight ~94 kg	a) Decreased by 1.2% b) Decreased by 1.6% c) Decreased by 0.8%	a) Reduced by 3.5 kg b) Reduced by 5.2 kg b) Increased by 1.2 kg	a) Systolic blood pressure decreased by 3.0 mmHg, and pulse rate increased by 2.4 beats/min b) Systolic blood pressure decreased by 3.5 mmHg, and pulse rate increased by 3.2 beats/min c) No effect	Severe or blood-glucose confirmed hypoglycemia: a) 4%, b) 6%, c) 11%. Nausea: a) 21%, b) 22%, c) 4%.
SUSTAIN 5 30 weeks [19]	Basal insulin alone or in combination with metformin a) Placebo	397 subjects with a mean duration of diabetes ~13 years HbA1c 8.4%	a) Decreased by 0.1% b) Decreased by 1.4% c) Decreased by 1.8%	a) Reduced by 1.4 kg b) Reduced by 3.6 kg	a) Systolic blood pressure decreased by 1.1 mmHg and pulse rate decreased by 0.8 beats/min	Severe or blood-glucose confirmed hypoglycemia: a) 5.3%, b) 8.3%, c) 10.7%.

	b) Semaglutide 0.5 mg sc/once weekly c) Semaglutide 1.0 mg sc/once weekly	Body weight ~92 kg		c) Reduced by 6.4 kg	b) Systolic blood pressure decreased by 4.3 mmHg and pulse rate increased by 0.8 beats/min c) Systolic blood pressure decreased by 7.3 mmHg and pulse rate decreased by 4.0 beats/min	
SUSTAIN 6 104 weeks [7]	Standard care plus a) Placebo b) Semaglutide 0.5 mg sc/once weekly c) Semaglutide 1.0 mg sc/once weekly	3297 subjects with cardiovascular disease or cardiovascular risk factor Mean age ~65 years HbA1c 8.7% Body weight 92 kg	a) Decreased by 0.4% b) Decreased by 1.1% c) Decreased by 1.4%	a) Reduced by ~0.6 kg b) Reduced by 3.6 kg c) Reduced by 4.9 kg	a) Systolic blood pressure reduced by ~2.5 mmHg with no change in pulse rate b) Systolic blood pressure decreased by 3.4 mmHg and pulse rate increased by 2.1 beats/min c) Systolic blood pressure decreased by 5.4 mmHg and pulse rate increased by 2.4 beats/min	Occurrence rates of severe hypoglycemia confirmed by plasma glucose testing were similar at ~21% in all groups. Gastrointestinal disorders were lower with placebo (~3%) than with semaglutide (~4.5%)

Table 2 Effects on HbA1c, body weight and cardiovascular outcomes for GLP-1R agonists in subjects with type 2 diabetes

Trial	Groups	Population	HbA1c	Body weight	Cardiovascular outcomes
Lixisenatide in ELIXA [5]	a) Placebo b) Lixisenatide, 10-20 µg, sc, daily	6,068 subjects who had had a myocardial infarction or unstable angina Mean age 60 years HbA1c ~7.65% Body weight 85 kg	Decreased by ~0.3%, compared with placebo	Reduced by 0.6 kg, compared to placebo	Primary outcome of cardiovascular death, myocardial infarction, stroke, or hospitalization for unstable angina occurred in 13.4% in the placebo group and 13.2% in the lixisenatide group, which was non-inferior, but not superior to placebo
Liraglutide in LEADER [6]	a) Placebo b) Liraglutide, 1.8 mg, sc, daily	9,340 subjects with high cardiovascular risk Mean age ~64 years HbA1c 8.7% Body weight 92 kg	Decreased by ~0.4%, compared with placebo	Reduced by 2.3 kg, compared to placebo	Primary outcome of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke occurred in 14.9% in the placebo group, and 13.0% in the liraglutide group, which was non-inferior and superior to placebo Composite of renal or retinal microvascular events was lower in liraglutide than placebo group; 7.6% vs 8.9%, due to reduction in renal events, and no effect on retinal events
Exenatide in EXSCEL [7]	a) Placebo b) Extended-release exenatide 2 mg, sc, once-weekly	14,752 subjects (10,782 with previous cardiovascular disease) Mean age 62 years HbA1c 8.0% BMI 32 kg/m ²	Decreased by 0.6% and 0.5%, in comparison with placebo at 6 months and 5 years, respectively	Reduced by 1.27 kg, compared to placebo	Primary outcome of first occurrence of cardiovascular death, non-fatal myocardial infarction or non-fatal stroke occurred in 12.2% in placebo group and 11.4% in the exenatide group, which was non-inferior, but not superior to placebo