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Comparative efficacy, safety, and cardiovascular outcomes with once-weekly subcutaneous semaglutide in the treatment of type 2 diabetes: Insights from the SUSTAIN 1–7 trials

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Abstract

In individuals with type 2 diabetes, glycaemic control and cardiovascular risk factor management reduces the likelihood of late-stage diabetic complications. Guidelines recommend treatment goals targeting HbA_{1c}, body weight, blood pressure, and low-density lipoprotein cholesterol. Development of new treatments for type 2 diabetes requires an understanding of their mechanism and efficacy, as well as their relative effects compared to other treatment choices, plus demonstration of cardiovascular safety. Subcutaneous semaglutide is a glucagon-like peptide-1 receptor agonist currently approved in several countries for once-weekly treatment of type 2 diabetes. Semaglutide works via the incretin pathway, stimulating insulin and inhibiting glucagon secretion from the pancreatic islets, leading to lower blood glucose levels. Semaglutide also decreases energy intake by reducing appetite and food cravings, and lowering relative preference for fatty, energy-dense foods. Semaglutide was evaluated in the SUSTAIN clinical trial program in over 8,000 patients across the spectrum of type 2 diabetes. This review details the efficacy and safety profile of semaglutide in the SUSTAIN 1–5 and 7 trials, and its cardiovascular safety profile in the SUSTAIN 6 trial. Semaglutide consistently demonstrated superior and sustained glycemic control and weight loss vs all comparators evaluated. In SUSTAIN 6, involving patients at high risk of cardiovascular disease, semaglutide significantly decreased the occurrence of cardiovascular events compared with placebo/standard of care (hazard ratio 0.74, $p<0.001$ for noninferiority). Through a comprehensive phase 3 clinical trial program, we have a detailed understanding of semaglutide's efficacy, safety, cardiovascular effects and comparative role in the treatment of type 2 diabetes.

Keywords: Cardiovascular; Efficacy; Glucagon-like peptide-1 receptor agonist; Semaglutide, SUSTAIN; Type 2 diabetes

Introduction

In individuals with type 2 diabetes (T2D), adequate glycaemic control and cardiovascular (CV) risk factor management reduces the likelihood of late-stage diabetic micro- and macro-vascular complications [1].

However, despite efforts with lifestyle intervention, most patients still require additional pharmacological therapy to achieve and maintain glycaemic control [1]. Although there are numerous pharmacological therapies available for the treatment of T2D, it is estimated that a third to nearly a half of patients still fail to meet their targets for glycaemic control, blood pressure, and low-density lipoprotein cholesterol (LDL-C) levels [2]. Furthermore, there is a need for treatments that maximize efficacy, adherence and improvement in CV risk as well as quality of life [3].

The vast majority (~86%) of patients with T2D are overweight or obese [4]. In such patients, modest (≥5% of body weight) and sustained weight loss has been shown to improve glycaemic control and reduce the need for glucose-lowering medications [5, 6].

Diabetes significantly increases the risk of atherosclerotic CV disease [7, 8]. Since 2008, a number of CV outcomes trials have completed, evaluating the safety profile of new treatments for T2D [9-20]. Differential effects of treatments on glycaemia, weight, hypertension and dyslipidaemia may further influence CV risk [8, 21, 22]. The recent joint ADA/EASD Consensus Report highlights the importance of considering CV disease history early in the diabetes treatment pathway. This is based on the evidence that several SGLT-2 inhibitors and GLP-1RAs improve CV outcomes and progression of renal impairment in patients with T2D at high CV risk [23].

Semaglutide has 94% amino acid sequence homology with native human GLP-1, with several modifications that enable increased binding of albumin and slowed degradation in plasma [24]. Subcutaneous semaglutide is a GLP-1RA currently approved by the FDA [25], EMA [26], Health Canada [27], and Japan's Ministry of Health, Labour and Welfare [28] for the once-weekly treatment of T2D. The phase 3 program (PIONEER) for an oral form of semaglutide is underway with full results from PIONEER 1–6 expected in 2019.

Semaglutide works via the incretin pathway, which stimulates insulin and inhibits glucagon secretion from the pancreatic islets in a glucose-dependent manner, leading to lower blood glucose levels with low risk for hypoglycaemia [29]. Treatment with semaglutide results in weight loss, the mechanism of which is not fully understood, although studies in animal models have shown that liraglutide, another GLP-1RA, can access the central nervous system and likely mediates weight loss through its action on POMC/CART-expressing ARC neurons [30]. Clinically, semaglutide has been shown to lower energy intake by reducing appetite and food cravings, improve control of eating and meal portion size management, and lower relative preference for fatty, energy-dense foods [31].

The SUSTAIN (Semaglutide Unabated Sustainability in Treatment of Type 2 Diabetes) clinical trial program included seven randomized controlled phase 3 trials involving more than 8,000 patients with T2D [14, 32-37]. Six efficacy trials, SUSTAIN 1–5 and SUSTAIN 7, were designed to evaluate the efficacy and safety of semaglutide vs comparators, and covered a broad range of the T2D treatment continuum [32-37]. SUSTAIN 6 was a safety trial designed to evaluate CV and other long-term outcomes with semaglutide in patients with T2D who were at high CV risk [14]. Here, we provide an overview of the efficacy and safety profile of semaglutide in the SUSTAIN 1–5 and 7 clinical trials, as well as its CV safety profile in the SUSTAIN 6 trial.

Overview of the SUSTAIN 1–7 trials

The designs and patient baseline characteristics of the SUSTAIN 1–7 trials have been published previously, and are summarized in Table S1 and S2 (see supplementary materials associated with this article on line) [14, 32-37]. In brief, the six efficacy trials were randomized, parallel-group, multicentre, controlled trials representing a broad range of the continuum of type 2 diabetes care (Table S1 and S2 (see supplementary materials associated with this article on line) [32-37]. SUSTAIN 1, 2 and 5 were double-blinded trials, while SUSTAIN 3, 4, and 7 were open-label. Comparators were placebo (SUSTAIN 1, 5 and 6), sitagliptin (SUSTAIN 2), exenatide extended release (ER) (SUSTAIN 3), insulin glargine (IGlar) (SUSTAIN 4), and dulaglutide (SUSTAIN 7). Two doses of semaglutide were evaluated (0.5 mg and 1.0 mg), except in SUSTAIN 3 where only semaglutide 1.0 mg was evaluated. All semaglutide-treated patients followed a fixed dose-escalation regimen from a starting dose of semaglutide 0.25 mg, with dose doubling every 4 weeks until the trial dose was achieved.

Primary endpoints for SUSTAIN 1–5 and 7 were changes in HbA_{1c} from baseline to the end of treatment [32-37]. Secondary endpoints included changes from baseline in FPG, mean SMBG and SMBG increment [32-37].

Efficacy analyses for SUSTAIN 1–5 and 7 were based on all randomized and exposed patients using on-treatment data collected prior to onset of rescue medication [32-37]. Safety analyses for SUSTAIN 1–5 and 7 were based on all randomized patients who had received ≥1 dose of randomized semaglutide s.c. or placebo [32-37]. Standard safety reporting was performed for all adverse events (AEs). Severe or blood glucose (BG)-confirmed symptomatic hypoglycaemia was defined as an episode that is severe according to the American Diabetes Association classification [38] or BG-confirmed by a plasma glucose value <3.1 mmol/L (56 mg/dL; 1 mmol/L = 18.02 mg/dL), with symptoms consistent with hypoglycaemia.

SUSTAIN 6 was a multicentre, double-blinded CV outcomes trial in which semaglutide 0.5 mg and 1.0 mg was compared against placebo (Table S1; see supplementary materials associated with this article on line) [14]. To date, SUSTAIN 6 is the longest trial with semaglutide, lasting 104 weeks [14]. The primary endpoint was time to first occurrence of a major adverse CV event (MACE), defined as death from CV causes, nonfatal myocardial infarction or nonfatal stroke. In SUSTAIN 6, the primary hypothesis was non-inferiority, compared with placebo. This is confirmed if the upper boundary of the two-sided 95% confidence interval of the hazard ratio is below the non-inferiority margin of 1.8, in line with FDA guidance on the evaluation of CV risk in new therapies for T2D [39]. Testing for superiority for the primary outcome was not pre-specified and there was no adjustment for multiplicity.

Clinical evidence

Baseline characteristics and patient disposition across the SUSTAIN 1–7 trials are summarized in Table S2 (see supplementary materials associated with this article on line) [14, 32-37, 40, 41]. Eight thousand four hundred and sixteen patients with T2D were randomized to once-weekly subcutaneous semaglutide 0.5 mg or 1.0 mg or comparators [14, 32-37]. Over 90% of patients completed each trial [14, 32-37].

Glycaemic control

Changes in HbA_{1c} from baseline to the end of the trial in all the SUSTAIN trials are summarized in **Table I** and **Figure 1a** [14, 32-37]. Across SUSTAIN 1–5 and 7, mean HbA_{1c} decreased from baseline (range 8.1–8.4%) by 1.2–1.5% with semaglutide 0.5 mg and 1.5–1.8% with semaglutide 1.0 mg, vs <0.1–0.4% with placebo and 0.5–1.4% with full doses of active

comparators including sitagliptin, exenatide ER, insulin glargine (treated to target defined as pre-breakfast SMBG of 4.0 to 5.5 mmol/L (72 to 99 mg/dL), with no maximum insulin dose specified) and dulaglutide (**Table I** and **Figure 1a**, all $P < 0.0001$ vs comparators) [32-37]. In SUSTAIN 6, where adjustment of background medications was permitted in all groups, there was still a significant reduction in HbA_{1c} with semaglutide 0.5 mg and 1.0 mg vs placebo (-1.1% vs -0.4% and -1.4% vs 0.4%, respectively) at Week 104 (**Table I** and **Figure 1a**) [14]. Additional analyses of a composite endpoint showed that across SUSTAIN 1–5 and 7, significantly more patients achieved $HbA_{1c} < 7.0\%$ with no weight gain and no severe or BG-confirmed symptomatic hypoglycaemia when treated with semaglutide 0.5 mg (47–66%) and semaglutide 1.0 mg (56–74%) once-weekly vs comparators (7% and 19% with placebo, and 16–58% with active comparators) (all $P \leq 0.0001$) (**Figure 2**) [32-37, 42]. Results for mean FPG, mean SMBG and SMBG increment are shown in Table S3; see supplementary materials associated with this article on line.

Body weight and waist circumference

Across the SUSTAIN trials, semaglutide consistently demonstrated significantly greater body weight reductions from baseline to end of treatment vs all comparators (**Table I** and **Figure 1b**, all $P < 0.0001$) [14, 32-37]. In SUSTAIN 1–5 and 7 (baseline range from 89—95 kg), mean body weight decreased by 3.5–4.6 kg with semaglutide 0.5 mg and 4.5–6.5 kg with semaglutide 1.0 mg, vs a weight reduction of 1.0–1.4 kg with placebo, and 3.0 kg with dulaglutide (SUSTAIN 7) or 1.9 kg with sitagliptin and exenatide ER (SUSTAIN 2 and 3), to a 1.2 kg weight increase with basal insulin (SUSTAIN 4) (**Table I** and **Figure 1b**, all $P < 0.0001$ vs comparators) [32-37]. In SUSTAIN 6, there was also a significant reduction in body weight, from a baseline of 92 kg, of 3.6 kg with semaglutide 0.5 mg and 4.9 kg with semaglutide 1.0 mg vs 0.5 kg and 0.7 kg with placebo at Week 104 ($P < 0.0001$) (**Table I** and **Figure 1b**) [14]. The proportion of patients achieving ≥ 5% or ≥ 10% weight loss was significantly higher in patients treated with semaglutide vs comparators. For example, the proportion of patients achieving ≥ 5% weight loss across SUSTAIN 1–5 and 7 was 37–46% with 0.5 mg semaglutide and 45–66% with semaglutide 1.0 mg, compared with 7–11% with placebo and 5–30% with active comparators ($P < 0.0001$ for all pairwise comparisons between semaglutide 0.5 mg and 1.0 mg vs comparators, **Table I**) [32-37].

Across SUSTAIN 1–5 and 7 trials, semaglutide reduced mean waist circumference from baseline to end of treatment by 3.2–4.3 cm with semaglutide 0.5 mg (SUSTAIN 1, 2, 4, 5 and 7), 4.1–6.0 cm with semaglutide 1.0 mg (SUSTAIN 1–5 and 7), vs 1.9–2.0 cm with placebo

(SUSTAIN 1 and 5), and 2.9 cm with dulaglutide 1.5 mg (SUSTAIN 7) to an increase of 0.2 cm with insulin glargine (SUSTAIN 4) [32-37].

Combined effect on HbA_{1c} and body weight

In a secondary analysis of SUSTAIN 1–5, more patients treated with semaglutide achieved reductions in both HbA_{1c} and body weight vs comparators [32-36, 43]. Across the SUSTAIN trials, between 78% (SUSTAIN 1) and 93% (SUSTAIN 5) of patients receiving 1.0 mg semaglutide showed a reduction in both HbA_{1c} and body weight, while ≤ 2% of patients had no reduction in either. A scatter plot of the individual changes from baseline in HbA_{1c} (%) at end-of-treatment and change from baseline in body weight (%) at end of treatment across SUSTAIN 1–5 is shown in **Figure 3** [32-36, 43].

Blood pressure, pulse and lipid parameters

Across SUSTAIN 1–5 and 7, treatment with semaglutide 0.5 mg and 1.0 mg resulted in similar or significantly greater reductions in systolic blood pressure vs placebo and active comparators (**Table I**) [32-37]. Changes from baseline in diastolic blood pressure were similar between semaglutide 0.5 mg, 1.0 mg, and comparators (**Table I**). Treatment with semaglutide 0.5 mg and 1.0 mg led to an increase in pulse rate of between 0.8 bpm and 4.0 bpm vs changes of -0.8 bpm to 2.4 bpm with placebo and active comparators.

Across SUSTAIN 1–5 and 7, treatment with semaglutide 0.5 mg and 1.0 mg also resulted in similar or significantly improved total cholesterol, LDL-cholesterol, HDL-cholesterol, and triglyceride levels vs placebo and active comparators (**Table I**) [32-37].

CV endpoints

In SUSTAIN 6, the primary outcome of CV death, non-fatal myocardial infarction (MI) or non-fatal stroke occurred in 108 of 1,648 patients in the semaglutide group vs 146 of 1,659 patients in the placebo group (hazard ratio 0.74; 95% confidence interval 0.58–0.95; $P < 0.001$ for non-inferiority). The trial was not powered to show superiority [14]. Analysis of the three components of the MACE composite endpoint showed that semaglutide significantly reduced the risk of non-fatal stroke vs placebo, but not non-fatal myocardial infarction and CV death [14].

Safety profile

The overall incidences of serious AEs across SUSTAIN 1–5 and 7 trials were similar between semaglutide arms vs comparators (Table S4; see supplementary materials associated with this article on line) [32-37]. The proportion of patients reporting an adverse event was similar or higher than comparators, primarily as a result of greater prevalence of GI disorders. The proportion of patients reporting GI disorders ranged from 27% to 44% with semaglutide and 15% (placebo) to 48% (1.5 mg dulaglutide) with comparators (Table S4; see supplementary materials associated with this article on line**; Figure 4**) [32-37, 44]. GI disorders, notably nausea, vomiting and diarrhea, were the most common AE reported by patients receiving semaglutide (Table S4; see supplementary materials associated with this article on line) [32-37]. Most nausea events were generally mild to moderate in severity, and improved over time for most patients [32-37]. In SUSTAIN 6, similar proportions of patients experienced AEs and serious AEs in all four treatment groups (semaglutide 0.5 mg, semaglutide 1.0 mg, placebo 0.5 mg and placebo 1.0 mg) [14]. Incidences of malignant neoplasms, cholelithiasis, elevated lipase and pancreatitis, in SUSTAIN 6 are summarized in Table S4; see supplementary materials associated with this article on line**.**

Across SUSTAIN 1–5 and 7, the reporting of diabetic retinopathy adverse events (AEs) were comparable across treatments and all events were mild to moderate – there were no serious AEs. These trials excluded patients with pre-existing proliferative retinopathy and maculopathy requiring acute treatment [32-37]. However, in SUSTAIN 6, in which there were no exclusion criteria related to diabetic retinopathy and therefore a higher number of patients had diabetic retinopathy at baseline vs other SUSTAIN trials, a greater proportion of diabetic retinopathy adverse events was reported in patients receiving semaglutide vs placebo (Table S4; see supplementary materials associated with this article on line) [14]. This may be linked to semaglutide treatment in SUSTAIN 6 resulting in a more rapid and pronounced reduction in HbA_{1c} vs placebo [45].

Across SUSTAIN 1–7, the proportion of patients who experienced an AE leading to premature treatment discontinuation was higher in those who received semaglutide vs comparators (5–14% vs 1–8% with placebo in SUSTAIN 1, 5 and 6, and 1–7% with active comparators in SUSTAIN 2, 3, 4 and 7, Table S4 (see supplementary materials associated with this article on line) [14, 32-37].

The proportions of subjects who experienced severe or BG-confirmed symptomatic hypoglycaemia across SUSTAIN 1–7 were generally similar or lower with semaglutide vs comparators (**Figure 5**) [14, 32-37]. In SUSTAIN 4, more patients receiving sulfonylureas at

baseline experienced hypoglycaemia vs those who did not receive sulfonylureas at baseline (**Figure 5**) [35]. This was also the case in SUSTAIN 3, in which the majority of hypoglycaemia events were reported in subjects concomitantly receiving sulfonylureas in both the semaglutide and exenatide ER groups [34].

In SUSTAIN 5, where only patients treated with insulin were enrolled, those with baseline $HbA_{1c} \leq 8.0\%$ at screening had a higher rate of severe or BG-confirmed hypoglycaemia with semaglutide compared with placebo, although the proportion of patients in this category who experienced any hypoglycaemia was similar to those with $HbA_{1c} > 8.0\%$ at screening [36].

SUSTAIN 2, 3 and 6 are the only SUSTAIN trials with published data on anti-semaglutide antibodies to date [14, 33, 34]. In SUSTAIN 2, six semaglutide-treated participants developed anti-semaglutide antibodies, which crossed-reacted with endogenous GLP-1 in three participants [33]. These antibodies did not have an *in-vitro* neutralizing effect on semaglutide or endogenous GLP-1 in any patients [33]. In SUSTAIN 3, anti-semaglutide antibodies developed in 13 subjects; none were neutralizing to semaglutide or endogenous GLP-1 [34]. In SUSTAIN 6, antibodies against semaglutide were detected in 30 patients treated with semaglutide [14]. In the majority of patients, antibody formation was transient and only four patients tested positive during follow-up [14].

In trials where injection-site reaction data were published, events with semaglutide ranged from 0–2% in SUSTAIN 3, 6 and 7, vs 12% for exenatide ER (SUSTAIN 3), 1—2% for placebo (SUSTAIN 6) and 1—3% for dulaglutide (SUSTAIN 7) [14, 34, 37].

Patient-reported outcomes were assessed in all trials, with a limitation in interpretation being the open-label design of SUSTAIN 3, 4 and 7. However, these outcomes were assessed in a double-blinded manner in SUSTAIN 2. In this trial, improvements in overall diabetes treatment satisfaction, as measured by the Diabetes Treatment Satisfaction Questionnaire were significantly greater for semaglutide vs sitagliptin (SUSTAIN 2) (P <0.05); the same was true for self-perceived hyperglycaemia (i.e., where the participant felt that their blood sugars had been unacceptably high; $P < 0.05$) with similar observations in the open-label SUSTAIN 3 (vs exenatide ER; $P < 0.05$) and 4 (vs insulin glargine; $P < 0.03$) trials [33-35, 37]. Overall, patients in SUSTAIN 2 were significantly more satisfied with semaglutide as their current treatment vs sitagliptin ($P < 0.05$) and vs exenatide ER and insulin glargine in SUSTAIN 3 and 4 ($P < 0.05$ and $P < 0.03$, respectively) [33-35]. Significantly more patients in SUSTAIN 2 and 3 would recommend semaglutide to others with T2D [33, 34] while significantly more patients in SUSTAIN 3 were satisfied to continue treatment with semaglutide over exenatide

ER [34]. In the open-label SUSTAIN 7 trial, semaglutide 0.5 mg and 1.0 mg demonstrated similar improvements from baseline in patient-reported outcomes as dulaglutide 0.75 mg and 1.5 mg, respectively [37]. Patient perception of unacceptable hyperglycaemia was significantly improved with semaglutide 0.5 mg vs dulaglutide 0.75 mg (ETD −0.32 [95% CI −0.60;−0.04], *P* = 0.0254) and semaglutide 1.0 mg vs dulaglutide 1.5 mg (ETD −0.40 [95% CI −0.68;−0.12], *P* = 0.0049) [37].

Discussion

GLP-1RAs are considered efficacious agents for treating T2D with the added benefit of weight loss and a low risk for hypoglycaemia [1]. In the SUSTAIN 1–5 and 7 trials, semaglutide consistently reduced HbA_{1c}, improved FPG and SMBG profiles, and induced greater weight loss vs comparators, with a lower risk of hypoglycaemia (excluding placebo and sitagliptin) in patients with T2D [32-37]. The SUSTAIN program included head-to-head trials comparing semaglutide with current clinical choices for treatment intensification, with semaglutide demonstrating superior glycaemic control vs a DPP-4 inhibitor (sitagliptin), other once-weekly GLP-1RAs (exenatide ER and dulaglutide), and basal insulin (IGlar) [32-37].

As well as helping patients achieve glycaemic control, it is also important for novel treatments for T2D to demonstrate CV safety [1]. To date, an SGLT-2 inhibitor (empagliflozin) and a GLP-1RA (liraglutide once daily) are the only treatments approved for reducing the risk of CV disease for patients with T2D [1]. The use of agents with proven CV benefits from the SGLT-2 inhibitor and GLP-1RA classes in populations at high CV risk is also highlighted in the 2018 update of the ADA/EASD Consensus Report [23].

Overall, there are now seven CV outcomes trials of GLP-1RAs, three of which have demonstrated CV safety but not superiority (lixisenatide, ITCA 650, and exenatide ER) [15, 16, 46], and four that have demonstrated both CV safety and superiority (liraglutide, semaglutide, albiglutide, and dulaglutide), in terms of MACE reduction [13, 14, 18, 19]. Of the SGLT-2 inhibitors, two have demonstrated CV safety and superiority [11, 12], and one has demonstrated CV safety [20, 47].

In SUSTAIN 6, semaglutide demonstrated CV safety vs placebo [14] and, although not currently indicated [48-50]**,** demonstrated significant reduction in CV events vs placebo/standard-of-care [1]. In the EXSCEL trial, once-weekly exenatide ER showed safety compared with placebo, but did not show superiority (hazard ratio 0.91; 95% confidence interval 0.83–1.00; *P* = 0.06 for superiority) in reducing the incidence of the three-component

MACE outcome [19]. The once-weekly GLP-1RA albiglutide has demonstrated a significant reduction in MACE (hazard ratio 0.78; 95% confidence interval 0.68–0.90; *P* = 0.0006 for superiority) in patients with T2D and established CV disease in the Harmony Outcomes trial [18].

In the LEADER trial the once-daily GLP-1RA liraglutide, showed a 13% reduction in the primary composite endpoint of CV death, non-fatal MI or non-fatal stroke and a 22% reduction vs placebo in death from CV causes with liraglutide vs placebo [13]. However, SUSTAIN 6 had a shorter trial duration than LEADER (2.1 vs 3.8 years) and involved fewer subjects (3,297 vs 9,340) [13, 14]. Hence, further studies with semaglutide may be required to provide additional information on outcomes such as CV death. In addition, the PIONEER 6 trial (NCT02692716) is investigating the CV safety of oral semaglutide in subjects with T2D; this trial completed in 2018 and results are expected in 2019.

These results suggest that semaglutide and liraglutide may share similar mechanisms for the reduction of CV risk by attenuating atherosclerotic progression, which differs from the effect of SGLT-2 inhibitors on CV death [11-14]. This may also be a general effect of the GLP-1RA class, although further research is required to confirm this hypothesis [51].

Another difference between the SGLT-2 inhibitor and GLP-1RA classes is with regards to heart failure (HF). Three SGLT-2 inhibitors have demonstrated a significant reduction in the risk of hospitalization for HF vs placebo in CV outcomes trials: empagliflozin, canagliflozin, and dapagliflozin [11, 12, 20]. Furthermore, in patients with T2D and HF, the use of SGLT-2 inhibitors as second-line treatment is preferred [23]. In the LIVE study, which investigated patients with chronic HF with or without T2D, there was no direct effect of liraglutide on left ventricular systolic function and an increased risk of serious cardiac events was observed [52]. In CV outcomes trials of patients with T2D, the GLP-1RAs liraglutide, semaglutide and albiglutide have shown no significant effect on the risk of hospitalization for HF [13, 14, 18].

Finally, effects of GLP-1RAs on renal outcomes have also gained increasing interest. Both LEADER and SUSTAIN 6 demonstrated a significant reduction in renal outcomes with liraglutide and semaglutide, respectively, with a slower decline in eGFR seen with both liraglutide and semaglutide (*post hoc* analysis of SUSTAIN 6), compared with placebo [13, 14, 53]. In addition, both have demonstrated safety in populations with GFR ≥ 15 mL/min/1.73 m^2 [54]. Furthermore, lower proportions of subjects experienced new or worsening nephropathy with semaglutide vs placebo [14], which may be suggestive of a potential renal protective effect. Current data supporting SGLT-2 inhibitor-mediated

reductions in chronic kidney disease progression are compelling however, and the use of SGLT-2 inhibitors as second-line treatment is preferred in patients with T2D and chronic kidney disease [23].

In addition to the improvements in glycaemic control and in CV safety demonstrated with semaglutide treatment, the clinically meaningful reductions in body weight vs comparators shown in the SUSTAIN 1–5 and 7 trials [32-37] are also key, given the benefits of weight loss on glycaemic control, insulin sensitivity and risk of CV disease [1]. The degree of weight loss achieved with semaglutide 0.5 mg and 1.0 mg was also numerically higher than that reported previously with other GLP-1RAs [55]. These data have been incorporated into treatment guidelines, which now advocate preferential use of semaglutide before other GLP-1RAs if there is a need to promote weight loss [23]. Comprehensively, the semaglutide phase 3 program indicates that semaglutide is efficacious across different background treatments and stages in the treatment continuum [32-37]. Recently, a pooled analysis of the SUSTAIN trials demonstrated that semaglutide treatment had a comparable efficacy and safety profile in elderly (≥ 65 years) patients with T2D vs non-elderly (< 65 years) patients [56].

Safety findings were generally consistent with known effects of GLP-1 RA. Fewer than 10% of patients discontinued treatment with semaglutide due to adverse events, reflecting an overall favourable safety and tolerability profile across the SUSTAIN 1–7 trials [14, 32-37]. As expected for a therapy with a glucose-dependent mechanism of action, rates of hypoglycaemia were generally low. Severe or BG-confirmed symptomatic hypoglycaemia events were fewer or similar with semaglutide vs comparators, irrespective of background OAD treatment, except when combined with sulfonylurea or insulin (SUSTAIN 3, 4 and 5) where higher rates of hypoglycaemia were observed [14, 32-37]. In addition, the rates of pancreatitis-related events across SUSTAIN 1–7 were low and comparable between semaglutide, placebo, and active comparators [14, 32-37].

In SUSTAIN 6, a greater proportion of patients randomized to semaglutide had diabetic retinopathy events vs placebo [14]. However, rates of diabetic retinopathy were balanced between treatments across SUSTAIN 1–5 and 7 [32-37]. In SUSTAIN 6, a greater proportion of patients who experienced worsening diabetic retinopathy had diabetic retinopathy at baseline vs the general trial population [14]. Similar findings have also been reported in the Diabetes Control and Complications Trial (DCCT) for patients with type 1 diabetes, and in the UK Prospective Diabetes Study (UKPDS 33) in newly diagnosed T2D patients; in these studies, rapid and marked reductions in HbA_{1c}, resulting in improved glycaemic control were

associated with transitory worsening of diabetic retinopathy [57, 58]. A *post hoc* mediation analysis suggested that the increase in diabetic retinopathy complications with semaglutide vs placebo may be associated with the large and rapid decline in HbA_{1c} during the first 16 weeks of treatment. Furthermore, most patients with diabetic retinopathy complications had a longer diabetes disease duration, higher HbA_{1c} at baseline and had a history of insulin treatment compared with those who did not [59]. However, further evidence is required to fully understand the effect of semaglutide on diabetic retinopathy. In the meantime, physicians should be aware of the risk of worsening diabetic retinopathy in association with rapid and large glycaemic reductions, particularly in patients also receiving insulin [59]. All patients with a history of diabetic retinopathy should be closely monitored for progression of diabetic retinopathy when a rapid drop in HbA_{1c} is achieved [49].

While each trial was robust in terms of their respective sample sizes to power individual statistical analyses, disparities in trial designs such as varying treatment durations and baseline characteristics among patients across the SUSTAIN 1–7 trials limits any direct between-trial comparisons. Conversely, this is one of the largest analyses of patients treated with a GLP-1RA to date, involving more than 8,000 patients.

Additional trials exploring the potential for semaglutide as an oral therapy for T2D (NCT02863328), and as a potential treatment for obesity (NCT02453711) are planned or ongoing. Also of interest will be the results of SUSTAIN 8, an ongoing phase 3b trial comparing semaglutide and the SGLT2 inhibitor canagliflozin (NCT03136484) and SUSTAIN 9, comparing semaglutide versus placebo as an add-on to SGLT2 inhibitor monotherapy or in combination with either metformin or sulfonylurea (NCT03086330).

Conclusion

In a comprehensive phase 3 clinical trial program with over 8,000 participants, once-weekly semaglutide, a newly approved GLP-1RA, consistently demonstrated greater glycaemic efficacy combined with greater weight loss than comparator therapies, across a broad range of patients with T2D vs all comparators evaluated. The safety profile of semaglutide was similar to that of other GLP-1RAs [60], and the CV safety of semaglutide is now well established. In the SUSTAIN 6 trial involving patients at high risk of CV disease, semaglutide lowered the risk of adverse CV outcomes compared with placebo added to standard of care. Forthcoming and ongoing studies include evaluation of oral semaglutide for T2D, of

subcutaneous semaglutide for the treatment of obesity, and of subcutaneous semaglutide once weekly vs an SGLT2 inhibitor in a head-to-head trial. As the landscape of diabetes therapeutics continues to expand and evolve, it is important for new agents to be evaluated in a way that will inform clinical practice, as has been done with semaglutide, offering an understanding of its comparative efficacy, safety, and cardiovascular effects in patients with T2D.

Appendix supplementary material

Supplementary materials (Table S1-S2-S3-S4) associated with this article can be found at http://www.scincedirect.com at doi . . .

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Declaration of interests

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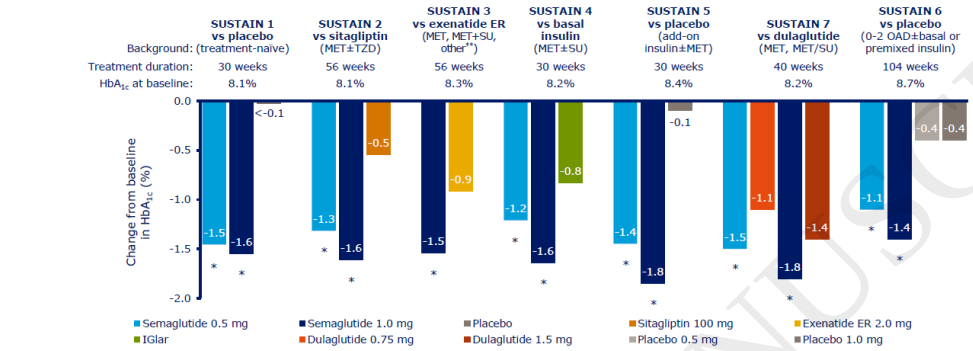
Figure legends

Figure 1. Effect of semaglutide vs comparators in SUSTAIN 1–7 on mean change from baseline in HbA1c (A) and body weight (B)

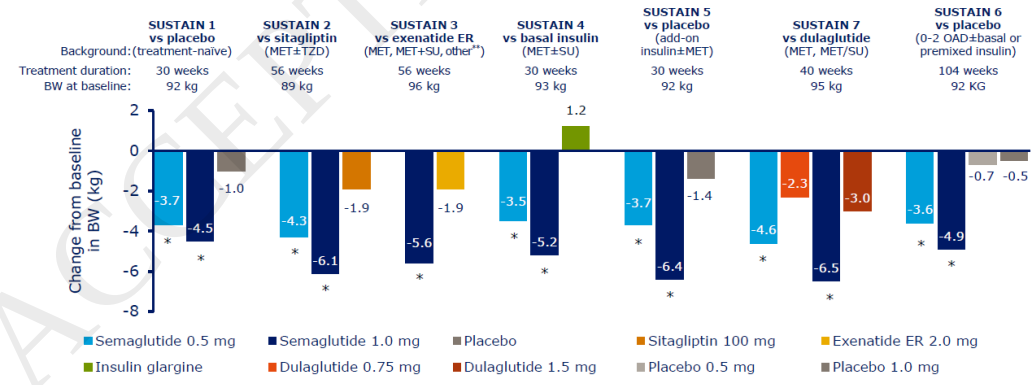
(Figure 1 to be reproduced in colour in print)

FIGURE 1a



*p<0.0001 vs comparator. **TZD, MET+TZD or SU+TZD.
Exenatide ER, exenatide extended release; IGlar, insulin glargine; met, metformin, OAD, oral antidiabetic drug; SU, sulfonylurea; TZD, thiazolidinedione.

FIGURE 1b

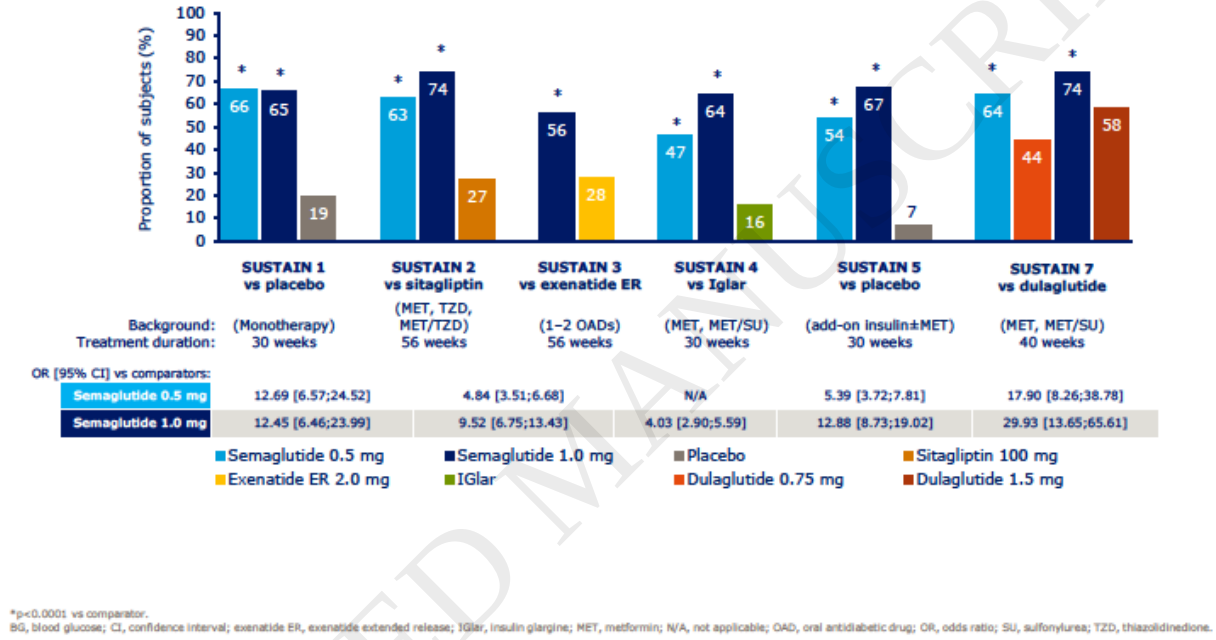


*p<0.0001 vs comparator. **TZD, MET+TZD or SU+TZD.
BW, body weight; exenatide ER, exenatide extended release; MET, metformin; OAD, oral antidiabetic drug; SU, sulfonylurea; TZD, thiazolidinedione.

Figure 2. Patients achieving HbA1c <7.0% with no weight gain and no severe or blood glucose-confirmed symptomatic hypoglycaemia

(Figure 2 to be reproduced in colour in print)

FIGURE 2



*p<0.0001 vs comparator.
BG, blood glucose; CI, confidence interval; exenatide ER, exenatide extended release; IGlar, insulin glargine; MET, metformin; N/A, not applicable; OAD, oral antidiabetic drug; OR, odds ratio; SU, sulfonylurea; TZD, thiazolidinedione.

Figure 3. Scatter plot of individual change from baseline in HbA1c (%) and body weight (%) at end-of-treatment in SUSTAIN 1–5

(Figure 3 to be reproduced in colour in print)

FIGURE 3

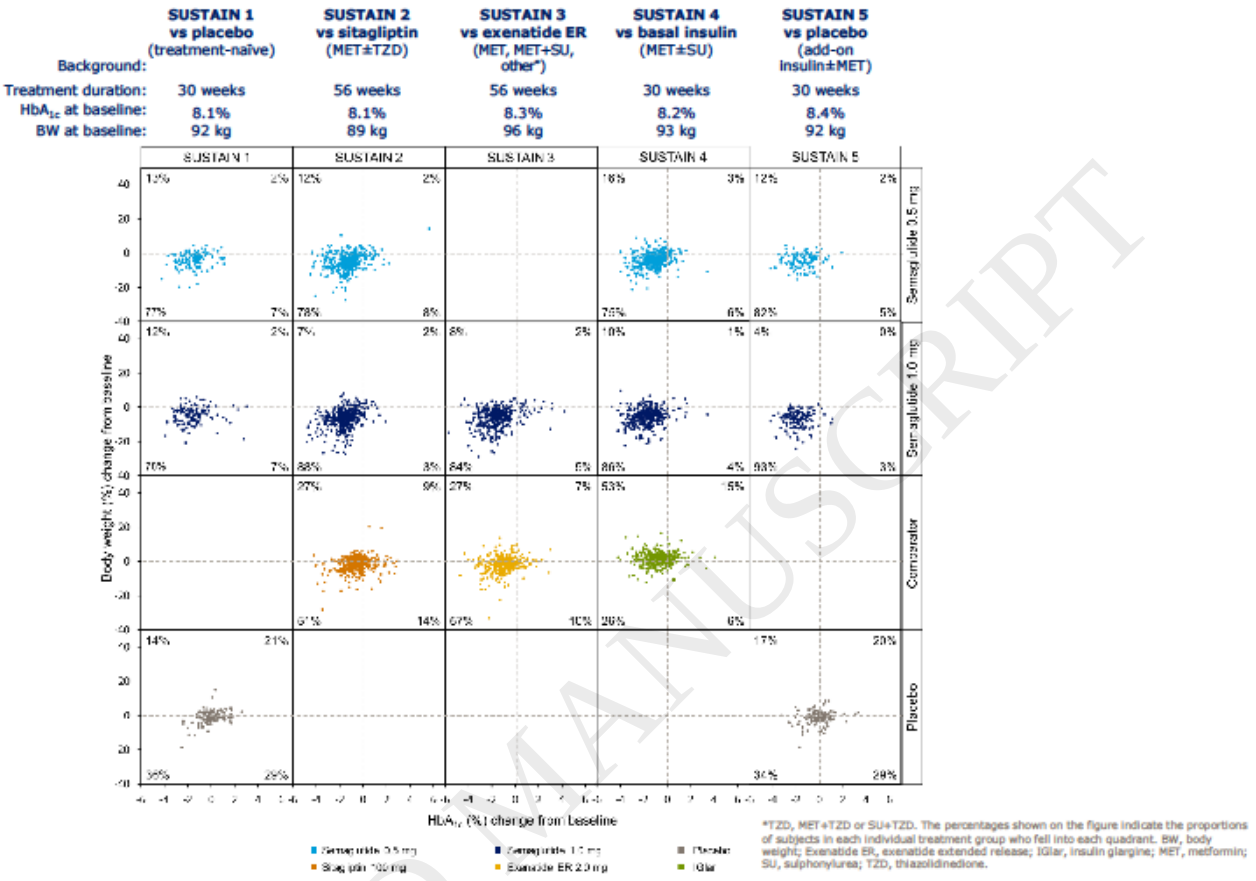
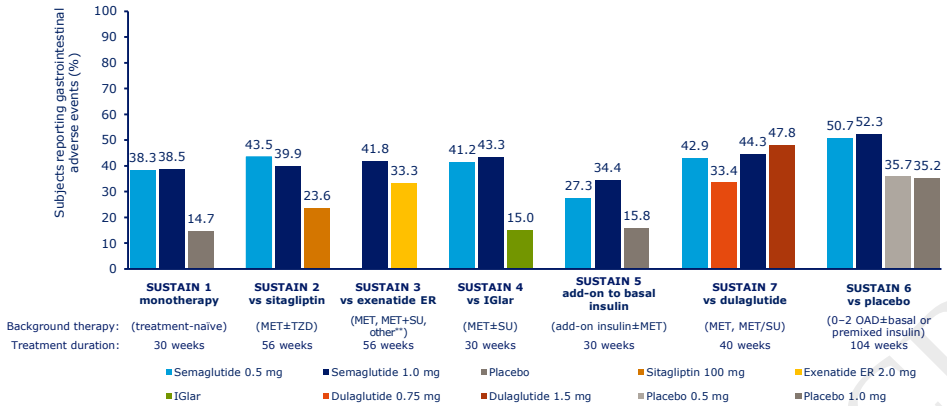


Figure 4. Gastrointestinal disorders in SUSTAIN 1–7

(Figure 4 to be reproduced in colour in print)

FIGURE 4

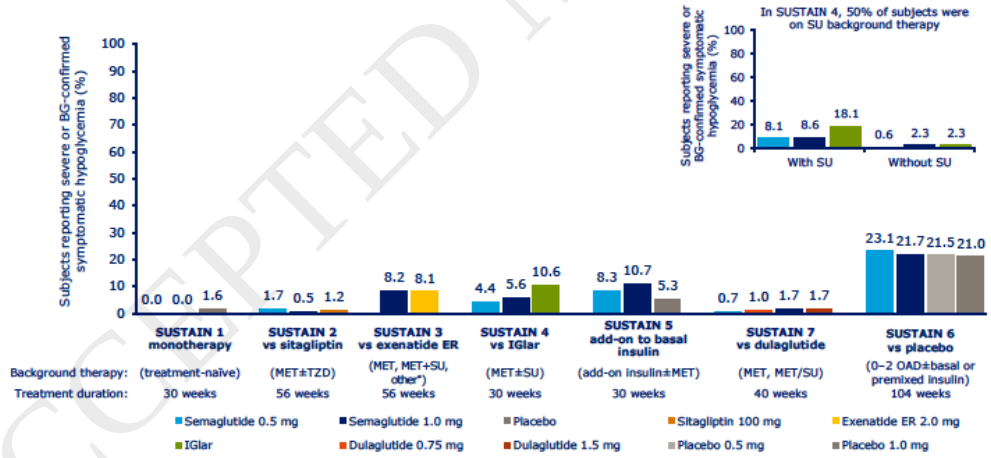


*TZD, MET+TZD or SU+TZD.
ER, exenatide extended release; IGlar, insulin glargine; MET, metformin; OAD, oral antidiabetic drug; SU, sulfonylurea; TZD, thiazolidinedione.

Figure 5. Severe or blood glucose-confirmed symptomatic hypoglycaemia in SUSTAIN 1–7

(Figure 5 to be reproduced in colour in print)

FIGURE 5



*TZD, MET+TZD or SU+TZD.
BG, blood glucose; ER, exenatide extended release; IGlar, insulin glargine; MET, metformin; OAD, oral antidiabetic drug; SU, sulfonylurea; TZD, thiazolidinedione.

Table

Table 1. Change from baseline in HbA_{1c}, body weight, blood pressure, and lipid parameters across SUSTAIN 1-7 and proportion of patients achieving targets

	SUSTAIN 1 monotherapy 30 weeks			**SUSTAIN 2 vs sitagliptin** 56 weeks			**SUSTAIN 3 vs exenatide ER** 56 weeks		**SUSTAIN 4 vs IGlar** 30 weeks			**SUSTAIN 5 add on to basal insulin** 30 weeks			**SUSTAIN 7 vs dulaglutide** 40 weeks				**SUSTAIN 6 vs placebo** 104 weeks			
	Sema 0.5 mg	**Sema** 1.0 mg	**PBO**	**Sema** 0.5 mg	**Sema** 1.0 mg	**Sita** 100 mg	**Sema** 1.0 mg	**Exe** 2.0 mg	**Sema** 0.5 mg	**Sema** 1.0 mg	**IGlar**	**Sema** 0.5 mg	**Sema** 1.0 mg	**PBO**	**Sema** 0.5 mg	**Dula** 0.75 mg	**Sema** 1.0 mg	**Dula** 1.5 mg	**Sema** 0.5 mg	**Sema** 1.0 mg	**PBO** 0.5 mg	**PBO** 1.0 mg
Change from baseline																						
HbA_{1c} (%)	-1.5*	-1.6*	<-0.1	-1.3*	-1.6*	-0.5	-1.5*	-0.9	-1.2*	-1.6*	-0.8	-1.4*	-1.8*	-0.1	-1.5*	-1.1	-1.8*	-1.4	-1.1*	-1.4*	-0.4	-0.4
Body weight (kg)	-3.7*	-4.5*	-1.0	-4.3*	-6.1*	-1.9	-5.6*	-1.9	-3.5*	-5.2*	1.2	-3.7*	-6.4*	-1.4	-4.6*	-2.3	-6.5*	-3.0	-3.6*	-4.9*	-0.7	-0.5
SBP (mmHg)	-2.6	-2.7	-1.7	-5.1*	-5.6*	-2.3	-4.6*	-2.2	-4.7*	-5.2*	-1.7	-4.3	-7.3*	-1.0	-2.4	-2.2	-4.9	-2.9	-3.4	-5.4*	-2.2	-2.8
DBP (mmHg)	-0.5	0.2	0.4	-2.0	-1.9	-1.1	-1.0	-0.1	-1.4	-1.0	-1.4	-1.8	-1.5	-2.2	-0.6	-0.3	-2.0*	<-0.1	-1.4	-1.6	-1.4	-1.7
Pulse (bpm)	2.3	2.4	-0.5	1.6	1.8	0.6	2.1	1.1	2.3	3.1	<-0.1	0.8	4.0	-0.8	2.1	1.6	4.0	2.4	2.1	2.4	0.1	-0.1
Estimated treatment ratio (semaglutide versus comparator)																						
Total cholesterol	0.97	0.92*		0.98	0.98		0.98		0.96*	0.96*		0.95*	0.97		0.96		0.97		0.97*	0.99		
Triglycerides	0.93	0.92		0.98	0.92*		0.87*		0.96	0.94*		0.92	0.90*		0.91		0.86		0.97	0.93*		
HDL	1.01	0.97		1.00	1.04*		1.02		1.00	1.02*		0.99	1.01		0.99		1.01		1.00	1.04*		
LDL	0.99	0.92*		0.96	0.97		0.99		0.94*	0.93*		0.93	0.98		0.97		1.00		0.96*	0.99		
Proportion of patients achieving HbA_{1c} target, composite endpoint and weight loss responses (%)																						
HbA_{1c} <7.0%	74%	72%	25%	69%	78%	36%	67%	40%	57%	73%	38%	61%	79%	11%	68%	52%	79%	67%	NR	NR	NR	NR
Composite endpoint HbA_{1c} <7.0%, no weight gain, no severe or	66%	65%	19%	63%	74%	27%	56%	28%	47%	64%	16%	54%	67%	7%	64%	44%	74%	58%	NR	NR	NR	NR

BG-confirmed hypoglycemia																						
Body weight ≥5%	37%	45%	7%	46%	62%	18%	52%	17%	37%	51%	5%	42%	66%	11%	44%	23%	63%	30%	NR	NR	NR	NR
Body weight ≥10%	8%	13%	2%	13%	24%	3%	21%	4%	8%	16%	2%	9%	26%	3%	14%	3%	27%	8%	NR	NR	NR	NR

*p<0.05 vs (dose-matched) comparator (SUSTAIN 7: semaglutide 0.5 mg vs dulaglutide 0.75 mg and semaglutide 1.0 mg vs dulaglutide 1.5 mg). DBP, diastolic blood pressure; Dula, dulaglutide; ETR, estimated treatment ratio vs (dose-matched) comparators (SUSTAIN 7: semaglutide 0.5 mg vs dulaglutide 0.75 mg and semaglutide 1.0 mg vs dulaglutide 1.5 mg); Exe, exenatide extended release; HDL, high-density lipoprotein cholesterol; IGlar, insulin glargine; LDL, low-density lipoprotein cholesterol; NR, not reported; PBO, placebo; SBP, systolic blood pressure; Sema, semaglutide; Sita, sitagliptin.