Title page

Title: Efficacy and safety of once-weekly semaglutide monotherapy versus placebo in subjects with type 2 diabetes (SUSTAIN 1): a randomised, placebo-controlled phase 3a trial

Authors: Christopher Sorli MD,[1] Shin-ichi Harashima MD PhD,[2] George M Tsoukas MD,[3] Jeffrey Unger MD,[4] Julie Derving Karsbøl MD,[5] Thomas Hansen PhD,[5] Stephen C Bain FRCP[6]

Author affiliations: [1]Billings Clinic Research Center, Billings, MT, USA; [2]Graduate School of Medicine, Kyoto University, Kyoto, Japan; [3]Department of Medicine, McGill University, Montreal, Canada; [4]Catalina Research Institute, Chino, CA, USA; [5]Novo Nordisk A/S, Søborg, Denmark; [6]School of Medicine, Swansea University, Wales, UK

Contact details for corresponding author:

Address: Billings Clinic North 30th, 1045 North 30th Street, Billings, Montana 59101, USA

Tel: +1 406 425 3318

Email: chrissorli@gmail.com

Panel: Research in context

Evidence before this study

- *This study was designed on the basis of evidence collected from the clinical development of semaglutide, including in vitro receptor studies, carcinogenicity studies, pre- and postnatal development toxicity studies, phase 1 single-dose and multi-dose pharmacokinetics/pharmacodynamics studies, and a phase 2 dose-finding trial. A number of long-acting glucagon-like peptide-1 receptor agonists (GLP-1RAs) with pharmacokinetic properties suitable for once-weekly dosing have been approved for the treatment of type 2 diabetes. The currently available products include albiglutide, exenatide extended release and dulaglutide. Biochemical methods of protraction differ and it is currently unknown if the molecular properties of long-acting GLP-1RAs will have differential influences on efficacy or safety parameters. The authors note there is a risk of bias in this literature search, in that mainly positive results may have been publicly reported for compounds with therapeutic implications.*

Added value of this study

- *Semaglutide is a novel once-weekly GLP-1RA. This study demonstrates that semaglutide combines a high degree of glycaemic control with weight loss, without an increased risk of hypoglycaemia. The safety profile of semaglutide appears to be similar to currently available GLP-1RAs, consisting primarily of gastrointestinal events.*

Implications of all the available evidence

- *Semaglutide appears to be a promising treatment for patients with type 2 diabetes. Compared with other currently available once-weekly GLP-1RAs, semaglutide has a low molecular weight and a distinctive method of protraction based on its affinity to albumin. Early results indicate significant improvements in glycaemic control in patients with type 2 diabetes. Indirect comparison of data from this study with other similar GLP-1RA monotherapy trials indicate that the improvements in glycaemic control are at least comparable. The extent of weight loss observed thus far with semaglutide is greater than has been reported for other GLP-1RAs. However, head-to-head trials are needed to draw firm conclusions on the relative efficacy of semaglutide and other GLP-1RAs. The SUSTAIN 2–5 trials assessed the efficacy and safety of once weekly s.c. semaglutide versus widely used active comparators, sitagliptin, exenatide extended release, insulin glargine and as add-on to insulin. Furthermore, the long-term effects of semaglutide on*

efficacy, safety and cardiovascular risk were assessed in the SUSTAIN 6 trial; a dedicated cardiovascular outcomes trial in adults with type 2 diabetes at high risk of cardiovascular disease. This comprehensive clinical trial programme will establish the role for semaglutide as part of the diabetes treatment armamentarium.

Summary

Background

Despite a broad range of pharmacological options for the treatment of type 2 diabetes, optimal glycaemic control remains challenging for many patients and new therapies remain necessary. Semaglutide is a glucagon-like peptide-1 (GLP-1) analogue in phase 3 development for type 2 diabetes. The objectives of this trial were to evaluate the efficacy, safety and tolerability of semaglutide monotherapy compared with placebo, in treatment-naïve subjects with type 2 diabetes who had insufficient glycaemic control on diet and exercise alone.

Methods

SUSTAIN 1 (NCT02054897) was a double-blind, randomised, placebo-controlled phase 3a trial. Treatment-naïve participants aged ≥18 years, diagnosed with type 2 diabetes and with a baseline HbA_{1c} of 7·0–10·0% were recruited and randomised 2:2:1:1 to receive once-weekly subcutaneous semaglutide 0·5 mg, semaglutide 1·0 mg, or volume-matched placebo for 30 weeks. The primary endpoint was change in mean HbA_{1c} from baseline to week 30. The confirmatory secondary endpoint was change in mean body weight from baseline to week 30.

Findings

Subjects were recruited between 3 February 2014 and 21 August 2014. A total of 388 adults were randomised. From a mean baseline HbA_{1c} of 8·1%, 0·5 mg and 1·0 mg semaglutide achieved superior reductions of 1·5% (estimated treatment difference vs placebo [ETD] −1·43%; 95% confidence interval [CI] −1·71, −1·15]; p<0·0001) and 1·6% (ETD −1·53%; 95% CI −1·81, −1·25; p<0·0001) respectively, versus no change for placebo. From a mean baseline of 91·9 kg, 0·5 mg and 1·0 mg semaglutide achieved superior weight loss of 3·7 kg and 4·5 kg, respectively, versus 1·0 kg for placebo (p<0·0001). Drug discontinuation rates due to adverse events were 6% and 5% for 0·5 mg and 1·0 mg semaglutide, compared with 2% for placebo.

Interpretation

Semaglutide was associated with superior improvements in HbA_{1c} and body weight, and demonstrated a similar safety profile to currently available GLP-1RAs, representing a promising treatment option for patients with type 2 diabetes.

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Introduction

Type 2 diabetes is a complex disorder that requires individualised treatment strategies. In addition to diet and lifestyle changes, pharmacotherapy is usually required.[1] A range of therapies are now available for treatment of type 2 diabetes, including orally administered and injectable options.[1] Guidelines recommend avoidance of both hypoglycaemia and weight gain as important therapeutic considerations in selecting treatment and individualising treatment goals.[1,2]

Glucagon-like peptide-1 receptor agonists (GLP-1RAs) stimulate insulin secretion and inhibit the release of glucagon in a glucose-dependent manner, which results in improved blood glucose levels combined with a relatively low risk of hypoglycaemia.[3] Unlike many other therapies for type 2 diabetes, GLP-1RAs have been shown to reduce body weight,[4] as a consequence of reduced appetite and energy intake,[5] as well as to modify the perception of food.[6]

Short-acting GLP-1RAs, requiring dosing once or twice daily, were the first to be developed. Recent efforts have focused on developing GLP-1RAs that require less frequent dosing, with a view to reducing treatment burden and improving patient adherence.[7] Currently three GLP-1RAs are available that can be administered once-weekly; exenatide extended release, albiglutide, and dulaglutide.[4]

Semaglutide is a GLP-1 analogue currently in development for the treatment of type 2 diabetes. It has 94% structural homology to native GLP-1, and is based on the same technology as liraglutide.[8] Structural modifications make semaglutide more resistant to degradation by dipeptidyl peptidase-4 (DPP-4) and improve binding to albumin.[8] These modifications result in a half-life of approximately one week, making semaglutide appropriate for once-weekly subcutaneous (s.c.) administration.[8] Semaglutide has a low molecular weight, making it likely to reach the brain in a similar manner as described for liraglutide.[9]

This article reports the findings of a phase 3a trial, SUSTAIN 1, which evaluated once-weekly s.c. semaglutide at doses of 0·5 mg and 1·0 mg. The objectives of the trial were to evaluate the efficacy, safety and tolerability of semaglutide monotherapy compared with placebo, in treatment-naïve subjects with type 2 diabetes who had insufficient glycaemic control on diet and exercise alone.

Methods

Study design

This was a phase 3a, randomised, double-blind, parallel-group, multinational, multicentre trial [SUSTAIN 1; ClinicalTrials.gov registration NCT02054897]. Participating sites were located in Canada, Italy, Japan, Mexico, Russia, South Africa, UK, and USA. The trial was conducted in compliance with the International Conference on Harmonisation Good Clinical Practice guidelines and the Declaration of Helsinki.

Participants

Patients were ≥18 years of age, had received a diagnosis of type 2 diabetes, and had been treated with diet and exercise alone for ≥30 days before screening when enrolled. Eligible subjects had HbA_{1c} 7·0–10·0% (53–86 mmol/mol). Key exclusion criteria included treatment with glucose-lowering agents in the 90 days prior to screening (except for short-term treatment of ≤7 days with insulin), history of chronic or idiopathic acute pancreatitis, personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2, impaired renal function (estimated glomerular filtration rate, eGFR <30 ml/min/1·73 m^2), screening calcitonin values ≥50 ng/L (pg/mL), heart failure (New York Heart Association class IV), or any acute coronary or cerebrovascular events in the 90 days prior to randomisation. Full eligibility criteria are included in Supplementary Table 1. Written informed consent was obtained from all participants before commencement of any study-related activities.

Randomisation and masking

Subjects were randomly assigned, using an interactive voice/web response system, with a 2:2:1:1 ratio to receive once-weekly s.c. semaglutide (0·5 mg or 1·0 mg) or once-weekly volume-matched placebo, ensuring blinding within dose. Both semaglutide placebo and active drug were provided in PDS290 pen-injectors and were identical with regards to appearance, taste and smell, and equal volume of placebo and active drug were administered within each dose-level. The investigators, subjects and sponsor were blinded throughout the trial.

Procedures

Following a two-week screening period, subjects received s.c. semaglutide 0·5 mg or 1·0 mg or volume-matched placebo (0·5 mg or 1·0 mg) once-weekly for 30 weeks, followed by

a 5-week follow-up period (Supplementary Figure 1). The trial implemented complete follow-up on all subjects, including those who discontinued treatment prematurely. All subjects in the semaglutide arms followed a fixed-dose escalation regimen, with a corresponding volume-matched escalation in the placebo arms. In the semaglutide 0·5 mg arm, the maintenance dose was reached after 4 weeks of 0·25 mg semaglutide once-weekly. In the semaglutide 1·0 mg arm, the maintenance dose was reached after 4 weeks of 0·25 mg semaglutide, followed by 4 weeks of 0·5 mg semaglutide. All doses were administered using 1·5 mL prefilled PDS290 pen-injectors. Injections could be administered in the thigh, abdomen or upper arm, at any time of day and irrespective of meals, provided they were on the same day of the week. Subjects were encouraged to inject in the same area throughout the trial as data on semaglutide concentration were collected for future population pharmacokinetic analyses to show an equivalence between injection sites. Subjects with unacceptable hyperglycaemia were to be offered metformin (first choice) or other antidiabetic medications (not GLP-1RA or DPP-4 inhibitors) as add-on to their randomised treatment (rescue medication) at the discretion of the investigator, in accordance with American Diabetes Association (ADA)/European Association for the Study of Diabetes (EASD) treatment guidelines.[1]

Outcomes

The primary endpoint was the change in HbA_{1c} levels from baseline to week 30, assessed at a central laboratory. The confirmatory secondary endpoint was the change in body weight from baseline to week 30. Other secondary efficacy endpoints included: proportion of subjects who achieved HbA_{1c} <7·0% (53 mmol/mol) or HbA_{1c} ≤6·5% (48 mmol/mol) by end of treatment; a composite endpoint of HbA_{1c} <7·0% with no severe or blood glucose (BG)-confirmed hypoglycaemia (defined as severe according to the ADA classification[10] or confirmed by a BG value <3·1 mmol/L [56 mg/dL] with symptoms consistent with hypoglycaemia) and no weight gain; change from baseline to week 30 in fasting plasma glucose (FPG); self-measured plasma glucose (SMPG) 7-point profiles and prandial increments (over all meals); laboratory measurements associated with β-cell function and glycaemic control (insulin, c-peptide, pro-insulin, glucagon, proinsulin/insulin ratio, and homeostasis model assessment of β-cell function [HOMA-B] and insulin resistance [HOMA-IR], all fasting); proportion of subjects who achieved ≥5% and ≥10% weight-loss from baseline to week 30; body-mass index (BMI); waist circumference; fasting blood lipids; and systolic and diastolic blood pressure.

Safety endpoints included the number of treatment-emergent adverse events (AEs) and the number of severe or BG-confirmed symptomatic hypoglycaemic episodes during exposure, and pulse rate. Other safety measurements were change in laboratory parameters (haematology, biochemistry, calcitonin, urinalysis, and urinary albumin-to-creatinine ratio) and examinations (ECG and physical examination) at week 30, the occurrence and level of anti-semaglutide antibodies, and semaglutide pharmacokinetics (to be included in a future population pharmacokinetic analyses across semaglutide phase 3a trials).

According to US Food and Drug Administration (FDA) requirements, and in an independent and blinded manner, an external event adjudication committee (EAC) validated predefined events (Supplementary Table 2).

Statistical analysis

The two placebo arms were pooled for the efficacy and safety evaluations. The trial was designed with 80% power to establish superiority jointly for both doses of semaglutide versus pooled placebo (hereafter referred to as placebo) for both HbA_{1c} and body weight at week 30 with a one-sided alpha of 2·5%, assuming treatment differences versus placebo of 0·45% and 2·25 kg, respectively, for each semaglutide dose level and standard deviations (SD) of 1·1% and 4·0 kg, respectively. The type-I error probability was controlled at 2·5% (one-sided) across the four confirmatory superior hypotheses in a hierarchical testing strategy. HbA_{1c} superiority versus placebo was tested first, starting with semaglutide 1·0 mg followed by 0·5 mg, followed by body weight superiority versus placebo in the same dose order (supplementary material).

The evaluation of efficacy was based on a modified intention to treat analysis, comprising all randomised subjects who were exposed to at least one dose of trial product; the evaluation used data collected before initiation of any rescue medication or before premature treatment discontinuation. Safety was evaluated based on the same set of subjects. For the safety evaluation, only data collected before premature treatment discontinuation with an ascertainment window of 42 days were used to identify treatment-emergent AEs. Supportive analyses using all data collected during the trial were performed for both efficacy and safety.

Analysis methods for HbA_{1c} and body weight and other continuous endpoints assessed over time included a mixed model for repeated measurements (MMRM), with factors for

treatment, country and baseline value, all nested within visits. All p-values are two-sided of the null hypothesis of no treatment difference.

The robustness of the analyses of HbA_{1c} and body weight was assessed by handling missing data in various ways in analyses, including a placebo-based multiple imputation model where missing data points were imputed as if the subject was treated with placebo. Sensitivity analyses also included an MMRM analysis on the FAS population using all data, regardless of whether obtained while the subjects had discontinued trial product and/or whether the subject had been administered rescue medication (supplementary materials).

Role of the funding source

The sponsor participated in discussions regarding study design and protocol development, and provided logistical support during the trial. The sponsor obtained the data, which were assessed jointly by the authors and the sponsor. The authors interpreted the data, and wrote the report together with medical writing services provided by the sponsor. The corresponding author had full access to all data and had final responsibility for the decision to submit for publication.

Results

Subjects were recruited between 3 February 2014 and 21 August 2014. In total, 388 subjects were randomised and 387 exposed to trial medication (Figure 1). The proportion of subjects administered rescue medication was 5% with each of semaglutide 0·5 mg and 1·0 mg, compared with 21% with placebo. The proportion of subjects discontinuing treatment prematurely was 13% with semaglutide 0·5 mg, 12% with semaglutide 1·0 mg, and 11% with placebo. The main reason for premature treatment discontinuation was AEs (Figure 1).

Baseline characteristics were similar between the three groups (Table 1) in regard to mean diabetes duration, HbA_{1c}, BMI and eGFR. Mean body weight was higher in the semaglutide 1·0 mg group (96·9 kg [range), compared with the semaglutide 0·5 mg (89·8 kg) and placebo (89·1 kg) groups. There was also a higher percentage of males in the semaglutide 1·0 mg group (61·5%), compared with the semaglutide 0·5 mg (46·9%) and placebo (54·3%) groups.

Mean HbA_{1c} (baseline 8·1%, standard deviation [SD] 0·85) decreased at a similar rate over time in both semaglutide groups (Figure 2A and Supplementary Figure 2A). At week 30, HbA_{1c} was significantly decreased with semaglutide 0·5 mg and 1·0 mg by 1·5% and 1·6%, respectively, versus <0·1% in the placebo group. The estimated treatment difference (ETD) versus placebo [95% confidence interval] was –1·43% [–1·71; –1·15] and –1·53% [–1·81; –1·25], respectively; p<0·0001 for both (Figure 2B, Table 2). HbA_{1c} <7·0% was achieved by 74% and 72% of 0·5 mg and 1·0 mg semaglutide-treated subjects, respectively, versus 25% in the placebo group (p<0·0001 for both; Table 2). This target was achieved without severe or BG-confirmed hypoglycaemia and without weight gain in 66% and 65% of subjects in the 0·5 mg and 1·0 mg semaglutide groups, respectively, compared with 19% in the placebo group (Table 2). HbA_{1c} ≤6·5% was achieved by 59% and 60% of 0·5 mg and 1·0 mg semaglutide-treated subjects, respectively, versus 13% in the placebo group (p<0·0001 for both; Table 2).

At week 30, mean FPG was significantly reduced with semaglutide 0·5 mg and 1·0 mg by 2·5 mmol/L and 2·3 mmol/L, respectively, versus 0·6 mmol/L with placebo (ETD –1·96 mmol/L and –1·79 mmol/L; p<0·0001 for both; Table 2). Mean 7-point SMPG was significantly reduced with semaglutide 0·5 mg and 1·0 mg, compared with placebo (ETD –1·68 mmol/L and –1·99 mmol/L; p<0·0001 for both; Table 2). The mean 7-point SMPG post-meal increment was significantly reduced with semaglutide 1·0 mg (ETD –0·74 mmol/L

p=0·0014), but the reduction in the semaglutide 0·5 mg group was not significant (ETD –0·41 mmol/L; p=0·08; Table 2).

Proinsulin and proinsulin/insulin ratio were significantly reduced, and c-peptide and HOMA-B were significantly increased, with both doses of semaglutide versus placebo. HOMA-IR was significantly reduced with semaglutide 1·0 mg compared with placebo, but this decrease was not significantly greater for semaglutide 0·5 mg versus placebo. No significant changes in fasting insulin or plasma glucagon levels were observed (Supplementary Table 3).

At week 30, body weight was significantly decreased with semaglutide 0·5 mg and 1·0 mg by 3·7 kg and 4·5 kg, respectively, versus 1·0 kg in the placebo group (ETD –2·75 kg and –3·56 kg; p<0·0001 for both; Figure 2D, Table 2). A similar pattern of weight change over time was observed in both semaglutide groups (Figure 3C and Supplementary Figure 2B). A body weight reduction of ≥5% was achieved by 37% and 45% of 0·5 mg and 1·0 mg semaglutide-treated subjects, respectively, versus 7% in the placebo group (p<0·0001 for both; Table 2). A body weight reduction of ≥10% was achieved by 8% and 13% of 0·5 mg and 1·0 mg semaglutide-treated subjects, respectively, versus 2% in the placebo group (p=0·0363 for 0·5 mg, p=0·0018 for 1·0 mg; Table 2).

BMI and waist circumference were reduced with both doses of semaglutide compared with placebo (Table 2). Total cholesterol, LDL-cholesterol and FFA were significantly reduced with semaglutide 1·0 mg, compared with placebo. No significant difference in HDL-cholesterol, triglycerides and VLDL-cholesterol was observed between semaglutide 0·5 mg, 1·0 mg and placebo arms (Supplementary Table 3). Changes in blood pressure were comparable between the semaglutide 0·5 mg, 1·0 mg and placebo groups (Table 2).

The proportion of subjects reporting any AEs was higher with semaglutide 0·5 mg versus placebo, while serious AEs (SAEs) were broadly similar between all groups: 64·1%, 56·2% and 53·5% of subjects reported AEs with semaglutide 0·5 mg, 1·0 mg and placebo, and 5·5%, 5·4% and 3·9% reported SAEs, respectively (Table 3; Supplementary Table 4). No deaths were reported in any of the groups. The majority of AEs reported were of mild or moderate severity (Table 3). The proportion of subjects prematurely discontinuing treatment due to AEs was 6·3% for semaglutide 0·5 mg, 5·4% for semaglutide 1·0 mg and 2·3% for placebo (Supplementary Figure 3).

The most frequent AEs in the semaglutide groups were gastrointestinal (GI) AEs, and these were also responsible for the majority of AEs leading to premature treatment

discontinuation (Table 3). In subjects receiving semaglutide 0·5 and 1·0 mg, 20·3% and 23·8% reported nausea, respectively, versus 7·8% in the placebo group. The rate of nausea was observed to decrease over time (Supplementary Figure 3). Vomiting was reported by 3·9% and 6·9% of subjects in the semaglutide 0·5 and 1·0 mg groups respectively, compared with 1·6% in the placebo group. In subjects receiving semaglutide 0·5 and 1·0 mg, 12·5% and 10·8% reported diarrhoea, respectively, versus 2·3% in the placebo group. The majority of GI AEs were mild to moderate (Table 3).

No episodes of severe or BG-symptomatic confirmed hypoglycaemia were reported in either semaglutide group; three events were reported in two subjects (1·6%) in the placebo group. All three events occurred after first dose of rescue medication.

No episodes of pancreatitis were reported in the trial. Lipase significantly increased by 18% with semaglutide 0.5 mg and 22% with semaglutide 1.0 mg, compared with a 6% decrease with placebo. Corresponding changes for amylase were 11%, 16% and 0%, respectively (Supplementary Figure 5). A total of four cases of cholelithiasis were reported: three in subjects receiving semaglutide 0·5 mg and one in a subject receiving semaglutide 1·0 mg. In one of the subjects receiving semaglutide 0·5 mg, this was categorised as an SAE. No cases of cholelithiasis were reported in the placebo arm (Table 3).

The pulse rate increased significantly with both doses of semaglutide by 2·4 bpm, compared with a 0·5 bpm decrease with placebo by week 30 (Table 2). EAC-confirmed neoplasms were reported by five subjects treated with semaglutide 0·5 mg, four treated with semaglutide 1·0 mg and none in the placebo arm. These neoplasms included four malignant cases. Single cases of squamous cell carcinoma of skin and breast cancer were confirmed in the semaglutide 0·5 mg group, and single cases of basal cell carcinoma and prostate cancer were confirmed in the semaglutide 1·0 mg treatment group. There were no cases of pancreatic cancer reported (Table 3). Calcitonin levels in both semaglutide arms were consistently low and comparable to placebo, and no C-cell abnormalities were observed.

A total of 11 subjects developed anti-semaglutide antibodies; none were observed to exhibit *in vitro* neutralising effects on semaglutide or endogenous GLP-1.

There were no clinically relevant changes in other safety laboratory assessments, physical examination or electrocardiograms.

Discussion

In this multicentre, randomised controlled phase 3a trial, both doses of once-weekly semaglutide (0·5 mg and 1·0 mg) significantly improved glycaemic control in treatment-naïve patients with type 2 diabetes, compared with placebo. Nearly three-quarters of subjects in the semaglutide groups reached the ADA recommended HbA_{1c} target of <7·0%,[11] and almost 60% achieved the more stringent American Association of Clinical Endocrinologists (AACE) / National Institute for Health and Care Excellence (NICE) target of 6·5%.[2,12] These findings are consistent with observations in an earlier 12-week dose-finding study for semaglutide in 415 subjects with type 2 diabetes treated with diet and exercise, with or without a stable metformin regimen, where up to 81% of the participants on semaglutide 0·1–1·6 mg achieved an HbA_{1c} level of <7·0% (up to 63% for the ≤6·5% target).[13]

As a dose response was evident in the dose finding study, it was surprising that there was no apparent dose-related difference in glycaemic control with semaglutide in this study. However, although both doses produced similar mean HbA_{1c} reductions from baseline, the decrease in HbA_{1c} was consistently more pronounced in the 1·0 mg semaglutide arm than in the 0·5 mg semaglutide arm in all prespecified sensitivity analyses (supplementary figure 4). A possible explanation could be that the low mean HbA_{1c} achieved by the end of treatment, and the high percentage of subjects achieving HbA_{1c} levels of less than 7·0%, may have reduced the visibility of a dose-dependent treatment difference in this treatment-naïve type 2 diabetes population. Furthermore, because the sample size was relatively small, the dose-response effect may have been skewed due to 13 subjects who had undetectable plasma semaglutide levels throughout the trial, indicating that they had not routinely administered the drug. Ten of these subjects were randomised to the 1·0 mg semaglutide arm and several had an increase in HbA_{1c}, thereby attenuating the mean HbA_{1c} reduction in the 1·0 mg arm. In contrast to HbA_{1c}, weight loss with semaglutide 1·0 mg was numerically higher than for semaglutide 0·5 mg. However, GLP-1RA effects on glycaemic control and body weight appear to be independent,[14] with glycaemic control primarily mediated by pancreatic GLP-1 receptors and weight loss by GLP-1 receptors in the brain.[15-17] This supports the proposal that glycaemic effects show different dose-response relationships than body weight.

In this study, both doses of semaglutide led to significant weight loss, compared with placebo. This is a particularly relevant finding, because many current treatments for

diabetes are either weight-neutral or associated with weight gain. [18-20] Current treatment guidelines from ADA/EASD and AACE stress the importance of avoiding weight gain and minimising the risk of treatment-emergent hypoglycaemia while managing patients with type 2 diabetes. Weight gain and obesity are associated with an increase in the risk of cardiovascular complications[21] and other comorbidities,[22] as well as a reduction in quality of life.[23] Furthermore, weight gain may contribute to patient frustration and lack of motivation, and lead to reduced compliance with medication.[24] Studies also suggest that individuals with type 2 diabetes are reluctant to begin treatments associated with an increased risk of weight gain.[1,25] Even the perception that regular use of diabetes therapy would result in weight gain is associated with a reduced adherence to treatment in individuals with type 2 diabetes.[25]

Although populations and trial durations may have varied, indirect comparison of the findings from this trial with those from similar monotherapy trials with other GLP-1RAs indicate that the improvements in glycaemic control and body weight are at least comparable – and potentially greater – with semaglutide. The proportions of patients achieving the ADA HbA_{1c} target have been reported as 40–49% with albiglutide (30 or 50 mg); 43–51% with liraglutide (1·2 or 1·8 mg); 62–63% with dulaglutide (0·75 or 1·5 mg); and 63% with exenatide extended release (2 mg), compared with 72–74% with semaglutide in this trial.[26-29] Similarly, the magnitude of the change from baseline in body weight (–3·7 to –4·5 kg) is numerically higher than that seen for other GLP-1RAs (reported at –0·4 to –2·5 kg),[26–29] similar to the weight loss reported with semaglutide in an earlier phase 2 dose-finding study.[13] The high proportion of subjects in this trial who achieved the ADA HbA_{1c} target of <7·0% without weight gain or hypoglycaemia suggests that semaglutide may potentially ameliorate several of the negative health consequences of type 2 diabetes. Head-to-head trials comparing semaglutide with other GLP-1RAs are needed to draw firm conclusions on potential differences.

The profile of AEs with semaglutide was similar to that seen with other GLP-1RAs, with GI AEs the most frequent.[30] These were largely mild-to-moderate and led to treatment discontinuation in only a small percentage of subjects; the frequency of nausea peaked shortly after treatment initiation and diminished over time. Dose escalation has previously been shown to partially ameliorate GI AEs associated with GLP-1RA use,[13] as was reflected in the trial design. Although lipase and amylase levels increased with semaglutide, there is no evidence of an association with pancreatitis, and no episodes of pancreatitis were reported in the trial.

The modest elevation in pulse rate relative to placebo is also in line with findings for other GLP-1RAs, although the decrease in systolic blood pressure also seen with other GLP-1RAs, was not statistically significant in this trial.[31] In addition, the SUSTAIN 6 trial, designed to assess cardiovascular safety in patients with type 2 diabetes, has demonstrated a significant reduction in cardiovascular risk with semaglutide. The first occurrence of cardiovascular death, nonfatal myocardial infarction or nonfatal stroke taking place in 6.6% of subjects treated with semaglutide 0.5 mg or 1.0 mg and 8.9% with placebo group (hazard ratio [HR] 0.74; 95% CI 0.58, 0.95; P<0.001 for noninferiority).[32]

In this trial, there was a numerical imbalance in the reporting of neoplasm, although based on very low numbers (2 in each of the semaglutide arms versus none in the placebo arm). However, in the much larger and longer SUSTAIN 6 trial, malignant neoplasms were equally distributed with semaglutide and placebo (HR 0.94; 95% CI 0.67, 1.32), with no apparent differences for any types of malignant neoplasms.[32]

A limitation of the trial is its short duration, which may not have allowed sufficient time for the full effects, on body weight in particular, to be evaluated. Furthermore, this trial had a relative small sample size, which carries the risk of not having completely balanced baseline characteristics. This was seen for baseline weight and gender distribution. It could be speculated that this slightly higher number of heavy males in the 1.0 mg arm could have impacted the weight loss results. Results from the remaining phase 3a trials are needed to confirm consistency in the results. Another limitation was the frequent use of rescue medication, particularly in the placebo arm, which led to missing data in more than 30% of placebo subjects. An advantage of this trial design was that use of a volume-matched placebo allowed for blinding within each dose for both the clinician and the patient, reducing the risk of bias. GLP-1RAs are not generally used as monotherapies but are typically started in combination with metformin, which may be another consideration.[1]

In conclusion, once-weekly semaglutide monotherapy at a dose of 0·5 mg or 1·0 mg was associated with superior glycaemic control and superior reductions in body weight in subjects with type 2 diabetes, compared with placebo. AEs were predominantly GI-related and the safety and tolerability profile was consistent with previous observations with other GLP-1RAs. These findings support a favourable benefit–risk profile of semaglutide in patients with type 2 diabetes.

Authors' contributions

All authors participated in the trial design. CS, SH, GMT, JU and SCB took part in the conduct of the trial and the data collection. JDKA and TH took part in the data analysis. All authors interpreted the data and participated in writing the manuscript together with medical writing services provided by the sponsor. All the authors have read the manuscript critically and approved the submitted version.

Conflicts of interest

In conducting this study, CS has received travel expenses from Novo Nordisk and SCB has received personal fees from Novo Nordisk. SH, GMT and JU have previously received honoraria and SCB has previously received research grants from Novo Nordisk. SH has previously received honoraria from Astellas, AstraZeneca, Boehringer Ingerheim, Dainippon Sumitomo, Eli Lilly, Mitsubishi Tanabe, MSD, Sanofi, Taisho Toyama, and research grants from AstraZeneca, MSD and Sanofi. SCB has previously received honoraria and research grants (paid to his institution) from Boehringer Ingerheim, Cellnovo, Eli Lilly, Jensen, MSD and Sanofi. JDK and TH are full-time employees of Novo Nordisk A/S, and JDK holds stock in Novo Nordisk.

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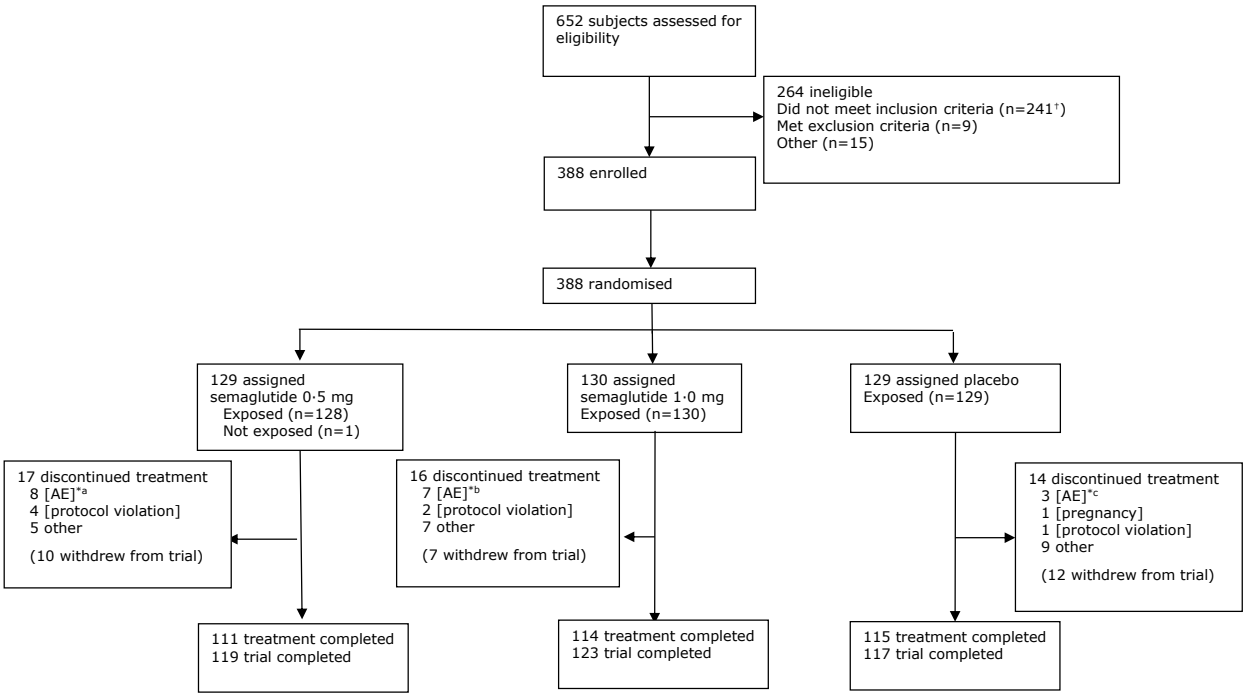
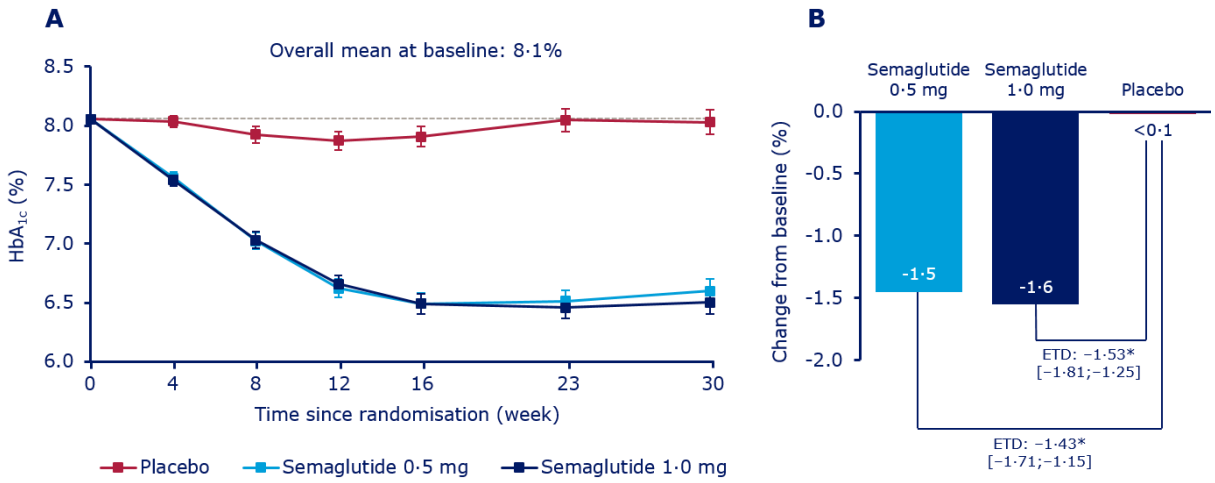
Figures

Figure 1. Participant flow.

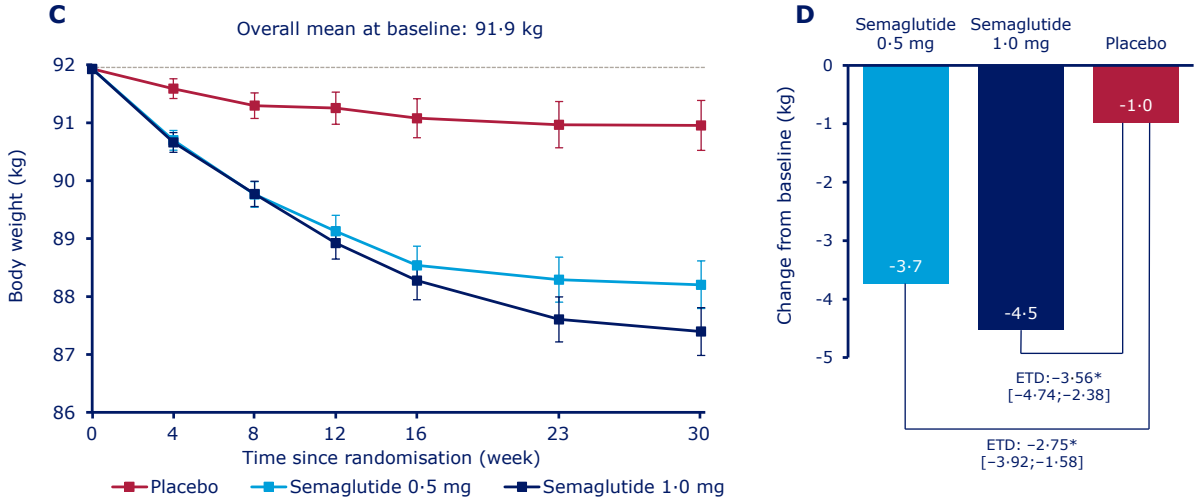


AE, adverse event; GI, gastrointestinal.
**Reflects primary reason for treatment discontinuation, as judged by the investigator; †Subjects did not have an HbA_{1c} within the specified range; [a]3 subjects discontinued due to GI AEs and 5 subjects due to other AEs; [b]3 subjects discontinued due to GI AEs and 4 subjects due to other AEs; [c]No subjects discontinued due to GI AEs and 3 subjects due to other AEs.*

Figure 2. Semaglutide 0·5 mg and 1·0 mg once-weekly, compared with placebo, change in mean HbA_{1c} by week (A), mean HbA_{1c} after 30 weeks (B), the proportion of subjects achieving HbA_{1c} targets of <7·0% (C) and ≤6·5% (D), change in mean body weight by week (E), and mean body weight after 30 weeks (F)



*Indicates significance (p-value <0·0001). Values are estimated means (+/- standard errors) from a mixed model for repeated measurements analysis using 'on-treatment without rescue medication' data from subjects in the full analysis set. Dotted line is the overall mean value at baseline.
ETD, estimated treatment difference.



*Indicates significance (p-value <0·0001). Values are estimated means (+/- standard errors) from a mixed model for repeated measurements analysis using 'on-treatment without rescue medication' data from subjects in the full analysis set. Dotted line is the overall mean value at baseline.
ETD, estimated treatment difference.

Table 1. Baseline characteristics.

	Semaglutide 0·5 mg	Semaglutide 1·0 mg	Placebo
Age,* years (min–max)	54·6 (30–80)	52·7 (26–80)	53·9 (18–88)
HbA_{1c}			
% (min–max)	8·1 (6·5–10·3)	8·1 (6·4–10·2)	8·0 (6·5–10·2)
mmol/mol (min–max)	64·9 (47·5–89·1)	65·3 (46·5–88·0)	63·4 (47·5–88·0)
Diabetes duration,* years (Min–Max)	4·9 (0·1–34·5)	3·7 (0·1–28·1)	4·1 (0·1–33·4)
Body weight,* kg (min–max)	89·8 (39·8–174·8)	96·9 (53·7–185·3)	89·1 (42·8–176·7)
BMI,* kg/m^2 (min–max)	32·5 (16·4–62·2)	33·9 (18·6–71·8)	32·4 (17·6–56·6)
eGFR (MDRD),* mL/min/1·73 m^2 (min–max)	95·9 (35·0–191·0)	100·9 (35·0–195·0)	100·2 (31·0–218·0)
Sex (%)			
Female	68 (53·1)	50 (38·5)	59 (45·7)
Male	60 (46·9)	80 (61·5)	70 (54·3)

Ethnicity (%)			
Hispanic or Latino	34 (26·6)	45 (34·6)	36 (27·9)
Not Hispanic or Latino	94 (73·4)	85 (65·4)	93 (72·1)
Race (%)			
White	83 (64·8)	88 (67·7)	78 (60·5)
Black or African American	11 (8·6)	11 (8·5)	9 (7·0)
Asian	26 (20·3)	25 (19·2)	32 (24·8)

* Values are means

BMI, body-mass index; MDRD, Modification of Diet in Renal Disease

Table 2. Study endpoints by treatment group.

	Semaglutide 0·5 mg			**Semaglutide 1·0 mg**	
	Change from baseline at Week 30 [SE]	ETD [95% CI]	p	Change from baseline at Week 30 [SE]	ETD [95% CI]
Glycaemia endpoints					
Mean HbA_{1c} (%)	1·5 [0·10]	−1·43 [-1·71; 1·15]	<0·0001	1·6 [0·10]	−1·53 [−1·81; −1·25]
Mean HbA_{1c} (mmol/mol)	15·9 [1·08]	−15·63 [−18·72; −12·53]	<0·0001	17·0 [1·07]	−16·69 [−19·77; −13·61]
Mean FPG (mmol/L)	−2·5 [0·19]	−1·96 [−2·49; −1·43]	<0·0001	−2·3 [0·18]	−1·79 [−2·31; −1·26]
7-point SMPG (mmol/L)					
Mean	−2·4 [0·17]	−1·68 [−2·18; −1·18]	<0·0001	−2·7 [0·17]	−1·99 [−2·48; −1·50]

Increment	−0·8 [0·16]	−0·41 [−0·87; 0·05]	0·0807	−1·1 [0·15]	−0·74 [−1·19; −0·29]
Body weight endpoints					
Mean body weight(kg)	3·7	−2·75 [−3·92; −1·58]	<0·0001	4·5	−3·56 [−4·74; −2·38]
Mean BMI (kg/m^2)	−1·4 [0·15]	−0·98 [−1·40; −0·56]	<0·0001	−1·6 [0·14]	−1·23 [−1·65; −0·82]
Mean waist circumference (cm)	−3·7 [0·55]	−1·84 [−3·40; −0·28]	0·0206	−4·1 [0·55]	−2·18 [−3·74; −0·61]
Blood pressure and pulse rate					
Mean DBP (mmHg)	−0·5 [0·66]	−0·89 [−2·81; 1·02]	0·36	0·2 [0·65]	−0·21 [−2·12; 1·69]
Mean SBP (mmHg)	−2·6 [1·13]	−0·86 [−4·15; 2·43]	0·6	−2·7 [1·12]	−1·03 [−4·29; 2·24]
Mean pulse rate (bpm)	2·4 [0·77]	2·89 [0·74; 5·04]	0·0086	2·4 [0·77]	2·97 [0·83; 5·12]

Treatment targets					
	Semaglutide 0·5 mg			Semaglutide 1·0 mg	
	Subjects achieving target	OR [95% CI]	p	Subjects achieving target	OR [95% CI]
Proportion achieving HbA_{1c} targets, n (%)					
<7·0% (<53 mmol/mol)	95 (74)	16·92 [8·44; 33·89]	<0·0001	94 (72)	15·70 [8·00; 30·83]
≤6·5% (≤48 mmol/mol)	76 (59)	15·99 [7·82; 32·68]	<0·0001	78 (60)	18·34 [8·96; 37·54]
Proportion achieving body weight reduction, n (%)					
≥5%	47 (37)	7·88 [3·65; 17·04]	<0·0001	58 (45)	12·01 [5·53; 26·07]
≥10%	10 (8)	3·60 [1·09; 11·95]	0·0363	17 (13)	6·23 [1·98; 19·61]
Proportion achieving HbA_{1c} <7·0% without severe or BG–confirmed hypoglycaemia and without weight gain, n (%)	85 (66)	12·69 [6·57; 24·52]	<0·0001	85 (65)	12·45 [6·46; 23·99]

BG, blood glucose; BMI, body-mass index; bpm, beats per minute; CI, confidence interval; DBP, diastolic b
estimated treatment difference vs placebo; FPG, fasting plasma glucose; HBA_{1c}, glycosylated haemoglobin;
SBP, systolic blood pressure; SD, standard deviation; SE, standard error; SMPG, self-monitored plasma glu
are two-sided of the null-hypothesis of no treatment difference.

Table 3. Adverse events overview.

	Semaglutide 0·5 mg			Semaglutide 1·0mg			
	N	(%)	E	N	(%)	E	N
Number of subjects	**128**	-	-	**130**	-	-	**129**
Serious adverse events	**7**	**5.5**	**10**	**7**	**5.4**	**8**	**5**
Fatal	**0**	**-**	**-**	**0**	**-**	**-**	**0**
Any adverse events	**82**	**64·1**	**364**	**73**	**56·2**	**269**	**69**
Severe	9	7.0	13	8	6.2	12	4
Moderate	35	27.3	102	31	23.8	80	26
Mild	71	55.5	249	60	46.2	177	58
GI adverse events	**49**	**38.3**	**141**	**50**	**38.5**	**115**	**19**
Severe	1	0.8	1	2	1.5	2	0
Moderate	19	14.8	33	17	13.1	35	5
Mild	38	29.7	107	41	31.5	78	16
Adverse events leading to premature treatment discontinuation	**8**	**6·3**	**16**	**7**	**5·4**	**11**	**3**
All GI adverse events	5	3·9	7	4	3·1	5	1
Nausea	2	1·6	2	2	1·5	2	1
Vomiting	1	0·8	1	2	1·5	2	0
Diarrhoea	3	2·3	3	0	-	-	0
Adverse events by preferred term (≥5% of subjects)							
Nausea	26	20·3	44	31	23·8	46	10

Diarrhoea	16	12·5	27	14	10·8	19	3
Headache	15	11·7	43	9	6·9	18	8
Lipase increased	8	6·3	10	5	3·8	5	5
Constipation	8	6·3	9	5	3·8	5	1
Dyspepsia	7	5·5	13	5	3·8	5	3
Nasopharyngitis	6	4·7	7	6	4·6	9	7
Vomiting	5	3·9	11	9	6·9	15	2
Other adverse events							
Pancreatitis	0	-	-	0	-	-	0
Cholelithiasis	3	2.3	3*	1	0.8	1	0
Malignant neoplasms	2	1.6	2	2	1.5	2	0
Squamous cell carcinoma of the skin	1	0.8	1	0	-	-	0
Breast cell carcinoma	0	-	-	1	0.8	1	0
Breast cancer	1	0.8	1	0	-	-	0
Prostate cancer	0	-	-	1	0.8	1	0
Benign neoplasms	3	2.3	3	2	1.5	2	0

E, episodes; GI, gastrointestinal; *1 serious adverse event

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