Efficacy and safety of once-weekly semaglutide versus once-daily sitagliptin as an add-on to metformin, thiazolidinediones, or both, in patients with type 2 diabetes (SUSTAIN 2): a 56-week, double-blind, phase 3a, randomised trial

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Summary

Background Semaglutide is a novel glucagon-like peptide-1 (GLP-1) analogue, suitable for once-weekly subcutaneous administration, in development for treatment of type 2 diabetes. We assessed the efficacy and safety of semaglutide versus the dipeptidyl peptidase-4 (DPP-4) inhibitor sitagliptin in patients with type 2 diabetes inadequately controlled on metformin, thiazolidinediones, or both.

Methods We did a 56-week, phase 3a, randomised, double-blind, double-dummy, active-controlled, parallel-group, multinational, multicentre trial (SUSTAIN 2) at 128 sites in 18 countries. Eligible patients were aged at least 18 years (or at least 20 years in Japan) and diagnosed with type 2 diabetes, with insufficient glycaemic control (HbA_{1c} 7·0–10·5% [53·0–91·0 mmol/mol]) despite stable treatment with metformin, thiazolidinediones, or both. We randomly assigned participants (2:2:1:1) using an interactive voice or web response system to 56 weeks of treatment with subcutaneous semaglutide 0·5 mg once weekly plus oral sitagliptin placebo once daily, subcutaneous semaglutide 1·0 mg once weekly plus oral sitagliptin placebo once daily, oral sitagliptin 100 mg once daily plus subcutaneous semaglutide placebo 0·5 mg once weekly, or oral sitagliptin 100 mg once daily plus subcutaneous semaglutide placebo 1·0 mg once weekly. The two oral sitagliptin 100 mg groups (with semaglutide placebo 0·5 mg and 1·0 mg) were pooled for the analyses. The primary endpoint was change in HbA_{1c} from baseline to week 56, assessed in the modified intention-to-treat population (all randomly assigned participants who received at least one dose of study drug); change in bodyweight from baseline to week 56 was the confirmatory secondary endpoint. Safety endpoints included adverse events and hypoglycaemic episodes. This trial is registered with ClinicalTrials.gov, number NCT01930188.

Findings Between Dec 2, 2013, and Aug 5, 2015, we randomly assigned 1231 participants; of the 1225 included in the modified intention-to-treat analysis, 409 received semaglutide 0·5 mg, 409 received semaglutide 1·0 mg, and 407 received sitagliptin 100 mg. Mean baseline HbA_{1c} was 8·1% (SD 0·93); at week 56, HbA_{1c} was reduced by 1·3% in the semaglutide 0·5 mg group, 1·6% in the semaglutide 1·0 mg group, and 0·5% with sitagliptin (estimated treatment difference *vs* sitagliptin –0·77% [95% CI –0·92 to –0·62] with semaglutide 0·5 mg and –1·06% [–1·21 to –0·91] with semaglutide 1·0 mg; p<0·0001 for non-inferiority and for superiority, for both semaglutide doses *vs* sitagliptin). Mean baseline bodyweight was 89·5 kg (SD 20·3); at week 56, bodyweight reduced by 4·3 kg with semaglutide 0·5 mg, 6·1 kg with semaglutide 1·0 mg, and 1·9 kg with sitagliptin (estimated treatment difference *vs* sitagliptin –2·35 kg [95% CI –3·06 to –1·63] with semaglutide 0·5 mg and –4·20 kg [–4·91 to –3·49] with semaglutide 1·0 mg; p<0·0001 for superiority, for both semaglutide doses *vs* sitagliptin). The proportion of patients who discontinued treatment because of adverse events was 33 (8%) for semaglutide 0·5 mg, 39 (10%) for semaglutide 1·0 mg, and 12 (3%) for sitagliptin. The most frequently reported adverse events in both semaglutide groups were gastrointestinal in nature: nausea was reported in 73 (18%) who received semaglutide 0·5 mg, 72 (18%) who received semaglutide 1·0 mg, and 30 (7%) who received placebo, and diarrhoea was reported in 54 (13%) who received semaglutide 0·5 mg, 53 (13%) who received semaglutide 1·0 mg, and 29 (7%) who received placebo. Seven (2%) patients in the semaglutide 0·5 mg group, two (<1%) in the semaglutide 1·0 mg group, and five (1%) in the sitagliptin group had blood-glucose confirmed hypoglycaemia. There were six fatal events (two in the semaglutide 0·5 mg group, one in the semaglutide 1·0 mg group, and three in the sitagliptin group); none were considered likely to be related to the trial drugs.

Interpretation Once-weekly semaglutide was superior to sitagliptin at improving glycaemic control and reducing bodyweight in participants with type 2 diabetes on metformin, thiazolidinediones, or both, and had a similar safety profile to that of other GLP-1 receptor agonists. Semaglutide seems to be an effective add-on treatment option for this patient population.

Funding Novo Nordisk A/S.

Lancet Diabetes Endocrinol 2017; 5: 341–54

Published Online
April 3, 2017
http://dx.doi.org/10.1016/S2213-8587(17)30092-X

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Research in context

Evidence before this study

We designed this trial on the basis of preclinical evidence from the development of semaglutide and early (phase 1 and 2) clinical studies of the drug. Various long-acting glucagon-like peptide-1 (GLP-1) receptor agonists and drugs from other classes that are suitable for once-weekly dosing are approved for use in the treatment of type 2 diabetes. Because the biochemical methods of protraction differ between GLP-1 receptor agonists and drugs from other classes, the molecular properties of the different medications might have differential effects on efficacy or safety parameters in clinical use that remain to be established.

Added value of this study

The results of this trial show that, compared with oral sitagliptin given once daily, subcutaneous semaglutide given once weekly provides superior glycaemic control and greater weight loss, without an increased risk of hypoglycaemia, in patients with type 2 diabetes inadequately controlled on metformin, thiazolidinediones, or both. The safety profile of semaglutide appears to be similar to available GLP-1 receptor agonists, consisting mainly of gastrointestinal events.

Implications of all the available evidence

Semaglutide seems to be a promising treatment option for participants with type 2 diabetes. Clinical trial results reported so far suggest significant improvements in glycaemic control compared with placebo or established standards of care in participants with type 2 diabetes, as well as substantial weight loss, and findings from a separate dedicated cardiovascular outcomes trial have shown a reduction in cardiovascular events in high-risk patients. A comprehensive phase 3b clinical trial programme is planned to further investigate the efficacy and safety of subcutaneous semaglutide versus several other active comparators (including dulaglutide and canagliflozin).

Introduction

Type 2 diabetes is a complex, progressive disease; despite the wide range of treatment options available,[1] many patients with type 2 diabetes do not achieve recommended blood glucose concentrations[2] (HbA_{1c} <7·0% [53·0 mmol/mol];[3] HbA_{1c} ≤6·5% [48·0 mmol/mol]).[4] Achievement of target blood glucose concentrations is a key goal of diabetes management because improved glycaemic control reduces the risk of associated microvascular and macrovascular complications.[5] Weight reduction is also recommended in overweight patients as it is known to improve glycaemic control and cardiovascular risk factors.[6]

Several treatment options exist for improving glycaemic control in patients with type 2 diabetes. However, there are challenges associated with these options, including adverse events and other factors that can compromise adherence. Complex dosing regimens are known to affect adherence to therapy and might hinder achievement of glycaemic targets.[7] Furthermore, many people with type 2 diabetes are overweight or obese and some drug regimens are associated with weight gain or an increased risk of hypoglycaemia.[8] These drawbacks, together with regimen complexity when using several compounds, might contribute to poor adherence and reduce the proportion of patients achieving their HbA_{1c} targets.[1]

Both glucagon-like peptide-1 (GLP-1) receptor agonists and dipeptidyl peptidase-4 (DPP-4) inhibitors can be used as second-line therapy when first-line therapy (mainly metformin) alone is insufficient for achieving glycaemic control.[1] DPP-4 inhibitors and GLP-1 receptor agonists have different mechanisms of action by which they mediate their effects. DPP-4 inhibitors extend the half-life of endogenous GLP-1, whereas GLP-1 receptor agonists, resistant to DPP-4 degradation, provide supraphysiological stimulation of GLP-1 receptors.[9] GLP-1 receptor agonists improve glycaemic control by stimulating insulin secretion and inhibiting the release of glucagon in a glucose-dependent manner, targeting the pathophysiological factors underlying the islet cell dysfunction associated with type 2 diabetes.[10] Importantly, GLP-1 receptor agonists also reduce bodyweight, by reducing appetite and energy intake.[11] DPP-4 is an enzyme known to act on various pharmacological and physiological substrates, including its inactivation of the incretin hormones GLP-1 and gastric inhibitory polypeptide, plus other hormones.[12] DPP-4 is targeted by DPP-4 inhibitors, which increase insulin secretion and suppress glucagon release through the increased half-life of endogenous GLP-1. Their specific modes of action result in different efficacy and tolerability profiles from those of GLP-1 receptor agonists. Furthermore, unlike GLP-1 receptor agonists, DPP-4 inhibitors do not generally reduce bodyweight.[13,14]

For first-generation GLP-1 receptor agonists, twice-daily or daily dosing is required.[15] Recent efforts have focused on developing GLP-1 receptor agonists for once-weekly administration, which could improve patient adherence and health-related quality of life.[16] Six GLP-1 receptor agonists have been approved for treatment of type 2 diabetes: exenatide (twice daily), lixisenatide and liraglutide (both once daily), and exenatide extended-release, albiglutide, and dulaglutide (all once weekly).[10]

Semaglutide, a novel GLP-1 receptor agonist with 94% structural homology to native GLP-1, is currently in development for the treatment of type 2 diabetes. It is similar in structure to liraglutide,[17] but important structural modifications make semaglutide less susceptible to degradation by the enzyme DPP-4, and thus more enzymatically stable.[17] These modifications also improve the specific high-affinity binding to albumin

and, overall, result in a half-life of about 1 week, making semaglutide appropriate for once-weekly subcutaneous administration.[17]

The efficacy and safety of subcutaneous semaglutide have been assessed as part of a large phase 3 trial programme (SUSTAIN). In SUSTAIN 1, a double-blind, randomised, international trial, the efficacy and safety of once-weekly subcutaneous semaglutide monotherapy compared with placebo in treatment-naive patients with type 2 diabetes was assessed over 30 weeks. The results showed that both semaglutide 0·5 mg and 1·0 mg significantly improved HbA_{1c} and bodyweight compared with placebo ($p<0·0001$ for all).[18] Similarly, in the 2-year SUSTAIN 6 cardiovascular outcomes trial of semaglutide treatment in patients with type 2 diabetes at high cardiovascular risk, semaglutide was associated with improvements in HbA_{1c} and sustained reductions in bodyweight compared with placebo, as well as reductions in the rate of cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke.[19]

Here we report the findings from SUSTAIN 2, a phase 3a clinical trial that assessed the efficacy and safety of semaglutide compared with a commonly used DPP-4 inhibitor, sitagliptin, as add-on treatment in patients with type 2 diabetes inadequately controlled on metformin, thiazolidinediones, or both.

Methods

Study design and participants

We did a 56-week, phase 3a, randomised, double-blind, double-dummy, active-controlled, parallel-group, multinational, multicentre trial (SUSTAIN 2) at 128 sites (hospitals, clinical institutions, or private practices) in Europe (Bulgaria, Czech Republic, Hungary, Norway, Portugal, Romania, Spain, Sweden, Turkey, and Ukraine), Argentina, Hong Kong, India, Japan, Mexico, Russia, South Africa, and Thailand.

Patients were eligible for inclusion if they were aged 18 years or older (or aged 20 years or older in Japan) and diagnosed with type 2 diabetes, with insufficient glycaemic control (HbA_{1c} 7·0–10·5% [53·0–91·0 mmol/mol]) for a period of 90 days before screening while on stable treatment with either metformin (≥1500 mg), pioglitazone (≥30 mg), rosiglitazone (≥4 mg), or a combination of either metformin and pioglitazone or metformin and rosiglitazone. For patients unable to tolerate these doses, a maximum tolerated dose was used.

Exclusion criteria included treatment with glucose-lowering drugs other than those defined in the eligibility criteria in the 90 days before screening (except for short-term treatment [≤7 days] with insulin related to diabetes); history of chronic or idiopathic acute pancreatitis; a screening calcitonin value of 50 ng/L (50 pg/mL) or greater; personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2; impaired renal function (estimated glomerular filtration [eGFR] <60 mL/min/1·73 m²); an acute coronary or cerebrovascular event within 90 days before randomisation or heart failure at any time (New York Heart Association class IV); and a BMI of less than 18 mg/kg² (post-commencement protocol amendment, applied in India only, according to local requirements). Full eligibility criteria are provided in the appendix. This trial was done in compliance with the International Conference on Harmonisation Good Clinical Practice Guideline and the Declaration of Helsinki and was approved by local ethics committees. We obtained written informed consent from all participants included in the trial.

See Online for appendix

Randomisation and masking

We randomly assigned participants (2:2:1:1) to receive second-line therapy, irrespective of background medication or baseline HbA_{1c}, with subcutaneous semaglutide (Novo Nordisk, Bagsværd, Denmark) 0·5 mg once weekly plus oral sitagliptin placebo (allphamed Pharbil Arzneimittel GmbH, Göttingen, Germany) once daily, subcutaneous semaglutide 1·0 mg once weekly plus oral sitagliptin placebo once daily, oral sitagliptin (Merck Sharp & Dohme Ltd, Northumberland, UK) 100 mg once daily plus subcutaneous semaglutide placebo (Novo Nordisk) 0·5 mg once weekly, or oral sitagliptin 100 mg once daily plus subcutaneous semaglutide placebo 1·0 mg once weekly, using an interactive voice or web response system. Semaglutide placebo was matched in volume to each dose of semaglutide, and sitagliptin placebo was identical in appearance, taste, and smell to sitagliptin, to ensure double-blinding (appendix). The two sitagliptin groups (one given 0·5 mg semaglutide placebo and one given 1·0 mg semaglutide placebo per week) were pooled for all analyses. The investigator, patients, and study funder remained masked to treatment assignment throughout the trial.

Procedures

After a 2-week screening period, participants received subcutaneous semaglutide for 56 weeks, followed by a 5-week follow-up period (appendix). Follow-up was planned for all participants for the duration of the trial, including those who discontinued treatment prematurely.

Participants in the semaglutide groups followed a fixed dose-escalation regimen. For semaglutide 0·5 mg, the maintenance dose was reached after 4 weeks of semaglutide 0·25 mg once weekly. For semaglutide 1·0 mg, the maintenance dose was reached after 4 weeks of semaglutide 0·25 mg, followed by 4 weeks of semaglutide 0·5 mg.

Once-weekly semaglutide or semaglutide placebo was taken on the same day of the week and injections could be administered in the thigh, abdomen, or upper arm. Both semaglutide and sitagliptin could be taken at any time of day, irrespective of meals.

Background medications, not exceeding the maximum approved dose in that country, were used in accordance

with treatment guidelines or the local label at the discretion of the investigator. Participants continued background medications during the whole treatment period, maintained at the stable, pre-trial dose and frequency. Participants with unacceptable hyperglycaemia, despite treatment with trial product and background medication, were offered treatment intensification (rescue medication) according to prespecified rescue criteria at the discretion of the investigator (excluding GLP-1 receptor agonists, DPP-4 inhibitors, and pramlintide) as add-on to their randomly assigned trial product (appendix).

Outcomes

The primary outcome was change in HbA_{1c} from baseline at week 56, and the confirmatory secondary outcome (included in the hierarchical testing and in the power calculation) was change in bodyweight from baseline to week 56. Other secondary efficacy outcomes were the proportion of participants who, at week 56, had achieved an HbA_{1c} of less than 7·0% (53·0 mmol/mol),[3] an HbA_{1c} of less than 7·0% (53·0 mmol/mol) without severe or blood glucose-confirmed symptomatic hypoglycaemia and no weight gain, or HbA_{1c} of 6·5% (48·0 mmol/mol) or lower;[4] change from baseline to week 56 in fasting plasma glucose; self-measured plasma glucose (mean seven-point profile and mean postprandial increment, over all meals); insulin, C-peptide, glucagon, pro-insulin concentrations, pro-insulin–to-insulin ratio, homoeostatic model assessment of β-cell function and insulin resistance (HOMA-B/IR; all fasting); the proportion of participants at week 56 who achieved weight loss of at least 5% or at least 10%; change from baseline to week 56 in BMI, waist circumference (three consecutive waist measurements were taken at visit 2 [week 0] and visits 3, 5–9, and 11–13 [weeks 4, 8, 12, 16, 23, 30, 40, 48, and 56, respectively]), fasting blood lipids (measured at visits 2 [week 0], 9 [week 30], and 13 [week 56]) and systolic and diastolic blood pressure (measured at every visit including screening, except for phone visits at weeks 6 and 35), C-reactive protein concentration (measured at randomisation [visit 2; week 0] and end of treatment [visit 13, week 56]), patient-reported outcome questionnaires Short-Form (36) health survey version 2 (at randomisation and end of treatment), and Diabetes Treatment Satisfaction Questionnaire status (at randomisation and end of treatment).

Safety outcomes included the number of treatment-emergent adverse events; number of treatment-emergent severe or blood glucose-confirmed symptomatic hypoglycaemic episodes (defined as severe according to the American Diabetes Association [ADA] classification [event requiring assistance of another person to actively administer carbohydrates, glucagon, or take other corrective actions][20] or confirmed by a blood glucose value of <3·1 mmol/L [56 mg/dL] with symptoms consistent with hypoglycaemia); change in pulse rate after 56 weeks of treatment; and occurrence of anti-semaglutide antibodies during the trial. Treatment-emergent adverse events were defined as adverse events with an onset date (or increase in severity) on or after the first day of randomly assigned treatment and no later than the end of treatment, plus an ascertainment window of 42 days.

According to US Food and Drug Administration (FDA) requirements, and in an independent and blinded manner, an external event adjudication committee (EAC) validated reports of pancreatitis, neoplasms, and cardiovascular and fatal events (appendix). Blood samples were taken during site visits at all timepoints (except at week 48) and analysed at a central laboratory to assess levels of efficacy variables including HbA_{1c}, and fasting concentrations of plasma glucose, insulin, C-peptide, glucagon, pro-insulin, and lipids. Anti-semaglutide antibodies (measured at visits 2, 7, 9, 11, and 13 [weeks 0, 16, 30, 40, and 56, respectively]) and semaglutide plasma concentrations (measured at visits 3, 5, 7, 9, and 13 [weeks 4, 8, 16, 30, and 56, respectively]) were analysed at a specialist laboratory. Other laboratory analyses were done by the central laboratory. These clinical laboratory tests were based on both urine and blood samples and comprised haematology (eg, haemoglobin, haematocrit, and differential cell count), urinalysis (eg, urinary albumin:creatinine ratio, protein, and ketones), hormones (ie, calcitonin), biochemistry (eg, creatinine kinase, albumin, sodium, and potassium), and pregnancy (ie, β-human chorionic gonadotropin). Tests were done throughout the study between visits 1 and 14 (weeks –2 to 61), but not every variable was tested on every visit. Physical examination of body systems was done at screening (visit 1) and end of treatment (visit 13). An electrocardiogram was done at randomisation (visit 2), week 30 (visit 9), end of treatment (visit 13), and follow-up (visit 14). Adverse events were recorded during each contact with site staff (every visit from randomisation to follow-up, at weeks 0, 4, 6, 8, 12, 16, 23, 30, 35, 40, 48, 56, and 61). Questionnaires were completed at randomisation and end-of-treatment visits. Assessment of safety laboratory parameters, physical examination, and electrocardiogram readings were also done.

Statistical analysis

The trial was designed with 80% power to jointly establish non-inferiority and superiority with respect to the primary outcome (change in HbA_{1c} at week 56) and superiority with respect to the confirmatory secondary outcome (change in bodyweight at week 56) when comparing both semaglutide doses to a pooled sitagliptin group under the following assumptions for HbA_{1c}: no treatment difference, a non-inferiority margin of 0·3%, an SD of 1·1%, one-sided 2·5% significance level, and 30% premature treatment discontinuation. For bodyweight, the assumptions were a treatment difference of 1·5 kg and an SD of 4 kg. On this basis, 1200 participants were required to be randomly assigned in a 2:2:1:1 ratio.

Non-inferiority and superiority for the primary and confirmatory secondary outcomes (six tests in total) were assessed in a hierarchical manner to preserve the overall type-I error rate: non-inferiority in change in HbA_{1c} for semaglutide 1·0 mg versus sitagliptin; non-inferiority in change in HbA_{1c} for semaglutide 0·5 mg versus sitagliptin; superiority in change in HbA_{1c} for semaglutide 1·0 mg versus sitagliptin; superiority in change in bodyweight for semaglutide 1·0 mg versus sitagliptin; superiority in change in bodyweight for semaglutide 0·5 mg versus sitagliptin; and superiority in change in HbA_{1c} for semaglutide 0·5 mg versus sitagliptin (appendix). In the hierarchy, non-inferiority of HbA_{1c} was confirmed if the upper boundary of the two-sided 95% CI of the estimated treatment difference was below the non-inferiority margin of 0·3%, and HbA_{1c} superiority and bodyweight superiority were confirmed if below 0% and 0 kg, respectively. All p values were two-sided, and a p value of less than 0·05 was considered to indicate significance.

Data from the two sitagliptin groups (sitagliptin 100 mg plus semaglutide placebo 1·0 mg and sitagliptin 100 mg plus semaglutide placebo 0·5 mg) were pooled in the efficacy and safety assessments. Efficacy was assessed in a modified intention-to-treat analysis. The modified intention-to-treat and safety analysis sets included all randomised participants exposed to at least one dose of trial product. Continuous outcomes were analysed with a mixed model for repeated measurements with factors for treatment, country, and the corresponding baseline value all nested within visit. Efficacy analyses, assessing an efficacy (de jure) estimate, were based on the modified intention-to-treat population and included data obtained before or at initiation of rescue medication (for those receiving rescue medication) or premature discontinuation of trial product. The robustness of the conclusions from the primary and confirmatory secondary analyses were assessed in several sensitivity analyses, including an analysis based on all data recorded after randomisation, assessing an effectiveness (de facto) estimate and a comparator multiple imputation analysis (appendix).

Responder outcomes were HbA_{1c} less than 7·0%; HbA_{1c} less than or equal to 6·5%; weight loss of 5% or greater; weight loss of 10% or greater; and HbA_{1c} of less than 7·0% without severe or blood glucose-confirmed symptomatic hypoglycaemia and no weight gain, all at week 56.

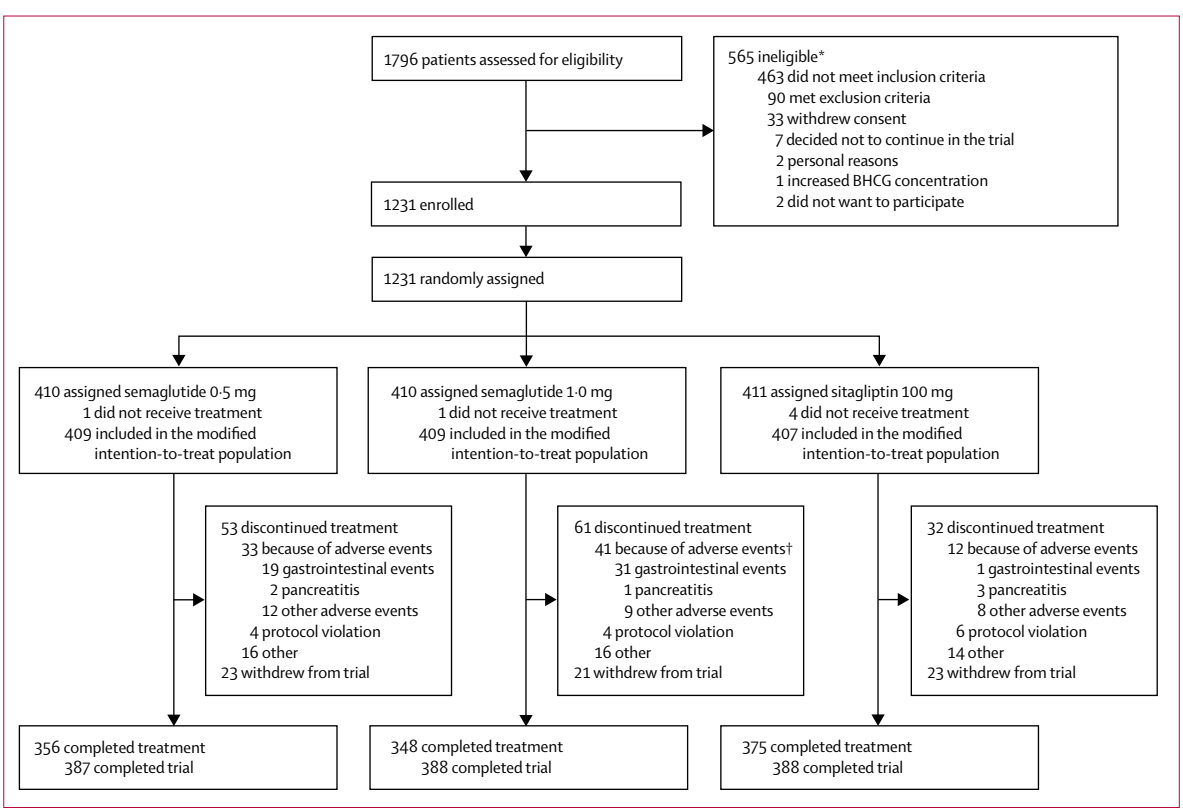

***Figure 1*: Trial profile**

Trial completers calculated as all subjects with a follow-up visit. BHCG=β-human chorionic gonadotropin.*Participants could have been ineligible for more than one reason. † Note that this number (n=41) differs from the corresponding number in table 3 (n=39). For one participant, the primary reason for premature treatment discontinuation was due to an adverse event, but the action to the drug was recorded as 'drug interrupted' rather than 'drug withdrawn'. Hence, this participant was recorded as having an adverse event, but this adverse event did not lead to premature treatment discontinuation. In an additional participant, the adverse event that led to premature treatment discontinuation was reported outside the on-treatment period (day –5) and thus is not included in the on-treatment adverse event summary tables.

	Semaglutide 0·5 mg (n=409)	Semaglutide 1·0 mg (n=409)	Sitagliptin 100 mg (n=407)
Age (years)	54·8 (10·2)	56·0 (9·4)	54·6 (10·4)
HbA_{1c}* (%)	8·0% (0·9)	8·0% (0·9)	8·2% (0·9)
HbA_{1c}* concentration (mmol/mol)	64·1 (10·1)	64·4 (10·2)	65·8 (10·1)
Fasting plasma glucose concentration (mmol/L)	9·3 (2·4)	9·3 (2·2)	9·6 (2·2)
Fasting plasma glucose concentration (mg/dL)	168·1 (43·0)	167·4 (39·9)	172·9 (38·8)
Diabetes duration (years)	6·4 (4·7)	6·7 (5·6)	6·6 (5·1)
Bodyweight (kg)	89·9 (20·4)	89·2 (20·7)	89·3 (19·7)
BMI (kg/m^2)	32·4 (6·2)	32·5 (6·6)	32·5 (5·8)
eGFR (MDRD; mL/min/1·73 m^2)	97·00 (60·0–317·0)	97·00 (55·0–171·0)	98·00 (53·0–194·0)
Sex			
Women	202 (49%)	204 (50%)	199 (49%)
Men	207 (51%)	205 (50%)	208 (51%)
Ethnic origin			
Hispanic or Latino	69 (17%)	67 (16%)	73 (18%)
Not Hispanic or Latino	340 (83%)	342 (84%)	334 (82%)
Race			
White	279 (68%)	279 (68%)	281 (69%)
Black or African American	18 (4%)	24 (6%)	17 (4%)
Asian	106 (26%)	99 (24%)	102 (25%)
Diabetes medications at randomisation			
Metformin	404 (99%)	407 (100%)	405 (100%)
Sulfonylureas†	1 (<1%)	0	1 (<1%)
Thiazolidinediones	23 (6%)	20 (5%)	23 (6%)
Metformin plus thiazolidinediones	20 (5%)	18 (4%)	22 (5%)
Combinations of oral blood glucose-lowering drugs‡	0	0	1 (<1%)
Other concomitant medications at randomisation (≥5% in any group)			
Proton-pump inhibitors	43 (11%)	20 (5%)	37 (9%)
Platelet aggregation inhibitors§	70 (17%)	85 (21%)	83 (20%)
Thiazides	40 (10%)	28 (7%)	28 (7%)
Sulfonamides	46 (11%)	47 (11%)	37 (9%)
β-blocking drugs, selective	68 (17%)	71 (17%)	79 (19%)
Dihydropyridine derivatives	67 (16%)	53 (13%)	62 (15%)
ACE inhibitors	95 (23%)	107 (26%)	109 (27%)
ACE inhibitors and diuretics	15 (4%)	25 (6%)	15 (4%)
Angiotensin II receptor antagonists	82 (20%)	69 (17%)	69 (17%)
Angiotensin II receptor antagonists and diuretics	27 (7%)	21 (5%)	20 (5%)
HMG CoA reductase inhibitors (statins)	154 (38%)	158 (39%)	155 (38%)
Fibrates	26 (6%)	23 (6%)	17 (4%)
Thyroid hormones	29 (7%)	23 (6%)	22 (5%)

Data are mean (SD), median (range), or n (%). eGFR=estimated glomerular filtration rate. MDRD=Modification of Diet in Renal Disease. ACE=angiotensin-converting enzyme. *Minimum or maximum HbA_{1c} might be outside the range specified in the inclusion criteria as the baseline measurement was made at the randomisation visit rather than recruitment. †Both participants on sulfonylureas were randomly assigned in error and discontinued treatment within 8 days of randomisation to study drug. ‡One patient was receiving Mopaday, a tablet containing pioglitazone and metformin. §Excludes heparin.

***Table 1*: Baseline characteristics at randomisation**

Responder outcomes were analysed by logistic regression, where missing response data were imputed from the mixed model for repeated measurements applied to the underlying continuous data, and subsequently dichotomised. Patient-reported outcomes, mean seven-point profile, and mean of the postprandial increments at week 56 were analysed by an ANCOVA model with treatment and country as fixed factors and the associated baseline value as a covariate, because these were only measured at baseline and at the end of treatment. Apart from HbA_{1c}, bodyweight, fasting plasma glucose, BMI, waist circumference, self-measured plasma glucose, patient-reported outcomes, pulse rate, blood pressure, glucose metabolism, and β-cell function (HOMA-B and HOMA-IR), the values of the variables were log transformed before analysis.

Safety outcomes were summarised and assessed by descriptive statistics for all randomly assigned participants exposed to at least one dose of trial product. Supportive safety analyses using all data collected during the trial were also done.

The need for a data monitoring committee was considered by the trial sponsor in accordance with FDA and European Medicines Agency guidance; however, the trial was not considered to meet the need for a data monitoring committee. All statistical analyses were done with SAS version 9.3.

This trial is registered with ClinicalTrials.gov, number NCT01930188.

Role of the funding source

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

Results

Between Dec 2, 2013, and Aug 5, 2014, we randomly assigned 1231 participants to treatment; of the 1225 participants exposed to at least one dose of study drug and included in the efficacy and safety analyses, 409 received once-weekly semaglutide 0·5 mg, 409 received once-weekly semaglutide 1·0 mg, and 407 received sitagliptin 100 mg once daily (203 in the semaglutide 0·5 mg placebo group and 204 in the semaglutide 1·0 mg placebo group; figure 1). 1163 (94%) participants completed the trial, which ended on Oct 12, 2015, at 61 weeks, in accordance with the protocol. 1079 (88%) of the 1225 participants completed treatment; 356 in the semaglutide 0·5 mg group, 348 in the semaglutide 1·0 mg group, and 375 in the sitagliptin 100 mg group. Rescue medication was provided to

22 (5%) of 409 participants in the semaglutide 0·5 mg group, nine (2%) of 409 participants in the 1·0 mg group, and 80 (20%) of 407 participants in the sitagliptin group. Baseline characteristics were broadly similar between the three groups (table 1), although mean baseline HbA_{1c} was slightly higher in the sitagliptin group (8·2%) than in the semaglutide 0·5 mg and 1·0 mg groups (8·0% in both groups; table 1).

The overall mean HbA_{1c} at baseline was 8·1% (SD 0·93). At week 56, mean HbA_{1c} had significantly decreased with semaglutide 0·5 mg and 1·0 mg by 1·3% and 1·6%, respectively, versus 0·5% with sitagliptin (table 2, figure 2). The estimated treatment difference versus sitagliptin was –0·77% (–0·92 to –0·62) with semaglutide 0·5 mg and –1·06% (–1·21 to –0·91) with semaglutide 1·0 mg; p<0·0001 for non-inferiority and for superiority, for both semaglutide doses versus sitagliptin. All sensitivity analyses resulted in similar and significant estimated treatment differences with corresponding 95% CIs (appendix). The cumulative distribution function for change in HbA_{1c} is shown in the appendix. The proportions of patients achieving HbA_{1c} concentrations of less than 7·0% or less than or equal to 6·5% was also significantly higher in both semaglutide groups than in the sitagliptin group (figure 2, appendix).

The reduction in mean fasting plasma glucose was significantly greater with semaglutide 0·5 mg and semaglutide 1·0 mg than with sitagliptin (table 2). Mean seven-point self-measured plasma glucose was also decreased significantly with both semaglutide doses compared with sitagliptin; incremental seven-point self-measured plasma glucose decreased significantly with semaglutide 1·0 mg compared with sitagliptin, but the difference between semaglutide 0·5 mg and sitagliptin was not significant (table 2).

There were significant reductions in fasting plasma glucagon, pro-insulin, pro-insulin or insulin ratio, and HOMA-IR, and a significant increase in HOMA-B with both semaglutide doses versus sitagliptin; fasting C-peptide was increased significantly with semaglutide

	Overall baseline (SD)	Semaglutide 0·5 mg (n=409)			Semaglutide 1·0 mg (n=409)			Sitagliptin 100 mg (n=407), change from baseline at week 56 (95% CI)
		Change from baseline at week 56 (95% CI)	Estimated treatment difference versus sitagliptin (95% CI)	p value	Change from baseline at week 56 (95% CI)	Estimated treatment difference versus sitagliptin (95% CI)	p value	
Glycaemia outcomes								
Mean HbA_{1c} (%)	8·1% (0·9)	–1·3% (–1·42 to –1·21)	–0·77% (–0·92 to –0·62)	<0·0001	–1·6% (–1·71 to –1·51)	–1·06% (–1·21 to –0·91)	<0·0001	–0·5% (–0·65 to –0·44)
Mean HbA_{1c} (mmol/mol)	64·8 (10·1)	–14·4 (–15·53 to –13·25)	–8·42 (–10·05 to –6·78)	<0·0001	–17·6 (–18·72 to –16·46)	–11·62 (–13·25 to –9·99)	<0·0001	–6·0 (–7·14 to –4·80)
Mean fasting plasma glucose (mmol/L)	9·4 (2·3)	–2·1 (–2·27 to –1·88)	–0·97 (–1·26 to –0·69)	<0·0001	–2·6 (–2·79 to –2·40)	–1·49 (–1·77 to –1·21)	<0·0001	–1·1 (–1·31 to –0·90)
Seven-point self-measured plasma glucose (mmol/L)								
Mean	10·8 (2·3)	–2·1 (–2·24 to –1·88)	–0·97 (–1·23 to –0·72)	<0·0001	–2·4 (–2·59 to –2·23)	–1·33 (–1·59 to –1·07)	<0·0001	–1·1 (–1·27 to –0·90)
Increment	2·8 (2·1)	–0·8 (–0·95 to –0·66)	–0·18 (–0·39 to 0·03)	0·09	–1·0 (–1·15 to –0·86)	–0·38 (–0·59 to –0·17)	0·0004	–0·6 (–0·77 to –0·47)
Bodyweight outcomes								
Mean bodyweight (kg)	89·5 (20·3)	–4·3 (–4·78 to –3·78)	–2·35 (–3·06 to –1·63)	<0·0001	–6·1 (–6·63 to –5·63)	–4·20 (–4·91 to –3·49)	<0·0001	–1·9 (–2·44 to –1·42)
Mean BMI (kg/m²)	32·5 (6·2)	–1·6 (–1·76 to –1·39)	–0·90 (–1·16 to –0·64)	<0·0001	–2·3 (–2·44 to –2·08)	–1·58 (–1·84 to –1·32)	<0·0001	–0·7 (–0·86 to –0·49)
Mean waist circumference (cm)	106·3 (14·3)	–4·3 (–4·91 to –3·78)	–2·10 (–2·91 to –1·29)	<0·0001	–5·9 (–6·49 to –5·36)	–3·67 (–4·48 to –2·87)	<0·0001	–2·2 (–2·83 to –1·67)
Blood pressure and pulse rate								
Mean systolic blood pressure (mm Hg)	132·6 (14·9)	–5·1 (–6·32 to –3·82)	–2·78 (–4·59 to –0·97)	0·0026	–5·6 (–6·85 to –4·38)	–3·32 (–5·13 to –1·52)	0·0003	–2·3 (–3·60 to –0·98)
Mean diastolic blood pressure (mm Hg)	80·7 (9·2)	–2·0 (–2·84 to –1·18)	–0·90 (–2·10 to 0·30)	0·14	–1·9 (–2·73 to –1·08)	–0·80 (–2·00 to 0·40)	0·19	–1·1 (–1·98 to –0·23)
Mean pulse rate (beats per min)	75·7 (9·9)	1·6 (0·76 to 2·40)	1·02 (–0·12 to 2·17)	0·08	1·8 (1·00 to 2·65)	1·27 (0·11 to 2·42)	0·0314	0·6 (–0·24 to 1·36)

Data are mean (SD), mean (95% CI), or treatment difference (95% CI). Overall, 1231 participants were randomly assigned; 1225 participants were exposed to treatment and included in the modified intention-to-treat analysis. Continuous outcomes were analysed using a mixed model for repeated measurements.

***Table 2*: Study outcomes by treatment group**

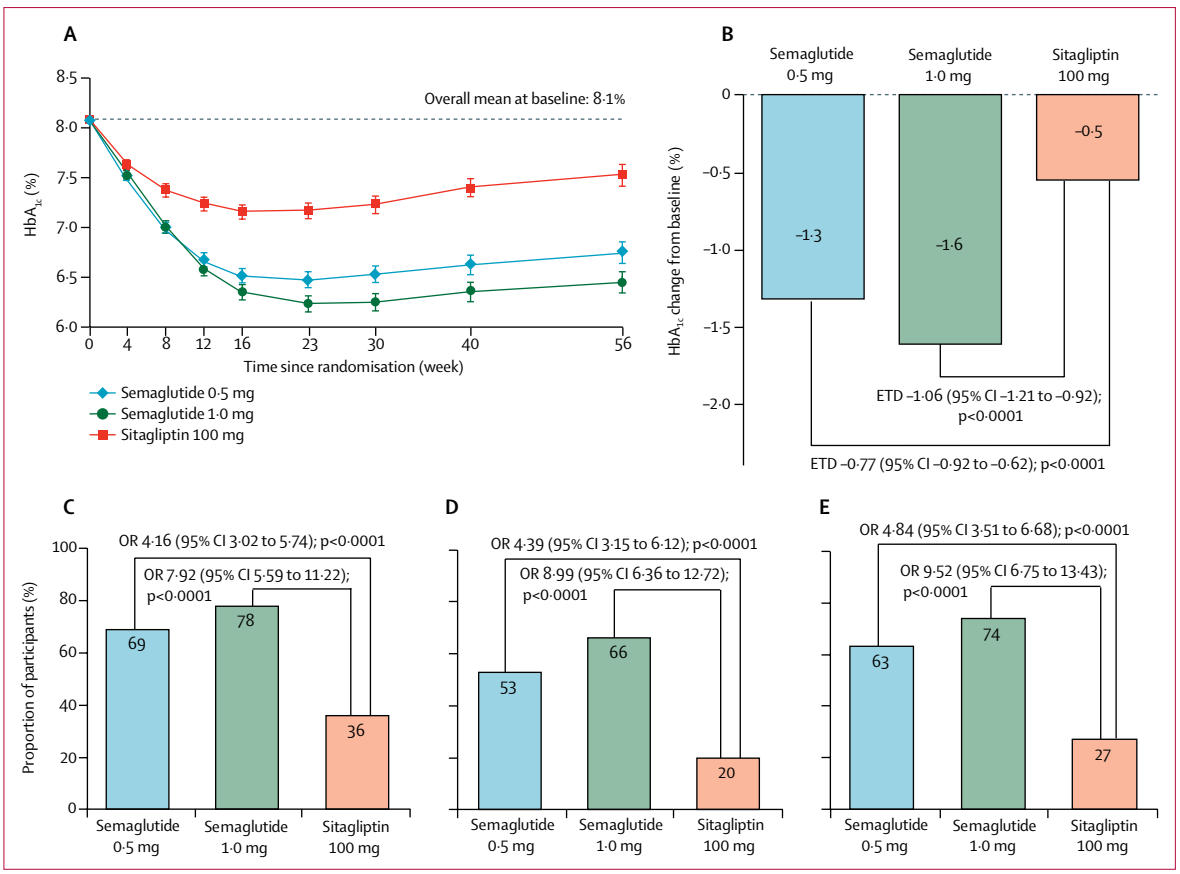

***Figure 2*: Efficacy outcomes of semaglutide 0·5 mg and 1·0 mg once weekly, compared with sitagliptin 100 mg**
Change in mean HbA_{1c} by week (A), change in mean HbA_{1c} after 56 weeks (B), proportion of participants achieving the HbA_{1c} target of less than 7·0% (C) and HbA_{1c} less than or equal to 6·5% (D), and proportion of participants achieving HbA_{1c} less than 7·0% without severe or blood glucose-confirmed symptomatic hypoglycaemia and with no weight gain (E). Data in (C), (D), and (E) were analysed with a logistic regression model. Data in (A) and (B) are estimated mean values (95% CIs, where shown) and ETDs from a mixed model for repeated measurements. All analyses used on-treatment without rescue medication data from participants in the modified intention-to-treat population. Blood glucose confirmed as less than or equal to 3·1 mmol/L (E). ETD=estimated treatment difference. OR=odds ratio.

0·5 mg compared with sitagliptin, but the difference was not significant between semaglutide 1·0 mg and sitagliptin (appendix). The decrease in fasting insulin at the end of treatment was not significantly different between either dose of semaglutide and sitagliptin (appendix).

Mean bodyweight was reduced by 4·3 kg with semaglutide 0·5 mg and 6·1 kg with semaglutide 1·0 mg versus a reduction of 1·9 kg with sitagliptin (estimated treatment difference –2·35 kg and –4·20 kg, respectively, both p<0·0001; table 2, figure 3). All sensitivity analyses resulted in similar and significant estimated treatment differences with corresponding 95% CIs (appendix). Weight-loss responses of 5% or greater and 10% or greater were achieved by more patients in the semaglutide groups than in the sitagliptin group (figure 3, appendix). BMI and waist circumference were also significantly reduced with both doses of semaglutide compared with sitagliptin (table 2).

The proportion of participants achieving HbA_{1c} of less than 7·0% (53·0 mmol/mol) without severe or blood glucose-confirmed symptomatic hypoglycaemia and with no weight gain was 63% in the semaglutide 0·5 mg group and 74% in the semaglutide 1·0 mg group, versus 27% in the sitagliptin group (figure 2, appendix).

Semaglutide 1·0 mg also slightly improved various lipid parameters compared with sitagliptin (appendix). HDL cholesterol was significantly increased, while triglycerides, VLDL cholesterol, and free fatty acids were significantly reduced with semaglutide 1·0 mg compared with sitagliptin. No significant differences were noted between semaglutide 0.5 mg and sitagliptin. No significant difference in change in LDL cholesterol and total cholesterol between either dose of semaglutide and sitagliptin was observed. Decreases in systolic blood pressure and diastolic blood pressure were significantly greater with semaglutide 0·5 mg and semaglutide 1·0 mg than with sitagliptin (table 2). Baseline C-reactive protein concentrations were similar across the three groups (geometric mean 2·33 mg/L; appendix). In all treatment groups, C-reactive protein concentrations decreased from baseline to week 56, with a significantly

greater reduction with both semaglutide doses than with sitagliptin (appendix).

Overall diabetes treatment satisfaction, as measured by the Diabetes Treatment Satisfaction Questionnaire, improved significantly more in the semaglutide 0·5 mg and semaglutide 1·0 mg groups than in the sitagliptin group, as did self-perceived hyperglycaemia (ie, where the participant felt that their blood sugars had been unacceptably high recently; appendix). Several health-related quality-of-life aspects, as measured by the Short-Form (36) health survey version 2, improved significantly with semaglutide versus sitagliptin (appendix), and none worsened.

The proportions of participants reporting any treatment-emergent adverse events and serious adverse events were similar between groups (table 3). The proportion of participants discontinuing treatment prematurely because of adverse events was similar with semaglutide 0·5 mg and semaglutide 1·0 mg, although both were higher than with sitagliptin (table 3, appendix). Proportions of participants discontinuing treatment prematurely for any reason are shown in the appendix, as are details of serious adverse events reported in the trial.

Two fatal events occurred in the semaglutide 0·5 mg group (one ischaemic cardiomyopathy and one cardiovascular disorder), one in the semaglutide 1·0 mg group (cardiorespiratory arrest), and three in the sitagliptin group (one ischaemic stroke, one road traffic accident, and one sudden death). All events were considered by the investigator to be unrelated to the trial drugs.

The most frequent adverse events were gastrointestinal adverse events (table 3). 73 (18%) of 409 participants in the semaglutide 0·5 mg group and 72 (18%) of 409 participants in the semaglutide 1·0 mg group versus 30 (7%) of

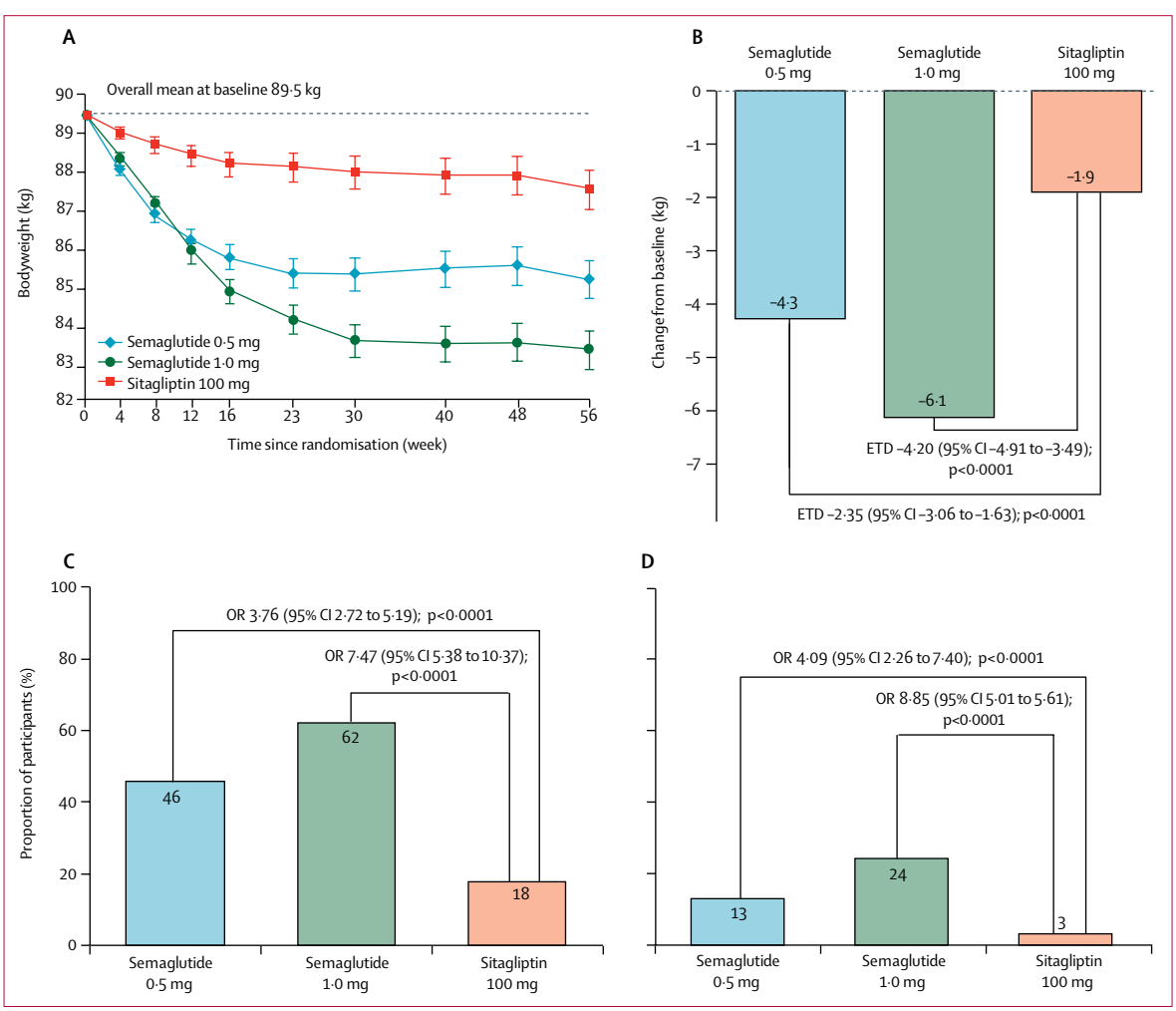

***Figure 3*: Bodyweight outcomes of semaglutide 0·5 mg and 1·0 mg once weekly, compared with sitagliptin 100 mg**

Change in mean bodyweight by week (A), change in mean bodyweight after 56 weeks (B), proportion of participants achieving 5% or greater weight loss (C) and 10% or greater weight loss (D). Data in (C) and (D) were analysed with a logistic regression model. Data in (A) and (B) were estimated mean values (95% CIs, where shown) and ETDs from a mixed model for repeated measurements. All analyses used on-treatment without rescue medication data from participants in the modified intention-to-treat population. ETD=estimated treatment difference. OR=odds ratio.

	Semaglutide 0·5 mg (n=409)		Semaglutide 1·0 mg (n=409)		Sitagliptin 100 mg (n=407)	
	Number of participants	Number of events	Number of participants	Number of events	Number of participants	Number of events
Any treatment-emergent adverse events	306 (75%)	1453	292 (71%)	1358	292 (72%)	1064
Serious adverse events	30 (7%)	55	30 (7%)	37	29 (7%)	39
Fatal adverse events*	2 (<1%)	2	1 (<1%)	1	3 (1%)	3
Severe adverse events†	26 (6%)	42	21 (5%)	31	21 (5%)	27
Moderate adverse events	122 (30%)	290	109 (27%)	300	114 (28%)	219
Mild adverse events	268 (66%)	1121	265 (65%)	1027	260 (64%)	818
Gastrointestinal adverse events	178 (44%)	462	163 (40%)	549	96 (24%)	175
Severe	13 (3%)	18	11 (3%)	17	4 (1%)	6
Moderate	56 (14%)	99	50 (12%)	132	22 (5%)	36
Mild	152 (37%)	345	144 (35%)	400	83 (20%)	133
Adverse events leading to premature discontinuation	33 (8%)	57	39‡ (10%)	70	12 (3%)	21
All gastrointestinal adverse events	27 (7%)	42	31 (8%)	51	3 (1%)	5
Nausea	11 (3%)	11	12 (3%)	15	2 (<1%)	2
Diarrhoea	10 (2%)	10	9 (2%)	9	0	..
Vomiting	3 (1%)	3	10 (2%)	10	0	..
Adverse events occurring in ≥5% of participants in one or more treatment groups by preferred term						
Nausea	73 (18%)	110	72 (18%)	140	30 (7%)	38
Diarrhoea	54 (13%)	92	53 (13%)	85	29 (7%)	35
Nasopharyngitis	50 (12%)	63	29 (7%)	33	42 (10%)	51
Vomiting	33 (8%)	49	41 (10%)	119	11 (3%)	16
Lipase increased§	33 (8%)	41	32 (8%)	38	29 (7%)	33
Headache	26 (6%)	81	29 (7%)	42	17 (4%)	29
Decreased appetite	27 (7%)	29	27 (7%)	29	11 (3%)	11
Influenza	18 (4%)	23	22 (5%)	25	27 (7%)	30
Dyspepsia	26 (6%)	28	20 (5%)	27	9 (2%)	11
Constipation	18 (4%)	20	23 (6%)	29	8 (2%)	9
Other adverse events						
EAC-confirmed pancreatitis (acute)	3 (1%)¶	3	..	..	..	..
EAC-confirmed pancreatitis (chronic)	..	..	1 (<1%)	1	..	..
Cholelithiasis	1 (<1%)	1	7 (2%)	7	6 (1%)	6
EAC-confirmed neoplasm	4 (1%)	4	10 (2%)	11	11 (3%)	13
Malignant neoplasms	0	..	2 (<1%)	2	2 (<1%)	2
Thyroid (papillary)	..	..	1 (<1%)	1	..	..
Neuroendocrine	0	..	0	..	1 (<1%)	1
Bladder	..	..	1 (<1%)	1	0	..
Undetermined	0	..	0	..	1 (<1%)	1
Benign neoplasms	4 (1%)	4	8 (2%)	9	9 (2%)	10
Diabetic retinopathy	1 (<1%)	1	0	..	3 (1%)	3

Preferred term events were based on the total percentage of subjects experiencing at least one event, unless indicated (≥5 were events reported by at least 5% of participants in one or more treatment groups). On-treatment summary of adverse events by preferred term includes events that are collected from first exposure to the follow-up visit scheduled at 42 days (5 weeks plus 1 week visit window) after last treatment dose. EAC=event adjudication committee. *All fatal adverse events were assessed as unlikely to be related to treatment by the investigator. †26 severe adverse events in the semaglutide 0.5 mg group, 14 in the semaglutide 1.0 mg group and 23 in the sitagliptin group (63/100) were assessed as unlikely to be related to treatment by the investigator. ‡This number (n=39) differs from the corresponding number in figure 1 (n=41). For one participant, the primary reason for premature treatment discontinuation was due to an adverse event, but the action to the drug was recorded as 'drug interrupted' rather than 'drug withdrawn'. Hence, this participant was recorded as having an adverse event, but this did not lead to premature treatment discontinuation. In an additional participant, the adverse event that led to premature treatment discontinuation was reported outside the on-treatment period (day –5) and thus was not included in the on-treatment adverse events summary tables. §More than the upper limit of normal (reference range 16–63 U/L). ¶One acute pancreatitis event was reported as severe.

***Table 3*: Adverse events overview in the safety analysis set**

407 participants in the sitagliptin group reported nausea; the proportion of patients with nausea diminished over time in the semaglutide groups (appendix). Diarrhoea was reported by 54 (13%) participants in the semaglutide 0·5 mg group and 53 (13%) participants in the semaglutide 1·0 mg group versus 30 (7%) in the sitagliptin group.

33 (8%) participants receiving semaglutide 0·5 mg and 41 (10%) receiving semaglutide 1·0 mg reported vomiting, compared with 11 (3%) in the sitagliptin group (table 3). The gastrointestinal adverse events in the semaglutide groups were mainly mild or moderate in severity.

The proportions of participants with blood glucose-confirmed hypoglycaemia were seven (2%) in the semaglutide 0·5 mg group, two (<1%) in the semaglutide 1·0 mg group, and five (1%) in the sitagliptin group. No participants in the semaglutide groups had severe events of hypoglycaemia, while two participants (<1%) receiving sitagliptin had one severe event of hypoglycaemia each (one case was judged as a serious adverse event, but was regarded as unrelated to the trial drug, and the participant subsequently recovered).

There were three events of acute pancreatitis in three participants in the semaglutide 0·5 mg group and one event of chronic pancreatitis in the semaglutide 1·0 mg group (all EAC-confirmed); no pancreatitis events were reported in the sitagliptin group (table 3). One of the participants receiving semaglutide 0·5 mg had acute, severe necrotising pancreatitis (with a history of diet inaccuracy) and the other two participants (both of whom had a history of gallstone disease) had mild, acute pancreatitis. The chronic pancreatitis reported in one patient in the semaglutide 1·0 mg group occurred in a participant with a history of gallstone disease and cholecystectomy. Amylase and lipase levels increased similarly with both semaglutide doses compared with sitagliptin (appendix).

Pulse rate increased by 1·6 beats per min with semaglutide 0·5 mg and 1·8 beats per min with semaglutide 1·0 mg versus 0·6 beats per min with sitagliptin (table 2); compared with sitagliptin, the increases in the semaglutide groups were not significant.

EAC-confirmed neoplasms were reported by four participants (1%) in the semaglutide 0·5 mg group, ten participants (2%) in the semaglutide 1·0 mg group, and 11 participants (3%) in the sitagliptin group. No malignant neoplasms were reported in the semaglutide 0·5 mg group, two were reported in the semaglutide 1·0 mg group (papillary thyroid cancer [n=1]; bladder cancer [n=1]), and two were reported in the sitagliptin group (metastatic neoplasm [n=1] and metastatic neuroendocrine carcinoma [n=1]; table 3). Calcitonin concentrations were similar between groups, with no apparent change during the trial.

Diabetic retinopathy was reported in one participant in the semaglutide 0·5 mg group and in three participants in the sitagliptin group (table 3). Six semaglutide-treated participants developed anti-semaglutide antibodies; in three participants, these antibodies cross-reacted with endogenous GLP-1. These antibodies did not have an in-vitro neutralising effect on semaglutide or endogenous GLP-1 in any of these patients. No clinically relevant changes in other safety laboratory assessments (eg, haematology, creatine kinase, and other biochemistry values), physical examination of body systems, or lectrocardiograms were reported (data not shown).

Discussion

In this phase 3a trial, semaglutide 0·5 mg and semaglutide 1·0 mg were superior to sitagliptin in improving glycaemic control and reducing bodyweight, leading to reductions of up to three times (with semaglutide 1·0 mg) compared with sitagliptin in HbA_{1c} and bodyweight, from baseline. The results from the primary analysis were substantiated by all sensitivity analyses. Improvements in glycaemic control and reductions in bodyweight in the semaglutide groups were associated with a low risk of hypoglycaemia, similar to that seen with sitagliptin.

Mean HbA_{1c} decreased over time in all three treatment groups, with reductions from baseline occurring as early as the first assessment at week 4. HbA_{1c} reductions with sitagliptin after 56 weeks were similar to those reported in other studies comparing a GLP-1 receptor agonist with sitagliptin.[21–23] More than three-quarters of participants in the semaglutide 1·0 mg and more than two-thirds of participants in the semaglutide 0·5 mg groups reached the ADA target of HbA_{1c} concentration less than 7·0% (53·0 mmol/mol),[3] compared with just over a third of participants in the sitagliptin group. The sitagliptin group did have a slightly higher baseline HbA_{1c} compared with the semaglutide groups, which might have contributed to the differences in the proportions of participants achieving HbA_{1c} targets. The results achieved with semaglutide are of clinical relevance because improvements in glycaemic control have been shown to reduce the risk of both diabetes-related complications and mortality.[24]

Head-to-head studies are not available, so direct comparisons are not possible; however, indirect comparisons of data from this trial with those from studies of other GLP-1 receptor agonists and DPP-4 inhibitors suggest that glycaemic control with semaglutide is potentially better than with other drugs in these classes. For example, although such indirect comparisons should be treated with caution, in terms of the proportion of participants achieving the composite outcome of an HbA_{1c} concentration lower than 7·0% (53·0 mmol/mol) with no weight gain and no hypoglycaemia, our findings for semaglutide seem to be favourable compared with data for another GLP-1 receptor agonist (dulaglutide).[25] In the SUSTAIN 1 trial in treatment-naive patients, at week 30, significant decreases (from baseline) in HbA_{1c} of 1·45% ($p<0·0001$ *vs* placebo) with semaglutide 0·5 mg and 1·55% ($p<0·0001$ *vs* placebo) with semaglutide 1·0 mg were reported versus a non-significant decrease of 0·02% with placebo, in individuals with type 2 diabetes. The proportions of participants achieving HbA_{1c} targets with semaglutide in this trial are similar to those reported for SUSTAIN 1.[18] Our results are also consistent with previous findings that suggested greater efficacy in

lowering HbA_{1c} with GLP-1 receptor agonists compared with DPP-4 inhibitors, which might be linked with mechanistic differences between the two classes (eg, greater stimulation of GLP-1 receptors with GLP-1 receptor agonists).[14,22,23]

For individuals with type 2 diabetes who are overweight or obese, weight losses of 5–10% are considered clinically meaningful and are associated with improvements in cardiovascular risk factors.[26] In this trial, about half of the participants achieved clinically meaningful weight loss with semaglutide, which was maintained until the end of treatment. These findings are consistent with the results of the SUSTAIN 1 trial, in which bodyweight was significantly decreased by 3·73 kg with semaglutide 0·5 mg and 4·53 kg with semaglutide 1·0 mg (both p<0·0001) versus a clinically non-significant decrease of 0·98 kg with placebo.[18] Sustained weight loss in patients with type 2 diabetes has been shown to improve glycaemic control and reduce the need for glucose-lowering medications.[27] Whether there was an association between bodyweight reduction and improved glycaemia was not analysed in the present study, since such an analysis was not prespecified. However, such analysis is planned for the future. In trials with other GLP-1 receptor agonists, the reductions in HbA_{1c} and bodyweight seem to be less than with semaglutide; however, these trials involved patients with different baseline characteristics and included different background antidiabetic therapies, so the results are not directly comparable.[21,23,28,29]

Semaglutide was well tolerated in this trial, with an adverse event profile consistent with the known class effects of the GLP-1 receptor agonists.[30] Similar proportions of participants reported adverse events and serious adverse events across treatment groups. There was a similar rate of premature treatment discontinuation between semaglutide doses, although the rates were higher than with sitagliptin; this difference was mainly caused by gastrointestinal adverse events. The proportion of participants experiencing gastrointestinal adverse events with semaglutide was higher than with sitagliptin, but was similar to that seen with other commonly used GLP-1 receptor agonists such as liraglutide.[31] The frequency of nausea diminished over time, as has been seen with other GLP-1 receptor agonists.[31] Four cases of pancreatitis (three acute and one chronic) were reported in participants receiving semaglutide. Results from the SUSTAIN 6 trial, a long-term cardiovascular outcomes and safety trial of semaglutide in participants with type 2 diabetes (at high cardiovascular risk, with HbA_{1c} ≥7%, and not treated with an antihyperglycaemic drug, or treated with ≤2 oral antihyperglycaemic drugs, with or without insulin), showed a similarly low rate of pancreatitis, which was similar to that seen with placebo.[19] One case of diabetic retinopathy was reported in a participant receiving semaglutide in the present trial, and three cases in participants receiving sitagliptin. Worsening of retinopathy has been associated with rapid glucose lowering in patients with insulin-dependent diabetes,[32,33] and results from the SUSTAIN 6 trial showed that semaglutide treatment resulted in a higher risk of diabetic retinopathy complications than placebo.[19] However, this finding might be related to the fast reduction in glucose concentrations, rather than a direct effect of semaglutide treatment.

An increase in pulse rate, a known class effect for GLP-1 receptor agonists, was seen with semaglutide at both doses in the present trial; however, this change was not significantly different from that seen with sitagliptin. Moreover, the pulse rate increase should be considered in the context of other effects on the cardiovascular risk profile seen with semaglutide in this trial, including the reduction in systolic blood pressure and the improvements in several lipid parameters compared with sitagliptin. The results of the SUSTAIN 6 trial[19] have provided further evidence concerning cardiovascular outcomes and the long-term safety profile of semaglutide. The rates of first occurrence of a composite outcome of death from cardiovascular causes, non-fatal stroke, or non-fatal myocardial infarction were 26% lower with semaglutide compared with placebo in participants with type 2 diabetes with high cardiovascular risk; this effect was driven by differences in non-fatal stroke and non-fatal myocardial infarction.[19] Whether these findings are applicable to a population with no or fewer cardiovascular risk factors remains to be seen.

Strengths of the trial included the head-to-head comparison of semaglutide with sitagliptin, with parallel treatment groups and the randomised, double-blind, double-dummy, controlled design, which was chosen to provide robust assessment of the effects of semaglutide. There was a high level of treatment adherence (based on measures of exposure, semaglutide plasma concentrations, and protocol deviations; data not shown) and the protocol deviations did not affect the overall conclusions of the trial. Although higher with semaglutide compared with sitagliptin, the rate of premature treatment discontinuation because of adverse events was less than 10% in all groups, with a high proportion of participants completing the trial and treatment. A higher number of participants completed treatment without receiving rescue medication with semaglutide (both doses) compared with sitagliptin, reflecting the greater efficacy of semaglutide versus sitagliptin treatment.

The double-blind, double-dummy design of this trial—although a clear advantage in allowing an unbiased comparison of the trial product—might also have limited the interpretation of patient-reported outcomes. The trial products assessed here had differing modes of administration (injectable and oral), so any differences in treatment satisfaction are likely to reflect the pharmacological effects isolated from the mode of administration. Thus, this design might have inadvertently masked any potential difference in satisfaction associated with administration methods. However, studies have

shown that, generally, patients do not necessarily associate injectable therapies with a negative effect on treatment satisfaction if efficacy is greater.[22,34]

Although the trial was sufficiently long in duration to assess the primary outcome of HbA_{1c}, it was short in view of the chronic nature of diabetes and also underpowered to assess differences between treatments for rare safety issues, such as alterations of the exocrine pancreas and thyroid. Longer and more extensive trial data will be needed to further assess the safety of semaglutide. Additionally, although the inclusion criteria included participants receiving stable treatment with metformin, pioglitazone, or rosiglitazone alone, or a combination of metformin and pioglitazone or rosiglitazone, very few participants were enrolled on thiazolidinediones, whether alone or in combination. Thus, the findings in this study subpopulation should be interpreted with caution. Finally, participants enrolled in this trial were generally younger than 60 years, had normal renal function, and a BMI lower than 30 kg/m², which might be different from clinical practice.

In summary, once-weekly semaglutide 0·5 mg and semaglutide 1·0 mg were superior to sitagliptin, providing up to three times greater glycaemic control and weight loss, in participants with type 2 diabetes on metformin, thiazolidinediones, or both, after 56 weeks of treatment. Semaglutide was well tolerated, with a safety profile similar to that of other GLP-1 receptor agonists. On the basis of these results, we conclude that once-weekly semaglutide is a promising treatment option as an add-on to metformin or thiazolidinediones when these drugs alone are insufficient to achieve glycaemic control in participants with type 2 diabetes.

Contributors

All authors participated in the trial design. BA, LM, HK, MS, and FC contributed to the conduct of the trial and the data collection. JDK and SHJ contributed to the data analysis. All authors interpreted the data and participated in writing the report, with the support of medical writing services provided by the funder. All authors read and approved the submitted version of the report.

Declaration of interests

In conducting this trial, BA has received honoraria for lecturing, consultancy, or both from GlaxoSmithKline, Merck Sharp & Dohme, Novartis, Novo Nordisk, and Sanofi. LM has received honoraria from Novo Nordisk, Sanofi, Janssen, Abbott, and Merck in his capacity as an advisor. HK has received research grants from Novo Nordisk and personal fees from Novo Nordisk and Eli Lilly. MS has received research grants from Novo Nordisk and AstraZeneca. JDK is a full-time employee of Novo Nordisk A/S and holds stock in the company. SHJ holds stock in Novo Nordisk A/S and, at the time of the trial, was an employee of the company. FC has received research grants from Novo Nordisk, Takeda Pharmaceuticals, and Boehringer Ingelheim and honoraria for advisory panels from Novo Nordisk, AstraZeneca, and Eli Lilly.

Acknowledgments

The trial was funded by Novo Nordisk A/S, Denmark. We thank all the participants, investigators, and trial-site staff who were involved in the conduct of the trial. We also thank Sayeh Tadayon and Uffe Jon Ploug (both from Novo Nordisk A/S, Søborg, Denmark) for their review of the draft report and input into the submitted report, and Lisa Langley (AXON Communications, London, UK) for medical writing and editorial assistance; they all received compensation from Novo Nordisk.

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