Efficacy and safety of once-weekly semaglutide versus once-daily insulin glargine as add-on to metformin (with or without sulfonylureas) in insulin-naive patients with type 2 diabetes (SUSTAIN 4): a randomised, open-label, parallel-group, multicentre, multinational, phase 3a trial

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Summary

Background Several pharmacological treatment options are available for type 2 diabetes; however, many patients do not achieve optimum glycaemic control and therefore new therapies are necessary. We assessed the efficacy and safety of semaglutide, a glucagon-like peptide-1 (GLP-1) analogue in clinical development, compared with insulin glargine in patients with type 2 diabetes who were inadequately controlled with metformin (with or without sulfonylureas).

Methods We did a randomised, open-label, non-inferiority, parallel-group, multicentre, multinational, phase 3a trial (SUSTAIN 4) at 196 sites in 14 countries. Eligible participants were insulin-naive patients with type 2 diabetes, aged 18 years and older, who had insufficient glycaemic control with metformin either alone or in combination with a sulfonylurea. We randomly assigned participants (1:1:1) to either subcutaneous once-weekly 0·5 mg or 1·0 mg semaglutide (doses reached after following a fixed dose-escalation regimen) or once-daily insulin glargine (starting dose 10 IU per day, then titrated weekly to a pre-breakfast self-measured plasma glucose target of 4·0–5·5 mmol/L [72–99 mg/dL]) for 30 weeks. In all treatment groups, previous background metformin and sulfonylurea treatment was continued throughout the trial. We did the randomisation using an interactive voice or web response system. The primary endpoint was change in mean HbA_{1c} from baseline to week 30 and the confirmatory secondary endpoint was the change in mean bodyweight from baseline to week 30. We assessed efficacy and safety in the modified intention-to-treat population (mITT; all randomly assigned participants who were exposed to at least one dose of study drug) and used a margin of 0·3% to establish non-inferiority in HbA_{1c} reduction. This trial is registered with ClinicalTrials.gov, number NCT02128932.

Findings Between Aug 4, 2014, and Sept 3, 2015, we randomly assigned 1089 participants to treatment; the mITT population consisted of 362 participants assigned to 0·5 mg semaglutide, 360 to 1·0 mg semaglutide, and 360 to insulin glargine. 49 (14%) participants assigned to 0·5 mg semaglutide discontinued treatment prematurely, compared with 55 (15%) assigned to 1·0 mg semaglutide, and 26 (7%) assigned to insulin glargine. Most discontinuations were due to adverse events—mostly gastrointestinal with semaglutide, and others such as skin and subcutaneous tissue disorders (eg, rash, pruritus, and urticaria) with insulin glargine. From a mean baseline HbA_{1c} of 8·17% (SD 0·89), at week 30, 0·5 and 1·0 mg semaglutide achieved reductions of 1·21% (95% CI 1·10–1·31) and 1·64% (1·54–1·74), respectively, versus 0·83% (0·73–0·93) with insulin glargine; estimated treatment difference versus insulin glargine –0·38% (95% CI –0·52 to –0·24) with 0·5 mg semaglutide and –0·81% (–0·96 to –0·67) with 1·0 mg semaglutide (both p<0·0001). Mean bodyweight at baseline was 93·45 kg (SD 21·79); at week 30, 0·5 and 1·0 mg semaglutide achieved weight losses of 3·47 kg (95% CI 3·00–3·93) and 5·17 kg (4·71–5·66), respectively, versus a weight gain of 1·15 kg (0·70–1·61) with insulin glargine; estimated treatment difference versus insulin glargine –4·62 kg (95% CI –5·27 to –3·96) with 0·5 mg semaglutide and –6·33 kg (–6·99 to –5·67) with 1·0 mg semaglutide (both p<0·0001). Severe or blood glucose-confirmed hypoglycaemia was reported by 16 (4%) participants with 0·5 mg semaglutide and 20 (6%) with 1·0 mg semaglutide versus 38 (11%) with insulin glargine (p=0·0021 and p=0·0202 for 0·5 mg and 1·0 mg semaglutide *vs* insulin glargine, respectively). Severe hypoglycaemia was reported by two (<1%) participants with 0·5 mg semaglutide, five (1%) with 1·0 mg semaglutide, and five (1%) with insulin glargine. Six deaths were reported: four (1%) in the 0·5 mg semaglutide group (three cardiovascular deaths, one pancreatic carcinoma, which was assessed as being possibly related to study medication) and two (<1%) in the insulin glargine group (both cardiovascular death). The most frequently reported adverse events were nausea with semaglutide, reported in 77 (21%) patients with 0·5 mg and in 80 (22%) with 1·0 mg, and nasopharyngitis reported in 44 (12%) patients with insulin glargine.

Interpretation Compared with insulin glargine, semaglutide resulted in greater reductions in HbA_{1c} and weight, with fewer hypoglycaemic episodes, and was well tolerated, with a safety profile similar to that of other GLP-1 receptor agonists.

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Research in context

Evidence before this study

The design of this phase 3a trial of the novel glucagon-like peptide-1 (GLP-1) analogue semaglutide was based on findings from preclinical safety and pharmacology studies and clinical phase 1 and 2 trials. Results from a phase 2 dose-finding trial and one of the phase 1 trials suggested that an adjusted dose-escalation regimen was likely to offer a more acceptable gastrointestinal tolerability profile, while maintaining efficacy, than starting at the final dose.

Added value of this study

The findings from this study show that semaglutide given once weekly leads to substantial lowering of HbA_{1c} with substantial weight loss compared with basal insulin glargine as a reference active comparator. The safety profile of gradually titrated semaglutide appears to be similar to currently available GLP-1 receptor agonists, with adverse events consisting mainly of gastrointestinal events such as nausea and diarrhoea, with a lower risk of hypoglycaemia than insulin glargine.

Implications of all the available evidence

Semaglutide given once weekly seems to be a beneficial treatment for patients with type 2 diabetes who are inadequately controlled on metformin, with or without sulfonylureas. It both significantly improves glycaemic control and leads to weight loss that seems potentially greater than has been reported for other GLP-1 receptor agonists, although indirect comparisons should be treated with caution. Semaglutide has a safety profile that is similar to those of other GLP-1 receptor agonists.

Introduction

Type 2 diabetes is a complex disorder that requires individualised treatment strategies. Because of its progressive nature, most patients with type 2 diabetes will require treatment intensification, which can be in the form of additional antihyperglycaemic agents either as oral or injectable therapies.[1] Currently, the most commonly used injectable treatments for patients who do not meet glycaemic targets on oral therapy are basal insulins or glucagon-like peptide-1 (GLP-1) receptor agonists.[1] Basal insulin, although effective in controlling hyperglycaemia for many patients,[2,3] is associated with adverse effects such as hypoglycaemia and weight gain.[4] By contrast, GLP-1 receptor agonists stimulate insulin secretion and inhibit the release of glucagon from pancreatic islets in a glucose-dependent manner,[5] resulting in effective glucose lowering that is similar to that achieved with basal insulin therapy but without the increased risk of hypoglycaemia.[6] These drugs have also been shown to reduce bodyweight.[6] Although GLP-1 receptor agonists were initially used once or twice per day, more recent efforts have focused on the development of once-weekly GLP-1 receptor agonists (including exenatide extended release, albiglutide, and dulaglutide), with the potential to improve treatment adherence and quality of life for patients.[6,7]

Semaglutide, a GLP-1 analogue currently in development, is structurally similar to liraglutide, an approved once-daily GLP-1 analogue. Structural modifications of the semaglutide molecule include aminoacid substitutions at position 8 (alanine to α-aminoisobutyric acid) and position 34 (lysine to arginine), and acylation of the lysine at position 26 with a spacer and C-18 fatty diacid chain.[8] The substitution at position 8 renders semaglutide less susceptible to degradation by dipeptidyl peptidase-4 (DPP-4), and the lysine acylation improves binding to albumin.[8] These modifications extend the half-life of semaglutide to roughly 1 week,[8] enabling its once-weekly administration.[9,10]

The findings from the phase 3a SUSTAIN 1 trial[11] showed that 0·5 mg and 1·0 mg semaglutide significantly improved HbA_{1c} and bodyweight in treatment-naive patients with type 2 diabetes compared with placebo and showed a similar safety profile to that of other GLP-1 receptor agonists. Here, we report the findings from the SUSTAIN 4 phase 3a trial, which assessed the efficacy, safety, and tolerability of 0·5 mg and 1·0 mg semaglutide compared with insulin glargine in insulin-naive patients with type 2 diabetes who had inadequate glycaemic control with metformin alone or in combination with a sulfonylurea.

Methods

Study design and participants

We did a phase 3a, randomised, open-label, non-inferiority, active-controlled, parallel-group, multicentre, multinational, three-armed trial (SUSTAIN 4) at 196 sites (including hospitals, clinical research units, and private offices) in Argentina, Croatia, France, Germany, India, Macedonia, Mexico, the Netherlands, Romania, Slovakia, Slovenia, South Africa, the UK, and the USA. The study protocol was approved by either institutional review boards or ethics committees at each site, according to local practice.

Eligible participants were insulin-naive patients with type 2 diabetes (HbA_{1c} 7·0%–10·0% [53–86 mmol/mol]), aged 18 years or older, on stable treatment with metformin alone or in combination with a sulfonylurea for at least 90 days before screening. Key exclusion criteria included a history of chronic or idiopathic acute pancreatitis, a screening calcitonin value of at least 50 ng/L, any personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2, severely impaired renal function (estimated glomerular filtration rate [eGFR] <30 mL/min per 1·73 m²), heart failure (New York Heart Association class IV) or any acute coronary or cerebrovascular events

within the previous 90 days before screening, and known proliferative retinopathy or maculopathy requiring acute treatment (any cases of retinopathy identified in the trial were likely to be new; however, retinopathy was not monitored as a trial procedure). Full eligibility criteria are in the appendix. Written informed consent was obtained from all participants.

Randomisation and masking

Participants were randomly assigned (1:1:1) to receive 0·5 mg semaglutide, 1·0 mg semaglutide, or insulin glargine via an interactive, automated voice or web response system without human involvement. Patients were stratified based on their pretrial medication (metformin, or metformin and a sulfonylurea). Investigators and participants were unmasked, apart from members of an external event adjudication committee who validated predefined events in a masked manner (appendix). The trial had an open-label design because of the different dosing frequencies and titration of insulin glargine compared with semaglutide.

Procedures

After a 2-week screening period, participants received once-weekly subcutaneously injected semaglutide (0·5 mg or 1·0 mg; Novo Nordisk A/S, Bagsværd, Denmark) or once-daily subcutaneously injected insulin glargine (Lantus U100, Sanofi, Gentilly, France) for 30 weeks, followed by a 5-week follow-up. Participants who stopped treatment prematurely were encouraged to remain in the trial and complete follow-up. We selected semaglutide dosing on the basis of findings from the phase 2 dose-finding trial,[12] and participants followed a fixed dose-escalation regimen. For those allocated to 0·5 mg semaglutide, this dose was reached after 4 weeks of once-weekly 0·25 mg semaglutide. The 1·0 mg semaglutide dose was reached after 4 weeks of once-weekly 0·25 mg, followed by 4 weeks of once-weekly 0·5 mg.

Participants assigned to insulin glargine started on a dose of 10 IU once daily. Protocol instructions were to titrate the insulin dose weekly to a pre-breakfast self-measured plasma glucose (SMPG) target of 4·0–5·5 mmol/L (72–99 mg/dL; appendix). Titration was according to the lowest value of each participant's fasting one-point profile SMPG concentrations 3 days before visits or phone contacts. All insulin adjustments were at the discretion of the investigators and were not reinforced by a titration committee. Patients administered their own injections in the thigh, abdomen, or upper arm. For semaglutide administration, injections (via prefilled PDS290 injectors [Novo Nordisk A/S, Denmark]) could be done at any time of the day, but on the same day each week. Participants were encouraged to inject in the same area throughout the trial for future semaglutide pharmacokinetic analyses of equivalence between injection sites. For insulin glargine, injection sites had to be rotated within a given injection area from one injection to the next. The time of administration was up to the patient but it had to be the same time every day. In all treatment groups, previous metformin treatment, with or without a sulfonylurea, was continued throughout the trial.

See Online for appendix

Participants with unacceptable hyperglycaemia (defined as any fasting SMPG measurement >15·0 mmol/L [270 mg/dL] from randomisation to end of week 5, 13·3 mmol/L [240 mg/dL] from week 6 to end of week 11, or 11·1 mmol/L [200 mg/dL] after week 12) were to be offered rescue treatment (intensification of existing background medication or initiation of new medication, preferably excluding GLP-1 receptor agonists, DPP-4 inhibitors, or amylin analogues) as an add-on to their randomised treatment at the discretion of the investigator, in accordance with treatment guidelines from the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD).[1]

Outcomes

The primary endpoint was the change in mean HbA_{1c} from baseline to week 30 (end of treatment). The confirmatory secondary endpoint was change in bodyweight from baseline to week 30. Other secondary efficacy endpoints measured at week 30 were the proportion of participants who achieved HbA_{1c} of less than 7·0% (53 mmol/mol)[13] or HbA_{1c} of 6·5% or less (48 mmol/mol)[14] by the end of treatment; the proportion of participants achieving HbA_{1c} of less than 7·0% without severe hypoglycaemia according to the ADA classification[15] (ie, an event requiring assistance of another person to actively administer carbohydrates, glucagon, or take other corrective actions) or blood glucose-confirmed symptomatic hypoglycaemia (plasma glucose ≤3·1 mmol/L [56 mg/dL]) and no weight gain; change from baseline to week 30 in mean fasting plasma glucose (FPG), mean 8-point SMPG profiles, and postprandial increment; proportions of participants who achieved a weight loss of at least 5% and at least 10% by the end of treatment; and the changes from baseline in BMI, waist circumference, fasting blood lipids (total cholesterol, LDL cholesterol, HDL cholesterol, VLDL cholesterol, triglycerides, and free fatty acids), systolic and diastolic blood pressure, plasminogen activator inhibitor-1, C-reactive protein, and patient-reported outcomes (Short Form [SF]-36 version 2 health survey and Diabetes Treatment Satisfaction Questionnaire [DTSQ]).

Safety endpoints were the number of treatment-emergent adverse events and the number of treatment-emergent severe or blood glucose-confirmed symptomatic hypoglycaemic episodes during exposure, and pulse rate. Other safety measurements were changes in laboratory variables (haematology, biochemistry, calcitonin, urinalysis, and urinary albumin-to-creatinine ratio) and

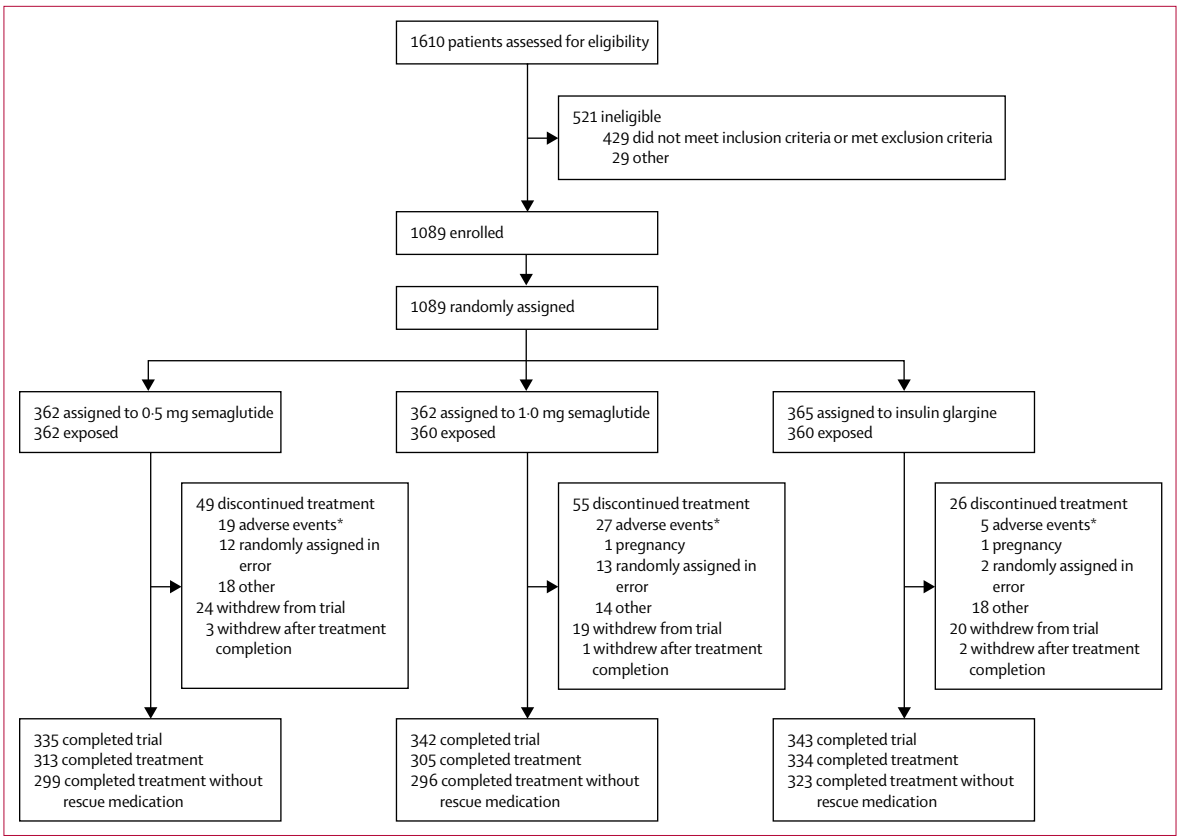

Figure 1: **Trial profile**
Patients who completed the trial were defined as those with at least one follow-up visit. Reasons for patients not being exposed to treatment were withdrawal by the patient or loss to follow-up. *Main reason for treatment discontinuation, as judged by the investigator.

examinations (electrocardiogram and physical examination) at week 30, the occurrence and concentration of antisemaglutide antibodies, and semaglutide pharmacokinetics (to be included in future population pharmacokinetic analyses).

Statistical analysis

The trial was powered for the primary endpoint (change in HbA_{1c} at 30 weeks) to assess non-inferiority for both doses of semaglutide, separately tested against insulin glargine, under the following assumptions: no treatment difference; a non-inferiority margin of 0·3%; 1:1:1 randomisation; SD 1·1%; a one-sided significance level of 0·025; and 30% dropout. On the basis of these assumptions, a sample size of 1047 participants was specified, which would ensure at least 90% power for each of the HbA_{1c} non-inferiority tests. Furthermore, this sample size ensured 99% power to detect a difference between 1·0 mg semaglutide versus insulin glargine of 1·5 kg change in bodyweight (SD 4·0 kg). With a conservative assumption of independence between the two endpoints, the joint power was 80%.

To preserve the overall type I error rate, we used a prespecified hierarchical testing approach (appendix): non-inferiority for the change in HbA_{1c} for 1·0 mg semaglutide versus insulin glargine; superiority in the change in bodyweight for 1·0 mg semaglutide versus insulin glargine; non-inferiority in the change in HbA_{1c} for 0·5 mg semaglutide versus insulin glargine; superiority in the change in HbA_{1c} for 1·0 mg semaglutide versus insulin glargine; superiority in the change in bodyweight for 0·5 mg semaglutide versus insulin glargine; and superiority in the change in HbA_{1c} for 0·5 mg semaglutide versus insulin glargine. Superiority for either change in HbA_{1c} or bodyweight was considered established if the upper limit of the two-sided 95% CI for the estimated differences was less than 0% or 0 kg, respectively.

We assessed efficacy in the modified intention-to-treat (mITT) population, which consisted of all randomly assigned participants who were exposed to at least one dose of study drug, as specified in the trial protocol; the assessment used data obtained before the initiation of any rescue medication or before premature treatment discontinuation. We assessed safety in the same mITT population. For safety, we used only data obtained before premature treatment discontinuation, with an ascertainment window of 42 days to define treatment-emergent adverse events. We also did supportive sensitivity analyses using all data obtained during the trial for both efficacy and safety.

Analysis methods for HbA_{1c}, bodyweight, and other continuous endpoints assessed over time included a mixed model for repeated measurements, with factors for treatment, country, stratum (metformin with or without a sulfonylurea), and baseline value, all nested within visits. An unstructured covariance matrix was assumed for measurements within the same participant. Outcomes assessing the secondary HbA_{1c} and bodyweight targets were analysed with logistic regression. All p values are from two-sided tests of the null hypothesis of no treatment difference; a value of 0·05 was regarded as significant. The robustness of the analyses of HbA_{1c} and bodyweight was assessed by handling missing data in several ways, including a comparator-based multiple imputation model in which missing data points were imputed on the basis of observed data in the insulin glargine group. Prespecified sensitivity analyses included a mixed model for repeated measurements analysis of the mITT population using all data, irrespective of whether they were obtained while the participants had discontinued the study drug or whether the participant had been given rescue medication (appendix). We used SAS version 9.3 for all statistical analyses. A data safety monitoring committee was not involved in this study. This trial is registered with ClinicalTrials.gov, number NCT02128932.

Role of the funding source

The funder of the study designed the trial and developed the protocol in consultation with VRA and JHDV. The funder provided logistical support during the trial and obtained the data. 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 the data in the study and had final responsibility for the decision to submit for publication.

	0·5 mg semaglutide (n=362)	1·0 mg semaglutide (n=360)	Insulin glargine (n=360)	Total (n=1082)
Age (years)	56·5 (10·3)	56·7 (10·4)	56·2 (10·6)	56·5 (10·4)
Sex				
Female	165 (46%)	178 (49%)	165 (46%)	508 (47%)
Male	197 (54%)	182 (51%)	195 (54%)	574 (53%)
HbA_{1c} (%)	8·1 (0·8)	8·3 (0·9)	8·1 (0·9)	8·2 (0·9)
HbA_{1c} (mmol/mol)	65·4 (9·3)	66·6 (10·3)	65·4 (9·6)	65·8 (9·7)
Diabetes duration (years)	7·8 (5·1)	9·3 (7·2)	8·6 (6·3)	8·6 (6·3)
Bodyweight (kg)	93·7 (21·4)	94·0 (22·5)	92·6 (21·5)	93·5 (21·8)
BMI (kg/m²)	33·1 (6·5)	33·0 (6·5)	33·0 (6·5)	33·0 (6·5)
eGFR (MDRD; mL/min per 1·73 m²)	97·9 (25·9)	98·0 (27·5)	99·7 (26·5)	98·5 (26·6)
Oral antidiabetes treatment†				
Metformin monotherapy	176 (49%)	175 (49%)	172 (48%)	523 (48%)
Metformin plus a sulfonylurea	186 (51%)	185 (51%)	188 (52%)	559 (52%)
Ethnic origin				
Hispanic or Latino	61 (17%)	74 (21%)	78 (22%)	213 (20%)
Not Hispanic or Latino	301 (83%)	286 (79%)	281 (78%)	868 (80%)
NA‡	0	0	1 (<1%)	1 (<1%)
Race				
Native American or Alaska Native	1 (<1%)	0	1 (<1%)	2 (<1%)
Asian	42 (12%)	39 (11%)	38 (11%)	119 (11%)
Black or African American	32 (9%)	34 (9%)	33 (9%)	99 (9%)
White	279 (77%)	279 (78%)	276 (77%)	834 (77%)
Other	3 (<1%)	3 (<1%)	5 (1%)	11 (1%)
NA‡	5 (1%)	5 (1%)	7 (2%)	17 (2%)

Data are mean (SD) or n (%). eGFR=estimated glomerular filtration rate. MDRD=modification of diet in renal disease. NA=not applicable. *The modified intention-to-treat population comprised all randomly assigned participants who were exposed to at least one dose of study drug. †Metformin doses ≥1500 mg or maximum tolerated dose were allowed. Sulfonylurea doses ≥half the maximum dose allowed according to national label. ‡One patient at a US site chose not to report their ethnic origin, and data about race were not collected in sites in France (all counted as NA).

Table 1*: Baseline characteristics of the modified intention-to-treat population

Results

We did the trial from August 4, 2014, to Sept 3, 2015, with participant recruitment taking place between Aug 4, 2014, and Dec 16, 2014. We randomly assigned 1089 participants, of whom 1082 (99%) were exposed to a study drug (figure 1). 1020 (94%) randomly assigned participants completed the trial and 952 (88%) completed their assigned treatment. The mITT population consisted of 362 participants assigned to 0·5 mg semaglutide, 360 assigned to 1·0 mg semaglutide, and 360 assigned to insulin glargine. The numbers of participants who completed assigned treatment without the need for rescue medication were 299 (83%) with 0·5 mg semaglutide, 296 (82%) with 1·0 mg semaglutide, and 323 (91%) with insulin glargine. Numerically more participants discontinued treatment prematurely in the semaglutide groups compared with the insulin glargine group (figure 1); most discontinuations were due to adverse events (mostly gastrointestinal with semaglutide and from other causes with insulin glargine, including skin and subcutaneous tissue disorders such as rash, pruritus, and urticaria). Baseline characteristics were similar between all groups (table 1; appendix).

Mean HbA_{1c} (baseline 8·17% [SD 0·89]) decreased over time in all three groups, with most of the decrease occurring by week 12 (figure 2). By week 30, mean HbA_{1c} decreased by 1·21% (95% CI 1·10–1·31) with 0·5 mg semaglutide and 1·64% (1·54–1·74) with 1·0 mg semaglutide, versus 0·83% with insulin glargine (0·73–0·93); estimated treatment differences versus insulin glargine –0·38% (95% CI –0·52 to –0·24) with 0·5 mg semaglutide and –0·81% (–0·96 to –0·67) with 1·0 mg semaglutide (both p<0·0001; figure 2, table 2). The mean insulin glargine dose at the end of treatment was 29·2 IU per day (SD 16·0). Results from the sensitivity analyses for HbA_{1c} supported the primary analysis results (appendix).

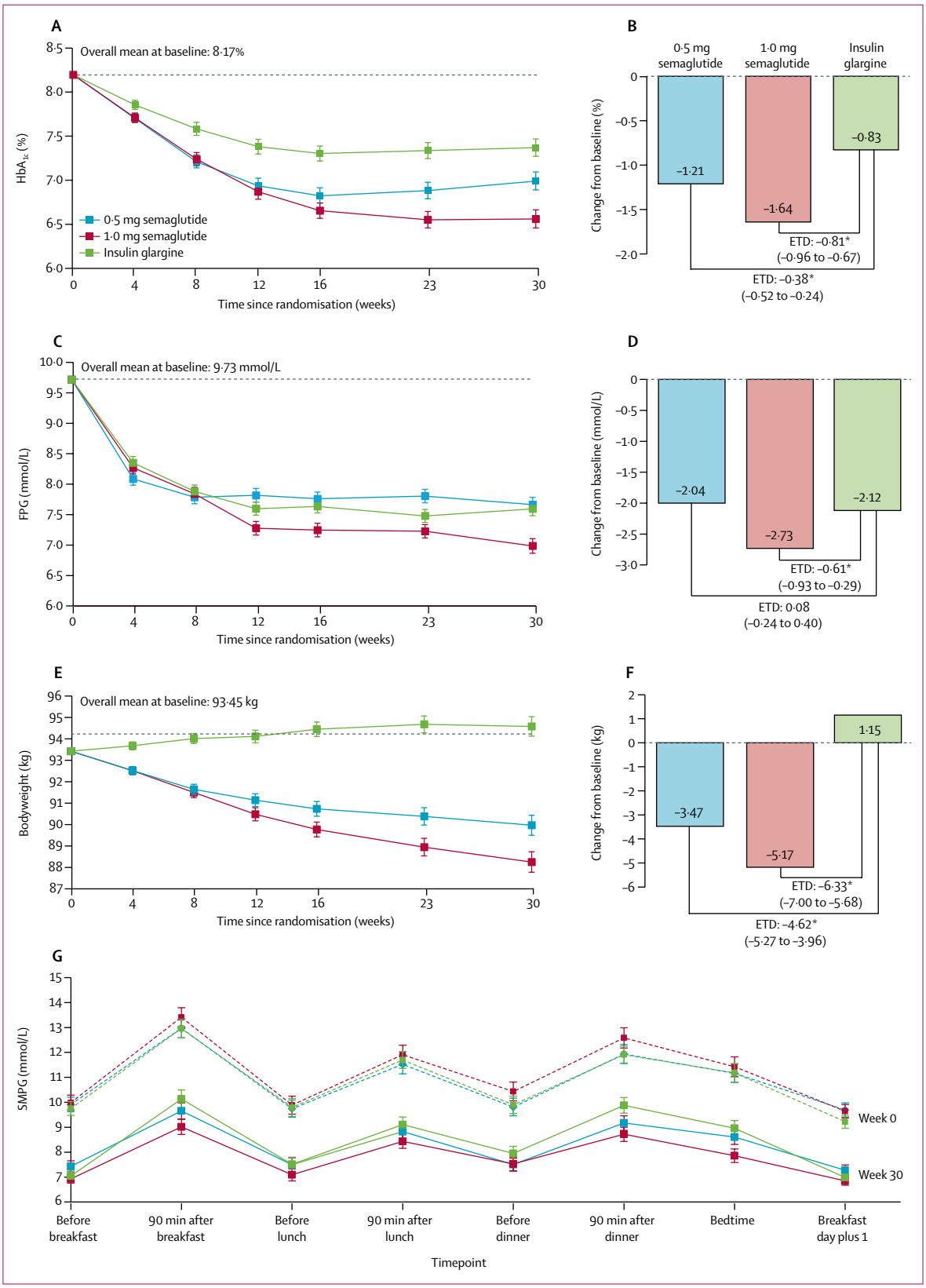

***Figure 2*: Efficacy outcomes**
Semaglutide 0·5 mg and 1·0 mg once weekly, compared with insulin glargine: change in mean HbA_{1c} by week (A), mean HbA_{1c} after 30 weeks (B), overall mean fasting plasma glucose over time (C), mean fasting plasma glucose (FPG) after 30 weeks (D), change in mean bodyweight by week (E), mean bodyweight after 30 weeks (F), and mean 8-point self-monitored plasma glucose (SMPG) profile at baseline and week 30 (G). Panels A–F: *indicates significance (p <0·0001); values are estimated means (95% CIs) from a mixed model for repeated measurements analysis using on-treatment without rescue medication data from participants in the full analysis set; dotted lines are the overall mean value at baseline. Panel G: values are observed means (95% CIs) based on on-treatment without rescue medication data from participants in the full analysis set. ETD=estimated treatment difference.

	Overall baseline* value (mean [SD])	0·5 mg semaglutide (n=362)			1·0 mg semaglutide (n=360)			Insulin glargine (n=360); change from baseline at week 30 (mean [95% CI])
		Change from baseline at week 30 (mean [95% CI])	Estimated treatment difference *vs* insulin glargine (95% CI)	p value	Change from baseline at week 30 (mean [95% CI])	Estimated treatment difference *vs* insulin glargine (95% CI)	p value	
Glycaemia endpoints								
HbA_{1c} (%)	8·2 (0·9)	−1·21 (−1·31 to −1·10)	−0·38 (−0·52 to −0·24)	<0·0001	−1·64 (−1·74 to −1·54)	−0·81 (−0·96 to −0·67)	<0·0001	−0·83 (−0·93 to −0·73)
HbA_{1c} (mmol/mol)	65·8 (9·7)	−13·22 (−14·32 to −12·08)	−4·16 (−5·72 to −2·60)	<0·0001	−17·93 (−19·06 to −16·79)	−8·87 (−10·45 to −7·30)	<0·0001	−9·06 (−10·14 to −7·97)
FPG (mmol/L)	9·7 (2·8)	−2·04 (2·28 to −1·82)	0·08 (−0·24 to 0·40)	0·6243	−2·73 (−2·96 to −2·50)	−0·61 (−0·93 to −0·29)	0·0002	−2·12 (−2·34 to −1·90)
8–point SMPG (mmol/L)								
Mean	10·9 (2·5)	−2·40 (−2·61 to −2·23)	−0·04 (−0·30 to 0·23)	0·7816	−2·94 (−3·12 to −2·75)	−0·57 (−0·83 to −0·31)	<0·0001	−2·37 (−2·55 to −2·18)
Postprandial increments	2·4 (2·0)	−0·59 (−0·78 to −0·41)	−0·39 (−0·65 to −0·13)	0·0029	−0·85 (−1·04 to −0·66)	−0·65 (−0·91 to −0·39)	<0·0001	−0·20 (−0·38 to −0·02)
Bodyweight endpoints†								
Bodyweight (kg)	93·5 (21·8)	−3·47 (−3·93 to −3·00)	−4·62 (−5·27 to −3·96)	<0·0001	−5·17 (−5·66 to −4·71)	−6·33 (−6·99 to −5·67)	<0·0001	1·15 (0·70 to 1·61)
BMI (kg/m^2)	33·0 (6·5)	−1·23 (−1·40 to −1·07)	−1·66 (−1·89 to −1·43)	<0·0001	−1·85 (−2·02 to −1·69)	−2·27 (−2·51 to −2·04)	<0·0001	0·42 (0·26 to 0·59)
Waist circumference (cm)	109·2 (15·2)	−3·20 (−3·79 to −2·61)	−3·42 (−4·24 to −2·59)	<0·0001	−4·54 (−5·16 to −3·96)	−4·76 (−5·59 to −3·93)	<0·0001	0·22 (−0·35 to 0·79)
Blood pressure and pulse rate								
DBP (mm Hg)	79·9 (8·5)	−1·38 (−2·22 to −0·52)	0·06 (−1·12 to 1·24)	0·9183	−0·98 (−1·85 to −0·12)	0·45 (−0·74 to 1·64)	0·4545	−1·44 (−2·26 to −0·63)
SBP (mm Hg)	132·1 (15·3)	−4·65 (−6·01 to −3·20)	−2·97 (−4·92 to −1·03)	0·0028	−5·17 (−6·62 to −3·76)	−3·50 (−5·46 to −1·54)	0·0005	−1·68 (−3·02 to −0·33)
Pulse rate (beats per min)	74·5 (10·2)	2·31 (1·38 to 3·24)	2·36 (1·07 to 3·65)	0·0004	3·14 (2·20 to 4·09)	3·19 (1·88 to 4·50)	<0·0001	−0·05 (−0·95 to 0·85)

p values are from a two-sided test of the null hypothesis that there is no treatment difference. FPG=fasting plasma glucose. SMPG=self-monitored plasma glucose. DBP=diastolic blood pressure. SBP=systolic blood pressure. *Baseline is for the entire trial population. †Missing bodyweight data imputed by a mixed model for repeated measurements.

***Table 2*: Primary and selected secondary endpoints by treatment group**

More participants in the semaglutide groups achieved an HbA_{1c} of less than 7% (53 mmol/mol), or an HbA_{1c} of 6·5% (48 mmol/mol) or less, than in the insulin glargine group (p<0·0001 for all; table 3). Additionally, more participants achieved an HbA_{1c} of less than 7% without severe or blood glucose-confirmed hypoglycaemia and without weight gain in the semaglutide groups than in the insulin glargine group (p<0·0001 for both comparisons; table 3).

Mean FPG and 8-point SMPG were reduced in all three groups (table 2, figure 2), but the estimated treatment differences were significant for only 1·0 mg semaglutide versus insulin glargine (p=0·0002 and <0·0001, respectively; table 2). Greater decreases in mean 8-point SMPG postprandial increments were noted in the semaglutide groups compared with insulin glargine (p<0·0001 for both; table 2).

Mean bodyweight at baseline was 93·45 kg (SD 21·79); at week 30, the 0·5 mg and 1·0 mg semaglutide groups achieved weight losses of 3·47 kg (95% CI 3·00–3·93) and 5·17 kg (4·71–5·66), respectively, versus a gain of 1·15 kg (0·70–1·61) with insulin glargine; estimated treatment difference versus insulin glargine –4·62 kg (95% CI –5·27 to –3·96) with 0·5 mg semaglutide and –6·33 kg (–6·99 to –5·67) with 1·0 mg semaglutide (both p<0·0001; figure 2, table 2). Bodyweight reductions of at least 5% occurred in more participants in the semaglutide groups than in the insulin glargine group (p<0·0001 for both; table 3); likewise, bodyweight reductions of at least 10% occurred in more participants in the 0·5 mg semaglutide group (p=0·0002) and in the 1·0 mg semaglutide group (p<0·0001; table 3). Results from the sensitivity analyses for bodyweight supported these findings (appendix). Greater reductions in BMI and waist circumference were also noted with both doses of semaglutide than with insulin glargine (table 2).

All measured lipid concentrations except for free fatty acids were significantly decreased at week 30 in the 1·0 mg semaglutide group compared with insulin glargine; however, only total cholesterol and LDL cholesterol were significantly decreased in the 0·5 mg semaglutide group compared with insulin glargine (appendix). The cardiovascular risk markers C-reactive protein and plasminogen activator inhibitor-1 were significantly reduced in both semaglutide groups at

	0·5 mg semaglutide (n=362)			1·0 mg semaglutide (n=360)			Insulin glargine (n=360); participants achieving target (%)
	Participants achieving target (%)	Odds ratio (95% CI)	p value	Participants achieving target (%)	Odds ratio (95% CI)	p value	
Participants achieving HbA_{1c} targets							
<7·0% (<53 mmol/mol)	208 (57%)	2·39 (1·73–3·28)	<0·0001	264 (73%)	5·78 (4·08–8·19)	<0·0001	137 (38%)
≤6·5% (≤48 mmol/mol)	135 (37%)	3·02 (2·11–4·33)	<0·0001	195 (54%)	6·86 (4·76–9·89)	<0·0001	63 (18%)
Participants achieving bodyweight reduction targets*							
≥5% reduction	134 (37%)	13·37 (7·71–23·20)	<0·0001	183 (51%)	23·94 (13·80–41·50)	<0·0001	17 (5%)
≥10% reduction	28 (8%)	6·35 (2·42–16·69)	0·0002	57 (16%)	14·51 (5·70–36·92)	<0·0001	6 (2%)
Participants achieving HbA_{1c} <7·0% without severe or blood glucose-confirmed hypoglycaemia and without weight gain	169 (47%)	5·39 (3·72–7·81)	<0·0001	231 (64%)	12·88 (8·73–19·02)	<0·0001	56 (16%)

Odds ratios were calculated from logistic regression models adjusted for treatment, country, stratification, and baseline HbA_{1c}. p values are from a two-sided test of the null hypothesis that there is no treatment difference. *Missing bodyweight data imputed by a mixed model for repeated measurements.

***Table 3*: Participants achieving study endpoints by treatment group**

week 30 compared with insulin glargine (appendix). Systolic blood pressure, but not diastolic blood pressure, decreased in both semaglutide groups compared with insulin glargine; pulse rate was increased in both semaglutide groups (table 2).

Overall treatment satisfaction (as per DTSQ; baseline mean 26·9 [SD 7·01]) improved by 4·6 points with 0·5 mg semaglutide, 5·6 points with 1·0 mg semaglutide, and 3·7 points with insulin glargine (p=0·0254 and p=0·0005, respectively; appendix). Results from the SF-36 questionnaire showed improvement with semaglutide 1·0 mg compared with insulin glargine in two of eight domains (role-emotional and general health); no differences were noted with 0·5 mg semaglutide compared with insulin glargine (appendix).

Six deaths were reported (table 4): four (1%) in the semaglutide 0·5 mg semaglutide group (three cardiovascular deaths confirmed by the event adjudication committee, and one pancreatic carcinoma detected 149 days into the trial and assessed as possibly related to study medication) and two (<1%) in the insulin glargine group (both cardiovascular deaths confirmed by the event adjudication committee). The most frequently reported adverse events were nausea with semaglutide, reported in 77 (21%) patients with 0·5 mg and in 80 (22%) with 1·0 mg, and nasopharyngitis with insulin glargine, reported in 44 (12%) patients (table 4). Diabetic retinopathy was reported by one (<1%) participant in the 0·5 mg semaglutide group, one (<1%) participant in the insulin glargine group, and none in the 1·0 mg semaglutide group. One participant (<1%) in the insulin glargine group reported proliferative retinopathy.

Treatment discontinuation because of adverse events occurred for 20 (6%) participants in the 0·5 mg semaglutide group, 27 (8%) in the 1·0 mg semaglutide group, and four (1%) in the insulin glargine group (table 4, appendix). The most frequent adverse events and most adverse events leading to premature treatment discontinuation in the semaglutide groups were gastrointestinal events. In the insulin glargine group, the adverse events most commonly leading to premature treatment discontinuation were skin and subcutaneous tissue disorders (eg, rash, pruritus, and urticaria). In the semaglutide groups, gastrointestinal events were mainly mild or moderate in severity and diminished in frequency over time (figure 3). Compared with insulin glargine, lipase and amylase concentrations were greater in both semaglutide groups, without a clear dose-dependent effect (appendix).

Severe or blood glucose-confirmed hypoglycaemia was reported by 16 (4%) participants with 0·5 mg semaglutide and 20 (6%) with 1·0 mg semaglutide versus 38 (11%) with insulin glargine (p=0·0021 and p=0·0202 for 0·5 mg and 1·0 mg semaglutide *vs* insulin glargine, respectively). Most episodes were reported in participants receiving sulfonylurea as background medication (15 [8%], 16 [9%], and 34 [18%] of participants in the 0·5 mg semaglutide, 1·0 mg semaglutide, and insulin glargine groups receiving a sulfonylurea as background medication, respectively, had severe or blood glucose-confirmed hypoglycaemia compared with 1 [<1%], 4 [2%], and 4 [2%] of those not receiving a sulfonylurea).

Severe hypoglycaemia was reported by two (<1%) participants with 0·5 mg semaglutide, five (1%) with 1·0 mg semaglutide, and five (1%) with insulin glargine. Nocturnal severe or blood glucose-confirmed hypoglycaemia was reported by four (1%) participants with 0·5 mg semaglutide, three (1%) with 1·0 mg semaglutide, and eight (2%) with insulin glargine.

Three cases of cholelithiasis were reported (none classified as severe); one (<1%) with 0·5 mg semaglutide and two (1%) with 1·0 mg semaglutide. Two pancreatic adverse events were reported, both in the 0·5 mg

semaglutide group, and were adjudicated as mild, acute pancreatitis. Both participants discontinued treatment prematurely and symptoms resolved after treatment discontinuation. Neoplasms confirmed by the event adjudication committee were reported by eight (2%) participants in the 0·5 mg semaglutide group (one participant had two events), two (1%) in the 1·0 mg semaglutide group, and three (1%) in the insulin glargine group (one participant had two events). These included four (1%) participants with malignant neoplasms in the 0·5 mg semaglutide group, no malignant neoplasms in the 1·0 mg semaglutide group, and one (<1%) in the insulin glargine group. Calcitonin concentrations were similar between groups with no apparent change during the trial. A decline in eGFR occurred in all three groups during the first 12 weeks of treatment, and then stayed stable over the rest of the trial (appendix). Cardiovascular adverse events confirmed by the event adjudication committee are in the appendix, with no non-fatal events in the semaglutide 0·5 mg group, three in the semaglutide 1·0 mg group, and two in the insulin glargine group.

Discussion

30 weeks' treatment with 0·5 mg and 1·0 mg semaglutide achieved reductions in HbA_{1c} and bodyweight that were superior compared with those achieved with insulin glargine.

More participants in both semaglutide groups achieved HbA_{1c} targets set by the ADA, EASD, and the American Association of Clinical Endocrinologists than those in the insulin glargine group. This result compares favourably with previous findings for liraglutide[16] as well as existing once-weekly GLP-1 receptor agonists such as dulaglutide and exenatide.[17,18] Furthermore, semaglutide led to substantial weight loss (–3·5 to –5·2 kg *vs* baseline), with more participants receiving 0·5 mg and 1·0 mg semaglutide having a clinically significant (≥5%) weight reduction than those receiving insulin glargine. Trials with other GLP-1 receptor agonists have reported reductions of –0·4 to –2·5 kg.[19–22] The weight reduction achieved with semaglutide versus insulin glargine (–4·6 to –6·3 kg) also compared favourably with that reported with other long-acting GLP-1 receptor agonists (–2·6 to –4·0 kg).[17,18,23] However, comparisons of findings from these trials should be made with caution because of the differences in study design and patient populations between individual trials.

Consistent with these findings, HbA_{1c} of less than 7% without severe or blood glucose-confirmed symptomatic hypoglycaemia and without weight gain was achieved by nearly half the participants receiving 0·5 mg semaglutide and nearly two-thirds receiving 1·0 mg semaglutide versus less than a fifth receiving insulin glargine. The combination of glycaemic control and bodyweight reduction with a low potential for hypoglycaemia, delivered with a once-weekly injection of semaglutide, is a promising finding given that a high proportion of patients with type 2 diabetes are overweight or obese and many other treatments either do not affect weight or are associated with weight gain accompanied by hypoglycaemia or the need to be injected daily.[2,24] The

	0·5 mg semaglutide (n=362)		1·0 mg semaglutide (n=360)		Insulin glargine (n=360)	
	n (%)	Events	n (%)	Events	n (%)	Events
Any adverse events	253 (70%)	1026	264 (73%)	1151	235 (65%)	743
Serious adverse events	22 (6%)	31	17 (5%)	23	18 (5%)	21
Fatal adverse events	4 (1%)	4	0	-	2 (1%)	2
Severe adverse events	27 (7%)	48	20 (6%)	33	10 (3%)	12
Moderate adverse events	108 (30%)	201	110 (31%)	233	104 (29%)	196
Mild adverse events	221 (61%)	777	230 (64%)	885	193 (54%)	535
GI adverse events	149 (41%)	345	156 (43%)	525	54 (15%)	91
Severe	7 (2%)	10	6 (2%)	11	2 (1%)	2
Moderate	36 (10%)	49	51 (14%)	90	15 (4%)	17
Mild	132 (36%)	286	137 (38%)	424	44 (12%)	72
Adverse events leading to premature treatment discontinuation*	20 (6%)	29	27 (8%)	45	4 (1%)†	5
All GI adverse events	11 (3%)	15	19 (5%)	31	0	NA
Nausea	3 (1%)	3	7 (2%)	7	0	NA
Vomiting	3 (1%)	3	7 (2%)	7	0	NA
Diarrhoea	1 (<1%)	1	9 (3%)	9	0	NA
Adverse events by preferred term (in ≥5% of patients)						
Nausea	77 (21%)	101	80 (22%)	117	13 (4%)	16
Diarrhoea	59 (16%)	67	69 (19%)	118	16 (4%)	18
Nasopharyngitis	45 (12%)	58	29 (8%)	37	44 (12%)	51
Lipase increased	36 (10%)	39	30 (8%)	32	15 (4%)	17
Decreased appetite	25 (7%)	34	23 (6%)	23	1 (<1%)	1
Vomiting	24 (7%)	28	37 (10%)	119	11 (3%)	13
Headache	19 (5%)	40	23 (6%)	33	20 (6%)	26
Dyspepsia	12 (3%)	24	24 (7%)	39	2 (1%)	2
Back pain	11 (3%)	11	18 (5%)	20	7 (2%)	10
Upper respiratory tract infection	10 (3%)	10	14 (4%)	16	24 (7%)	25
Gastro-oesophageal reflux disease	4 (1%)	4	19 (5%)	20	3 (1%)	4
Other adverse events						
Pancreatitis	2 (1%)	2	0	NA	0	NA
Cholelithiasis	1 (<1%)	1	2 (1%)	2	0	NA
Cardiovascular	3 (1%)	3	3 (1%)	4	4 (1%)	4
Malignant neoplasms	4 (1%)	4	0	NA	1 (<1%)	1
Skin	1 (<1%)	1	0	NA	1 (<1%)	1
Nasopharyngeal	1 (<1%)	1	0	NA	NA	NA
Pancreatic	1 (<1%)	1	0	0	0	NA
Renal or adrenal	1 (<1%)	1	0	NA	0	NA
Benign neoplasms	5 (1%)	5	2 (1%)	4	3 (1%)	4

Summary of treatment-emergent adverse events includes events that were collected from first exposure to the follow-up visit scheduled at 5 weeks (plus 1-week visit window) after last dose of study drug. 5% is calculated on the basis of the total number of patients in the safety analysis set. GI=gastrointestinal. NA=not applicable. *Includes all participants who discontinued treatment after an adverse event, even if this was not the main reason (might differ from figure 1). † One additional patient cited adverse events as the main reason after discontinuing treatment prematurely (figure 1).

Table 4: **Adverse events overview**

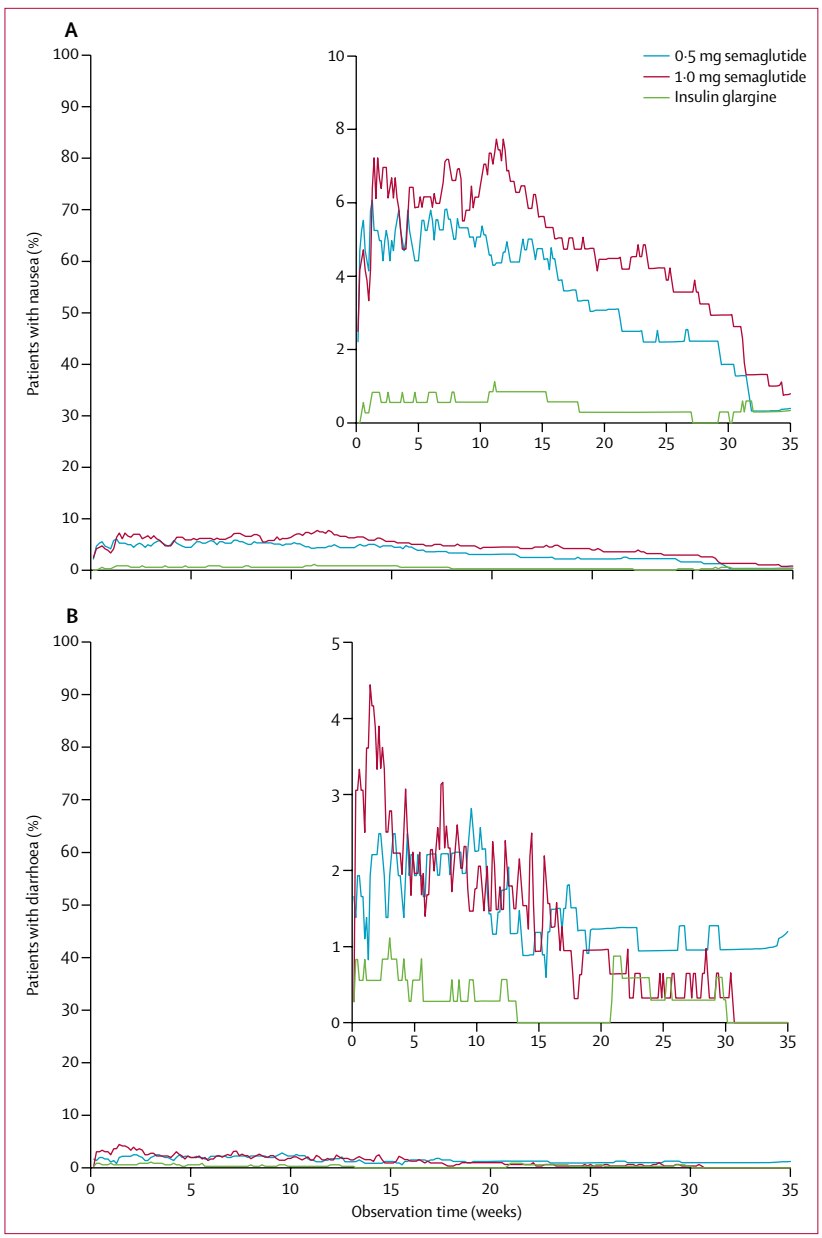

***Figure 3*: Time course of nausea (A) and diarrhoea (B)**
Treatment-emergent adverse events by week.

efficacy profile shown in this trial was consistent with that reported in the phase 3a SUSTAIN 1 trial,[11] comparing semaglutide monotherapy with placebo in treatment-naive patients with type 2 diabetes.

We identified no new safety issues for semaglutide, and its safety profile seems similar to that of other GLP-1 receptor agonists. As expected for a therapy with a glucose-dependent mechanism of action, numerically fewer episodes of hypoglycaemia occurred in the semaglutide groups than in the insulin glargine group, consistent with previous findings both for once-daily[16] and once-weekly[25] GLP-1 receptor agonists. Furthermore, most of the hypoglycaemic events were reported in participants receiving background sulfonylurea medication in addition to metformin, suggesting that the background therapy might have contributed to these events.[4]

Similar proportions of participants reported serious adverse events across all three treatment groups. As previously reported with other GLP-1 receptor agonists,[17,18,22] the main gastrointestinal side-effects reported in the semaglutide groups were nausea and diarrhoea, and gastrointestinal adverse event profiles with semaglutide were higher than with insulin glargine. The frequency of these events diminished over time, as with liraglutide.[16,26] Premature treatment discontinuation was more frequent with semaglutide than with insulin glargine, driven primarily by gastrointestinal events; however, dose escalation has been shown to partly ameliorate such adverse events.[6,9,12] Reports of diarrhoea in this trial were higher than have been previously reported for liraglutide[26] or exenatide.[17] Heart rate increased and systolic blood pressure decreased in the semaglutide groups, consistent with results in previous trials of other long-acting GLP-1 receptor agonists.[6] Both liraglutide (LEADER trial)[27] and semaglutide (SUSTAIN 6 trial)[28] have been shown to reduce cardiovascular outcomes in patients with high cardiovascular risk. A potential mechanism of this reduced risk might relate to modification of the progression of atherosclerosis; the contribution of cardiovascular risk factors to this outcome requires further research.[27,28]

The occurrence of pancreatitis in our trial was low, with two events reported with 0·5 mg semaglutide. Although acute pancreatitis has been reported after treatment with GLP-1 receptor agonists, a causal link has not been shown.[29] Lipase and amylase concentrations increased with semaglutide; these increases were similar to those seen with other GLP-1 receptor agonists.[30] In the SUSTAIN 6 cardiovascular outcome trial,[28] the occurrence of acute pancreatitis was not increased with semaglutide compared with placebo despite higher lipase and amylase concentrations. The occurrence of cholelithiasis in our trial was also low, with only three cases reported in participants receiving semaglutide. The numbers of neoplasms confirmed by an event adjudication committee were generally low and balanced between treatment groups, with no apparent clustering of the malignant neoplasms by tissue. Additionally, findings from the larger and longer SUSTAIN 6 trial[27] showed that malignant neoplasms were equally distributed between semaglutide and placebo groups (hazard ratio 0·94, 95% CI 0·67–1·32), with no apparent differences in neoplasm types.

Our trial population was heterogeneous, encompassing a broad range in terms of age, duration of diabetes, and level of HbA_{1c} at baseline. The population was also ethnically diverse compared with other phase 3a clinical trial programmes in patients with type 2 diabetes.

The limitations of this trial included the open-label design, which was because of the different dosing frequencies and titration of insulin glargine compared with semaglutide. This design should be especially considered when interpreting endpoints that are prone to subjectivity, such as gastrointestinal adverse events and the patient-reported outcomes of quality of life, although the reduced frequency of dosing with semaglutide might improve both adherence and quality of life compared with once-daily treatments and is perceived to do so by patients.[6,7] The trial duration was short, restricting the conclusions that can be drawn regarding the long-term efficacy and tolerability of semaglutide compared with insulin glargine. Additionally, real-world patient populations might be expected to have received several oral antidiabetic therapies before being considered for insulin treatment. Research in populations with longer baseline diabetes duration and a longer history of treatment might therefore be of relevance.

Another limitation of the current trial was the extent to which insulin glargine was titrated. The mean prebreakfast fasting SMPG at week 30 (7·1 mmol/L) suggests that a more rigorous titration could have been enforced, but that might possibly have been achieved at the expense of more hypoglycaemia and gain in bodyweight. The overall mean insulin dose reported here was in line with that reported in trials comparing other weekly GLP-1 receptor agonists and insulin glargine,[18,23] and the insulin dose at the end of the trial (29·2 IU per day at 30 weeks) seems to be consistent with clinical practice. However, more frequent titrations might have allowed more aggressive insulin titration.

In summary, semaglutide was associated with superior glycaemic control and reduced bodyweight, with few episodes of hypoglycaemia, compared with insulin glargine in patients with type 2 diabetes receiving metformin with or without a sulfonylurea. However, insulin glargine did not achieve titration targets, reflecting a potential limitation of titration often seen in clinical practice. No unexpected safety issues were identified and semaglutide had a similar safety profile to that of other GLP-1 receptor agonists. Combined with its cardiovascular risk reduction effect noted in SUSTAIN 6,[28] semaglutide seems to be an effective once-weekly therapeutic option for patients with type 2 diabetes who are unable to achieve glycaemic control on metformin with or without a sulfonylurea.

Contributors

VRA, JHDV, and MA participated in the trial design. VRA, SCB, BC, MP, LR, and JHDV undertook the trial and the data collection. MA and ER took part in the data analysis. All authors interpreted the data and participated in writing the report together with medical writing services provided by the funder. All the authors read the report critically and approved the submitted version.

Declaration of interests

In doing this study, SCB received personal fees from Novo Nordisk. VRA (to her institution), SCB, BC, MP, LR, and JHDV have previously received honoraria, and VRA (to her institution), SCB (to his institution), and JHDV have previously received research grants, from Novo Nordisk. VRA has previously received honoraria from Adocia, the American Diabetes Association, AstraZeneca, Janssen, Medscape, Sanofi, and Tufts (all paid to her institution), and research grants from AstraZeneca, Bristol-Myers Squibb, Calibra, Eisai, Elcelyx, Janssen, Sanofi, and Theracos (all paid to her institution). SCB has previously received honoraria and research grants (paid to his institution) from Boehringer Ingelheim, Cellnovo, Jensen, Lilly, Merck Sharpe Dohme (MSD), and Sanofi. BC has previously received honoraria from Amgen, AstraZeneca, Lilly, Merck, Novartis, and Sanofi-Regeneron, and research grants from Pfizer, Sanofi and Sanofi-Regeneron. MP has previously received honoraria from Lilly. LR has previously received honoraria from AstraZeneca and Lilly. MA is a full-time employee of, and owns stock in, Novo Nordisk A/S, and ER is a full-time employee of Novo Nordisk. JHDV has previously received honoraria from GlaxoSmithKline and MSD, and funding from Lilly (to his institution).

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