



Efficacy and safety of once-weekly semaglutide versus daily canagliflozin as add-on to metformin in patients with type 2 diabetes (SUSTAIN 8): a double-blind, phase 3b, randomised controlled trial

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Summary

Background Existing guidelines for management of type 2 diabetes recommend a patient-centred approach to guide the choice of pharmacological agents. Although glucagon-like peptide-1 (GLP-1) receptor agonists and sodium-glucose cotransporter-2 (SGLT2) inhibitors are increasingly used as second-line agents, direct comparisons between these treatments are insufficient. In the SUSTAIN 8 trial, we compared the efficacy and safety of semaglutide (a GLP-1 receptor agonist) with canagliflozin (an SGLT2 inhibitor) in patients with type 2 diabetes.

Methods This was a double-blind, parallel-group, phase 3b, randomised controlled trial done at 111 centres in 11 countries. Eligible patients were at least 18 years old and had uncontrolled type 2 diabetes (HbA_{1c} 7.0–10.5% [53–91 mmol/mol]) on stable daily metformin therapy. Patients were randomly assigned (1:1) by use of an interactive web response system to subcutaneous semaglutide 1.0 mg once weekly or oral canagliflozin 300 mg once daily. The primary endpoint was change from baseline in HbA_{1c} , and the confirmatory secondary endpoint was change from baseline in bodyweight, both at week 52. The primary analysis population included all randomly assigned patients, using on-treatment data collected before initiation of rescue medication. The safety analysis was done on a population that included all patients exposed to at least one dose of trial product. The trial was powered for HbA_{1c} and bodyweight superiority under reasonable assumptions. This trial is registered with ClinicalTrials.gov, NCT03136484.

Findings Between March 15, 2017, and Nov 16, 2018, 788 patients were randomly assigned to semaglutide 1.0 mg (394 patients) or canagliflozin 300 mg (394 patients). 739 patients completed the trial (367 in the semaglutide group and 372 in the canagliflozin group). From overall baseline mean, patients receiving semaglutide had significantly greater reductions in HbA_{1c} and bodyweight than those receiving canagliflozin (HbA_{1c} estimated treatment difference [ETD] -0.49 percentage points, 95% CI -0.65 to -0.33 ; -5.34 mmol/mol, 95% CI -7.10 to -3.57 ; $p < 0.0001$; and bodyweight ETD -1.06 kg, 95% CI -1.76 to -0.36 ; $p = 0.0029$). Gastrointestinal disorders, most commonly nausea, were the most frequently reported adverse events with semaglutide, occurring in 184 (47%) of 392 patients; whereas infections and infestations (defined using the Medical Dictionary for Regulatory Activities, version 21.0), most commonly urinary tract infections, occurred more frequently with canagliflozin, in 136 (35%) of 394 patients. Premature treatment discontinuation because of adverse events occurred in 38 (10%) of 392 patients with semaglutide and in 20 (5%) of 394 patients with canagliflozin. One fatal adverse event confirmed unlikely to be caused by treatment occurred in the semaglutide group.

Interpretation Once-weekly semaglutide 1.0 mg was superior to daily canagliflozin 300 mg in reducing HbA_{1c} and bodyweight in patients with type 2 diabetes uncontrolled on metformin therapy. These outcomes might guide treatment intensification choices.

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Introduction

Existing guidelines for the comprehensive management of type 2 diabetes recommend a patient-centred approach to guide the choice of pharmacological agents.^{1–3} Beyond optimising glycaemic control, several other treatment considerations influence treatment choice, including effect on weight, hypoglycaemia risk, and comorbidities (including cardiovascular status).² Both glucagon-like peptide-1 (GLP-1)⁴ receptor agonists and sodium-glucose

co-transporter-2 (SGLT2)⁵ inhibitors are preferred add-on treatment options for patients with cardiovascular disease and poorly controlled HbA_{1c} after first-line metformin therapy and lifestyle modifications.^{1–3}

Semaglutide is a GLP-1 receptor agonist with efficacy across the continuum of diabetes care, as shown in the SUSTAIN (Semaglutide Unabated Sustainability in Treatment of Type 2 Diabetes) clinical trial programme, in which subcutaneous once-weekly semaglutide showed

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Research in context

Evidence before this study

Glucagon-like peptide-1 (GLP-1) receptor agonists and sodium-glucose co-transporter-2 (SGLT2) inhibitors are increasingly being used as preferred second-line agents after metformin for the management of type 2 diabetes because of additional effects beyond HbA_{1c} lowering, including weight loss and improvements in cardiovascular outcomes. The Joint Guidelines of the American Diabetes Association and the European Association for the Study of Diabetes recommend second-line therapy with GLP-1 receptor agonists for patients with type 2 diabetes who have atherosclerotic heart disease and SGLT2 inhibitors for those with heart failure. However, to our knowledge, there are insufficient comparative data on the second-line use of GLP-1 receptor agonists versus SGLT2 inhibitors in patients with type 2 diabetes inadequately controlled with metformin alone and who do not have cardiovascular conditions. This scarcity of data can complicate physician decision making.

Added value of this study

The results of the SUSTAIN 8 trial showed that subcutaneous semaglutide 1.0 mg once weekly was superior to oral canagliflozin 300 mg daily in reducing HbA_{1c} and bodyweight

in adults with type 2 diabetes inadequately controlled with daily metformin therapy. Similar proportions of patients reported adverse events with semaglutide and canagliflozin, with some adverse events occurring at a higher rate with each treatment, as expected (gastrointestinal adverse events with semaglutide, and genital and perineal infections with canagliflozin). Rates of hypoglycaemia were low with both treatments.

Implications of the available evidence

SUSTAIN 8 provides direct evidence of the superiority of semaglutide 1.0 mg over canagliflozin 300 mg in reducing HbA_{1c} and bodyweight in patients with type 2 diabetes on metformin therapy, as well as showing similar safety profiles between the two agents. These findings support the use of semaglutide as an alternative to canagliflozin in second-line treatment of patients with type 2 diabetes who need treatment intensification after metformin. However, decisions on treatment intensification should always consider individual patient factors, such as presence of atherosclerotic disease, and history or high risk of heart failure, as well as patient and physician preferences.

See Online for appendix

superior HbA_{1c} and bodyweight reductions compared with those of placebo, sitagliptin, exenatide extended release, insulin glargine, and dulaglutide.^{6–11} Canagliflozin, a once-daily oral SGLT2 inhibitor, also has efficacy in glycaemic control and weight loss compared with that of placebo and active comparators.^{12–15} Both semaglutide and canagliflozin provide cardiovascular benefits in patients with type 2 diabetes at high risk of cardiovascular disease.^{16,17}

Although GLP-1 receptor agonists and SGLT2 inhibitors are increasingly used as second-line agents, comparative data on the second-line use of GLP-1 receptor agonists versus SGLT2 inhibitors are insufficient. With many available treatment options, but little robust data to support an evidence-based choice, an individualised approach to patient care can be difficult. Therefore, we did the SUSTAIN 8 study to compare the effect of semaglutide 1.0 mg with canagliflozin 300 mg on reductions in HbA_{1c} and bodyweight in individuals with uncontrolled type 2 diabetes. SUSTAIN 8 was powered to show superiority of semaglutide in reducing HbA_{1c} and bodyweight compared with canagliflozin.

Methods

Study design and participants

SUSTAIN 8 was a 52-week, phase 3b, randomised, double-blind, double-dummy, active-comparator, two-arm, parallel-group trial. Patients were screened by investigators at 115 sites, and the trial was done at 111 centres (hospitals and specialised research centres) in 11 countries (Argentina, Brazil, Canada, India, Ireland, Lebanon,

Malaysia, Mexico, Sweden, the UK, and the USA). Trial design and a list of investigators are provided in the appendix (pp 2, 10–11). Eligible participants were aged 18 years or older with type 2 diabetes, had HbA_{1c} levels of 7.0–10.5% (53–91 mmol/mol), were on a stable daily dose of metformin (≥1500 mg or maximum tolerated dose) for at least 90 days before screening, and had an estimated glomerular filtration rate (eGFR) of 60 mL/min per 1.73 m² or higher. Key exclusion criteria included history or presence of pancreatitis (acute or chronic), history of diabetic ketoacidosis, myocardial infarction, stroke, hospital admission for unstable angina, or transient ischaemic attack within 180 days before screening, and heart failure (New York Heart Association Class IV). Metformin was the only background diabetes medication allowed; patients continued the pre-trial dose throughout the treatment period, unless rescue medication was required. Patients receiving medication for diabetes or obesity other than those stated in the inclusion criteria within 90 days before screening were excluded, except for short-term insulin use for a maximum of 14 days before screening. A full list of inclusion and exclusion criteria is provided in the appendix (pp 12–13). The trial was done in compliance with the International Conference on Harmonisation Good Clinical Practice Guidelines and the Declaration of Helsinki. Prior to trial initiation, the protocol, the consent form, and the patient information sheet were reviewed and approved according to local regulations by appropriate health authorities, and by an independent ethics committee/institutional review board. All patients provided written informed consent.

Randomisation and masking

Eligible patients were randomly assigned (1:1) through an interactive web response system to receive semaglutide 1.0 mg once weekly or canagliflozin 300 mg once daily (these doses were the final doses in SUSTAIN 8 after dose escalation). Randomisation was stratified according to participation in a body composition sub-study (results reported separately), and the allocation of trial products was accomplished by use of an interactive web response system. The interactive web response system was supplied by Perceptive eClinical Limited; they had no clinical involvement. Patients and investigators remained masked throughout the trial; unmasking occurred only when required for medical emergencies. To fulfil masking of the trial, a double-dummy design was implemented: all patients randomly assigned to semaglutide also received placebo tablets to mimic canagliflozin administration, while patients randomly assigned to canagliflozin also received placebo injections to mimic semaglutide administration.

Procedures

A screening period of 2 weeks was followed by 52 weeks of treatment and a 5-week follow-up. The maintenance dose of semaglutide 1.0 mg was reached after an 8-week fixed dose-escalation period. Semaglutide was administered once weekly subcutaneously in the thigh, abdomen, or upper arm at any time of day, irrespective of meals, on the same day of the week. Canagliflozin was administered once daily as oral tablets, preferably taken before the first meal of the day; the maintenance dose of canagliflozin 300 mg once daily was reached after an 8-week fixed dose escalation. In patients whose eGFR fell persistently to lower than 60 mL/min per 1.73 m², the dose of canagliflozin or canagliflozin placebo was reduced to 100 mg once daily and re-escalated if eGFR increased to 60 mL/min per 1.73 m² or higher. All investigational treatments were discontinued if eGFR was reduced to lower than 45 mL/min per 1.73 m².

Rescue medication was offered to patients with confirmed fasting plasma glucose levels higher than 13.3 mmol/L (240 mg/dL) from week 8 to the end of week 13 and higher than 11.1 mmol/L (200 mg/dL) from week 14 to end of study treatment, or to patients with confirmed HbA_{1c} higher than 8.5% (69.4 mmol/mol) from week 26 to end of study treatment. Choice of rescue medication was at the investigator's discretion and excluded GLP-1 receptor agonists, dipeptidyl peptidase-4 inhibitors, amylin analogues, and SGLT2 inhibitors. All events meeting the definition of an adverse event observed by the investigator, or spontaneously reported by the patients, were evaluated by the investigator and recorded on an adverse event form. This included events occurring from the first trial-related activity after the patient had signed the informed consent form, until the end of the post-treatment follow-up period. Procedures

and assessments for primary and secondary outcome measures are summarised in the appendix (pp 14–15).

Outcomes

The primary endpoint was change in HbA_{1c} percentage point from baseline to week 52. The confirmatory secondary endpoint was change in bodyweight (kg) from baseline to week 52. Prespecified supportive secondary efficacy endpoints included the following: achievement of target HbA_{1c} levels established by the American Diabetes Association (ADA; <7.0% [<53 mmol/mol])¹⁸ and the American Association of Clinical Endocrinologists (AAACE; $\leq 6.5\%$ [≤ 48 mmol/mol]);¹ weight-loss responses of at least 3%, at least 5%, or at least 10%; a composite endpoint of HbA_{1c} lower than 7.0% (<53 mmol/mol), no weight gain, and no severe hypoglycaemia (ADA classification)¹⁸ or blood glucose—confirmed symptomatic hypoglycaemic episodes; and a composite endpoint of HbA_{1c} reduction of at least 1 percentage point and weight loss of at least 5%. A post-hoc analysis assessed weight-loss responses of at least 15%.

Other prespecified secondary efficacy endpoints were change from baseline to week 52 in fasting plasma glucose, 7-point self-measured blood glucose profile, systolic and diastolic blood pressure, fasting blood lipids (total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides), and patient-reported outcomes assessed with the Diabetes Treatment Satisfaction Questionnaire (DTSQs), Control of Eating Questionnaire (CoEQ), and Short-Form health survey (SF-36, version 2).

Supportive safety endpoints included treatment-emergent adverse events and severe or blood glucose-confirmed symptomatic hypoglycaemic episodes. All patients were required to have fundus photography or dilated fundoscopy before enrolment, and all new or worsening diabetic retinopathy events required the completion of a specific event form; these events were identified by a predefined Medical Dictionary for Regulatory Activities search with the “eye disorders” system organ class and “diabetic retinopathy” preferred term, during the in-trial observation period.

Statistical analysis

The primary estimand was defined as the treatment difference between semaglutide and canagliflozin at week 52 for all randomly assigned patients if all patients completed treatment and did not start rescue medication. A sample size of 784 patients would ensure a power greater than 90% for the primary analysis and retrieved dropout sensitivity analysis for confirming superiority of semaglutide versus canagliflozin for HbA_{1c} and bodyweight under reasonable assumptions (HbA_{1c} −0.32% and bodyweight −2.4 kg for efficacy [primary analysis]; HbA_{1c} −0.26% and bodyweight −2.0 kg for in-trial treatment effect [retrieved dropout analysis]; and SD 1.1% for HbA_{1c} and 4.0 kg for bodyweight). We used a closed

testing procedure to control the overall type-1 error at a nominal two-sided 5% level (appendix p 3).

Analysis populations included the full analysis population of all patients randomly assigned to treatment and the safety analysis population of all patients exposed to at least one dose of trial product. The primary estimand was based on the full analysis population by using post-baseline measurements up to and including week 52 from the observation period termed on-treatment without rescue medication (defined as the period when patients were exposed to trial product and had not initiated any rescue medication); an ANCOVA with treatment, stratification, region, and baseline value as fixed effects; and multiple imputation for missing data. We imputed missing values using observed data within the same treatment group by use of Markov Chain Monte Carlo for intermittent missing values and a sequential regression approach for monotone missing values. For each post-baseline visit, missing data were imputed with a regression model including region and stratification factor as categorical effects and data from baseline and all previous visits as covariates. In total,

500 datasets were generated, each of which was analysed with the described ANCOVA; results were then combined with use of Rubin's rule to draw inference.

We did sensitivity analyses to support robustness of conclusions from the primary analysis, including the following: a tipping-point analysis (pattern-mixture model) based on the full analysis population using the on-treatment without rescue medication observation period; a retrieved dropout analysis based on the full analysis population using post-baseline measurements up to and including week 52 from the in-trial observation period (defined as the period in which people were considered to be within the trial, regardless of trial product discontinuation or initiation of rescue medicine); a statistical non-inferiority sensitivity analysis based on the per protocol analysis set; and multiple imputation for missing data, in which missing values were imputed using observed data within the same group.

To calculate odds ratios (ORs), we analysed all binary endpoints using a logistic regression model with treatment, region, and stratification factor as fixed factors and baseline value as a covariate. Before analysis, we imputed missing data for individual components separately, using observed data from patients within the same group (defined by randomised treatment), by use of a regression model including region and stratification factor as categorical effects, and data from baseline and all previous visits as covariates; these data were subsequently dichotomised.

All analyses, including sensitivity analyses, were prespecified in the statistical analysis plan, except for a post-hoc analysis of weight-loss responses of 15% or greater, and performed with Statistical Analysis System version 9.4. Before data were released for statistical analysis, a blinded review of all data took place to identify protocol deviations that might potentially have affected the results. No data monitoring committee was involved. This trial is registered with ClinicalTrials.gov, NCT03136484.

Role of the funding source

The sponsor designed the study and did site monitoring, data collection, data analysis, and data interpretation. Site investigators gathered data. All authors had full access to all data, and the lead author had final responsibility for the decision to submit for publication. The sponsor funded editorial support, provided by a professional medical writer.

Results

The study began on March 15, 2017, and ended on Nov 16, 2018. 1212 patients were screened, of whom 788 were enrolled and randomly assigned to semaglutide 1.0 mg or canagliflozin 300 mg (full analysis population, $n=394$ in each treatment group), with 786 (>99%) exposed to treatment (figure 1). Two patients were randomly assigned to semaglutide but not exposed (reasons unknown).

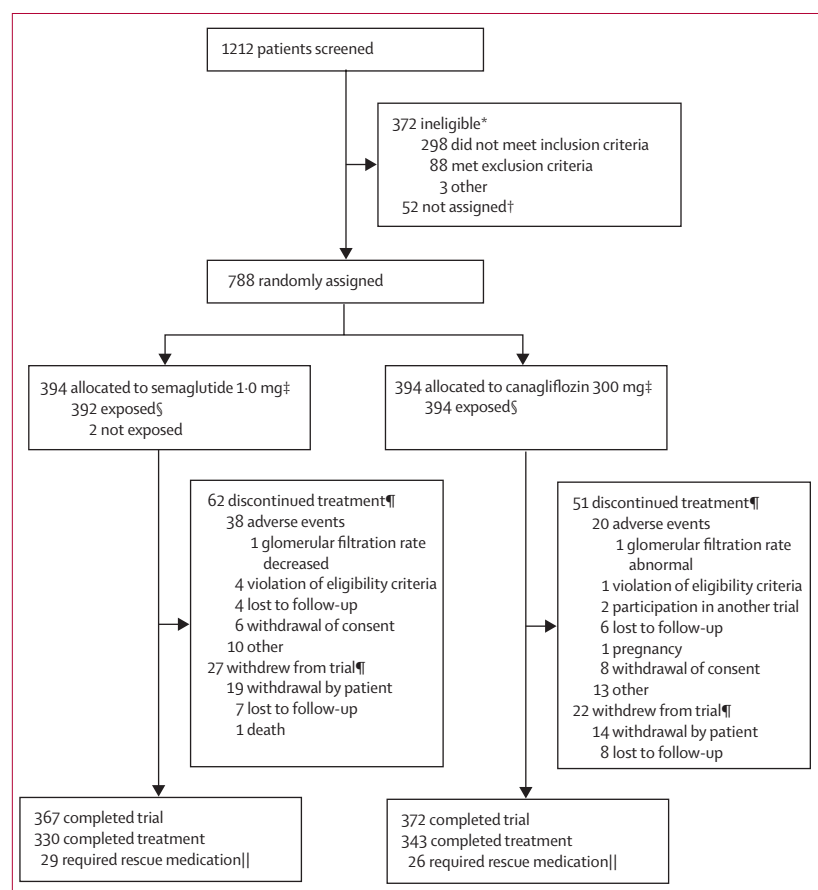


Figure 1: Trial profile

*Patients could meet more than one exclusion criteria. †Includes patients who withdrew consent before randomisation. ‡The full analysis population was defined as all patients randomly assigned and allocated to semaglutide or canagliflozin. §The safety analysis population was defined as all patients who were exposed to at least one dose of trial product. ¶Patients who discontinued treatment and who withdrew from the study were partly overlapping. ||Number of patients who completed treatment requiring rescue medication.

In the full analysis population, 673 (85%) of 788 patients completed treatment (330 in the semaglutide group and 343 in the canagliflozin group) and 739 (94%) completed the trial (367 in semaglutide and 372 in canagliflozin). Overall, 29 (7%) of 394 patients in the semaglutide group and 27 (7%) of 394 patients in the canagliflozin group received rescue medication. Most patients initiating rescue medication had baseline HbA_{1c} higher than 8.5% (>69 mmol/mol). The most commonly used rescue medication was sulphonylurea (25 [86%] of 29 patients in the semaglutide group; 19 [70%] of 27 patients in the canagliflozin group). Baseline characteristics were similar across treatment groups, including the number of patients with complications from diabetes at screening (table 1).

For both treatment groups, mean baseline HbA_{1c} decreased over time from a pooled baseline average of 8.3% (SD 1.0) (66.7 mmol/mol, SD 10.9; figure 2A). Treatment with semaglutide led to superior reductions in HbA_{1c} compared with those with canagliflozin, with an estimated change from baseline to week 52 of -1.5 percentage points (SE 0.06; -16.0 mmol/mol, SE 0.65) with semaglutide and -1.0 percentage points (0.06; -10.7 mmol/mol, 0.61) with canagliflozin. The estimated treatment difference (ETD) was -0.49 percentage points (95% CI -0.65 to -0.33; -5.34 mmol/mol, 95% CI -7.10 to -3.57; $p < 0.0001$). Greater proportions of patients achieved prespecified HbA_{1c} targets with semaglutide than with canagliflozin (66% vs 45% achieved HbA_{1c} <7.0% [<53 mmol/mol], OR 2.77, 95% CI 1.98–3.85, $p < 0.0001$; 53% vs 24% achieved HbA_{1c} ≤6.5% [≤ 48 mmol/mol], 4.19, 2.97–5.92, $p < 0.0001$; appendix p 4).

Semaglutide also resulted in superior reductions in bodyweight from baseline to week 52 (figure 2B). From an overall mean baseline of 90.2 kg (SD 22.6), estimated change in bodyweight was -5.3 kg (SE 0.26) with semaglutide and -4.2 kg (0.24) with canagliflozin (ETD -1.06 kg, 95% CI -1.76 to -0.36; $p = 0.0029$). Greater proportions of patients achieved weight loss of 3% or greater, 5% or greater (appendix p 5), and 10% or greater with semaglutide compared with those with canagliflozin, although only the difference in the proportion of patients achieving 10% or greater weight loss was significant (22% vs 9%; OR 2.99, 95% CI 1.89–4.75; $p < 0.0001$; appendix p 6). A post-hoc analysis showed that a weight loss of 15% or greater was achieved by a greater proportion of patients receiving semaglutide than those receiving canagliflozin (7% vs 1%; OR 7.45, 95% CI 2.45–22.63; $p = 0.0004$; appendix p 6).

The per-protocol analysis and the retrieved dropout analysis all returned significant ETDs, supporting the conclusions from the analyses of the primary and confirmatory secondary endpoints (appendix p 18). The results of all sensitivity analyses are available in the appendix (pp 16–18). Additionally, more patients receiving semaglutide than those receiving canagliflozin achieved

	Semaglutide 1.0 mg (n=394)	Canagliflozin 300 mg (n=394)	Total (n=788)
Age (years)	55.7 (11.1)	57.5 (10.7)	56.6 (10.9)
Sex			
Men	223 (57%)	201 (51%)	424 (54%)
Women	171 (43%)	193 (49%)	364 (46%)
Ethnicity			
Hispanic or Latino	156 (40%)	137 (35%)	293 (37%)
Not Hispanic or Latino	238 (60%)	257 (65%)	495 (63%)
Race			
Native American or Alaska Native	1 (<1%)	3 (1%)	4 (1%)
Asian	62 (16%)	63 (16%)	125 (16%)
Black or African-American	28 (7%)	30 (8%)	58 (7%)
White	297 (75%)	290 (74%)	587 (74%)
Other	6 (2%)	7 (2%)	13 (2%)
Not applicable	0	1 (<1%)	1 (<1%)
HbA _{1c} (%)	8.3 (1.0)	8.2 (1.0)	8.3 (1.0)
HbA _{1c} (mmol/mol)	67.1 (11.1)	66.3 (10.6)	66.7 (10.9)
Glucose (mmol/L)			
Fasting plasma glucose	9.4 (2.7)	9.4 (2.6)	9.4 (2.7)
Mean 7-point SMBG*	10.3 (2.4)	10.6 (2.6)	10.4 (2.5)
Postprandial SMBG increments	2.1 (1.9)	2.2 (1.8)	2.2 (1.8)
Diabetes duration (years)	7.5 (5.9)	7.2 (5.4)	7.4 (5.6)
Bodyweight (kg)	90.6 (22.6)	89.8 (22.6)	90.2 (22.6)
Body-mass index (kg/m ²)	32.2 (6.8)	32.5 (6.9)	32.3 (6.8)
Systolic blood pressure (mm Hg)	129.4 (14.7)	131.4 (14.8)	130.4 (14.8)
Diastolic blood pressure (mm Hg)	78.9 (9.3)	79.5 (9.0)	79.2 (9.2)
Pulse rate (beats per min)	74.1 (10.2)	74.2 (10.2)	NA
Lipids (mmol/L)†			
Total cholesterol	4.5 (22.6)	4.4 (24.9)	4.4 (23.7)
HDL cholesterol	1.1 (24.6)	1.1 (23.9)	1.1 (24.3)
LDL cholesterol	2.4 (37.6)	2.4 (42.3)	2.4 (40.0)
Triglycerides	1.8 (53.3)	1.7 (51.5)	1.8 (52.4)
Renal function (eGFR)‡			
Normal	285 (72%)	275 (70%)	560 (71%)
Mild renal impairment	107 (27%)	117 (30%)	224 (28%)
Moderate renal impairment	2 (1%)	2 (1%)	4 (1%)
Severe renal impairment or end-stage renal disease	0	0	0
Diabetic complications			
Diabetic neuropathy	44 (11%)	45 (11%)	89 (11%)
Diabetic retinopathy§	33 (8%)	32 (8%)	65 (8%)
Macroangiopathy	19 (5%)	19 (5%)	38 (5%)
Diabetic nephropathy	11 (3%)	17 (4%)	28 (4%)
Macular oedema	2 (1%)	2 (1%)	4 (1%)
Anti-diabetes medication at screening			
Biguanides	394 (100%)	394 (100%)	788 (100%)
Insulin and analogues for injection¶	1 (<1%)	0	1 (<1%)

Data are n (%) or mean (SD), unless otherwise specified. eGFR=estimated glomerular filtration rate. NA=data not available. SMBG=self-measured blood glucose. *Mean 7-point SMBG profile was calculated as the area under the profile divided by the measurement time. †Geometric mean (coefficient of variation). ‡Renal function was defined as normal (eGFR ≥90 mL/min per 1.73 m²), mild renal impairment (eGFR ≥60 to <90 mL/min per 1.73 m²), moderate renal impairment (eGFR ≥30 to <60 mL/min per 1.73 m²), severe renal impairment (eGFR ≥15 to <30 mL/min per 1.73 m²), and end-stage renal disease (eGFR <15 mL/min per 1.73 m²). §All patients were required to have fundus photography or dilated funduscopy before enrolment to identify baseline diabetic retinopathy. ¶Patient randomly assigned in error.

Table 1: Baseline characteristics

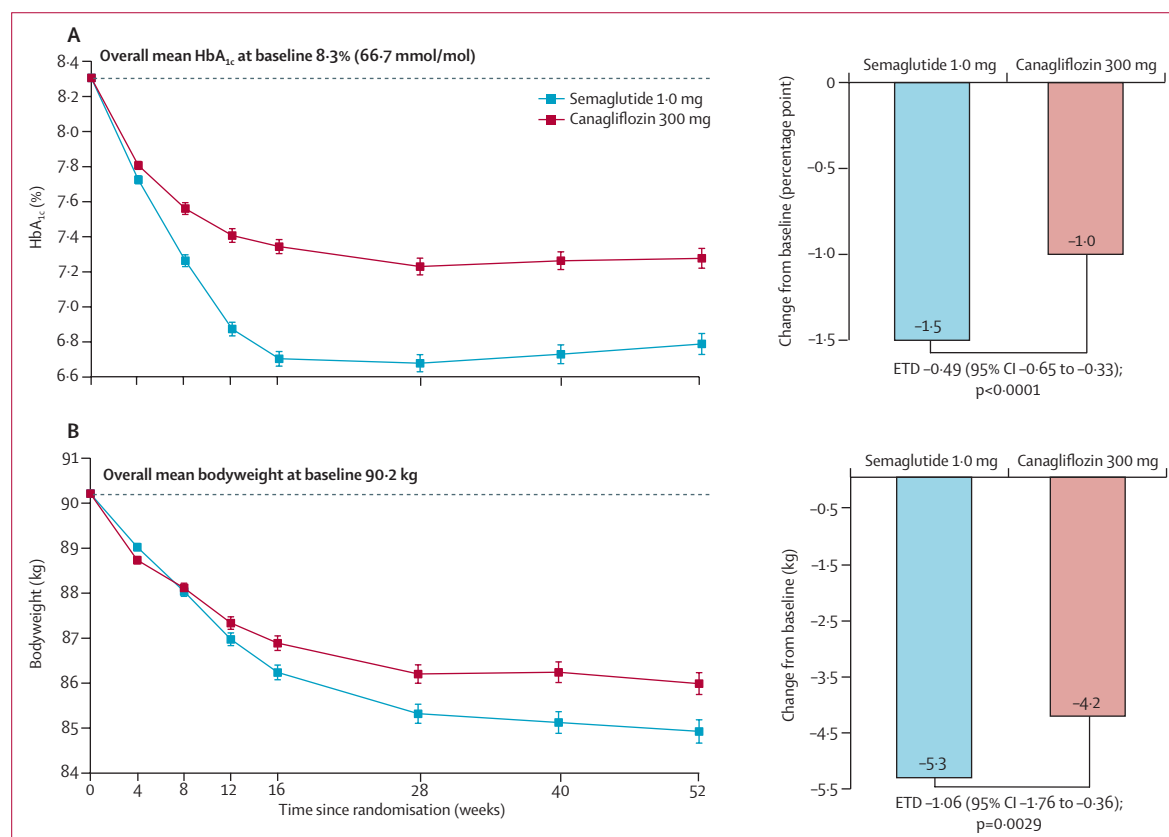


Figure 2: Glycaemic and bodyweight outcomes

On-treatment without rescue medication period data for all patients randomly assigned to treatment. Error bars are SE 1 of the means and dashed lines indicate the overall mean values at baseline. All site visits, except screening visits, were to be completed with patients in a fasting state. (A) Estimated mean HbA_{1c} by week and change in HbA_{1c} from overall baseline to week 52. Mean estimates are from an ANCOVA with treatment, region, and stratification factor as fixed factors and baseline value as covariate, in which missing data were multiple imputed using data from patients within the same group defined by randomised treatment using a regression model including region and stratification factor as categorical effects and data from baseline and all previous visits as covariates. The missing data patterns were examined to detect unexpected patterns. (B) Estimated mean bodyweight by week and change in bodyweight from overall baseline to week 52. ETD=estimated treatment difference.

the composite endpoints of HbA_{1c} lower than 7.0% (<53 mmol/mol), no weight gain, and no severe or blood glucose-confirmed hypoglycaemia (60% vs 40%; OR 2.56, 95% CI 1.84–3.54; p<0.0001) and HbA_{1c} reduction of at least 1.0 percentage point (≥10.4 mmol/mol) and weight loss of 5% or greater (39% vs 24%; 1.99, 1.43–2.76; p<0.0001; data not supplied).

Reductions in mean fasting plasma glucose and self-measured blood glucose (mean 7-point profile and mean postprandial increments) from baseline to week 52 were all greater with semaglutide than with canagliflozin (table 2). Both treatments resulted in reductions in blood pressure and fasting lipids. Canagliflozin reduced systolic and diastolic blood pressure versus semaglutide from baseline to week 52 (table 2). Pulse rate increased by a mean of 2.7 beats per min (SE 0.4) with semaglutide compared with a mean reduction of 0.6 beats per min (0.4) with canagliflozin (ETD 3.3, 95% CI 2.1–4.5; p<0.0001). Semaglutide reduced total serum cholesterol, LDL cholesterol and triglycerides compared with canagliflozin from baseline to week 52 (table 2; appendix p 19).

Canagliflozin increased HDL cholesterol compared with semaglutide from baseline to week 52 (table 2).

We observed no difference in DTSQ score (overall and individual components) between semaglutide and canagliflozin, except for the category “satisfaction with current treatment”, in which the score was in favour of semaglutide (ETD 0.13, 95% CI 0.00–0.26; p<0.05; appendix p 8). For the CoEQ, we found no difference between semaglutide and canagliflozin in any domain, except for the savoury craving domain score, in which the score was in favour of semaglutide (ETD -0.28, 95% CI -0.54 to -0.03; p=0.030; appendix p 9). Results of the SF-36 questionnaire showed no differences between treatment groups for changes in overall health-related quality of life (data not shown).

In total, 1189 adverse events were reported by 298 (76%) of 392 patients in the semaglutide group, and 1138 adverse events were reported by 283 (72%) of 394 patients in the canagliflozin group (table 3). Most adverse events were mild (occurring in 262 [67%] of 392 patients with semaglutide and in 252 [64%] of 394 with canagliflozin) or

	Change from baseline			Ratio to baseline		
	Semaglutide 1.0 mg (n=394)	Canagliflozin 300 mg (n=394)	Estimated treatment difference (95% CI; p value)	Semaglutide 1.0 mg (n=394)	Canagliflozin 300 mg (n=394)	Estimated treatment ratio (95% CI; p value)
Glucose (mmol/mol)						
FPG	-2.3 (0.10)	-2.0 (0.10)	-0.36 (-0.62 to -0.09; p=0.0094)
Mean 7-point SMBG profile*	-2.8 (0.10)	-2.0 (0.10)	-0.86 (-1.14 to -0.58; p<0.0001)
Postprandial SMBG increments	-0.7 (0.09)	-0.4 (0.09)	-0.26 (-0.49 to -0.02; p=0.036)
Systolic blood pressure (mm Hg)	-3.5 (0.7)	-5.5 (0.7)	2.0 (0 to 4.0; p=0.045)
Diastolic blood pressure (mm Hg)	-1.0 (0.5)	-3.0 (0.5)	2.0 (0.7 to 3.4; p=0.003)
Pulse rate (beats per min)	2.7 (0.4)	-0.6 (0.4)	3.3 (2.1 to 4.5; p<0.0001)
Lipids (mmol/L)						
Total cholesterol	0.97 (0.01)	1.03 (0.01)	0.94 (0.92 to 0.97; p<0.0001)
LDL cholesterol	0.97 (0.02)	1.05 (0.02)	0.92 (0.88 to 0.96; p=0.0004)
HDL cholesterol	1.04 (0.01)	1.08 (0.01)	0.96 (0.94 to 0.98; p=0.0001)
Triglycerides	0.87 (0.02)	0.92 (0.02)	0.95 (0.90 to 1.00; p=0.040)

Data are from the on-treatment without rescue medication observation period. Values are mean (SE). Responses were analysed using an ANCOVA with treatment, region, and stratification factor as fixed factors and baseline value as covariate. Before analysis, we multiple imputed missing data using observed data from patients within the same group defined by randomised treatment, using a regression model including region and stratification factor as categorical effects and data from baseline and all previous visits as covariates. For lipids, the response and baseline values were log transformed before ANCOVA analysis. FPG=fasting plasma glucose. SMBG=self-measured blood glucose. * Mean 7-point SMBG profile was calculated as the area under the profile divided by the measurement time.

Table 2: Glucose, blood pressure, pulse rate, and lipids at 52 weeks

moderate (occurring in 139 [35%] of 392 patients with semaglutide and in 118 [30%] of 394 with canagliflozin) in severity for both groups. 30 serious adverse events were reported by 18 (5%) of 392 patients receiving semaglutide, and 35 serious adverse events were reported by 21 (5%) of 394 patients receiving canagliflozin (table 3). The most frequent adverse events with semaglutide were gastrointestinal disorders (occurring in 184 [47%] of 392 patients with semaglutide vs 110 [28%] of 394 with canagliflozin), most commonly nausea (89 [23%] of 392 vs 26 [7%] of 394), whereas with canagliflozin, infections and infestations were the most frequent adverse events (occurring in 136 [35%] of 394 patients with canagliflozin vs 114 [29%] of 392 with semaglutide), most commonly urinary tract infections (18 [5%] of 394 vs 18 [5%] of 392 with semaglutide). No cases of Fournier's gangrene were reported. A higher proportion of patients in the semaglutide group prematurely discontinued treatment because of an adverse event compared with that in the canagliflozin group (38 [10%] of 392 with semaglutide vs 20 [5%] of 394 with canagliflozin). This was primarily driven by gastrointestinal adverse events in the semaglutide group (26 [7%] of 392 vs four [1%] of 394). The most common reason for premature treatment discontinuation in the canagliflozin group was infections and infestations (six [2%] of 394 patients with canagliflozin vs one [$<1\%$] of 392 with semaglutide). Severe or blood glucose-confirmed symptomatic hypoglycaemia occurred in six (2%) patients with semaglutide and in five (1%)

patients with canagliflozin. Two events in one patient ($<1\%$) from the semaglutide group on trial days 75 and 76 were considered severe. The first event was associated with physical activity, and no information was provided on the second event; both resolved after treatment with oral carbohydrates. New or worsening diabetic retinopathy was diagnosed in nine (2%) of 392 patients with semaglutide compared with 15 (4%) of 394 with canagliflozin during the in-trial observation period. No amputations occurred in the trial. One ($<1\%$) fatal adverse event that did not meet the criteria for a coronary event occurred in the semaglutide group and was confirmed by the Event Adjudication Committee as sudden cardiac death unlikely to be caused by the treatment. We observed no clinically relevant changes in other safety parameters.

Discussion

In SUSTAIN 8, we have shown the superiority of once-weekly semaglutide 1.0 mg versus daily canagliflozin 300 mg in reductions in HbA_{1c} and bodyweight in patients with uncontrolled type 2 diabetes on a background of metformin therapy, although both treatments led to improvements in glycaemia and weight loss. These results add to those observed in the SUSTAIN clinical trial programme, in which treatment with semaglutide led to superior improvements in glycaemic control and weight loss compared with those with placebo, sitagliptin, exenatide extended release, insulin glargine, and dulaglutide.^{6–11}

	Semaglutide 1.0 mg (n=392)			Canagliflozin 300 mg (n=394)		
	Number of patients*	Number of events	Event rate per 100 exposure-years	Number of patients*	Number of events	Event rate per 100 exposure-years
All adverse events	298 (76%)	1189	307.4	283 (72%)	1138	286.7
Serious adverse events	18 (5%)	30	7.8	21 (5%)	35	8.8
Fatal adverse events†	1 (<1%)	1	0.3	0	0	NA
Adverse events leading to premature treatment discontinuation‡	38 (10%)	46	11.9	20 (5%)	24	6.0
GI adverse events leading to premature treatment discontinuation	26 (7%)	28	7.2	4 (1%)	4	1.0
GI adverse events	184 (47%)	458	118.4	110 (28%)	208	52.4
GI adverse events occurring in ≥5% of patients						
Nausea	89 (23%)	127	32.8	26 (7%)	30	7.6
Diarrhoea	60 (15%)	95	24.6	37 (9%)	58	14.6
Vomiting	50 (13%)	77	19.9	9 (2%)	9	2.3
Dyspepsia	22 (6%)	23	5.9	8 (2%)	8	2.0
Constipation	20 (5%)	20	5.2	23 (6%)	23	5.8
Infections and infestations	114 (29%)	172	44.5	136 (35%)	241	60.7
Genital and perineal infections	10 (3%)	11	2.8	48 (12%)	69	17.4
Urinary tract infections	18 (5%)	21	5.4	18 (5%)	18	4.5
Hypoglycaemia§	53 (14%)	122	31.5	32 (8%)	68	17.1
Severe or BG-confirmed hypoglycaemia	6 (2%)	25	6.5	5 (1%)	6	1.5
Severe	1 (<1%)	2	0.5	0	0	NA
Adverse events potentially leading to lower limb amputation¶	14 (4%)	15	3.6	24 (6%)	27	6.4
Nervous system disorders	8 (2%)	9	2.1	16 (4%)	18	4.3
Infections and infestations	0	0	NA	4 (1%)	5	1.2
Vascular disorders	3 (1%)	3	0.7	1 (<1%)	1	0.2
Injury, poisoning, and procedural complications (wound)	0	0	NA	2 (1%)	2	0.5
Skin and subcutaneous tissue disorders (skin ulcer)	2 (1%)	2	0.5	0	0	NA
Metabolism and nutrition disorders (dehydration)	0	0	NA	1 (<1%)	1	0.2
Musculoskeletal and connective tissue disorders (osteitis)	1 (<1%)	1	0.2	0	0	NA
Other adverse events of clinical interest						
New or worsening diabetic retinopathy	9 (2%)	10	2.4	15 (4%)	16	3.8
Medication errors and overdose	8 (2%)	8	2.1	2 (1%)	2	0.5
Acute renal failure	4 (1%)	4	1.0	0	0	NA
Malignant neoplasms**	2 (1%)	3	0.7	4 (1%)	4	0.9

Data are n (%), unless otherwise specified. Adverse events were identified using MedDRA, version 21.0. ADA=American Diabetes Association. BG=blood glucose.

GI=gastrointestinal. MedDRA=Medical Dictionary for Regulatory Activities. NA=not applicable. *Number of patients who had at least one event. †One (<1%) sudden cardiac death (confirmed by the Event Adjudication Committee) occurred in the semaglutide 1.0 mg treatment group on trial day 369; this was considered unlikely to be caused by treatment. ‡Adverse events leading to premature treatment discontinuation in the semaglutide group (38 patients) were due to GI disorders (26 patients), investigations (five), metabolism and nutrition disorders (four), nervous system disorders (two), urinary tract infection (one), malaise (one), ureterolithiasis (one), feeling of despair (one), palpitations (one), back pain (one), and arterial disorder (one); in the canagliflozin group (20 patients), such adverse events were due to infections and infestation (six patients), GI disorders (four), skin and subcutaneous tissue disorders (three), investigations (two), general disorders and administration site conditions (two), renal and urinary disorders (two), skin and subcutaneous tissue disorders (two), motor dysfunction (one), irritability (one), vertigo (one), vulvovaginal pruritus (one), and epistaxis (one). §ADA classification (<3.9 mmol/L [<70 mg/dL]); severe or BG-confirmed symptomatic hypoglycaemia was defined as an episode that was severe according to the ADA classification or was BG-confirmed by a plasma glucose value (<3.1 mmol/L [56 mg/dL]), with symptoms consistent with hypoglycaemia. ¶A signal of increased risk of lower limb amputations has been associated with the use of canagliflozin; while the review of this risk by health authorities is ongoing, participants at risk were excluded from this trial, and assessment of leg and foot was required at every site visit; adverse events potentially leading to lower limb amputation were those observed during the in-trial observation period (defined as the period where people were considered within the trial, regardless of trial product discontinuation or initiation of rescue medicine) according to a predefined MedDRA search. ||Adverse events are based on a predefined MedDRA search; new or worsening diabetic retinopathy were adverse events observed during the in-trial observation period. **Malignant neoplasms were events confirmed by the Event Adjudication Committee and observed during the in-trial observation period.

Table 3: Overview of adverse events

Achieving the targets of HbA_{1c} lower than 7.0% (<53 mmol/mol)¹⁸ or 6.5% or lower (≤48 mmol/mol)¹ is crucial for substantially reducing the development and progression of microvascular complications in type 2 diabetes.¹⁸ Both semaglutide^{6–11} and canagliflozin^{12–15} were previously shown to have efficacy in reducing HbA_{1c} to target levels. In SUSTAIN 8, the 1.5 percentage point (16.0 mmol/mol) reduction in HbA_{1c} with semaglutide is consistent with reported mean reductions of 1.5–1.8 percentage points in previous trials.¹⁹ Similarly, the 1.0 percentage point (10.7 mmol/mol) reduction in HbA_{1c} achieved with canagliflozin is consistent with the 0.80–1.03 percentage point reductions reported in the literature.^{20,21} Approximately two-thirds of patients receiving semaglutide achieved the ADA target of HbA_{1c} lower than 7.0% (<53 mmol/mol) and over half of patients met the more ambitious AACE target of HbA_{1c} 6.5% or lower (≤48 mmol/mol), compared with fewer than half achieving the ADA target and fewer than a quarter achieving the AACE target in those receiving canagliflozin. These results are similar to those from responder analyses of the global SUSTAIN clinical trial programme for semaglutide²² and phase 3 studies with canagliflozin^{12,13} and reflect the findings of a network meta-analysis assessing the comparative efficacy of semaglutide and canagliflozin in patients with type 2 diabetes inadequately controlled with metformin therapy.²³

In SUSTAIN 8, twice as many patients achieved weight loss of at least 10% with semaglutide than those with canagliflozin after 1 year of treatment. Because the SUSTAIN 1–5 and 7 trials assessing 5% and 10% weight loss have repeatedly shown superior responses with semaglutide compared with those with comparators, and because semaglutide can consistently provide 15% weight loss in some patients,²⁴ we did a post-hoc analysis to investigate if a more stringent weight loss target of at least 15% was attainable by a meaningful proportion of patients with semaglutide. The analysis found that 7% of patients were so-called super-responders, achieving at least 15% weight loss. This highlights the potential benefit of a 15% weight loss to patients and health-care professionals, as well as reassuring them that this is a recognised effect of semaglutide and should not be a cause for undue concern. These results are similar to the greater proportions of weight-loss responders with semaglutide compared with those receiving comparators that were observed in SUSTAIN 1–5 and 7. Factors contributing to the magnitude of weight loss observed with semaglutide are not fully understood. In SUSTAIN 9, the addition of semaglutide to an SGLT2 inhibitor significantly reduced bodyweight compared with placebo (ETD −3.81 kg, 95% CI −4.70 to −2.93),²⁵ an additive effect that suggests a difference in the mechanism of action for weight loss between drug classes and a possible synergy when these classes are used concomitantly. The effect of GLP-1 receptor agonists on weight loss is believed to be centrally mediated,²⁶ with reduced energy intake as a

potential result of reduced appetite and food cravings, better control of eating, and a lower preference for fatty food.²⁷ SGLT2 inhibitors are generally considered to cause weight loss by glucose excretion (calorie loss) in the kidneys, although this glucosuria can elicit adaptive compensatory increases in energy intake to mitigate excessive weight loss.²⁸ Surprisingly, patient-reported outcomes in SUSTAIN 8 showed improved control of cravings in both groups, although semaglutide significantly decreased the desire for savoury food compared with that with canagliflozin (appendix p 9); the reasons for this result are not known.

In SUSTAIN 8, both canagliflozin and semaglutide reduced blood pressure, although the reduction with canagliflozin was significantly greater. Semaglutide reduced levels of total cholesterol, LDL cholesterol, and triglycerides compared with canagliflozin, results that have been observed against other comparators in previous trials,^{6,8–11,16,25} whereas canagliflozin increased HDL cholesterol compared with semaglutide. Hyperlipidaemia is a well known risk factor for cardiovascular disease and a particular concern for patients with type 2 diabetes.²⁹ The beneficial effects of semaglutide on lipids might have had a role in the cardiovascular risk reduction shown in SUSTAIN 6, in which treatment with semaglutide significantly decreased the occurrence of major cardiovascular events compared with that of placebo in patients at high risk of cardiovascular disease.¹⁶

The results of SUSTAIN 8 showed low rates of serious adverse events for both semaglutide and canagliflozin. The reported higher incidence of gastrointestinal adverse events with semaglutide was expected, with rates similar to those across the SUSTAIN programme.^{6–11} Likewise, the higher incidence of genital and perineal infections with canagliflozin was expected and has been reported previously.^{12–15} Severe or blood glucose-confirmed hypoglycaemia was low and similar in both treatment groups. These results, combined with consistently low rates of hypoglycaemic events reported across the SUSTAIN trials,^{6–11} might offer further reassurance to patients with type 2 diabetes for whom fear of hypoglycaemia might be a barrier to achieving glycaemic control.

The superiority of semaglutide on HbA_{1c} and weight loss compared with canagliflozin was consistent with indirect evidence from clinical trials investigating the efficacy of GLP-1 receptor agonists compared with that of SGLT2 inhibitors.³⁰ In a network meta-analysis that indirectly compared the efficacy of semaglutide with SGLT2 inhibitors (including canagliflozin and dapagliflozin) in patients with type 2 diabetes inadequately controlled with metformin therapy, semaglutide outperformed SGLT2 inhibitor comparators in both glycaemic control and weight loss.²³ Similarly, another network meta-analysis showed superiority of GLP-1 receptor agonists versus SGLT2 inhibitors.³¹ More recently, the PIONEER-2 trial has shown significantly greater effects of once-daily oral

semaglutide on glycaemic control and weight loss compared with those of empagliflozin at 52 weeks.³²

Overall, the results of SUSTAIN 8 provide a robust head-to-head comparison of a GLP-1 receptor agonist and an SGLT2 inhibitor, show that semaglutide is an efficacious, well tolerated second-line treatment option for patients with type 2 diabetes, and provide important comparative second-line data on GLP-1 receptor agonists versus SGLT2 inhibitors in patients with type 2 diabetes uncontrolled by metformin therapy who do not have atherosclerotic heart disease. However, treatment intensification should always consider individual patient factors, such as presence of atherosclerotic disease and history or high risk of heart failure,³ as well as patient and physician preferences.

SUSTAIN 8 has several strengths, including its substantial size, global population, double-blind nature, relatively long treatment period, and relevant head-to-head comparison with a well-established glucose-lowering medication. However, our study also has several limitations. As with any randomised controlled trial with multiple eligibility criteria and frequent, intensive follow-ups between health-care professionals and patients, the population of SUSTAIN 8 will not accurately reflect clinical practice or a real-world, heterogeneous population with type 2 diabetes. Additionally, although this trial had a sufficiently long duration to assess the effect of trial products on glycaemic control and weight loss, the evaluation of long-term effects, including persistence and potential complications and comorbidities, would require longer studies to assess fully. Finally, although assessment of patient-reported outcomes is an important strength of SUSTAIN 8, a consideration when interpreting these is the double-blind, double-dummy trial design, which meant that patients receiving oral canagliflozin also received a weekly injection of semaglutide-mimicking placebo. While this minimised study bias, it also limited the true effect of each treatment on patient-reported outcomes, particularly DTSQ (which assesses treatment satisfaction, flexibility, and convenience), because of receipt of an injection in both treatment groups.

In summary, treatment with once-weekly semaglutide 1.0 mg was superior to that with daily canagliflozin 300 mg in reducing HbA_{1c} and bodyweight in patients with uncontrolled type 2 diabetes on a background of metformin treatment. Both treatments were well tolerated, with low rates of hypoglycaemia. These results add to a body of evidence from the SUSTAIN clinical trial programme showing that semaglutide is an effective glucose-lowering medication offering additional benefits, such as weight loss and cardiovascular-protective effects. These study outcomes might be used to guide decisions about treatment intensification after metformin therapy in this patient population.

Contributors

IL, A-MC, HK, CWIR, DT, AV, and RJM participated in the design of this analysis. IL, A-MC, JPF, HK, CWIR, DT, AV, and RJM contributed

to the conduct and data collection of the primary trial. NLL 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

IL received research grants to her institution and consulting fees from Novo Nordisk, and received grants, personal fees, or both from AstraZeneca, Boehringer Ingelheim, Eli Lilly, GI Dynamics, Intarcia, Mannkind, Merck, Mylan, Novartis, Novo Nordisk, Pfizer, Sanofi, TARGET PharmaSolutions, and Valeritas. A-MC, NLL, and DT are full-time employees of Novo Nordisk. JPF reports grants and personal fees from Novo Nordisk, and grants and personal fees from AstraZeneca, Eli Lilly, Pfizer, Sanofi, Merck, Boehringer Ingelheim, and Bristol-Myers Squibb. HK reports grants and non-financial support from Novo Nordisk. CWIR reports grants and other support from the Health Research Board, the Science Foundation Ireland, and the Irish Research Council, and reports grants, personal fees, and other support from AnaBio, AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Eli Lilly, GI Dynamics, Janssen, Johnson & Johnson, Keyron, Novo Nordisk, and Sanofi. AV reports grants and other support from AstraZeneca, Boehringer Ingelheim, Eli Lilly, MSD, Napp, Novo Nordisk, and Sanofi, and non-financial support from Amgen, AstraZeneca, Eli Lilly, Novartis, Novo Nordisk, Regeneron, and Sanofi. RJM reports personal fees from Eli Lilly, Novo Nordisk, and Sanofi.

Data sharing

Individual participant data will be shared in datasets in a de-identified format, including datasets from Novo Nordisk-sponsored clinical research completed after 2001 for product indications approved in both the EU and the USA. The study protocol and redacted clinical study report will be available according to Novo Nordisk data sharing commitments. Data will be available permanently after research completion and approval of product and product use in the EU and the USA. Data will only be shared with bona fide researchers submitting a research proposal and requesting access to data, for use as approved by the independent review board and according to its charter. The access request proposal form and the access criteria can be found online. Data will be made available on a specialised Statistical Analysis System data platform.

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