# Semaglutide once weekly as add-on to SGLT-2 inhibitor therapy in type 2 diabetes (SUSTAIN 9): a randomised, placebo-controlled trial

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## Summary

**Background** Semaglutide is a once-weekly glucagon-like peptide-1 (GLP-1) analogue for type 2 diabetes. Few clinical trials have reported on the concomitant use of GLP-1 receptor agonists with sodium-glucose cotransporter-2 (SGLT-2) inhibitors. We aimed to investigate the efficacy and safety of semaglutide when added to SGLT-2 inhibitor therapy in patients with inadequately controlled type 2 diabetes.

**Methods** The SUSTAIN 9 double-blind, parallel-group trial was done at 61 centres in six countries (Austria, Canada, Japan, Norway, Russia, and the USA). Adults with type 2 diabetes and $HbA_{1c}$ 7·0–10·0% (53–86 mmol/mol), despite at least 90 days of treatment with an SGLT-2 inhibitor, were randomly assigned (1:1) to receive subcutaneous semaglutide 1·0 mg or volume-matched placebo once weekly for 30 weeks, after a dose-escalation schedule of 4 weeks of 0·25 mg semaglutide or placebo and 4 weeks of 0·5 mg semaglutide or placebo. Existing antidiabetic medications, including SGLT-2 inhibitor treatment, were continued for the duration of the trial. Rescue medication, defined as intensification of background antidiabetic treatment or the initiation of new glucose-lowering medications, could be given to patients meeting specific criteria at the discretion of the investigator. The primary outcome was change in $HbA_{1c}$ from baseline at week 30, assessed in the full analysis set (all patients randomly allocated to treatment) using on-treatment data collected before rescue medication was started. The confirmatory secondary outcome was change in bodyweight from baseline to week 30. Safety was also assessed in the safety analysis set (all patients who received at least one dose of treatment). The trial was registered with ClinicalTrials.gov (NCT03086330).

**Findings** Between March 15, and Dec 4, 2017, 302 patients were enrolled and randomly assigned to receive semaglutide 1·0 mg or placebo (full analysis set), of whom 301 received at least one dose of treatment (safety analysis set). One patient was assigned to semaglutide but was not treated (reason unknown). 294 (97·4%) patients completed the trial and 267 (88·4%) completed treatment. Baseline characteristics were generally comparable between groups. In addition to randomised medication and SGLT-2 inhibitor, 216 (71·5%) patients were taking metformin and 39 (12·9%) were taking sulphonylurea. Patients given semaglutide had greater reductions in $HbA_{1c}$ (estimated treatment difference –1·42% [95% CI –1·61 to –1·24]; –15·55 mmol/mol [–17·54 to –13·56]) and bodyweight (–3·81 kg [–4·70 to –2·93]) versus those randomised to placebo (both p<0·0001). 356 adverse events were reported by 104 (69·3%) patients in the semaglutide group, and 247 adverse events were reported by 91 (60·3%) patients in the placebo group. Gastrointestinal adverse events were most common and were reported in 56 (37·3%) patients in the semaglutide group and 20 (13·2%) in the placebo group. Serious adverse events occurred in seven (4·7%) patients in the semaglutide group and six (4·0%) in the placebo group. Severe or blood glucose-confirmed hypoglycaemic events were reported in four patients on semaglutide (2·7%). 16 patients stopped treatment early because of an adverse event, 13 of whom were in the semaglutide group. There were no deaths during the trial.

**Interpretation** Adding semaglutide to SGLT-2 inhibitor therapy significantly improves glycaemic control and reduces bodyweight in patients with inadequately controlled type 2 diabetes, and is generally well tolerated.

**Funding** Novo Nordisk.



## Introduction

The 2018 report on the management of type 2 diabetes from the American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD),[1] and the 2019 ADA Standards of Care treatment guidelines[2] emphasise the use of treatment regimens that take patients' characteristics into account. Notably, this report and guidelines highlight glucagon-like peptide-1 (GLP-1) receptor agonists and sodium-glucose cotransporter-2 (SGLT-2) inhibitors as preferred agents after metformin in patients with type 2 diabetes and established cardiovascular disease.[1,2] In addition to improving glycaemic control, some drugs in each of these classes lower the risk of major cardiovascular events, reduce the

## Research in context

### Evidence before this study

Glucagon-like peptide-1 (GLP-1) receptor agonists and sodium-glucose co-transporter-2 (SGLT-2) inhibitors have been highlighted in the 2018 American Diabetes Association/European Association for the Study of Diabetes consensus report as preferred agents after metformin in patients with established cardiovascular disease. However, to date, few data from clinical trials are available to help physicians and patients to make informed decisions about the concomitant use of these drugs.

### Added value of this study

The results of the SUSTAIN 9 trial show that the addition of subcutaneous semaglutide, a once-weekly GLP-1 analogue, to existing SGLT-2 inhibitor therapy significantly improves glycaemic control and reduces bodyweight. Additionally, the trial shows that most patients tolerate concomitant treatment well.

### Implications of all the available evidence

SUSTAIN 9 is the second clinical trial to show that the concomitant use of GLP-1 receptor agonists and SGLT-2 inhibitors is effective and generally well tolerated in patients with type 2 diabetes. Combining the distinct modes of action of these two drug classes has beneficial effects on glucose and weight outcomes. Specifically, the findings of the SUSTAIN 9 trial show that the addition of semaglutide 1·0 mg appears to be an effective, well tolerated treatment option for patients who have not reached their therapeutic goals, despite treatment with an SGLT-2 inhibitor.

progression of chronic kidney disease, minimise the risk of hypoglycaemia, and reduce bodyweight.[3–8] GLP-1 receptor agonists and SGLT-2 inhibitors are increasingly used for the treatment of type 2 diabetes, but there is scarce information from clinical trials on the efficacy and safety of their concomitant use.

Semaglutide is a long-acting GLP-1 analogue approved for once-weekly treatment of type 2 diabetes.[9,10] The efficacy and safety of semaglutide have been established in the SUSTAIN clinical trial programme across the continuum of care in patients with type 2 diabetes.

During the SUSTAIN programme, semaglutide has been directly compared with various antidiabetic drugs, and has been studied both as monotherapy and in combination with other agents. Semaglutide has consistently shown superior $HbA_{1c}$ and bodyweight reductions versus placebo[11,12] and a range of active comparators,[13–16] and has a safety profile similar to that of other GLP-1 receptor agonists.[13,15,16] Furthermore, in SUSTAIN 6,[3] semaglutide significantly reduced the risk of major adverse cardiovascular events compared with placebo, in patients with type 2 diabetes and high cardiovascular risk. The benefits of semaglutide have also been shown when used in addition to various combinations of oral antidiabetic drugs (eg, metformin, with or without sulphonylureas or thiazolidinediones).[3,13–16] Semaglutide has also shown superiority over placebo when used in combination with basal insulin (with or without metformin), in terms of effects on both $HbA_{1c}$ and bodyweight.[12]

As changes to international guidelines begin to be implemented at national and local levels, it is likely that concomitant treatment with GLP-1 receptor agonists and SGLT-2 inhibitors will become more common. However, at present, there are only scarce data from randomised controlled trials to inform such concomitant use,[17,18] and even less evidence relating to the specific clinical situation in which a GLP-1 receptor agonist is added to existing SGLT-2 inhibitor treatment.[17]

The SUSTAIN 9 trial aimed to investigate the efficacy and safety of semaglutide in patients with type 2 diabetes who were inadequately controlled on SGLT-2 inhibitor-based treatment.

## Methods

### Study design and participants

SUSTAIN 9 was a 30-week, phase 3b, randomised, double-blind, parallel-group, placebo-controlled trial, done at 61 centres (including hospitals, clinical research units, and private offices) in six countries (Austria, Canada, Japan, Norway, Russia, and the USA). The design of the trial is shown in the appendix.

See Online for appendix

Patients were considered for enrolment if they were aged 18 years or older (≥20 years in Japan), had type 2 diabetes, and had an $HbA_{1c}$ level of 7·0–10·0% (53–86 mmol/mol) at the time of screening. Eligible patients were required to be on stable treatment with an SGLT-2 inhibitor (as monotherapy, or with a sulphonylurea or metformin [≥1500 mg/day, or the maximum tolerated dose]), and to have started SGLT-2 inhibitor treatment at least 90 days before screening. Key exclusion criteria were an estimated glomerular filtration rate (eGFR) of less than 60 mL/min per 1·73 m² and the presence of New York Heart Association class IV heart failure. Patients with proliferative retinopathy or maculopathy requiring acute treatment, verified by fundus photography or dilated fundoscopy within 90 days before randomisation, were also excluded. Full inclusion and exclusion criteria are listed in the appendix.

SUSTAIN 9 was done in compliance with the International Conference on Harmonisation Good Clinical Practice guidelines[19] and the Declaration of Helsinki.[20] The trial protocol was approved by the institutional review board and ethics committee at each participating centre, and patients provided written informed consent before trial-related activities started. The protocol is available in the appendix.

### Randomisation and masking

Enrolled patients were randomised (1:1) to receive either semaglutide 1·0 mg (Novo Nordisk, Bagsværd, Denmark), administered subcutaneously once weekly, or volume-matched placebo. Randomisation was done via an interactive web response system. We stratified patients according to antidiabetic medication at screening (sulphonylurea use: yes or no) and region (Japan or other).

Semaglutide and placebo were prepared in visually identical dosage units to maintain masking throughout the trial. Patients and site personnel were masked to treatment. Events of interest were reviewed by an event adjudication committee in a masked manner. Masking was performed in accordance with Good Clinical Practice.

### Procedures

A screening period of up to 2 weeks was followed by 30 weeks of treatment and 5 weeks of follow-up. For the first 8 weeks, patients followed a fixed dose-escalation schedule, in which the maintenance dose of semaglutide (1·0 mg once weekly) was reached after 4 weeks of semaglutide 0·25 mg followed by 4 weeks of semaglutide 0·5 mg. Patients in the placebo group followed the same dose-escalation schedule to maintain masking.

Trial medications were administered subcutaneously, using a prefilled pen injector, into the thigh, abdomen, or upper arm. Injections were given on the same day each week at any time of day, irrespective of meals.

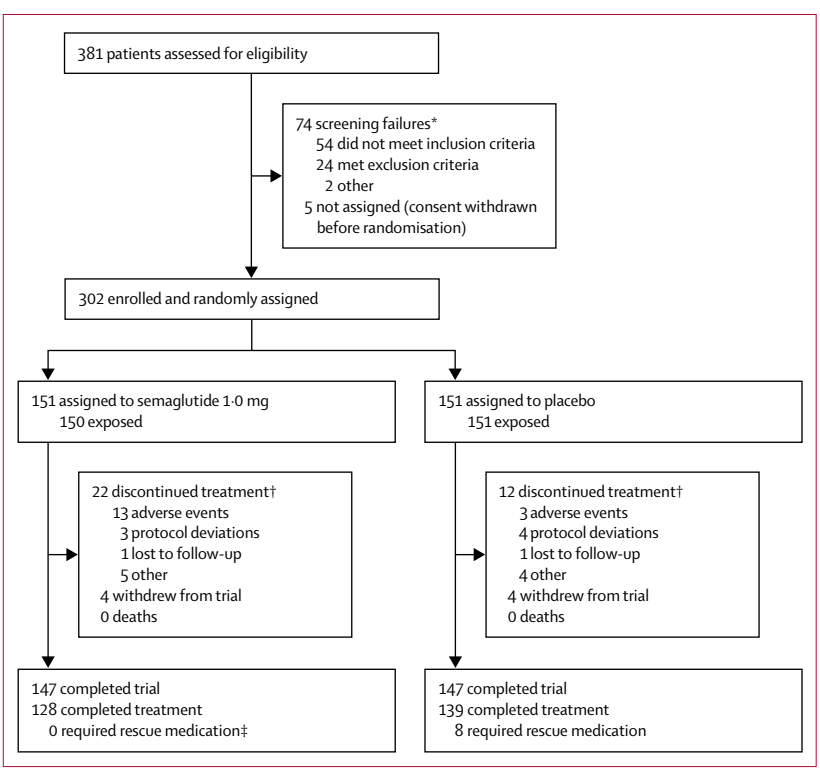


***Figure 1:*** **Trial profile**
Completed trial refers to patients who attended the follow-up visit. Completed treatment refers to patients who did not discontinue treatment prematurely (with or without the addition of rescue medication). *Some patients had more than one reason for screening failure. †Reflects the primary reason for treatment discontinuation, as judged by the investigator. ‡One patient that did not complete treatment required rescue medication.

Existing antidiabetic medications, including SGLT-2 inhibitor treatment, were continued for the duration of the trial. Rescue medication, defined as intensification of background antidiabetic treatment or the initiation of new glucose-lowering medications, was administered at the discretion of the investigator and was consistent with ADA/EASD guidelines.[1] Such medication could be offered to patients with confirmed fasting plasma glucose concentrations of greater than 13·3 mmol/L (240 mg/dL) from week 8 to the end of week 13, or greater than 11·1 mmol/L (200 mg/dL) from week 14 to the end of the trial. Rescue medication was added on to study treatment. GLP-1 receptor agonists, dipeptidyl peptidase-4 inhibitors, and amylin analogues were not permitted.

### Outcomes

The primary outcome was change in $HbA_{1c}$ from baseline to week 30, and the confirmatory secondary outcome was change in bodyweight over the same period. Other prespecified secondary outcomes endpoints included change from baseline to week 30 in fasting plasma glucose concentration; mean (across all meals) seven-point self-measured blood glucose concentration, and mean postprandial glucose increment; fasting blood lipid (total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides) concentrations; BMI and waist circumference; systolic and diastolic blood pressure; and patient-reported outcome questionnaire scores (Short Form 36 version 2 and Diabetes Treatment Satisfaction Questionnaire status version [DTSQs]).

Prespecified clinical treatment targets included proportions of patients achieving the following at week 30: $HbA_{1c}$ less than 7·0% (<53 mmol/mol; ADA);[21] $HbA_{1c}$ less than or equal to 6·5% (≤48 mmol/mol; American Association of Clinical Endocrinologists);[22] bodyweight loss of at least 5% or at least 10%; the composite endpoint of $HbA_{1c}$ less than 7·0% (<53 mmol/mol) without severe (ADA classification[23]) or blood glucose-confirmed (<3·1 mmol/L; <55·8 mg/dL) symptomatic hypoglycaemia and no weight gain; and composite endpoints of a decrease in $HbA_{1c}$ ≥1·0% (≥11 mmol/mol) with weight loss of at least 3%, 5%, or 10%. We also did a post-hoc analysis on the composite endpoint of $HbA_{1c}$ less than 7·0% (<53 mmol/mol) and weight loss of at least 5%, without severe or blood glucose-confirmed symptomatic hypoglycaemia. A complete list of prespecified supportive secondary outcomes is included in the appendix.

Safety endpoints included the number of treatment-emergent adverse events, incidence of severe or blood glucose-confirmed symptomatic hypoglycaemic episodes, eGFR, and pulse rate. Fundus photography or dilated fundoscopy was done at baseline and week 30, or upon premature discontinuation, to allow comparison with baseline and the identification of diabetic retinopathy

| | Semaglutide 1·0 mg (n=151) | Placebo (n=151) | Total (n=302) |
|---|---|---|---|
| Age, years | 57·5 (8·9) | 56·6 (10·1) | 57·0 (9·5) |
| Sex | | | |
| Male | 89 (58·9%) | 87 (57·6%) | 176 (58·3%) |
| Female | 62 (41·1%) | 64 (42·4%) | 126 (41·7%) |
| Race | | | |
| White | 100 (66·2%) | 109 (72·2%) | 209 (69·2%) |
| Asian | 36 (23·8%) | 35 (23·2%) | 71 (23·5%) |
| Black or African American | 9 (6·0%) | 4 (2·6%) | 13 (4·3%) |
| American Indian or Alaska native | 2 (1·3%) | 0 | 2 (0·7%) |
| Other* | 4 (2·6%) | 3 (2·0%) | 7 (2·3%) |
| Ethnicity | | | |
| Hispanic or Latino | 9 (6·0%) | 13 (8·6%) | 22 (7·3%) |
| Not Hispanic or Latino | 142 (94·0%) | 138 (91·4%) | 280 (92·7%) |
| $HbA_{1c}$, % | 8·0 (0·8) | 8·1 (0·8) | 8·0 (0·8) |
| $HbA_{1c}$, mmol/mol | 64·1 (8·8) | 64·5 (9·1) | 64·3 (9·0) |
| Fasting plasma glucose, mmol/L | 9·1 (2·1) | 8·9 (2·2) | 9·0 (2·1) |
| Seven-point SMBG, mmol/L | 9·9 (1·9) | 9·7 (1·7) | 9·8 (1·8) |
| Seven-point SMBG, increment across meals, mmol/L | 2·4 (2·0) | 2·3 (1·9) | 2·4 (2·0) |
| Time since diabetes diagnosis, years | 9·8 (6·3) | 9·6 (5·9) | 9·7 (6·1) |
| Bodyweight, kg | 89·6 (19·5) | 93·8 (22·3) | 91·7 (21·0) |
| BMI, $kg/m^2$ | 31·1 (6·2) | 32·7 (6·9) | 31·9 (6·6) |
| Waist circumference, cm | 105·3 (14·0) | 109·2 (16·8) | 107·2 (15·5) |
| eGFR, mL/min per 1·73 $m^2$† | 94·5 (15·3) | 96·0 (15·1) | 95·2 (15·2) |
| Lipids, mmol/L‡ | | | |
| Total cholesterol | 4·4 (25·7) | 4·5 (25·5) | 4·5 (25·5) |
| HDL cholesterol | 1·1 (28·6) | 1·2 (23·3) | 1·1 (26·0) |
| LDL cholesterol | 2·3 (40·6) | 2·3 (45·7) | 2·3 (43·1) |
| Triglycerides | 1·7 (60·6) | 1·9 (51·4) | 1·8 (56·2) |
| Systolic blood pressure, mm Hg | 127·2 (14·0) | 128·6 (15·0) | 127·9 (14·5) |
| Diastolic blood pressure, mm Hg | 77·8 (8·0) | 79·9 (9·5) | 78·8 (8·8) |
| Pulse rate, beats per min | 73·7 (11·1) | 74·6 (9·6) | 74·1 (10·4) |
| Smoking status | | | |
| Current | 23 (15·2%) | 22 (14·6%) | 45 (14·9%) | |
| Never | 89 (58·9%) | 82 (54·3%) | 171 (56·6%) | |
| Previous | 39 (25·8%) | 47 (31·1%) | 86 (28·5%) | |
| Haemoglobin, mmol/L‡ | 8·9 (9·2) | 9·0 (10·3) | NA | |
| Leukocytes, $\times 10^9$/L‡ | 6·8 (23·3) | 6·7 (26·0) | NA | |
| Antidiabetic medication at screening | | | |
| SGLT-2 inhibitor§ | 150 (99·3%) | 151 (100%) | 301 (99·7%) | |
| Metformin¶ | 106 (70·2%) | 110 (72·8%) | 216 (71·5%) | |
| Sulphonylurea | 19 (12·6%) | 20 (13·2%) | 39 (12·9%) | |

(Table 1 continues in next column)

(Continued from previous column)

| | Semaglutide 1·0 mg (n=151) | Placebo (n=151) | Total (N=302) |
|---|---|---|---|
| Diabetes complications | | | |
| Diabetic neuropathy | 25 (16·6%) | 34 (22·5%) | 59 (19·5%) |
| Diabetic nephropathy | 14 (9·3%) | 11 (7·3%) | 25 (8·3%) |
| Macroangiopathy‖ | 8 (5·3%) | 8 (5·3%) | 16 (5·3%) |
| Diabetic retinopathy | 13 (8·6%) | 25 (16·6%) | 38 (12·6%) |
| Proliferative | 1 (0·7%) | 0 | 1 (0·3%) |
| Non-proliferative | 12 (7·9%) | 25 (16·6%) | 37 (12·3%) |

Data are mean (SD) or n (%) for the full analysis set, unless otherwise stated. SMBG=self-measured blood glucose. eGFR=estimated glomerular filtration rate. NA=not available. SGLT-2=sodium–glucose cotransporter-2. *Guyanese (n=1), Indian (n=1), Latino (n=1), Metis (n=2), Turkish (n=1), and West Indian (n=1). †eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration formula in serum and is expressed as geometric mean (coefficient of variation). ‡Data expressed as geometric mean (coefficient of variation). §Includes 68 patients on canagliflozin, 106 on dapagliflozin, 102 on empagliflozin, and 25 on other SGLT-2 inhibitors available only in Japan. ¶Metformin or metformin hydrochloride. ||Including peripheral vascular disease.

***Table 1:*** **Baseline characteristics**

adverse events. All adverse events were coded using version 21.0 of the Medical Dictionary for Regulatory Activities. The protocol contains a full list of all safety endpoints (appendix).

### Statistical analysis

We calculated that a sample size of 300 would achieve at least 99% power for testing the superiority of semaglutide versus placebo in change from baseline in $HbA_{1c}$ and bodyweight (primary and confirmatory secondary hypotheses). The sample size was determined on the basis of the need to collect safety data from patients treated with the combination of semaglutide and SGLT-2 inhibitor, with either metformin or sulphonylurea.

We tested the primary and confirmatory secondary endpoints using a closed testing procedure. In multiple imputation analyses, missing values were imputed using a sequential regression approach for each treatment group separately, assuming that missing data are missing at random. ANCOVA was used, with treatment and stratification factors (use of a sulphonylurea at screening [yes or no] and region [Japan or other]) as categorical effects, and baseline $HbA_{1c}$ (for primary analyses) and bodyweight (for confirmatory secondary analyses) as covariates. We used Rubin's rule to combine the results from multiple-imputed data (appendix).

Two methodologically distinct sensitivity analyses were done to test the robustness of the efficacy results. We used a tipping point analysis to test the sensitivity of the results to the missing at random assumption for missing data. Further sensitivity analyses, using retrieved dropout methodology (including responses of patients who stopped study treatment and started an alternative

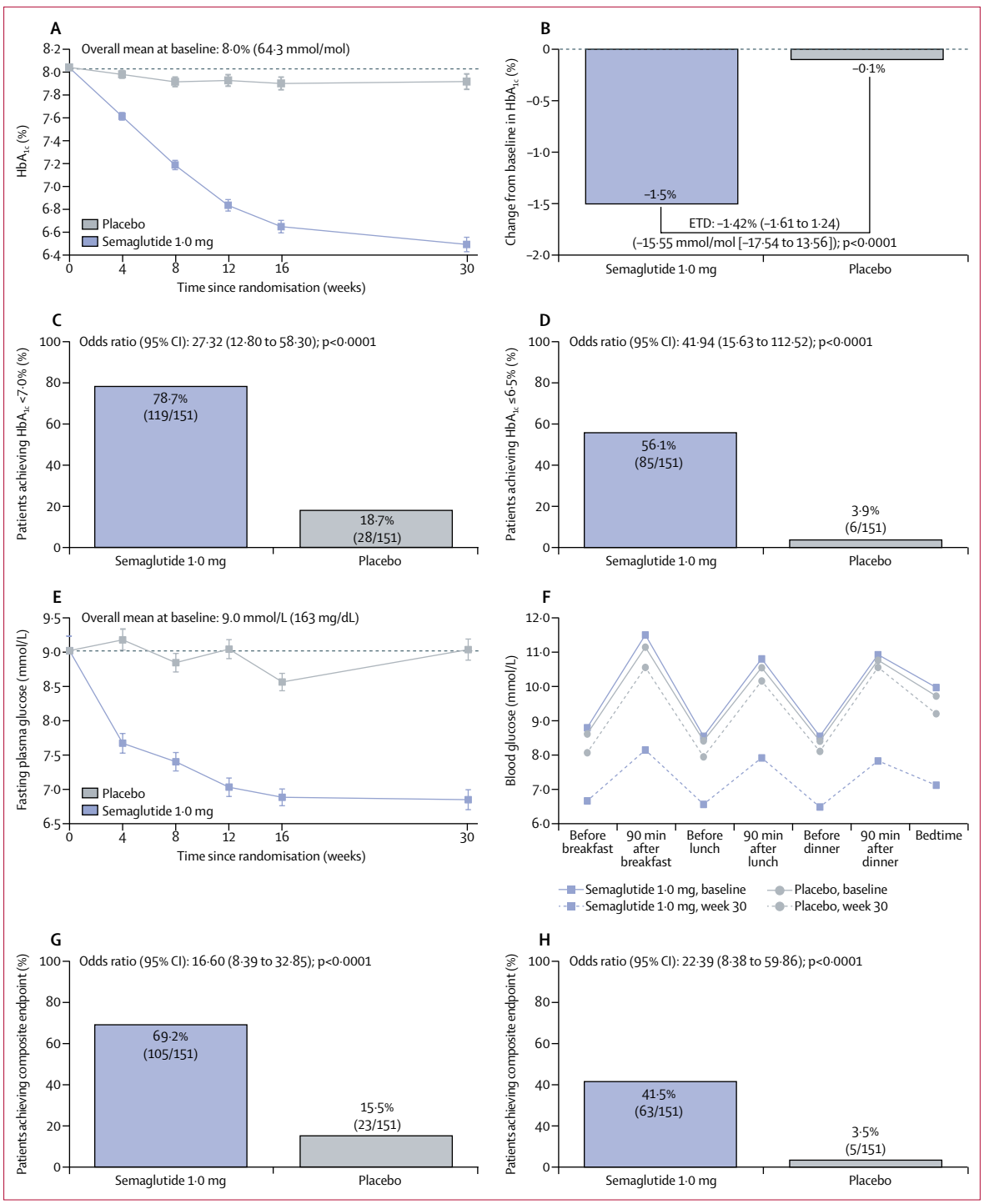


***Figure 2:*** **Glycaemic and composite outcomes with semaglutide 1·0 mg and placebo at week 30**
Data are estimated (A, B, D, E) or observed (SEs; F) means from a multiple imputation analysis, or proportion (%) of patients (C, D, G, H) from an analysis of covariance, with treatment and stratification factors (use of a sulphonylurea at baseline [yes or no], and region [Japan or other]) as categorical effects, and baseline $HbA_{1c}$ and bodyweight as covariates. Proportion of patients achieving the composite outcome of $HbA_{1c}$ <7·0% (<53 mmol/mol), with no weight gain and no severe or blood glucose-confirmed hypoglycaemia (G) or with weight loss ≥5% and no severe or blood glucose-confirmed hypoglycaemia (H). The proportions of patients (C, D, G, H) were calculated using multiple imputed observations, with 500 observations for a patient at week 30 combined into one observation per patient per visit using the mean procedure. Data are for all patients in the full analysis set, except those who discontinued treatment or required rescue medication. Dashed horizontal lines indicate the overall mean value at baseline. Results of the retrieved dropout sensitivity analyses corresponding to the data shown in figures 2C and 2D are shown in the appendix. ETD=estimated treatment difference.

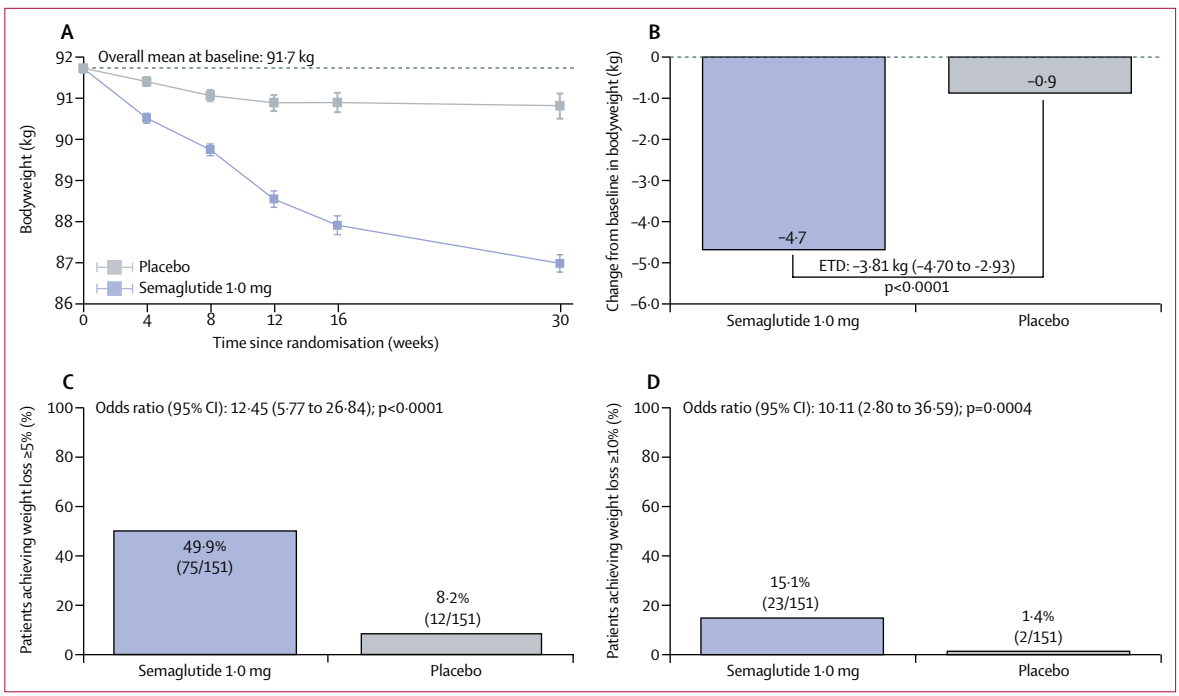


***Figure 3:*** **Bodyweight outcomes with semaglutide 1·0 mg and placebo at week 30**
Data are estimated means from a multiple imputation analysis or proportion of patients from an analysis of covariance, with treatment and stratification factors (use of a sulphonylurea at baseline [yes or no], and region [Japan or other]) as categorical effects, and baseline $HbA_{1c}$ and bodyweight as covariates. The proportions of patients (C and D) were calculated using multiple imputed observations, with 500 observations for a patient at week 30 combined into one observation per patient per visit using the mean procedure. Data are for all patients in the full analysis set, except those who discontinued treatment or required rescue medication. The horizontal dashed line indicates the overall mean value at baseline. Results of the retrieved dropout sensitivity analyses corresponding to the data in figures 3C and 3D are shown in the appendix. ETD=estimated treatment difference.

regimen) were prespecified on the primary and confirmatory secondary endpoints, and were also done as post-hoc analyses on several other measures of efficacy, including fasting plasma glucose, self-measured blood glucose, and the proportion of patients achieving $HbA_{1c}$ targets and weight loss responses (appendix). This sensitivity analysis used data from the in-trial observation period.

Safety outcomes were summarised descriptively, using on-treatment data, for all patients who received at least one dose of treatment (semaglutide or placebo; ie, the safety analysis set). Fatal events, cardiovascular events confirmed by an event adjudication committee, neoplasms, and diabetic retinopathy were summarised descriptively using data for all patients in the safety analysis set obtained from randomisation to the end of the trial, regardless of treatment exposure or usage of rescue medication (in-trial data). We used Statistical Analysis System version 9·4 for all statistical analyses.

The trial is registered with ClinicalTrials.gov, number NCT03086330.

### Role of the funding source

The funder of the study designed the trial, was responsible for site monitoring, data collection, and data analysis and interpretation, and funded the preparation and submission of the manuscript with the assistance of medical writers. Data were gathered by the site investigators. The first author (BZ) had full access to all the data in the study and had final responsibility for the decision to submit for publication.

## Results

Between March 15, and Dec 4, 2017, 302 patients were enrolled and randomly assigned to semaglutide 1·0 mg (n=151) or placebo (n=151; the full analysis set), of whom 301 received at least one dose of treatment (the safety analysis set; figure 1). One patient was assigned to semaglutide but was not treated (reason unknown).

Of the full analysis set, 294 (97·4%) patients completed the trial and 267 (88·4%) completed treatment. Eight patients (5·3%) received rescue medication in the placebo group, all of whom completed treatment. One patient (0·7%) received rescue medication in the semaglutide group and subsequently discontinued treatment.

Baseline characteristics of the two groups were similar (table 1), with the exception of mean bodyweight, which was higher in the placebo group than in the semaglutide group. Baseline values for mean $HbA_{1c}$ were 8·0% (64·1 mmol/mol) for semaglutide and 8·1% (64·5 mmol/mol) for placebo. The trial population was

predominantly white and included more men than women. In addition to randomised medication and an SGLT-2 inhibitor, 216 (71·5%) patients were also taking metformin, and 39 (12·9%) were taking a sulphonylurea.

The prevalence of diabetes complications was similar between the semaglutide and placebo groups at baseline. However, there were fewer patients with a history of diabetic retinopathy in the semaglutide group than in the placebo group; most patients with diabetic retinopathy at screening had non-proliferative disease.

The change in mean $HbA_{1c}$ from baseline to week 30 was –1·5% (SE 0·06; –16·9 mmol/mol [0·69]) for semaglutide and –0·1% (SE 0·07; –1·4 mmol/mol [0·73]) for placebo, yielding an estimated treatment difference of –1·42% (95% CI –1·61 to –1·24; –15·55 mmol/mol [–17·54 to –13·56], p<0·0001; figure 2). Semaglutide was also superior to placebo with respect to the confirmatory secondary endpoint of change in bodyweight from baseline to week 30 (–4·7 kg [SE 0·32] for semaglutide *vs* –0·9 kg [SE 0·31] for placebo), with an estimated treatment difference of –3·81 kg (–4·70 to –2·93; p<0·0001; figure 3). The results of the primary analysis were supported by sensitivity analyses (appendix).

Greater proportions of patients achieved $HbA_{1c}$ less than 7·0% (<53 mmol/mol) or $HbA_{1c}$ less than or equal to 6·5% (≤48 mmol/mol) with semaglutide than with placebo (figure 2; both p<0·0001). Most patients assigned to semaglutide achieved $HbA_{1c}$ less than 7·0% without experiencing weight gain or severe or blood glucose-confirmed hypoglycaemia (figure 2). Reductions in fasting plasma glucose and self-measured blood glucose (mean and seven-point postprandial increment) from baseline to week 30 were greater with semaglutide than with placebo (table 2; p<0·0001 for all comparisons between treatment groups). Seven-point self-measured blood glucose profiles at baseline and week 30 are shown in figure 2.

More patients achieved mean weight reductions of at least 5% or 10% at week 30 with semaglutide than with placebo (p<0·0001 for ≥5%; p=0·0004 for ≥10%; figure 3), with the odds ratios for both endpoints being greater than 10. Reductions in mean BMI and waist circumference from baseline to week 30 were also greater with semaglutide than with placebo (both p<0·0001; table 2).

The proportions of patients who achieved both a reduction in $HbA_{1c}$ of at least 1·0% (11 mmol/mol) and weight loss of at least 3%, 5%, or 10% with semaglutide were 53·6%, 39·1%, and 13·5%, respectively (appendix). By contrast, fewer than 10% of patients assigned to placebo achieved any of these endpoints.

Patients randomised to semaglutide had favourable changes, overall, in blood pressure and lipid concentrations (table 2). Although semaglutide was associated with a reduction of 4·7 mm Hg in mean systolic blood pressure at week 30, there was a slight increase

| | Overall baseline, mean (SD) | Semaglutide 1·0 mg (n=151) | Placebo (n=151) | Estimated treatment difference (95% CI) | Estimated treatment ratio (95% CI) | p value |
|---|---|---|---|---|---|---|
| **Change from baseline to week 30** | | | | | | |
| Fasting plasma glucose, mmol/L | 9·0 (2·1) | –2·2 (0·1) | 0·0 (0·2) | –2·20 (–2·62 to –1·78) | .. | <0·0001 |
| Seven-point SMBG, mmol/L | 9·8 (1·8) | –2·4 (0·2) | –0·4 (0·2) | –2·06 (–2·49 to –1·62) | .. | <0·0001 |
| Seven-point SMBG, increment across meals, mmol/L | NA | –1·0 (0·1) | 0·0 (0·1) | –1·05 (–1·44 to –0·65) | .. | <0·0001 |
| BMI, kg/m² | 31·9 (6·6) | –1·7 (0·1) | –0·3 (0·1) | –1·35 (–1·66 to –1·04) | .. | <0·0001 |
| Waist circumference, cm | 107·2 (15·5) | –4·5 (0·5) | –1·7 (0·4) | –2·83 (–4·08 to –1·59) | .. | <0·0001 |
| Systolic blood pressure, mm Hg | 127·9 (14·5) | –4·7 (1·0) | 1·6 (1·0) | –6·32 (–9·12 to –3·52) | .. | <0·0001 |
| Diastolic blood pressure, mm Hg | 78·8 (8·8) | –0·9 (0·6) | 0·5 (0·6) | –1·43 (–3·04 to 0·19) | .. | 0·0831 |
| Pulse rate, beats per min | 74·1 (10·4) | 3·4 (0·7) | 0·3 (0·7) | 3·06 (1·06 to 5·07) | .. | 0·0027 |
| **Ratio, week 30 to baseline*** | | | | | | |
| eGFR†, mL/min per 1·73 m² | 95·2 (15·2) | 0·99 (7·7) | 1·00 (7·6) | .. | NA | NA |
| Total cholesterol, mmol/L | 4·5 (25·5)‡ | 0·91 (0·01) | 1·03 (0·02) | .. | 0·88 (0·85 to 0·92) | <0·0001 |
| HDL cholesterol, mmol/L | 1·1 (26·0)‡ | 0·99 (0·01) | 1·01 (0·01) | .. | 0·98 (0·95 to 1·02) | 0·2846 |
| LDL cholesterol, mmol/L | 2·3 (43·1)‡ | 0·90 (0·02) | 1·04 (0·02) | .. | 0·87 (0·81 to 0·93) | <0·0001 |
| Triglycerides, mmol/L | 1·8 (56·2)‡ | 0·80 (0·03) | 0·98 (0·03) | .. | 0·82 (0·75 to 0·90) | <0·0001 |

Unless otherwise stated, data are mean (SE) change from overall baseline mean, estimated treatment difference (ie, semaglutide–placebo), or estimated treatment ratio (ie, semaglutide/placebo; 95% CI), from a multiple imputation analysis, using data for all randomised patients (full analysis set) obtained while on treatment and before onset of rescue medication. For pulse rate and eGFR safety endpoints, data are estimated means and estimated treatment difference using observed and imputed (pulse rate) or observed (eGFR) data for all patients randomly assigned to treatment who received at least one dose of treatment (safety analysis set) while on treatment. SMBG=self-measured blood glucose. eGFR=estimated glomerular filtration rate. NA=not available. *Ratios for eGFR are expressed as geometric mean (coefficient of variation) and, for lipids, as mean (SE). Changes from baseline to week 30 for both eGFR and lipids are shown in the appendix. †eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration formula in serum. ‡Ratio data expressed as geometric mean (coefficient of variation).

***Table 2:*** **Selected secondary outcomes**

| | Semaglutide 1·0 mg (n=150) | | | Placebo (n=151) | | |
|---|---|---|---|---|---|---|
| | n (%) | Events (n) | Event rate per 100 years of exposure | n (%) | Events (n) | Event rate per 100 years of exposure |
| All adverse events | 104 (69·3%) | 356 | 385·3 | 91 (60·3%) | 247 | 256·6 |
| Serious adverse events | 7 (4·7%) | 13 | 14·1 | 6 (4·0%) | 6 | 6·2 |
| Fatal adverse events | 0 | .. | .. | 0 | .. | .. |
| Adverse events leading to premature treatment discontinuation | 13 (8·7%) | 23 | 24·9 | 3 (2·0%) | 3 | 3·1 |
| Gastrointestinal adverse events leading to premature treatment discontinuation | 10 (6·7%) | 17 | 18·4 | 0 | .. | .. |
| Gastrointestinal adverse events | 56 (37·3%) | 133 | 144·0 | 20 (13·2%) | 42 | 43·6 |
| Severe | 2 (1·3%) | 3 | 3·2 | 0 | .. | .. |
| Moderate | 21 (14·0%) | 42 | 45·5 | 5 (3·3%) | 5 | 5·2 |
| Mild | 46 (30·7%) | 88 | 95·2 | 16 (10·6%) | 37 | 38·4 |
| Gastrointestinal adverse events in ≥5% of patients by preferred term | | | | | | |
| Nausea | 29 (19·3%) | 37 | 40·0 | 5 (3·3%) | 7 | 7·3 |
| Diarrhoea | 17 (11·3%) | 21 | 22·7 | 9 (6·0%) | 11 | 11·4 |
| Vomiting | 14 (9·3%) | 21 | 22·7 | 3 (2·0%) | 3 | 3·1 |
| Constipation | 10 (6·7%) | 10 | 10·8 | 0 | .. | .. |
| Other adverse events of clinical interest | | | | | | |
| Hypoglycaemia* | 17 (11·3%) | 28 | 30·3 | 3 (2·0%) | 4 | 4·2 |
| Severe or blood glucose-confirmed hypoglycaemia | 4 (2·7%) | 4 | 4·3 | 0 | .. | .. |
| Diabetic retinopathy | 3 (2·0%) | 3 | 3·2 | 8 (5·3%)† | 10 | 10·4 |
| Neoplasms | 4 (2·7%) | 4 | 4·0 | 4 (2·6%) | 5 | 4·9 |
| Cardiovascular events | 7 (4·7%) | 10 | 10·0 | 4 (2·6%) | 4 | 4·0 |
| Medication errors and overdose | 2 (1·3%) | 2 | 2·2 | 0 | .. | .. |
| Acute renal failure | 1 (0·7%) | 1 | 1·1 | 0 | .. | .. |
| Hypovolaemia | 0 | .. | .. | 1 (0·7%) | 1 | 1·0 |
| Urinary tract infection | 3 (2·0%) | 3 | 3·2 | 0 | .. | .. |
| Adverse events potentially leading to lower limb amputation‡ | 6 (4·0%) | 7 | 7·6 | 3 (2·0%) | 3 | 3·1 |

Adverse events included events that had onset, or increase in severity, from first exposure to the planned follow-up visit scheduled 5 weeks (with a 7-day visit window) after the end of treatment visit at week 30 (in-trial data). Severity of adverse events was defined as follows: mild, transient symptoms that do not interfere with daily activities; moderate, marked symptoms that moderately interfere with daily activities; and severe, unacceptable symptoms that considerably interfere with daily activities. Severe or blood glucose-confirmed hypoglycaemia was defined as an episode that was severe according to the American Diabetes Association classification;[23] blood glucose-confirmed by a plasma glucose value below 3·1 mmol/L (55·8 mg/dL) with symptoms consistent with hypoglycaemia. All adverse events were coded using the most recent version of the Medical Dictionary for Regulatory Activities. *American Diabetes Association classified, including hypoglycaemia episodes classified as severe, documented symptomatic, asymptomatic, probable symptomatic, and pseudo-hypoglycaemia. †Includes two patients with established diabetic retinopathy at baseline. ‡Diabetic neuropathy, hypoaesthesia, occlusive peripheral arterial disease, osteonecrosis, paraesthesia, and peripheral neuropathy. This was a predefined MedDRA search.

***Table 3:*** **Adverse events**

(1·6 mm Hg) in the placebo group, resulting in an estimated treatment difference of –6·32 mm Hg (p<0·0001). The groups did not differ in terms of change in mean diastolic blood pressure. Mean total cholesterol, LDL cholesterol, and triglyceride concentrations decreased between baseline and week 30 in the semaglutide group, but not in the placebo group (between-group difference p<0·0001 for all three lipids; table 2). Mean HDL cholesterol concentrations did not differ between groups.

Mean pulse rate increased from baseline to week 30 with semaglutide but not with placebo (table 2). No clinically relevant changes in other safety parameters, including laboratory assessments, physical examinations and electrocardiogram readings, were observed.

Semaglutide was associated with greater overall treatment satisfaction compared with placebo, as assessed by the DTSQs (appendix). Changes in overall DTSQs score favoured semaglutide, as did changes in score for the individual components of the DTSQs, except for patients'

perceived frequency of hypoglycaemia (which favoured placebo) and satisfaction with diabetes understanding (which did not favour either group). Among patients not taking a sulphonylurea at baseline, perceptions of low blood sugar did not differ between groups (estimated treatment difference 0·26; –0·04 to 0·56; p=0·09; appendix).

Changes in health-related quality of life score (assessed using the Short Form 36 version 2) numerically favoured semaglutide over placebo. However, significance was only achieved for the general health domain (appendix).

In the post-hoc analysis, a greater proportion of patients in the semaglutide group (than in the placebo group) achieved $HbA_{1c}$ of less than 7·0% (<53 mmol/mol) and weight loss of at least 5% without severe or blood glucose-confirmed hypoglycaemia (figure 2).

356 adverse events were reported by 104 (69·3%) patients in the semaglutide group, and 247 adverse events were reported by 91 (60·3%) patients in the placebo group (table 3).

Most adverse events were mild or moderate in severity. Serious adverse events, and premature treatment discontinuations due to an adverse event, were uncommon. Serious adverse events were reported by seven patients (4·7%; 13 adverse events) in the semaglutide group and six patients (4·0%; six adverse events) in the placebo group. One patient in the semaglutide group accounted for seven of the serious adverse events in that group. 16 patients stopped treatment early because of an adverse event, 13 of whom were in the semaglutide group. There were no deaths during the trial.

The most common adverse events in both groups were gastrointestinal system disorders, which were experienced by 56 (37·3%) patients in the semaglutide group and 20 (13·2%) patients in the placebo group (table 3). The most frequent gastrointestinal adverse event was nausea, followed by diarrhoea, vomiting, and constipation; all were more common among those receiving semaglutide compared with placebo. Most gastrointestinal events with semaglutide were mild or moderate in severity (table 3), with the highest incidence during the first 12 weeks of the trial (data not shown).

Severe or blood glucose-confirmed symptomatic hypoglycaemia was rare, with four events occurring in four (2·7%) patients in the semaglutide group, one of whom was receiving a sulphonylurea (table 3). Only one of these events was considered severe, according to ADA criteria,[23] and occurred in a patient who was not on a sulphonylurea. No such events were reported in the placebo group. No cases of incident pancreatitis (acute or chronic) were reported during the trial.

Adverse events related to diabetic complications were infrequent. Events related to diabetic retinopathy were reported in three (2·0%) patients in the semaglutide group and eight (5·3%) patients in the placebo group. These events, which were identified during routine examination, were mainly mild in severity, and all were reported as non-proliferative. None required acute treatment. Notably, of the 11 events related to diabetic retinopathy, only two (both in the placebo group) occurred in patients who had diabetic retinopathy at screening. There were no reports of incident microalbuminuria or macroalbuminuria, and mean eGFR did not change between baseline and week 30 in either group (table 2). There was one event (0·7%) of acute renal failure (in the semaglutide group), which resolved completely and was not temporally associated with either the dose-escalation period or the occurrence of gastrointestinal adverse events. No lower limb amputations were reported during the trial.

Neoplasm-related adverse events were reported by four patients in each group (a total of nine events). Events were mainly benign, only one (a laryngeal squamous cell carcinoma in a patient assigned to placebo, confirmed by an event adjudication committee) was considered malignant. None were classified as severe, nor were any considered to be related to study medication.

## Discussion

The SUSTAIN 9 trial shows that adding semaglutide to existing SGLT-2 inhibitor therapy results in significant and clinically relevant reductions in both $HbA_{1c}$ and bodyweight, compared with placebo, in patients with uncontrolled type 2 diabetes. Our findings are consistent with those of previous trials in the SUSTAIN programme,[3,12–16] showing that the addition of semaglutide to existing antidiabetic treatment significantly improves glycaemic control and promotes weight loss.

Among patients assigned to semaglutide, the reductions in mean $HbA_{1c}$ and bodyweight were 1·5% (16·9 mmol/mol) and 4·7 kg, from overall baseline values of 8·0% (64 mmol/mol) and 91·7 kg, respectively. The estimated treatment difference for bodyweight (–3·81 kg) is notable because patients in the placebo group had a higher baseline mean bodyweight than did those in the semaglutide group. The observed weight reduction was supported by a significant reduction in waist circumference with semaglutide relative to placebo.

SUSTAIN 9 showed that the addition of semaglutide 1·0 mg to SGLT-2 inhibitor treatment was associated with significant reductions in total and LDL cholesterol concentrations, and in systolic blood pressure, versus placebo. The observed reductions in systolic blood pressure were additional to any changes already achieved with SGLT-2 inhibitor treatment before enrolment in the trial. Improvements in cholesterol concentrations and blood pressure could be explained by reductions in bodyweight and glucose, but GLP-1 receptor agonists have also been shown to regulate cholesterol and triglyceride concentrations via several distinct pathways.[24] Additionally, numerous mechanisms by which GLP-1 receptor agonists might reduce blood pressure, involving the vasculature, myocardium, kidney, and central nervous system, have been proposed.[25] However, these pathways have not been

adequately defined, and other mechanisms might also be involved.

Selected GLP-1 receptor agonists (including semaglutide) and SGLT-2 inhibitors reduce the risk of major adverse cardiovascular events or other cardiovascular outcome measures in patients with uncontrolled type 2 diabetes.[3–8] In SUSTAIN 6,[3] semaglutide was associated with a 26% reduction in the combined risk of non-fatal myocardial infarction, non-fatal stroke, or cardiovascular death, versus placebo, in patients with a high baseline level of cardiovascular risk. Given the additional effect of semaglutide on cardiovascular risk factors in patients already receiving SGLT-2 inhibitor therapy, one could speculate that the concomitant use of these agents might lead to greater reductions in cardiovascular events than expected with either class of agent alone. However, as yet, there are no data from prospective cardiovascular outcomes trials of concomitant therapy with a GLP-1 receptor agonist and an SGLT-2 inhibitor.

Concomitant therapy with a GLP-1 receptor agonist and an SGLT-2 inhibitor is an attractive therapeutic approach in type 2 diabetes, for various reasons. First, these drug classes reduce glucose concentrations via distinct and complementary mechanisms of action. Additionally, both have glucose-dependent effects on glycaemic control,[26,27] which translates into low rates of hypoglycaemia, and both promote weight loss,[28,29] albeit to differing degrees. Agents in both classes have been shown to have significant favourable effects on cardiovascular risk factors or cardiovascular outcomes, or both.[3–8]

SUSTAIN 9 is the second randomised, placebo-controlled trial to report on the addition of a GLP-1 receptor agonist to existing SGLT-2 inhibitor therapy. In the other published trial, AWARD-10,[17] dulaglutide 0·75 mg or 1·5 mg once weekly was added to SGLT-2 inhibitor therapy (with or without metformin), and was associated with significantly greater reductions in $HbA_{1c}$ compared with placebo over 24 weeks (–1·21% [–13·2 mmol/mol] and –1·34% [–14·7 mmol/mol] for low-dose and high-dose dulaglutide, respectively, *vs* –0·54% [–5·9 mmol/mol] for placebo). Estimated treatment differences versus placebo were –0·66% (–7·2 mmol/mol) and –0·79% (–8·6 mmol/mol) for dulaglutide 0·75 mg and 1·5 mg, respectively (p<0·0001 for both). Patients randomised to dulaglutide 1·5 mg lost significantly more weight, compared with those on placebo (–3·1 kg *vs* –2·1 kg; p=0·028), but the difference between dulaglutide 0·75 mg and placebo was not significant. Differences between GLP-1 receptor agonist and placebo were more modest in AWARD-10 than in SUSTAIN 9. A possible explanation for this is that the full clinical effects of SGLT-2 inhibitor treatment had not yet been reached at the time of randomisation in AWARD-10. Although both AWARD-10 and SUSTAIN 9 required patients to have been taking an SGLT-2 inhibitor for at least 90 days before enrolment, only 11% of patients in AWARD-10 had been on SGLT-2 inhibitor treatment for 12 months or more; most (62%) had been taking it for at least 3 months but less than 6 months. By contrast, the mean duration of prior treatment with SGLT-2 in SUSTAIN 9 was about 11 months (data not shown).

In addition to SUSTAIN 9 and AWARD-10, another randomised controlled trial, DURATION-8,[18] has investigated the effects of concomitant therapy with GLP-1 receptor agonists and SGLT-2 inhibitors. However, in DURATION-8, treatment with the GLP-1 receptor agonist and the SGLT-2 inhibitor was coinitiated in those randomly assigned to concomitant treatment. Additionally, patients had higher baseline $HbA_{1c}$ levels than in SUSTAIN 9, owing to the exclusion of those with $HbA_{1c}$ less than 8·0% (<64 mmol/mol).

The effects of GLP-1 receptor agonists as an add-on to SGLT-2 inhibitor therapy have been investigated in two other trials that have yet to report their results. The main results of these trials, LIRA-ADD2SGLT2i (NCT02964247) and PIONEER 4 (NCT02863419), are expected in 2019, and will further add to our understanding of the efficacy and safety of concomitant GLP-1 receptor agonist and SGLT-2 inhibitor therapy.

The safety profiles of both GLP-1 receptor agonists and SGLT-2 inhibitors are well characterised, with the adverse events most commonly associated with these drugs being transient gastrointestinal effects and mycotic genital infections, respectively. In the present study, treatment with semaglutide and an SGLT-2 inhibitor appeared to be well tolerated, with low rates of serious adverse events and adverse event-related premature treatment discontinuations. Gastrointestinal adverse events were mostly mild or moderate in severity, and tended to occur during the initial phase of treatment; these effects are well known to occur during dose escalation with semaglutide.[10] As predicted from the glucose-dependent mode of action of semaglutide, hypoglycaemia was uncommon, with only one severe hypoglycaemic episode reported. The safety and tolerability profiles of semaglutide in SUSTAIN 9 were consistent with those seen in previous trials in the SUSTAIN programme, and with other GLP-1 receptor agonists.[3,11–16] No new or unexpected safety concerns were identified.

The SUSTAIN 9 trial has limitations. The trial was of relatively short duration in the context of type 2 diabetes, and it is not possible to draw conclusions beyond 30 weeks. Additionally, further analysis is required to establish whether our findings remain valid for specific subgroups (defined, among other criteria, by race, baseline $HbA_{1c}$, and duration of diabetes or type of SGLT-2 inhibitor).

As noted above, GLP-1 receptor agonists and SGLT-2 inhibitors can lower the risk of major cardiovascular events in people with type 2 diabetes. Although not analysed in SUSTAIN 9, we believe that cardiovascular biomarkers, such as NT-proBNP concentrations, and cardiovascular outcomes in patients receiving concomitant treatment with a GLP-1 receptor agonist and an SGLT-2 inhibitor

warrant further research. Additionally, concomitant use of these drug classes could lead to complementary or synergistic effects (or both), which would be an interesting topic for further study.

In summary, SUSTAIN 9 found that subcutaneous semaglutide 1·0 mg once weekly, added on to SGLT-2 inhibitor-based oral antidiabetic treatment, resulted in significant and clinically important improvements in glycaemic control and reductions in bodyweight over 30 weeks in patients with uncontrolled type 2 diabetes. The addition of semaglutide 1·0 mg appears to be an effective, well tolerated option for patients who have not met their therapeutic goals despite treatment with an SGLT-2 inhibitor.

#### Contributors

BZ and IH were responsible for the conduct of the trial and interpreting the data. VB analysed the data. All authors reviewed and commented on several drafts of the manuscript and approved the final version for publication.

#### Declaration of interests

BZ reports research grants (to his institution) and personal fees for advisory board participation from Novo Nordisk, during the course of the study; research grants (to his institution) from Boehringer Ingelheim and Novo Nordisk; and personal fees for advisory board attendance from AstraZeneca, Boehringer Ingelheim, Eli Lilly, Janssen, Merck, Novo Nordisk, and Sanofi, outside of the submitted work. VB, IH, and DT are full-time employees of Novo Nordisk. RB reports research support from AstraZeneca, Novo Nordisk and Sanofi, and fees for speakers' bureaus from AstraZeneca, Eli Lilly, Novo Nordisk, and Sanofi, outside of the submitted work. BL reports research grants (to his institution) and personal fees from Amgen, Boehringer Ingelheim, Eli Lilly, MSD, Novartis, Novo Nordisk, Roche, Sanofi, and Takeda, outside of the submitted work. JT reports research grants (to his institution) from AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Lexicon, Medtronic, Novo Nordisk, and Sanofi, outside of the submitted work; personal fees for participation in advisory boards or speaking engagements (or both) for AstraZeneca, Lexicon and Sanofi; fees for data safety monitoring board participation from Medtronic; and publication support from Boehringer Ingelheim. VW reports research grants (to his institution) and personal fees for advisory board participation from Novo Nordisk, during the course of the study. AP-T reports research grants (to her institution); unpaid consultancy work for AstraZeneca, Genentech, Janssen, Merck, Novo Nordisk, and Sanofi; and unpaid advisory panel work for Dexcom and Voluntis, outside of the submitted work.

#### Data sharing

Individual participant data will be shared in datasets in a deidentified format, including datasets from Novo Nordisk-sponsored clinical research completed after 2001 for product indications approved in both the European Union 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 European Union 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.

For the **independent review board charter** see http://www.novonordisk-trials.com

For the **form and criteria** see http://www.novonordisk-trials.com

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