Semaglutide versus dulaglutide once weekly in patients with type 2 diabetes (SUSTAIN 7): a randomised, open-label, phase 3b trial

Richard E Pratley, Vanita R Aroda, Ildiko Lingvay, Jörg Lüdemann, Camilla Andreassen, Andrea Navarria, Adie Viljoen, on behalf of the SUSTAIN 7 investigators

Summary

Background Despite common mechanisms of actions, glucagon-like peptide-1 receptor agonists differ in structure, pharmacokinetic profile, and clinical effects. This head-to-head trial compared semaglutide with dulaglutide in patients with inadequately controlled type 2 diabetes.

Methods This was an open-label, parallel-group, phase 3b trial done at 194 hospitals, clinical institutions or private practices in 16 countries. Eligible patients were aged 18 years or older and had type 2 diabetes with HbA_{1c} 7·0–10·5% (53·0–91·0 mmol/mol) on metformin monotherapy. Patients were randomly assigned (1:1:1:1) by use of an interactive web-response system to once a week treatment with either semaglutide 0·5 mg, dulaglutide 0·75 mg, semaglutide 1·0 mg, or dulaglutide 1·5 mg subcutaneously. The primary endpoint was change from baseline in percentage HbA_{1c}; the confirmatory secondary endpoint was change in bodyweight, both at week 40. The primary analysis population included all randomly assigned patients exposed to at least one dose of trial product obtained while on treatment and before the onset of rescue medication. The safety population included all randomly assigned patients exposed to at least one dose of trial product obtained while on treatment. The trial was powered for HbA_{1c} non-inferiority (margin 0·4%) and bodyweight superiority. This trial is registered with ClinicalTrials.gov, number NCT02648204.

Findings Between Jan 6, 2016, and June 22, 2016, 1201 patients were randomly assigned to treatment; of these, 301 were exposed to semaglutide 0·5 mg, 299 to dulaglutide 0·75 mg, 300 to semaglutide 1·0 mg, and 299 to dulaglutide 1·5 mg. 72 (6%) patients withdrew from the trial (22 receiving semaglutide 0·5 mg, 13 receiving dulaglutide 0·75 mg, 21 receiving semaglutide 1·0 mg, and 16 receiving dulaglutide 1·5 mg). From overall baseline mean, mean percentage HbA_{1c} was reduced by 1·5 (SE 0·06) percentage points with semaglutide 0·5 mg versus 1·1 (0·05) percentage points with dulaglutide 0·75 mg (estimated treatment difference [ETD] –0·40 percentage points [95% CI –0·55 to –0·25]; p<0·0001) and by 1·8 (0·06) percentage points with semaglutide 1·0 mg versus 1·4 (0·06) percentage points with dulaglutide 1·5 mg (ETD –0·41 percentage points [–0·57 to –0·25]; p<0·0001). From overall baseline mean, mean bodyweight was reduced by 4·6 kg (SE 0·28) with semaglutide 0·5 mg compared with 2·3 kg (0·27) with dulaglutide 0·75 mg (ETD –2·26 kg [–3·02 to –1·51]; p<0·0001) and by 6·5 kg (0·28) with semaglutide 1·0 mg compared with 3·0 kg (0·27) with dulaglutide 1·5 mg (ETD –3·55 kg [–4·32 to –2·78]; p<0·0001). Gastrointestinal disorders were the most frequently reported adverse event, occurring in 129 (43%) of 301 patients receiving semaglutide 0·5 mg, 133 (44%) of 300 patients receiving semaglutide 1·0 mg, 100 (33%) of 299 patients receiving dulaglutide 0·75 mg, and in 143 (48%) of 299 patients receiving dulaglutide 1·5 mg. Gastrointestinal disorders were also the most common reason for discontinuing treatment with semaglutide and dulaglutide. There were six fatalities: one in each semaglutide group and two in each dulaglutide group.

Interpretation At low and high doses, semaglutide was superior to dulaglutide in improving glycaemic control and reducing bodyweight, enabling a significantly greater number of patients with type 2 diabetes to achieve clinically meaningful glycaemic targets and weight loss, with a similar safety profile.

Funding Novo Nordisk.

Lancet Diabetes Endocrinol 2018

Published Online
January 31, 2018
http://dx.doi.org/10.1016/S2213-8587(18)30024-X

See Online/Comment
http://dx.doi.org/10.1016/S2213-8587(18)30049-4

Florida Hospital Translational Research Institute for Metabolism and Diabetes, Orlando, FL, USA (R E Pratley MD); **MedStar Health Research Institute, Hyattsville, MD, USA** (V R Aroda MD); **UT Southwestern Medical Center, Dallas, TX, USA** (I Lingvay MD); **diabetes-falkensee, Diabetes Centre and Centre for Clinical Studies, Falkensee, Germany** (J Lüdemann MD); **Novo Nordisk, Søborg, Denmark** (C Andreassen PhD, A Navarria MD); **and Lister Hospital, Stevenage, UK** (A Viljoen MMed)

Correspondence to:
Dr Richard E Pratley, Translational Research Institute for Metabolism and Diabetes, Orlando, FL 32804, USA
richard.pratley@flhosp.org

Introduction

Despite considerable advances in treatment options for type 2 diabetes, a significant proportion of patients do not achieve recommended glycaemic targets[1] and are, therefore, at risk of developing several chronic complications of diabetes, including cardiovascular disease.[2] Additionally, obesity, a comorbidity that affects about 85% of patients with type 2 diabetes,[3] promotes insulin resistance and is associated with poor long-term clinical outcomes.[4,5]

Glucagon-like peptide-1 receptor (GLP-1R) agonists are an established treatment option for type 2 diabetes. These drugs are effective antihyperglycaemic treatments that carry a low risk of hypoglycaemia and promote weight loss.[6] Treatments with these drugs once a week have been associated with better adherence to therapy

Research in context

Evidence before this study

The clinical profile of glucagon-like peptide-1 receptor (GLP-1R) agonists—including improved glycaemic control, a low risk of hypoglycaemia, and the potential for clinically relevant weight loss—make this class a useful option for patients and has led to its incorporation into guidelines for the treatment of type 2 diabetes. There are several once-weekly GLP-1R agonists with various molecular structures and different clinical profiles. The SUSTAIN 7 trial directly compared semaglutide once a week with dulaglutide, another GLP-1R agonist taken once a week in patients with type 2 diabetes inadequately controlled on metformin.

Added value of this study

The findings from this study show that, after 40 weeks of treatment, semaglutide 0·5 mg was superior to dulaglutide 0·75 mg when taken once a week and semaglutide 1·0 mg was superior to dulaglutide 1·5 mg in reducing HbA_{1c} and bodyweight in patients on metformin monotherapy. The incidence of gastrointestinal disorders was similar between both doses of semaglutide and high-dose dulaglutide, and lower with low-dose dulaglutide. The overall safety profile was similar between treatments.

Implications of all the available evidence

Within the GLP-1R agonist class, dulaglutide 1·5 mg has previously been shown to be superior to exenatide when taken twice a day in the AWARD 1 study and has also been shown to be non-inferior to liraglutide 1·8 mg when taken once a day in AWARD 6. Meanwhile, once-weekly semaglutide 1·0 mg was superior to exenatide extended-release 2·0 mg taken once a week in the SUSTAIN 3 trial. Semaglutide is approved by the US Food and Drug Administration as an adjunct to diet and exercise to improve glycaemic control in adults with type 2 diabetes, and is currently under review by several regulatory agencies, including the European Medicines Agency and the Japanese Pharmaceuticals and Medical Devices Agency. On the basis of the available evidence, semaglutide is a highly effective treatment option for patients with type 2 diabetes compared with other GLP-1R agonists.

than regimens requiring once a day administration.[7] Several GLP-1R agonists are available that are dosed once a week, and randomised trials have shown that these agonists vary in efficacy and tolerability.[8]

Semaglutide (Novo Nordisk, Denmark) is a new GLP-1R agonist approved by the US Food and Drug Administration as an adjunct to diet and exercise to improve glycaemic control in adults with type 2 diabetes and is currently under review by several regulatory agencies, including the European Medicines Agency and the Japanese Pharmaceuticals and Medical Devices Agency. The GLP-1 moiety of semaglutide is modified by the addition of a fatty diacid chain and two aminoacid substitutions. These modifications prolong its half-life through enhanced binding to albumin and inhibition of degradation by dipeptidyl peptidase-4, facilitating dosing once a week.[9] Dulaglutide (Eli Lilly and Company, USA) is another GLP-1R agonist comprising two substituted GLP-1R agonists covalently linked to a modified IgG4-Fc domain that, because of slow clearance, confers a long half-life.[10] Both semaglutide and dulaglutide are dosed once a week.[9,11]

See Online for appendix

Both semaglutide and dulaglutide have been compared with placebo and antihyperglycaemic drugs in phase 3 trials.[12–17] Semaglutide at 0·5 mg and 1·0 mg provided superior improvements in glycaemic control and bodyweight versus placebo, sitagliptin, insulin glargine, and the GLP-1R agonist exenatide extended-release in head-to-head trials when given once a week.[12–16] Dulaglutide 1·5 mg was superior in reducing glycated haemoglobin (HbA_{1c}), compared with placebo, metformin, sitagliptin, insulin glargine, and exenatide when given twice a day,[17] and significantly reduced bodyweight compared with placebo, sitagliptin, and insulin glargine,[17] but was non-inferior to and resulted in less bodyweight loss than liraglutide 1·8 mg once a day.[18] Dulaglutide has not previously been tested against another once-weekly GLP-1R agonist.

In this head-to-head trial, we compared the efficacy and safety of semaglutide and dulaglutide at low doses (semaglutide 0·5 mg *vs* dulaglutide 0·75 mg) and high doses (semaglutide 1·0 mg *vs* dulaglutide 1·5 mg) when given once a week to patients with type 2 diabetes inadequately controlled with metformin monotherapy. Dulaglutide is approved at two dose levels (0·75 mg and 1·5 mg once a week) and semaglutide has been developed at two dose levels (0·5 mg and 1·0 mg once a week). Therefore, a pairwise treatment strategy investigating two dose levels of semaglutide and dulaglutide was implemented to ensure a thorough assessment of clinical efficacy and tolerability.

Methods

Study design and participants

SUSTAIN 7 was a 40-week, phase 3b, randomised, open-label, active-controlled, parallel group, four-armed trial (appendix) done at 194 sites (hospitals, clinical institutions, or private practices) in 16 countries (Bulgaria, Croatia, Finland, Germany, Greece, Hong Kong, India, Ireland, Latvia, Lithuania, Portugal, Romania, Slovakia, Spain, the UK, and the USA; appendix). This trial was done in compliance with the International Conference on Harmonisation Good Clinical Practice guidelines[19] and the Declaration of Helsinki.[20] The trial protocol, available with the full text of this Article online, was approved by the institutional review board and ethics committee at each participating centre.

Adults aged 18 years or older with type 2 diabetes and an HbA_{1c} of 7·0–10·5% (53·0–91·0 mmol/mol), who were on

stable treatment with metformin at a minimum dose of 1500 mg per day or a maximal tolerated dose for at least 90 days before screening were eligible for the study. Key exclusion criteria included history of pancreatitis, heart failure (New York Heart Association Class IV), chronic kidney disease stage 3 and above,[21] and proliferative retinopathy or maculopathy requiring acute treatment (appendix). We chose a treatment duration of 40 weeks for adequate comparison of efficacy on both primary and confirmatory secondary endpoints, and of safety, tolerability, and patient satisfaction between semaglutide and dulaglutide. Patients provided written informed consent before trial-related activities commenced.

Randomisation and masking

Patients were randomly assigned (1:1:1:1) by use of an interactive web response system to receive: semaglutide 0·5 mg, dulaglutide 0·75 mg, semaglutide 1·0 mg, or dulaglutide 1·5 mg, once a week. Randomisation was not stratified. The open-label design was necessary because of the different patented devices used to administer the trial products, which were supplied by Novo Nordisk.

Procedures

After a 2-week screening period, patients received study medication subcutaneously for 40 weeks, followed by follow-up for 5 weeks (appendix). Injections were self-administered in the thigh, abdomen, or upper arm, at any time of day irrespective of meals. Injections were administered on the same day of the week.[10] A fixed dose-escalation procedure was used for semaglutide: the dose was doubled every 4 weeks from a starting dose of 0·25 mg until the trial maintenance dose (0·5 or 1·0 mg) was reached. Patients randomised to dulaglutide received 0·75 or 1·5 mg without dose escalation, in accordance with the dulaglutide clinical development programme and clinical product labelling.[10,17] Once trial maintenance doses were reached, they were not changed during the course of the trial. Patients were required to continue their pre-trial dose of metformin throughout the trial. Patients who had persistent and unacceptable hyperglycaemia according to protocol-defined fasting plasma glucose criteria were offered rescue medication at the investigator's discretion (appendix). Blood samples to measure HbA_{1c} were analysed in a central laboratory.

Outcomes

The primary endpoint was change in percentage HbA_{1c} from baseline to week 40. The confirmatory secondary endpoint (included in the hierarchical testing and in the power calculation) was change in bodyweight from baseline to week 40. Other prespecified secondary efficacy endpoints assessed were change from baseline to week 40 in: fasting plasma glucose, seven-point self-measured blood glucose (SMBG) profile, mean and postprandial increment across the 7-point scale (calculated by the average of the postprandial blood glucose value minus the preprandial blood glucose value [before breakfast, 90 min after the start of breakfast, before lunch, 90 min after the start of lunch, before dinner, 90 min after the start of dinner, and at bedtime]),[22] body-mass index (BMI), waist circumference, blood pressure, fasting blood lipids (total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglycerides), and patient-reported outcome questionnaires (Short-Form health survey 36 version 2, and Diabetes Treatment Satisfaction Questionnaire) status. Predefined clinical treatment targets or goals were also assessed, including percentage of patients who achieved the following at week 40: HbA_{1c} of less than 7·0%,[23] of 6·5% or less,[24] or HbA_{1c} reduction of more than 1 percentage point, weight loss responses of more than 3%, more than 5%, or more than 10%; a composite endpoint of HbA_{1c} less than 7·0% without severe or blood glucose-confirmed symptomatic hypoglycaemia and no weight gain; a composite endpoint of HbA_{1c} reduction of more than 1 percentage point and weight loss of more than 3%.

Blood samples to test HbA_{1c} (on all visits), fasting plasma glucose (on all visits) and lipids (visit 2 at week 0, visit 7 at week 16, and visit 9 at week 40) were analysed at a central laboratory. 7-point SMBG was measured at visit 2 at week 0, visit 7 at week 16, and visit 9 at week 40. Bodyweight and blood pressure were measured at all visits. Waist circumference was measured and an echocardiogram was done at visit 2 at week 0, visit 7 at week 16, and visit 9 at week 40. Questionnaires were completed at randomisation and end-of-treatment visits. Height was measured at visit 2 at week 0. Adverse events were recorded during each contact with site staff (all visits from randomisation to follow-up).

Safety endpoints included the number of treatment-emergent adverse events and number of severe[25] or blood glucose-confirmed (<3·1 mmol/L) symptomatic hypoglycaemic episodes; and change in heart rate at week 40 during the trial. An independent external event adjudication committee that was masked to treatment provided validation of predefined adverse events, in line with US Food and Drug Administration requirements (appendix).

Other laboratory blood sample analyses were done by the central laboratory, and comprised haematology (eg, haemoglobin, haematocrit, and differential cell count), hormones (ie, calcitonin), biochemistry (eg, creatinine, liver enzymes, albumin, bilirubin, sodium, and potassium), anti-semaglutide antibodies, and pregnancy testing (ie, β-human chorionic gonadotropin). Tests were done throughout the study between visits 1 and 9, but not every variable was tested on every visit.

Statistical analysis

The enrolment of 1196 patients was planned, with 299 in each group, as this would yield 90% power to confirm HbA_{1c} non-inferiority and bodyweight superiority between

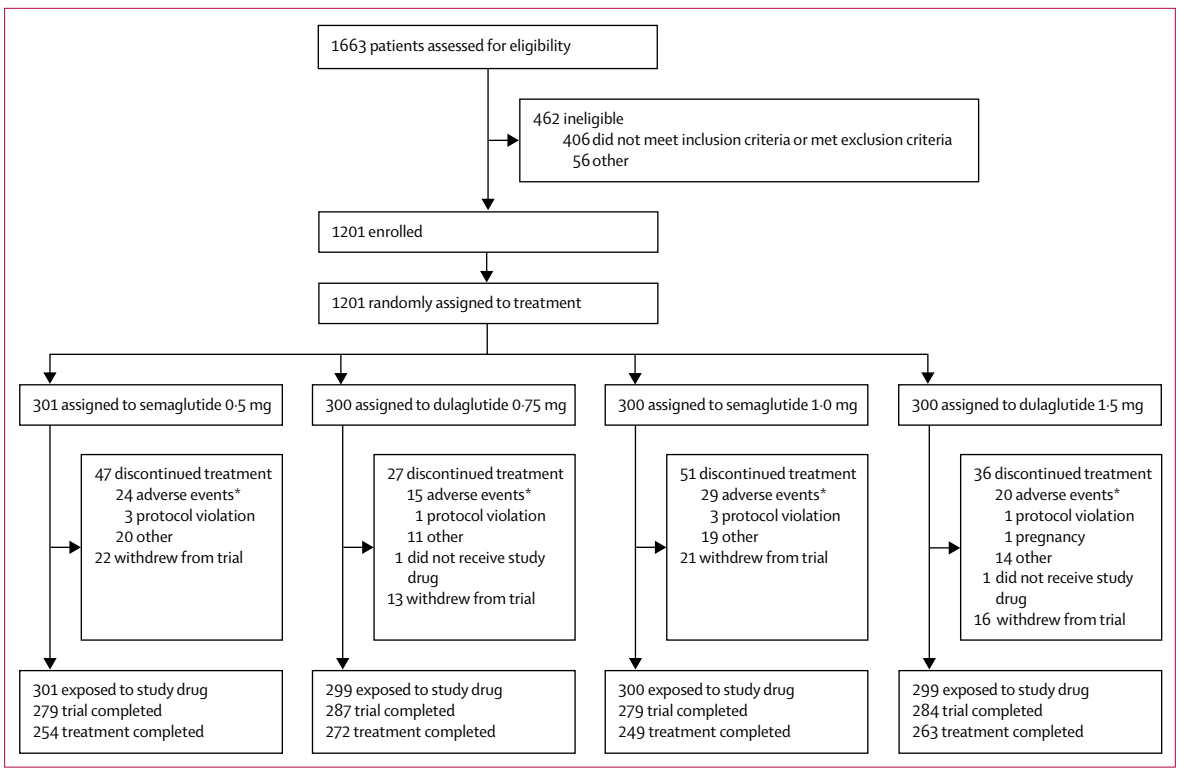

Figure 1: **Trial profile**
Completed trial refers to those patients who attended the follow-up visit. Completed treatment refers to those patients who did not discontinue treatment prematurely (with or without the addition of rescue medication). *Reflects primary reason for treatment discontinuation, as judged by the investigator.

semaglutide and dulaglutide at both dose levels (appendix). All of the six prespecified confirmatory hypotheses are assumed to be independent. The SD for HbA_{1c} was assumed to be 1·1% and the for bodyweight assumed to be 4 kg. Treatment difference in HbA_{1c} of semaglutide compared with dulaglutide at week 40 within both dose levels was assumed to be zero. Treatment difference in bodyweight of semaglutide compared with dulaglutide at week 40 within both dose levels was assumed to be 1·5 kg. A 50% smaller effect on bodyweight was assumed in the 25% of patients expected to prematurely discontinue treatment or initiate rescue medication leading to an adjusted treatment effect of 1·35 kg. The rate of premature treatment discontinuation or initiation of rescue medication was expected to be similar across treatment groups. The sample size was calculated using the calcPower function in the R package, gMCP1, using 10 000 simulations.

We used a mixed model for repeated measurements for the analysis of the primary outcome of change in continuous endpoints at week 40 from each individual baseline using data for all patients randomly assigned to treatment and exposed to at least one dose of trial product (full analysis set) obtained while on treatment and before onset of rescue medication. The primary HbA_{1c} and confirmatory bodyweight endpoints were adjusted for multiple testing. To be able to draw conclusions for each of the two dose levels independently, the overall alpha level of 5% (two-sided) was split equally between a hierarchical testing strategy comparing semaglutide 0·5 mg versus dulaglutide 0·75 mg and semaglutide 1·0 mg versus dulaglutide 1·5 mg.[26] For both dose levels, the hierarchy started with testing HbA_{1c} non-inferiority (0·4% margin), followed by bodyweight and HbA_{1c} superiority (appendix).

Prespecified sensitivity analyses were done for HbA_{1c} and bodyweight (appendix) by use of alternative data selections and methods for handling missing data. p values for exploratory endpoints were two-sided, testing the null hypothesis of no difference. Safety outcomes were summarised descriptively by use of data for all patients randomised to treatment who were exposed to at least one dose of trial product (safety analysis set, equivalent to the full analysis set) obtained while on treatment (on-treatment data). Fatal events, confirmed cardiovascular events by the event adjudication committee, confirmed malignant neoplasms, and diabetic retinopathy were summarised descriptively by use of 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). All statistical analyses were done with SAS version 9.4. See appendix for extended statistical methods. This trial is registered with ClinicalTrials.gov, NCT02648204.

Role of the funding source
The sponsor, Novo Nordisk, designed the study. Data were gathered by the site investigators. The sponsor did site monitoring, data collection, and data analysis. The first author had full access to all the data in the study and had final responsibility for the decision to submit for publication. The sponsor also funded editorial support, which was provided by an independent medical writer.

Results

Between Jan 6, 2016, and June 22, 2016, 1201 patients were randomly assigned to treatment; 1199 were exposed to treatment and included in the efficacy and safety analyses; 301 in the semaglutide 0·5 mg group, 299 in the dulaglutide 0·75 mg group, 300 in the semaglutide 1·0 mg group, and 299 in the dulaglutide 1·5 mg group. Of these, 1038 (87%) completed treatment and 1129 (94%) completed the trial, with the final patient visit on May 19, 2017 (figure 1). Baseline characteristics were similar between treatment groups (table 1). Throughout the trial, 47 (16%) of 301 patients discontinued treatment prematurely with semaglutide 0·5 mg, 27 (9%) of 299 patients with dulaglutide 0·75 mg, 51 (17%) of 300 in the semaglutide 1·0 mg group, and 36 (12%) of 299 in the dulaglutide 1·5 mg group. Three patients (1%) initiated rescue medication due to hyperglycaemia with semaglutide 0·5 mg, 14 (5%) with dulaglutide 0·75 mg, seven (2%) with semaglutide 1·0 mg, and six (2%) with dulaglutide 1·5 mg.

From baseline, mean percentage HbA_{1c} was reduced by 1·5 (SE 0·06) percentage points with semaglutide 0·5 mg versus 1·1 (0·05) percentage points with dulaglutide 0·75 mg. At the higher doses, semaglutide 1·0 mg reduced HbA_{1c} by 1·8 (SE 0·06) percentage points versus 1·4 (0·06) percentage points with dulaglutide 1·5 mg. The estimated treatment difference (ETD) for semaglutide 0·5 mg versus dulaglutide 0·75 mg was –0·40 percentage points (95% CI –0·55 to –0·25) and for semaglutide 1·0 mg versus dulaglutide 1·5 mg was –0·41 percentage points (–0·57 to –0·25); both p<0·0001 for non-inferiority and superiority (figure 2, table 2). Prespecified sensitivity analyses all supported the conclusions of the primary analysis (appendix).

From baseline, mean bodyweight was reduced at week 40 by 4·6 kg (SE 0·28) with semaglutide 0·5 mg versus 2·3 kg (0·27) with dulaglutide 0·75 mg (treatment difference –2·26 [95% CI –3·02 to –1·51]; p<0·0001), and by 6·5 kg (0·28) with semaglutide 1·0 mg versus 3·0 kg (0·27) with dulaglutide 1·5 mg (–3·55 kg [–4·32 to –2·78]; p<0·0001; figure 2, table 2). These results were supported by all prespecified statistical sensitivity analyses (appendix).

Significantly more patients with semaglutide than dulaglutide, at both dose levels, achieved the predefined HbA_{1c} treatment targets of less than 7·0% and less than or equal to 6·5% at week 40 (p<0·0001 for the low-dose comparison and p=0·0021 for the high-dose comparison; table 3, appendix). Mean fasting plasma glucose was reduced to a similar degree with semaglutide 0·5 mg and dulaglutide 0·75 mg (ETD –0·31 mmol/L [95% CI –0·63 to 0·01]; p=0·0603), whereas semaglutide 1·0 mg provided a significantly greater reduction than did dulaglutide 1·5 mg (ETD –0·58 mmol/L [–0·91 to –0·26]; p=0·0005; figure 2, table 2). The mean 7-point SMBG concentration was also significantly reduced with semaglutide 0·5 mg versus with dulaglutide 0·75 mg (ETD –0·44 mmol/L [95% CI –0·71 to –0·17]; p=0·0014; figure 2, table 2) and with semaglutide 1·0 mg versus with dulaglutide 1·5 mg (ETD –0·63 mmol/L [–0·90 to –0·35]; p<0·0001; figure 2, table 2). The mean postprandial increment in blood glucose across all meals, calculated by the average of the postprandial blood glucose value minus the preprandial blood glucose value across the three main meals, was

	Semaglutide 0·5 mg (n=301)	Dulaglutide 0·75 mg (n=299)	Semaglutide 1·0 mg (n=300)	Dulaglutide 1·5 mg (n=299)
Age (years)	56 (10·9)	55 (10·4)	55 (10·6)	56 (10·6)
HbA_{1c} (%)	8·3 (0·9)	8·2 (0·9)	8·2 (0·9)	8·2 (0·9)
HbA_{1c} (mmol/mol)	67·5 (10·5)	65·7 (9·9)	66·2 (10·1)	66·1 (9·7)
Fasting plasma glucose (mg/dL)	176·3 (45·7)	173·9 (47·7)	177·1 (46·5)	172·5 (41·2)
Fasting plasma glucose (mmol/L)	9·8 (2·5)	9·7 (2·6)	9·8 (2·6)	9·6 (2·3)
7-point self-measured blood glucose (mmol/L)	10·6 (2·5)	10·2 (2·3)	10·4 (2·3)	10·4 (2·5)
7-point self-measured blood glucose, increment across meals (mmol/L)	2·1 (1·8)	2·1 (1·8)	2·4(1·8)	2·3 (1·9)
Diabetes duration (years)	7·7 (5·9)	7·0 (5·5)	7·3 (5·7)	7·6 (5·6)
Bodyweight (kg)	96·4 (24·4)	95·6 (23·0)	95·5 (20·9)	93·4 (21·8)
Body-mass index (kg/m²)	33·7 (7·1)	33·6 (6·9)	33·6 (6·5)	33·1 (6·6)
Waist circumference (cm)	111 (16·9)	111 (14·8)	111 (14·4)	109 (14·9)
Estimated glomerular filtration rate (mL/min per 1·73 m² [CV])	96 (16·7)	96 (17·5)	97 (17·2)	95 (18·0)
Systolic blood pressure (mm Hg)	134 (14·8)	133 (14·0)	133 (14·5)	132 (13·6)
Diastolic blood pressure (mm Hg)	81 (9·0)	81 (8·9)	82 (9·1)	80 (8·7)
Heart rate (bpm)	75 (10·1)	75 (10·2)	76 (10·6)	75 (10·5)
Sex				
Male	169 (56%)	160 (54%)	162 (54%)	171 (57%)
Female	132 (44%)	139 (46%)	138 (46%)	128 (43%)
Race				
White	233 (77%)	232 (78%)	243 (81%)	220 (74%)
Black or African American	17 (6%)	17 (6%)	18 (6%)	18 (6%)
Asian	50 (17%)	48 (16%)	38 (13%)	55 (18%)
Other	1 (<1%)	2 (1%)	1 (<1%)	6 (2%)
Ethnic origin				
Hispanic or Latino	29 (10%)	31 (10%)	35 (12%)	43 (14%)
Not Hispanic or Latino	272 (90%)	268 (90%)	265 (88%)	256 (86%)

Values are mean (SD) or n (%) unless otherwise stated. Estimated glomerular filtration rate is calculated by use of the Chronic Kidney Disease Epidemiology Collaboration formula. CV=coefficient of variation.

Table 1: **Baseline characteristics**

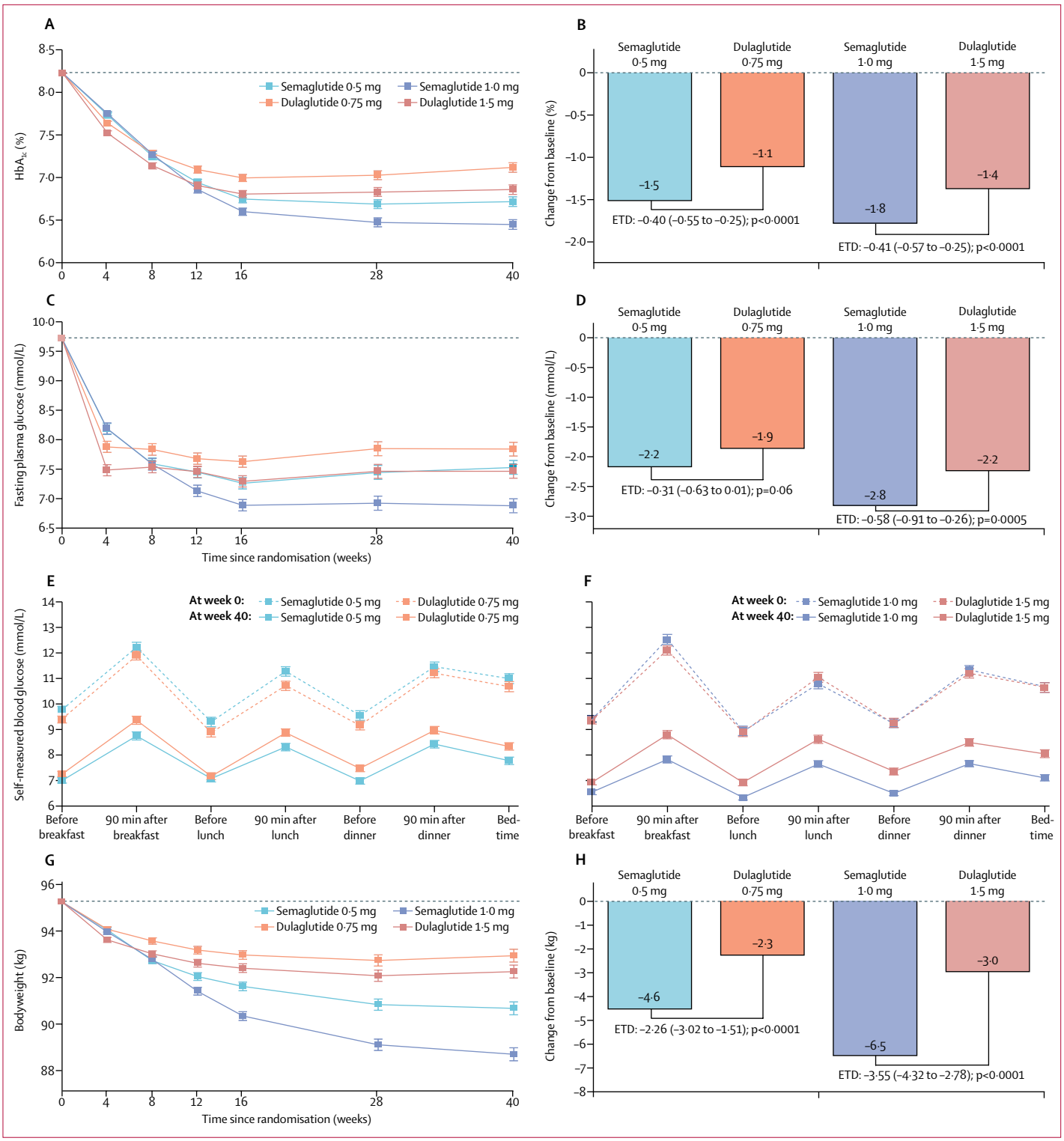

Figure 2: **Efficacy outcomes of semaglutide 0·5 mg versus dulaglutide 0·75 mg and semaglutide 1·0 mg versus dulaglutide 1·5 mg at week 40**
Change in HbA_{1c} by week (A); change in HbA_{1c} from overall baseline mean at week 40 (B); fasting plasma glucose by week (C); change in fasting plasma glucose from overall baseline mean at week 40 (D); self-measured blood glucose curves for low-dose (E) and high-dose (F) comparisons; change in bodyweight by week (G) and change in bodyweight from overall baseline mean at week 40 (H). Values are estimated means with associated ETDs and 95% CIs (A, B, C, D, G, and H) or observed means (SEs; E and F) from a mixed model for repeated measurements analysis using data from all randomised patients exposed to at least one dose of trial product (full analysis set) using data obtained while on treatment and prior to onset of rescue medication. Dashed line (A, C, and G) indicates the overall mean value at baseline. ETD=estimated treatment difference.

	Overall baseline	Low dose				High dose			
		Semaglutide 0·5 mg (n=301)	Dulaglutide 0·75 mg (n=299)	Estimated treatment difference (95% CI)	p value	Semaglutide 1·0 mg (n=300)	Dulaglutide 1·5 mg (n=299)	Estimated treatment difference (95% CI)	p value
Glycaemic outcomes									
Mean HbA_{1c} (%)	8·2 (0·9)	−1·5 (0·06)	−1·1 (0·05)	−0·40 (−0·55 to −0·25)	<0·0001	−1·8 (0·06)	−1·4 (0·06)	−0·41 (−0·57 to −0·25)	<0·0001
Mean HbA_{1c} (mmol/mol)	66·4 (10·0)	−16·5 (0·61)	−12·1 (0·60)	−4·37 (−6·06 to −2·69)	<0·0001	−19·4 (0·62)	−14·9 (0·61)	−4·47 (−6·18 to −2·77)	<0·0001
Mean fasting plasma glucose (mmol/L)	9·7 (2·5)	−2·2 (0·12)	−1·9 (0·12)	−0·31 (−0·63 to 0·01)	0·0603	−2·8 (0·12)	−2·2 (0·12)	−0·58 (−0·91 to −0·26)	0·0005
Mean 7-point self-measured blood glucose (mmol/L)	10·4 (2·4)	−2·4 (0·10)	−2·0 (0·10)	−0·44 (−0·71 to −0·17)	0·0014	−3·0 (0·10)	−2·3 (0·10)	−0·63 (−0·90 to −0·35)	<0·0001
Mean 7-point self-measured blood glucose, increment across meals (mmol/L)	2·2 (1·8)	−0·8 (0·08)	−0·4 (0·08)	−0·33 (−0·55 to −0·10)	0·0053	−0·9 (0·09)	−0·6 (0·08)	−0·30 (−0·53 to −0·06)	0·013
Bodyweight outcomes									
Mean bodyweight (kg)	95·2 (22·6)	−4·6 (0·28)	−2·3 (0·27)	−2·26 (−3·02 to −1·51)	<0·0001	−6·5 (0·28)	−3·0 (0·27)	−3·55 (−4·32 to −2·78)	<0·0001
Mean body-mass index (kg/m^2)	33·5 (6·8)	−1·6 (0·10)	−0·8 (0·10)	−0·81 (−1·08 to −0·54)	<0·0001	−2·3 (0·10)	−1·1 (0·10)	−1·25 (−1·52 to −0·98)	<0·0001
Mean waist circumference (cm)	110 (15·3)	−4·3 (0·34)	−2·4 (0·33)	−1·91 (−2·84 to −0·98)	<0·0001	−5·2 (0·34)	−2·9 (0·33)	−2·27 (−3·21 to −1·33)	<0·0001
Blood pressure and heart rate									
Mean systolic blood pressure (mm Hg)	133·0 (14·3)	−2·4 (0·76)	−2·2 (0·75)	−0·28 (−2·37 to 1·81)	0·79	−4·9 (0·77)	−2·9 (0·75)	−2·02 (−4·14 to 0·09)	0·0607
Mean diastolic blood pressure (mm Hg)	81·0 (8·9)	−0·6 (0·48)	−0·3 (0·47)	−0·22 (−1·54 to 1·10)	0·74	−2·0 (0·49)	<−0·1 (0·47)	−2·02 (−3·35 to −0·68)	0·0031
Mean heart rate (bpm)	75·0 (10·3)	2·1 (0·51)	1·6 (0·49)	0·53 (−0·84 to 1·91)	0·45	4·0 (0·51)	2·4 (0·50)	1·55 (0·15 to 2·95)	0·0304

Data are mean (SE) change from overall baseline mean (SD) or mean (95% CI) estimated treatment difference from a mixed model for repeated measurements analysis using data for all randomised patients exposed to at least one dose of trial product (full analysis set) obtained while on treatment and before onset of rescue medication. For heart rate, which was a safety endpoint, values are estimated means and estimated treatment differences from a mixed model for repeated measurements analysis using data for all patients randomly assigned to treatment who were exposed to at least one dose of trial product (safety analysis set) obtained while on treatment.

Table 2: **Efficacy outcomes measured as change from baseline at week 40**

	Low dose				High dose			
	Semaglutide 0·5 mg (n=301)	Dulaglutide 0·75 mg (n=299)	Estimated odds ratio (95% CI)	p value	Semaglutide 1·0 mg (n=300)	Dulaglutide 1·5 mg (n=299)	Estimated odds ratio (95% CI)	p value
Glycaemic targets								
HbA_{1c} <7·0%	206 (68%)	156 (52%)	2·47 (1·68–3·64)	<0·0001	236 (79%)	199 (67%)	1·96 (1·28–3·00)	0·0021
HbA_{1c} ≤6·5%	148 (49%)	102 (34%)	2·18 (1·50–3·17)	<0·0001	200 (67%)	141 (47%)	2·18 (1·50–3·18)	<0·0001
HbA_{1c} reduction ≥1%	233 (77%)	161 (54%)	2·42 (1·64–3·57)	<0·0001	250 (83%)	202 (68%)	2·04 (1·34–3·12)	0·0009
Weight loss responses								
≥3% reduction	194 (64%)	109 (36%)	2·82 (1·98–4·02)	<0·0001	230 (77%)	133 (45%)	3·17 (2·19–4·60)	<0·0001
≥5% reduction	132 (44%)	68 (23%)	2·40 (1·65–3·47)	<0·0001	189 (63%)	90 (30%)	3·03 (2·11–4·34)	<0·0001
≥10% reduction	43 (14%)	10 (3%)	4·79 (2·38–9·65)	<0·0001	80 (27%)	23 (8%)	4·55 (2·73–7·59)	<0·0001
Composite endpoints								
HbA_{1c} ≥1% reduction and weight loss ≥3%	160 (53%)	75 (25%)	2·82 (1·95–4·08)	<0·0001	205 (68%)	104 (35%)	3·11 (2·17–4·46)	<0·0001
HbA_{1c} <7·0% without severe or blood glucose-confirmed symptomatic hypoglycaemia and no weight gain	194 (64%)	132 (44%)	2·65 (1·81–3·87)	<0·0001	222 (74%)	174 (58%)	2·15 (1·45–3·19)	0·0001

Data are n (%) unless otherwise stated. Severe or blood glucose-confirmed hypoglycaemia was defined as an episode that was severe according to the American Diabetes Association classification[23] or blood glucose-confirmed by a plasma glucose value below 3·1 mmol/L (56 mg/dL) with symptoms consistent with hypoglycaemia. The proportions are calculated using observed data for all randomised patients exposed to at least one dose of trial product (full analysis set) obtained while on treatment and before onset of rescue medication. For patients with no data at week 40, missing data were imputed from a mixed model for repeated measurements analysis and subsequently classified. The odds ratios and associated CIs are estimated from a logistic regression model.

Table 3: **Proportion of patients achieving glycaemic targets and weight loss responses at week 40**

significantly reduced with semaglutide 0·5 mg versus with dulaglutide 0·75 mg (ETD −0·33 mmol/L [95% CI −0·55 to −0·10]; p=0·0053; figure 2, table 2) and with semaglutide 1·0 mg versus with dulaglutide 1·5 mg (ETD −0·30 mmol/L [−0·53 to −0·06]; p=0·013; figure 2, table 2).

More patients with semaglutide than dulaglutide, at both dose levels, achieved weight loss responses of at least 5% or at least 10% at week 40 (all p<0·0001; table 3, appendix).

Significantly more semaglutide-treated patients than dulaglutide-treated patients at each dose level achieved

	Semaglutide 0·5 mg (n=301)			Dulaglutide 0·75 mg (n=299)			Semaglutide 1·0 mg (n=300)			Dulaglutide 1·5 mg (n=299)		
	n (%)	Events	Rate of events per 100 patient-years	n (%)	Events	Rate of events per 100 patient-years	n (%)	Events	Rate of events per 100 patient-years	n (%)	Events	Rate of events per 100 patient-years
All adverse events												
Adverse events	204 (68%)	966	412·7	186 (62%)	802	326·2	207 (69%)	1015	439·7	221 (74%)	957	402·6
Serious adverse events	17 (6%)	23	9·8	24 (8%)	34	13·8	23 (8%)	27	11·7	22 (7%)	33	13·9
Fatal events*†	1 (<1%)	1	0·4	2 (1%)	2	0·8	1 (<1%)	1	0·4	2 (1%)	5	2·0
Adverse events leading to premature treatment discontinuation	24 (8%)	46	19·7	14 (5%)	23	9·4	29 (10%)	66	28·6	20 (7%)	51	21·5
Gastrointestinal adverse events leading to premature treatment discontinuation	16 (5%)	27	11·5	6 (2%)	8	3·3	18 (6%)	37	16·0	14 (5%)	37	15·6
Gastrointestinal adverse events	129 (43%)	394	168·3	100 (33%)	257	104·5	133 (44%)	498	215·7	143 (48%)	393	165·4
Severe	9 (3%)	20	8·5	3 (1%)	3	1·2	8 (3%)	13	5·6	8 (3%)	13	5·5
Moderate	40 (13%)	57	24·4	20 (7%)	29	11·8	48 (16%)	122	52·8	39 (13%)	80	33·7
Mild	108 (36%)	317	135·4	85 (28%)	223	90·7	113 (38%)	363	157·2	125 (42%)	300	126·2
Adverse events occurring in ≥5% patients by preferred term												
Nausea	68 (23%)	145	62·0	39 (13%)	66	26·8	63 (21%)	192	83·2	60 (20%)	108	45·4
Diarrhoea	43 (14%)	79	33·8	23 (8%)	42	17·1	41 (14%)	96	41·6	53 (18%)	75	31·6
Vomiting	31 (10%)	51	21·8	12 (4%)	16	6·5	31 (10%)	48	20·8	29 (10%)	40	16·8
Decreased appetite	25 (8%)	26	11·1	9 (3%)	12	4·9	27 (9%)	27	11·7	31 (10%)	36	15·1
Headache	25 (8%)	35	15·0	12 (4%)	20	8·1	22 (7%)	30	13·0	19 (6%)	30	12·6
Lipase increased	20 (7%)	24	10·3	16 (5%)	17	6·9	17 (6%)	17	7·4	17 (6%)	20	8·4
Nasopharyngitis	15 (5%)	16	6·8	17 (6%)	20	8·1	14 (5%)	16	6·9	20 (7%)	24	10·1
Upper respiratory tract infection	14 (5%)	19	8·1	21 (7%)	26	10·6	10 (3%)	11	4·8	16 (5%)	21	8·8
Constipation	16 (5%)	18	7·7	10 (3%)	10	4·1	14 (5%)	14	6·1	15 (5%)	18	7·6
Other adverse events of clinical interest												
Severe or blood glucose-confirmed hypoglycaemia	2 (1%)	3	1·3	3 (1%)	3	1·2	5 (2%)	7	3·0	5 (2%)	5	2·1
Event adjudication committee-confirmed cardiovascular events*	3 (1%)	3	1·2	5 (2%)	5	2·0	2 (1%)	2	0·8	6 (2%)	6	2·4
Committee-confirmed malignant neoplasms (including thyroid)*‡	3 (1%)	3	1·2	1 (<1%)	1	0·4	3 (1%)	3	1·2	3 (1%)	3	1·2
Committee-confirmed thyroid neoplasms*	1 (<1%)	1	0·4	0	..	..	0	..	..	1 (<1%)	1	0·4
Committee-confirmed thyroidectomy events	0	..	..	0	..	..	0	..	..	1 (<1%)	1	0·4
Committee-confirmed pancreatitis	0	..	..	0	..	..	0	..	..	0	..	..
Gallbladder disorders	2 (1%)	2	0·9	4 (1%)	4	1·6	4 (1%)	5	2·2	8 (3%)	9	3·8
Cholelithiasis	0	..	..	1 (<1%)	1	0·4	2 (1%)	2	0·9	2 (1%)	2	0·8
Diabetic retinopathy*	2 (1%)	2	0·8	2 (1%)	2	0·8	2 (1%)	2	0·8	3 (1%)	3	1·2
Allergic reactions	8 (3%)	12	5·1	15 (5%)	22	8·9	8 (3%)	9	3·9	6 (2%)	7	2·9
Injection-site reactions	4 (1%)	5	2·1	4 (1%)	9	3·7	6 (2%)	6	2·6	8 (3%)	17	7·2

Adverse events include events that had an 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 40 (on-treatment data). *Adverse events include events that had an onset, or increase in severity, from randomisation to the end of trial regardless of treatment or rescue medication status (in-trial data). †See the appendix for further details of fatal cases; one patient receiving dulaglutide 1·5 mg had four events resulting in a fatal outcome. ‡One additional malignant neoplasm was reported by a patient receiving dulaglutide 1·5 mg after the trial observation period: see the appendix. Severity of adverse events was defined as follows: mild (transient symptoms, no interference with patient's daily activities); moderate (marked symptoms, moderate interference with patient's daily activities); severe (considerable interference with patient's daily activities, unacceptable). Severe or blood glucose-confirmed hypoglycaemia was defined as an episode that was severe according to the American Diabetes Association classification[25] or blood glucose-confirmed by a plasma glucose value below 3·1 mmol/L (56 mg/dL) with symptoms consistent with hypoglycaemia. All adverse events were coded using the most recent version of the Medical Dictionary for Regulatory Activities.

Table 4: **Adverse events overview**

the two composite endpoints of: HbA_{1c} of less than 7·0% without severe or blood glucose-confirmed symptomatic hypoglycaemia and no weight gain; and at least a 1 percentage point HbA_{1c} reduction and at least 3% weight loss, respectively (all p≤0·0001; table 3, appendix). Mean systolic and mean diastolic blood pressure were reduced with both semaglutide and dulaglutide. The change in diastolic blood pressure was significantly greater for semaglutide 1·0 mg versus dulaglutide 1·5 mg (ETD –2·02 [95% CI –3·35 to –0·68]; p=0·003); all other blood pressure comparisons between semaglutide and dulaglutide were non-significant (table 2). No clinically relevant differences in lipid parameters were observed between treatments (appendix). Improvements in patient-reported outcomes from baseline to week 40 were similar for both the high-dose and low-dose treatment group comparisons (appendix). Patient perception of unacceptable hyperglycaemia was significantly improved with both semaglutide doses compared with respective dulaglutide doses (low-dose comparison: ETD –0·32 [95% CI –0·60 to –0·04]; p=0·0254; high-dose comparison: ETD –0·40 [–0·68 to –0·12]; p=0·0049; appendix).

Adverse events were reported by 204 (68%) of 301 patients receiving semaglutide 0·5 mg, 186 (62%) of 299 patients receiving dulaglutide 0·75 mg, 207 (69%) of 300 patients receiving semaglutide 1·0 mg, and 221 (74%) of 299 patients receiving dulaglutide 1·5 mg (table 4). There were six deaths: one in each semaglutide group and two in each dulaglutide group (table 4, appendix). The frequency of serious adverse events was similar between treatment groups (table 4; see appendix for full list). Adverse events leading to premature treatment discontinuation occurred in 24 (8%) of 301 patients receiving semaglutide 0·5 mg, 14 (5%) of 299 patients receiving dulaglutide 0·75 mg, 29 (10%) of 300 patients receiving semaglutide 1·0 mg, and 20 (7%) of 299 patients receiving dulaglutide 1·5 mg (table 4, appendix). Most adverse events leading to treatment discontinuation occurred early on in the trial.

Gastrointestinal disorders were the most frequent adverse events, and occurred in similar proportion of patients receiving semaglutide 0·5 mg (129 patients [43%]), semaglutide 1·0 mg (133 [44%]), and dulaglutide 1·5 mg (143 [48%]); fewer patients had gastrointestinal disorders with dulaglutide 0·75 mg (100 [33%]; table 4). Gastrointestinal disorders were the most common reason for premature treatment discontinuation. Nausea was reported by 68 (23%) of 301 patients receiving semaglutide 0·5 mg, 39 (13%) of 299 patients receiving dulaglutide 0·75 mg, 63 (21%) of 300 patients receiving semaglutide 1·0 mg, and 60 (20%) of 299 patients receiving dulaglutide 1·5 mg (table 4); most events were mild or moderate in severity and diminished over time (appendix). The proportions of patients with vomiting and diarrhoea over time are also shown in the appendix.

Event adjudication committee-confirmed cardiovascular events were reported by three patients (1%) receiving semaglutide 0·5 mg, five patients (2%) receiving dulaglutide 0·75 mg, two patients (1%) receiving semaglutide 1·0 mg, and six patients (2%) receiving dulaglutide 1·5 mg (table 4). From baseline, mean heart rate increased by 2·1 bpm (SE 0·51) with semaglutide 0·5 mg versus 1·6 bpm (0·49) with dulaglutide 0·75 mg (ETD 0·53 bpm [95% CI –0·84 to 1·91]; p=0·45) and by 4·0 bpm (0·51) with semaglutide 1·0 mg versus 2·4 bpm (0·50) with dulaglutide 1·5 mg (ETD 1·55 bpm [0·15 to 2·95]; p=0·0304; table 2).

Episodes of severe or blood glucose-confirmed symptomatic hypoglycaemia were reported by two patients (1%) receiving semaglutide 0·5 mg and three patients (1%) receiving dulaglutide 0·75 mg, and five patients each (2%) in the semaglutide 1·0 mg and dulaglutide 1·5 mg groups (table 4).

Overall, 11 event adjudication committee-confirmed malignant neoplasms, evenly distributed across treatment groups, were reported during the study, with no clustering of any event type (table 4, appendix). There were no event adjudication committee-confirmed events of pancreatitis (table 4). Calcitonin concentrations were similar between groups, with no apparent change from baseline during the trial.

Adverse events of diabetic retinopathy were reported by two patients (1%) receiving semaglutide 0·5 mg, two patients (1%) receiving dulaglutide 0·75 mg, two patients (1%) receiving semaglutide 1·0 mg, and three patients (1%) receiving dulaglutide 1·5 mg (table 4).

Discussion

The clinical profile of GLP-1R agonists—including improved glycaemic control, a low risk of hypoglycaemia, and the potential for clinically relevant weight loss—makes this drug class a useful option for patients and has led to its incorporation into guidelines for the treatment of type 2 diabetes.[23] Variability in efficacy and tolerability within the drug class is well documented.[8] Accordingly, in the present study, we compared two once-weekly GLP-1R agonists at two dose levels and showed that semaglutide was superior to dulaglutide in reducing HbA_{1c} at 40 weeks, enabling a significantly greater number of patients receiving semaglutide to achieve recommended HbA_{1c} targets. Weight loss was observed across all treatment groups; however, the magnitude of weight loss achieved with semaglutide was double the amount achieved with dulaglutide at both dose levels. Accordingly, twice as many semaglutide-treated patients achieved clinically relevant weight loss of more than 5% as did dulaglutide-treated patients.

The magnitude of the reductions in HbA_{1c} and bodyweight observed for semaglutide and dulaglutide in this study were consistent with those observed for semaglutide in SUSTAIN 1–5 and also for dulaglutide in AWARD 1–9 clinical trials,[12–17] which support the

robustness of these results. The findings complement those from the SUSTAIN 3 trial, in which semaglutide was superior to exenatide extended-release in improving glycaemic control and reducing bodyweight at 56 weeks.[14] Comparative studies allow clinicians to make informed treatment decisions about choice of GLP-1R agonist therapy, supporting patients to reach personalised treatment goals.[27]

Both doses of semaglutide led to significantly greater improvements in mean blood glucose postprandial increment across all meals and in mean 7-point SMBG than with dulaglutide. This finding, combined with the greater reduction in fasting plasma glucose observed with semaglutide versus dulaglutide, is likely to have contributed to the marked reductions in HbA_{1c} observed with semaglutide compared with dulaglutide. These findings are in line with those of the SUSTAIN 1–5 trials,[12–16,28] and further support that long-acting GLP-1R agonists can affect postprandial glucose concentrations.

Insulin sensitivity and β-cell function were not investigated during this study; however, semaglutide has been shown to improve insulin sensitivity primarily via weight loss.[29] A bodyweight-mediated effect on insulin sensitivity and β-cell function might have also contributed to the greater improvement in glycaemic control observed with semaglutide compared with dulaglutide.[30] A potential explanation for the superior bodyweight reduction observed with semaglutide than with dulaglutide might be differences in centrally mediated effects on appetite regulation. Although both compounds[10,31] are likely to activate peripheral pathways that modulate glucose homoeostasis, preclinical studies of mouse animal models indicate that semaglutide activates GLP-1 receptors in the brain.[32] It is not known if the larger molecular weight of dulaglutide hinders access to important body compartments, such as specific brain areas involved in appetite regulation. Further research on both compounds is required to understand the causes of the differences in efficacy, including a direct comparison of their pharmacokinetic profiles to identify the variability in exposure over time, which were not tested in this study.

The overall safety profiles of semaglutide and dulaglutide were similar. The proportions of patients reporting gastrointestinal adverse events were similar for both doses of semaglutide and high-dose dulaglutide. Although the proportion of premature treatment discontinuation due to occurrence of adverse events was less than 10% in all treatment groups, it was higher for each dose level of semaglutide compared with the respective dose level of dulaglutide. The most frequently reported adverse events that led to discontinuation of treatment were gastrointestinal disorders. The higher proportion of discontinuation caused by adverse events with semaglutide 1·0 mg might be due to the higher prevalence of moderate gastrointestinal events than occurred in the other treatment groups. Most events that led to discontinuation of treatment generally occurred early in the trial for high-dose dulaglutide and both semaglutide doses. Importantly, there were no differences in overall treatment satisfaction in this trial despite high satisfaction scores at baseline, suggesting that both treatments were equally suited to patients' day-to-day life.

A modest but significant increase in heart rate (1·55 bpm)—a known GLP-1R agonist class effect[33]—was observed with high-dose semaglutide compared with high-dose dulaglutide. Although the mechanism for this increase has not been fully elucidated, it might be mediated directly via GLP-1Rs on the sinoatrial node of the heart.[33] Crucially, the cardiovascular studies reported to date suggest that this increased heart rate observed with all agents in the GLP-1R agonist class has no effect on long-term cardiovascular outcomes. Indeed, in the 2-year cardiovascular outcomes trial, SUSTAIN 6,[34] despite an increase in heart rate of 2·0–2·5 bpm versus placebo, semaglutide treatment significantly reduced the rate of major adverse cardiovascular events (composite endpoint of cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke) by 26% compared with placebo in patients with type 2 diabetes who were at high risk of cardiovascular events. The cardiovascular safety of dulaglutide is currently under investigation in the REWIND trial (NCT01394952), with an estimated primary completion date in 2018.[35]

An increase in diabetic retinopathy complications was observed in SUSTAIN 6 in patients at high risk of cardiovascular events who were treated with semaglutide versus placebo,[34] which is considered to be consistent with the phenomenon of early worsening of pre-existing diabetic retinopathy associated with rapid improvements in glycaemic control.[36] Notably, there was no increased risk in patients without pre-existing retinopathy with semaglutide compared with placebo.[36] The SUSTAIN 7 trial investigated semaglutide in a different population to SUSTAIN 6, and excluded patients with pre-existing proliferative retinopathy and maculopathy requiring acute treatment. In accordance with the results from SUSTAIN 1–5 trials,[12–16] relatively few events related to diabetic retinopathy were reported in SUSTAIN 7; they were evenly distributed across semaglutide and dulaglutide treatment groups.

Limitations to this study include the open-label design, implemented because masking of the patented administration device of dulaglutide would have required the use of a different device from the one that is clinically available, which would have reduced the clinical relevance of the findings. Additionally, enrolled patients were treated with metformin only and had relatively normal renal function or mild renal impairment, thereby limiting the generalisability of the study findings to other populations. Also, a study of longer duration might have provided further insights, particularly as the reduction in bodyweight for semaglutide 1·0 mg did not appear to plateau by week 40. Finally, although the use of multiple doses is a strength of this study, its design was limited to the comparison between semaglutide and dulaglutide

within respective dose levels only (ie, high-dose and low-dose comparisons).

Semaglutide was superior to dulaglutide in improving glycaemic control and reducing bodyweight in patients with type 2 diabetes. The incidence of gastrointestinal disorders was similar between semaglutide and high-dose dulaglutide, although lower with low-dose dulaglutide. The overall safety profile was similar between treatment groups. These data provide evidence to further inform clinical decision making and care in this patient population.

Contributors

All authors participated in the trial design. REP, VRA, IL, JL, and AV contributed to the conduct of the trial and the data collection. AN and CA 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

REP received research grants (to his institution) from Novo Nordisk, and has previously received speaker and consultancy fees (to his institution) from AstraZeneca and Takeda; consultancy fees (to his institution) from Boehringer Ingelheim, GlaxoSmithKline, Hanmi Pharmaceutical Co, Janssen, Ligand Pharmaceuticals, Eli Lilly, Merck, Novo Nordisk, Pfizer, and Eisai; and research grants from Gilead Sciences, Lexicon Pharmaceuticals, Ligand Pharmaceuticals, Eli Lilly, Merck, Novo Nordisk, Sanofi-Aventis US, and Takeda. VRA received research grants and meeting attendance and travel support from MedStar Health Research Institute, and has previously received consultancy fees from Adocia, Janssen, Novo Nordisk, Sanofi, American Diabetes Association, Tufts, AstraZeneca, and Medscape; and has pending clinical trial contracts with AstraZeneca/BMS, Calibra, Eisai, Elcelyx, Janssen, Novo Nordisk, Sanofi-Aventis, and Theracos. IL received grants and consulting fees (paid to her institution) and travel support from Novo Nordisk, and has previously received research grants (to her institution) from Novartis, GI Dynamics, Pfizer, Merck, and Novo Nordisk; and consulting fees and editorial support from AstraZeneca, Sanofi, Eli Lilly, and Novo Nordisk, and editorial support from Boehringer Ingelheim. JL received grants, personal fees, and travel support from Novo Nordisk, and has previously received research grants (to his institution), personal fees, and support for Advisory Board attendance and speaker's bureaus from Novo Nordisk, and research grants (to his institution), personal fees and support for Advisory Board attendance speaker's bureaus and congress travel from Eli Lilly. CA and AN report that they are full-time employees of Novo Nordisk. AV received honoraria (to his institution) from Novo Nordisk, and has previously received research grants (to his institution) from Sanofi-Aventis and personal fees for clinical trial support from AstraZeneca, Regeneron, Amgen, Sanofi-Aventis, and Novo Nordisk, for speaker bureaus from AstraZeneca, Boehringer Ingelheim, Eli Lilly, Merck Sharpe & Dohme, Amgen, Sanofi-Aventis, and Novo Nordisk, and for Advisory Boards for Boehringer Ingelheim, Merck Sharpe & Dohme, Amgen, Sanofi-Aventis, Novo Nordisk, and Pfizer.

Acknowledgments

This study was supported by Novo Nordisk. We thank all the patients, investigators, and trial-site staff members who were involved in the completion of the trial; Desirée Thielke (Novo Nordisk), for review and suggestions for revising the manuscript; and Nicole Antonio (AXON Communications), for medical writing and editorial assistance.

References

1 Lipska KJ, Yao X, Herrin J, et al. Trends in drug utilization, glycemic control, and rates of severe hypoglycemia, 2006–2013. *Diabetes Care* 2017; **40:** 468–75.

2 The ADVANCE Collaborative Group. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *N Engl J Med* 2008; **358:** 2560–72.

3 Centers for Disease Control and Prevention (CDC). Prevalence of overweight and obesity among adults with diagnosed diabetes—United States, 1988–1994 and 1999–2002. *MMWR Morb Mortal Wkly Rep* 2004; **53:** 1066–68.

4 Tobias DK, Pan A, Jackson CL, et al. Body-mass index and mortality among adults with incident type 2 diabetes. *N Engl J Med* 2014; **370:** 233–44.

5 Scheen AJ, Van Gaal LF. Combating the dual burden: therapeutic targeting of common pathways in obesity and type 2 diabetes. *Lancet Diabetes Endocrinol* 2014; **2:** 911–22.

6 Leiter LA, Nauck MA. Efficacy and safety of GLP-1 receptor agonists across the spectrum of type 2 diabetes mellitus. *Exp Clin Endocrinol Diabetes* 2017; **125:** 419–35.

7 Johnston SS, Nguyen H, Felber E, et al. Retrospective study of adherence to glucagon-like peptide-1 receptor agonist therapy in patients with type 2 diabetes mellitus in the United States. *Adv Ther* 2014; **31:** 1119–33.

8 Zaccardi F, Htike ZZ, Webb DR, Khunti K, Davies MJ. Benefits and harms of once-weekly glucagon-like peptide-1 receptor agonist treatments: a systematic review and network meta-analysis. *Ann Intern Med* 2016; **164:** 102–13.

9 Lau J, Bloch P, Schaffer L, et al. Discovery of the once-weekly glucagon-like peptide-1 (GLP-1) analogue semaglutide. *J Med Chem* 2015; **58:** 7370–80.

10 Eli Lilly. Trulicity (dulaglutide) SmPC. 2017. www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002825/WC500179470.pdf (accessed June 26, 2017).

11 Amblee A. Mode of administration of dulaglutide: implications for treatment adherence. *Patient Prefer Adherence* 2016; **10**: 975–82.

12 Sorli C, Harashima SI, Tsoukas GM, et al. Efficacy and safety of once-weekly semaglutide monotherapy versus placebo in patients with type 2 diabetes (SUSTAIN 1): a double-blind, randomised, placebo-controlled, parallel-group, multinational, multicentre phase 3a trial. *Lancet Diabetes Endocrinol* 2017; **5:** 251–60.

13 Ahrén B, Masmiquel L, Kumar H, et al. Efficacy and safety of once-weekly semaglutide versus once-daily sitagliptin as an add-on to metformin, thiazolidinediones, or both, in patients with type 2 diabetes (SUSTAIN 2): a 56-week, double-blind, phase 3a, randomised trial. *Lancet Diabetes Endocrinol* 2017; **5:** 341–54.

14 Ahmann AJ, Capehorn M, Charpentier G, et al. Efficacy and safety of once-weekly semaglutide versus exenatide ER in subjects with type 2 diabetes (SUSTAIN 3): a 56-week, open-label, randomized clinical trial. *Diabetes Care* 2018; **41:** 258–66.

15 Aroda VR, Bain SC, Cariou B, et al. Efficacy and safety of once-weekly semaglutide versus once-daily insulin glargine as add-on to metformin (with or without sulfonylureas) in insulin-naive patients with type 2 diabetes (SUSTAIN 4): a randomised, open-label, parallel-group, multicentre, multinational, phase 3a trial. *Lancet Diabetes Endocrinol* 2017; **5:** 355–66.

16 Rodbard H, Lingvay I, Reed J, et al. Efficacy and safety of semaglutide once-weekly vs placebo as add-on to basal insulin alone or in combination with metformin in subjects with type 2 diabetes (SUSTAIN 5). *Diabetologia* 2016; **59** (suppl 1)**:** S364–65.

17 Jendle J, Grunberger G, Blevins T, Giorgino F, Hietpas RT, Botros FT. Efficacy and safety of dulaglutide in the treatment of type 2 diabetes: a comprehensive review of the dulaglutide clinical data focusing on the AWARD phase 3 clinical trial program. *Diabetes Metab Res Rev* 2016; **32:** 776–90.

18 Dungan KM, Povedano ST, Forst T, et al. Once-weekly dulaglutide versus once-daily liraglutide in metformin-treated patients with type 2 diabetes (AWARD-6): a randomised, open-label, phase 3, non-inferiority trial. *Lancet* 2014; **384:** 1349–57.

19 International Conference on Harmonisation Working Group. ICH harmonised tripartite guideline: guideline for good clinical practice E6 (R1). International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use; Washington, DC; June 10, 1996. https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R1_Guideline.pdf (accessed June 26, 2017).

20 World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. *JAMA* 2013; **310:** 2191.

21 Stevens PE, Levin A, Kidney Disease: Improving Global Outcomes Chronic Kidney Disease Guideline Development Work Group Members. Evaluation and management of chronic kidney disease: synopsis of the kidney disease: improving global outcomes 2012 clinical practice guideline. *Ann Intern Med* 2013; **158:** 825–30.

22 International Diabetes Federation Guideline Development Group. Guideline for management of postmeal glucose in diabetes. *Diabetes Res Clin Pract* 2014; **103:** 256–68.

23 American Diabetes Association. Standards of Medical Care in Diabetes. *Diabetes Care* 2017; **40** (suppl 1)**:** S1–135.

24 Handelsman Y, Bloomgarden ZT, Grunberger G, et al. American Association of Clinical Endocrinologists and American College of Endocrinology—clinical practice guidelines for developing a diabetes mellitus comprehensive care plan—2015. *Endocr Pract* 2015; **21** (suppl 1)**:** 1–87.

25 Seaquist ER, Anderson J, Childs B, et al. Hypoglycemia and diabetes: a report of a workgroup of the American Diabetes Association and the Endocrine Society. *Diabetes Care* 2013; **36:** 1384–95.

26 Bretz F, Maurer W, Brannath W, Posch M. A graphical approach to sequentially rejective multiple test procedures. *Stat Med* 2009; **28:** 586–604.

27 Fiore LD, Lavori PW. Integrating randomized comparative effectiveness research with patient care. *N Engl J Med* 2016; **374:** 2152–58.

28 Aroda V, Unger J, Cariou B, Birch S, Tadayon S, Jódar E. Semaglutide consistently reduces both fasting and postprandial glucose levels across SUSTAIN 1–5 clinical trials. *Endocr Rev* 2017; **38** (suppl)**:** abstr 622.

29 Fonseca V, Capehorn M, Garg S, et al. Semaglutide-induced reductions in insulin resistance are mediated primarily via weight loss in subjects with type 2 diabetes (SUSTAIN 1–3). *Diabetologia* 2017; **60** (suppl 1)**:** S375–76.

30 Kapitza C, Dahl K, Jacobsen JB, Axelsen MB, Flint A. Effects of semaglutide on beta cell function and glycaemic control in participants with type 2 diabetes: a randomised, double-blind, placebo-controlled trial. *Diabetologia* 2017; **60:** 1390–99.

31 Hjerpsted JB, Flint A, Brooks A, Axelsen MB, Kvist T, Blundell J. Semaglutide improves postprandial glucose and lipid metabolism, and delays first-hour gastric emptying in subjects with obesity. *Diabetes Obes Metab* 2017; published online Sept 23. DOI:10.111/dom.13120.

32 Jensen C, Secher A, Hecksher-Sørensen J, et al. Quantification of semaglutide distribution and action in mouse brain regions associated with reward and food intake. *Diabetes* 2017; **66** (suppl 1)**:** A305.

33 Lorenz M, Lawson F, Owens D, et al. Differential effects of glucagon-like peptide-1 receptor agonists on heart rate. *Cardiovasc Diabetol* 2017; **16:** 6.

34 Marso SP, Bain SC, Consoli A, et al. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med* 2016; **375:** 1834–44.

35 ClinicalTrials.gov. Researching cardiovascular events with a weekly incretin in diabetes (REWIND). https://clinicaltrials.gov/ct2/show/NCT01394952?term=dulaglutide+rewind&rank=1 (accessed July 31, 2017).

36 Vilsbøll T, Bain SC, Leiter LA, et al. Semaglutide, reduction in glycated haemoglobin and the risk of diabetic retinopathy. *Diabetes Obes Metab* 2018; published online Jan 8. DOI:10.1111/dom.13172.