Efficacy and safety of once-weekly semaglutide 2·0 mg versus 1·0 mg in patients with type 2 diabetes (SUSTAIN FORTE): a double-blind, randomised, phase 3B trial

Juan P Frías, Pernille Auerbach, Harpreet S Bajaj, Yasushi Fukushima, Ildiko Lingvay, Stanislava Macura, Anette L Søndergaard, Tsvetalina I Tankova, Nikolaos Tentolouris, John B Buse

Summary

Background Semaglutide is an effective treatment for type 2 diabetes; however, 20–30% of patients given semaglutide 1·0 mg do not reach glycaemic treatment goals. We aimed to investigate the efficacy and safety of once-weekly semaglutide 2·0 mg versus 1·0 mg in adults with inadequately controlled type 2 diabetes on a stable dose of metformin with or without a sulfonylurea.

Methods We did a 40-week, randomised, active-controlled, parallel-group, double-blind, phase 3B trial (SUSTAIN FORTE) at 125 outpatient clinics in ten countries. Participants (≥18 years) with inadequately controlled type 2 diabetes (HbA_{1c} 8·0–10·0%) with metformin and with or without sulfonylurea were randomly assigned (1:1) by an interactive web-response system to 2·0 mg or 1·0 mg once-weekly semaglutide. Participants, site personnel, the clinical study group, and investigators were masked to the randomised treatment. Outcomes included change from baseline at week 40 in HbA_{1c} (primary outcome) and bodyweight (secondary confirmatory outcome), evaluated through trial product estimand (no treatment discontinuation or without rescue medication) and treatment policy estimand (regardless of treatment discontinuation or rescue medication) strategies. This study is registered with ClinicalTrials.gov, NCT03989232; EudraCT, 2018-004529-96; and WHO, U1111-1224-5162.

Findings Between June 19 and Nov 28, 2019, of 1515 adults assessed for eligibility, 961 participants (mean age 58·0 years [SD 10·0]; 398 [41%] women) were included. Participants were randomly assigned to once-weekly semaglutide 2·0 mg (n=480 [50%]) or 1·0 mg (n=481 [50%]); 462 (96%) patients in the semaglutide 2·0 mg group and 471 (98%) in the semaglutide 1·0 mg group completed the trial. Mean baseline HbA_{1c} was 8·9% (SD 0·6; 73·3 mmol/mol [SD 6·9]) and BMI was 34·6 kg/m² (SD 7·0). Mean change in HbA_{1c} from baseline at week 40 was –2·2 percentage points with semaglutide 2·0 mg and –1·9 percentage points with semaglutide 1·0 mg (estimated treatment difference [ETD] –0·23 percentage points [95% CI –0·36 to –0·11]; p=0·0003; trial product estimand) and –2·1 percentage points with semaglutide 2·0 mg and –1·9 percentage points with semaglutide 1·0 mg (ETD –0·18 percentage points [–0·31 to –0·04]; p=0·0098; treatment policy estimand). Mean change in bodyweight from baseline at week 40 was –6·9 kg with semaglutide 2·0 mg and –6·0 kg with semaglutide 1·0 mg (ETD –0·93 kg [95% CI –1·68 to –0·18]; p=0·015; trial product estimand) and –6·4 kg with semaglutide 2·0 mg and –5·6 kg with semaglutide 1·0 mg (ETD –0·77 kg [–1·55 to 0·01]; p=0·054; treatment policy estimand). Gastrointestinal disorders were the most commonly reported adverse events (163 [34%] in the 2·0 mg group and 148 [31%] in the 1·0 mg group). Serious adverse events were similar between treatment groups, reported for 21 (4%) participants given semaglutide 2·0 mg and 25 (5%) participants given semaglutide 1·0 mg. Three deaths were reported during the trial (one in the semaglutide 1·0 mg group and two in the semaglutide 2·0 mg group).

Interpretation Semaglutide 2·0 mg was superior to 1·0 mg in reducing HbA_{1c}, with additional bodyweight loss and a similar safety profile. This higher dose provides a treatment intensification option for patients with type 2 diabetes treated with semaglutide in need of additional glycaemic control.

Funding Novo Nordisk.

Lancet Diabetes Endocrinol 2021; 9: 563–74

Published Online July 19, 2021 https://doi.org/10.1016/S2213-8587(21)00174-1

See Comment page 546

Clinical Research, National Research Institute, Los Angeles, CA, USA (J P Frías MD); **Novo Nordisk, Søborg, Denmark** (P Auerbach MD, S Macura MD, A L Søndergaard PhD); **LMC Diabetes and Endocrinology, Brampton, ON, Canada** (H S Bajaj MD); **Fukuwa Clinic, Tokyo, Japan** (Y Fukushima MD); **Department of Internal Medicine/Endocrinology** (I Lingvay MD) **and Department of Population and Data Sciences** (I Lingvay), **University of Texas Southwestern Medical Center, Dallas, TX, USA; Department of Endocrinology, Medical University of Sofia, Sofia, Bulgaria** (T I Tankova MD); **Diabetes Centre, First Department of Propaedeutic Internal Medicine, Medical School, National and Kapodistrian University of Athens, Laiko General Hospital, Athens, Greece** (N Tentolouris MD); **Department of Medicine, University of North Carolina School of Medicine, Chapel Hill, NC, USA** (J B Buse MD)

Correspondence to: Dr Juan P Frías, Clinical Research, National Research Institute, Los Angeles, CA 90057, USA **juan.frias@nritrials.com**

Introduction

GLP-1 receptor agonists are an established treatment option for type 2 diabetes, providing effective glycaemic lowering by stimulating insulin secretion and inhibiting the release of glucagon in a glucose-dependent manner.[1,2] They also decrease bodyweight by reducing appetite and food intake.[1,2] Owing to structural differences between the available GLP-1 receptor agonists, differences exist in the efficacy profile within the class regarding improvements in glycaemia and bodyweight and cardiovascular risk reduction.[1,2]

Once-weekly subcutaneous semaglutide, a GLP-1 receptor agonist, is available for the treatment of type 2 diabetes in two doses: 0·5 mg and 1·0 mg.[3,4] The efficacy

Research in context

Evidence before this study

We searched PubMed on June 28, 2021, using the term "semaglutide" with no date or language restrictions. The results were reviewed and publications reporting phase 3 clinical trials of once-weekly semaglutide were included. Once-weekly subcutaneous semaglutide, at doses of 0·5 mg and 1·0 mg, are available for the treatment of type 2 diabetes and were investigated in the global, phase 3, SUSTAIN clinical trial programme. Despite superior HbA_{1c} reductions compared with comparators, including other GLP-1 receptor agonists, in the SUSTAIN programme 20–30% of participants did not reach a target HbA_{1c} of less than 7·0% (53 mmol/mol) with semaglutide 1·0 mg. In a phase 2 trial, done after the phase 3 SUSTAIN trial programme was initiated, which evaluated semaglutide doses exceeding 1·0 mg once weekly, additional, dose-dependent HbA_{1c} and bodyweight reductions were observed with higher doses, with no new safety concerns.

Added value of this study

In the SUSTAIN FORTE trial, superior glycaemic control was observed with semaglutide 2·0 mg compared with 1·0 mg with two estimand strategies (trial product and treatment policy); clinically relevant reductions in bodyweight were observed with both doses—greater bodyweight reduction was confirmed by the trial product estimand but not by the treatment policy estimand. A greater proportion of participants attained glycaemic and weight-loss responses with semaglutide 2·0 mg compared with semaglutide 1·0 mg. Safety and tolerability of the two doses were similar and there were no safety concerns following dose escalation from semaglutide 1·0 mg to 2·0 mg.

Implications of all the available evidence

The findings of the SUSTAIN FORTE trial show that once-weekly semaglutide 2·0 mg is more efficacious than 1·0 mg, with a similar safety profile, for people with type 2 diabetes. The 2·0 mg dose should provide a simple intensification option for patients given semaglutide in need of additional glycaemic control via escalating their existing treatment.

and safety of these doses were investigated in the comprehensive SUSTAIN phase 3 clinical development programme, which included participants with type 2 diabetes across the continuum of care and treated with multiple oral anti-hyperglycaemic drugs or insulin.[5–14] In the SUSTAIN programme, clinically relevant and superior reductions in both HbA_{1c} and bodyweight were shown with semaglutide versus all commonly used anti-hyperglycaemic treatments, including other GLP-1 receptor agonists (exenatide extended-release 2·0 mg, dulaglutide 0·75 and 1·5 mg, and liraglutide 1·2 mg), dipeptidyl peptidase-4 inhibitors (sitagliptin 100 mg), SGLT2 inhibitors (canagliflozin 300 mg), and basal insulin (insulin glargine).[5–14] In addition, the safety profile of semaglutide in the SUSTAIN programme was consistent with that of the GLP-1 receptor agonist class.[5–15] Furthermore, in SUSTAIN 6, a cardiovascular outcomes trial, a significant 26% reduction in the risk of major adverse cardiovascular events was shown with semaglutide (0·5 mg and 1·0 mg pooled) versus placebo in participants with type 2 diabetes at high risk of, or with established, cardiovascular disease (non-inferiority, prespecified; superiority, not prespecified).[10] However, despite the superior HbA_{1c} lowering efficacy of semaglutide versus comparators, across the SUSTAIN trials, approximately 20–30% of participants given once-weekly semaglutide 1·0 mg did not reach the treatment target of HbA_{1c} less than 7·0%.[16,17] The proportion of participants given semaglutide 1·0 mg reaching this glycaemic target was lower in those with higher baseline HbA_{1c}, with 40–61% of those with baseline values greater than 9·0% reaching glycaemic targets.[18]

See Online for appendix

In a phase 2 trial, initiated after the phase 3 programme evaluating semaglutide 0·5 mg and 1·0 mg had started, the efficacy and safety of a wider dose range of semaglutide was investigated in adults with type 2 diabetes.[19] With a 4-week dose-escalation regimen, doses of 0·05, 0·1, 0·2, and 0·3 mg per day of semaglutide (corresponding to 0·35–2·1 mg per week) showed dose-dependent improvements in both glycaemic control and bodyweight.[19] Weekly doses exceeding 1·0 mg were generally well tolerated with no new safety concerns.[19]

We aimed to investigate the efficacy and safety of a 2·0 mg dose of once-weekly semaglutide compared with the highest currently available maintenance dose of 1·0 mg in adults with type 2 diabetes. Based on the aforementioned phase 2 trial, it was anticipated that a higher 2·0 mg dose of once-weekly semaglutide would decrease HbA_{1c} and bodyweight to a greater extent than the 1·0 mg dose.

Methods

Study design and participants

We did a 40-week, randomised, multicentre, multinational, active-controlled, parallel-group, double-blind, two-armed phase 3B trial (SUSTAIN FORTE) at 125 sites (hospitals, clinical research units, private offices) in ten countries. The number of trial sites in each country is shown in the appendix (p 10).

Adults (≥18 years) with type 2 diabetes for at least 180 days before screening, inadequately controlled (HbA_{1c} 8·0–10·0%; 64–86 mmol/mol) on a stable dose of metformin therapy (≥1500 mg or maximum tolerated or effective dose) alone or in combination with a sulfonylurea (half or more of maximum approved dose according to

local label or maximum tolerated or effective dose) for at least 90 days before screening were enrolled. Exclusion criteria included estimated glomerular filtration rate of less than 30 mL/min per 1·73 m²;[20] treatment with diabetes or obesity medications other than metformin or sulfonylurea therapy within 90 days before screening, except for short-term (≤14 days) insulin treatment for acute illnesses; uncontrolled and potentially unstable diabetic retinopathy or maculopathy (verified by a fundus examination); presence or history of chronic or acute pancreatitis; or presence of New York Heart Association class IV heart failure. Additional exclusion criteria are shown in the appendix (p 1).

The trial was done in compliance with the International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use Good Clinical Practice guidelines, and the Declaration of Helsinki. Participants provided written informed consent before the commencement of any trial-related activities. The trial protocol was approved by the institutional review board and ethics committee for each participating trial site (appendix p 11). Major amendments to the protocol after trial commencement are shown in the appendix (p 1).

Randomisation and masking

Participants were randomly assigned (1:1) to semaglutide 2·0 mg or 1·0 mg, administered subcutaneously once weekly. Randomisation was done centrally using an interactive web response system (Calyx, Nottingham, UK), with stratification by country (Japan or not Japan). Investigators at each site accessed the interactive web response system to randomly assign participants. For the first 12 weeks, during dose escalation, all participants received once-weekly semaglutide open-label in a prefilled pen injector. From week 13, participants received an additional masked pen injector containing either semaglutide 1·0 mg or placebo (visually identical to semaglutide 1·0 mg to maintain masking) and administered two injections each week (semaglutide 1·0 mg plus semaglutide 1·0 mg or semaglutide 1·0 mg plus placebo). Participants, site personnel, the clinical study group, and investigators were masked to the randomised treatment.

Procedures

A screening period of up to 2 weeks was followed by 40 weeks of treatment and 7 weeks of follow-up (appendix p 6). Treatment was initiated with semaglutide 0·25 mg for 4 weeks, followed by 4 weeks of semaglutide 0·5 mg and 4 weeks of semaglutide 1·0 mg. Subsequently, participants were either escalated to semaglutide 2·0 mg, as two injections of semaglutide 1·0 mg, or remained on semaglutide 1·0 mg and received placebo (see appendix p 6 for details on dose escalation). In the case of tolerability concerns in which the participant would otherwise discontinue treatment, at the investigator's discretion, participants could revert to the previously tolerated lower dose before attempting re-escalation. To mitigate hypoglycaemia risk, at randomisation the sulfonylurea dose could be reduced by approximately 50%, at the investigator's discretion; otherwise, background medications were to be kept stable throughout the trial, except for safety reasons or if rescue medication was required. Glycaemic rescue medication could be implemented from week 16 onwards in the case of persistent hyperglycaemia (appendix p 2) and there could be, at the investigators' discretion, intensification of a background therapy or initiation of a new anti-hyperglycaemic drug other than a GLP-1 receptor agonist, dipeptidyl peptidase-4 inhibitor, or amylin analogue.

Outcomes

The primary outcome was change from baseline at week 40 in HbA_{1c} (percentage points). The secondary confirmatory outcome was change from baseline at week 40 in bodyweight (kg). Key secondary efficacy outcomes were: change from baseline at week 40 in fasting plasma glucose (mmol/L), BMI (kg/m²), and waist circumference (cm); whether a participant reached HbA_{1c} less than 7·0% or 6·5% or lower or a loss of baseline bodyweight of 5% or more or 10% or more at week 40 (yes or no). Analyses specified post hoc were relative weight loss (%); whether a participant reached the following composite outcomes (yes or no): HbA_{1c} less than 7·0% with bodyweight reduction from baseline of 5% or greater; and HbA_{1c} less than 7·0% with bodyweight reduction from baseline of 5% or greater without level 2 or 3 hypoglycaemia at week 40. Subgroup analyses of change from baseline at week 40 in HbA_{1c} (percentage points) or bodyweight (kg) according to background oral anti-hyperglycaemic drug use at baseline (metformin alone or metformin and sulfonylurea) were also defined and performed post hoc.

Safety outcomes included the number and severity of treatment-emergent adverse events. All adverse events were coded using the Medical Dictionary for Regulatory Activities (version 23.0). Key supportive secondary safety outcomes included change in pulse rate (beats per minute [bpm]) from baseline at week 40.[16] Hypoglycaemia defined according to the American Diabetes Association classification (ie, level 1, 2, or 3) was analysed post hoc.[16] The incidence of hypoglycaemia according to baseline sulfonylurea use was also evaluated post hoc. Blood pressure was not a protocol-defined outcome but was assessed and is presented for completeness.

964 participants randomly assigned were required to provide a power of 87% to detect a treatment difference of –0·22 percentage points anticipating an SD of 1·1 percentage point, at a significance level of 0·05 (appendix p 2).

Data were collected in an electronic data capture system (Inform, Oracle America, Redwood City, CA, USA). Relevant data from participant diaries were transcribed to the electronic case report form by site personnel. Data

quality checks were done with electronic and manual verification methods.

Statistical analysis

Two analysis populations were defined (appendix p 2): the full analysis population included all randomly assigned participants (used for efficacy outcome analyses) and the safety analysis population included all participants exposed to one or more doses of trial product (used for safety outcome analyses). The full analysis population was analysed according to the treatment to which participants were randomly assigned and the safety analysis population according to the trial product that participants had received for the majority of the time they were on treatment. Observation periods included the in-trial period (the time from random assignment to last contact with a trial site, regardless of treatment discontinuation or initiation of rescue medication), the on-treatment period, and the on-treatment without rescue medication period (the time during which participants received treatment and had not initiated rescue medication).

Two complementary estimand strategies were defined to evaluate treatment effect from different scientific perspectives and, thus, provide a more complete assessment of the effect; this approach is consistent with the updated regulatory guidelines of the International Council for Harmonisation.[21,22] The trial product estimand strategy evaluated treatment effect in all randomly assigned participants based on data collected up to and including week 40 from the on-treatment without rescue medication observation period, regardless of change in treatment dose (corresponding to the hypothetical estimand). The trial product estimand was considered the primary estimand except in the USA, to accommodate the US Food and Drug Administration (FDA) preference for a treatment policy estimand strategy. The treatment policy estimand strategy evaluated treatment effect in all randomly assigned participants based on data collected up to and including week 40 from the in-trial observation period, regardless of treatment discontinuation or initiation of rescue medication or change in treatment dose, which is consistent with an intention-to-treat analysis. Multiplicity was controlled separately for the two estimand strategies. To preserve an overall 5% significance level within each estimand, the conclusion of superiority of semaglutide 2·0 mg versus semaglutide 1·0 mg on glycaemic control and weight management was evaluated hierarchically (appendix p 6). The primary and secondary confirmatory outcomes were evaluated using both estimand strategies, and the

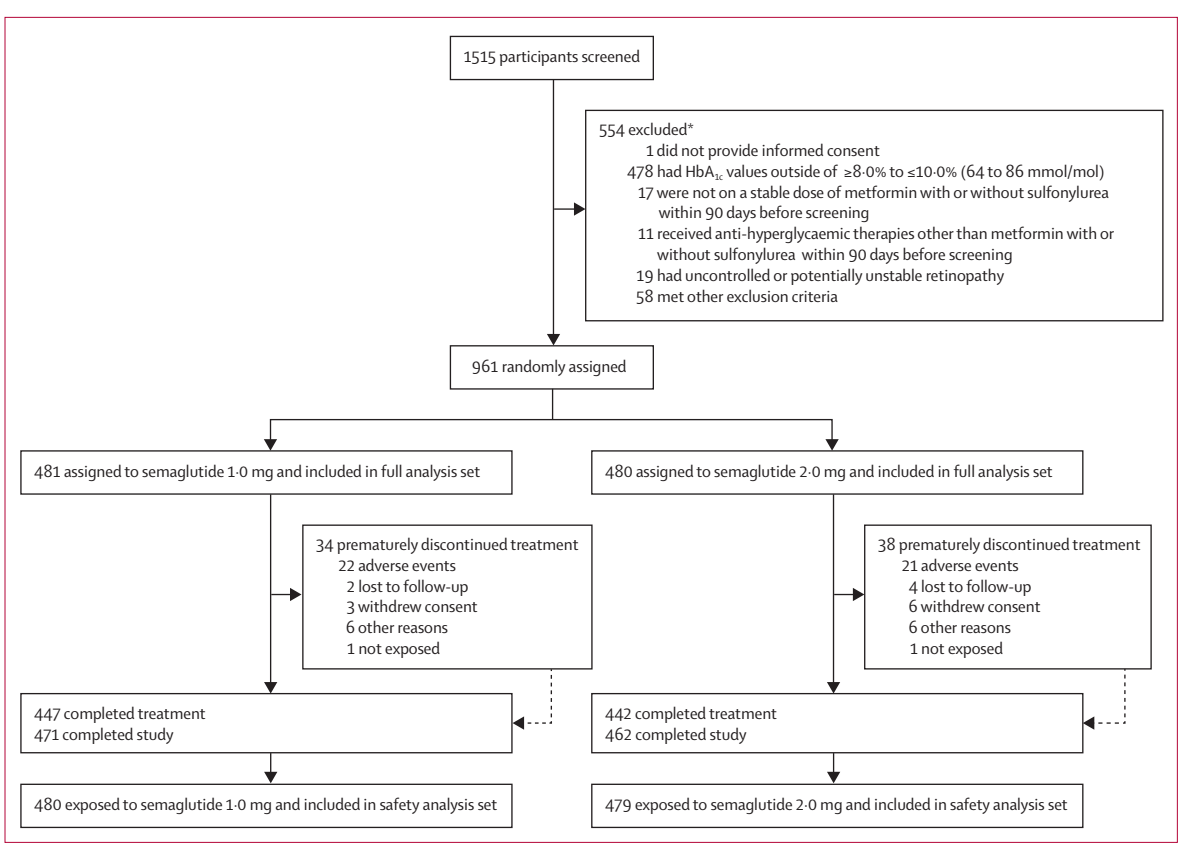

Figure 1: **Trial profile**
*Participants could contribute to more than one exclusion criteria.

trial product estimand strategy was prespecified for all supportive secondary outcomes. The statistical testing strategy was done for the primary analysis of each of the two estimands separately. The trial product estimand is reported first throughout this manuscript as it corresponds to the analysis reported for previous SUSTAIN clinical trials.

Continuous endpoints (including the primary and secondary confirmatory endpoints) were analysed by ANCOVA, with randomised treatment and stratification (Japan or not Japan) as factors and baseline value of response as a covariate. The results were described by the estimated treatment difference (ETD) with associated two-sided 95% CIs and p values corresponding to two-sided tests of no difference. Missing data were handled by multiple imputation, assuming that such data were missing at random (appendix p 3). Tipping point analyses were done to test the sensitivity of the superiority claims to assumptions about missing data (appendix p 3). Dichotomous secondary outcomes were analysed using logistic regression with treatment and stratification (Japan or not Japan) as fixed factors and baseline underlying continuous variable as covariate. The results were described by the odds ratio between treatments and the associated 95% CI and p value for no treatment difference. Dichotomous endpoints were derived on the basis of the observed and imputed data for the underlying continuous variable.

Safety outcomes were summarised descriptively, based on the safety analysis population, with use of data from the on-treatment observation period (including events occurring up to 49 days after the last day on trial drug to account for the half-life of semaglutide). Safety focus areas included cardiovascular events, benign and malignant neoplasms, and diabetic retinopathy (appendix p 4), and these were reported with data from the in-trial observation period due to the long latency of these events. The analysis of change in pulse rate from baseline at week 40 was based on the safety analysis population with use of data from the on-treatment observation period; missing data were imputed by multiple imputation and assumed data were missing at random. Summaries of treatment-emergent level 1, 2, or 3 hypoglycaemic episodes were presented descriptively. There was no data monitoring committee for the SUSTAIN FORTE trial. Analyses were done using SAS, version 9.4M5. This study is registered with ClinicalTrials.gov, NCT03989232; EudraCT, 2018-004529-96; and WHO, U1111-1224-5162.

Role of the funding source

The funder of the study conceived and designed the trial, and was responsible for site monitoring, data collection from investigators, and data analysis. The authors interpreted the data and wrote the report with editorial support from an independent medical writer supported by the funder.

Results

Between June 19 and Nov 28, 2019, of 1515 adults assessed for eligibility, 961 participants were included. The last patient last visit was on Nov 9, 2020. The outbreak of the COVID-19 pandemic did not substantially affect the conduct of the trial and is not considered to have affected results (appendix p 4).

	Semaglutide 1·0 mg (n=481)	Semaglutide 2·0 mg (n=480)	Overall (n=961)
Age, years	58·2 (9·9)	57·9 (10·0)	58·0 (10·0)
Gender			
Women	197 (41%)	201 (42%)	398 (41%)
Men	284 (59%)	279 (58%)	563 (59%)
Race			
American Indian or Alaska native	1 (<1%)	0	1 (<1%)
Asian*	36 (7%)	33 (7%)	69 (7%)
Black or African American	17 (4%)	26 (5%)	43 (4%)
White	427 (89%)	420 (88%)	847 (88%)
Other	0	1 (<1%)	1 (<1%)
Country			
Bulgaria	50 (10%)	46 (10%)	96 (10%)
Canada	11 (2%)	9 (2%)	20 (2%)
Czech Republic	8 (2%)	7 (1%)	15 (2%)
Greece	18 (4%)	19 (4%)	37 (4%)
Hungary	81 (17%)	75 (16%)	156 (16%)
Japan	25 (5%)	25 (5%)	50 (5%)
Poland	68 (14%)	68 (14%)	136 (14%)
Slovakia	40 (8%)	52 (11%)	92 (10%)
Ukraine	20 (4%)	30 (6%)	50 (5%)
USA	160 (33%)	149 (31%)	309 (32%)
Diabetes duration, years			
Mean	9·8 (6·2)	9·2 (6·2)	9·5 (6·2)
Median (IQR)	9·6 (4·9–13·4)	7·9 (4·7–12·1)	8·7 (4·8–12·8)
HbA_{1c}, %	8·8 (0·6)	8·9 (0·6)	8·9 (0·6)
HbA_{1c}, mmol/mol	73·1 (6·9)	73·4 (6·9)	73·3 (6·9)
Fasting plasma glucose, mmol/L	10·9 (2·7)	10·7 (2·8)	10·8 (2·8)
Bodyweight, kg	98·6 (24·4)	100·1 (22·6)	99·3 (23·5)
BMI, kg/m²	34·4 (7·2)	34·8 (6·8)	34·6 (7·0)
Waist circumference, cm	112·2 (16·4)	113·4 (16·4)	112·8 (16·4)
Estimated glomerular filtration rate, mL/min per 1·73 m²	93·0 (17·5)	93·9 (16·4)	93·4 (16·9)
≥90 mL/min per 1·73 m²	309 (64%)	316 (66%)	625 (65%)
60 to <90 mL/min per 1·73 m²	147 (31%)	150 (31%)	297 (31%)
30 to <60 mL/min per 1.73 m²	25 (5%)	14 (3%)	39 (4%)
Systolic blood pressure, mm Hg	134 (14)	134 (14)	134 (14)
Diastolic blood pressure, mm Hg	80 (10)	81 (9)	81 (9)
Pulse rate, beats per minute	75·4	76·4	75·9
Diabetic retinopathy	37 (8%)	50 (10%)	87 (9%)
Anti-diabetes medication at randomisation			
Metformin	481 (100%)	480 (100%)	961 (100%)
Sulfonylurea	259 (54%)	253 (53%)	512 (53%)

Data are mean (SD) or n (%) unless otherwise indicated. *Further breakdown of the Asian subgroup is not available.

Table 1: **Baseline characteristics**

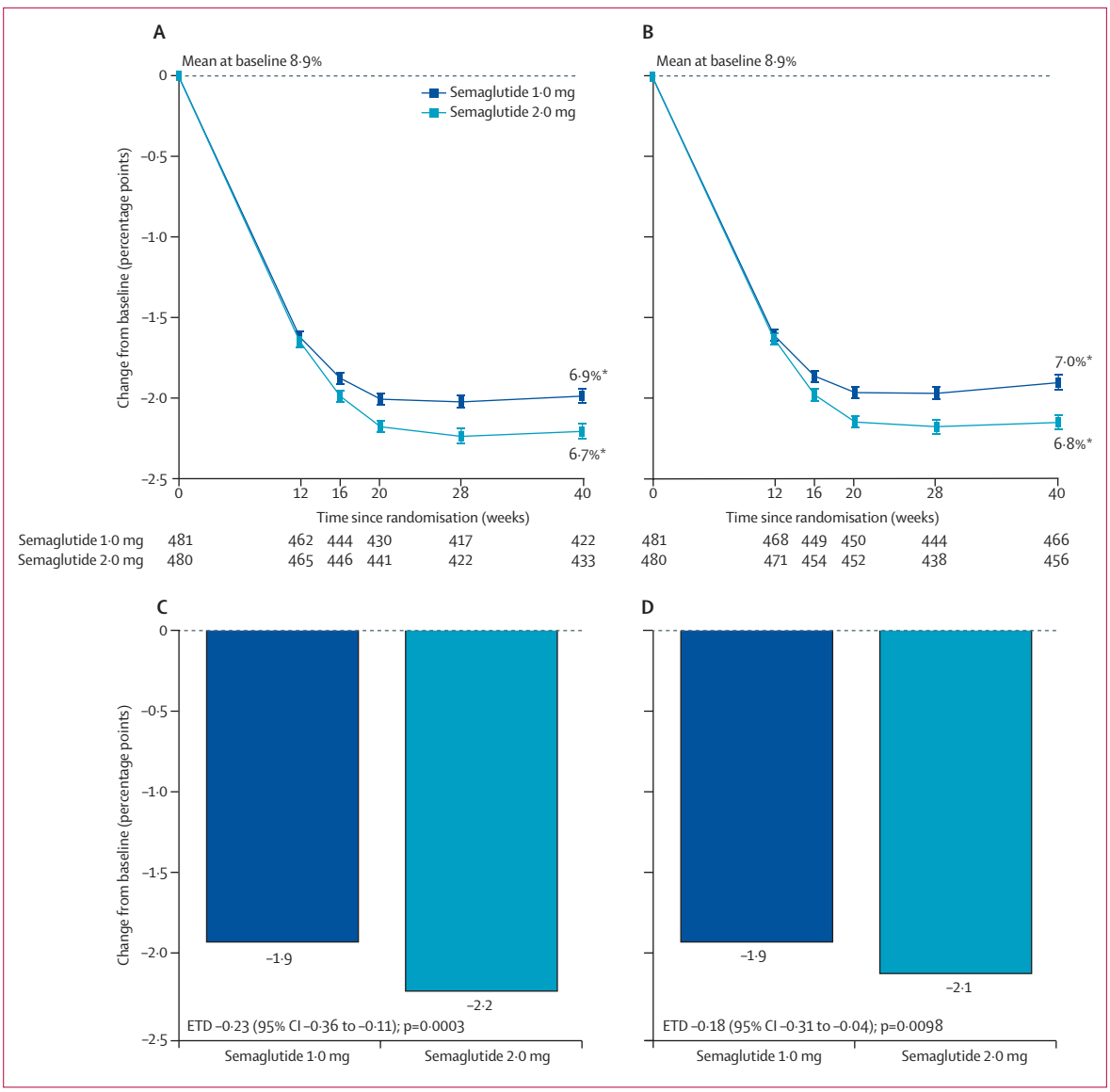

Figure 2: **HbA_{1c} outcomes with once-weekly semaglutide 2·0 mg versus 1·0 mg during 40 weeks of treatment**
Observed mean change from baseline in HbA_{1c} over time in (A) the trial product estimand and (B) treatment policy estimand. Estimated mean change in HbA_{1c} from baseline at week 40 in (C) the trial product estimand and (D) treatment policy estimand. Error bars are SEM. Numbers shown below the line graph represent the number of participants contributing to the means. Superiority was confirmed for semaglutide 2·0 versus 1·0 mg with both estimand strategies. ETD=estimated treatment difference. *Data shown are estimated mean HbA_{1c} at end of treatment in the full analysis set.

480 (50%) participants were randomly assigned to semaglutide 2·0 mg and 481 (50%) were randomly assigned to semaglutide 1·0 mg (figure 1). Of participants randomly assigned, 462 (96%) participants in the semaglutide 2·0 mg group and 471 (98%) participants in the semaglutide 1·0 mg group completed the trial, 442 (92%) participants in the semaglutide 2·0 mg group and 447 (93%) participants in the semaglutide 1·0 mg group completed treatment, and 435 (91%) participants in the semaglutide 2·0 mg group and 428 (89%) participants in the semaglutide 1·0 mg group completed treatment without rescue medication. The safety analysis population included 479 participants in the semaglutide 2·0 mg group and 480 participants in the semaglutide 1·0 mg group. At any specific trial visit, in each treatment group, more than 95% of participants were receiving semaglutide at the planned target dose (appendix p 7).

Table 1 shows baseline characteristics, including use of anti-hyperglycaemic medication. Semaglutide 2·0 mg was superior to 1·0 mg in reducing HbA_{1c} when assessed using either the trial product or the treatment policy estimand. Mean changes from baseline at week 40 in HbA_{1c} were –2·2 percentage points for semaglutide 2·0 mg and –1·9 percentage points for semaglutide 1·0 mg when

assessed using the trial product estimand (ETD –0·23 percentage points [95% CI –0·36 to –0·11]; p=0·0003; figure 2A, C). When assessed using the treatment policy estimand, mean changes from baseline at week 40 in HbA_{1c} were –2·1 percentage points for semaglutide 2·0 mg and –1·9 percentage points for semaglutide 1·0 mg (ETD –0·18 percentage points [95% CI –0·31 to –0·04]; p=0·0098; figure 2B, D). The results of these analyses were supported by the tipping-point sensitivity analyses (appendix p 12). The greater effect on HbA_{1c} with semaglutide 2·0 mg than with semaglutide 1·0 mg was observed in participants with or without use of sulfonylurea at baseline, with no significant interaction between treatment effect and baseline sulfonylurea use (appendix p 13). At week 40, a greater proportion of participants receiving semaglutide 2·0 mg than those receiving 1·0 mg reached HbA_{1c} less than 7·0% (p=0·0010) and 6·5% or lower (p<0·0001) (table 2). Once-weekly semaglutide 2·0 mg and 1·0 mg each reduced mean fasting plasma glucose from baseline, with a significantly greater reduction with semaglutide 2·0 mg than 1·0 mg (trial product estimand; ETD –0·33 mmol/L [95% CI –0·61 to –0·04]; p=0·026; table 2). Eight (2%) participants receiving semaglutide 2·0 mg and 20 (4%) participants receiving semaglutide 1·0 mg initiated rescue medication.

Semaglutide 2·0 mg was superior to 1·0 mg in reducing bodyweight when assessed using the trial product estimand; mean changes from baseline at week 40 in bodyweight were –6·9 kg for semaglutide 2·0 mg and –6·0 kg for semaglutide 1·0 mg (ETD –0·93 kg [95% CI –1·68 to –0·18; p=0·015; figure 3A, C). These results were also supported by a tipping-point sensitivity analysis (appendix p 12). When assessed using the treatment policy estimand, superiority of semaglutide 2·0 mg could not be confirmed; mean changes from baseline at week 40 in bodyweight were –6·4 kg for semaglutide 2·0 mg and –5·6 kg for semaglutide 1·0 mg (ETD –0·77 kg [95% CI –1·55 to 0·01]; p=0·054; figure 3B, D). The relative weight loss from baseline at week 40 was 7·2% with semaglutide 2·0 mg and 6·2% with 1·0 mg with the trial product estimand (ETD –0·98% [95% CI –1·75 to –0·20]; p=0·013). The greater effect on bodyweight with semaglutide 2·0 mg compared with semaglutide 1·0 mg was observed in participants with or without sulfonylurea use at baseline, with no significant interaction between treatment effect and baseline sulfonylurea use (appendix p 13). Across both semaglutide treatment groups, participants receiving a sulfonylurea had numerically smaller reductions in bodyweight than those not receiving one. At week 40, a greater proportion of participants receiving semaglutide 2·0 mg than those receiving 1·0 mg had weight loss of 5% or more (p=0·012 for odds ratio of reaching target) and 10% or more from baseline (p=0·031 for odds ratio of reaching target; table 2). Once-weekly semaglutide 2·0 mg and 1·0 mg reduced mean BMI from baseline, with a significantly greater reduction shown with semaglutide 2·0 mg than 1·0 mg (p=0·026; table 2). Waist circumference was reduced from baseline with either semaglutide 2·0 mg or 1·0 mg, with no difference in effect between the treatment groups (p=0·18; table 2).

A greater proportion of participants receiving semaglutide 2·0 mg than those receiving 1·0 mg reached the post-hoc composite outcomes of HbA_{1c} less than 7·0% with weight loss of 5% or greater or HbA_{1c} less than 7·0% with weight loss of 5% or greater without level 2 or 3 hypoglycaemia (appendix p 13).

Mean changes in blood pressure observed from baseline at week 40 were –5·3 mm Hg (SD 14·9) systolic and –0·8 mm Hg (8·9) diastolic with semaglutide 2·0 mg and –4·5 mm Hg (14·0) systolic and –0·4 mm Hg (9·0) diastolic with semaglutide 1·0 mg.

272 (57%) participants in the semaglutide 2·0 mg group and 251 (52%) in the semaglutide 1·0 mg group had at least one treatment-emergent adverse event (table 3). Most events were mild-to-moderate in severity. Serious adverse events were similar between treatment groups, with 21 (4%) in participants given semaglutide 2·0 mg and 25 (5%) in participants given semaglutide 1·0 mg. There was no clustering of serious adverse events in any of the system organ classes (appendix p 14). Three deaths occurred during the conduct of the trial, two participants died in the semaglutide 2·0 mg group (cause of death head injury or unknown) and one in the semaglutide 1·0 mg group (cause of death neuromyelitis optica spectrum disorder; appendix p 4). The fatal events in the semaglutide 2·0 mg group were judged as unlikely to be related to the study product by the investigator and sponsor, whereas the death in the participant given semaglutide 1·0 mg was judged as possibly related to the study product by the investigator and unlikely to be related to the study product by the sponsor.

The most common adverse events were gastrointestinal (including nausea, diarrhoea, and vomiting), reported in 163 (34%) participants given semaglutide 2·0 mg and

	Semaglutide 1·0 mg (n=481)	Semaglutide 2·0 mg (n=480)	Estimated treatment difference or OR (95% CI)	p value
Estimated mean change from baseline at week 40				
Fasting plasma glucose, mmol/L	–3·1	–3·4	–0·33 (–0·61 to –0·04)*	p=0·026
BMI, kg/m²	–2·1	–2·4	–0·30 (–0·57 to –0·04)*	p=0·026
Waist circumference, cm	–5·2	–5·8	–0·54 (–1·34 to 0·26)*	p=0·18
Participants reaching outcome at week 40				
HbA_{1c} <7·0%†	57·5	67·6	OR 1·60 (1·21 to 2·13)‡	p=0·0010
HbA_{1c} ≤6·5%§	38·5	51·7	OR 1·80 (1·36 to 2·36)‡	p<0·0001
Weight loss ≥5%	51·3	59·2	OR 1·41 (1·08 to 1·84)‡	p=0·012
Weight loss ≥10%	22·6	28·4	OR 1·40 (1·03 to 1·90)‡	p=0·031

Analyses include both observed and imputed data. ETD=estimated treatment difference. OR=odds ratio. *Once-weekly semaglutide 2·0 mg minus once-weekly semaglutide 1·0 mg. †American Diabetes Association target. ‡Estimated odds ratio of reaching outcome at week 40 with semaglutide 2·0 mg compared with semaglutide 1·0 mg. §American Association of Clinical Endocrinologists target.

Table 2: **Supportive secondary outcomes, trial product estimand**

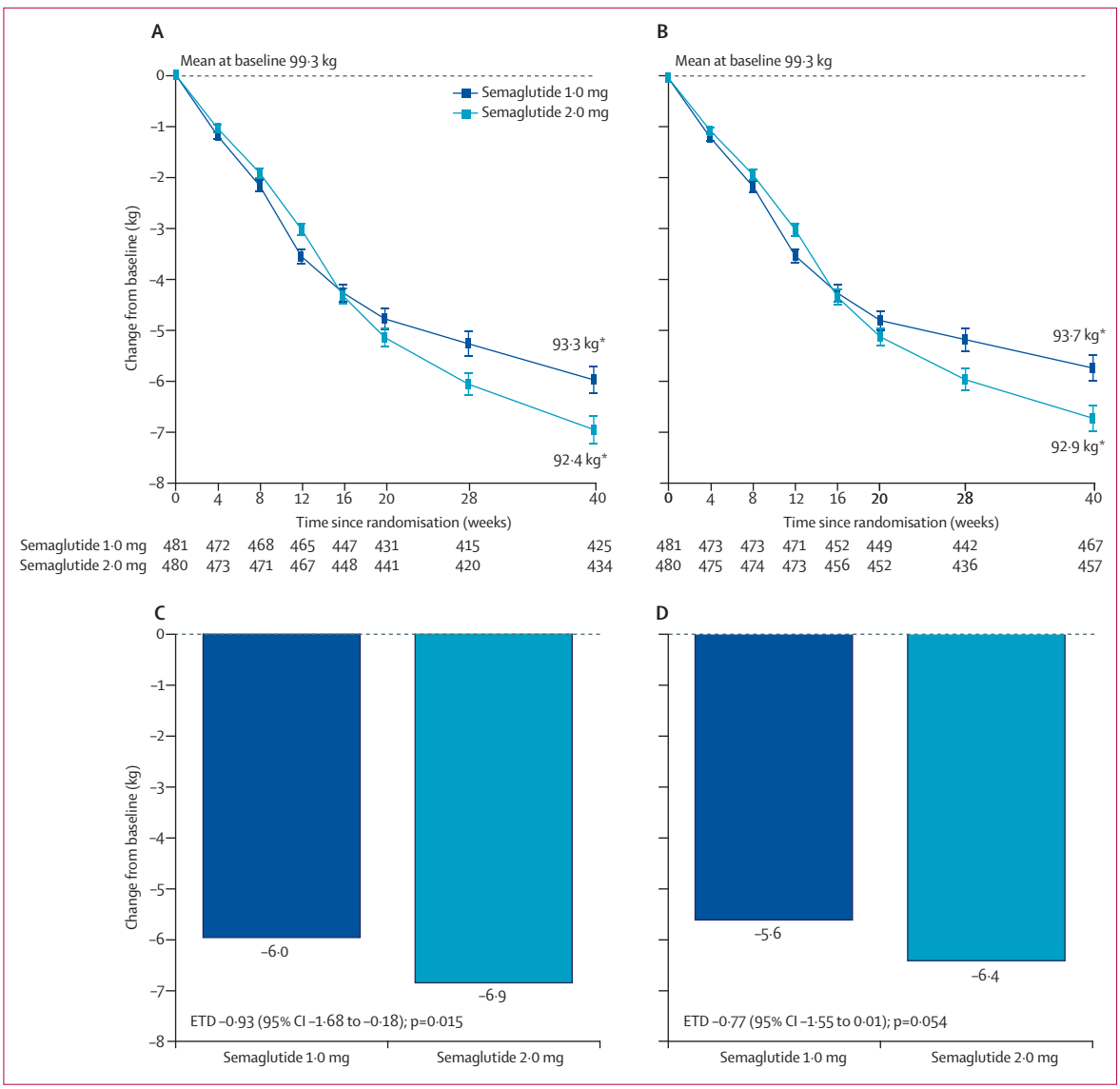

Figure 3: **Bodyweight outcomes with once-weekly semaglutide 2·0 mg versus 1·0 mg during 40 weeks of treatment**
Observed mean change in bodyweight over time in the (A) trial product estimand and (B) treatment policy estimand. Estimated mean change in bodyweight from baseline at week 40 in the (C) trial product estimand and (D) treatment policy estimand. Error bars are SEM. Numbers shown below the line graph represent the number of participants contributing to the means. Superiority was confirmed for semaglutide 2·0 versus 1·0 mg with the trial product estimand strategy only. ETD=estimated treatment difference. *Data shown are estimated mean bodyweight at end of treatment in the full analysis set.

148 (31%) participants given semaglutide 1·0 mg (table 3). Most adverse events were mild-to-moderate and the incidence was highest during the dose-escalation period (appendix p 8).

Premature treatment discontinuation due to adverse events was low and similar in both treatment groups; 21 (4%) participants in the semaglutide 2·0 mg group and 22 (5%) in the semaglutide 1·0 mg group (appendix p 15). Gastrointestinal adverse events were the most common reasons for premature trial drug discontinuation, reported in 16 (3%) participants in the semaglutide 2·0 mg group and 13 (3%) in the semaglutide 1·0 mg group.

The mean change in pulse rate from baseline at week 40 was similar with semaglutide 2·0 mg and semaglutide 1·0 mg (3·6 bpm *vs* 2·6 bpm; p=0·055; appendix p 9). The proportions of participants reporting level 1, 2, and 3 hypoglycaemic events were similar with semaglutide 2·0 mg and 1·0 mg (table 3). All but three of the 30 participants who reported level 2 episodes were concomitantly receiving a sulfonylurea (appendix p 15). Three episodes of severe (level 3) hypoglycaemia were reported: two in the semaglutide 2·0 mg treatment group, with one occurring in combination with a sulfonylurea, and a second after premature treatment

discontinuation during the 7-week safety follow-up while receiving treatment with a sulfonylurea; one in the semaglutide 1·0 mg treatment group occurred after premature treatment discontinuation during the 7-week safety follow-up while receiving treatment with insulin.

A full overview of adverse events relating to safety focus areas, including diabetic retinopathy, is shown in the appendix (p 16). No adverse events related to pancreatitis were reported (appendix p 16).

Discussion

In this 40-week, randomised, double-blind, active-comparator clinical trial, participants with inadequately controlled type 2 diabetes on a stable dose of metformin alone or in combination with a sulfonylurea showed superior glycaemic control when given semaglutide 2·0 mg than 1·0 mg, with greater proportions of participants assigned to semaglutide 2·0 mg reaching HbA_{1c} targets of less than 7·0% and 6·5% or lower. The improvements in glycaemic control were met together with clinically meaningful reductions in bodyweight and waist circumference, and a similar safety profile was observed for the two treatment groups.

Two estimand strategies (trial product and treatment policy) were used to assess efficacy endpoints.[21,22] The two estimand strategies are considered complementary in understanding the treatment effect in different clinical scenarios. The trial product estimand strategy provides an estimate of the mean treatment effect in the overall population assuming participants had not discontinued treatment and had not initiated rescue medications; it reflects what might be observed in clinical practice for an individual who is adherent to treatment and does not initiate additional anti-diabetic medication. The treatment policy estimand strategy provides an estimate of the mean treatment effect in the overall population irrespective of treatment discontinuation or use of rescue medication, indicating the mean treatment effect at a population level. The trial product estimand was considered the primary estimand except in the USA, to accommodate the FDA preference for a treatment policy estimand strategy.

Superior HbA_{1c} reductions with semaglutide 2·0 mg compared with semaglutide 1·0 mg were shown across the estimands and were supported by sensitivity analyses. Although 67–79% of participants reached HbA_{1c} less than 7·0% with semaglutide 1·0 mg in the SUSTAIN programme,[5–9,11–14] a subgroup analysis of the SUSTAIN 1–5 trials has shown that a smaller proportion of participants with higher baseline HbA_{1c} reached this treatment target than those with lower baseline HbA_{1c}.[18] It is therefore clinically relevant that in this trial with a mean baseline HbA_{1c} of 8·9%, a larger proportion of participants reached treatment targets of HbA_{1c} less than 7·0% and 6·5% or lower with semaglutide 2·0 mg than 1·0 mg, with significantly greater odds of reaching these important targets. Additionally, the reduction in fasting plasma glucose was significantly greater with the 2·0 mg than the 1·0 mg dose and, although there was low use of rescue medication in both treatment groups, fewer participants required use of rescue medication among those receiving semaglutide 2·0 mg than those receiving semaglutide 1·0 mg, underscoring superior glycaemic efficacy of the higher dose.

The magnitude of mean HbA_{1c} reduction of 1·9 percentage points (trial product estimand) with the 1·0 mg dose of semaglutide in SUSTAIN FORTE is consistent with that previously reported in the SUSTAIN clinical trial programme (1·5–1·8 percentage points; on-treatment without rescue medication analysis), with the greater reduction likely to be related to the higher baseline HbA_{1c} concentration in SUSTAIN FORTE (mean baseline HbA_{1c} 8·9% [SUSTAIN FORTE] versus 8·0–8·4% [SUSTAIN 1–5 and 7–10]).[5–14] The greater glycaemic

	Semaglutide 1·0 mg (n=480)			Semaglutide 2·0 mg (n=479)		
	n (%)	Events	Events per 100 patient-years of exposure	n (%)	Events	Events per 100 patient-years of exposure
Treatment-emergent adverse events	251 (52%)	828	201·4	272 (57%)	775	189·1
Severity						
Mild	199 (41%)	575	139·8	215 (45%)	552	134·7
Moderate	111 (23%)	216	52·5	108 (23%)	194	47·3
Severe	26 (5%)	37	9·0	19 (4%)	29	7·1
Serious	25 (5%)	40	9·7	21 (4%)	29	7·1
Deaths*	1 (<1%)	1	0·2	2 (<1%)	2	0·5
Treatment-emergent adverse events leading to premature treatment discontinuation						
Overall	22 (5%)	22	5·4	21 (4%)	21	5·1
Gastrointestinal adverse events	13 (3%)	13	3·2	16 (3%)	16	3·9
Gastrointestinal adverse events						
Overall	148 (31%)	353	85·8	163 (34%)	346	84·4
Mild	121 (25%)	250	60·8	134 (28%)	247	60·3
Moderate	54 (11%)	92	22·4	47 (10%)	79	19·3
Severe	8 (2%)	11	2·7	12 (3%)	20	4·9
Treatment-emergent adverse events in >5% in any treatment group by preferred term						
Nausea	70 (15%)	99	24·1	69 (14%)	98	23·9
Diarrhoea	42 (9%)	83	20·2	45 (9%)	51	12·4
Vomiting	32 (7%)	41	10·0	37 (8%)	55	13·4
Dyspepsia	25 (5%)	26	6·3	16 (3%)	17	1·0
Decreased appetite	18 (4%)	18	4·4	29 (6%)	29	1·0
Hypoglycaemia†						
Level 1	54 (11%)	133	32·3	41 (9%)	82	20·0
Level 2	18 (4%)	24	5·8	12 (3%)	19	4·6
Level 3	1 (<1%)‡	1	0·2	2 (<1%)§	2	0·5

*Causes of death were head injury and unknown in the semaglutide 2·0 mg group, and an event of neuromyelitis optica spectrum disorder in the in the semaglutide 1·0 mg group (appendix p 4). †Definition based on International Hypoglycaemia Study Group.[16] ‡Reported after treatment discontinuation during 7-week follow-up, in combination with insulin. §Both in combination with sulfonylurea; one episode was reported after treatment discontinuation during 7-week follow-up.

Table 3: **Safety outcomes in the safety analysis set**

efficacy of semaglutide 2·0 mg versus 1·0 mg in SUSTAIN FORTE suggests that simple dose escalation would be possible for patients unable to reach treatment targets on the 1·0 mg dose, thus adding to the options available for treatment intensification.

For bodyweight reduction, with the trial product estimand, semaglutide 2·0 mg was superior to semaglutide 1·0 mg, but statistical superiority was not confirmed for the treatment policy estimand (p=0·054). The majority of participants in both treatment groups reached clinically relevant bodyweight loss from baseline of 5% or greater, with a greater proportion of participants seeing 5% or greater and 10% or greater bodyweight loss with semaglutide 2·0 mg versus semaglutide 1·0 mg. However, the treatment difference was less than what might have been expected based on the phase 2 study that evaluated doses of semaglutide exceeding 1·0 mg once weekly.[19] The bodyweight loss in the SUSTAIN FORTE trial should be considered in the context of the trial population, which had a higher baseline HbA_{1c} than in the phase 2 study. In addition, half of the participants were given a sulfonylurea, whereas there was no use of sulfonylurea in the phase 2 study. Such factors might have attenuated the magnitude of the weight loss, as they have previously been identified as affecting weight loss.[23–26] In addition, the weight loss curves with both semaglutide doses appear not to have plateaued at week 40.

Overall adverse event rates were similar with both doses. Consistent with the GLP-1 receptor agonist drug class, the most prevalent adverse events were gastrointestinal in nature in both treatment groups. Overall, there was a slightly higher proportion of participants reporting these types of events with semaglutide 2·0 mg versus 1·0 mg, with similar frequencies of the most commonly reported gastrointestinal events (ie, nausea, diarrhoea, and vomiting). Semaglutide 2·0 mg was well tolerated, with a low (<5%) proportion of participants discontinuing treatment prematurely due to adverse events in both treatment groups. Consistent with the GLP-1 receptor agonist class, there was a low risk of hypoglycaemia with semaglutide.[27] The proportion of participants having hypoglycaemic episodes, and the corresponding event rates, were low and occurred primarily in participants concomitantly given a sulfonylurea in both treatment groups, with no increased rates with the higher versus the lower dose.

Higher doses of the GLP-1 receptor agonist dulaglutide have also been investigated. In the AWARD-11 trial, dulaglutide 3·0 and 4·5 mg were compared with dulaglutide 1·5 mg in participants with type 2 diabetes inadequately controlled with metformin. At week 36, using the efficacy estimand (corresponding to the trial product estimand), HbA_{1c} was reduced from baseline (mean 8·6%) by 1·53, 1·71, and 1·87 percentage points with dulaglutide 1·5 mg, 3·0 mg, and 4·5 mg, respectively.[28] In the efficacy estimand, the ETD for dulaglutide was –0·17 percentage points (95% CI –0·29 to –0·06) for 1·5 mg versus 3·0 mg and –0·34 percentage points (–0·45 to –0·22) for 1·5 mg versus 4·5 mg. The bodyweight reduction at week 36 in the efficacy estimand was –3·1 kg with dulaglutide 1·5 mg, –4·0 kg with dulaglutide 3·0 mg, and –4·7 kg with dulaglutide 4·5 mg; the ETD for dulaglutide was –0·9 kg (95% CI –1·4 to –0·4) for 1·5 mg versus 3·0 mg and –1·6 kg (–2·1 to –0·9) for 1·5 mg versus 4·5 mg.[28] The results of the SUSTAIN FORTE trial were consistent with those of the AWARD-11 trial showing incremental benefits in HbA_{1c} and bodyweight reductions, with no safety concerns identified with the higher doses.

A strength of SUSTAIN FORTE was the use of an active comparator, with once-weekly semaglutide 2·0 mg showing superior glycaemic control versus the maximum currently available dose of 1·0 mg, which has proven superior glycaemic efficacy versus a range of anti-hyperglycaemic drugs in people with type 2 diabetes.[5–14] High trial and treatment completion rates at target dose support the robustness of the analyses. Similarity of the primary and secondary confirmatory outcomes with the two estimand strategies was observed, due to the low rate of treatment discontinuation due to adverse events and low use of rescue medication observed in both treatment groups in the trial.

The trial had some limitations. Although its 40-week duration enabled the assessment of the glycaemic effects of semaglutide 2·0 mg, as mean HbA_{1c} reductions plateaued around 20 weeks, the maximum effect on bodyweight reduction might not have been explored. In addition, the trial design was not reflective of how semaglutide 2·0 mg might be anticipated to be used in clinical practice, in which only those patients in need of further treatment intensification would escalate to the 2·0 mg dose of semaglutide from the 1·0 mg dose.

In conclusion, semaglutide 2·0 mg versus 1·0 mg in the SUSTAIN FORTE trial provided superior glycaemic control, with more participants reaching glycaemic treatment targets, together with clinically meaningful reductions in bodyweight for both doses and a similar safety profile. Semaglutide 2·0 mg offers a valuable treatment option for individuals with type 2 diabetes, in addition to already available 0·5 mg and 1·0 mg doses, and could be beneficial for those in need of treatment intensification while remaining on the existing therapy.

Contributors

JPF, HSB, YF, IL, NT, TIT, and JBB contributed to trial conduct and data collection as trial investigators. SM contributed to trial design as an employee of the sponsor. ALS, SM, and PA contributed to data analysis as employees of the sponsor. ALS and SM verified the data. All authors contributed to data interpretation and writing the manuscript (reviewing and editing) and approved the final version for publication. The authors had full access to all the data in the study and were responsible for the decision to submit for publication.

Declarations of interest

JPF reports grants and personal fees from Novo Nordisk; grants from AstraZeneca, BMS, Janssen, Novartis, Oramed, and Pfizer; and grants and personal fees from Boehringer Ingelheim, Eli Lilly, Merck KGaA,

and Sanofi. HSB reports trial fees paid to his institution by Novo Nordisk; speaking honoraria from Eli Lilly and Novo Nordisk; and trial fees paid to his institution by Amgen, AstraZeneca, Boehringer Ingelheim, Ceapro, Eli Lilly, Gilead, Janssen, Kowa Pharmaceuticals, Madrigal Pharmaceuticals, Merck KGaA, Novo Nordisk, Pfizer, Sanofi, and Tricida. IL reports grants, personal fees, and non-financial support from Novo Nordisk; grants, personal fees, and non-financial support from Novo Nordisk and Sanofi; personal fees and non-financial support from Eli Lilly, Sanofi, AstraZeneca, Boehringer Ingelheim, and Janssen; personal fees from Intercept, Intarcia, TARGETPharma, Mannkind, Valeritas, Bayer, and Zealand Pharma, grants; and non-financial support from Merck and Pfizer, and grants from Mylan. TIT reports lecture fees and advisory board membership for Boehringer Ingelheim, AstraZeneca, Novo Nordisk, Sanofi, Eli Lilly, Novartis, and MSD. NT reports consultation fees from MSD, clinical trial fees from AstraZeneca, Eli Lilly, Boehringer Ingelheim, Sanofi, and Novo Nordisk, and unrestricted grants from Eli Lilly, Boehringer Ingelheim, ELPEN, and TrigoCare. ALS, PA, and SM are full-time employees of Novo Nordisk and own shares in the company. JBB reports a grant and non-financial support from Novo Nordisk; contracted consulting fees and travel support paid to the University of North Carolina (contract between University of North Carolina and the companies) from Adocia, AstraZeneca, Eli Lilly, Fractyl, Intarcia Therapeutics, Lexicon, MannKind, Metavention, Novo Nordisk, Sanofi, Senseonics, vTv Therapeutics, and Zafgen; research contracts, largely for clinical trials, and travel support paid to the University of North Carolina (contract between University of North Carolina and the companies) from AstraZeneca, Eli Lilly, Intarcia Therapeutics, Johnson & Johnson, Lexicon, NovaTarg, Novo Nordisk, Sanofi, Theracos, Tolerion, and vTv Therapeutics; consulting fees from Cirius Therapeutics, Fortress Biotech, Moderna, Pendulum Therapeutics, and Zealand Pharma; stock or options in lieu of payments for consulting and travel support for consulting activities from Mellitus Health, Pendulum Therapeutics, PhaseBio, Praetego, and Stability Health; and grants and non-financial support from the National Institutes of Health, Juvenile Diabetes Research Foundation International, Patient Centered Outcomes Research Institute, and the American Diabetes Association. YF declares no competing interests. The authors have not been paid or received compensation for their authorship.

Data sharing

Individual participant data will be shared in datasets in a de-identified format, including datasets from Novo Nordisk-sponsored clinical research completed after 2001 for product indications approved in both the EU and USA. The trial protocol and redacted clinical trial report will be available according to Novo Nordisk data sharing commitments. Data will be available permanently after research completion and approval of product and product use in the EU and 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.

Acknowledgments

We thank all the participants, investigators, and trial site staff members who were involved in the conduct of the trial and Alexander Jones, AXON Communications, for medical writing and editorial assistance (funded by Novo Nordisk).

References

1 Sheahan KH, Wahlberg EA, Gilbert MP. An overview of GLP-1 agonists and recent cardiovascular outcomes trials. *Postgrad Med J* 2020; **96:** 156–61.

2 American Diabetes Association. 9. Pharmacologic approaches to glycemic treatment: standards of medical care in diabetes—2021. *Diabetes Care* 2021; **44** (suppl 1)**:** S111–24.

3 Novo Nordisk. Ozempic semaglutide injection 0.5 mg / 1.0 mg. 2020. https://www.novo-pi.com/ozempic.pdf (accessed March 3, 2021).

4 European Medicines Agency. Ozempic. 2021. https://www.ema.europa.eu/en/medicines/human/EPAR/ozempic (accessed March 17, 2021).

5 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.

6 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.

7 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.

8 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.

9 Rodbard HW, Lingvay I, Reed J, et al. Semaglutide added to basal insulin in type 2 diabetes (SUSTAIN 5): a randomized, controlled trial. *J Clin Endocrinol Metab* 2018; **103:** 2291–301.

10 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.

11 Pratley RE, Aroda VR, Lingvay I, et al. Semaglutide versus dulaglutide once weekly in patients with type 2 diabetes (SUSTAIN 7): a randomised, open-label, phase 3b trial. *Lancet Diabetes Endocrinol* 2018; **6:** 275–86.

12 Lingvay I, Catarig AM, Frias JP, et al. Efficacy and safety of once-weekly semaglutide versus daily canagliflozin as add-on to metformin in patients with type 2 diabetes (SUSTAIN 8): a double-blind, phase 3b, randomised controlled trial. *Lancet Diabetes Endocrinol* 2019; **7:** 834–44.

13 Zinman B, Bhosekar V, Busch R, et al. Semaglutide once weekly as add-on to SGLT-2 inhibitor therapy in type 2 diabetes (SUSTAIN 9): a randomised, placebo-controlled trial. *Lancet Diabetes Endocrinol* 2019; **7:** 356–67.

14 Capehorn MS, Catarig AM, Furberg JK, et al. Efficacy and safety of once-weekly semaglutide 1.0mg vs once-daily liraglutide 1.2 mg as add-on to 1-3 oral antidiabetic drugs in subjects with type 2 diabetes (SUSTAIN 10). *Diabetes Metab* 2020; **46:** 100–09.

15 Hussein H, Zaccardi F, Khunti K, et al. Efficacy and tolerability of sodium-glucose co-transporter-2 inhibitors and glucagon-like peptide-1 receptor agonists: a systematic review and network meta-analysis. *Diabetes Obes Metab* 2020; **22:** 1035–46.

16 American Diabetes Association. 6. Glycemic targets: standards of medical care in diabetes—2021. *Diabetes Care* 2021; **44** (suppl 1)**:** S73–84.

17 Davies MJ, D'Alessio DA, Fradkin J, et al. Management of hyperglycemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care* 2018; **41:** 2669–701.

18 Bain SC, Araki E, Desouza C, et al. Semaglutide reduces HbA_{1c} across baseline HbA_{1c} subgroups across SUSTAIN 1–5 clinical trials. 77th Scientific Sessions of the American Diabetes Association. June 9–13, 2017. San Diego, CA, USA; 2017 (poster 1123-P).

19 Lingvay I, Desouza CV, Lalic KS, et al. A 26-week randomized controlled trial of semaglutide once daily versus liraglutide and placebo in patients with type 2 diabetes suboptimally controlled on diet and exercise with or without metformin. *Diabetes Care* 2018; **41:** 1926–37.

20 Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med* 2009; **150:** 604–12.

21 Aroda VR, Saugstrup T, Buse JB, Donsmark M, Zacho J, Davies MJ. Incorporating and interpreting regulatory guidance on estimands in diabetes clinical trials: the PIONEER 1 randomized clinical trial as an example. *Diabetes Obes Metab* 2019; **21:** 2203–10.

22 International Council for Harmonisation (ICH) of Technical Requirements for Pharmaceuticals for Human Use. ICH Harmonised Guideline E9 (R1): Estimands and Sensitivity Analysis in Clinical Trials. 2017. https://www.ema.europa.eu/en/documents/scientific-guideline/ich-e9-r1-addendum-estimands-sensitivity-analysis-clinical-trials-guideline-statistical-principles_en.pdf (accessed March 3, 2021).

23 Qian D, Zhang T, Tan X, et al. Comparison of antidiabetic drugs added to sulfonylurea monotherapy in patients with type 2 diabetes mellitus: a network meta-analysis. *PLoS One* 2018; **13:** e0202563.

24 Dahlqvist S, Ahlén E, Filipsson K, et al. Variables associated with HbA_{1c} and weight reductions when adding liraglutide to multiple daily insulin injections in persons with type 2 diabetes (MDI Liraglutide trial 3). *BMJ Open Diabetes Res Care* 2018; **6:** e000464.

25 Aroda VR, Capehorn MS, Chaykin L, et al. Impact of baseline characteristics and beta-cell function on the efficacy and safety of subcutaneous once-weekly semaglutide: a patient-level, pooled analysis of the SUSTAIN 1-5 trials. *Diabetes Obes Metab* 2020; **22:** 303–14.

26 Pi-Sunyer FX. Weight loss in type 2 diabetic patients. *Diabetes Care* 2005; **28:** 1526–27.

27 Trujillo JM, Nuffer W, Ellis SL. GLP-1 receptor agonists: a review of head-to-head clinical studies. *Ther Adv Endocrinol Metab* 2015; **6:** 19–28.

28 Frias JP, Bonora E, Nevarez Ruiz L, et al. Efficacy and safety of dulaglutide 3.0 mg and 4.5 mg versus dulaglutide 1.5 mg in metformin-treated patients with type 2 diabetes in a randomized controlled trial (AWARD-11). *Diabetes Care* 2021; **44:** 765–73.