# Efficacy and safety of oral semaglutide with flexible dose adjustment versus sitagliptin in type 2 diabetes (PIONEER 7): a multicentre, open-label, randomised, phase 3a trial

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## Summary

**Background** Oral semaglutide is the first oral formulation of a glucagon-like peptide-1 (GLP-1) receptor agonist developed for the treatment of type 2 diabetes. We aimed to compare the efficacy and safety of flexible dose adjustments of oral semaglutide with sitagliptin 100 mg.

**Methods** In this 52-week, multicentre, randomised, open-label, phase 3a trial, we recruited patients with type 2 diabetes from 81 sites in ten countries. Patients were eligible if they were aged 18 years or older (19 years or older in South Korea), had type 2 diabetes (diagnosed ≥90 days before screening), $HbA_{1c}$ of 7·5–9·5% (58–80 mmol/mol), and were inadequately controlled on stable daily doses of one or two oral glucose-lowering drugs (for 90 days or more before screening). Participants were randomly assigned (1:1) by use of an interactive web-response system, stratified by background glucose-lowering medication at screening, to oral semaglutide with flexible dose adjustments to 3, 7, or 14 mg once daily or sitagliptin 100 mg once daily. To approximate treatment individualisation in clinical practice, oral semaglutide dose could be adjusted on the basis of prespecified $HbA_{1c}$ and tolerability criteria. Two efficacy-related estimands were prespecified: treatment policy (regardless of treatment discontinuation or use of rescue medication) and trial product (on treatment and without use of rescue medication) for participants randomly assigned to treatment. The primary endpoint was achievement of $HbA_{1c}$ of less than 7% (53 mmol/mol) at week 52 and the confirmatory secondary efficacy endpoint was change in bodyweight from baseline to week 52. Safety was assessed in all participants who received at least one dose of study drug. This trial is registered with ClinicalTrials.gov, number NCT02849080, and European Clinical Trials Database, EudraCT number 2015-005593-38, and an open-label extension is ongoing.

**Findings** Between Sept 20, 2016, and Feb 7, 2017, of 804 patients assessed for eligibility, 504 were eligible and randomly assigned to oral semaglutide (n=253) or sitagliptin (n=251). Most participants were male (285 [57%] of 504) with a mean age of 57·4 years (SD 9·9). All participants were given at least one dose of their allocated study drug except for one participant in the sitagliptin group. From a mean baseline $HbA_{1c}$ of 8·3% (SD 0·6%; 67 mmol/mol [SD 6·4]), a greater proportion of participants achieved an $HbA_{1c}$ of less than 7% with oral semaglutide than did with sitagliptin (treatment policy estimand: 58% [134 of 230] *vs* 25% [60 of 238]; and trial product estimand: 63% [123 of 196] *vs* 28% [52 of 184]). The odds of achieving an $HbA_{1c}$ of less than 7% was significantly better with oral semaglutide than sitagliptin (treatment policy estimand: odds ratio [OR] 4·40, 95% CI 2·89–6·70, p<0·0001; and trial product estimand: 5·54, 3·54–8·68, p<0·0001). The odds of decreasing mean bodyweight from baseline to week 52 were higher with oral semaglutide than with sitagliptin (estimated mean change in bodyweight, treatment policy estimand: –2·6 kg [SE 0·3] *vs* –0·7 kg [SE 0·2], estimated treatment difference [ETD] –1·9 kg, 95% CI –2·6 to –1·2; p<0·0001; and trial product estimand: –2·9 kg [SE 0·3] *vs* –0·8 kg [SE 0·3], ETD –2·2 kg, –2·9 to –1·5; p<0·0001). Adverse events occurred in 197 (78%) of 253 participants in the oral semaglutide group versus 172 (69%) of 250 in the sitagliptin group, and nausea was the most common adverse event with oral semaglutide (53 [21%]). Two deaths occurred in the sitagliptin group during the trial.

**Interpretation** Oral semaglutide, with flexible dose adjustment, based on efficacy and tolerability, provided superior glycaemic control and weight loss compared with sitagliptin, and with a safety profile consistent with subcutaneous GLP-1 receptor agonists.

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## Introduction

Semaglutide, a human glucagon-like peptide-1 (GLP-1) analogue, is available as a once weekly subcutaneous injection that has been shown to significantly decrease glycated haemoglobin ($HbA_{1c}$) levels and bodyweight in people with type 2 diabetes,[1–6] and decrease the risk of cardiovascular events among those at high cardiovascular risk.[7]

## Research in context

### Evidence before this study

GLP-1 receptor agonists are an established class of drugs that have been shown to have high glucose-lowering efficacy and to induce decreases in bodyweight. Available GLP-1 receptor agonists include dulaglutide, exenatide, liraglutide, lixisenatide, and semaglutide, all of which are only available in subcutaneous formulations. Subcutaneous semaglutide has been extensively studied in comparison with placebo and various active comparators in patients with type 2 diabetes in the phase 3 SUSTAIN trial programme. The SUSTAIN 2 trial has shown improved glycaemic control and decreased bodyweight with subcutaneous semaglutide compared with sitagliptin in type 2 diabetes, when added to metformin or thiazolidinediones, or both. We searched PubMed on Jan 17, 2019, with no date or language restrictions to identify relevant clinical trials using the search term "oral semaglutide". This search revealed only clinical pharmacology studies and a phase 2 dose-finding trial with oral semaglutide, which were used to inform the design of the current phase 3a PIONEER 7 trial.

### Added value of this study

To our knowledge, the PIONEER 7 trial is the first to assess the efficacy and safety of oral semaglutide using a flexible dose-adjustment approach to approximate clinical practice. We found that in patients with type 2 diabetes on one or two glucose-lowering drugs, once-daily oral semaglutide with flexible dose adjustment (guided by glycaemic efficacy and gastrointestinal tolerability) provides superior glycaemic control and decreases in bodyweight compared with the DPP-4 inhibitor, sitagliptin, even though not all patients received or needed the highest dose of oral semaglutide to achieve the target $HbA_{1c}$ of less than 7% (53 mmol/mol). The safety profile of oral semaglutide was consistent with that expected for the GLP-1 receptor agonist class.

### Implications of all the available evidence

This trial is one of the first phase 3 trials to compare an oral GLP-1 receptor agonist with a DPP-4 inhibitor. Additionally, the flexible dose-adjustment approach to the administration of oral semaglutide might be more relevant to clinical practice. Furthermore, our results suggest that oral semaglutide could become a promising new oral treatment option for patients with type 2 diabetes. Further insights into the efficacy of oral semaglutide compared with other glucose-lowering drugs are anticipated from additional studies in the comprehensive PIONEER clinical trial programme.

To expand treatment options for patients, semaglutide has been developed as an oral formulation. To improve its bioavailability after oral administration, semaglutide is co-formulated into a tablet with an absorption enhancer, sodium N-(8-[2-hydroxylbenzoyl] amino) caprylate, which is designed to protect peptides, such as semaglutide, from proteolytic degradation and promote absorption across the gastric mucosa.[8] In the first completed phase 3 trial to investigate oral semaglutide, PIONEER 1,[9,10] monotherapy with once-daily oral semaglutide at doses of 3, 7, and 14 mg provided superior and dose-dependent decreases in $HbA_{1c}$ compared with placebo, and superior decreases in bodyweight at the highest dose, in patients with type 2 diabetes whose glycaemia was insufficiently controlled on diet and exercise. Oral semaglutide 7 mg and 14 mg doses have also shown superior decreases in $HbA_{1c}$ and bodyweight compared with sitagliptin in the PIONEER 3 trial.[11]

The phase 3a trial reported herein, PIONEER 7, sought to assess the efficacy and safety of once-daily oral semaglutide, administered according to an individualised and flexible dose-adjustment approach, compared with a fixed dose of an established once-daily oral drug, the dipeptidyl peptidase-4 (DPP-4) inhibitor sitagliptin. The flexible dose-adjustment approach for oral semaglutide was designed to mimic the individualised approach used in clinical practice, with treatment dose being increased or decreased depending on glycaemic efficacy and gastrointestinal tolerability, rather than the fixed-dose schedule typically used in clinical trials. To further reflect clinical practice and consensus recommendations,[12] the trial enrolled patients who were already receiving one or two oral glucose-lowering drugs.

## Methods

### Study design

This randomised, open-label, active-controlled, multicentre, phase 3a trial was undertaken at 81 sites in Argentina (three sites), Austria (three sites), Belgium (seven sites), Brazil (two sites), Egypt (four sites), Norway (five sites), South Korea (seven sites), Switzerland (eight sites), Turkey (eight sites), and the USA (34 sites).

Two different scientific questions associated with efficacy were addressed through the definition of two estimands: treatment policy and trial product. Both estimands were defined on the basis of interactions with regulatory agencies.

The treatment policy estimand assesses the treatment effect for all randomly assigned participants regardless of treatment discontinuation or use of rescue medication. The treatment policy estimand was the primary estimand for all efficacy endpoints. This estimand reflects the intention-to-treat principle as defined in International Conference on Harmonisation Guidelines for Good Clinical Practice (ICH) E9.[13] The estimand reflects the effect of initiating treatment with oral semaglutide compared with initiating treatment with sitagliptin, both potentially followed by discontinuation of study drug, or addition of or switch to another glucose-lowering medication.

The trial product estimand assesses the treatment effect for all randomly assigned participants under the assumption that all participants remained on treatment (oral semaglutide or sitagliptin) for the entire planned duration of the trial and did not use rescue medication. The trial product estimand was the secondary estimand for all efficacy endpoints. This estimand aims to reflect the effect of oral semaglutide compared with sitagliptin without the confounding effect of rescue medication. The statistical analysis that was applied to estimate this estimand is similar to that applied in many phase 3a diabetes trials. Results from such analyses are currently included in many product labels (eg, US prescribing information, and European Union summary of product characteristics [SmPC]) for glucose-lowering drugs (eg, the SmPC for Ozempic).[14]

Study drug discontinuation and initiation of rescue medication are accounted for by the treatment policy strategy for the treatment policy estimand and by the hypothetical strategy for the trial product estimand as defined in draft ICH E9(R1).[13] Further details on the estimands are in the appendix (pp 2–3).

The trial was undertaken in accordance with ICH Good Clinical Practice, the Declaration of Helsinki, and all applicable regulatory requirements. The trial protocol was approved by the relevant local institutional review boards and independent ethics committees. A redacted protocol is in the appendix (pp 22–164).

See Online for appendix

## Participants

Eligible patients were aged 18 years or older (or 19 years or older in South Korea) with type 2 diabetes (diagnosed ≥90 days before screening), $HbA_{1c}$ of 7·5–9·5% (58–80 mmol/mol), and receiving stable daily doses of one or two glucose-lowering drugs (metformin, sulphonylureas, sodium glucose co-transporter-2 [SGLT2] inhibitors, or thiazolidinediones) for 90 days or more before screening. As determined by the investigator, patients also needed to be healthy enough to aim for an $HbA_{1c}$ treatment target of less than 7·0% (53 mmol/mol). Key exclusion criteria included renal impairment (estimated glomerular filtration rate [eGFR] of <60 mL/min per 1·73 m²); New York Heart Association class IV heart failure;[15] proliferative retinopathy or maculopathy requiring acute treatment; history of pancreatitis; family or personal history of multiple endocrine neoplasia type 2 or medullary thyroid carcinoma; and a history of malignant neoplasms within the past 5 years. Full eligibility criteria are in the appendix (pp 4–5).

All patients provided written informed consent before undertaking any trial-related activities.

## Randomisation and masking

Eligible patients were randomly assigned (1:1) to either oral semaglutide once daily with flexible dose adjustment or oral sitagliptin 100 mg once daily, in addition to existing background glucose-lowering medication. Randomisation was stratified according to background glucose-lowering medication at screening (with or without sulphonylureas) and using an interactive web-response system. Due to the nature of the intervention and so that investigators could escalate the dose of oral semaglutide as prespecified, the trial was open label.

## Procedures

After a 2-week screening period, participants were randomly assigned to receive oral semaglutide once daily with flexible dose adjustment or oral sitagliptin 100 mg once daily for the 52-week treatment period (appendix p 9). During the treatment phase, participants attended study site visits at weeks 4, 8, 16, 24, 32, 40, 48, and 52 regardless of treatment group. After 52 weeks, participants could either undergo a 5-week follow-up period and complete the trial or, after re-consenting, they could continue in a 52-week extension phase. In this Article we report on the first 52-week, flexible dose-adjustment phase of the trial.

All participants who were assigned to oral semaglutide were initiated at a 3 mg dose, which they were given until week 8. At week 8 and every 8 weeks thereafter, the oral semaglutide dose was adjusted on the basis of their $HbA_{1c}$ (measured by a point-of-care device) and gastrointestinal tolerability. For the purposes of dose adjustment, three dose levels were available (3, 7, and 14 mg). At each study visit, the current dose of oral semaglutide was maintained if $HbA_{1c}$ was less than 7·0% (53 mmol/mol) and escalated to the next dose level if $HbA_{1c}$ was 7·0% (53 mmol/mol) or higher, unless participants had reported moderate-to-severe nausea or vomiting for 3 or more days in the week before the scheduled visit. If participants reported moderate-to-severe nausea or vomiting, the oral semaglutide dose was maintained or decreased to a minimum of 3 mg once daily, irrespective of the $HbA_{1c}$ level and at the investigator's discretion. Participants were instructed to take the oral semaglutide tablet in the morning, in a fasted state, with up to 120 mL of water, at least 30 min before any other food, beverage, or other oral medication.

Patients with persistent or unacceptable hyperglycaemia were to be offered treatment intensification with rescue medication at the investigator's discretion. From week 32, persistent or unacceptable hyperglycaemia was defined as $HbA_{1c}$ of 8·5% (69·4 mmol/mol) or higher, assessed at a central laboratory (ICON Laboratory Services, Dublin, Ireland). Rescue medication was selected in accordance with American Diabetes Association (ADA) or European Association for the Study of Diabetes guidelines,[16] excluding use of GLP-1 receptor agonists, DPP-4 inhibitors, and amylin analogues. Participants who discontinued study drug prematurely were switched to an alternative glucose-lowering drug at the investigator's discretion, including drugs not permitted as rescue medication. All participants were followed up throughout

the 52-week trial period irrespective of use of rescue medication or premature discontinuation of the assigned trial drug, except for those who withdrew consent.

Bodyweight was assessed at baseline and weeks 8, 16, 24, 32, 40, 48 and 52, or within 3 days of study drug discontinuation. Blood samples were drawn at baseline and then every 8 weeks, with $HbA_{1c}$ assessed at these timepoints by the central laboratory. Blood samples were also assessed for fasting plasma glucose and fasting lipid profile. Details of other efficacy assessments are in the appendix (p 6).

We recorded adverse events at every visit, including a 5-week safety follow-up visit at week 57 or within 3 days of study drug discontinuation and again 5 weeks after study drug discontinuation. All adverse events were coded by use of the Medical Dictionary for Regulatory Activities (version 20.1). Adverse events were defined as any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered associated with the product. A serious adverse event was defined as any event that resulted in death, a life-threatening experience, in-patient hospitalisation or extension of existing hospital admissions; a full list of eligible events is in the appendix (p 6). Details of all safety assessments are in the appendix (p 6). An independent external event adjudication committee was established for masked validation of selected adverse events (death, acute coronary syndrome, cerebrovascular event, heart failure requiring admission to hospital, acute pancreatitis, malignant neoplasm, malignant thyroid neoplasm or C-cell hyperplasia, acute kidney injury, and lactic acidosis).

## Outcomes

The primary endpoint was achievement of the $HbA_{1c}$ target of less than 7·0% (53 mmol/mol) at week 52. The confirmatory secondary efficacy endpoint was change from baseline to week 52 in bodyweight. Supportive secondary efficacy endpoints were change from baseline to week 52 in $HbA_{1c}$, fasting plasma glucose, BMI, bodyweight percentage, waist circumference, lipid profile, patient-reported outcomes (Diabetes Treatment Satisfaction Questionnaire [DTSQ]; Short Form-36 [SF-36] version 2 health survey [acute version]); and achievement of $HbA_{1c}$ less than or equal to 6·5% (48 mmol/mol),[17] bodyweight loss of 5% or more or 10% or more by week 52, and time to use of rescue medication. Composite supportive secondary endpoints assessed achievement at week 52 of $HbA_{1c}$ of less than 7% without hypoglycaemia (treatment-emergent severe or confirmed by blood glucose concentration [<3·1 mmol/L or 56 mg/dL] symptomatic hypoglycaemia) or weight gain; and a $HbA_{1c}$ decrease of 1% (10·9 mmol/mol) or more with weight loss of 3% or more. Severe hypoglycaemia was defined in accordance with the ADA classification (an episode requiring assistance of another person to actively administer carbohydrate, glucagon, or take other corrective actions).[18]

Supportive secondary safety endpoints were the number of treatment-emergent adverse events, the number of symptomatic hypoglycaemic episodes that were treatment-emergent severe or confirmed by blood glucose concentration, and whether a participant had a symptomatic hypoglycaemic episode that was treatment-emergent severe or confirmed by blood glucose concentration up to 52 weeks (yes or no). Other safety assessments included changes from baseline to week 52 in laboratory results, vital signs, electrocardiograms, and physical examinations, including eye examinations.

## Statistical analysis

We used descriptive statistics to summarise baseline demographic information for all participants who were randomly assigned to a study drug. We calculated the trial sample size to ensure at least 90% power to confirm superiority of oral semaglutide versus sitagliptin for the primary endpoint (treatment policy estimand), with planned enrolment of 500 patients and random assignment to treatment to ensure this power was achieved. We assumed an absolute difference in proportions of 15% and that the proportion of sitagliptin responders was distributed around 20–50%.

We used a hierarchical closed-testing strategy to control the overall type 1 error for the confirmation of efficacy of oral semaglutide for the achievement of $HbA_{1c}$ of less than 7% at week 52 and in decrease in bodyweight from baseline to week 52 when assessed by use of the treatment policy estimand.

We analysed the primary endpoint using a logistic regression model with treatment, region (Africa, Asia, Europe, North America, or South America), and stratification factor (ie, with or without background use of sulphonylurea) as fixed effects and baseline $HbA_{1c}$ as a covariate for both estimands. The treatment effect is presented as an odds ratio (OR) with corresponding 95% CI.

We estimated the treatment policy estimand using a pattern mixture model with multiple imputation to handle missing data at week 52. Data collected at week 52 from all participants who were randomly assigned to treatment, irrespective of premature discontinuation of treatment and initiation of rescue medication, were included in the statistical analysis. We did imputation within groups defined by study drug and treatment status at week 52. This imputation was based on an analysis of covariance model, whereas we did the statistical analysis using a logistic regression model as described for the primary endpoint. We combined the results using Rubin's rule.[19]

We estimated the trial product estimand using a mixed model for repeated measurements that used data collected before premature discontinuation of study drug or initiation of rescue medication from all participants

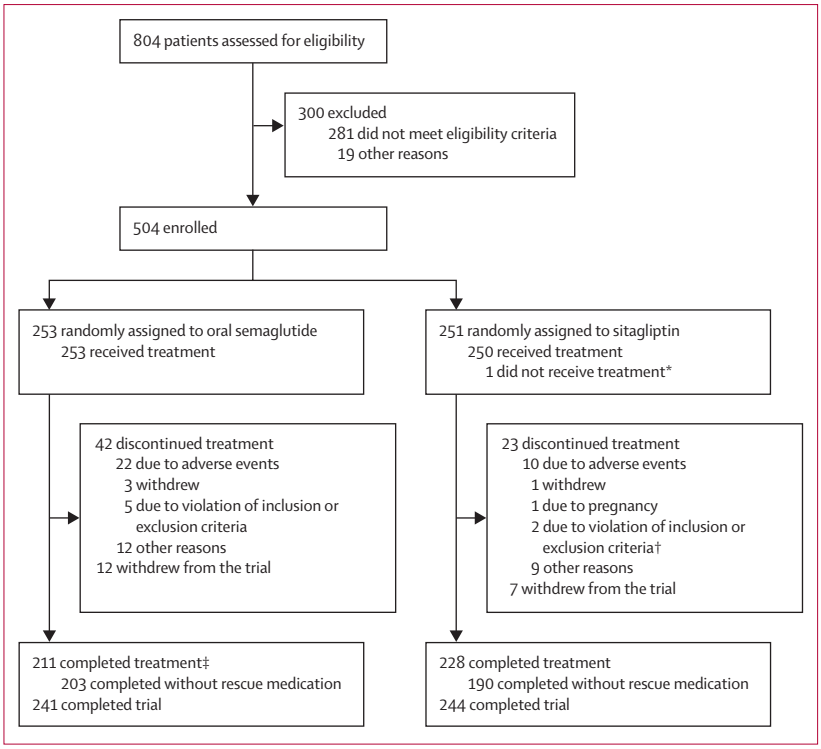


***Figure 1:*** **Trial profile**
*This participant was included in the analysis for the treatment policy estimand, but excluded from the safety analysis set. †Includes the one participant who was not exposed to study drug. ‡Excludes one participant with missing visit 10 (week 52) data and who reported discontinuation of study drug after the end of trial date.

who were randomly assigned to study drug. Further details on the statistical analyses are in the appendix (pp 7–8).

We analysed time from random assignment to additional glucose-lowering medication using a Cox proportional hazards model with treatment, region, and stratification factor as categorical fixed effects and baseline $HbA_{1c}$ as a covariate.

We assessed all safety endpoints using data from all participants exposed to at least one dose of study drug (safety analysis set), and analysed for two observation periods: in-trial period (duration in the trial regardless of premature discontinuation of study drug) and on-treatment period (duration on assigned study drug).

We did all analyses using SAS Version 9.4M2. This trial is registered with ClinicalTrials.gov, number NCT02849080, and the European Clinical Trials Database, EudraCT number 2015-005593-38.

### Role of the funding source

The funder developed the protocol, provided logistical support during the trial, and compiled the data. Data were assessed jointly by the authors and the funder. The authors interpreted the data and wrote the manuscript, with the help of medical writing services funded by the sponsor. All authors had full access to the trial data and provided final approval to submit the manuscript for publication, and the corresponding author had final responsibility for the decision to submit.

## Results

Between Sept 20, 2016, and Feb 7, 2017, of 804 patients assessed for eligibility, 504 were enrolled and randomly assigned to treatment with once-daily oral semaglutide with flexible dose adjustment (n=253; all at an initial dose of 3 mg) or sitagliptin 100 mg (n=251; figure 1). All participants were given at least one dose of their allocated study drug, except one in the sitagliptin group. 241 (95%) of 253 participants in the oral semaglutide group and 244 (97%) of 251 in the sitagliptin group completed the 52-week trial. The treatment schedule was completed by 211 (83%) participants in the oral semaglutide group and 228 (91%) in the sitagliptin group; and 203 (80%) participants in the oral semaglutide group and 190 (76%) in the sitagliptin group completed the trial without receiving rescue medication. Adverse events were the main reason for premature discontinuation of study drug. Demographic and baseline characteristics were similar in the two treatment groups (table 1). Overall, most participants were male (285 [57%] of 504) with a mean age of 57·4 years (SD 9·9), mean duration of diabetes of 8·8 years (SD 6·2), mean $HbA_{1c}$ of 8·3% (SD 0·6%; 67 mmol/mol [SD 6·4]), mean bodyweight of 88·6 kg (SD 19·8), and mean BMI of 31·5 kg/m² (SD 6·3). Overall, 203 (40%) of 504 participants were receiving one concomitant glucose-lowering drug at baseline (primarily metformin), 299 (59%) were receiving two concomitant glucose-lowering drugs (mostly metformin plus a sulphonylurea), and two (<1%) were receiving three concomitant glucose-lowering drugs (protocol violation, participants included in full analysis set; table 1).

In the oral semaglutide group, 185 (73%) of 253 patients were escalated to the 7 mg dose at week 8 (appendix p 10). Of 212 participants on treatment at week 52, 19 (9%) were receiving 3 mg, 64 (30%) were receiving 7 mg, and 126 (59%) were receiving 14 mg of oral semaglutide (dose information was missing for the remaining three [1%] patients at week 52, but the last known dose was 7 mg for one participant and 14 mg for two participants). Twice as many participants were given additional glucose-lowering drugs and more than four-times as many partipants were given rescue medication in the sitagliptin group compared with the oral semaglutide group (appendix p 14).

For the treatment policy estimand, the $HbA_{1c}$ target of less than 7% (53 mmol/mol) at week 52 was achieved by 134 (58%) of 230 participants in the oral semaglutide group versus 60 (25%) of 238 participants with sitagliptin (figure 2). The odds of achieving $HbA_{1c}$ of less than 7% were higher with oral semaglutide than with sitagliptin (OR 4·40, 95% CI 2·89–6·70; p<0·0001). For the trial product estimand, $HbA_{1c}$ of less than 7% at

| | Oral semaglutide group (n=253) | Sitagliptin group (n=251) |
|---|---|---|
| **Demographic** | | |
| Age, years | 56·9 (9·7) | 57·9 (10·1) |
| Sex | | |
| Female | 108 (43%) | 111 (44%) |
| Male | 145 (57%) | 140 (56%) |
| Race | | |
| White | 195 (77%) | 186 (74%) |
| Black or African American | 22 (9%) | 25 (10%) |
| Asian | 34 (13%) | 38 (15%) |
| Other | 2 (1%) | 2 (1%) |
| Ethnicity | | |
| Hispanic or Latino | 48 (19%) | 57 (23%) |
| Not Hispanic or Latino | 205 (81%) | 194 (77%) |
| **Clinical** | | |
| $HbA_{1c}$, % | 8·3 (0·6) | 8·3 (0·6) |
| $HbA_{1c}$, mmol/mol | 67·0 (6·3) | 67·2 (6·5) |
| Duration of diabetes, years | 8·6 (6·3) | 9·0 (6·2) |
| Fasting plasma glucose, mmol/L | 9·8 (2·4) | 9·8 (2·6) |
| Bodyweight, kg | 88·9 (19·6) | 88·4 (20·1) |
| BMI, kg/m² | 31·5 (6·5) | 31·5 (6·1) |
| eGFR, mL/min per 1·73 m²* | 97·0 (14·4) | 95·3 (15·6) |
| **Background medication at baseline** | | |
| Participants receiving one type of concomitant glucose-lowering drug | 106 (42%) | 97 (39%) |
| Metformin | 102 (40%) | 87 (35%) |
| Sulphonylurea | 3 (1%) | 6 (2%) |
| SGLT2 inhibitor | 1 (<1%) | 3 (1%) |
| Thiazolidinedione | 0 | 1 (<1%) |
| Participants receiving two types of concomitant glucose-lowering drugs | 146 (58%) | 153 (61%) |
| Metformin plus sulphonylurea | 119 (47%) | 116 (46%) |
| Metformin plus SGLT2 inhibitor | 16 (6%) | 31 (12%) |
| Metformin plus thiazolidinedione | 9 (4%) | 3 (1%) |
| Metformin plus other | 1 (<1%) | 0 |
| Sulphonylurea plus other | 1 (<1%) | 3 (1%) |
| Participants receiving three types of concomitant glucose-lowering drugs† | | |
| Metformin plus SGLT2 inhibitor plus sulphonylurea | 1 (<1%) | 1 (<1%) |

Data are mean (SD) or n (%). eGFR=estimated glomerular filtration rate. $HbA_{1c}$=glycated haemoglobin. SGLT2=sodium-glucose co-transporter 2. *Estimated using the Chronic Kidney Disease-Epidemiology Collaboration formula. †Participants receiving three drugs at baseline were protocol violations (of these patients, one in the oral semaglutide group received study drug for 10 days before discontinuation, and one in the sitagliptin group received study drug for 30 days before discontinuation; both participants continued in the trial until week 52).

***Table 1:*** **Baseline characteristics of all participants randomly assigned to treatment (full analysis set)**

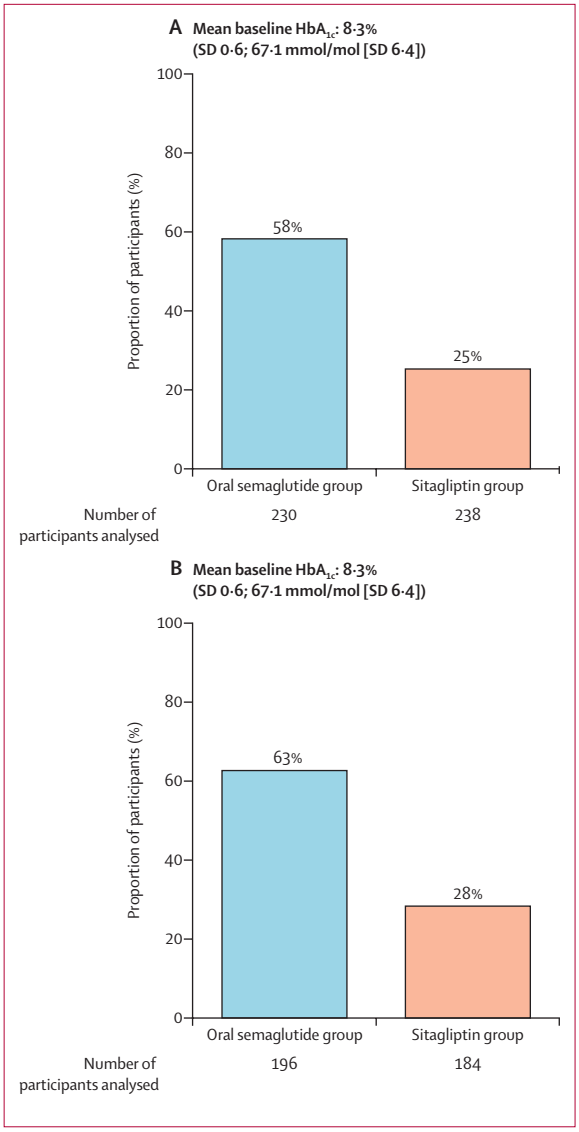


***Figure 2:*** **Proportion of participants achieving $HbA_{1c}$ target of less than 7% (53 mmol/mol) at week 52 for the treatment policy estimand (A) and the trial product estimand (B)**
Proportions of participants achieving $HbA_{1c}$ of less than 7% are based on observed data, with number of participants analysed being the number with non-missing information—ie, who attended the week 52 visit and contributed to the proportions. $HbA_{1c}$=glycated haemoglobin.

week 52 was achieved by 123 (63%) of 196 participants in the oral semaglutide group and 52 (28%) of 184 participants in the sitagliptin group (figure 2). The odds of achieving $HbA_{1c}$ of less than 7% at week 52 were significantly better with oral semaglutide than with sitagliptin (OR 5·54, 95% CI 3·54–8·68; p<0·0001).

Oral semaglutide was superior to sitagliptin in decreasing bodyweight from baseline to week 52 (treatment policy estimand: estimated treatment difference [ETD] –1·9 kg, 95% CI –2·6 to –1·2; p<0·0001; and trial product estimand: ETD –2·2 kg, –2·9 to –1·5; p<0·0001; figure 3).

Estimated mean $HbA_{1c}$ levels at week 52 were 7·0% (SE 0·1; 53 mmol/mol [SE 1]) with oral semaglutide and 7·5% (SE 0·1; 59 mmol/mol [SE 1]) with sitagliptin for

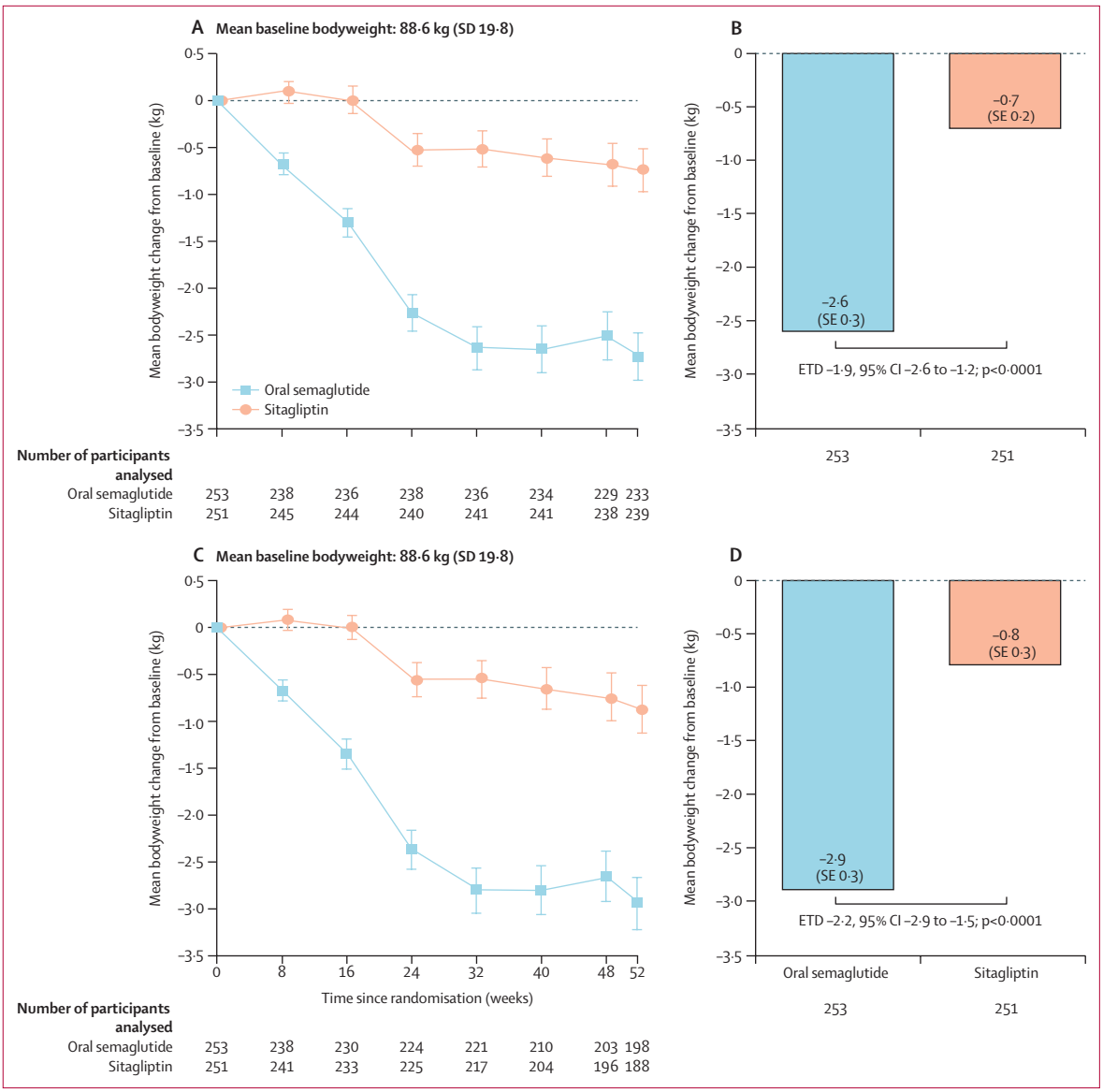


***Figure 3:*** **Changes in bodyweight with oral semaglutide compared with sitagliptin by use of the treatment policy estimand (A and B) and trial product estimand (C and D)**

(A and C) Observed change in mean bodyweight over time from baseline by week, and (B and D) estimated mean change in bodyweight from baseline to week 52. For panels A and C, error bars are the SEM. For panels B and D, n are number of participants contributing to the proportions. ETD=estimated treatment difference.

the treatment policy estimand and 6·9% (SE 0·1; 52 mmol/mol [SE 1]) versus 7·6% (SE 0·1; 60 mmol/mol [SE 1]) for the trial product estimand. Oral semaglutide resulted in significantly greater decreases in $HbA_{1c}$ than sitagliptin did at week 52 (treatment policy estimand: ETD –0·5%, 95% CI –0·7 to –0·4 [–6 mmol/mol, 95% CI –7 to –4], p<0·0001; trial product estimand: ETD –0·7%, –0·9 to –0·5 [–8 mmol/mol, –9 to –6], p<0·0001; figure 4).

More participants achieved a bodyweight loss of 5% or more and 10% or more with oral semaglutide than did with sitagliptin, and the odds of achieving these weight losses were significantly better with oral semaglutide than with sitagliptin (for ≥5% bodyweight loss, p<0·0001 for both estimands; for ≥10% bodyweight loss, p=0·0156 for treatment policy estimand and p=0·0065 for trial product estimand; appendix pp 12–13). Additionally, fasting plasma glucose was decreased from baseline significantly more with oral semaglutide than with sitagliptin at week 52 (treatment policy estimand, p=0·0002; trial product estimand, p<0·0001; appendix pp 12–13). Further data for supportive secondary endpoints, including change from baseline to week 52 in BMI, bodyweight

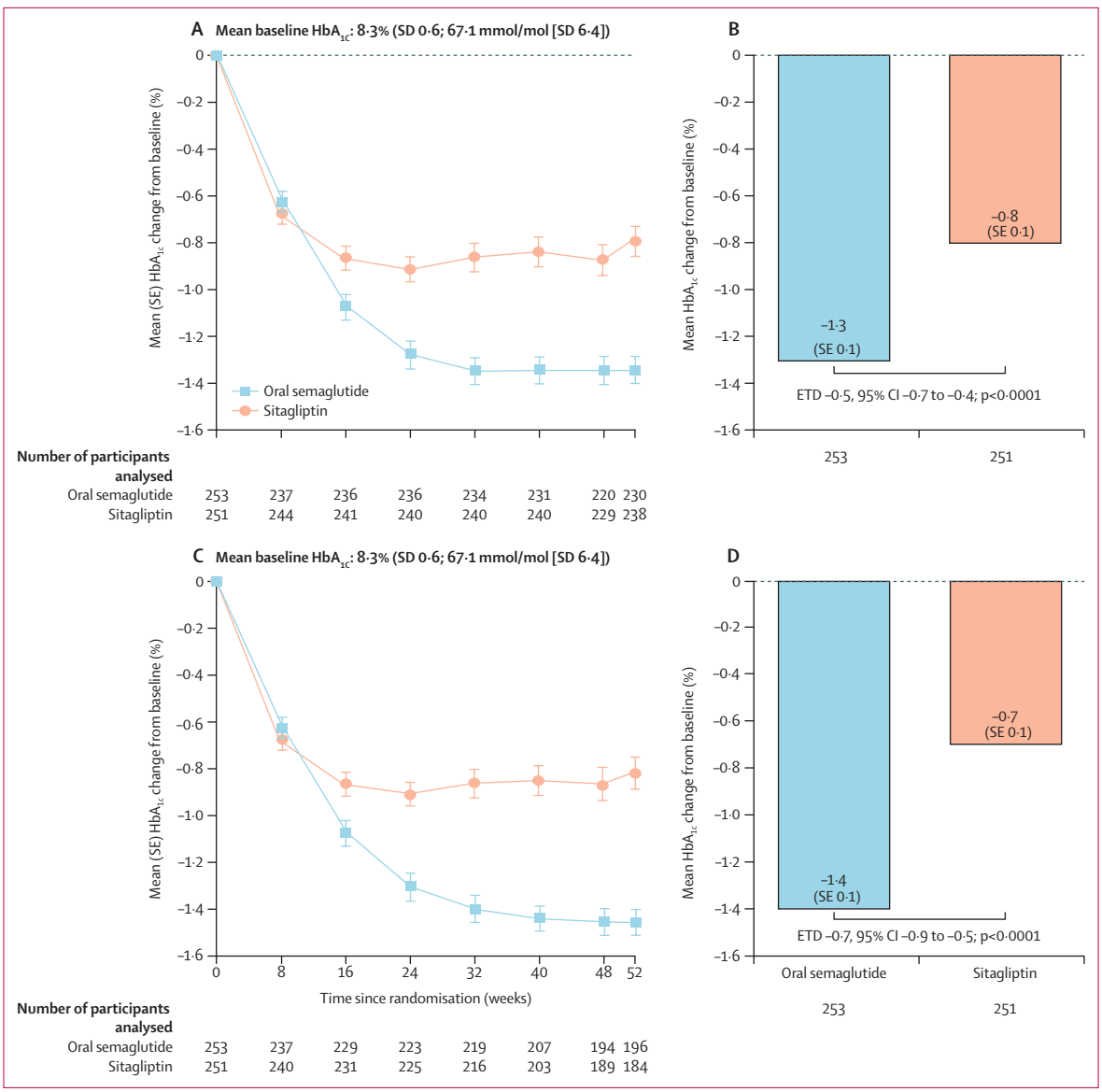


***Figure 4:*** **Changes in $HbA_{1c}$ with oral semaglutide versus sitagliptin by use of the treatment policy estimand (A and B) and trial product estimand (C and D)**
(A and C) Observed change in mean $HbA_{1c}$ over time from baseline by week, and (B and D) estimated mean change in $HbA_{1c}$ from baseline to week 52. For panels A and C, error bars are SEMs. For panels B and D, n are number of participants contributing to the proportions. Changes from baseline (67·1 mmol/mol) in $HbA_{1c}$ in mmol/mol for the treatment policy estimand were –14 mmol/mol with oral semaglutide and –8 mmol/mol for sitagliptin, and for the trial product estimand were –15 mmol/mol with oral semaglutide and –8 mmol/mol for sitagliptin. ETD=estimated treatment difference. $HbA_{1c}$=glycated haemoglobin.

percentage, waist circumference, and lipid profile, and proportion of patients achieving $HbA_{1c}$ of 6·5% (48 mmol/mol) or less, are reported in the appendix (pp 12–13). The results of these supportive secondary endpoints are consistent with those of the primary and confirmatory secondary endpoints.

For patient-reported outcomes, change from baseline to week 52 in DTSQ scores, satisfaction with treatment, convenience and flexibility of treatment, and total treatment satisfaction appeared similar for oral semaglutide and sitagliptin with no significant differences for either estimand (appendix p 11). The ETD significantly favoured oral semaglutide over sitagliptin with regard to decreased feelings of unacceptably high blood sugars for both estimands. No differences were seen in the SF-36 version 2 health survey responses between groups (appendix p 11).

The odds for achieving the composite supportive secondary endpoints ($HbA_{1c}$ less than 7% [53 mmol/mol], without hypoglycaemic episodes and without increase in bodyweight; and decrease of $HbA_{1c}$ of 1% or more with weight loss of 3% or more) were significantly better with oral semaglutide than with sitagliptin (p<0·0001 for both estimands and both endpoints; appendix pp 12–13).

| | Oral semaglutide group (n=253) | | Sitagliptin group (n=250) | |
|---|---|---|---|---|
| | Participants with at least one event | Number of events | Participants with at least one event | Number of events |
| All adverse events | 197 (78%) | 768 | 172 (69%) | 519 |
| Serious adverse events | 24 (9%) | 28 | 24 (10%) | 30 |
| Fatal events | 0 | .. | 1 (<1%)* | 1* |
| Adverse event severity | | | | |
| Severe | 16 (6%) | 31 | 18 (7%) | 20 |
| Moderate | 104 (41%) | 196 | 75 (30%) | 143 |
| Mild | 167 (66%) | 541 | 144 (58%) | 356 |
| Premature discontinuation of study drug due to adverse events | 22 (9%) | 35 | 8 (3%) | 13 |
| Most frequent cause of premature study drug discontinuation by system organ class† | | | | |
| Gastrointestinal disorders | 14 (6%) | 19 | 2 (1%) | 2 |
| Most frequent adverse events ‡ | | | | |
| Nausea | 53 (21%) | 83 | 6 (2%) | 8 |
| Nasopharyngitis | 26 (10%) | 30 | 13 (5%) | 15 |
| Headache | 25 (10%) | 33 | 15 (6%) | 15 |
| Diarrhoea | 22 (9%) | 25 | 8 (3%) | 11 |
| Abdominal pain upper | 16 (6%) | 17 | 3 (1%) | 3 |
| Vomiting | 14 (6%) | 21 | 2 (1%) | 2 |
| Dyspepsia | 13 (5%) | 13 | 2 (1%) | 4 |
| Upper respiratory tract infection | 9 (4%) | 9 | 15 (6%) | 16 |

*An additional in-trial fatal adverse event occurred in the sitagliptin group, which occurred 78 days after premature discontinuation of the study drug; both fatal events were cardiovascular deaths in participants with a history of cardiovascular disease. †Occurring in ≥3% of participants in either group. ‡Occurring in ≥5% of participants in either group, defined by use of Medical Dictionary for Regulatory Activities (version 20·1) preferred term.

*Table 2:* **On-treatment adverse events (safety analysis set)**

Fewer participants in the oral semaglutide group required rescue medication than did in the sitagliptin group (appendix p 14). Additional glucose-lowering medications used during the trial for the full analysis set are reported in the appendix (p 14). Time to first dose of rescue medication was significantly longer with oral semaglutide than with sitagliptin (hazard ratio [HR] 0·18, 95% CI 0·09–0·39; p<0·0001), as was the time to additional glucose-lowering drug or rescue medication (HR 0·58, 0·37–0·91; p=0·0175).

The number of adverse events and proportion of participants who had adverse events were higher in the oral semaglutide group (197 [78%] of 253) than in the sitagliptin group (172 [69%] of 250) during the on-treatment period (table 2). The most frequently reported adverse events were gastrointestinal events (appendix p 15), most commonly nausea and diarrhoea that were predominantly mild-to-moderate in severity and of short duration, and occurred more frequently in the oral semaglutide group than in the sitagliptin group (table 2). Most adverse events were mild-to-moderate in severity in both treatment groups. The incidence of serious adverse events was similar in the oral semaglutide and sitagliptin groups during the on-treatment period (table 2). More participants in the oral semaglutide group than in the sitagliptin group prematurely discontinued their allocated study drug because of adverse events, primarily gastrointestinal events. Most discontinuations in the oral semaglutide group occurred within the first 8 weeks of the trial (data not shown). No deaths occurred in the oral semaglutide group, and two deaths occurred during the trial in the sitagliptin group, both of which were cardiovascular deaths in participants with a history of cardiovascular disease and were judged by the investigator to be unlikely related to study drug (one during the on-treatment phase, the other during the in-trial phase; table 2; appendix p 16).

No severe hypoglycaemic episodes occurred during the trial (appendix p 17). The proportion of participants who had symptomatic hypoglycaemic episodes that were confirmed by blood glucose concentration was low and similar between treatment groups, and most episodes occurred in participants who were receiving background therapy with a sulphonylurea (appendix p 17).

Adverse events associated with diabetic retinopathy were reported in the same proportion of participants in both groups (oral semaglutide: six [2%] of 253; sitagliptin: six [2%] of 250; in-trial period; appendix p 18). Event adjudication committee-confirmed malignant neoplasms were reported in eight (3%) of 253 participants in the oral semaglutide group and in two (1%) of 250 in the sitagliptin group, and with no clustering of malignancies to specific organ systems (appendix p 15). No cases of pancreatitis were reported. Mean lipase and amylase concentrations were increased in both treatment groups compared with baseline, with no difference between groups (data not shown). No other clinically relevant changes in blood pressure, pulse rate, or eGFR were reported (appendix p 19).

## Discussion

In this trial, oral semaglutide with flexible dose adjustment (3, 7, or 14 mg) was found to be superior to sitagliptin 100 mg for achievement of an $HbA_{1c}$ target of less than 7% (53 mmol/mol) after 52 weeks when added to existing therapy with one or two glucose-lowering drugs in patients with type 2 diabetes. The proportion of participants who achieved this target with oral semaglutide was over twice that in the sitagliptin group despite the flexible dose-adjustment approach and despite twice as many participants receiving additional glucose-lowering drugs in the sitagliptin group compared with the oral semaglutide group. Additionally, oral semaglutide with flexible dose adjustment was superior to sitagliptin in decreasing bodyweight. In the present trial, patient-reported total treatment satisfaction, treatment convenience, and flexibility with once-daily oral semaglutide were similar to those reported for once-daily sitagliptin, which could suggest that the dosing conditions for oral semaglutide had little effect on treatment convenience or satisfaction. These data

suggest that treatment with oral semaglutide can be individualised and, even though at week 52 more than a third of participants were not receiving the maximum dose, it can help more patients achieve $HbA_{1c}$ targets than sitagliptin can.

The most frequently reported adverse events were gastrointestinal in nature, most commonly nausea and diarrhoea, which were typically mild to moderate. The overall safety profile of oral semaglutide in our trial was similar to that previously reported in a phase 2 trial,[20] in the phase 3 PIONEER 1[9,10] and PIONEER 3[11] trials, and with that of subcutaneous semaglutide[1–3] and other GLP-1 receptor agonists.[21,22] In the present study, hypoglycaemic episodes occurred in a similar proportion of participants between the oral semaglutide group and the sitagliptin group, few with blood glucose concentrations below 3·1 mmol/L, and almost all occurred in participants receiving background sulphonylurea treatment. Notably, approximately half of participants enrolled were treated with sulphonylurea, alone or in combination with another glucose-lowering drug. Although the increased risk of hypoglycaemia with GLP-1 receptor agonists is low,[23] caution and close monitoring of patients is advisable when adding a GLP-1 receptor agonist to an existing treatment associated with hypoglycaemia.

Individualised dose adjustments of semaglutide could be expected to help mitigate adverse events and minimise treatment discontinuation. However, flexible dose adjustment did not decrease the prevalence of study drug discontinuations due to adverse events compared with that observed in other oral semaglutide studies.[10,11,20] Indeed, in PIONEER 3, study drug discontinuation due to adverse events over 78 weeks occurred in 6% (26 of 466) of participants on 3 mg once-daily oral semaglutide, 6% (27 of 464) on 7 mg, and 12% (54 of 465) on 14 mg.[10,11] In our trial, 9% of participants in the oral semaglutide group prematurely discontinued study drug due to adverse events. However, this was an open-label study of shorter duration (52 weeks) than PIONEER 3 (78 weeks), and participants were asked about adverse events at all visits, which could have influenced their decisions to discontinue treatment and might have influenced clinician or investigator focus on gastrointestinal tolerability when discussing with participants. Most adverse events that led to study drug discontinuation in the present trial occurred within the first 8 weeks of the trial, before any dose adjustment, and few additional participants discontinued therapy after the main dose escalation timepoints (immediately after weeks 8 and 16). This observation suggests that clinicians seeking increased effect in glycaemic control or weight loss might consider further escalation of oral semaglutide if tolerability is not a factor after the first few weeks of treatment.

Several considerations and potential limitations need to be addressed when interpreting these results. A strength of this trial is that it implements the estimand concept, which is now recommended by regulatory bodies.[13] The two estimands used here are complementary and provide insight into treatment effects that are relevant for regulators and payers focusing on comparing treatment policies (the treatment policy estimand: data from all patients regardless of study drug discontinuation or use of rescue medication), and physicians seeking to understand the anticipated treatment effect attributable to the study drug (the trial product estimand: data from all participants that were randomly assigned to a study drug and not initiating rescue medication). In the present trial, the conclusions from the two estimands were broadly consistent, reflecting the high proportion of participants in both groups who completed treatment without use of rescue medication.

Another strength of the current trial is that it provides information that is clinically relevant for physicians who are treating patients with diabetes. This relevance was achieved by the use of a clinically important primary endpoint (achievement of the $HbA_{1c}$ target of less than 7% [53 mmol/mol]) and also by implementing a flexible dose-adjustment approach that more closely replicates the individualised approach of adjusting dose according to efficacy and tolerability that might be used for oral semaglutide in future clinical practice. Additionally, all participants were required to be taking stable doses of one or two glucose-lowering drugs at enrolment, with the study drugs added to this background therapy. This patient population reflects current treatment consensus, which recommends GLP-1 receptor agonists as add-on therapy after initial glucose-lowering therapy with metformin,[12] and supports the relevance of the trial results for clinical practice. The trial was open-label and therefore knowledge of the administered treatment could have influenced participant and investigator behaviour during the trial, including adverse event reporting. A further limitation of this trial is that the criteria for dose adjustment specified in the protocol restricted physicians to maintaining the current dose once participants reached the glycaemic targets. Consequently, the maximum potential benefits of treatment with oral semaglutide might not have been achieved in all participants.

In conclusion, this study shows the superiority of flexible dose adjustment with oral semaglutide compared with a fixed dose of the DPP-4 inhibitor sitagliptin in terms of both achievement of target $HbA_{1c}$ and decrease in bodyweight. These benefits were observed despite the lower use of additional glucose-lowering drugs with oral semaglutide than with sitagliptin. Oral semaglutide had a safety profile consistent with the GLP-1 receptor agonist class.

### Contributors

JBB, TRP, CLH, SORW, and EC contributed to the trial design. JBB, BB, AM, YMC, EC, and TRP contributed to the conduct of the trial and the data collection. EC and SORW contributed to the data analysis. All authors interpreted the data and participated in writing the manuscript, 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

TRP reports board membership and personal fees from Novo Nordisk, Sanofi, AstraZeneca, Arecor, and Adocia, and payment for lectures from Novo Nordisk. BB reports personal fees from Novo Nordisk, Sanofi, Lilly, AstraZeneca, Boehringer Ingelheim, Janssen, Adocia, Intarcia, Medtronic, Mannkind, and Senseonics; grant support from Novo Nordisk, Sanofi, Lilly, Boehringer Ingelheim, Janssen, Diasome, Medtronic, Mannkind, Senseonics, and DexCom; and holds shares in Aseko. AM reports board membership and consultancy fees paid to KU Leuven (Leuven, Belgium) from Novo Nordisk, Sanofi, Merck Sharp & Dome, and AstraZeneca, and payment for lectures from Novo Nordisk, Sanofi, Eli Lilly, Amgen, AstraZeneca, Novartis, Boehringer Ingelheim, Merck Sharp & Dome, and Johnson & Johnson. YMC reports grants from Sanofi, AstraZeneca, and LG, and consulting fees from Hanmi. EC, CLH, and SORW are employees of Novo Nordisk. EC and CLH hold shares in Novo Nordisk. JBB reports contracted consulting fees paid to the University of North Carolina (Chapel Hill, NC, USA) from Adocia, AstraZeneca, Dance Biopharm, Dexcom, Elcelyx Therapeutics, Eli Lilly, Fractyl, GI Dynamics, Intarcia Therapeutics, Lexicon, MannKind, Metavention, NovaTarg, Novo Nordisk, Orexigen, PhaseBio, Sanofi, Senseonics, Shenzhen HighTide, Takeda, vTv Therapeutics, and Zafgen; grant support from AstraZeneca, Eli Lilly, GI Dynamics, GlaxoSmithKline, Intarcia Therapeutics, Johnson & Johnson, Lexicon, Medtronic, Novo Nordisk, Orexigen, Sanofi, Scion NeuroStim, Takeda, Theracos, vTv Therapeutics, and the US National Institutes of Health (UL1TR002489); personal fees from Neurimmune AG; and holds stock options in Mellitus Health, PhaseBio, and Stability Health.

### Data sharing

Data will be shared with researchers submitting a research proposal approved by the independent review board. Access request proposals can be found at www.novonordisk-trials.com. Data will be made available after research completion, and approval of the product and product use in the European Union and the USA. Individual participant data will be shared in data sets in a de-identified and anonymised format. There will not be any limitations on how these data can be used.

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