Oral semaglutide versus subcutaneous liraglutide and placebo in type 2 diabetes (PIONEER 4): a randomised, double-blind, phase 3a trial

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Summary

Background Glucagon-like peptide-1 (GLP-1) receptor agonists are effective treatments for type 2 diabetes, lowering glycated haemoglobin (HbA_{1c}) and weight, but are currently only approved for use as subcutaneous injections. Oral semaglutide, a novel GLP-1 agonist, was compared with subcutaneous liraglutide and placebo in patients with type 2 diabetes.

Methods In this randomised, double-blind, double-dummy, phase 3a trial, we recruited patients with type 2 diabetes from 100 sites in 12 countries. Eligible patients were aged 18 years or older, with HbA_{1c} of 7·0–9·5% (53–80·3 mmol/mol), on a stable dose of metformin (≥1500 mg or maximum tolerated) with or without a sodium-glucose co-transporter-2 inhibitor. Participants were randomly assigned (2:2:1) with an interactive web-response system and stratified by background glucose-lowering medication and country of origin, to once-daily oral semaglutide (dose escalated to 14 mg), once-daily subcutaneous liraglutide (dose escalated to 1·8 mg), or placebo for 52 weeks. Two estimands were defined: treatment policy (regardless of study drug discontinuation or rescue medication) and trial product (assumed all participants were on study drug without rescue medication) in all participants who were randomly assigned. The treatment policy estimand was the primary estimand. The primary endpoint was change from baseline to week 26 in HbA_{1c} (oral semaglutide superiority *vs* placebo and non-inferiority [margin: 0·4%] and superiority *vs* subcutaneous liraglutide) and the confirmatory secondary endpoint was change from baseline to week 26 in bodyweight (oral semaglutide superiority *vs* placebo and liraglutide). Safety was assessed in all participants who received at least one dose of study drug. This trial is registered on Clinicaltrials.gov, number NCT02863419, and the European Clinical Trials registry, number EudraCT 2015-005210-30.

Findings Between Aug 10, 2016, and Feb 7, 2017, 950 patients were screened, of whom 711 were eligible and randomly assigned to oral semaglutide (n=285), subcutaneous liraglutide (n=284), or placebo (n=142). 341 (48%) of 711 participants were female and the mean age was 56 years (SD 10). All participants were given at least one dose of study drug, and 277 (97%) participants in the oral semaglutide group, 274 (96%) in the liraglutide group, and 134 (94%) in the placebo group completed the 52-week trial period. Mean change from baseline in HbA_{1c} at week 26 was –1·2% (SE 0·1) with oral semaglutide, –1·1% (SE 0·1) with subcutaneous liraglutide, and –0·2% (SE 0·1) with placebo. Oral semaglutide was non-inferior to subcutaneous liraglutide in decreasing HbA_{1c} (estimated treatment difference [ETD] –0·1%, 95% CI –0·3 to 0·0; p<0·0001) and superior to placebo (ETD –1·1%, –1·2 to –0·9; p<0·0001) by use of the treatment policy estimand. By use of the trial product estimand, oral semaglutide had significantly greater decreases in HbA_{1c} than both subcutaneous liraglutide (ETD –0·2%, 95% CI –0·3 to –0·1; p=0·0056) and placebo (ETD –1·2%, –1·4 to –1·0; p<0·0001) at week 26. Oral semaglutide resulted in superior weight loss (–4·4 kg [SE 0·2]) compared with liraglutide (–3·1 kg [SE 0·2]; ETD –1·2 kg, 95% CI –1·9 to –0·6; p=0·0003) and placebo (–0·5 kg [SE 0·3]; ETD –3·8 kg, –4·7 to –3·0; p<0·0001) at week 26 (treatment policy). By use of the trial product estimand, weight loss at week 26 was significantly greater with oral semaglutide than with subcutaneous liraglutide (–1·5 kg, 95% CI –2·2 to –0·9; p<0·0001) and placebo (ETD –4·0 kg, –4·8 to –3·2; p<0·0001). Adverse events were more frequent with oral semaglutide (n=229 [80%]) and subcutaneous liraglutide (n=211 [74%]) than with placebo (n=95 [67%]).

Interpretation Oral semaglutide was non-inferior to subcutaneous liraglutide and superior to placebo in decreasing HbA_{1c}, and superior in decreasing bodyweight compared with both liraglutide and placebo at week 26. Safety and tolerability of oral semaglutide were similar to subcutaneous liraglutide. Use of oral semaglutide could potentially lead to earlier initiation of GLP-1 receptor agonist therapy in the diabetes treatment continuum of care.

Funding Novo Nordisk A/S.

Published **Online** June 8, 2019 http://dx.doi.org/10.1016/S0140-6736(19)31271-1

See **Online/Comment** http://dx.doi.org/10.1016/S0140-6736(19)31350-9

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Research in context

Evidence before this study

Glucagon-like peptide-1 (GLP-1) receptor agonists currently available for the treatment of type 2 diabetes, which include dulaglutide, exenatide, liraglutide, lixisenatide, and semaglutide, are all administered by subcutaneous injection. Within the class, substantial differences in structure, dosing interval, and efficacy exist. In previous comparisons of once-weekly GLP-1 receptor agonists, subcutaneous semaglutide had superior glycaemic control and weight loss compared with exenatide and dulaglutide. An oral formulation of semaglutide is in development, which is co-formulated with the absorption enhancer sodium N-(8-[2-hydroxybenzoyl] amino) caprylate to overcome the low bioavailability typical of oral peptides and facilitate semaglutide absorption across the gastric mucosa. We did a PubMed search on Jan 17, 2019, with no date or language restrictions for clinical trials using the search term "oral semaglutide" and found only clinical pharmacology studies, a phase 2 dose-finding trial with oral semaglutide, and a phase 3 trial in which oral semaglutide at 7 mg and 14 mg per day resulted in significantly greater decreases in HbA_{1c} and bodyweight over 26 weeks versus the dipeptidyl peptidase-4 inhibitor sitagliptin in patients with type 2 diabetes uncontrolled with metformin with or without sulfonylurea.

Added value of this study

To our knowledge, the PIONEER 4 trial is the first study to compare the efficacy and safety of oral semaglutide with a subcutaneously injected GLP-1 receptor agonist, liraglutide. The results of this trial show that once daily oral semaglutide is non-inferior to once-daily subcutaneous injections of the highest approved dose of liraglutide and superior to placebo in decreasing HbA_{1c}, and superior to both liraglutide and placebo in decreasing bodyweight, after 26 weeks of treatment in patients with type 2 diabetes uncontrolled on metformin with or without a sodium-glucose co-transporter-2 inhibitor. Significant decreases in HbA_{1c} and bodyweight with oral semaglutide versus both subcutaneous liraglutide and placebo at week 52 suggest a long-term benefit with continued oral semaglutide therapy. Safety and tolerability of oral semaglutide were consistent with subcutaneous liraglutide and the GLP-1 receptor agonist class.

Implications of all the available evidence

This trial is the first comparison of orally and subcutaneously administered GLP-1 receptor agonists for the treatment of type 2 diabetes. Oral semaglutide is an effective treatment option, potentially leading to earlier initiation of GLP-1 receptor agonist therapy in the diabetes treatment continuum of care.

Introduction

Glucagon-like peptide-1 (GLP-1) receptor agonists that are currently available for the treatment of type 2 diabetes are all administered by subcutaneous injection.[1] Within the class, substantial differences in structure, dosing interval, and efficacy exist. Liraglutide is a once-daily GLP-1 receptor agonist that decreases glycated haemoglobin (HbA_{1c}) and bodyweight in patients with type 2 diabetes across the continuum of care.[2,3] Among once-weekly GLP-1 receptor agonists, subcutaneous semaglutide has superior glycaemic control and weight loss compared with exenatide and dulaglutide.[4,5] Both liraglutide and subcutaneous semaglutide have shown a cardiovascular benefit and are recommended for patients with type 2 diabetes and cardiovascular disease.[6–8]

An oral formulation of semaglutide is in development. Orally delivered peptides typically have low bioavailability and so oral semaglutide is co-formulated with the absorption enhancer, sodium N-(8-[2-hydroxybenzoyl] amino) caprylate, which facilitates semaglutide absorption across the gastric mucosa.[9] In previous trials, oral semaglutide showed significantly greater decreases in HbA_{1c} and bodyweight compared with placebo in patients with type 2 diabetes uncontrolled by diet and exercise.[10,11] Oral semaglutide at 7 mg and 14 mg per day also resulted in significantly greater decreases in HbA_{1c} and bodyweight over 26 weeks versus the dipeptidyl peptidase-4 inhibitor sitagliptin in patients with type 2 diabetes uncontrolled on metformin with or without sulfonylurea.[12]

This phase 3a trial, PIONEER 4, is the first to compare the efficacy and safety of oral semaglutide with a subcutaneously injected GLP-1 receptor agonist, liraglutide, and placebo in patients with type 2 diabetes uncontrolled on background metformin with or without a sodium-glucose co-transporter-2 (SGLT2) inhibitor.

Methods

Study design

PIONEER 4 was a 52-week, randomised, double-blind, double-dummy, active-controlled, and placebo-controlled phase 3a trial undertaken at 100 trial sites in 12 countries (Croatia, Czech Republic, Germany, Hungary, Japan, Latvia, Poland, Slovakia, South Africa, Ukraine, United Arab Emirates, and the USA).

Two different questions related to efficacy were addressed through the definition of two estimands: the treatment policy estimand and the trial product estimand, which were defined on the basis of interactions with regulatory agencies.

The treatment policy estimand (primary estimand) assessed the treatment effect for all participants randomly assigned to treatment regardless of study drug discontinuation or use of rescue medication. It reflects the intention-to-treat principle as defined in International Conference on Harmonisation (ICH) E9.[13] This estimand reflects the effect of initiating treatment with oral semaglutide compared with initiating treatment with subcutaneous liraglutide or placebo, all potentially followed by either discontinuation of study drug or

addition of or switch to another glucose-lowering drug, or both.

The trial product estimand (secondary estimand) assessed the treatment effect for all participants randomly assigned to treatment under the assumption that all participants remained on study drug for the entire planned duration of the trial and did not use rescue medication. It aims to reflect the effect of oral semaglutide compared with subcutaneous liraglutide or placebo without the confounding effect of rescue medication. The statistical analysis applied with this estimand is similar to how many phase 3a diabetes trials have been assessed in the past.

Discontinuation of study drug 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).[14] Further details on the estimands can be found in the appendix (p 4).

The trial protocol was approved by the Institutional Review Board or Independent Ethics Committees at each site, and the trial was undertaken in accordance with ICH Good Clinical Practice guidelines and the Declaration of Helsinki. A redacted protocol is in the appendix (pp 29–162).

Participants

Eligible patients were aged 18 years or older with type 2 diabetes and HbA_{1c} of 7·0–9·5% (53–80·3 mmol/mol), on a stable dose of metformin (≥1500 mg or maximum tolerated) with or without an SGLT2 inhibitor. Key exclusion criteria included taking any medication for diabetes or obesity within 90 days of screening (other than metformin, SGLT2 inhibitor, or short-term insulin [≤14 days]); renal impairment (estimated glomerular filtration rate <60 mL/min per 1·73 m^2); proliferative retinopathy or maculopathy requiring acute treatment; and history of acute or chronic pancreatitis. Full eligibility criteria are in the appendix (p 14).

All participants provided written, informed consent before any trial-related activities.

Randomisation and masking

Participants were randomly assigned (2:2:1) to oral semaglutide, subcutaneous liraglutide, or placebo once-daily (appendix p 7) in addition to existing background glucose-lowering medication. Randomisation was done with an interactive web-response system that allocated dispensing unit numbers for each participant, and was stratified by glucose-lowering background medication (metformin alone or metformin with an SGLT2 inhibitor) and participants' country of origin (Japanese or non-Japanese). We used a double-blind, double-dummy design in which participants received both a tablet (active or placebo) and an injection (active or placebo). For both oral semaglutide and subcutaneous liraglutide, the active and corresponding placebo products were visually identical to maintain masking of participants and site staff.

Procedures

Participants assigned to oral semaglutide initiated once-daily treatment at 3 mg with dose escalation to 7 mg at 4 weeks and to the maintenance dose of 14 mg at 8 weeks, whereas those assigned to subcutaneous liraglutide initiated treatment at 0·6 mg once-daily with dose escalation to 1·2 mg after 1 week and to the maintenance dose of 1·8 mg after 2 weeks. Participants were to continue on the maximum tolerated dose for the remaining weeks of the 52-week trial period. Because the presence of food and fluid in the stomach impairs absorption of oral semaglutide,[15] participants were instructed to take the study drug tablet in the morning in a fasted state, with up to half a glass of water, and wait 30 min or longer before their first meal, any other drinks, and taking any other oral medication.

Participants continued glucose-lowering background medication throughout the trial at the same dose and frequency as at baseline unless rescue medication was needed or in response to safety concerns. Rescue medication (ie, additional glucose-lowering medication prescribed as add-on to study drug) was prescribed to participants with persistent or unacceptable hyperglycaemia (ie, >13·3 mmol/L [240 mg/dL] from weeks 8–13, >11·1 mmol/L [200 mg/dL] from week 14 to end of treatment, or HbA_{1c} >8·5% [69·4 mmol/mol]) from week 26 onwards) at the investigator's discretion in accordance with international guidelines.[16,17] Participants were assessed for hyperglycaemia at all visits.

See Online for appendix

Patients who prematurely discontinued study drug could be switched to any marketed glucose-lowering drug (other than GLP-1 receptor agonists) at the investigator's discretion. All participants continued in the trial unless they withdrew consent, were lost to follow-up, or died.

At baseline, we recorded participant demographics, weight, body-mass index (BMI) and HbA_{1c}; we repeated weight and HbA_{1c} measurements at weeks 4, 8, 14, 20, 26, 32, 38, 45, and 52 (within 3 days either side of scheduled visit day) or on the day of study drug discontinuation if applicable. Participants recorded their own blood-glucose concentration using a blood-glucose meter (Abbott, Wiesbaden, Germany) provided by Novo Nordisk to each participant, and results were recorded by participants in study diaries. Blood samples were taken and assessment of lipid profile and other laboratory parameters (including haematology, biochemistry, antibodies) at baseline and at weeks 4, 8, 14, 26, 38, and 52 (within 3 days either side of scheduled visit day) or on the day of study drug discontinuation if applicable, and at follow-up 5 weeks after the end of treatment or discontinuation, as applicable. At baseline and 26 and 52 weeks, or on the day of study drug discontinuation as applicable, participants completed the Diabetes Treatment Satisfaction Questionnaire status version (DTSQs). Physical examinations were done at baseline and at week 52 or the day of study drug discontinuation, as applicable. Physical examinations

were done according to local procedures but had to include general appearance, head, ears, eyes, nose, throat, neck, thyroid gland, respiratory, cardiovascular and gastrointestinal systems (including mouth), musculoskeletal system, central and peripheral nervous system, skin and lymph node palpation. An electrocardiogram (ECG) was done at baseline and at weeks 26 and 52 (within 3 days either side of scheduled visit day) or on the day of study drug discontinuation if applicable, and at follow-up 5 weeks after the end of treatment or discontinuation, as applicable.

We recorded adverse events at each visit. Adverse events were defined with definitions in Medical Dictionary for Regulatory Activities (version 20.1). Serious adverse events were defined as an experience that resulted in any of the following: death; a life-threatening event; inpatient admission to hospital or extension of hospital stay; a persistent or substantial disability or incapacitation; and a congenital anomaly or birth defect. A medical event that might not result in death, be life-threatening, or require admission to hospital could be considered a serious adverse event, on the basis of appropriate medical judgement, if it might jeopardise the participant's health or might require medical or surgical intervention to prevent one of the outcomes listed here. A severe episode of hypoglycaemia was defined according to the American Diabetes Association classification,[18] requiring assistance of another person to actively administer carbohydrate, glucagon, or take other corrective actions. Symptomatic hypoglycaemia was confirmed by blood glucose concentration of less than 3·1 mmol/L (<56 mg/dL) with symptoms consistent with hypoglycaemia. Participants were followed up for adverse events until 5 weeks after the end of treatment or study drug discontinuation, as applicable. An independent external event adjudication committee did masked validation of predefined adverse events, including deaths, selected cardiovascular events, acute pancreatitis, malignant neoplasms, and acute kidney injury.

Outcomes

The primary endpoint was change from baseline to week 26 in HbA_{1c}. The confirmatory secondary endpoint was change from baseline to week 26 in bodyweight. Supportive secondary endpoints included change from baseline to week 52 in HbA_{1c} and bodyweight; change from baseline to weeks 26 and 52 in fasting plasma glucose, seven-point self-measured blood-glucose concentration, and fasting lipids; whether at weeks 26 and 52 a participant achieved an HbA_{1c} target of less than 7·0% (53 mmol/mol), an HbA_{1c} target of 6·5% (48 mmol/mol) or less, or weight loss of 5% or more or 10% or more; and treatment satisfaction as measured with DTSQs scores. A full list of secondary endpoints is in the appendix (p 4).

Safety endpoints were the number of treatment-emergent adverse events during exposure to study drug assessed up to 57 weeks; number of treatment-emergent symptomatic hypoglycaemic episodes that were severe as classified by the American Diabetes Association[18] or confirmed by blood-glucose concentration, assessed up to 57 weeks; change from baseline to week 26 and 52 in haematology, biochemistry, calcitonin, pulse rate, systolic and diastolic blood pressure, ECG category, physical examination (week 52 only), and eye examination category (week 52 only); and any occurrence of anti-semaglutide antibodies up to approximately 57 weeks.

Statistical analysis

We used a weighted Bonferroni closed-testing strategy[19] to control the overall type 1 error for five confirmatory hypotheses for the treatment policy estimand only (see appendix pp 5–6). We based our statistical testing strategy on the following two principles: superiority regarding change in HbA_{1c} of oral semaglutide 14 mg versus placebo was to be established before testing for glycaemic effect versus liraglutide 1·8 mg; and non-inferiority regarding change in HbA_{1c} of oral semaglutide 14 mg versus liraglutide 1·8 mg (margin: 0·4%) was to be established before testing for added benefits in terms of HbA_{1c} superiority versus liraglutide 1·8 mg and bodyweight superiority versus liraglutide 1·8 mg and placebo. The sample size calculation ensured a power of at least 90% for jointly confirming all hypotheses except superiority of oral semaglutide versus liraglutide 1·8 mg. Superiority of oral semaglutide versus placebo regarding change in HbA_{1c} was first tested at the overall significance level (5%) while allocating a 0% local significance level to the remaining hypotheses. For this hypothesis, and in general, if a hypothesis was confirmed, the significance level was reallocated to the next hypothesis in the testing strategy (see appendix pp 5–6). We tested each of the following hypotheses at their local significance level (α-local). We repeated this process until no further hypotheses could be confirmed.

We estimated the treatment policy estimand by ANCOVA for continuous endpoints and logistic regression for binary endpoints, using data irrespective of discontinuation of trial product or initiation of rescue medication. We used a pattern mixture model with multiple imputation to handle missing data at week 26 for the primary endpoint and the confirmatory secondary endpoint. We included all data collected at week 26 from all participants who were randomly assigned in the statistical analysis, irrespective of premature discontinuation of study drug or initiation of rescue medication. We did data imputation in groups defined by study drug and treatment status at week 26. We based both the imputation and the analysis on ANCOVA models. We combined the results using Rubin's rule.[20] Before testing for non-inferiority versus subcutaneous liraglutide, we added a value of 0·4% (the non-inferiority margin) to imputed values at week 26 for the oral semaglutide group only to minimise the potential bias

towards equivalence in the estimation of the treatment policy.[21]

We estimated the trial product estimand using a mixed model for continuous endpoints, logistic regression for binary endpoints, and repeated measurements that used data collected before early discontinuation of study drug or initiation of rescue medication from all participants who were randomly assigned. We excluded data collected after discontinuation of study drug or initiation of rescue medication. For binary endpoints, we imputed missing values from participants randomly assigned to same treatment group using sequential multiple imputation.

We assessed safety endpoints in all participants exposed to at least one dose of trial drug (safety analysis set) and evaluated for both the on-treatment period (duration participant was on assigned study drug) and in-trial period (duration participant was in trial regardless of early discontinuation of study drug).

We did sensitivity analyses to estimate the robustness of the primary endpoint as listed in the appendix (p 9).

No deviations from the assumption behind the statistical model led to additional analyses or changes to the pre-specified statistical analysis models. The variables included in the model are described in the appendix (pp 5–6) and included baseline measure of the endpoint and stratification variables. We included all reported secondary and sensitivity analyses in the protocol and the statistical analysis plan and all analyses were done according to the statistical analysis plan. Further details on statistical analyses can be found in the appendix (pp 5–6).

p values are unadjusted two-sided p values for the test of no difference. We did all analyses using SAS version 9.4M2. This trial is registered with Clinicaltrials.gov, identifier NCT02863419, and the European Clinical Registry, identifier EudraCT 2015-005210-30.

Role of the funding source

The funder designed the trial, monitored trial sites, and collected and analysed data. The manuscript was drafted by the corresponding author with medical writing and editorial support and under the guidance of the authors. All authors had full access to all the data in the study, actively contributed to all drafts of the manuscript, and made the decision to submit the manuscript for publication.

Results

Between Aug 10, 2016, and Feb 7, 2017, 950 patients were screened, of whom 711 were enrolled and randomly assigned to oral semaglutide (n=285), subcutaneous liraglutide (n=284), or placebo (n=142). 277 (97%) participants in the oral semaglutide group, 274 (96%) in the liraglutide group, and 134 (94%) in the placebo group completed the 52-week trial period. All participants were given at least one dose of assigned treatment and treatment was completed without rescue medication for 223 (78%) of 285 participants in the oral semaglutide group, 231 (81%) of 284 in the liraglutide group, and 83 (58%) of 142 in the placebo group (figure 1).

Baseline demographic and clinical characteristics were similar between the groups (table 1). 341 (48%) of 711 participants were female, mean age was 56 years (SD 10), mean diabetes duration was 7·6 years (SD 5·5), mean HbA_{1c} was 8·0% (SD 0·7; 64 mmol/mol [SD 8]), mean fasting plasma glucose was 9·28 mmol/L (SD 2·23; 167·2 mg/dL [SD 40·2]), and mean BMI was 33·0 kg/m² (SD 6·3). Up to 26 weeks, rescue medication was required for ten (4%) participants in the oral semaglutide group, nine (3%) in the liraglutide group, and 11 (8%) in the placebo group; and up to week 52, rescue medication was required for 20 (7%) participants in the oral semaglutide group, 18 (6%) in the liraglutide group, and 43 (30%) in the placebo group (appendix p 15). Use of rescue medication over time is shown in the appendix (p 8). Premature discontinuation of study drug in the oral semaglutide and liraglutide groups mainly occurred during the dose escalation period, and generally occurred earlier with liraglutide than with oral semaglutide.

Mean change from baseline in HbA_{1c} at week 26 was –1·2% (SE 0·1) for oral semaglutide, –1·1% (SE 0·1) for liraglutide, and –0·2% (SE 0·1) for placebo for the treatment policy estimand (figure 2). Oral semaglutide

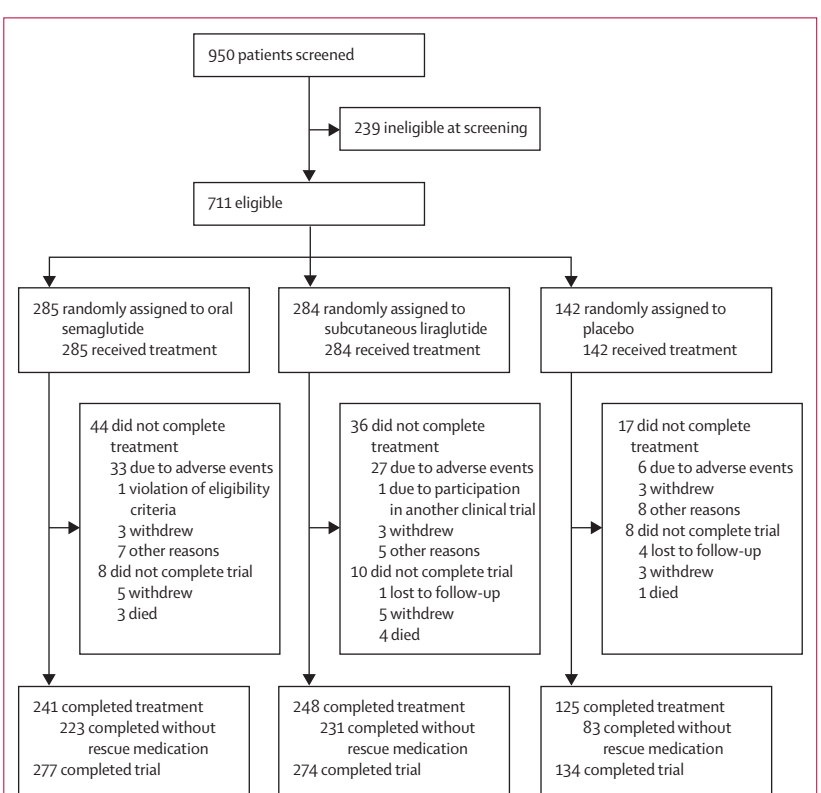

Figure 1: **Trial profile**

	Oral semaglutide 14 mg (n=285)	Liraglutide 1·8 mg (n=284)	Placebo (n=142)	Total (n=711)
Age, years	56 (10)	56 (10)	57 (10)	56 (10)
Sex				
Female	138 (48%)	135 (48%)	68 (48%)	341 (48%)
Male	147 (52%)	149 (52%)	74 (52%)	370 (52%)
Race				
White	208 (73%)	212 (75%)	99 (70%)	519 (73%)
Black or African American	12 (4%)	9 (3%)	8 (6%)	29 (4%)
Asian	39 (14%)	36 (13%)	19 (13%)	94 (13%)
Other*	3 (1%)	10 (4%)	4 (3%)	17 (2%)
Not available†	23 (8%)	17 (6%)	12 (8%)	52 (7%)
Ethnicity				
Hispanic or Latino	17 (6%)	18 (6%)	5 (4%)	40 (6%)
Not Hispanic or Latino	268 (94%)	266 (94%)	137 (96%)	671 (94%)
Coutry of origin				
Japanese	31 (11%)	29 (10%)	15 (11%)	75 (11%)
Non-Japanese	254 (89%)	255 (90%)	127 (89%)	636 (89%)
HbA_{1c}, %	8·0% (0·7)	8·0% (0·7)	7·9% (0·7)	8·0% (0·7)
HbA_{1c}, mmol/mol	64 (8)	64 (7)	63 (8)	64 (8)
Fasting plasma glucose, mmol/L	9·27 (2·23)	9·30 (2·22)	9·25 (2·27)	9·28 (2·23)
Bodyweight, kg	92·9 (20·6)	95·5 (21·9)	93·2 (20·0)	94·0 (21·0)
BMI, kg/m²	32·5 (5·9)	33·4 (6·7)	32·9 (6·1)	33·0 (6·3)
Waist circumference, cm	108·3 (14·3)	109·1 (15·1)	108·0 (13·6)	108·6 (14·4)
eGFR,‡ mL/min per 1·73 m²	96 (15)	96 (15)	95 (15)	96 (15)
Duration of diabetes, years	7·8 (5·7)	7·3 (5·3)	7·8 (5·5)	7·6 (5·5)
On SGLT2 inhibitor treatment at baseline	74 (26%)	73 (26%)	36 (25%)	183 (26%)

Data are mean (SD) or n (%). HbA_{1c}=glycated haemoglobin. BMI=body-mass index. eGFR=estimated glomerular filtration rate. SGLT2=sodium-glucose cotransporter-2. *Includes American Indian or Alaskan Native, Native Hawaiian, or Pacific Islander, and other. †For participants in South Africa, race was not available. ‡eGFR was estimated using the Chronic Kidney Disease Epidemiology Collaboration formula.

Table 1: **Baseline demographic and clinical characteristics**

was non-inferior to subcutaneous liraglutide (margin of 0·4%; estimated treatment difference [ETD] –0·1%, 95% CI –0·3 to 0·0; p<0·0001 for non-inferiority) and superior to placebo (ETD –1·1%, –1·2 to –0·9]; p<0·0001) in decreasing HbA_{1c}. Superiority of oral semaglutide over subcutaneous liraglutide was not confirmed.

Assessed with the trial product estimand, oral semaglutide had significantly greater decreases in HbA_{1c} than both subcutaneous liraglutide (ETD –0·2%, 95% CI –0·3 to –0·1; p=0·0056) and placebo (ETD –1·2%, –1·4 to –1·0; p<0·0001) at week 26 (figure 2).

Oral semaglutide resulted in superior weight loss at week 26 (mean change –4·4 kg [SE 0·2]) compared with subcutaneous liraglutide (–3·1 kg [SE 0·2] ; ETD –1·2 kg, 95% CI –1·9 to –0·6; p=0·0003) and placebo (–0·5 kg [SE 0·3]; ETD –3·8 kg, –4·7 to –3·0; p<0·0001) when assessed with the treatment policy estimand (figure 3). When assessed with the trial product estimand, weight loss at week 26 was significantly greater with oral semaglutide than with subcutaneous liraglutide (–1·5 kg, 95% CI –2·2 to –0·9; p<0·0001) and placebo (ETD –4·0 kg, –4·8 to –3·2; p<0·0001; figure 3).

At 52 weeks, decreases in HbA_{1c} were significantly greater with oral semaglutide than with both subcutaneous liraglutide (ETD –0·3%, 95% CI –0·5 to –0·1; p=0·0002) and placebo (ETD –1·0%, –1·2 to –0·8; p<0·0001) with the treatment policy estimand; this trend was also seen with the trial product estimand (figure 2). At 52 weeks, significantly greater decreases in bodyweight were seen with oral semaglutide than with both subcutaneous liraglutide and placebo for both estimands (figure 3).

Mean fasting plasma glucose was significantly decreased with oral semaglutide compared with placebo at week 26 for both estimands but not with liraglutide and compared with both liraglutide and placebo at week 52 for both estimands (table 2; appendix p 10). Mean seven-point self-measured blood glucose profile was significantly decreased with oral semaglutide compared with liraglutide and placebo at weeks 26 and 52 for both estimands (table 2; appendix p 10).

The odds of achieving HbA_{1c} targets of less than 7·0% (53 mmol/mol) or 6·5% (48 mmol/mol) or less were not different between oral semaglutide and subcutaneous liraglutide at week 26, but significantly favoured oral semaglutide for the target of HbA_{1c} of 6·5% or less at week 52 for both estimands (figure 2; table 2). The odds of achieving both targets were significantly better with oral semaglutide than with placebo at weeks 26 and 52 (both estimands; figure 2; table 2).

The odds of achieving a bodyweight loss of 5% or more or 10% or more were significantly better with oral semaglutide than with liraglutide and placebo at weeks 26 and 52 for both estimands (figure 3; table 2).

Results for other supportive secondary endpoints are shown in table 2 and in the appendix (pp 16–21). Outcomes were similar or better for oral semaglutide than with liraglutide and generally favoured oral semaglutide over placebo. A significant difference in the total treatment satisfaction score, as measured with the DTSQs at weeks 26 and 52 for both treatment estimands, indicated that oral semaglutide was favoured over placebo and was similar to liraglutide (appendix pp 11–12).

The proportion of participants reporting an adverse event was 80% (229 of 285) in the oral semaglutide group, 74% (211 of 284) in the liraglutide group, and 67% (95 of 142) in the placebo group (table 3). The slightly higher occurrence of adverse events with oral semaglutide than with subcutaneous liraglutide was largely attributable to gastrointestinal events, with the most frequent being transient nausea (appendix p 13) and diarrhoea, which were generally mild to moderate in severity. Peak occurrence of nausea was earlier with subcutaneous liraglutide than with oral semaglutide (approximately week 2 compared with week 8), before decreasing in both groups.

31 (11%) participants in the oral semaglutide group, 26 (9%) in the liraglutide group, and five (4%) in the placebo group discontinued study treatment early due to adverse events (table 3; appendix p 22). Gastrointestinal

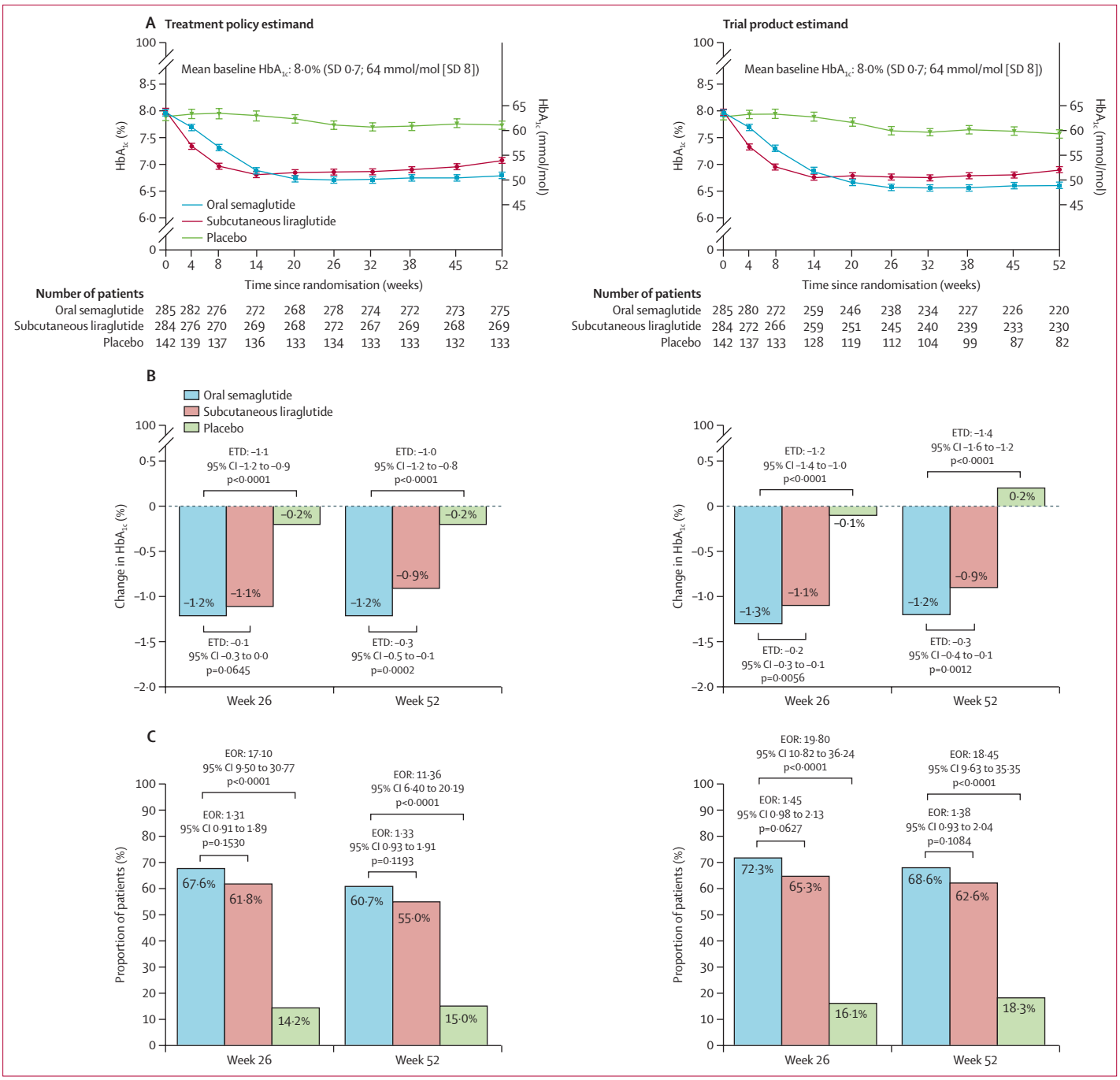

Figure 2: **Glycaemic control-related efficacy endpoints**
(A) Observed mean changes (SD) in HbA_{1c} over time with in-trial data for the treatment policy estimand and on-treatment without rescue medication data for the trial product estimand. (B) Estimated mean change from baseline in HbA_{1c} for the treatment policy estimand and trial product estimand at weeks 26 and 52. (C) Observed proportions of patients achieving HbA_{1c} target of less than 7·0% (53 mmol/mol) at weeks 26 and 52. EOR=estimated odds ratio. ETD=estimated treatment difference. HbA_{1c}=glycated haemoglobin.

side-effects were the main reason for discontinuations. The proportion of participants who had a serious adverse event was similar in the oral semaglutide and placebo groups, and lower in the liraglutide group (table 3). Eight deaths occurred during the trial (oral semaglutide group, n=3; liraglutide group, n=4; placebo group, n=1; appendix p 23). All deaths were judged as not treatment related by the investigator.

Severe or blood-glucose-confirmed symptomatic hypoglycaemic events occurred in two (1%) participants in the oral semaglutide group, seven (2%) in the liraglutide group, and three (2%) in the placebo group (table 3).

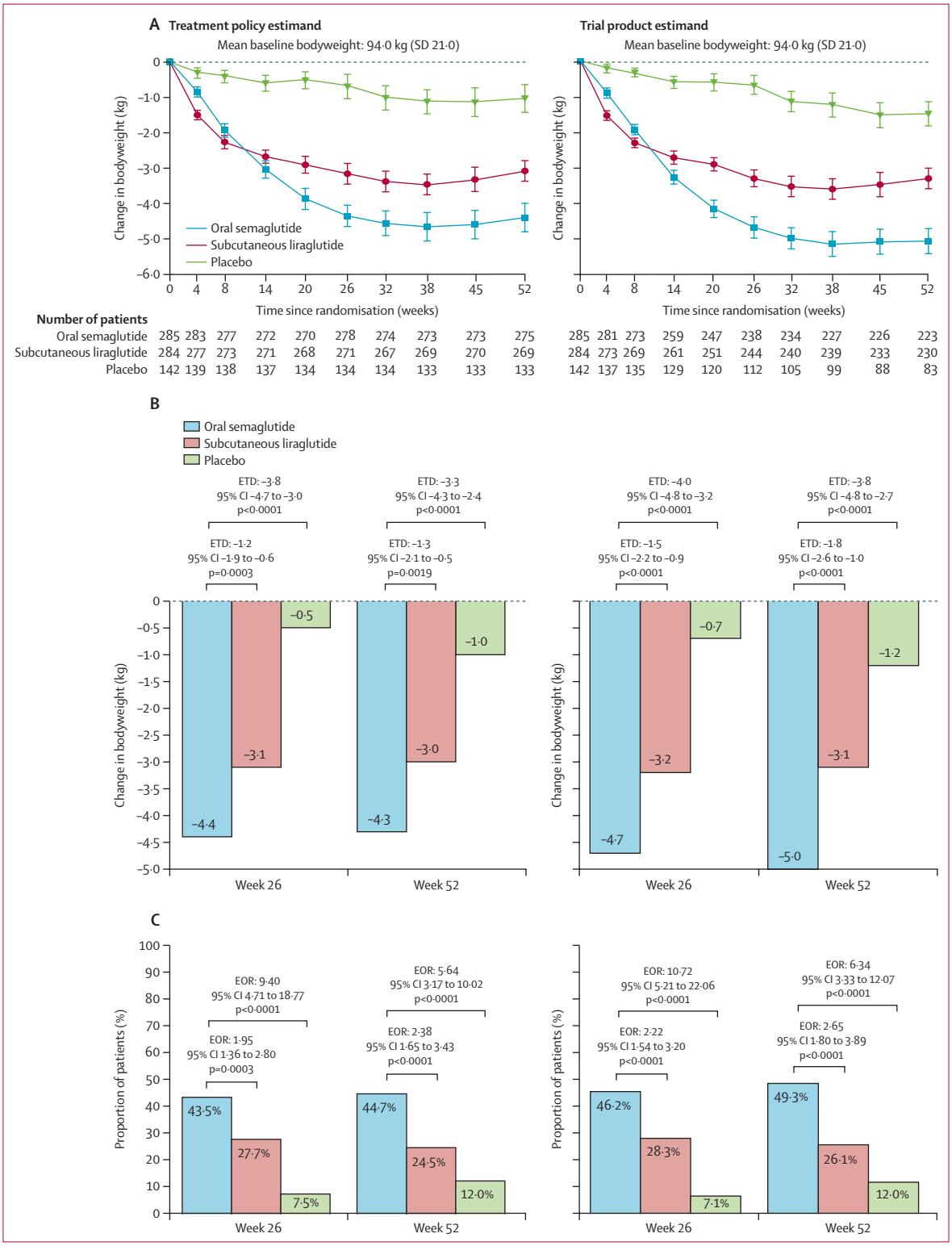

Figure 3: **Bodyweight-related efficacy endpoints**
(A) Observed mean changes (SD) from baseline in bodyweight over time with in-trial data for the treatment policy estimand and on-treatment without rescue medication data for the trial product estimand. (B) Estimated mean changes from baseline in bodyweight for the treatment policy estimand and the trial product estimand at weeks 26 and 52. (C) Observed proportions of patients achieving 5% or more weight loss at weeks 26 and 52. EOR=estimated odds ratio. ETD=estimated treatment difference.

	Treatment policy estimand			Trial product estimand		
	Oral semaglutide group (n=285)	Liraglutide group (n=284)	Placebo group (n=142)	Oral semaglutide group (n=285)	Liraglutide group (n=284)	Placebo group (n=142)
Fasting plasma glucose, mmol/L						
Week 26						
Number of participants analysed	276	269	133	236	243	111
Estimated mean	7·28 (SE 0·1)	7·41 (SE 0·1)	8·92 (SE 0·2)	7·20 (SE 0·1)	7·43 (SE 0·1)	9·00 (SE 0·1)
Estimated mean change from baseline	−2·00 (SE 0·1)	−1·87 (SE 0·1)	−0·36 (SE 0·2)	−2·08 (SE 0·1)	−1·85 (SE 0·1)	−0·28 (SE 0·1)
Estimated treatment difference	..	−0·13 (−0·41 to 0·14); p=0·3422	−1·64 (−1·99 to −1·28); p<0·0001	..	−0·22 (−0·50 to 0·06); p=0·1171	−1·80 (−2·14 to −1·45); p<0·0001
Week 52						
Number of participants analysed	273	269	132	220	229	83
Estimated mean	7·40 (SE 0·1)	7·81 (SE 0·1)	8·58 (SE 0·2)	7·40 (SE 0·1)	7·77 (SE 0·1)	8·98 (SE 0·2)
Estimated mean change from baseline	−1·88 (SE 0·1)	−1·47 (SE 0·1)	−0·70 (SE 0·2)	−1·87 (SE 0·1)	−1·51 (SE 0·1)	−0·30 (SE 0·2)
Estimated treatment difference	..	−0·41 (−0·74 to −0·08); p=0·0136	−1·19 (−1·58 to −0·79); p<0·0001	..	−0·36 (−0·71 to −0·02); p=0·0383	−1·58 (−2·03 to −1·13); p<0·0001
Seven-point SMBG, mmol/L						
Week 26						
Number of participants analysed	263	257	129	231	235	113
Estimated mean	7·7 (SE 0·1)	8·0 (SE 0·1)	9·1 (SE 0·1)	7·5 (SE 0·1)	7·9 (SE 0·1)	9·1 (SE 0·1)
Estimated mean change from baseline	−2·2 (SE 0·1)	−1·9 (SE 0·1)	−0·8 (SE 0·1)	−2·3 (SE 0·1)	−1·9 (SE 0·1)	−0·7 (SE 0·1)
Estimated treatment difference	..	−0·3 (−0·6 to −0·0); p=0·0294	−1·4 (−1·8 to −1·1); p<0·0001	..	−0·4 (−0·6 to −0·1); p=0·0032	−1·6 (−1·9 to −1·3); p<0·0001
Week 52						
Number of participants analysed	263	251	126	217	215	78
Estimated mean	7·8 (SE 0·1)	8·3 (SE 0·1)	8·9 (SE 0·1)	7·6 (SE 0·1)	8·1 (SE 0·1)	9·0 (SE 0·2)
Estimated mean change from baseline	−2·1 (SE 0·1)	−1·6 (SE 0·1)	−1·0 (SE 0·1)	−2·3 (SE 0·1)	−1·8 (SE 0·1)	−0·9 (SE 0·2)
Estimated treatment difference	..	−0·5 (−0·8 to −0·2); p=0·0008	−1·1 (−1·5 to −0·8); p<0·0001	..	−0·5 (−0·8 to −0·2); p=0·004	−1·4 (−1·8 to −1·0); p<0·0001
HbA_{1c} ≤6·5%						
Week 26						
Number of participants analysed	278	272	134	238	245	112
Participants reaching endpoint	133 (48%)	116 (43%)	7 (5%)	125 (53%)	113 (46%)	7 (6%)
Estimated odds ratio	..	1·22 (0·86 to 1·74); p=0·2687	21·42 (9·41 to 48·75); p<0·0001	..	1·31 (0·91 to 1·88); p=0·1494	23·66 (10·33 to 54·16); p<0·0001
Week 52						
Number of participants analysed	275	269	133	220	230	82
Participants reaching endpoint	119 (43%)	88 (33%)	5 (4%)	110 (50%)	87 (38%)	4 (5%)
Estimated odds ratio	..	1·63 (1·13 to 2·33); p=0·0084	21·38 (8·36 to 54·63); p<0·0001	..	1·65 (1·14 to 2·41); p=0·0088	29·76 (10·59 to 83·66); p<0·0001
Body-mass index, kg/m²						
Week 26						
Number of participants analysed	278	271	134	238	244	112
Estimated mean	31·4 (SE 0·1)	31·9 (SE 0·1)	32·8 (SE 0·1)	31·3 (SE 0·1)	31·8 (SE 0·1)	32·7 (SE 0·1)
Estimated mean change from baseline	−1·6 (SE 0·1)	−1·1 (SE 0·1)	−0·2 (SE 0·1)	−1·7 (SE 0·1)	−1·1 (SE 0·1)	−0·2 (SE 0·1)
Estimated treatment difference	..	−0·5 (−0·7 to −0·2); p=0·0002	−1·4 (−1·7 to −1·1); p<0·0001	..	−0·6 (−0·8 to −0·3); p<0·0001	−1·4 (−1·7 to −1·2); p<0·0001
Week 52						
Number of participants analysed	275	269	133	223	230	83
Estimated mean	31·4 (SE 0·1)	31·9 (SE 0·1)	32·6 (SE 0·2)	31·1 (SE 0·1)	31·9 (SE 0·1)	32·5 (SE 0·2)
Estimated mean change from baseline	−1·6 (SE 0·1)	−1·1 (SE 0·1)	−0·3 (SE 0·2)	−1·8 (SE 0·1)	−1·1 (SE 0·1)	−0·4 (SE 0·2)
Estimated treatment difference	..	−0·5 (−0·8 to −0·2); p=0·0006	−1·2 (−1·6 to −0·9); p<0·0001	..	−0·7 (−1·0 to −0·4); p<0·0001	−1·4 (−1·8 to −1·0); p<0·0001

(Table 2 continues on next page)

	Treatment policy estimand			Trial product estimand		
	Oral semaglutide group (n=285)	Liraglutide group (n=284)	Placebo group (n=142)	Oral semaglutide group (n=285)	Liraglutide group (n=284)	Placebo group (n=142)
(Continued from previous page)						
Bodyweight loss ≥10%						
Week 26						
Number of participants analysed	278	271	134	238	244	112
Participants reaching endpoint	39 (14%)	16 (6%)	0	36 (15%)	15 (6%)	0
Estimated odds ratio	..	2·45 (1·35 to 4·44); p=0·0032	39·88 (2·58 to 615·6); p=0·0083	..	2·77 (1·52 to 5·06); p=0·0009	42·92 (2·85 to 646·3); p=0·0066
Week 52						
Number of participants analysed	275	269	133	223	230	83
Participants reaching endpoint	45 (16%)	20 (7%)	4 (3%)	41 (18%)	18 (8%)	3 (4%)
Estimated odds ratio	..	2·31 (1·33 to 4·01); p=0·0028	5·74 (2·14 to 15·36); p=0·0005	..	2·91 (1·65 to 5·13); p=0·0002	42·92 (2·85 to 646·3); p=0·0066

Data are n, mean (SE), mean change (SE), n (%), or estimated treatment difference or estimated odds ratio with 95% CI in parentheses and p values. Number of participants analysed are the number with an observation at study visit. p values are unadjusted two-sided p values for the test of no difference. SMBG is reported as plasma equivalent values calibrated from capillary whole blood glucose. SMBG=self-monitored blood glucose. HbA_{1c}=glycated haemoglobin.

Table 2: **Selected supportive secondary endpoints**

	Oral semaglutide group (n=285)	Liraglutide group (n=284)	Placebo group (n=142)
Adverse events	229 (80%)	211 (74%)	95 (67%)
Severity			
Severe	23 (8%)	22 (8%)	7 (5%)
Moderate	120 (42%)	102 (36%)	32 (23%)
Mild	192 (67%)	180 (63%)	87 (61%)
Severe or blood-glucose-confirmed symptomatic hypoglycaemic episode*	2 (1%)	7 (2%)	3 (2%)
Most frequent adverse events†			
Nausea	56 (20%)	51 (18%)	5 (4%)
Diarrhoea	43 (15%)	31 (11%)	11 (8%)
Vomiting	25 (9%)	13 (5%)	3 (2%)
Constipation	22 (8%)	11 (4%)	4 (3%)
Abdominal pain	16 (6%)	6 (2%)	3 (2%)
Dyspepsia	16 (6%)	12 (4%)	0
Nasopharyngitis	41 (14%)	37 (13%)	15 (11%)
Headache	27 (9%)	17 (6%)	9 (6%)
Decreased appetite	16 (6%)	20 (7%)	0
Back pain	11 (4%)	18 (6%)	5 (4%)
Blood glucose increased	0	2 (1%)	9 (6%)
Serious adverse events	31 (11%)	22 (8%)	15 (11%)
Adverse events leading to early discontinuation of study drug	31 (11%)	26 (9%)	5 (4%)
Gastrointestinal adverse events leading to early discontinuation of study drug	22 (8%)	17 (6%)	3 (2%)

Data are n (%). *Hypoglycaemic episodes were reported on a separate form to adverse events. †Occurring in more than 5% of participants in any treatment group, categorised by preferred term (Medical Dictionary for Regulatory Activities, version 20.1).

Table 3: **On-treatment adverse events**

Adverse events associated with diabetic retinopathy were infrequent across groups (eight [3%] in the oral semaglutide group, four [1%] in the liraglutide group, and two [1%] in the placebo group; appendix p 24). Two pancreatitis events confirmed by the independent event adjudication committee were reported, one in the liraglutide group and one in the placebo group (appendix p 25). No lactic acidosis events occurred.

No clinically relevant changes in physical examinations or ECG readings were recorded in any groups. Data on vital signs and laboratory assessments are summarised in the appendix (pp 26–28). Blood pressure and pulse rate changes from baseline were generally similar between treatment groups. Lipase and amylase were generally similar between oral semaglutide and liraglutide but were significantly increased with oral semaglutide compared with placebo. Renal function remained stable in all treatment groups.

One participant in the oral semaglutide group tested positive for anti-semaglutide antibodies at baseline, but not at any measurements thereafter; the single positive sample was negative for cross-reacting antibodies and in-vitro neutralising effect.

Discussion

In PIONEER 4, oral semaglutide was compared with daily injections of subcutaneous liraglutide and placebo in patients with type 2 diabetes receiving metformin with or without an SGLT2 inhibitor. Using the treatment policy estimand, oral semaglutide was non-inferior to once-daily subcutaneous liraglutide given at the highest approved dose for the treatment of type 2 diabetes and superior to placebo in decreasing HbA_{1c} at week 26. Additionally, significantly greater decreases in HbA_{1c} were observed with oral semaglutide than with both liraglutide and placebo at week 52 using the treatment policy estimand. Using the trial product estimand, a significantly greater decrease in HbA_{1c} was seen with oral semaglutide than with both comparators at weeks 26 and 52. With respect to bodyweight, significant decreases

compared with subcutaneous liraglutide and placebo were seen for oral semaglutide at both weeks 26 and 52, assessed with both estimands.

Improvement in HbA_{1c} was more rapid with subcutaneous liraglutide compared with oral semaglutide, likely attributable to the faster dose escalation of liraglutide than oral semaglutide. Decrease in fasting plasma glucose concentration with oral semaglutide was similar to that seen with subcutaneous liraglutide at week 26, with a significantly greater decrease with oral semaglutide than with liraglutide seen at week 52, suggesting a long-term benefit with continued oral semaglutide therapy. By contrast, the slower dose escalation with oral semaglutide than with liraglutide did not hinder a superior decrease in bodyweight at week 26.

The double-blind, double-dummy, placebo-controlled design of the trial provides a high degree of robustness for safety assessment both within drug class (oral semaglutide *vs* subcutaneous liraglutide) and overall (oral semaglutide *vs* placebo). Adverse events were slightly more frequent with oral semaglutide than with subcutaneous liraglutide, but the safety and tolerability profile of oral semaglutide was consistent with the GLP-1 receptor agonist class. The most frequent adverse events were gastrointestinal in nature, most commonly mild-to-moderate and transient nausea, which occurred with a similar incidence in the oral semaglutide and subcutaneous liraglutide groups. The timing of nausea differed between treatment groups, with peak occurrence being earlier with subcutaneous liraglutide than with oral semaglutide, before decreasing in both groups. This result might reflect the slower dose escalation of oral semaglutide, leading to a more gradual increase in GLP-1 exposure than with the faster dose escalation schedule of liraglutide. Slightly more participants withdrew prematurely due to adverse events with oral semaglutide than with subcutaneous liraglutide, with discontinuations primarily due to gastrointestinal adverse events—in particular, nausea.

The robust design and high completion rate of this trial, and the use of a commonly employed subcutaneous GLP-1 receptor agonist as the active comparator, make the results of this study highly relevant to clinical practice. Nevertheless, larger population-based studies might be required to fully elucidate the effectiveness and safety of oral semaglutide in a broader population, including younger and older patients and those from more diverse racial, ethnic and social backgrounds.

In conclusion, oral semaglutide was non-inferior to daily injections of liraglutide and superior to placebo in decreasing HbA_{1c}, and superior in decreasing bodyweight over both comparators at week 26. Safety and tolerability of oral semaglutide were consistent with subcutaneous liraglutide. Because many patients are reluctant to initiate or intensify therapy by injection, oral semaglutide might be an effective treatment option, potentially leading to earlier initiation of GLP-1 receptor agonist therapy in the diabetes treatment continuum of care.

Contributors

RP, AA, TK, IL, MN, and JJM contributed to data collection (as study investigators). STH, KBP, and TS contributed to trial design and data analysis (as employees of the sponsor). All authors interpreted the data. The first draft of the manuscript was prepared by the corresponding author and all authors 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 manuscript.

Declaration of interests

RP reports lecture and consulting fees from AstraZeneca; consulting fees from Boehringer-Ingelheim, Eisai, GlaxoSmithKline, and Mundipharma; grants and lecture and consulting fees from Glytec, Janssen, Novo Nordisk, Pfizer, and Takeda; grants from Lexicon Pharmaceuticals; and grants and consulting fees from Ligand Pharmaceuticals, Lilly, Merck, and Sanofi-Aventis US outside of the submitted work. And except for consulting fees in February, 2018, and June, 2018, from Sanofi US Services, RP's fees for services were paid directly to AdventHealth, a non-profit organisation. AA reports personal fees related to advisory boards and lectures from Novo Nordisk, Sanofi (South Africa), AstraZeneca, Merck Sharp & Dohme, Lilly South Africa, Boehringer Ingelheim, Merck Biopharma, Novartis South Africa, Aspen Pharmacare, and Servier Laboratories. TK reports honoraria from Merck Sharpe & Dohme, Daiichi Sankyo, Takeda Pharmaceutical, Mitsubishi Tanabe Pharma Corporation, Kowa Pharmaceutical, Astellas Pharma, Ono Pharmaceutical, AstraZeneca KK, Sumitomo Dainippon Pharma, Sanofi KK, Eli Lilly Japan KK, Nippon Boehringer Ingelheim, Sanwa Kagaku Kenkyusho, Kyowa Hakko Kirin, and Taisho Pharmaceutical; research funds from Merck Sharpe & Dohme, Daiichi Sankyo, Novo Nordisk Pharma, Sanofi KK, and Takeda Pharmaceutical. TK's department has received annual fees of ¥1 million or higher that TK is substantially authorised to use from Takeda Pharmaceutical, TERUMO Corporation, Merck Sharpe & Dohme, Novo Nordisk Pharma, and Nippon Boehringer Ingelheim. IL reports consulting fees from Sanofi, AstraZeneca, Valeritas, Eli Lilly, Boehringer Ingelheim, TARGETPharma, Intarcia, and MannKind. IL's employer has received research funding or consulting fees from Novo Nordisk, Merck, Pfizer, Novartis, and Mylan. MN reports having served on advisory boards or consulted for AstraZeneca, Boehringer Ingelheim, Eli Lilly, Fractyl, GlaxoSmithKline, Intarcia, Menarini/Berlin Chemie, Merck Sharp & Dohme, and Novo Nordisk, and having served on speakers' bureau for AstraZeneca, Boehringer Ingelheim, Eli Lilly, GlaxoSmithKline, Menarini/Berlin Chemie, Merck Sharp & Dohme, Novo Nordisk A/S, and Sun Pharma. MN institution has received grant support from AstraZeneca, Boehringer Ingelheim, Eli Lilly, GlaxoSmithKline, Intarcia, Menarini/Berlin-Chemie, Merck Sharp & Dohme, Novartis, and Novo Nordisk A/S. JJM reports personal fees from Astra Zeneca, Eli Lilly, and Servier; and grants and personal fees from Boehringer Ingelheim, Merck Sharpe & Dohme, Novo Nordisk, and Sanofi outside of the submitted work. STH, KBP, and TS are employees of Novo Nordisk. STH and TS also own shares in Novo Nordisk.

Data sharing

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

Acknowledgments

This trial was funded by Novo Nordisk A/S, Denmark. We thank the patients who took part in this trial, the investigators, all trial site staff, and all Novo Nordisk employees involved in the trial. We thank Emisphere (Roseland, NJ, USA) for providing a license to the Eligen Technology— ie, the sodium N-(8-[2-hydroxylbenzoyl] amino) caprylate component of oral semaglutide. We also thank Andy Bond of Spirit Medical Communications Group for medical writing and editorial assistance (funded by Novo Nordisk A/S), and Brian Bekker Hansen of Novo Nordisk for reviewing the manuscript.

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