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Efficacy and safety of oral semaglutide in patients with type 2 diabetes and moderate renal impairment (PIONEER 5): a randomised, placebo-controlled phase 3a trial

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Summary

Background: Oral semaglutide has been developed as the first oral GLP-1 receptor agonist for glycaemic control of type 2 diabetes**.** Type 2 diabetes is commonly associated with renal impairment, limiting treatment options. The efficacy and safety of oral semaglutide in patients with type 2 diabetes and moderate renal impairment were investigated.

Methods: This 26-week, randomised, double-blind, phase 3a trial was conducted at 88 sites in eight countries. Patients with type 2 diabetes and estimated glomerular filtration rate 30–59 mL/min/1·73 m^2 received oral semaglutide 14 mg once daily or placebo for 26 weeks, added to background medication. Two efficacy-related estimands were defined: treatment policy (regardless of treatment discontinuation or rescue medication) and trial product (on treatment without rescue medication) in all randomised patients. Endpoints were change to week 26 in glycated haemoglobin (HbA_{1c}, primary endpoint) and body weight (confirmatory secondary endpoint). The trial is registered on ClinicalTrials.gov (NCT02827708) and EudraCT (2015-005326-19).

Findings: Oral semaglutide (n=163) was superior to placebo (n=161) in reducing HbA_{1c} (-1·0%-points *vs* -0·2%-points; estimated treatment difference [ETD]: -0·8 [95% confidence interval: -1·0, -0·6]; p<0·0001) and body weight (-3·4 kg *vs* -0·9 kg; ETD: -2·5 [-3·2, -1·8]; p<0·0001) by the treatment policy estimand. Statistically significant differences were seen for the trial product estimand: HbA_{1c} change -1·1%-points versus -0·1%-points (ETD: -1·0 [-1·2, -0·8]; p<0·0001); body weight -3·7 kg versus -1·1 kg (ETD: -2·7 [-3·5, -1·9]; p<0·0001). More patients taking oral semaglutide than placebo had adverse events (73·6% *vs* 65·2%), and discontinued treatment as a result (14·7% *vs* 5·0%). Gastrointestinal events, mainly mild-to-moderate nausea, were more common with oral semaglutide.

Interpretation: Oral semaglutide was effective in patients with type 2 diabetes and moderate renal impairment, potentially providing a new treatment option for this population. Safety, including renal safety, was consistent with the GLP-1 receptor agonist class.

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Keywords: clinical trial, GLP-1 receptor agonist, moderate renal impairment, oral semaglutide, phase 3, type 2 diabetes.

Research in context

Evidence before this trial

PubMed was searched for articles published in the last 5 years discussing type 2 diabetes and renal impairment or chronic kidney disease, and the prescribing information documents of approved glucose-lowering drugs were reviewed for dose adjustments and/or contraindications relating to renal function. Type 2 diabetes is often associated with renal impairment, but common oral glucose-lowering drugs have restrictions for use (e.g. sodium-glucose co-transporter [SGLT]-2 inhibitors), require increased monitoring (e.g. metformin) or dose adjustment (e.g. most dipeptidyl peptidase [DPP]-4 inhibitors), or are associated with an increased risk of hypoglycaemia and weight gain (sulfonylureas) in patients with reduced kidney function. Chronic kidney disease is a risk factor for hypoglycaemia, but many patients with renal impairment may be using insulin, sulfonylureas, and/or glinides for glycaemic control, which are also associated with an increased risk of hypoglycaemia as well as weight gain. Therefore, there is a need for improved glucose-lowering treatment options for these patients.

Added value of this trial

Oral semaglutide 14 mg taken once daily was superior to placebo in reducing glycated haemoglobin and body weight in patients with type 2 diabetes and moderate renal impairment who were uncontrolled on metformin and/or sulfonylureas, or basal insulin with/without metformin. The proportion of patients who achieved a target of glycated haemoglobin <7·0% was higher with oral semaglutide than placebo. Taking into account the population, oral semaglutide demonstrated a similar overall safety profile to that seen previously with the glucagon-like peptide-1 (GLP-1) receptor agonist class and did not adversely affect renal function.

Implications of all the available evidence

Some GLP-1 receptor agonists have demonstrated effective glycaemic control in patients with type 2 diabetes and impaired renal function (for example, liraglutide was superior to placebo, and dulaglutide was similarly effective to insulin, without a negative effect on renal function in either case). However, GLP-1 receptor agonists are all currently administered subcutaneously, which may not be ideal for some patients. Oral semaglutide is the first orally available GLP-1 receptor agonist and has the potential to expand the treatment options for patients with type 2 diabetes and moderate renal impairment, for whom current oral glucose-lowering treatment options are limited.

Introduction

Glucagon-like peptide (GLP)-1 receptor agonists act on multiple pathophysiological defects present in patients with type 2 diabetes.[1] Semaglutide is a GLP-1 analogue currently approved for once-weekly subcutaneous injection for treatment of type 2 diabetes,[2] and has been shown to reduce glycated haemoglobin (HbA_{1c}) and body weight effectively in patients uncontrolled on one or more oral glucose-lowering drugs.[3] Elimination of semaglutide occurs via multiple pathways, involving both the liver and kidneys.[4]

An oral semaglutide tablet has been developed, in which semaglutide is co-formulated with the absorption enhancer, sodium N-(8-[2-hydroxybenzoyl]amino) caprylate (SNAC), to facilitate semaglutide absorption across the gastric mucosa.[5] Oral semaglutide monotherapy has demonstrated significant HbA_{1c} and body weight reductions compared with placebo in patients with type 2 diabetes not controlled through diet and exercise,[6] and versus sitagliptin in addition to background metformin with or without sulfonylurea.[7]

Type 2 diabetes is commonly associated with renal impairment, which limits the use of some glucose-lowering medications and makes it challenging to achieve treatment targets. Insulin and sulfonylureas are associated with weight gain and increased risk of hypoglycaemia in patients with chronic kidney disease (CKD).[8,9] Metformin can be used with caution in patients with glomerular filtration rate >30 mL/min despite its association with lactic acidosis, a rare but serious complication.[10] Most sodium-glucose co-transporter (SGLT)-2 inhibitors are not recommended in patients with creatinine clearance <45 mL/min.[11] Dipeptidyl peptidase (DPP)-4 inhibitors can be used in patients with CKD (all stages, except CKD stage 5 for saxagliptin), although these agents (with the exception of linagliptin) must be given at a reduced dose dependent on the stage of CKD.[11] In contrast, the GLP-1 receptor agonists semaglutide, liraglutide, albiglutide, and dulaglutide do not require dose adjustment in patients with CKD stage 4 and above, and may represent a useful alternative.[11] Nevertheless, this class of medication is currently only available for subcutaneous injection, which may not be ideal for some patients.

In patients without diabetes, the pharmacokinetics of oral semaglutide were not affected by renal impairment.[12] However the efficacy and safety profile of oral semaglutide in patients with diabetes and renal impairment is unknown. Therefore, this phase 3a trial, PIONEER 5, compared the efficacy and safety of once-daily oral semaglutide versus placebo, added to existing background medication, in patients with type 2 diabetes and moderate renal impairment (estimated glomerular filtration rate [eGFR] 30–59 mL/min/1·73 m^2).

Methods

Study design

This 26-week, randomised, double-blind, placebo-controlled, parallel-group, multicentre, phase 3a trial was carried out at 88 sites in Denmark, Finland, Israel, Poland, Russia, Sweden, the United Kingdom, and the United States. Approval from the relevant Institutional Review Boards/Independent Ethics Committees was secured for each site prior to trial commencement, which was conducted according to applicable national requirements and in compliance with International Conference on Harmonisation Guidelines for Good Clinical Practice (ICH E6) and the Declaration of Helsinki.

Two different scientific questions related to the efficacy objectives were addressed through the definition of two estimands ('treatment policy' and 'trial product'). Both estimands were defined based on interactions with regulatory agencies. The treatment policy estimand was the protocol-defined primary estimand. Superiority testing was based on the treatment policy estimand only, and results were controlled for multiplicity. The trial product estimand was the protocol-defined secondary estimand and was used to assess the magnitude of an established treatment effect.

The treatment policy estimand evaluates the treatment effect for all randomised patients, regardless of trial product discontinuation or use of rescue medication. This estimand reflects the intention-to-treat principle as defined in ICH E9.[13] The estimand reflects the effect of initiating treatment with oral semaglutide compared with initiating treatment with placebo, both potentially followed by either discontinuation of trial product, or addition of or switch to another glucose-lowering drug.

The trial product estimand evaluates the treatment effect for all randomised patients, under the assumption that all patients remained on trial product (oral semaglutide or placebo) for the entire planned duration of the trial and did not use rescue medication. This estimand aims at reflecting the effect of oral semaglutide compared with placebo without the confounding effect of rescue medication. The statistical analysis that was applied to this estimand is similar to how many phase 3a diabetes trials have been evaluated. Results from such analyses are currently included in many product labels (e.g. European summary of product characteristics [SmPC]) for glucose-lowering drugs (e.g. Ozempic® SmPC).

Trial product 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).[14] Further details on the estimands can be found in the supplementary appendix.

Participants

Patients were aged ≥18 years with type 2 diabetes (diagnosed ≥90 days prior to screening), had HbA_{1c} 7·0–9·5% (53–80 mmol/mol) and moderate renal impairment (Chronic Kidney Disease-Epidemiology Collaboration [CKD-EPI] stage 3),[15] defined as eGFR 30–59 mL/min/1·73 m^2 (calculated using the CKD-EPI formula).[16] Patients were required to be treated with stable doses of one of the following regimens for 90 days prior to screening: metformin (≥1500 mg or maximum tolerated dose) and/or a sulfonylurea (at least half maximum approved dose, or maximum tolerated dose); or basal insulin, with or without metformin. All patients provided written informed consent before the conduct of any trial-related activity.

Patients were excluded if they had: rapidly progressing renal disease (as judged by the investigator) or known nephrotic albuminuria (>2200 mg/24 hours or >2200 mg/g); family or personal history of multiple endocrine neoplasia type 2 or medullary thyroid carcinoma; history of malignant neoplasms within the preceding 5 years; history of pancreatitis; myocardial infarction, stroke, or hospitalisation for unstable angina or transient ischaemic attack within the prior 180 days, or New York Heart Association Class IV heart failure; or proliferative retinopathy or maculopathy (determined by fundus photography or dilated fundoscopy at least 90 days before randomisation and requiring acute treatment). Full eligibility criteria are detailed in the supplementary appendix.

Randomisation and masking

Patients were randomised 1:1 to receive either once-daily oral semaglutide (14 mg) or placebo, added to their background medication (Figure S1). Randomisation was performed using an interactive web response system, which allocated dispensing unit numbers for each patient. Blinding of patients and site staff was maintained using visually identical oral semaglutide and placebo tablets. Randomisation was stratified based on background glucose-lowering medication (metformin alone, sulfonylurea ± metformin, or basal insulin ± metformin) and renal function (eGFR 45–59 [CKD-EPI stage 3A] or 30–44 [stage 3B] mL/min/1·73 m^2; at least 40% of patients had to be at stage 3B at screening).

Procedures

After a 2-week screening period, patients received once-daily oral semaglutide or placebo for 26 weeks, with a follow-up period of 5 weeks (Figure S1). Oral semaglutide was initiated at a 3 mg dose, then escalated to 7 mg at 4 weeks, and 14 mg at 8 weeks. No dose adjustment of trial product was permitted during the trial. Dose escalation was intended to improve gastrointestinal tolerability following experience with initiation at higher doses.[17] Absorption of oral semaglutide is affected by food and fluid in the stomach, so patients were instructed (for both oral semaglutide and placebo) to

take the medication in the morning in a fasted state with up to half a glass of water (approximately 120 mL), 30 minutes before the first meal of the day and taking any other oral medication.

Patients were required to continue background glucose-lowering medication throughout the trial. Those receiving metformin and sulfonylureas were required to maintain the same dose level and frequency as at trial entry; those receiving basal insulin were recommended to have the dose reduced by 20% at randomisation to minimise the risk of hypoglycaemic episodes. Up-titration of basal insulin (to a dose not exceeding that at randomisation) was permitted in weeks 10–16, after the maximum dose of oral semaglutide was reached.

Patients with persistent and unacceptable hyperglycaemia were offered treatment intensification with rescue medication, prescribed at the investigator's discretion and as an add-on to randomised treatment, in accordance with international guidelines.[18] Rescue medication, excluding GLP-1 receptor agonists, DPP-4 inhibitors, or amylin analogues, was recommended if fasting plasma glucose (confirmed at the central laboratory) exceeded 13·3 mmol/L (240 mg/dL) in weeks 12–16 or 11·1 mmol/L (200 mg/dL) from week 17 to end of treatment.

Blood samples were drawn at baseline and weeks 4, 8, 14, 20, 26 and 31 for assessment of glucose metabolism, lipid profile and other laboratory parameters. Renal function was assessed at baseline and weeks 14 and 26.

Patients prematurely discontinuing allocated trial product were switched to an appropriate locally approved treatment selected at the investigator's discretion, excluding GLP-1 receptor agonists. All patients were asked to complete the protocol-specified visit schedule, regardless of premature trial product discontinuation or rescue medication use, unless consent was withdrawn.

Outcomes

The primary and confirmatory secondary endpoints were change from baseline to week 26 in HbA_{1c} and body weight, respectively. Supportive secondary endpoints included achievement at week 26 of the targets of HbA_{1c} <7·0% (53 mmol/mol)[19] and ≤6·5% (48 mmol/mol),[20] and composite endpoints: HbA_{1c} <7·0% without treatment-emergent severe (American Diabetes Association [ADA] classification[21]) or blood glucose-confirmed (<3·1 mmol/L [56 mg/dL]) symptomatic hypoglycaemia, and without weight gain; and HbA_{1c} reduction ≥1·0% with weight loss ≥3% from baseline. Further endpoints included weight loss ≥5 or ≥10%, change from baseline to week 26 in: fasting plasma glucose; body mass index; waist circumference; fasting lipid profile; and C-reactive protein, and patient-reported outcomes (SF-36v2® Health Survey [acute version], and the status version of the Diabetes Treatment Satisfaction Questionnaire [DTSQs]). Exploratory and descriptive investigations of endpoints by eGFR strata were performed post hoc on the primary and secondary endpoints.

Safety endpoints included the number of treatment-emergent adverse events, and the number of severe and/or blood glucose-confirmed (<3·1 mmol/L [56 mg/dL]) symptomatic hypoglycaemic episodes. Severe hypoglycaemia was defined as the patient requiring third-party assistance to administer corrective treatment (ADA classification).[21] Additional safety endpoints encompassed changes from baseline in a range of laboratory assessments (including eGFR and urinary albumin to creatinine ratio [UACR]), electrocardiograms, physical examinations, vital signs, and eye examinations. An independent event adjudication committee (EAC) validated selected adverse events according to pre-defined diagnostic criteria, including cardiovascular events, in line with US Food and Drug Administration requirements. Blinded adjudication was performed for instances of acute coronary syndrome, acute kidney injury, acute pancreatitis, cerebrovascular events, death, heart failure requiring hospitalisation, lactic acidosis, malignant neoplasm, and malignant thyroid neoplasm or C-cell hyperplasia.

Statistical analysis

The sample size for the trial was calculated to ensure a power of ≥90% for testing HbA_{1c} superiority of oral semaglutide versus placebo for the treatment policy estimand. Based on data from previous trials, a treatment effect of -0·5% (standard deviation 1·1%) for HbA_{1c} for oral semaglutide versus placebo was assumed, requiring 324 patients to be randomised.

In the PIONEER 5 trial, the superiority of oral semaglutide versus placebo was tested in terms of change from baseline to week 26 in HbA_{1c} and body weight (the primary and confirmatory secondary endpoints, respectively). The confirmation of efficacy of oral semaglutide on change in HbA_{1c} and in body weight, both from baseline to week 26, was based on a hierarchical testing strategy to control the overall type 1 error for the hypotheses evaluated by the treatment policy estimand. The treatment policy estimand was estimated by a pattern mixture model using multiple imputation to handle missing week-26 data for both confirmatory endpoints. Data collected at week 26 from all randomised patients (the full analysis set) were included in the statistical analysis, irrespective of premature discontinuation of trial product or initiation of rescue medication. Imputation was done within groups defined by trial product and treatment status at week 26. Both the imputation and the analysis were based on analysis of covariance (ANCOVA) models, with region, stratification factors and the interaction between the two stratification factors as categorical fixed effects, and baseline HbA_{1c} measurement as a covariate. The results were combined by use of Rubin's rule.

The trial product estimand was estimated by a mixed model for repeated measurements (MMRM) that used data collected prior to premature trial product discontinuation or initiation of rescue medication from all randomised patients.

Binary endpoints were analysed by a logistic regression model. For the treatment policy estimand, missing data were imputed similarly as for the continuous endpoints, whereas missing data for the trial product estimand were imputed from patients randomised to the same trial product using a sequential multiple imputation method.

Sensitivity analyses were performed on the primary and confirmatory secondary endpoints, primarily to evaluate the impact of missing data. The evaluation of the robustness of the primary endpoint was mainly based on a pattern mixture model approach using multiple imputation.

All analyses were performed using SAS Version 9.4M2.

Safety endpoints were assessed during the on-treatment and in-trial periods, using data from all patients exposed to trial product (the safety analysis set). The in-trial period represented the period during which patients were considered to be in the trial, regardless of trial product discontinuation or rescue medication use; this period was used when reporting cardiovascular events, neoplasms, rare events, diabetic retinopathy, and deaths. The on-treatment period represented the period during which the patient was treated with trial product plus an ascertainment window of 35 days (for adverse events and hypoglycaemia) or 3 days (for laboratory assessments, physical examinations and vital signs) after the last date on trial product. Laboratory assessments of physical examinations and vital signs were evaluated until 3 days after the last date on trial product.

Further information on statistical methodology is given in the supplementary appendix.

Role of the funding source

The sponsor of the trial was involved in trial design, monitoring, data collection, data analysis, data interpretation, and writing of the report. The corresponding author had full access to all the data in the trial and had final responsibility for the decision to submit for publication. The trial is registered with the European Clinical Trials Database (No. 2015-005326-19) and Clinicaltrials.gov (NCT02827708).

Results

Between 20 September 2016 and 29 September 2017, 721 patients were screened, of whom 324 were randomised to oral semaglutide 14 mg (n=163) or placebo (n=161, Figure 1). Patient baseline demographics and disease characteristics were similar between the two treatment groups (Table 1, Table S1). The mean age was 70 years (standard deviation 8 years) and 168/324 patients (51·9%) were female. Mean diabetes duration was 14·0 (8·0) years, HbA_{1c} was 8·0% (0·7%), fasting plasma glucose was 9·1 (2·7) mmol/L (163·5 mg/dL), body mass index was 32·4 (5·4) kg/m^2 and eGFR was 48 (10) mL/min/1·73 m^2. Metformin was used by 242 patients (74·7%), sulfonylureas by 131 patients (40·4%), and basal insulin by 114 patients (35·2%), respectively (Table S2).

A similar proportion of patients completed the trial in both groups (96·9% in each). In total, 133 patients (81·6%) in the oral semaglutide group and 141 (87·6%) in the placebo group completed 26 weeks on treatment (Figure 1). The majority of patients who completed treatment did so without use of rescue medication. Over the treatment period, 7 patients in the oral semaglutide group [4.3%] and 16 patients in the placebo group [9.9%] required rescue medication (Table S3).

Oral semaglutide was superior to placebo in reducing HbA_{1c}. Mean changes from baseline in HbA_{1c} at week 26 were -1·0%-points (-11 mmol/mol) for oral semaglutide and -0·2%-points (-2 mmol/mol) for placebo (Figure 2A) when evaluated by the treatment policy estimand (estimated treatment difference [ETD] -0·8%-points [95% confidence interval [CI] -1·0, -0·6]; p<0·0001). Sensitivity analyses supported the results of the confirmatory analysis (Figure S2).

Similarly, when evaluated by the trial product estimand, oral semaglutide provided a significantly greater reduction in HbA_{1c} than placebo. Mean changes from baseline were -1·1%-points (-12 mmol/mol) and -0·1%-points (-1 mmol/mol), respectively (ETD -1·0%-points [95% CI -1·2, -0·8]; p<0·0001, Figure 2B). Observed change in HbA_{1c} over time was similar for patients in both eGFR subgroups (Figure S3).

More patients achieved at least a 1·0% reduction in HbA_{1c} with oral semaglutide compared with placebo (60·4% *vs* 20·0%, treatment policy estimand, Figure S4), and more achieved the targets of HbA_{1c} <7·0% and ≤6·5%. The odds of achieving both targets for both estimands were statistically significantly greater with oral semaglutide than placebo (p<0·0001, Figure S5).

Oral semaglutide was superior to placebo (ETD -2·5 kg [95% CI -3·2, -1·8]; p<0·0001) in reducing body weight. The mean change from baseline in body weight at week 26 was -3·4 kg for oral semaglutide and -0·9 kg for placebo for the treatment policy estimand (Figure 3A). A significant difference was also seen when evaluated by the trial product estimand. Mean changes from baseline were -3·7 kg and -1·1 kg, respectively (ETD -2·7 kg [95% CI -3·5, -1·9]; p<0·0001, Figure 3B). Results from

sensitivity analyses supported the results of the confirmatory analysis (Figure S2). Observed change in body weight over time was similar for patients in both eGFR subgroups (Figure S3).

More patients achieved weight losses ≥5% (55 patients [35·7%] *vs* 15 [9·7%] with placebo) and ≥10% (13 patients [8·4%] *vs* none with placebo) with oral semaglutide (treatment policy estimand). Compared with placebo, the odds of achieving weight loss were significantly better with oral semaglutide for thresholds of both ≥5% (p<0·0001 for both estimands, Table S4) and ≥10% (p=0·0086 [treatment policy estimand] and p=0·0040 [trial product estimand], Table S4).

Compared with placebo, more patients achieved the composite endpoint of HbA_{1c} <7·0% without severe or blood glucose-confirmed symptomatic hypoglycaemia or weight gain at week 26. Estimated odds ratios (EORs) significantly favoured oral semaglutide, compared with placebo, when evaluated by the treatment policy estimand (EOR 5·74, p<0·0001; Figure 4A) and the trial product estimand (EOR 9·04, p<0·0001; Figure 4B). The odds of achieving HbA_{1c} reduction ≥1·0%-points with weight loss ≥3% from baseline were also significantly better with oral semaglutide (p<0·0001, Figure S6).

Data for selected additional clinical outcomes can be found in Table S4.

Health-related quality of life, measured by SF-36v2 (acute version), significantly favoured oral semaglutide for the physical component summary (ETD 1·98; p=0·0058) and the domains role-physical (ETD 2·29; p=0·0079), bodily pain (ETD 2·28; p=0·0326) and social functioning (ETD 1·83; p=0·0350) compared with placebo (treatment policy estimand, Figure S7). In addition, there was a significantly lower patient-perceived frequency of hyperglycaemia compared with placebo (p<0·0001 for both estimands), as measured by the DTSQs (Figure S8).

Safety outcomes are summarised in Table 2 and further information can be found in the supplementary appendix (Tables S5–S7). A higher proportion of patients reported an adverse event with oral semaglutide (120 patients [73·6%]) compared with placebo (105 patients [65·2%]), with a similar proportion in each group experiencing serious adverse events (17 patients each, 10·4% *vs* 10·6%). The most frequent adverse events were mild-to-moderate gastrointestinal events, primarily nausea. Nausea was more common in patients receiving oral semaglutide with CKD stage 3A than stage 3B (Figure S9). The proportion of premature trial product discontinuations due to adverse events was higher in the oral semaglutide group than the placebo group (24 patients [14·7%] *vs* 8 patients [5·0%]), mainly due to gastrointestinal events (principally nausea, vomiting, abdominal pain, and dyspepsia).

Overall, renal function was unchanged throughout the trial period in both treatment groups (Figure S10); median eGFR ratios (week 31 follow-up to baseline) were 1·02 (range 0·27, 1·96) for oral semaglutide and 1·00 (0·68, 2·17) for placebo. Geometric mean UACRs (week 26 to baseline) were 0·86 (range 0·04, 56·71) for oral semaglutide and 1·19 (0·01, 79·59) for placebo (Figure S11). Two patients in the oral semaglutide group had three non-serious EAC-confirmed events of acute kidney injury (stage 1, recovered or recovering while remaining on trial product). One patient in the placebo group had a non-serious EAC-confirmed event of acute kidney injury (stage 2) and recovered.

The proportion of patients with a blood-glucose confirmed symptomatic hypoglycaemic episode while on trial product was low (9 patients [5·5%] with oral semaglutide *vs* 3 patients [1·9%] with placebo). There were no severe hypoglycaemic events. EAC-confirmed cardiovascular events (5 patients [3·1%] *vs* 3 patients [1·9%]) and diabetic retinopathy-related adverse events (5 patients [3·1%] *vs* 2 patients [1·2%]) during the in-trial period were infrequent with oral semaglutide and placebo. All cases of retinopathy were non-serious and mild or moderate in severity, and none required treatment or led to trial product discontinuation. Most of these events were discovered during routine end-of-treatment eye examination and were diagnosed as non-proliferative diabetic retinopathy.

There were three deaths during the in-trial period. One patient in each group died of cardiovascular causes (acute myocardial infarction [MI] in a patient receiving oral semaglutide who had a history of previous MI, and sudden cardiac death in a patient receiving placebo who had a history of cardiovascular disease). Another patient receiving placebo died without a confirmed cause of death.

There were no clinically relevant changes in laboratory assessments, physical examinations, or ECGs. Mean systolic blood pressure decreased by 7 mmHg from baseline to week 26 in the oral semaglutide group, compared with no change in the placebo group (ETD -7 mmHg [95% CI -9, -4]; p<0·0001, Table S8). Mean diastolic pressure decreased by 2 mmHg from baseline to week 26 with oral semaglutide, compared with an increase of 1 mmHg with placebo (ETD -3 [95% CI -5, -1]; p=0·0018, Table S8). Mean pulse rate was not significantly increased from baseline at week 26 with oral semaglutide (1 beat per minute) versus placebo (0 beats per minute), with treatment difference1 beat per minute; p=0·5648, Table S8).

Discussion

In the current randomised phase 3a trial, oral semaglutide was superior to placebo for reductions in HbA_{1c} and body weight at 26 weeks in patients with type 2 diabetes and moderate renal impairment who were receiving standard glucose-lowering medication (treatment policy estimand). Using the

trial product estimand, HbA_{1c} was reduced by 1·0%-points and body weight by 2·7 kg versus placebo, and approximately 58% of patients receiving oral semaglutide met the target of HbA_{1c} <7·0% at 26 weeks. More than 60% of patients achieved an HbA_{1c} reduction of ≥1·0%-points.

Type 2 diabetes is a common cause of CKD, and both conditions are associated with increased cardiovascular risk, especially in combination.[10] In the SUSTAIN-6 trial, in which 83% of patients had cardiovascular disease and/or CKD, subcutaneous semaglutide improved cardiovascular outcomes (significantly reducing the composite incidence of cardiovascular death, non-fatal MI and non-fatal stroke) and led to lower rates of nephropathy progression compared with placebo.[22] Oral semaglutide is the first oral GLP-1 receptor agonist and, once available, may be preferred to injections by some patients. Like liraglutide and subcutaneous semaglutide, the pharmacokinetics of oral semaglutide are not significantly affected by renal impairment,[12,23] making it potentially suitable for patients with CKD.

Renal impairment limits the choice and efficacy of medication for glycaemic control in patients with CKD. However, unlike SGLT-2 inhibitors (contraindicated when creatinine clearance is below 45 mL/min) and metformin (dose-adjusted below 60 mL/min and contraindicated below 30 mL/min), some GLP-1 receptor agonists, including subcutaneous semaglutide, can be used without dose adjustment in patients with creatinine clearance down to 15 mL/min.[10,11] In addition to their potential for improved renal safety and convenience in patients with CKD, GLP-1 receptor agonists provided better glycaemic control (liraglutide and dulaglutide) and weight loss (liraglutide) than regimens containing insulin.[24,25]

Unlike SGLT-2 inhibitors, DPP-4 inhibitors such as sitagliptin have a wider indication for usage in the setting of renal impairment. However, a meta-analysis of trials in patients with type 2 diabetes with moderate to severe CKD indicated that only modest reductions in HbA_{1c} are achieved with DPP-4 inhibitor therapy.[26] In a head-to-head comparison, albiglutide was significantly better for glycaemic control and weight loss than sitagliptin in patients with CKD, with similar tolerability.[27] In the recently published PIONEER 3 trial, oral semaglutide was superior to sitagliptin for glycaemic control and body weight reduction, albeit in a population with normal renal function.[7]

The results of PIONEER 5 were achieved with few hypoglycaemic episodes, an important advantage over insulin and sulfonylureas, and are consistent with those observed in the pivotal, randomised, placebo-controlled, 26-week PIONEER 1 trial.[6] In PIONEER 1, oral semaglutide 14 mg monotherapy resulted in reductions 1·5% in HbA_{1c} and 4·1 kg in body weight, and approximately 80% of patients achieved the target of HbA_{1c} <7·0% (according to the trial product estimand).[6] The greater magnitude of response in PIONEER 1 compared with the present trial is likely due to differences in

patient populations and trial design. Compared with PIONEER 5, patients in PIONEER 1 were on average younger, had a shorter duration of diabetes and were not receiving background glucose-lowering medications. Moreover, patients with eGFR <60 mL/min/1·73m^2 were excluded from PIONEER 1.[6]

The optimal target for HbA_{1c} in type 2 diabetes associated with kidney disease is uncertain. Meta-analyses of studies using intensive control (target HbA_{1c} 6·1–7·1%) showed that microalbuminuria and macroalbuminuria were reduced in patients with type 2 diabetes, but without significant impact on downstream clinical outcomes, such as progression to end stage or death from renal disease.[28,29] On the other hand, a more recent analysis of four large randomised trials did indicate clinical benefits on renal outcomes with tight glycaemic control, although glycaemic targets varied between the studies.[30] It should be noted that the patients analysed in all these analyses were receiving older classes of glucose-lowering medication, and different effects could be expected with GLP-1 receptor agonists.

In the present trial, oral semaglutide displayed acceptable safety and tolerability in most patients, and the adverse event profile was consistent with a type 2 diabetes population with moderate renal impairment and comorbidities. Therefore, compared with PIONEER 1, the proportions of serious adverse events were higher (in both groups).[6] The trial product discontinuation rates due to adverse events with oral semaglutide 14 mg and placebo (14·7% *vs* 5·0%) were approximately double those in PIONEER 1 (7·4% *vs* 2·2%),[6] but similar to that with liraglutide in the LIRA-RENAL trial (13·6% *vs* 2·9%).[24] There were few blood-glucose confirmed symptomatic hypoglycaemic episodes and none were severe. Unlike in LIRA-RENAL,[24] pulse rate was not significantly increased with GLP-1 receptor agonist therapy, but significant increases in heart rate have been reported with oral semaglutide in other trials.[6,7]

As in PIONEER 1,[6] and other phase 3 trials of oral semaglutide, a four-week dose-escalation schedule was used to minimise the anticipated gastrointestinal adverse events associated with GLP-1 receptor agonists. Similar to LIRA-RENAL,[24] gastrointestinal events were the most common adverse events, and these mostly manifested as mild-to-moderate and transient nausea. In the present study, nausea appeared to be more common in patients with better (stage 3A versus stage 3B CKD) renal function. Although this may have been a chance finding due to low patient numbers, it is consistent with the observation that gastrointestinal events were more common in patients with stage 3A versus stage 3B CKD in LIRA-RENAL.[24] There were few new or worsening episodes of diabetic retinopathy during the trial, and no cases of proliferative retinopathy.

All patients in this trial had moderate renal impairment (CKD-EPI stage 3, eGFR 30–59 mL/min/1·73 m^2). Exploratory observations suggested that reductions in HbA_{1c} and body weight seemed to be broadly consistent regardless of whether patients had CKD-EPI stage 3A (eGFR 45–59 mL/min/1·73 m^2) or 3B (30–44 mL/min/1·73 m^2). Overall, eGFR levels remained generally constant during the trial period overall and in both CKD subgroups (stage 3A and 3B). In the LEADER cardiovascular outcomes trial, patients with eGFR 30–60 mL/min/1·73m^2 at baseline who received liraglutide had significantly slower deterioration in renal function than those receiving placebo.[31] Similarly, in the AWARD-7 study, dulaglutide was associated with a reduced decline in eGFR compared with insulin glargine in patients with eGFR 15–60 mL/min/1·73m^2).[25] Although PIONEER 5 was a smaller and shorter trial and, unlike AWARD-7, did not enrol patients with CKD stage 4, these data collectively suggest a renoprotective effect that may apply to the GLP-1 class as a whole.

As observed in other trials of GLP-1 analogues, including liraglutide[24] and subcutaneous semaglutide,[32] oral semaglutide may have a positive effect on albuminuria. UACR, a risk marker for cardiovascular disease and kidney damage,[33,34] decreased during the current trial in the oral semaglutide group (based on the numerical ratio to baseline). However, no statistical evaluation was performed and more detailed study is needed to confirm the effect of oral semaglutide in relation to albuminuria and clinical outcomes in patients with CKD.

Of interest, mean diastolic and systolic blood pressure were reduced with oral semaglutide compared with placebo, which could represent an important benefit in populations with long-standing diabetes and CKD, often combined with hypertension.

A potential limitation of the current trial is that the efficacy and safety of oral semaglutide in patients with moderate renal impairment were evaluated against placebo, rather than an active comparator. However, all patients were receiving standard glucose-lowering agents as background medication. The trial size and duration were planned to allow glucose control analysis and not renal safety and efficacy, which require further evaluation. Although the duration of PIONEER 5 was only 26 weeks, further PIONEER trials are investigating the efficacy and safety of oral semaglutide for treatment durations of up to 78 weeks, albeit not in patients with renal impairment.

In conclusion, once-daily oral semaglutide 14 mg was superior to placebo in reducing HbA_{1c} and body weight in patients with type 2 diabetes and moderate renal impairment. The overall safety profile, including renal safety, was consistent with that seen for other GLP-1 receptor agonists, and there was a low occurrence of hypoglycaemic episodes. Oral semaglutide appears to provide an important addition to the currently suboptimal treatment options for patients with type 2 diabetes and moderate renal impairment.

References

1. DeFronzo RA. Banting Lecture. From the triumvirate to the ominous octet: a new paradigm for the treatment of type 2 diabetes mellitus. *Diabetes* 2009; **58**(4): 773–95.
2. Davies MJ, D'Alessio DA, Fradkin J, et al. Management of hyperglycaemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetologia* 2018; **61**(12): 2461–98.
3. Aroda VR, Ahmann A, Cariou B, et al. Comparative efficacy, safety, and cardiovascular outcomes with once-weekly subcutaneous semaglutide in the treatment of type 2 diabetes: Insights from the SUSTAIN 1-7 trials. *Diabetes Metab* 2019; pii: S1262-3636(18): 30222–2.
4. Jensen L, Helleberg H, Roffel A, et al. Absorption, metabolism and excretion of the GLP-1 analogue semaglutide in humans and nonclinical species. *Eur J Pharm Sci* 2017;**104**:31–41.
5. Buckley ST, Bækdal TA, Vegge A, et al. Transcellular stomach absorption of a derivatized glucagon-like peptide-1 receptor agonist. *Sci Transl Med* 2018; **10**(467) pii: eaar7047.
6. Aroda VR, Rosenstock J, Terauchi Y, et al. Effect and Safety of Oral Semaglutide Monotherapy in Type 2 Diabetes—PIONEER 1 Trial. *Diabetes* 2018; **67**(S1): 2-LB.
7. Rosenstock J, Allison D, Birkenfeld AL, et al. Effect of Additional Oral Semaglutide vs Sitagliptin on Glycated Hemoglobin in Adults With Type 2 Diabetes Uncontrolled With Metformin Alone or With Sulfonylurea: The PIONEER 3 Randomized Clinical Trial. *JAMA* 2019; published online Mar 23. DOI: 10.1001/jama.2019.2942.
8. Abdi H, Azizi F, Amouzegar A. Insulin Monotherapy Versus Insulin Combined with Other Glucose-Lowering Agents in Type 2 Diabetes: A Narrative Review. *Int J Endocrinol Metab* 2018; **16**(2): e65600.
9. Edridge CL, Dunkley AJ, Bodicoat DH, et al. Prevalence and Incidence of Hypoglycaemia in 532,542 People with Type 2 Diabetes on Oral Therapies and Insulin: A Systematic Review and Meta-Analysis of Population Based Studies. *PloS One* 2015; **10**(6): e0126427.
10. Ioannidis I. Diabetes treatment in patients with renal disease: Is the landscape clear enough? *World J Diabetes* 2014; **5**(5): 651–58.
11. Davies M, Chatterjee S, Khunti K. The treatment of type 2 diabetes in the presence of renal impairment: what we should know about newer therapies. *Clin Pharmacol* 2016; **8**: 61–81.
12. Granhall C, Sondergaard FL, Thomsen M, Anderson TW. Pharmacokinetics, Safety and Tolerability of Oral Semaglutide in Subjects with Renal Impairment. *Clin Pharmacokinet* 2018; **57**(12):1571–80.
13. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. ICH Harmonised Tripartite Guideline E9: Statistical Principles for Clinical Trials.

1998. https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E9/Step4/E9_Guideline.pdf (accessed 18 February 2019).

14. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. ICH Harmonised Guideline E9(R1): Estimands and Sensitivity Analysis in Clinical Trials. 2018. http://www.ich.org/products/guidelines/efficacy/article/efficacy-guidelines.html (accessed 18 February 2019).
15. National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Am J Kidney Dis* 2002; **39**(2 S1): S1–266.
16. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med* 2009; **150**(9): 604–12.
17. Davies M, Pieber TR, Hartoft-Nielsen ML, Hansen OKH, Jabbour S, Rosenstock J. Effect of Oral Semaglutide Compared With Placebo and Subcutaneous Semaglutide on Glycemic Control in Patients With Type 2 Diabetes: A Randomized Clinical Trial. *JAMA* 2017; **318**(15): 1460–70.
18. Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of hyperglycaemia in type 2 diabetes, 2015: a patient-centred approach. Update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetologia* 2015; **58**(3): 429–42.
19. American Diabetes Association. 8. Pharmacologic Approaches to Glycemic Treatment: Standards of Medical Care in Diabetes-2018. *Diabetes Care* 2018; **41**(S1): S73–S85.
20. Garber AJ, Abrahamson MJ, Barzilay JI, et al. Consensus Statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the Comprehensive Type 2 Diabetes Management Algorithm - 2018 Executive Summary. *Endocr Pract* 2018; **24**(1): 91–120.
21. Seaquist ER, Anderson J, Childs B, et al. Hypoglycemia and diabetes: a report of a workgroup of the American Diabetes Association and the Endocrine Society. *Diabetes Care* 2013; **36**(5): 1384–95.
22. Marso SP, Bain SC, Consoli A, et al. Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes. *N Engl J Med* 2016; **375**(19): 1834–44.
23. Marbury TC, Flint A, Jacobsen JB, Derving Karsbol J, Lasseter K. Pharmacokinetics and Tolerability of a Single Dose of Semaglutide, a Human Glucagon-Like Peptide-1 Analog, in Subjects With and Without Renal Impairment. *Clin Pharmacokinet* 2017; **56**(11): 1381–90.

24. Davies MJ, Bain SC, Atkin SL, et al. Efficacy and Safety of Liraglutide Versus Placebo as Add-on to Glucose-Lowering Therapy in Patients With Type 2 Diabetes and Moderate Renal Impairment (LIRA-RENAL): A Randomized Clinical Trial. *Diabetes Care* 2016; **39**(2): 222–30.
25. Tuttle KR, Lakshmanan MC, Rayner B, et al. Dulaglutide versus insulin glargine in patients with type 2 diabetes and moderate-to-severe chronic kidney disease (AWARD-7): a multicentre, open-label, randomised trial. *Lancet Diabetes Endocrinol* 2018; **6**(8): 605–17.
26. Singh-Franco D, Harrington C, Tellez-Corrales E. An updated systematic review and meta-analysis on the efficacy and tolerability of dipeptidyl peptidase-4 inhibitors in patients with type 2 diabetes with moderate to severe chronic kidney disease. *SAGE Open Med* 2016; **4**: 2050312116659090.
27. Leiter LA, Carr MC, Stewart M, et al. Efficacy and safety of the once-weekly GLP-1 receptor agonist albiglutide versus sitagliptin in patients with type 2 diabetes and renal impairment: a randomized phase III study. *Diabetes Care* 2014; **37**(10): 2723–30.
28. Coca SG, Ismail-Beigi F, Haq N, Krumholz HM, Parikh CR. Role of intensive glucose control in development of renal end points in type 2 diabetes mellitus: systematic review and meta-analysis intensive glucose control in type 2 diabetes. *Arch Intern Med* 2012; **172**(10): 761–69.
29. Rodriguez-Gutierrez R, Montori VM. Glycemic Control for Patients With Type 2 Diabetes Mellitus: Our Evolving Faith in the Face of Evidence. *Circ Cardiovasc Qual Outcomes* 2016; **9**(5): 504–12.
30. Zoungas S, Arima H, Gerstein HC, et al. Effects of intensive glucose control on microvascular outcomes in patients with type 2 diabetes: a meta-analysis of individual participant data from randomised controlled trials. *Lancet Diabetes Endocrinol* 2017; **5**(6): 431–37.
31. Mann JFE, Orsted DD, Brown-Frandsen K, et al. Liraglutide and Renal Outcomes in Type 2 Diabetes. *N Engl J Med* 2017; **377**(9): 839–48.
32. Bloomgarden Z. The kidney and cardiovascular outcome trials. *J Diabetes* 2018; **10**(2): 88–89.
33. Gerstein HC, Mann JF, Yi Q, et al. Albuminuria and risk of cardiovascular events, death, and heart failure in diabetic and nondiabetic individuals. *JAMA* 2001; **286**(4): 421–26.
34. Schmieder RE, Mann JF, Schumacher H, et al. Changes in albuminuria predict mortality and morbidity in patients with vascular disease. *J Am Soc Nephrol* 2011; **22**(7): 1353–64.

Contributors

OM, JWE, SH, RP, TS and CD contributed to data collection (as study investigators). TMB, SR, OHH contributed to trial design and data analysis (as employees of the sponsor). All authors interpreted the data and participated in writing the manuscript, with the support of medical writing services provided by the funder. The medical writer developed the manuscript drafts under the guidance of the authors. All authors read and approved the submitted version of the manuscript.

Declaration of interests

OM: Advisory Board for Novo Nordisk, Eli Lilly, Sanofi, MSD, Boehringer Ingelheim, AstraZeneca; Grants paid to institution as study physician by AstraZeneca; Research grant paid to institution from Novo Nordisk; Speaker's Bureau for AstraZeneca, Novo Nordisk, Eli Lilly, Sanofi, MSD, Boehringer Ingelheim.

TMB: Employee of Novo Nordisk A/S.

SR: Employee of Novo Nordisk A/S.

JWE: Personal fees from Novo Nordisk, AstraZeneca, Bayer, MSD and Sanofi. Grants from AstraZeneca and Bristol Myers Squibb.

SH: Fees paid to institution for consultancy by Eli Lilly, Novo Nordisk, Sanofi Aventis, Zealand Pharma, Boehringer Ingelheim, UN-EEG and Takeda; Speaker’s Bureau for Eli Lilly and Novo Nordisk.

OHH: Employee and Shareholder of Novo Nordisk A/S

RP: Grants and fees for lecturing and consultancy paid to institution by AstraZeneca, Boehringer Ingelheim, Eisai, GlaxoSmithKline, Glytec LLC, Janssen, Lexicon Pharmaceuticals, Ligand Pharmaceuticals, Eli Lilly, Merck, Mundipharma, Novo Nordisk, Pfizer, Sanofi Aventis US, Takeda and Sanofi US Services.

TS: Grants paid to institution as study physician by Novo Nordisk

CD: Grants, personal fees and non-financial support from Novo Nordisk; grants from National Institutes of Health, REPOWER, Sanofi and Theracos.

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Tables

Table 1. Demographics and baseline characteristics.

	Oral semaglutide 14 mg (N=163)	Placebo (N=161)	Total (N=324)
Age (years), mean (SD)	71 (8)	70 (8)	70 (8)
Female sex, n (%)	80 (49·1)	88 (54·7)	168 (51·9)
Race, n (%)			
White	158 (96·9)	152 (94·4)	310 (95·7)
Black or African American	4 (2·5)	9 (5·6)	13 (4·0)
Asian	1 (0·6)	0	1 (0·3)
Ethnicity, n (%)			
Hispanic or Latino	7 (4·3)	14 (8·7)	21 (6·5)
Duration of diabetes (years), mean (SD)	14·1 (8·6)	13·9 (7·4)	14·0 (8·0)
Body weight (kg), mean (SD)	91·3 (17·8)	90·4 (17·5)	90·8 (17·6)
Body mass index (kg/m2), mean (SD)	32·2 (5·4)	32·6 (5·5)	32·4 (5·4)
Waist circumference (cm), mean (SD)	106·8 (13·9)	107·9 (12·8)	107·3 (13·3)
HbA_{1c} (%), mean (SD)	8·0 (0·7)	7·9 (0·7)	8·0 (0·7)
HbA_{1c} (mmol/mol), mean (SD)	64 (8)	63 (8)	64 (8)
Fasting plasma glucose (mmol/l), mean (SD)	9·1 (2·7)	9·1 (2·8)	9·1 (2·7)
eGFR (mL/min/1·73 m2), mean (SD)	47 (10)	48 (10)	48 (10)
Stage 3A (45–<60 mL/min/1·73 m^2), n (%)	99 (60·7)	97 (60·2)	196 (60·5)
Stage 3B (30–<45 mL/min/1·73 m^2), n (%)	64 (39·3)	64 (39·8)	128 (39·5)
Urinary albumin to creatinine ratio (mg/g), mean (SD)	230·5 (776·7)	186·8 (489·4)	209·1 (651·1)
<30 mg/g, n (%)	96 (58·9)	105 (65·2)	201 (62·0)
30–≤300 mg/g, n (%)	44 (27·0)	25 (15·5)	69 (21·3)
>300 mg/g, n (%)	22 (13·5)	26 (16·1)	48 (14·8)
Unclassified	1 (0·6)	5 (3·1)	6 (1·9)

eGFR, estimated glomerular filtration rate; HbA_{1c}, glycated haemoglobin; SD, standard deviation.

Table 2. Summary of adverse events.

	Oral semaglutide 14 mg (N=163), n (%)	**Placebo (N=161), n (%)**
Adverse events (in trial)	122 (74·8)	109 (67·7)
Adverse events (on treatment)	120 (73·6)	105 (65·2)
Severe	10 (6·1)	15 (9·3)
Moderate	61 (37·4)	42 (26·1)
Mild	106 (65·0)	89 (55·3)
Serious adverse events		
In trial	20 (12·3)	18 (11·2)
On treatment	17 (10·4)	17 (10·6)
Severe* or blood glucose-confirmed** symptomatic hypoglycaemic episode† (on treatment)	9 (5·5)	3 (1·9)
Most frequent on-treatment adverse events occurring in >5% of patients in either group (preferred term‡)		
Nausea	31 (19·0)	12 (7·5)
Constipation	19 (11·7)	6 (3·7)
Vomiting	19 (11·7)	2 (1·2)
Diarrhoea	17 (10·4)	6 (3·7)
Dyspepsia	16 (9·8)	2 (1·2)
Decreased appetite	11 (6·7)	0
Headache	10 (6·1)	8 (5·0)
Back pain	1 (0·6)	9 (5·6)
On-treatment adverse events leading to premature trial product discontinuation (>3% in either treatment group)		
Gastrointestinal disorders	19 (11·7)	3 (1·9)
Fatal adverse events (in trial)	1 (0·6)	2 (1·2)

*American Diabetes Association classification; **Plasma glucose 3·1 mmol/l (<56 mg/dl); †Hypoglycaemic episodes were reported on a separate form to adverse events; ‡MedDRA version 20·1.

Figures

Figure 1. Patient disposition.

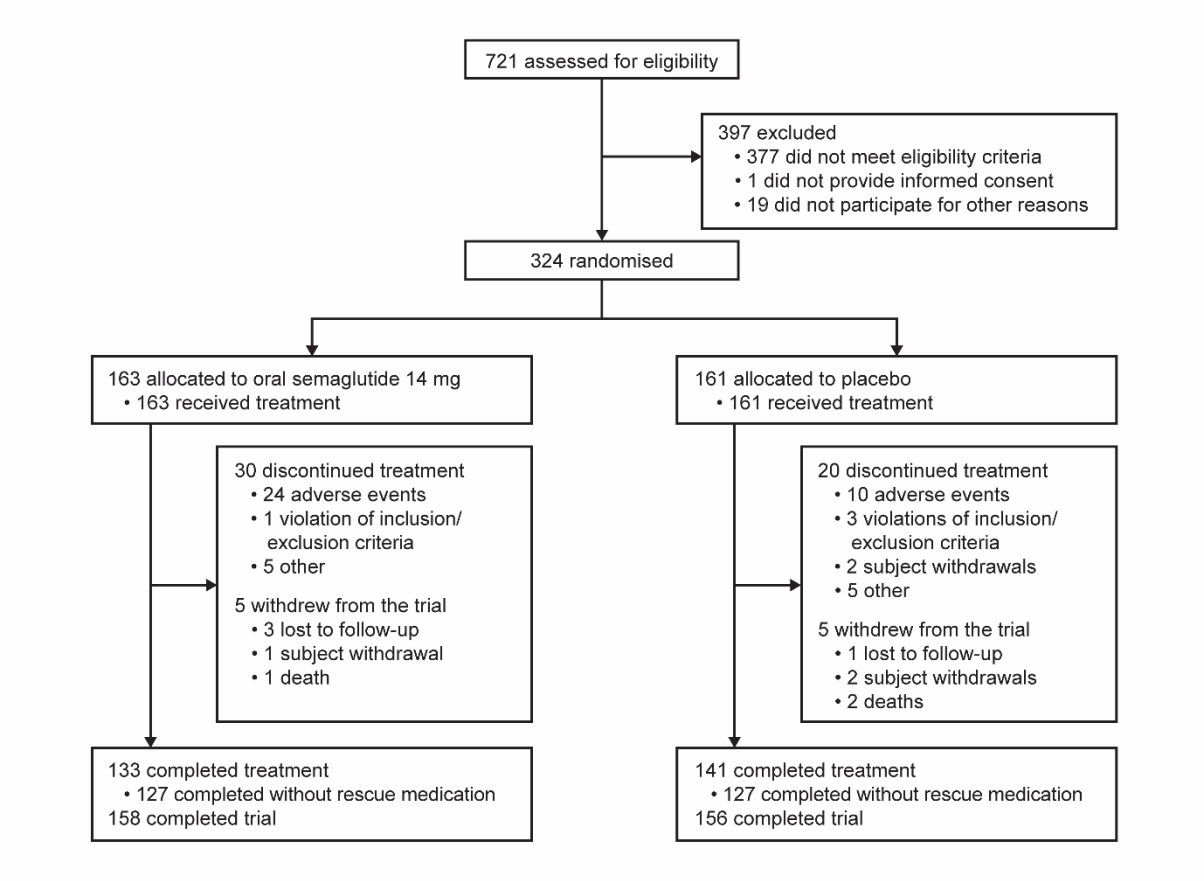
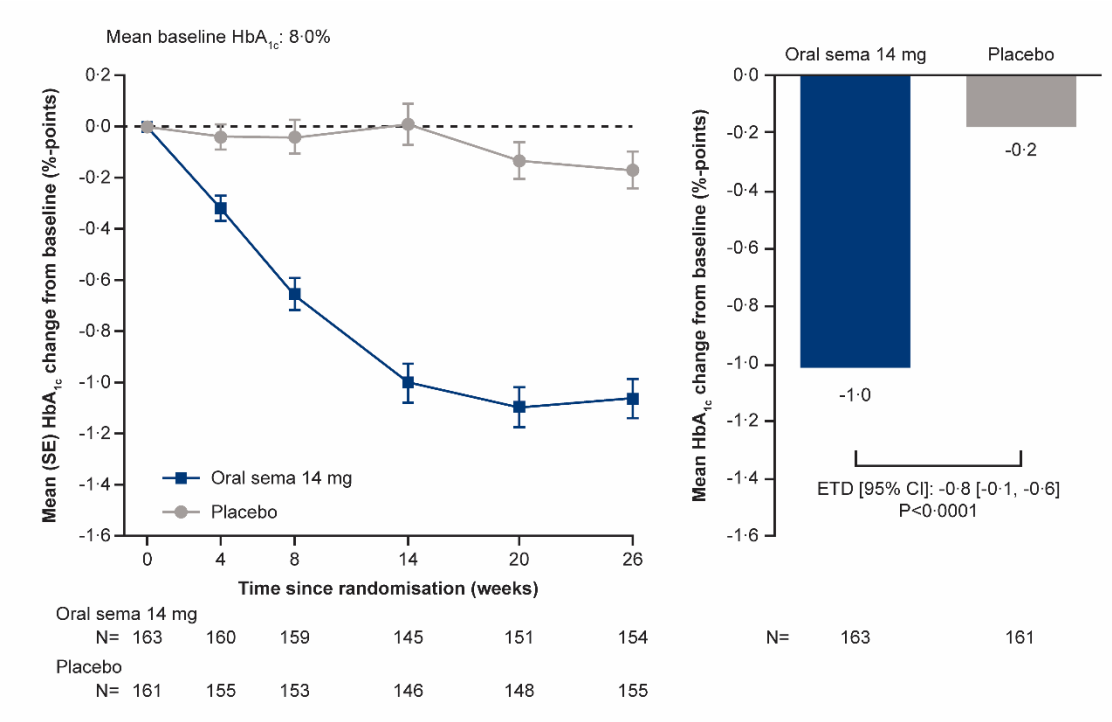
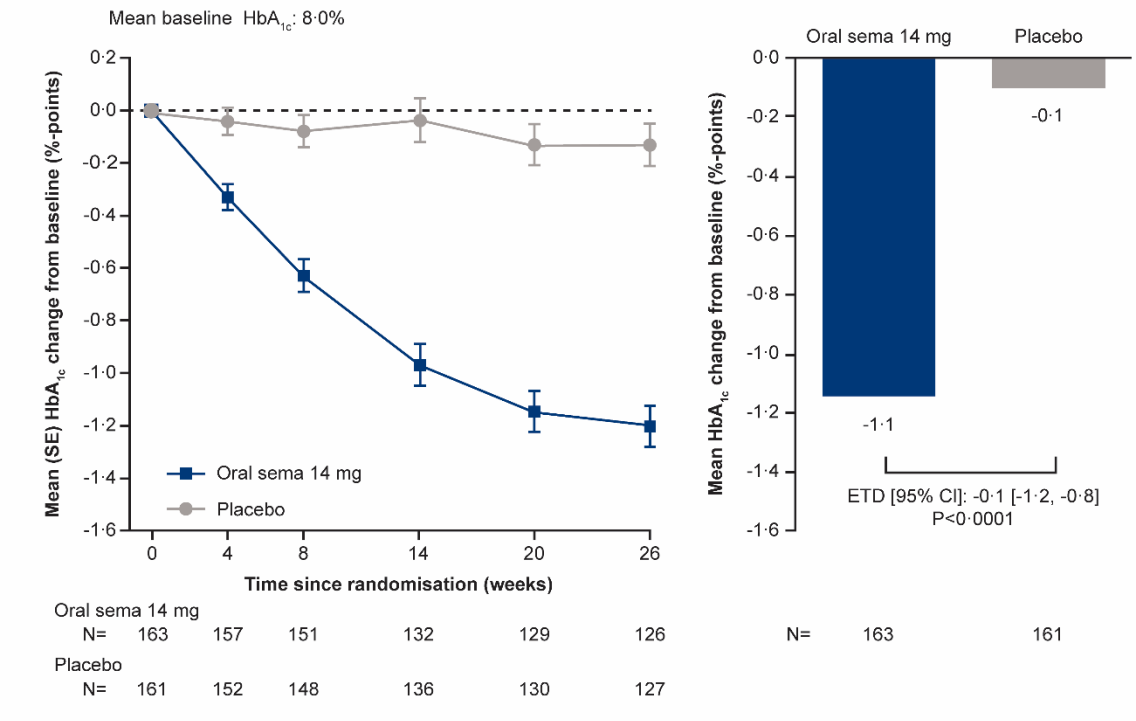


Figure 2. Mean change in glycated haemoglobin up to week 26: (A) treatment policy estimand; (B) trial product estimand.

(A)



(B)



Left-hand figures: Observed mean values; error bars are ± standard error of the mean. Right-hand figures: Estimated means and statistical analysis at week 26 from the primary analysis. N represents the number of patients contributing to the analysis.

Treatment policy estimand: analysis of covariance using data irrespective of discontinuation of trial product or initiation of rescue medication. Missing values were imputed by a pattern mixture model using multiple imputation. Patterns were defined by use of trial product and rescue medication.

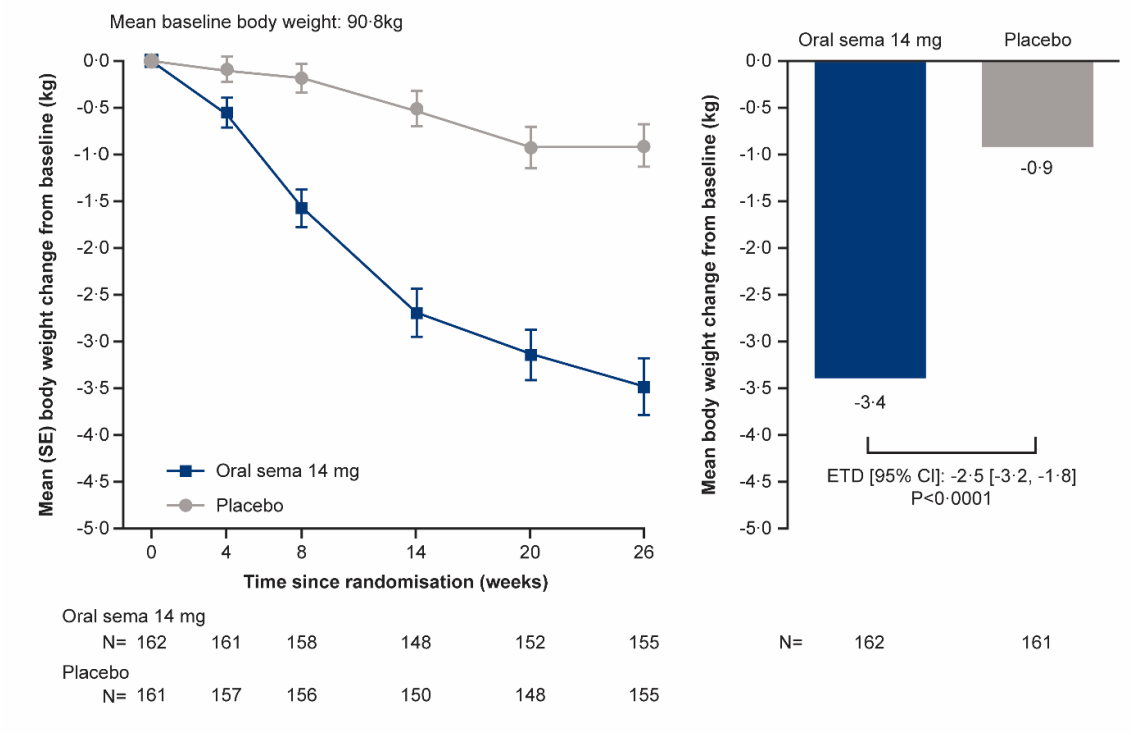
Trial product estimand: mixed model for repeated measurements. Data collected after discontinuation of trial product or initiation of rescue medication are excluded.

P-values are unadjusted two-sided p-value for the test of no difference.

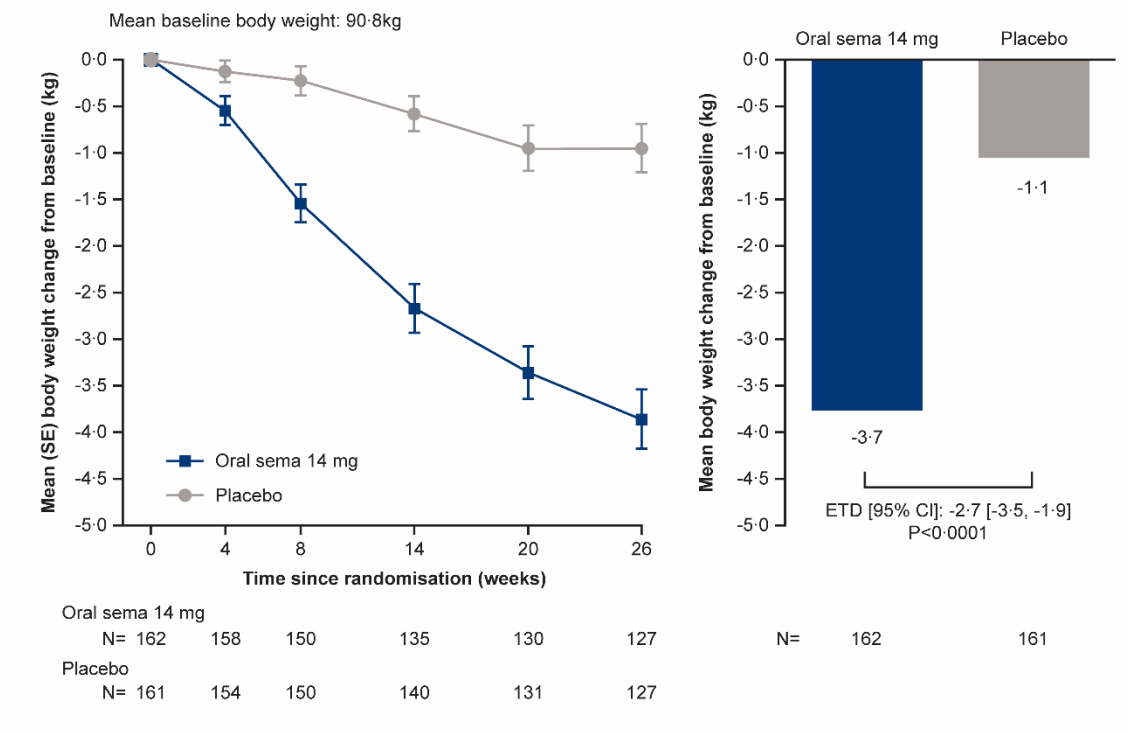
CI, confidence interval; ETD: Estimated treatment difference with 95% confidence interval; HbA_{1c}, glycated haemoglobin; SE, standard error; sema, semaglutide.

Figure 3. Mean change in body weight up to week 26: (A) treatment policy estimand; (B) trial product estimand.

(A)



(B)



Left-hand figures: Observed mean values; error bars are ± standard error of the mean. Right-hand figures: Estimated means and statistical analysis at week 26 from the primary analysis; N represents the number of patients contributing to the analysis.

Treatment policy estimand: analysis of covariance using data irrespective of discontinuation of trial product or initiation of rescue medication. Missing values were imputed by a pattern mixture model using multiple imputation. Patterns were defined by use of trial product and rescue medication.

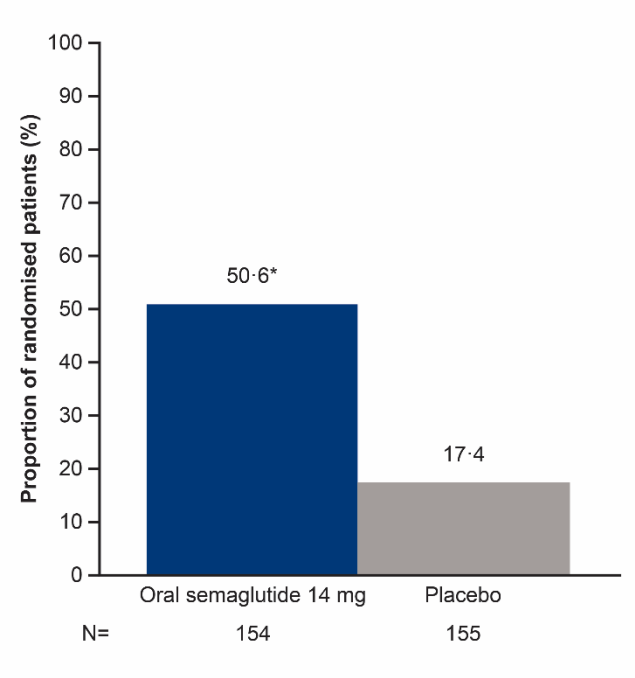
Trial product estimand: mixed model for repeated measurements. Data collected after discontinuation of trial product or initiation of rescue medication are excluded.

P-values are unadjusted two-sided p-value for the test of no difference.

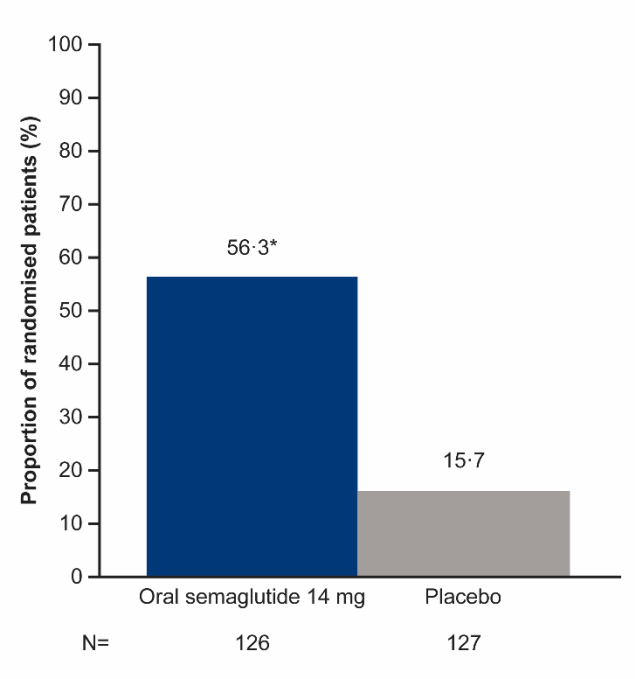
CI, confidence interval; ETD, estimated treatment difference; SE, standard error; sema, semaglutide.

Figure 4. Composite outcome of glycated haemoglobin <7·0% without hypoglycaemic episodes[†] or weight gain at week 26: (A) treatment policy estimand, (B) trial product estimand.

(A)



(B)



[†]Severe or blood glucose-confirmed (3·1 mmol/l [<56 mg/dL]) symptomatic event.

Odds ratio calculations were evaluated for the treatment policy estimand (Panel A; N=163 for oral semaglutide and N=161 for placebo) and the trial product estimand (Panel B; N=163 for oral semaglutide and N=161 for placebo). Proportions of patients achieving the composite outcomes are based on observed data (N values below the bars represents the number of patients with non-missing information, i.e. who

attended the week 26 visit and contributed to the proportions). The composite outcomes were analysed by a logistic regression model. For the treatment policy estimand, missing data was imputed similarly as for the continuous endpoints, whereas missing data for the trial product estimand was imputed from patients randomised to same trial product using a sequential multiple imputation method.

*The odds of achieving the targets were statistically significantly greater with oral semaglutide than placebo: treatment policy estimand, EOR 5·74 (95% CI 3·25, 10·16); p<0·0001; trial product estimand, EOR 9·04 (95% CI 4·77, 17·15); p<0·0001.

EOR, estimated odds ratio CI; confidence interval.