Efficacy and safety of once-daily oral semaglutide 25 mg and 50 mg compared with 14 mg in adults with type 2 diabetes (PIONEER PLUS): a multicentre, randomised, phase 3b trial

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Summary

Background Once-daily oral semaglutide is an effective type 2 diabetes treatment. We aimed to investigate a new formulation of oral semaglutide at higher investigational doses versus the approved 14 mg dose in adults with inadequately controlled type 2 diabetes.

Methods This global, multicentre, randomised, double-blind, phase 3b trial, carried out at 177 sites in 14 countries, enrolled adults with type 2 diabetes, glycated haemoglobin (HbA_{1c}) 8·0–10·5% (64–91 mmol/mol), a BMI of 25·0 kg/m² or greater, receiving stable daily doses of one to three oral glucose-lowering drugs. Participants were randomly assigned (1:1:1), by means of an interactive web response system, to once-daily oral semaglutide 14 mg, 25 mg, or 50 mg for 68 weeks. Investigators, site personnel, trial participants, and trial sponsor staff were masked to dose assignment throughout the trial. The primary endpoint was change in HbA_{1c} from baseline to week 52, evaluated with a treatment policy estimand in the intention-to-treat population. Safety was assessed in all participants who received at least one dose of trial drug. This trial is registered with ClinicalTrials.gov, NCT04707469, and the European Clinical Trials register, EudraCT 2020-000299-39, and is complete.

Findings Between Jan 15 and Sept 29, 2021, of 2294 people screened, 1606 (n=936 [58·3%] male; n=670 [41·7%] female; mean [SD] age 58·2 [10·8] years) received oral semaglutide 14 mg (n=536), 25 mg (n=535), or 50 mg (n=535). At baseline, mean (SD) HbA_{1c} was 9·0% (0·8; 74·4 mmol/L [SD 8·3]) and mean bodyweight was 96·4 kg (21·6). Mean changes (SE) in HbA_{1c} at week 52 were –1·5 percentage points (SE 0·05) with oral semaglutide 14 mg, –1·8 percentage points (0·06) with 25 mg (estimated treatment difference [ETD] –0·27, 95% CI –0·42 to –0·12; p=0·0006), and –2·0 percentage points (0·06) with 50 mg (ETD –0·53, –0·68 to –0·38; p<0·0001). Adverse events were reported by 404 (76%) participants in the oral semaglutide 14 mg group, 422 (79%) in the 25 mg group, and 428 (80%) in the 50 mg group. Gastrointestinal disorders, which were mostly mild to moderate, occurred more frequently with oral semaglutide 25 mg and 50 mg than with 14 mg. Ten deaths occurred during the trial; none were judged to be treatment related.

Interpretation Oral semaglutide 25 mg and 50 mg were superior to 14 mg in reducing HbA_{1c} and bodyweight in adults with inadequately controlled type 2 diabetes. No new safety concerns were identified.

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See Comment page 668

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Introduction

Achievement and maintenance of glycaemic control is considered an important therapeutic goal for the management of type 2 diabetes and a mainstay for the prevention of long-term, diabetes-related complications.[1] In addition, the consensus report by the American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD) recommends weight management as a crucial target for people with type 2 diabetes, alongside cardiorenal protection and cardiovascular risk reduction.[2]

GLP-1 receptor agonists are recommended for the treatment of type 2 diabetes owing to their ability to improve glycaemic control and reduce bodyweight, with some also having shown cardiovascular risk reduction.[3] Semaglutide, a long-acting human GLP-1 analogue, is approved for the treatment of type 2 diabetes as an adjunct to diet and exercise and is available both as once-weekly subcutaneous[4,5] (0·5 mg, 1·0 mg, and 2·0 mg doses) and once-daily oral (7 mg and 14 mg) formulations.[6,7] In the PIONEER clinical trial programme, once-daily oral semaglutide at doses of 7 mg and 14 mg resulted in significant reductions in glycated haemoglobin (HbA_{1c}), together with clinically relevant weight loss, compared with placebo and active comparators.[8–14] Oral glucose-lowering medications are preferred over injectable therapies by some patients and prescribers because of increased convenience and greater patient acceptance of medication.[15]

The availability of higher doses of GLP-1 receptor agonists might provide a more easily individualised option for treatment intensification in people with type 2

Research in context

Evidence before this study

We did a PubMed search on March 27, 2023, using the terms "oral semaglutide" and "type 2 diabetes", limited to clinical trials, and identified 23 relevant publications. These included ten phase 3 trials in the global PIONEER programme, which investigated oral semaglutide at doses of 7 mg and 14 mg daily. Oral semaglutide 14 mg daily resulted in significant reductions in glycated haemoglobin (HbA_{1c}; −1·0 to −1·4 percentage points after 26 or 52 weeks) compared with placebo and active comparators. However, in these studies, 33–47% of patients did not reach HbA_{1c} of less than 7·0%. In a 26-week phase 2 dose-finding trial, oral semaglutide showed dose-dependent reductions in HbA_{1c} and bodyweight at doses of up to 40 mg once daily. Exposure–response modelling analyses of oral and subcutaneous semaglutide trials suggested greater reductions in HbA_{1c} and bodyweight with increased drug exposure.

Added value of this study

The PIONEER PLUS trial showed superior glycaemic control with a new formulation of oral semaglutide at higher investigational doses of 25 mg and 50 mg once daily compared with the approved formulation and dose of oral semaglutide 14 mg once daily (mean changes of −1·8 percentage points with 25 mg, −2·0 percentage points with 50 mg, and −1·5 percentage points with 14 mg at 52 weeks). Higher doses of oral semaglutide also resulted in superior reductions in bodyweight. A greater proportion of participants treated with oral semaglutide 25 mg and 50 mg attained HbA_{1c} of less than 7·0% (51% and 63% for 25 mg and 50 mg, respectively, *vs* 39% for 14 mg) and clinically relevant bodyweight loss of at least 5% or 10% compared with the 14 mg dose. The higher doses were well tolerated, although gastrointestinal adverse events, which mostly occurred during dose escalation, were more frequent. There were no new safety concerns following dose escalation to the higher doses.

Implications of all the available evidence

For people with inadequately controlled type 2 diabetes on a stable dose of one to three oral glucose-lowering drugs, higher doses (25 mg and 50 mg) of once-daily oral semaglutide provided more effective glycaemic control and greater bodyweight loss than 14 mg semaglutide, without additional safety concerns. PIONEER PLUS is the first study to indicate that these higher doses might provide a highly effective oral option to improve both glycaemic control and weight loss in type 2 diabetes.

diabetes in need of additional glycaemic control. Previous studies of subcutaneous GLP-1 receptor agonists have reported improvements in glycaemia and bodyweight with higher doses.[16,17] Moreover, a phase 2 study of oral semaglutide showed dose-dependent reductions in HbA_{1c} and bodyweight at doses of up to 40 mg once daily in participants with type 2 diabetes uncontrolled by diet and exercise with or without metformin,[18] and exposure–response modelling analyses of oral and subcutaneous semaglutide trials suggested greater reductions in HbA_{1c} and bodyweight with increased drug exposure.[19]

The aim of this phase 3b PIONEER PLUS trial was to evaluate the efficacy, safety, and tolerability of once-daily oral semaglutide 25 mg and 50 mg in a new formulation compared with the highest approved 14 mg dose in adults with type 2 diabetes.

Methods

Study design

PIONEER PLUS was a 68-week, active-controlled, multinational, randomised, double-blind, three-armed, phase 3b trial. The trial was done at 177 sites in Australia, Bulgaria, Canada, Croatia, Czechia, Estonia, Germany, Hungary, India, Poland, Slovakia, Slovenia, Taiwan, and the USA. The trial protocol was approved by appropriate health authorities according to local guidelines and by an Institutional Review Board or Independent Ethics Committee for each participating trial site, and the trial was done in accordance with the Declaration of Helsinki and International Council on Harmonisation Good Clinical Practice guidelines. Protocol deviations are listed in the appendix (pp 14–15); these did not affect the trial conclusions. The protocol is included in the appendix.

See Online for appendix

Participants

Eligible individuals were male or female adults aged 18 years or older with type 2 diabetes, had an HbA_{1c} of 8·0–10·5% (64–91 mmol/mol), a BMI of 25·0 kg/m² or greater, and were on stable daily doses of one to three of the following oral glucose-lowering drugs: metformin, sulfonylurea, SGLT2 inhibitor, or DPP-4 inhibitor. Participants who were on treatment with a stable dose of a DPP-4 inhibitor at inclusion were asked to discontinue DPP-4 inhibitor treatment at randomisation. Sex was self-reported with options for male or female. Key exclusion criteria included treatment with any other medication for the indication of diabetes or obesity within 90 days of screening (other than short-term insulin treatment [≤14 days]), renal impairment (estimated glomerular filtration rate value of <30 mL/min per 1·73 m²), uncontrolled and potentially unstable diabetic retinopathy or maculopathy within 90 days of screening (verified by a fundus examination within 90 days of screening or between screening and randomisation, with pharmacological pupil dilation a requirement unless using a digital camera specified for non-dilated examination), personal or first-degree relative(s) history of multiple endocrine neoplasia type 2 or medullary thyroid carcinoma, history of major gastrointestinal surgery, and history of acute or chronic

pancreatitis. Full eligibility criteria can be found in the appendix (p 16). All participants provided written informed consent before commencement of any trial-related activities.

Randomisation and masking

Participants were randomly assigned (1:1:1) to receive once-daily oral semaglutide maintenance doses of 14 mg, 25 mg, or 50 mg (appendix p 6), in addition to existing glucose-lowering medication, except for DPP-4 inhibitors, which were discontinued at randomisation. Randomisation was done by means of an interactive web response system, which assigned a dispensing unit number to each participant, and stratified according to background glucose-lowering medication. Randomisation comprised eight strata for combinations of sulfonylureas, SGLT2 inhibitors, and discontinued DPP-4 inhibitors, these being: SGLT2 inhibitor only, discontinued DPP-4 inhibitor only, sulfonylurea only, SGLT2 inhibitor plus discontinued DPP-4 inhibitor, SGLT2 inhibitor plus sulfonylurea, discontinued DPP-4 inhibitor plus sulfonylurea (all these six strata with or without metformin), SGLT2 inhibitor plus discontinued DPP-4 inhibitor plus sulfonylurea (without metformin), and metformin only.

The oral semaglutide 25 mg and 50 mg tablets were a new formulation developed to enhance bioavailability compared with the 14 mg dose (appendix p 5). As the shape of the new formulation 25 mg and 50 mg tablets had minor differences to the 14 mg tablets, matching packaging was used for all treatment groups, regardless of dose, to maintain blinding of investigational products. For patients in the 14 mg group, dose escalation beyond 14 mg was simulated by providing tablets packaged in a high-density polyurethane bottle identical to the packaging of the new formulation 25 mg and 50 mg tablets, in place of the dose pack used for doses up to and including 14 mg during the initial dose escalation. A third party, who was only allowed to be involved in trial product handling, was responsible for drug accountability. It was recommended that the third party be responsible for dispensing of all trial products; in cases where site personnel or investigators needed to dispense trial products, they were only allowed to handle a trial product in its original packaging material (unbroken packaging). Investigators, site personnel, trial participants, and trial sponsor staff remained masked to trial product dose throughout the trial.

Procedures

All participants initiated once-daily oral semaglutide treatment at 3 mg, then escalated to 7 mg at week 4, and 14 mg at week 8. Participants assigned to the 25 mg group received their maintenance dose of 25 mg at week 12, whereas those assigned to the 50 mg treatment group received the 25 mg dose at week 12 then escalated to the maximum study dose of 50 mg at week 16. From week 12, participants were allowed to extend the dose escalation intervals or reduce the dose if they had had moderate-to-severe gastrointestinal adverse events. Dose reduction to below 14 mg was not permitted (to maintain dose blinding); the trial drug would have to be discontinued, but the participant could stay in the study.

Participants were instructed to take the once-daily study drug tablet in the morning in the fasting state with up to half a glass of water (120 mL) at least 30 min before intake of any other food, beverage, or oral medication. To mitigate potential sulfonylurea-induced hypoglycaemia, all participants treated with sulfonylureas, regardless of dose, were to reduce the sulfonylurea dose at randomisation by approximately 50%, at the discretion of the investigator. Participants were to continue all other background glucose-lowering medication (except for discontinued DPP-4 inhibitors) at the same dose and frequency throughout the trial unless changes were needed to mitigate any safety concerns, including hypoglycaemia. From week 26, participants with persistent and unacceptable hyperglycaemia (stable HbA_{1c} above 8·5% [69 mmol/mol] and considered unacceptably high according to investigator's assessment) were to be offered intensification of rescue medication but were to continue to follow the visit schedule and remain on randomised treatment unless the investigator judged that the participants' safety was jeopardised. Rescue medication was selected at the discretion of the investigator and in accordance with national and ADA–EASD guidelines at the time of study initiation,[20] excluding GLP-1 receptor agonists, DPP-4 inhibitors, and amylin analogues.

During the treatment period, participants attended the study site visits at weeks 4, 8, 12, 14, 16, 18, 20, 26, 32, 38, 44, 52, 60, and 68, regardless of treatment group. At the end of the treatment period, all participants entered a 5-week follow-up period. A summary of trial assessments and procedures is presented in the appendix (pp 17–18). Participants who prematurely discontinued the trial treatment were asked to complete the scheduled visits and assessments, unless consent was withdrawn.

Outcomes

The primary endpoint was change in HbA_{1c} (percentage point) from baseline to week 52 (analysed at a central laboratory), and the confirmatory secondary endpoint was change in bodyweight (kg) from baseline to week 52. Supportive secondary efficacy endpoints included were proportion of participants who reached an HbA_{1c} target of less than 7·0% (53 mmol/mol) or no more than 6·5% (48 mmol/mol) at week 52, change from baseline to week 52 in fasting plasma glucose, percentage change in bodyweight from baseline to week 52, proportion of participants who had weight loss of 5% or more or 10% or more at week 52, change in waist circumference (cm) at week 52, time to rescue medication, and change in fasting lipids at week 52. All efficacy endpoints were

also evaluated at week 68. Two estimands were predefined to comprehensively address trial efficacy objectives: the treatment policy (primary) estimand and the trial product estimand (further information is provided in the appendix p 5).

Supportive safety endpoints included number of adverse and serious adverse events (including diabetic retinopathy, gallbladder disease, hepatic events, neoplasm, acute pancreatitis, and acute kidney injury), gastrointestinal disorders, number of hypoglycaemic episodes, cardiovascular events, and death. Other safety assessments included changes from baseline to weeks 52 and 68 in vital signs, physical examinations, and eye examinations (fundus photography or slit-lamp biomicroscopy) and electrocardiogram assessments at randomisation and week 68. A post-hoc, exploratory analysis was done to assess hypoglycaemic episodes by baseline use of sulfonylureas.

Statistical analysis

A weighted Bonferroni-based closed testing procedure[21] was used to control the type 1 error for four confirmatory hypotheses for the treatment policy estimand (appendix p 7). For the primary endpoint and confirmatory secondary endpoint, the confirmatory one-sided hypotheses were tested to confirm superiority in HbA_{1c} and bodyweight for both oral semaglutide 50 mg and 25 mg versus 14 mg.

The superiority of oral semaglutide 50 mg versus 14 mg on change from baseline in HbA_{1c} was first tested at the overall significance level (5%) while allocating 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. Each of the four hypotheses was tested at their updated local significance level (α-local). This process was repeated until no further hypotheses could be confirmed. The sample size calculation was done considering the power for jointly confirming the superiority hypotheses with respect to HbA_{1c} for both oral semaglutide 50 mg and 25 mg versus oral semaglutide 14 mg for the primary estimand and to ensure enough participants would be exposed to assess safety and tolerability of the higher doses. The power to jointly confirm HbA_{1c} superiority for both dose levels would be 89% with 1620 subjects randomly assigned and a randomisation ratio of 1:1:1. Hypotheses to compare oral semaglutide 50 mg versus 25 mg were not prespecified and no statistical comparisons of these doses were done.

Evaluation of efficacy endpoints was based on the full analysis set, which included all randomly assigned participants (the intention-to-treat analysis), and evaluation of safety endpoints was based on the safety analysis set, which included all participants who received at least one dose of trial treatment. For the efficacy endpoints, the treatment policy estimands were evaluated on the basis of data from the in-trial observation period, and the trial product estimand was evaluated on the basis of data from the on-treatment without rescue medication observation period. The safety evaluation was primarily based on the on-treatment observation period, except for deaths and adverse event types with potentially long

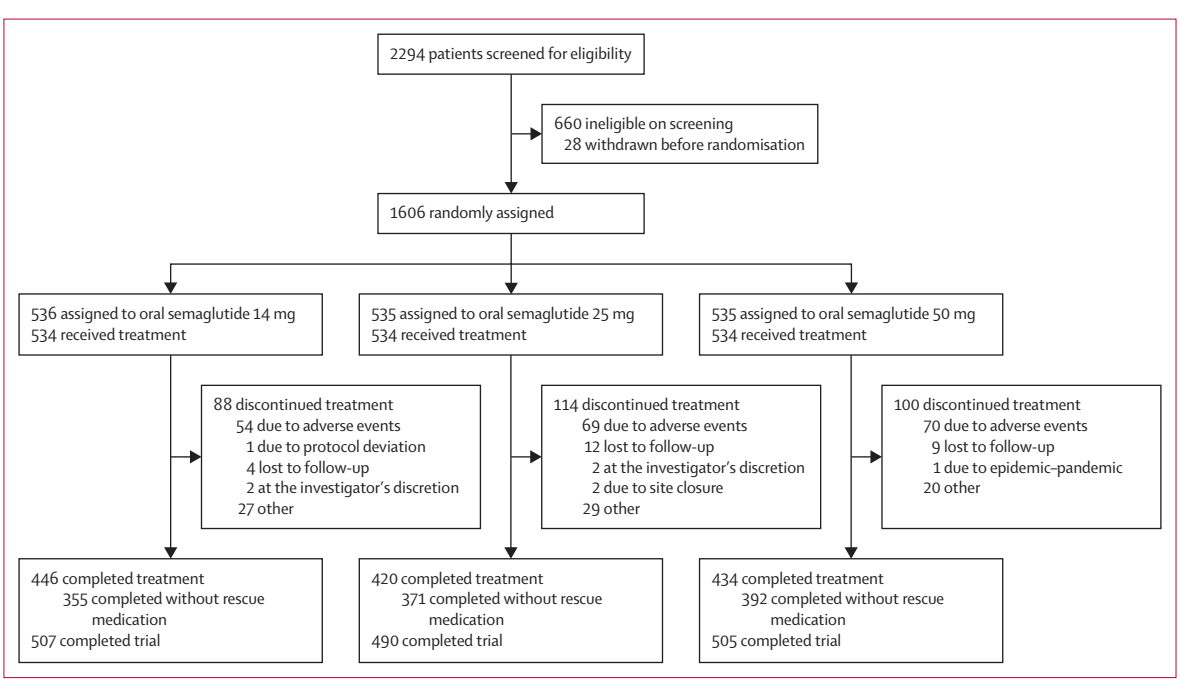

Figure 1: **Trial profile**
Completed treatment means attended week 68 visit while still on trial drug. Completed trial means attended follow-up visit.

latency between onset and diagnosis, for which the in-trial observation period was used.

A pattern mixture model with multiple imputation was used to handle missing at random data at week 52 for the treatment policy estimand. Imputation of missing week-52 data was done within six groups of participants defined by randomised treatment group, and whether participants at week 52 were still on treatment and had not initiated rescue medication or had discontinued treatment or initiated rescue medication. The complete datasets were analysed by means of an analysis of covariance model with treatment, stratification factor, and region as factors and baseline value as covariate. The results obtained from analysing the datasets were combined by means of Rubin's rule.[22]

A mixed model for repeated measurements analysis was used for the trial product estimand based on the full analysis set by means of observed post-baseline measurements up to, and including, week 52 from the on-treatment without rescue medication observation period. The model included treatment, stratification factor, and region as categorical fixed effects, and baseline value as a covariate, all nested within visit. An unstructured covariance matrix for measurements within the same participant was used, assuming measurements from different participants are independent.

Categorical endpoints were analysed by means of a logistic regression model with treatment, strata, and region as fixed effects and baseline value as covariate. Time from first dose of trial product to initiation of rescue medication was analysed by means of a Cox proportional hazards model with treatment, stratification factor and region as categorical fixed effects, and baseline HbA_{1c} as a covariate. Fasting lipid parameters were analysed on a log scale.

Analyses were done by means of SAS 9.4. There was no data monitoring committee. The trial was registered with ClinicalTrials.gov (NCT04707469) and the European Clinical Trials register (EudraCT 2020-000299-39).

Role of the funding source

The funder of the study was involved in study design and monitoring, data collection, data analysis, and data interpretation.

Results

Between Jan 15 and Sept 22, 2021, 2294 people were screened, of whom 1606 were enrolled and randomly assigned to oral semaglutide 14 mg (n=536), 25 mg (n=535), or 50 mg (n=535). The last participant last visit was on March 6, 2023. Treatment was completed by 446 (83%) participants in the 14 mg group, 420 (79%) in the 25 mg group, and 434 (81%) in the 50 mg group (figure 1). Oral semaglutide dose by visit is shown in the appendix (p 8). Participant demographics and baseline characteristics were similar between groups (table 1). There were more men (n=936; 58·3%) than women (n=670; 41·7%); mean (SD) age was 58·2 (10·8) years; mean diabetes duration was 9·3 years (SD 6·2), mean HbA_{1c} was 9·0% (SD 0·8; 74·4 mmol/L [SD 8·3]), mean bodyweight was 96·4 kg (SD 21·6), and mean BMI was 33·8 kg/m² (SD 6·3). Overall, at screening, 865 (54%) participants were treated with sulfonylureas, 484 (30%) with SGLT2 inhibitors, and 403 (25%) with DPP-4 inhibitors; 425 (26%) participants were treated with one oral glucose-lowering drug, 678 (42%) with two, and 503 (31%) with three.

HbA_{1c} improved from baseline to week 52 in all groups, with an estimated mean change of –1·5 percentage points (SE 0·05) for oral semaglutide 14 mg, –1·8 percentage points (0·06) for 25 mg, and –2·0 percentage points (0·06) for 50 mg (figure 2) for the treatment policy estimand. Changes were significantly greater with 25 mg and 50 mg compared with 14 mg, with estimated treatment differences (ETDs) of –0·27 percentage points (95% CI

	Oral semaglutide 14 mg group (n=536)	Oral semaglutide 25 mg group (n=535)	Oral semaglutide 50 mg group (n=535)
Age, years	58·4 (10·4)	58·8 (10·7)	57·6 (11·2)
Sex			
Female	211 (39%)	231 (43%)	228 (43%)
Male	325 (61%)	304 (57%)	307 (57%)
Race			
White	424 (79%)	432 (81%)	398 (74%)
Asian	85 (16%)	73 (14%)	111 (21%)
Black or African American	19 (4%)	22 (4%)	18 (3%)
American Indian or Alaska Native	1 (<1%)	0	0
Native Hawaiian or other Pacific Islander	0	2 (<1%)	0
Other	7 (1%)	6 (1%)	8 (1%)
Ethnicity			
Hispanic or Latinx	38 (7%)	37 (7%)	36 (7%)
Non-Hispanic or Latinx	498 (93%)	498 (93%)	499 (93%)
Duration of diabetes, years	9·4 (5·9)	9·7 (6·7)	8·9 (5·9)
HbA_{1c}			
mmol/mol	74·2 (8·5)	74·6 (8·2)	74·3 (8·2)
%	8·9 (0·8)	9·0 (0·8)	8·9 (0·7)
Fasting plasma glucose*			
mmol/L	10·8 (2·9)	11·0 (3·1)	10·8 (2·9)
mg/dL	195·1 (52·8)	198·0 (55·4)	195·5 (51·7)
Bodyweight, kg	96·4 (20·8)	96·6 (21·2)	96·1 (22·8)
BMI, kg/m²	33·7 (6·1)	34·1 (6·5)	33·7 (6·2)
Waist circumference, cm	112 (14)	113 (14)	112 (15)
Systolic blood pressure, mm Hg	132 (14)	133 (14)	132 (14)
Diastolic blood pressure, mm Hg	81 (9)	80 (9)	80 (8)
Concomitant glucose-lowering medication, n			
Metformin	514 (96%)	503 (94%)	507 (95%)
Sulfonylurea	291 (54%)	287 (54%)	287 (54%)
SGLT2 inhibitor	163 (30%)	162 (30%)	159 (30%)
DPP-4 inhibitor	134 (25%)	136 (25%)	133 (25%)

Data are mean (SD) or n (%). *Mean fasting plasma glucose measurements are based on 532, 526, and 530 participants for oral semaglutide 14 mg, 25 mg, and 50 mg, respectively.

Table 1: **Participant demographic and baseline characteristics**

–0·42 to –0·12; p=0·0006) for oral semaglutide 25 mg and –0·53 percentage points (–0·68 to –0·38; p<0·0001), for oral semaglutide 50 mg. Results were similar for the trial product estimand, with mean changes from baseline for the 14 mg, 25 mg, and 50 mg doses of –1·5 (SE 0·06), –1·9 (0·06; ETD *vs* 14 mg –0·41 [95% CI –0·56 to –0·25; p<0·0001]), and –2·2 percentage points (0·06; ETD *vs* 14 mg –0·77 [–0·93 to –0·61; p<0·0001]) respectively (figure 2). Reductions in HbA_{1c} were largely sustained until week 68 (appendix p 9).

The HbA_{1c} target of less than 7·0% (53 mmol/mol) at week 52 was reached by a greater proportion of participants receiving oral semaglutide 25 mg or 50 mg compared with 14 mg with the treatment policy estimand (194 [39%] of 497 for 14 mg, 240 [51%] of 475 for 25 mg, and 310 [63%] of 492 for 50 mg; estimated odds ratio [EOR] 1·55 [95% CI 1·19 to 2·01; p=0·0011] for 25 mg *vs* 14 mg; EOR 2·61 [2·01 to 3·40; p<0·0001] for 50 mg *vs* 14 mg). HbA_{1c} of no more than 6·5% (48 mmol/mol) at week 52 was also reached by a greater proportion of participants receiving oral semaglutide 25 mg or 50 mg compared with 14 mg with the treatment policy estimand (128 [26%] of 497 for 14 mg, 188 [40%] of 475 for 25 mg, and 252 [51%] of 492 for 50 mg; EOR 1·85 [1·40 to 2·44; p<0·0001] for 25 mg *vs* 14 mg; EOR 3·01 [2·28 to 3·96; p<0·0001] for 50 mg *vs* 14 mg; table 2).

In total, 194 participants (12%) required rescue medication during the trial (92 [17%] of 536 for 14 mg, 54 [10%] of 535 for 25 mg, and 48 [9%] of 535 for 50 mg). The time to rescue medication was significantly shorter in the 14 mg dose group compared with the 25 mg and 50 mg groups (p=0·0019 for 25 mg *vs* 14 mg and p=0·0001 for 50 mg *vs* 14 mg; appendix p 10).

Bodyweight loss was observed in all groups from baseline to week 52 with the treatment policy estimand (mean change –4·4 kg [SE 0·3] for oral semaglutide 14 mg, –6·7 kg [0·3] for 25 mg, and –8·0 kg [0·3] for 50 mg; figure 3). Change in bodyweight was significantly

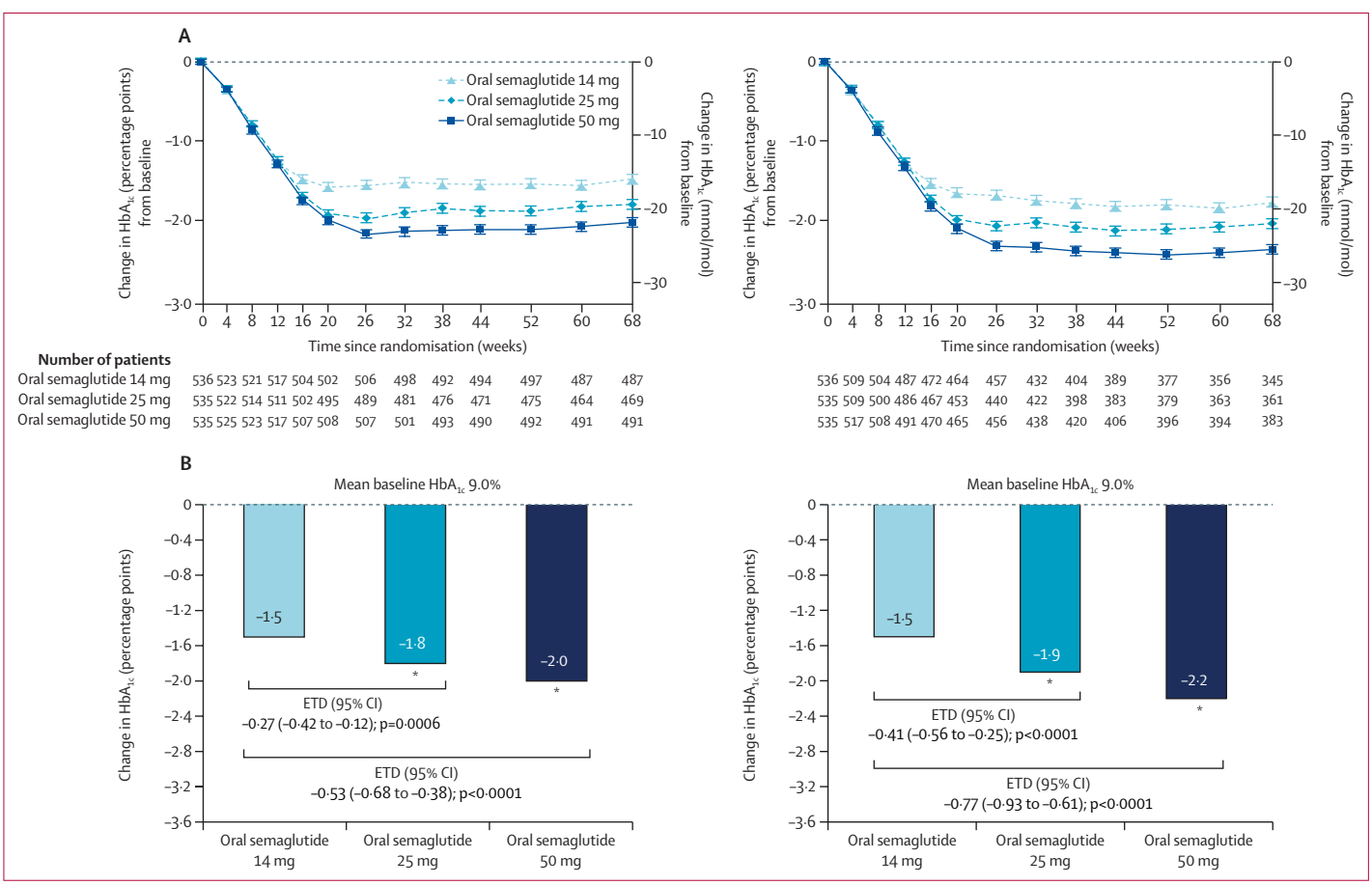

Figure 2: **Glycaemic control-related efficacy endpoints**

(A) Mean observed change (SEM) in HbA_{1c} (percentage points) over time with in-trial data for the treatment policy estimand (left) and on-treatment without rescue medication data for the trial product estimand (right). (B) Estimated change in HbA_{1c} from baseline to week 52 for the treatment policy (left) and trial product estimands (right). Estimated changes in HbA_{1c} (mmol/mol) from baseline to week 52 were –16·2, –19·2, and –22·0 mmol/mol, respectively, with oral semaglutide 14 mg, 25 mg, and 50 mg using the treatment policy estimand (ETD [95% CI], –2·94 mmol/mol [–4·62 to –1·26], p=0·0006 for 25 mg *vs* 14 mg; and –5·82 mmol/mol [–7·48 to –4·16], p<0·0001 for 50 mg *vs* 14 mg). For the trial product estimand, this was –15·9, –20·4, and –24·4 mmol/mol, respectively, with oral semaglutide 14 mg, 25 mg, and 50 mg (ETD [95% CI], –4·43 mmol/mol [–6·17 to –2·69], p<0·0001 for 25 mg *vs* 14 mg; and –8·43 mmol/mol [–10·16 to –6·70], p<0·0001 for 50 mg *vs* 14 mg). (C) Observed proportion of participants achieving HbA_{1c} target of <7·0% (53 mmol/mol) at week 52 for the treatment policy and trial product estimands. HbA_{1c}=glycated haemoglobin. ETD=estimated treatment difference. SEM=standard error of the mean. *Significant *vs* oral semaglutide 14 mg.

	Treatment policy estimand (primary estimand)			Trial product estimand		
	Oral semaglutide 14 mg group (n=536)	Oral semaglutide 25 mg group (n=535)	Oral semaglutide 50 mg group (n=535)	Oral semaglutide 14 mg group (n=536)	Oral semaglutide 25 mg group (n=535)	Oral semaglutide 50 mg group (n=535)
HbA_{1c} <7·0%, <53 mmol/mol						
N	497	475	492	377	379	396
n	194 (39%)	240 (51%)	310 (63%)	179 (47%)	226 (60%)	294 (74%)
Estimated odds ratio	..	1·55 (1·19 to 2·01)	2·61 (2·01 to 3·40)	..	1·73 (1·32 to 2·27)	3·32 (2·50 to 4·39)
p value	..	0·0011	<0·0001	..	<0·0001	<0·0001
HbA_{1c} ≤6·5%, ≤48 mmol/mol						
N	497	475	492	377	379	396
n	128 (26%)	188 (40%)	252 (51%)	121 (32%)	178 (47%)	246 (62%)
Estimated odds ratio	..	1·85 (1·40 to 2·44)	3·01 (2·28 to 3·96)	..	1·91 (1·44 to 2·55)	3·61 (2·71 to 4·82)
p value	..	<0·0001	<0·0001	..	<0·0001	<0·0001
Change from baseline in fasting plasma glucose, mg/dL						
N	494	460	482	374	369	388
Mean change from baseline	−42·8 (61·6)	−54·4 (62·4)	−57·3 (61·7)	−47·1 (58·4)	−56·2 (58·6)	−67·2 (53·0)
Estimated treatment difference	..	−8·24 (−14·23 to −2·25)	−14·81 (−20·72 to −8·89)	..	−10·58 (−16·12 to −5·03)	−19·82 (−25·32 to −14·33)
p value	..	0·007	<0·0001	..	0·0002	<0·0001
Change from baseline in fasting plasma glucose, mmol/L						
N	494	460	482	374	369	388
Mean change from baseline	−2·4 (3·4)	−3·0 (3·5)	−3·2 (3·4)	−2·6 (3·2)	−3·1 (3·3)	−3·7 (2·9)
Estimated treatment difference	..	−0·46 (−0·79 to −0·13)	−0·82 (−1·15 to −0·49)	..	−0·59 (−0·89 to −0·28)	−1·10 (−1·41 to −0·80)
p value	..	0·007	<0·0001	..	0·0002	<0·0001
Change from baseline in bodyweight, %						
N	503	480	495	381	383	399
Mean change from baseline	−4·7 (5·4)	−7·3 (6·6)	−8·5 (7·3)	−5·2 (5·2)	−7·8 (6·6)	−9·8 (7·1)
Estimated treatment difference	..	−2·29 (−3·09 to −1·48)	−3·63 (−4·43 to −2·82)	..	−2·51 (−3·35 to −1·67)	−4·72 (−5·56 to −3·89)
p value	..	<0·0001	<0·0001	..	<0·0001	<0·0001
Bodyweight loss ≥5%						
N	503	480	495	381	383	399
n	206 (41%)	288 (60%)	334 (67%)	168 (44%)	242 (63%)	302 (76%)
Estimated odds ratio	..	2·00 (1·55 to 2·58)	2·80 (2·16 to 3·63)	..	2·06 (1·57 to 2·70)	3·66 (2·75 to 4·88)
p value	..	<0·0001	<0·0001	..	<0·0001	<0·0001
Bodyweight loss ≥10%						
N	503	480	495	381	383	399
n	70 (14%)	139 (29%)	184 (37%)	60 (16%)	124 (32%)	175 (44%)
Estimated odds ratio	..	2·37 (1·72 to 3·27)	3·49 (2·55 to 4·77)	..	2·55 (1·84 to 3·54)	4·14 (3·01 to 5·70)
p value	..	<0·0001	<0·0001	..	<0·0001	<0·0001
Change in waist circumference, cm						
N	502	479	494	381	382	398
Mean change from baseline	−4 (7)	−5 (7)	−6 (7)	−4 (7)	−6 (6)	−7 (7)
Estimated treatment difference	..	−1·2 (−2·0 to −0·4)	−2·3 (−3·1 to −1·5)	..	−1·7 (−2·6 to −0·8)	−3·2 (−4·1 to −2·3)
p value	..	0·0039	<0·0001	..	0·0003	<0·0001

Data are n (%), mean (SD), or estimated treatment difference or estimated odds ratio with 95% CI. HbA_{1c}=glycated haemoglobin.

Table 2: **Supportive secondary endpoints at week 52**

greater for oral semaglutide 25 mg and 50 mg, respectively, versus 14 mg (ETD −2·32 kg [95% CI −3·11 to −1·53; p<0·0001] for oral semaglutide 25 mg and −3·63 kg [−4·42 to −2·84; p<0·0001] for oral semaglutide 50 mg). Bodyweight loss was also observed in all groups with the trial product estimand (figure 3). The percentage change in bodyweight from baseline to weeks 52 and 68 is shown in table 2 and the appendix (p 11). A significantly greater proportion of participants in the oral semaglutide 25 mg and 50 mg groups compared with the 14 mg group had bodyweight reduction of 5% or more (206 [41%] of 503 for 14 mg, 288 [60%] of 480 for 25 mg, and 334 [67%] of 495 for 50 mg) and 10% or more (70 [14%] of 503 for 14 mg, 139 [29%] of 480 for 25 mg, and 184 [37%] of 495 for 50 mg) at week 52 for the treatment policy estimand. Results were similar with the trial

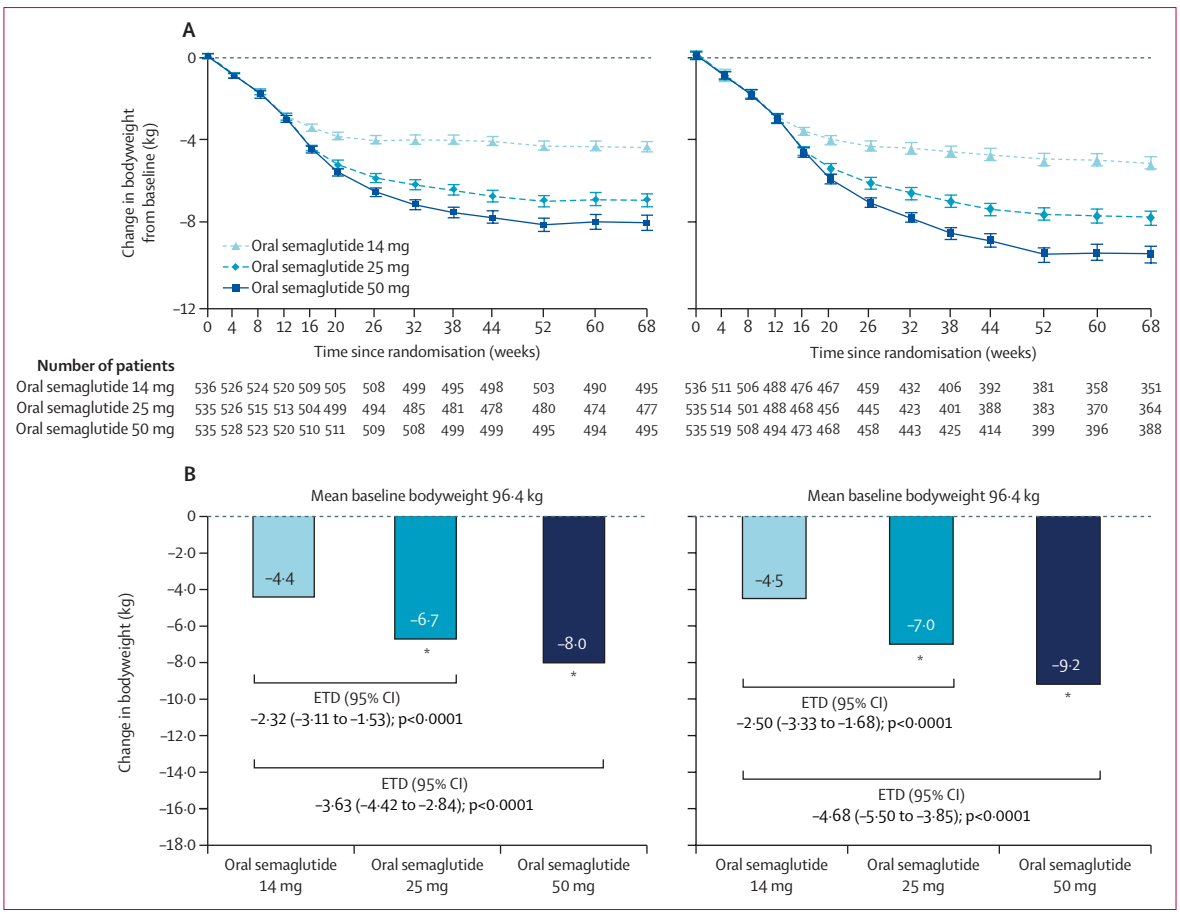

Figure 3: **Bodyweight-related efficacy endpoints**
(A) Mean observed change (SEM) in bodyweight (kg) over time with in-trial data for the treatment policy estimand (left) and on-treatment without rescue medication data for the trial product estimand (right). (B) Estimated change in bodyweight from baseline to week 52 for the treatment policy (left) and trial product estimands (right). (C) Observed proportion of participants achieving bodyweight loss of 10% or more at week 52 for the treatment policy and trial product estimands. *Significant *vs* oral semaglutide 14 mg. ETD=estimated treatment difference.

product estimand. Reductions in bodyweight were maintained through to week 68 (appendix p 12). Reductions in waist circumference were significantly greater with oral semaglutide 25 mg and 50 mg versus 14 mg. Results for other supportive secondary endpoints at weeks 52 and 68 are shown in tables 2 and the appendix (pp 19–20). Changes in fasting lipids were generally similar between groups, although greater reductions in triglycerides (both estimands) and greater increases in high-density lipoprotein cholesterol (trial product estimand only) were seen with oral semaglutide 50 mg versus 14 mg (appendix pp 21–22).

The proportion of participants reporting an adverse event was 404 (76%) of 534 in the 14 mg group, 422 (79%) of 534 in the 25 mg group, and 428 (80%) of 534 in the 50 mg group (table 3). Gastrointestinal disorders, in particular nausea, vomiting, and diarrhoea, were the most frequently reported adverse events, occurring in 42% (n=225) of the 14 mg group, 53% (n=282) of the 25 mg group, and 54% (n=286) of the 50 mg group. The majority of gastrointestinal disorders were mild to moderate in severity and occurred during dose escalation (appendix p 13). Adverse events leading to premature treatment discontinuation occurred in 10% (n=54) of participants in the 14 mg group, 12% (n=66) in the 25 mg group, and 13% (n=68) in the 50 mg group, and were predominantly gastrointestinal. Level 1–3 hypoglycaemic episodes were reported in 13% (n=70) of participants in the 14 mg group, 14% (n=74) in the 25 mg group, and 17% (n=90) in the 50 mg dose group (table 3); 4% in each group (n=24, 21 and 24, respectively) were considered clinically relevant and one episode (in the 50 mg group) was classified as severe (level 3). The majority of hypoglycaemic episodes reported were in participants treated with sulfonylurea at baseline (appendix p 23). Small decreases in diastolic and systolic blood pressure and increases in pulse rate were reported in all groups from baseline to weeks 52 and 68 (appendix p 24). No dose-dependent increases in other adverse events of special focus, including diabetic retinopathy, pancreatitis, acute

	Oral semaglutide 14 mg group (n=534)			Oral semaglutide 25 mg group (n=534)			Oral semaglutide 50 mg group (n=534)		
	n (%)	Events	Events per 100 patient-years	n (%)	Events	Events per 100 patient-years	n (%)	Events	Events per 100 patient-years
Total adverse events	404 (76%)	1641	244·7	422 (79%)	2055	317·6	428 (80%)	2115	319·9
Adverse events by severity									
Mild	344 (64%)	1117	166·5	345 (65%)	1386	214·2	357 (67%)	1449	219·2
Moderate	202 (38%)	450	67·1	226 (42%)	585	90·4	242 (45%)	604	91·4
Severe	47 (9%)	74	11·0	55 (10%)	84	13·0	46 (9%)	62	9·4
Total serious adverse events	53 (10%)	81	12·1	57 (11%)	81	12·5	44 (8%)	52	7·9
Adverse events leading to discontinuation of trial product	54 (10%)	104	15·5	66 (12%)	112	17·3	68 (13%)	125	18·9
Fatal events*	2 (<1%)	2	0·3	5 (<1%)	6	0·9	2 (<1%)	2	0·3
Hypoglycaemic episodes†	70 (13%)	323	48·2	74 (14%)	272	42·0	90 (17%)	288	43·6
Level 1	55 (10%)	254	37·9	65 (12%)	223	34·5	80 (15%)	237	35·9
Level 2	24 (4%)	65	9·7	21 (4%)	44	6·8	24 (4%)	35	5·3
Level 3	0	0	..	0	0	..	1 (<1%)	1	0·15
Most frequent adverse events occurring in ≥5% of participants in one or more treatment groups by Medical Dictionary for Regulatory Activities preferred term (on-treatment)									
Nausea	97 (18%)	120	17·9	145 (27%)	222	34·3	146 (27%)	218	33·0
Vomiting	54 (10%)	71	10·6	91 (17%)	156	24·1	97 (18%)	184	27·8
Diarrhoea	66 (12%)	84	12·5	69 (13%)	108	16·7	76 (14%)	150	22·7
COVID-19	66 (12%)	68	10·1	64 (12%)	68	10·5	69 (13%)	71	10·7
Decreased appetite	38 (7%)	43	6·4	39 (7%)	42	6·5	58 (11%)	61	9·2
Constipation	40 (7%)	46	6·9	35 (7%)	41	6·3	33 (6%)	39	5·9
Diabetic retinopathy	41 (8%)	44	6·6	26 (5%)	30	4·6	35 (7%)	40	6·1
Headache	34 (6%)	63	9·4	28 (5%)	81	12·5	38 (7%)	81	12·3
Dyspepsia	28 (5%)	32	4·8	30 (6%)	48	7·4	30 (6%)	50	7·6
Nasopharyngitis	24 (4%)	28	4·2	22 (4%)	27	4·2	27 (5%)	30	4·5
Abdominal pain upper	14 (3%)	17	2·5	32 (6%)	52	8·0	22 (4%)	55	8·3
Abdominal pain	15 (3%)	26	3·9	28 (5%)	35	5·4	21 (4%)	27	4·1
Safety focus areas									
Gastrointestinal disorders	225 (42%)	520	77·5	282 (53%)	821	126·9	286 (54%)	922	139·5
Renal disorders	2 (<1%)	2	0·3	6 (1%)	6	0·9	2 (<1%)	2	0·3
Acute kidney injury	2 (<1%)	2	0·3	3 (<1%)	3	0·5	2 (<1%)	2	0·3
Renal impairment	0	0	..	3 (<1%)	3	0·5	0	0	..
Drug-related hepatic disorders	14 (3%)	17	2·5	10 (2%)	12	1·9	11 (2%)	17	2·6
Gallbladder-related disorders	4 (<1%)	8	1·2	8 (1%)	8	1·2	4 (<1%)	6	0·9
Hepatobiliary disorders	4 (<1%)	8	1·2	7 (1%)	7	1·1	3 (<1%)	4	0·6
Cholelithiasis	2 (<1%)	3	0·4	3 (<1%)	3	0·5	3 (<1%)	3	0·5
Pancreatitis	2 (<1%)	2	0·3	1 (<1%)	1	0·2	1 (<1%)	1	0·2
Acute pancreatitis	0	0	..	1 (<1%)	1	0·2	1 (<1%)	1	0·2
Cardiovascular disorders	37 (7%)	54	7·4	42 (8%)	47	6·5	20 (4%)	29	4·0
Malignant neoplasm	6 (1%)	6	0·8	9 (2%)	11	1·5	6 (1%)	6	0·8
Thyroid cancer	0	0	..	0	0	..	0	0	..
Diabetic retinopathy‡	67 (13%)	80	10·9	53 (10%)	66	9·2	60 (11%)	73	10·0

Data are n (%). *In the 25 mg group, one participant had two fatal events (respiratory failure and circulatory collapse) reported simultaneously. One further participant in the 25 mg group had a fatal event (brain cancer) after product discontinuation. †Hypoglycaemic episodes were reported using a specific hypoglycaemic episode form and were classified according to the American Diabetes Association 2018/International Hypoglycaemia Study Group 2017 classification. ‡Eye examinations were done at screening, week 52, and week 68.

Table 3: **On-treatment adverse events (safety analysis set)**

gallbladder disease, and thyroid cancer, were observed (table 3). There were no new safety concerns with the 25 mg and 50 mg doses of oral semaglutide.

Serious adverse events were reported by 10% (n=53) of participants in the 14 mg group, 11% (n=57) in the 25 mg group, and 8% (n=44) in the 50 mg group. Ten deaths

occurred during the trial: two in the 14 mg group (pancreatic cancer or cardiac arrest), six in the 25 mg group (lung cancer, brain cancer, myocardial infarction, pulmonary embolism, respiratory failure–circulatory collapse, circulatory collapse), and two in the 50 mg group (COVID-19 infection and undetermined [presumed cardiovascular event]). Two of the six deaths in the 25 mg group occurred when the participant was on the 14 mg dose; one of the six occurred after discontinuation of oral semaglutide. All fatal events were judged unlikely to be related to the trial product by the investigator and sponsor.

Discussion

In this randomised, double-blind, active-controlled clinical trial, participants with inadequately controlled type 2 diabetes on a stable daily regimen of one to three oral glucose-lowering drugs at screening showed both superior glycaemic control and superior bodyweight reduction with once-daily oral semaglutide 25 mg or 50 mg compared with 14 mg. Significantly greater proportions of participants assigned to oral semaglutide 25 mg or 50 mg versus 14 mg reached HbA_{1c} targets of less than 7·0% (53 mmol/mol) and no more than 6·5% (48 mmol/mol) and weight loss of 5% or more and 10% or more. Reductions in HbA_{1c} and bodyweight were largely sustained through to week 68.

Oral semaglutide 14 mg has been extensively studied in eight international phase 3a PIONEER trials. Across the PIONEER phase 3a programme, this dose was associated with HbA_{1c} changes of –1·0 to –1·4 percentage points after 26 or 52 weeks,[8–12,14] compared with –1·5 percentage points with the 14 mg dose, –1·8 percentage points for the 25 mg dose, and –2·0 percentage points for the 50 mg dose in PIONEER PLUS, in which the population had a higher baseline HbA_{1c}. Fewer participants required rescue medication in the oral semaglutide 25 mg and 50 mg groups compared with the 14 mg group. This improved glycaemic efficacy suggests that dose escalation could be a valuable therapeutic strategy to improve outcomes for people with type 2 diabetes who do not reach glycaemic treatment targets with the 14 mg dose.

The higher doses of oral semaglutide increased the proportion of participants who reached an HbA_{1c} target of less than 7% (53 mmol/mol) compared with 14 mg in our trial. The proportion of participants reaching the HbA_{1c} target of less than 7% (53 mmol/mol) with oral semaglutide 14 mg was lower than reported with the same dose in previous trials (39% *vs* 53–77%).[8–14,23] This can, in part, be attributed to the inclusion criterion for HbA_{1c} in PIONEER PLUS resulting in participants having higher mean baseline HbA_{1c} than in previous PIONEER trials (9·0% *vs* 8·0–8·3%).[8–14,23] However, other differences between trial populations and procedures (eg, the use of other glucose-lowering medications, duration of type 2 diabetes) might also have contributed.

The magnitude of bodyweight reduction for both the 25 mg and 50 mg doses was superior to oral semaglutide 14 mg, and greater than reductions seen in previous PIONEER trials.[8–14,23] More than twice as many participants reached bodyweight loss from baseline of 10% or greater in both the 25 mg and 50 mg treatment groups compared with the 14 mg group. Approximately two-thirds of patients had bodyweight loss of 5% or more, a threshold considered clinically meaningful by the US Food and Drug Administration and others.[24,25] The weight reduction observed in the 50 mg treatment group was similar to that observed with subcutaneous semaglutide 2·4 mg once weekly in the STEP 2 trial of adults with overweight or obesity and type 2 diabetes.[26] The reduction in bodyweight in PIONEER PLUS aligns with the increased focus on weight management as a priority treatment target for people with type 2 diabetes, alongside cardiorenal protection and glycaemic control, which are seen across international recommendations.[2]

The findings of PIONEER PLUS might help to support treatment intensification with GLP-1 receptor agonists for people in need of additional glycaemic control. The 2023 ADA guidelines recommend selecting glucose-lowering medications on the basis of an individual's glycaemic and weight loss targets.[3] In addition, avoidance of therapeutic inertia (ie, the failure to initiate or intensify therapy in a timely manner), is essential to reach HbA_{1c} targets in people with type 2 diabetes, with early and sustained glycaemic control associated with a reduced risk of cardiovascular complications.[27,28] Dose escalation of existing glucose-lowering treatment provides a simple and accessible approach to support individualisation of pharmacotherapy according to need. Existing studies have shown the therapeutic potential of escalating injectable doses of GLP-1 receptor agonists.[16,17] However, many people might be reluctant to initiate therapy by injection. The utility of an oral GLP-1 receptor agonist option has been suggested by the higher-than-expected adoption of oral semaglutide reported in primary care in the USA.[29] PIONEER PLUS is the first study to confirm therapeutic benefit from intensification of oral semaglutide therapy from 14 mg to doses of 25 mg and 50 mg, and is therefore important and might help to support earlier treatment intensification.

The findings of PIONEER PLUS appear to be largely consistent with those of previous trials of higher-dose injectable GLP-1 receptor agonists, which reported dose-related decreases in HbA_{1c} and bodyweight;[16,17] however, differences in trial populations prevent direct comparisons. Previous trials have also not found any new safety concerns with the higher doses evaluated. This supports a wider range of dosing choices to reach individualised treatment goals.

The safety profile of oral semaglutide 25 mg and 50 mg reported in our study was consistent with the known profile of the GLP-1 receptor agonist class and with the profile reported across previous PIONEER trials.[8–14,23] Gastrointestinal adverse events were the most frequent and increased with increasing dose, and were primarily

responsible for the increase in premature treatment discontinuations seen with the higher oral semaglutide doses. However, these events were mostly mild or moderate in severity, of short duration, and occurred during the dose-escalation phase. Oral semaglutide was well tolerated across all three doses, although adverse events occurred at a slightly higher rate with the 25 mg and 50 mg doses versus the 14 mg dose. The rates of serious adverse events were similar across treatment groups, as were adverse events of special focus (eg, diabetic retinopathy, pancreatitis, and gallbladder-related disorders). Rates of diabetic retinopathy were higher than seen in most of the phase 3a PIONEER trials;[8–14,23] however, this was most likely due to the different methods applied in this trial. In PIONEER PLUS, more frequent eye examinations were done (at screening, week 52, and week 68), and a more comprehensive search strategy was used to capture events.

A strength of the PIONEER PLUS trial design is the use of an active comparator, with higher doses of oral semaglutide compared with the maximum currently available dose of 14 mg, which has been shown to improve glycaemic control and reduce bodyweight compared with other glucose-lowering drugs across the type 2 diabetes disease spectrum and across various patient groups.[8–12,14] The high proportions of participants completing the trial (94%) and treatment (81%) support the trial robustness, as does the similarity of the primary and secondary confirmatory outcomes with both estimands.

Limitations of the trial include that the dose-escalation period of up to 16 weeks meant that participants were only on the higher doses for 36–40 weeks before the primary and confirmatory secondary endpoints were assessed, which might not have been an adequate duration for the full effects to be seen. However, the reductions in HbA_{1c} and bodyweight at week 52 appeared to have plateaued and were largely sustained at week 68. In addition, dosing might not reflect clinical practice since participants were escalated to higher doses according to randomisation and irrespective of clinical need. The inability to reduce doses to below 14 mg because of the need to maintain masking might also not reflect real-world practice. Moreover, it is possible, although we consider it unlikely, that participants receiving 25 mg or 50 mg doses of oral semaglutide were aware that these tablets were slightly different in shape from the 14 mg dose and could have communicated this to their research team. In addition, it was not possible to assess whether the efficacy and tolerability of oral semaglutide were directly affected specifically by the new formulation. It is therefore possible that the additional benefit of the 25 mg and 50 mg doses was not only dose-related, but also reflected the higher bioavailability of this formulation. Also, the trial did not assess differences between the 25 mg and 50 mg doses. The predominantly White cohort in this trial (78%) is also a limitation, especially given the high prevalence of type 2 diabetes in other racial and ethnic groups.

The superior glycaemic control and bodyweight loss with oral semaglutide 25 mg and 50 mg compared with the current highest approved dose of 14 mg observed in PIONEER PLUS suggest that these higher doses might support individually tailored treatment goals, based not only on glucose-lowering but also bodyweight and cardiovascular risk factor reduction targets. The availability of a wider range of doses might allow individualised dose titration to the desired effect, and the ability to intensify treatment by increasing the dose of a single oral agent might help overcome therapeutic inertia. This might encourage improved management of type 2 diabetes earlier and in the primary care setting. Future real-world studies will be needed to investigate the clinical impact of the availability of higher doses of oral semaglutide.

Contributors

EC and LB contributed to trial design. VRA, JA, JBB, and SDP did the trial and collected the data. LB analysed the data. VRA, JA, LB, EC and SG verified the data. All authors participated in interpretation of data and revised the manuscript and approved the final version. 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.

Declaration of interests

VRA reports receiving consultancy fees from Applied Therapeutics, Fractyl, Novo Nordisk, Pfizer, and Sanofi, and research grant support (to their institution) from Applied Therapeutics, Eli Lilly, Fractyl, Novo Nordisk, and Sanofi. LB, EC, and SG are employees and shareholders in Novo Nordisk. JA reports consulting fees or speaking honoraria from Astra Zeneca, Boehringer Ingelheim, Lilly, and Novo Nordisk. FKK reports participating in scientific advisory panels or speakers' bureaus for, consulting fees, or receiving research support from Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Carmot Therapeutics, Eli Lilly, Gubra, Lupin, MedImmune, MSD–Merck, Mundipharma, Norgine, Novo Nordisk, Pharmacosmos, Sanofi, ShouTi, Zealand Pharma, and Zucara; is a minority shareholder in Antag Therapeutics, and co-owner of the weight loss clinic Medicinsk Vægttabsbehandling ApS. SDP reports consulting fees or speaking honoraria from Abbott, AstraZeneca, Bausch, Bayer, Boehringer Ingelheim, Dexcom, HLS, Janssen, Lilly, Merck, Novo Nordisk, Pfizer, and Sanofi; and research studies for AstraZeneca, Boehringer Ingelheim, Lilly, Medpace, and Novo Nordisk. JBB contracted consulting fees and travel support for contracted activities that are paid to the University of North Carolina by Novo Nordisk and vTv Therapeutics; has received grant support from Dexcom, NovaTarg, Novo Nordisk, Sanofi, Tolerion, and vTv Therapeutics; has received personal compensation for consultation from Alkahest, Altimmune, Anji, AstraZeneca, Bayer, Boehringer Ingelheim, Carmot Therapeutics, CeQur, Cirius Therapeutics, Corcept Therapeutics, Dasman Diabetes Institute (Kuwait), Eli Lilly, Fortress Biotech, GentiBio, Glycadia, Glyscend, Janssen, Mellitus Health, Moderna, Pendulum Therapeutics, Praetego, Sanofi, Stability Health, Terns, and Valo; has received payment for expert testimony from Medtronic; and in lieu of payment for consultation he has received stock or options in Glyscend, Mellitus Health, Pendulum Therapeutics, PhaseBio, Praetego, and Stability Health.

Data sharing

Individual participant data will be shared in datasets in a de-identified, anonymised format. Shared data will include datasets from clinical research sponsored by Novo Nordisk completed after 2001 for product indications approved in both the EU and the USA. The study protocol and redacted clinical study report will be made available according to Novo Nordisk data sharing commitments. These data will be available

permanently after research completion and approval of product and product use in both the EU and the USA (no end date). Data will be shared with bona fide researchers submitting a research proposal requesting access to data, for use as approved by the Independent Review Board (IRB) according to the IRB charter. These data can be accessed via an access request proposal form. The data will be made available on a specialised SAS data platform.

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