Effect of Additional Oral Semaglutide vs Sitagliptin on Glycated Hemoglobin in Adults with Type 2 Diabetes Uncontrolled with Metformin ± Sulfonylurea: the PIONEER 3 Randomized Clinical Trial

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Key points

Question: What is the efficacy of oral semaglutide (3, 7, or 14 mg daily) compared with sitagliptin 100 mg when added to metformin ± sulfonylurea in patients with uncontrolled type 2 diabetes?

Findings: In this randomized clinical trial that included 1864 adults, oral semaglutide 7 mg and 14 mg compared with sitagliptin resulted in statistically significantly greater reductions in glycated hemoglobin over 26 weeks (–1.0% and –1.3%, respectively, compared with –0.8%). There was no significant benefit with oral semaglutide 3 mg compared with sitagliptin.

Meaning: In this trial, oral semaglutide 7 mg and 14 mg daily, when added to metformin ± sulfonylurea, resulted in greater improvements in glycated hemoglobin than sitagliptin after 26 weeks.

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Abstract

Importance: This is the first published phase 3 trial to compare oral semaglutide, a novel glucagon-like peptide-1 receptor agonist, with another class of glucose-lowering therapy.

Objective: To demonstrate efficacy, and assess long-term adverse event profile, and tolerability of once-daily oral semaglutide 3, 7, and 14 mg versus sitagliptin 100 mg added-on to metformin ± sulfonylurea in patients with type 2 diabetes.

Design: 78-week, randomized, double-blind, double-dummy, parallel-group, phase 3a trial.

Setting: 206 sites in 14 countries conducted from February 2016 to March 2018.

Participants: Of 2463 patients screened, 1864 adults with type 2 diabetes uncontrolled on metformin ± sulfonylurea were randomized.

Interventions: Once-daily oral semaglutide 3 mg (N=466), 7 mg (N=466) or 14 mg (N=465), or sitagliptin (N=467). Oral semaglutide was initiated at 3 mg, and escalated every 4 weeks, first to 7 mg then 14 mg, until the randomized dose was achieved.

Main Outcomes and Measures: Two scientific questions were addressed by defining two estimands: a treatment policy estimand (regardless of trial product discontinuation, or rescue medication use), and a trial product estimand (on trial product without rescue medication use) in all randomized patients. Primary endpoint was change in glycated hemoglobin (HbA_{1c}), and key secondary endpoint was change in body weight, both from baseline to week 26; these endpoints were assessed at weeks 52 and 78 as additional secondary endpoints. Demonstration of efficacy was done by showing non-inferiority (margin 0.3%) with respect to HbA_{1c} prior to testing for superiority of HbA_{1c} and body weight, all based on the treatment policy estimand. Tolerability was also assessed.

Results: Among 1864 patients who were randomized (mean [standard deviation]: age 58 years [10], baseline HbA_{1c} 8.3% [0.9], body mass index 32.5 kg/m^2 [6.4]; 879 [47.2%] women), 1758 (94.3%) completed the trial and 298 (16.0%) prematurely discontinued treatment. Oral semaglutide 7 and 14 mg were superior to sitagliptin in reducing HbA_{1c}

(estimated treatment differences [ETD; 95% confidence interval (CI)]: –0.3% [–0.4, –0.1]; –0.5% [–0.6, –0.4], respectively; both P<.001) and body weight (ETD [95% CI]: –1.6 kg [–2.0, –1.1]; –2.5 kg [–3.0, –2.0], respectively; both P<.001) from baseline to week 26 (treatment policy estimand). Non-inferiority of oral semaglutide 3 mg with respect to HbA_{1c} was not demonstrated. Trial product estimand findings were consistent. Week 78 reductions in both endpoints were statistically significantly greater with oral semaglutide 14 mg versus sitagliptin (both estimands). The proportions of patients prematurely discontinuing trial product because of adverse events were 5.6%, 5.8%, 11.6% and 5.2% for oral semaglutide 3, 7, and 14 mg and sitagliptin, respectively, with gastrointestinal AEs being the most frequent cause in all groups.

Conclusions and Relevance: Among adults with type 2 diabetes uncontrolled with metformin ± sulfonylurea, oral semaglutide 7 mg and 14 mg compared with sitagliptin resulted in significantly greater reductions in HbA_{1c} over 26 weeks, but there was no significant benefit with the 3 mg dose. Further research is needed to assess effectiveness in a clinical setting.

Trial Registration: Funded by Novo Nordisk A/S; ClinicalTrials.gov: NCT02607865

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Keywords: clinical trial, DPP-4 inhibitor, GLP-1 receptor agonist, oral glucose-lowering agent, oral semaglutide, phase 3, sitagliptin, type 2 diabetes.

Introduction

Achieving and maintaining glycemic control is a key aim for the treatment of type 2 diabetes (T2D).[1] The recommended target glycated hemoglobin (HbA_{1c}) of <7.0%, is, however, not achieved by a sizable proportion of patients.[2] Following metformin, many second-line treatment options for T2D are available, with choice influenced by a variety of factors including the presence of comorbidities (eg, cardiovascular disease, renal disease), potential body weight effects, safety concerns (eg, risk of hypoglycemia), cost, and patient preferences.[1,3]

Glucagon-like peptide-1 receptor agonists (GLP-1RAs) and dipeptidyl peptidase-4 inhibitors (DPP-4is) are incretin-based therapies for the treatment of T2D. DPP-4is generally have modest glucose-lowering potential and a neutral effect on body weight and, in comparison, GLP-1RAs are associated with greater reductions in HbA_{1c}, and also reduce body weight.[4] Also, while no cardiovascular benefit has been demonstrated for DPP-4is,[5,6] some GLP-1RAs have been shown to improve cardiovascular outcomes,[7-9] and are recommended for patients with cardiovascular disease.[1] Based on their convenient oral administration and safety profile, DPP-4is continue to be widely prescribed.[10]

As peptides, GLP-1RAs are currently administered only via subcutaneous (s.c.) injection. Peptide medications have low oral bioavailability as they are subject to rapid enzymatic and pH-induced proteolytic degradation in the stomach, and are poorly absorbed by the gastrointestinal tract.[11] To overcome this, an oral tablet of the GLP-1RA semaglutide has been developed through co-formulation with the absorption enhancer sodium N-(8-[2-hydroxylbenzoyl] amino) caprylate (SNAC).[12] Oral semaglutide treatment has shown significant improvements in glycemic control and body weight when compared with placebo.[12,13]

This paper reports the results of PIONEER 3, a trial that compared the efficacy, long-term adverse event (AE) profile and tolerability of oral semaglutide with sitagliptin, a widely used DPP-4i, as add-on to metformin ± sulfonylurea in patients with T2D.

Methods

The trial protocol was approved by the Institutional Review Board/Independent Ethics Committees at each site, and the trial was conducted in accordance with International Council on Harmonisation (ICH) Good Clinical Practice guidelines and the Declaration of Helsinki.[14,15] All patients provided written informed consent prior to any trial-related intervention.

Patients

Adult patients diagnosed with T2D, with HbA_{1c} 7.0–10.5% inclusive, and on a stable dose of metformin ± sulfonylurea, were eligible. Exclusion criteria included treatment with any medication for diabetes or obesity ≤90 days before screening (other than metformin, sulfonylurea, or short-term insulin [≤14 days in total]), a history of pancreatitis, renal impairment, and proliferative retinopathy or maculopathy requiring acute treatment. Full eligibility criteria are provided in eTable 1.

Data on race and ethnicity were recorded in the electronic case report form (fixed categories supplemented by a free-text “other” field and a “not applicable” field) by the investigator at screening, in accordance with local regulations. These data were collected in part to address regulatory requests to assess efficacy and safety of an investigational product in patients of different races and ethnicities.

Randomization

Patients were randomized 1:1:1:1 to once-daily oral semaglutide (3, 7, or 14 mg) or once-daily oral sitagliptin 100 mg for 78 weeks (eFigure 1). Treatment codes were assigned by an interactive web response system, ensuring patients and investigators were blinded to treatment allocation. Randomization was done in blocks of size 8 and stratified by patients’ country of origin (Japanese or non-Japanese) and background medication (metformin ± sulfonylurea).

Interventions

Since food intake impairs absorption of oral semaglutide, patients were instructed to administer trial products (eAppendix 2) in the morning, in a fasting state, with ≤120 mL of water ≥30 minutes before breakfast and ≥30 minutes before any other oral medication (including background glucose-lowering medication). Oral semaglutide treatment was initiated with the 3 mg dose, then escalated to 7 mg after 4 weeks, and 14 mg after a further 4 weeks, until the randomized dose was achieved; sitagliptin was initiated and maintained at 100 mg. Patients also received background metformin ± sulfonylurea, maintained at the stable, pre-trial dosage. Intensification of existing background glucose-lowering medication and/or initiation of new glucose-lowering medication was prescribed as add-on to randomized treatment to patients with persistent or unacceptable hyperglycemia, based on predefined fasting plasma glucose (FPG) and/or HbA_{1c} criteria (eTable 2). All patients were to continue in the trial even if prematurely discontinuing trial product and/or receiving additional glucose-lowering medications. Patients prematurely discontinuing trial product could receive any glucose-lowering drug, excluding other GLP-1RAs or DPP-4is, before completion of the follow-up visit at the investigator's discretion.

Outcomes

The primary endpoint was the change in HbA_{1c}, and the key secondary endpoint was the change in body weight, both from baseline to week 26. All additional secondary endpoints were assessed at weeks 26, 52 and 78. These included change from baseline in HbA_{1c} and body weight, FPG, mean and mean post-prandial increment in self-measured blood glucose (SMBG) 7-point profile, body mass index (BMI), waist circumference, fasting lipid profile, and patient-reported outcomes (Impact of Weight on Quality of Life-Lite questionnaire Clinical Trial Version [IWQoL-Lite-CT], Short Form-36 Version 2 Health Survey [SF-36v2] [acute version], and Control of Eating Questionnaire [CoEQ]; described in eAppendix 3). Further secondary endpoints were whether patients achieved HbA_{1c} <7.0% (American Diabetes Association [ADA] target) and ≤6.5%, weight loss ≥5% and ≥10%, and composites of HbA_{1c}

<7.0% without hypoglycemia (severe or blood glucose-confirmed symptomatic hypoglycemia [56 mg/dL (3.1 mmol/mol)]) and without weight gain, and HbA_{1c} reduction ≥1% and weight loss ≥3%; and time to rescue medication and additional glucose-lowering medication.

Safety assessments included the number of AEs, number of severe (according to ADA classification) or blood-glucose confirmed (blood glucose value <56 mg/dL [3.1 mmol/L]) symptomatic hypoglycemic episodes, changes from baseline at weeks 26, 52 and 78 in laboratory parameters (amylase and lipase), vital signs (pulse, systolic and diastolic blood pressure), and eye examination category (week 52 and 78 only); and occurrence of anti-semaglutide antibodies. An independent external event adjudication committee (EAC) performed blinded validation of selected AEs (deaths, acute coronary syndrome, cerebrovascular events, heart failure requiring hospitalization, acute pancreatitis, malignant neoplasms, thyroid diseases [malignant thyroid neoplasms and C-cell hyperplasia], acute kidney injury, and lactic acidosis) according to predefined diagnostic criteria. Semaglutide plasma concentration was determined in approximately 50% of patients (data not reported in this manuscript). Tolerability was assessed as the rate of premature discontinuations of trial product, along with the primary reason for discontinuation.

Trial Design

This was a 78-week, randomized, double-blind, double-dummy, active-controlled, parallel-group, phase 3a trial conducted at 206 sites in 14 countries between February 2016 and March 2018.

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, including the Food and Drug Administration and the European Medicines Agency.

The treatment policy estimand evaluates the treatment effect for all randomized patients regardless of trial product discontinuation or use of rescue medication. This estimand

reflects the intention-to-treat principle as defined in International Council of Harmonisation (ICH) E9.[16] The estimand reflects the effect of initiating treatment with oral semaglutide compared with initiating treatment with sitagliptin, both potentially followed by either discontinuation of trial product and/or addition of, or switch to, another glucose-lowering drug.

The trial product estimand evaluates the treatment effect for all randomized patients under the assumption that all patients remained on trial product 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 sitagliptin without the confounding effect of trial product discontinuation or the use of rescue medication.

Trial product discontinuation and initiation of rescue medication are post-randomization events that 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).[17] For the treatment policy estimand, the event (trial product discontinuation or initiation of rescue medication) was considered irrelevant and data collected thereafter were included in the estimation. For the trial product estimand, any data collected after the event was discarded and the estimation relies on statistical modelling to estimate the treatment effect under the assumption that the event had not occurred. Further details on the estimands can be found in eAppendix 4.

Sample Size

A sample size of 465 patients per treatment group was calculated to provide 90% power to jointly demonstrate superiority of oral semaglutide 14 and 7 mg versus sitagliptin, and non-inferiority of oral semaglutide 3 mg versus sitagliptin in reducing HbA_{1c} at week 26.

Statistical Analysis

The demonstration of efficacy of oral semaglutide on change in HbA_{1c} and in body weight, both from baseline to week 26, was based on a weighted Bonferroni closed-testing

strategy[18] to control the overall type 1 error at a level of 5% (two-sided) for the hypotheses evaluated by the treatment policy estimand. The testing strategy was based on two principles: 1) within a dose level, non-inferiority with respect to HbA_{1c} had to be demonstrated before testing for added benefits in terms of superiority with respect to HbA_{1c} or to body weight; 2) non-inferiority with respect to HbA_{1c} had to be demonstrated on all higher dose levels before continuing testing hypotheses on lower dose levels (eAppendix 4).

Because of the potential for type 1 errors due to multiple comparisons, findings for analyses of additional secondary endpoints should be interpreted as exploratory.

The treatment policy estimand was estimated by a pattern mixture model using multiple imputation to handle missing week-26 data for both endpoints. Data collected at week 26, irrespective of premature discontinuation of trial product or initiation of rescue medication, were included in the statistical analysis. Missing data were imputed within groups defined by trial product and treatment status at week 26, and this assumed that the likely values of the missing data were best described by observed responses from patients with the same trial product and treatment status. Both the imputation and the analysis were based on analysis of covariance (ANCOVA) models with region and background medication as factors and baseline value as covariate. The results were combined by use of Rubin's rule.[19] Prior to testing for non-inferiority, a value of 0.3% (the non-inferiority margin) was added to imputed values at week 26 for the oral semaglutide treatment groups only, to ensure imputation of missing values would not increase the likelihood of demonstrating non-inferiority.[20]

The trial product estimand was estimated by a mixed model for repeated measurements (MMRM) with treatment, region and background medication as categorical fixed effects and baseline value as a covariate, all nested within visit. All data collected at scheduled visits prior to premature trial product discontinuation or initiation of rescue medication were included in the statistical analysis. An unstructured covariance matrix for endpoint measurements within the same patient was employed.

Safety and tolerability were assessed using the safety analysis set (all patients exposed to ≥1 dose of trial product) and evaluated both on-treatment (ie, while receiving trial product regardless of rescue medication use) and in-trial (ie, while in trial regardless of trial product discontinuation or rescue medication use).

Further details on the statistical analyses can be found in the eAppendix 4. All statistical analyses were pre-specified and performed using SAS v9.4M2. The analysis model for binary endpoints was changed *post hoc* to meet journal requirements.

Results

Patient Disposition and Baseline Characteristics

A total of 2463 patients were screened, with 1864 randomized to oral semaglutide 3 mg (N=466), 7 mg (N=466) or 14 mg (N=465), or sitagliptin (N=467) (Figure 1). The trial was completed by 94.3% (1758/1864) of patients. At week 26, rescue medication was initiated by 5.4% (25/466), 2.4% (11/465), and 1.1% (5/465) of patients for oral semaglutide 3, 7, and 14 mg, respectively, and 2.8% (13/467) for sitagliptin; these proportions increased throughout the trial (Figure 1, eTable 2). Treatment was completed without rescue medication by 52.1% (243/466), 64.6% (301/466), 72% (335/465), and 60.6% (283/467) of patients for oral semaglutide 3, 7, 14 mg, and sitagliptin, respectively.

Demographics and baseline disease characteristics were balanced across treatment groups (Table 1). Approximately half (52.8% [984/1864]) of all patients were male, and the majority were white (71.1% [1324/1864]). The mean age was 58 years, with a mean HbA_{1c} of 8.3%, duration of diabetes of 8.6 years, FPG of 9.49 mmol/L, body weight of 91.2 kg, and BMI of 32.5 kg/m^2. All patients were taking background metformin, with approximately half in each treatment group also receiving a sulfonylurea (Table 1).

Primary Endpoint

For the treatment policy estimand, the estimated mean changes from baseline in HbA_{1c} at week 26 were –0.6%, –1.0%, and –1.3% for oral semaglutide 3, 7, and 14 mg, respectively, and –0.8% for sitagliptin. Oral semaglutide 7 and 14 mg were superior to sitagliptin in reducing HbA_{1c} from baseline at week 26 (estimated treatment differences [ETD] [95% confidence interval (CI)] of –0.3% [–0.4%, –0.1%]; *P*<.001, and –0.5% [–0.6%, –0.4%]; *P*<.001, respectively; Figure 2). Non-inferiority of oral semaglutide 3 mg versus sitagliptin could not be demonstrated (ETD [95% CI]: 0.2% [0.1%, 0.3%]; *P*=.09), with HbA_{1c} reductions significantly favoring sitagliptin (*P*=.008). There were similar results for the trial product estimand (Figure 2). The robustness of the primary analyses was supported by sensitivity analyses (eTable 3, eFigure 2).

Key Secondary Endpoint

For the treatment policy estimand, the estimated mean changes from baseline in body weight at week 26 were –1.2 kg, –2.2 kg, and –3.1 kg for oral semaglutide 3, 7, and 14 mg, respectively, and –0.6 kg for sitagliptin. Oral semaglutide 7 and 14 mg doses were superior to sitagliptin in reducing body weight from baseline at week 26 (ETDs [95% CI] of –1.6 kg [–2.0 kg, –1.1 kg; *P*<.001] and –2.5 kg [–3.0 kg, –2.0 kg; *P*<.001], respectively; Figure 2). As non-inferiority with respect to HbA_{1c} was not demonstrated for oral semaglutide 3 mg, superiority with respect to body weight was not tested (ETD [95% CI]: –0.6 kg [–1.1 kg, –0.1 kg]; *P*=.02). There were similar results at week 26 for the trial product estimand. The primary analyses were supported by the sensitivity analyses (eTable 3, eFigure 2).

Additional Secondary Endpoints

At week 78, HbA_{1c} reductions from baseline were statistically significantly greater with oral semaglutide 7 mg (trial product estimand only) and 14 mg (both estimands) versus sitagliptin, with no significant differences observed with oral semaglutide 3 mg (Figure 2). For both estimands the body weight reductions at week 78 were statistically significantly greater

with all doses of oral semaglutide compared with sitagliptin (Figure 2). For FPG and mean SMBG, the reductions from baseline were significantly greater in the oral semaglutide 14 mg group at weeks 26 and 78 compared with sitagliptin (Table 2).

Significantly greater proportions of patients achieved HbA_{1c} <7.0%, body weight loss ≥5%, and the two composite outcomes (HbA_{1c} <7.0% without hypoglycemia and without weight gain, and HbA_{1c} reduction ≥1% and weight loss ≥3%) with oral semaglutide 7 and 14 mg compared with sitagliptin (Table 2).

Time to rescue medication and time to additional glucose-lowering medication were statistically significantly longer with oral semaglutide 7 and 14 mg compared with sitagliptin (eTable 4). The endpoints presented here are those considered most relevant for interpreting the clinical efficacy of oral semaglutide; all other secondary endpoints are reported in eTable 5 and eFigures 3–5.

Adverse Events and Tolerability

The overall proportions of patients experiencing at least one AE while on treatment were similar across treatments (Table 3). The most frequent AEs by system organ class were gastrointestinal disorders with oral semaglutide 14 mg, and infections and infestations with oral semaglutide 3 and 7 mg, and sitagliptin. Of the gastrointestinal AEs, the majority were of mild or moderate severity, and the most common with oral semaglutide 7 and 14 mg was nausea (eFigure 6; Table 3). The number and proportions of on-treatment serious AEs were also similar across treatments.

The proportions of patients who prematurely discontinued trial product for any reason were 16.7% (78/466), 15.0% (70/466), and 19.1% (89/465) for oral semaglutide 3, 7, and 14 mg, respectively, and 13.1% (61/467) for sitagliptin. AEs led to premature discontinuation for 5.6% (26/466), 5.8% (27/464), 11.6% (54/465), and 5.2% (24/466) of patients for oral semaglutide 3, 7, and 14 mg, and sitagliptin, respectively (Table 3), with gastrointestinal AEs being the primary cause in all treatment groups (eTable 6). For a substantial proportion of

patients in the oral semaglutide 7 and 14 mg groups who discontinued because of an AE, the onset of the causative event occurred during the dose-escalation period.

Severe or blood glucose-confirmed symptomatic hypoglycemic episodes were experienced by 4.9% (23/466), 5.2% (24/464), 7.7% (36/465), and 8.4% (39/466) of patients with oral semaglutide 3, 7, and 14 mg, and sitagliptin, respectively (Table 3); these episodes mainly occurred in patients on background metformin with sulfonylurea (eTable 7). Diabetic retinopathy-related AEs were infrequent and similar across all treatments (eTable 8) and were mostly mild or moderate in severity, reported at routine eye examinations, and did not require treatment. The frequencies of EAC-confirmed acute kidney injury, acute pancreatitis, cardiovascular events, and malignant neoplasms were similar across treatments (eTable 9). Other safety parameters are reported in eTable 10.

There were 12 deaths among exposed patients (eTable 9); five in the oral semaglutide 3 mg group, three in the 7 mg group, one in the 14 mg group, and three in the sitagliptin group. No pattern or clustering of causes of death was observed. Very few patients tested positive for anti-semaglutide antibodies (eTable 11).

Discussion

In this large, multicenter, randomized clinical trial in patients with T2D uncontrolled on metformin ± sulfonylurea, addition of once daily oral semaglutide 7 and 14 mg demonstrated superior reductions from baseline in HbA_{1c} and body weight than sitagliptin after 26 weeks. Non-inferiority of oral semaglutide 3 mg compared with sitagliptin could not be demonstrated with respect to HbA_{1c} reduction from baseline.

The greater effect with oral semaglutide for reducing HbA_{1c} and body weight compared with sitagliptin is consistent with other head-to-head trials that have demonstrated superior glycemic control and weight reduction with GLP-1RAs over DPP-4is.[21-24] This glucose-lowering effect was also reflected by the longer time to, and less use of, rescue medication with oral semaglutide 7 and 14 mg. The results achieved with oral semaglutide are of clinical

relevance as improved glycemic control is associated with better diabetes-related outcomes,[25] and because some patients may prefer oral medications to achieve this improved glycemic control.[26] Furthermore, clinically meaningful weight loss contributes to greater glycemic control and reduces cardiovascular risk factors,[27] which is particularly beneficial in a population that frequently has comorbid obesity.

The long-term AE profile of oral semaglutide in this trial was consistent with the GLP-1RA class as a whole.[28] The majority of gastrointestinal AEs were mild-to-moderate in severity, with nausea, vomiting or diarrhea the most frequently observed, and this is consistent with s.c. semaglutide[29] and other GLP-1RAs.[24,28,30] DPP-4is cause fewer gastrointestinal AEs than GLP-1RAs,[4] but in this trial similar proportions of patients prematurely discontinued because of these events with oral semaglutide 3 and 7 mg (but not 14 mg), and sitagliptin. Around twice as many patients prematurely discontinued with the oral semaglutide 14 mg dose due to any AE. Most AE-related discontinuations with oral semaglutide occurred during the dose-escalation period. The dose escalation was fixed according to the trial protocol and so may not reflect clinical practice, where dose-escalation would be based on individualized efficacy and tolerability. It was identified in the oral semaglutide phase 2 trial that initiating oral semaglutide at a low dose and escalating it slowly improves tolerability and helps minimize gastrointestinal AEs.[12] The proportions of AE-related premature discontinuations with oral semaglutide 14 mg were similar to that previously observed with s.c. semaglutide 1.0 mg,[23,31] and in previous trials of other GLP-1RAs.[22,24]

It should be noted that the 14 mg dose of oral semaglutide used in this trial is greater than the largest dose of s.c. semaglutide assessed in the SUSTAIN program.[23,31] As a result of their low oral bioavailability, larger doses of orally administered peptide medications are required in order to achieve comparable plasma concentrations to those achieved via other routes.

In this trial, two different scientific questions related to the efficacy were addressed through the definition of the two estimands. Treatment differences versus sitagliptin were smaller at

week 78 for the treatment policy estimand compared with the trial product estimand; a significant difference in HbA_{1c} reduction was not shown with the 7 mg dose at this time point, in line with the increasing use of rescue medication with sitagliptin.

The trial product estimand was estimated using a mixed model for repeated measurements approach, the appropriateness of which relies on the assumption of the missing data mechanism being 'missing at random' (MAR), i.e. that patients who discontinued trial product or initiated rescue medication had evolved similarly to patients still on the same trial product without rescue medication and having the same covariates and same trajectory prior to the time point of discontinuation of trial product or initiation of rescue medication. While this approach aims at reflecting the treatment effect without the confounding effect of trial product discontinuation and use of rescue medication, residual confounding due to unmeasured factors cannot be ruled out. Initiation of rescue medication was more frequent with oral semaglutide 3 mg and sitagliptin, and discontinuation of trial product was more frequent with oral semaglutide 14 mg.

A strength of this trial was the double-blind design, achieved using a double-dummy approach. This approach was used in an effort to ensure the comparisons of the trial products were unbiased, as oral semaglutide and sitagliptin tablets are not visually identical. An additional strength was the long duration and high retention rate, which allowed for the long-term efficacy, AE profile and tolerability of oral semaglutide to be investigated.

Limitations

This trial has several limitations. Firstly, as already noted, the fixed dose-escalation used in this trial is not reflective of expected use in a real-life clinical setting, and could have contributed to a higher rate of discontinuations because of AEs than what might have occurred in a real-life setting. Secondly, compliance with treatment was not formally measured in this trial, with patients instead routinely reminded to comply with trial procedures, and monitoring of drug accountability. It is therefore unknown if poor compliance with treatment affected results obtained in patients receiving oral semaglutide, given the

importance of correct administration on its absorption.[32] Thirdly, sitagliptin may not be the best active comparator for this trial because it has been documented that DPP-4is have modest glucose-lowering effects and minimal effect on body weight compared with GLP-1RAs.[4] However, they are widely used and are well tolerated. Other trials within the PIONEER phase 3 program will assess oral semaglutide against other glucose-lowering medications and with flexible dosing of oral semaglutide.

Conclusions

Among adults with T2D uncontrolled with metformin ± sulfonylurea, oral semaglutide 7 and 14 mg daily compared with sitagliptin daily, resulted in significantly greater reductions in HbA_{1c} over 26 weeks, but there was no significant benefit for semaglutide 3 mg daily. A greater proportion of patients prematurely discontinued treatment with oral semaglutide 14 mg versus 3 or 7 mg, or sitagliptin. Further research is needed to assess effectiveness in a clinical setting.

Data Sharing Statement: Supplement 1

Author Contributions

Julio Rosenstock and Melanie Davies had full access to all of the data in the trial and take responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: JR, MD

Acquisition, analysis, or interpretation of data: All authors

Statistical analysis: JBJ

Drafting the manuscript: All authors

Critical revision of the manuscript for important intellectual content: All authors

Conflicts of Interest Disclosures

JR has served on scientific advisory boards and received honorarium or consulting fees from Eli Lilly, Novo Nordisk, Sanofi, Janssen, Boehringer Ingelheim, and Intarcia, and has

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Authors' Access to Data

All authors had access to the final trial results.

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Role of the Funders/Sponsors

Representatives of Novo Nordisk (the sponsor) were involved in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, and approval of the manuscript. The decision to submit the manuscript for publication was taken by the authors, and the sponsor had no veto right to publish or to control the decision to which journal to submit.

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Figure Legends

Figure 1. Patient disposition overview (A) and over time (B).

[a] No assessments were performed.

[b] Received disallowed background medication (nateglinide).

[c] Did not provide informed consent.

[d] The bands represent the proportion of patients by treatment status until the planned end-of-treatment visit.

Figure 2. Glycemic control and body weight-related efficacy endpoints. A: Observed absolute HbA_{1c} over time, B: Estimated changes from baseline in HbA_{1c} at weeks 26, 52, and 78, C: Observed changes from baseline in body weight over time, D: Estimated changes from baseline in body weight at weeks 26, 52, and 78.

Abbreviation: CI, confidence interval; ETD, estimated treatment differences.

[a] Favored sitagliptin.

Observed absolute mean values (± confidence intervals) for the in-trial period and the period on-treatment without rescue medication (Panel A/C), and estimated mean change from baseline for value by the treatment policy estimand and the trial product estimand (Panel B/D) at weeks 26, 52 and 78. *P* values are unadjusted two-sided *P* values for the test of no difference.

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. Pattern was defined by randomized trial product and treatment status (premature trial product discontinuation and/or initiation of rescue medication).

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

585 **Tables**

586 Table 1. Demographics and baseline disease characteristics.

	Oral semaglutide			Sitagliptin 100 mg (N=467)
	3 mg (N=466)	7 mg (N=465)	14 mg (N=465)	
Sex, n (%)				
Male	254 (54.5)	245 (52.7)	247 (53.1)	238 (51.0)
Female	212 (45.5)	220 (47.3)	218 (46.9)	229 (49.0)
Age, mean (SD), y	58 (10.0)	58 (10.0)	57 (10.0)	58 (10.0)
Race, n (%)				
White	344 (73.8)	330 (71.0)	317 (68.2)	333 (71.3)
Black or African American	38 (8.2)	38 (8.2)	45 (9.7)	39 (8.4)
Asian	56 (12.0)	69 (14.8)	61 (13.1)	59 (12.6)
Other[a]	28 (6.0)	28 (6.0)	42 (9.0)	36 (7.7)
Ethnicity, n (%)				
Hispanic or Latino	76 (16.3)	77 (16.6)	75 (16.1)	93 (19.9)
Background medication, n (%)				
Metformin	466 (100.0)	465 (100.0)	465 (100.0)	467 (100.0)
Sulfonylurea	220 (47.2)	218 (46.9)	220 (47.3)	219 (46.9)
Glimepiride	93 (20.0)	88 (18.9)	107 (23.0)	97 (20.8)
Gliclazide	47 (10.1)	59 (12.7)	51 (11.0)	53 (11.3)
Glibenclamide	46 (9.9)	41 (8.8)	36 (7.7)	46 (9.9)
Glipizide	33 (7.1)	30 (6.5)	26 (5.6)	23 (4.9)
Gliquidone	1 (0.2)	0	0	0
Duration of diabetes, y				
Mean (SD)	8.4 (6.1)	8.3 (5.8)	8.7 (6.1)	8.8 (6.0)
Median (min–max)	7.3 (0.3–37.6)	7.5 (0.3–40.5)	7.4 (0.3–36.5)	7.9 (0.3–37.2)
Body weight, kg				
Mean (SD)	91.6 (22.0)	91.3 (20.8)	91.2 (21.7)	90.9 (21.0)
Median (min–max)	88.5 (42.1–167.2)	89.8 (44.0–168.3)	88.5 (42.0–188)	88.9 (45.0–171.9)
BMI, kg/m^2				
Mean (SD)	32.6 (6.7)	32.6 (6.4)	32.3 (6.3)	32.5 (6.2)
Median (min–max)	31.9 (18.3–67.9)	32.0 (19.5–56.6)	31.4 (17.5–61.0)	31.7 (16.1–57.6)
HbA_{1c}, %				
Mean (SD)	8.3 (1.0)	8.4 (1.0)	8.3 (0.9)	8.3 (0.9)
Median (min–max)	8.2 (6.5–10.9)	8.3 (6.3–12.0)	8.1 (6.5–11.5)	8.1 (5.4–10.7)
Fasting plasma glucose, mg/dL				
Mean (SD)	174.2 (50.5)	170.3 (42.9)	167.9 (45.1)	171.8 (41.9)

	Oral semaglutide			Sitagliptin 100 mg (N=467)
	3 mg (N=466)	7 mg (N=465)	14 mg (N=465)	
Median (min–max)	163.4 (58.7– 421.7)	161.8 (45.2–321.5)	160.1 (73.5–363.3)	165.5 (69.9–349.4)
Estimated glomerular filtration rate[b], mL/min/1.73 m^2				
Mean (SD)	96 (15)	96 (16)	95 (16)	96 (15)
Median (min–max)	96 (34–138)	97 (48–143)	97 (3–144)	98 (56–139)
Most frequent comorbidities affecting ≥10% of patients at screening in any treatment group (by MedDRA preferred term), n (%)				
Hypertension	348 (74.7)	328 (70.5)	357 (76.8)	339 (72.6)
Dyslipidemia	134 (28.8)	132 (28.4)	136 (29.2)	141 (30.2)
Obesity	125 (26.8)	142 (30.5)	119 (25.6)	133 (28.5)
Diabetic neuropathy	127 (27.3)	102 (21.9)	115 (24.7)	129 (27.6)
Hyperlipidemia	104 (22.3)	99 (21.3)	94 (20.2)	102 (21.8)
Gallbladder disease	75 (16.1)	66 (14.2)	84 (18.1)	85 (18.2)
Ischemic heart disease	73 (15.7)	76 (16.3)	77 (16.6)	81 (17.3)
Diabetic retinopathy	73 (15.7)	73 (15.7)	74 (15.9)	81 (17.3)
Osteoarthritis	67 (14.4)	61 (13.1)	74 (15.9)	59 (12.6)
Hepatic steatosis	55 (11.8)	47 (10.1)	56 (12.0)	55 (11.8)
Cholecystectomy	51 (10.9)	49 (10.5)	52 (11.2)	46 (9.9)
Cataract	45 (9.7)	46 (9.9)	54 (11.6)	45 (9.6)
Diabetic nephropathy	46 (9.9)	43 (9.2)	52 (11.2)	40 (8.6)
Menopause	52 (11.2)	59 (12.7)	38 (8.2)	46 (9.9)
Seasonal allergy	51 (10.9)	25 (5.4)	38 (8.2)	47 (10.1)
Back pain	39 (8.4)	30 (6.5)	36 (7.7)	48 (10.3)
Depression	37 (7.9)	47 (10.1)	36 (7.7)	32 (6.9)

Abbreviation: BMI, body mass index; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; MedDRA, Medical Dictionary for Regulatory Activities; SD, standard deviation.

[a] "Other" for oral semaglutide 3, 7, and 14 mg, and sitagliptin, respectively, n (%): American Indian or Alaska Native: 4 (0.9), 3 (0.6), 5 (1.1), 6 (1.3); Native Hawaiian or other Pacific Islander: 1 (0.2), 0, 0, 0; other: 13 (2.8), 11 (2.4), 20 (4.3), 12 (2.6); not applicable (for Brazil and France): 10 (2.1), 14 (3.0), 17 (3.7), 18 (3.9).

[b] Glomerular filtration rate was estimated by the CKD-EPI formula.

SI conversion factor: To convert fasting plasma glucose from mg/dL to mmol/L, multiply by 0.055494.

Table 2. Additional secondary endpoints.

	Treatment policy estimand				Trial product estimand			
	Oral semaglutide			Sitagliptin 100 mg (N=467)	Oral semaglutide			Sitagliptin 100 mg (N=467)
	3 mg (N=466)	7 mg (N=465)	14 mg (N=465)		3 mg (N=466)	7 mg (N=465)	14 mg (N=465)	
Fasting plasma glucose, mg/dL								
Week 26								
Estimated mean	157.5	149.8	140.5	155.6	160.3	150.2	136.4	157.1
Estimated mean change from baseline	–13.6	–21.3	–30.5	–15.4	–10.7	–20.8	–34.6	–13.9
ETD vs sitagliptin (95% CI)	1.9 (–3.6, 7.3)	–5.9 (–11.4, –0.3)	–15.1 (–20.6, –9.7)	–	3.2 (–1.9, 8.3)	–6.9 (–12.0, –1.8)	–20.7 (–25.8, –15.6)	–
P value	.50	.039	<.001	–	.22	.008	<.001	–
Week 52								
Estimated mean	155.2	149.1	138.5	153.0	162.8	149.6	137.2	158.4
Estimated mean change from baseline	–15.9	–22.0	–32.6	–18.1	–8.3	–21.5	–33.8	–12.7
ETD vs sitagliptin (95% CI)	2.2 (–3.3, 7.7)	–3.9 (–9.7, 1.9)	–14.5 (–20.0, –9.1)	–	4.4 (–1.1, 9.9)	–8.8 (–14.1, –3.5)	–21.2 (–26.5, –15.9)	–
P value	.44	.18	<.001	–	.12	.001	<.001	–
Week 78								
Estimated mean	154.0	153.0	140.3	156.1	162.9	152.7	139.3	161.3
Estimated mean change from baseline	–17.1	–18.1	–30.8	–15.0	–8.2	–18.4	–31.7	–9.8
ETD vs sitagliptin (95% CI)	–2.1 (–8.0, 3.9)	–3.1 (–9.3, 3.1)	–15.8 (–21.7, –9.9)	–	1.6 (–4.5, 7.7)	–8.6 (–14.5, –2.7)	–21.9 (–27.7, –16.1)	–
P value	.50	.33	<.001	–	.61	.004	<.001	–

	Treatment policy estimand				Trial product estimand			
	Oral semaglutide			Sitagliptin 100 mg (N=467)	Oral semaglutide			Sitagliptin 100 mg (N=467)
	3 mg (N=466)	7 mg (N=465)	14 mg (N=465)		3 mg (N=466)	7 mg (N=465)	14 mg (N=465)	
7-point self-measured blood glucose[a] mean, mg/dL								
Week 26								
Estimated mean	164.2	157.4	155.0	163.0	164.1	155.8	148.3	160.6
Estimated mean change from baseline	–20.0	–26.8	–29.3	–21.2	–19.0	–27.3	–34.8	–22.6
ETD vs sitagliptin (95% CI)	1.2 (–3.7, 6.1)	–5.6 (–10.4, –0.7)	–8.0 (–13.1, –2.9)	–	3.6 (–1.0, 8.2)	–4.8 (–9.3, –0.2)	–12.3 (–16.8, –7.7)	–
P value	.63	.03	.002	–	.13	.004	<.001	–
Week 52								
Estimated mean	162.5	157.3	151.1	159.5	161.6	156.1	146.9	161.9
Estimated mean change from baseline	–21.7	–26.9	–33.1	–24.7	–21.5	–27.0	–36.2	–21.2
ETD vs sitagliptin (95% CI)	3.0 (–1.8, 7.8)	–2.2 (–7.0, 2.6)	–8.4 (–13.2, –3.6)	–	–0.3 (–5.4, 4.8)	–5.8 (–10.7, –0.9)	–15.0 (–19.8, –10.1)	–
P value	.22	.37	.001	–	.90	.02	<.001	–
Week 78								
Estimated mean	161.6	158.9	153.9	161.6	164.9	157.3	150.9	160.6
Estimated mean change from baseline	–22.6	–25.3	–30.4	–22.7	–18.3	–25.9	–32.2	–22.5
ETD vs sitagliptin (95% CI)	0.0 (–5.0, 5.1)	–2.6 (–7.9, 2.6)	–7.7 (–12.7, –2.7)	–	4.3 (–1.1, 9.6)	–3.4 (–8.5, 1.8)	–9.7 (–14.8, –4.7)	–
P value	.99	.33	.003	–	.12	.20	<.001	–

	Treatment policy estimand				Trial product estimand			
	Oral semaglutide			Sitagliptin 100 mg (N=467)	Oral semaglutide			Sitagliptin 100 mg (N=467)
	3 mg (N=466)	7 mg (N=465)	14 mg (N=465)		3 mg (N=466)	7 mg (N=465)	14 mg (N=465)	
HbA_{1c} <7.0%								
Week 26								
Estimated proportion of patients, %	27	42	55	32	26	44	59	32
ETD vs sitagliptin (95% CI)	–5 (–11, 1)	10 (4, 17)	23 (17, 30)	–	–6 (–12, –0)	13 (6, 19)	27 (21, 34)	–
P value	.07	<.001	<.001	–	.04	<.001	<.001	–
Week 52								
Estimated proportion of patients, %	27	38	53	31	23	38	57	30
ETD vs sitagliptin (95% CI)	–4 (–10, 2)	7 (0, 13)	22 (16, 28)	–	–6 (–12, –0)	8 (2, 14)	27 (21, 34)	–
P value	.15	.04	<.001	–	.04	.01	<.001	–
Week 78								
Estimated proportion of patients, %	27	37	44	29	23	36	47	28
ETD vs sitagliptin (95% CI)	–2 (–8, 4)	8 (2, 14)	15 (8, 21)	–	–5 (–11, 1)	8 (2, 15)	19 (13, 26)	–
P value	.48	.01	<.001	–	.09	.009	<.001	–
Weight loss ≥5%								
Week 26								
Estimated proportion of patients, %	13	19	30	10	13	20	32	11
ETD vs sitagliptin (95% CI)	3 (–1, 7)	9 (4, 13)	20 (15, 25)	–	2 (–2, 6)	9 (4, 13)	21 (16, 27)	–
P value	.15	<.001	<.001	–	.39	<.001	<.001	–

	Treatment policy estimand				Trial product estimand			
	Oral semaglutide			Sitagliptin 100 mg (N=467)	Oral semaglutide			Sitagliptin 100 mg (N=467)
	3 mg (N=466)	7 mg (N=465)	14 mg (N=465)		3 mg (N=466)	7 mg (N=465)	14 mg (N=465)	
Week 52								
Estimated proportion of patients, %	17	27	34	12	17	26	38	12
ETD vs sitagliptin (95% CI)	5 (–0, 9)	15 (10, 20)	22 (16, 27)	–	4 (–1, 9)	14 (9, 20)	26 (20, 31)	–
P value	.06	<.001	<.001	–	.10	<.001	<.001	–
Week 78								
Estimated proportion of patients, %	21	27	33	14	23	27	36	15
ETD vs sitagliptin (95% CI)	7 (2, 12)	13 (8, 19)	19 (13, 24)	–	7 (1, 14)	12 (6, 18)	21 (15, 27)	–
P value	.01	<.001	<.001	–	.02	<.001	<.001	–
HbA_{1c} <7.0% without hypoglycemic episodes[b] and without body weight gain								
Week 26								
Estimated proportion of patients, %	20	34	46	20	19	35	50	20
ETD vs sitagliptin (95% CI)	–1 (–5, 4)	14 (8, 19)	26 (20, 32)	–	–1 (–6, 3)	15 (9, 20)	29 (23, 35)	–
P value	.80	<.001	<.001	–	.55	<.001	<.001	–
Week 52								
Estimated proportion of patients, %	20	30	43	20	18	30	46	20
ETD vs sitagliptin (95% CI)	–0 (–5, 5)	10 (5, 16)	23 (17, 29)	–	–2 (–7, 3)	10 (5, 16)	26 (20, 32)	–
P value	.97	<.001	<.001	–	.46	<.001	<.001	–
Week 78								
Estimated proportion of patients, %	20	31	34	19	17	30	37	19
ETD vs sitagliptin (95% CI)	1 (–4, 6)	11 (6, 17)	15 (9, 20)	–	–2 (–7, 3)	11 (5, 16)	17 (12, 23)	–

	Treatment policy estimand				Trial product estimand			
	Oral semaglutide			Sitagliptin 100 mg (N=467)	Oral semaglutide			Sitagliptin 100 mg (N=467)
	3 mg (N=466)	7 mg (N=465)	14 mg (N=465)		3 mg (N=466)	7 mg (N=465)	14 mg (N=465)	
P value	.80	<.001	<.001	–	.43	<.001	<.001	–
HbA_{1c} reduction ≥1% with weight loss ≥3%								
Week 26								
Estimated proportion of patients, %	13	26	37	9	12	27	40	10
ETD vs sitagliptin (95% CI)	4 (–1, 8)	17 (12, 22)	28 (23, 33)	–	3 (–2, 7)	17 (12, 22)	30 (25, 36)	–
P value	.09	<.001	<.001	–	.22	<.001	<.001	–
Week 52								
Estimated proportion of patients, %	17	24	36	12	15	23	38	11
ETD vs sitagliptin (95% CI)	5 (1, 10)	12 (7, 17)	24 (19, 30)	–	4 (–1, 8)	12 (7, 17)	27 (21, 32)	–
P value	.03	<.001	<.001	–	.12	<.001	<.001	–
Week 78								
Estimated proportion of patients, %	18	26	34	14	16	24	35	12
ETD vs sitagliptin (95% CI)	4 (–0, 9)	12 (7, 17)	20 (14, 25)	–	4 (–1, 9)	12 (6, 17)	23 (17, 28)	–
P value	.08	<.001	<.001	–	.12	<.001	<.001	–

Abbreviation: CI, confidence interval; ETD, estimated treatment difference.

[a] Self-monitored blood glucose is reported as plasma equivalent values of capillary whole blood glucose.

[b] Reported episodes were either severe (defined according to the American Diabetes Association classification) or confirmed by a blood glucose value <56 mg/dL (3.1 mmol/L), with symptoms consistent with hypoglycemia.

SI conversion factor: To convert glucose from mg/dL to mmol/L, multiply by 0.055494. *P* values are unadjusted two-sided *P* values for the test of no difference.

Treatment policy estimand: Analysis of covariance for continuous endpoints and generalized linear model with binomial distribution and identity link for binary endpoints, 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. Pattern was defined by randomized trial product and treatment status (premature trial product discontinuation and/or initiation of rescue medication).

Trial product estimand: Mixed model for repeated measurements for continuous endpoints and generalized linear model with binomial distribution and identity link for binary endpoints. Data collected after discontinuation of trial product or initiation of rescue medication were excluded. For binary endpoints, missing values were imputed from patients randomized to the same trial product using sequential multiple imputation.

606 Table 3. On-treatment adverse events.

	Oral semaglutide			Sitagliptin 100 mg (N=466)
	3 mg (N=466)	7 mg (N=464)	14 mg (N=465)	
Any AEs, n (%)	370 (79.4)	363 (78.2)	370 (79.6)	388 (83.3)
Severity, n (%)				
Mild	323 (69.3)	318 (68.5)	321 (69.0)	340 (73.0)
Moderate	186 (39.9)	171 (36.9)	199 (42.8)	197 (42.3)
Severe	47 (10.1)	37 (8.0)	40 (8.6)	53 (11.4)
SAEs, n (%)	64 (13.7)	47 (10.1)	44 (9.5)	58 (12.4)
AEs leading to premature trial product discontinuation, n (%)	26 (5.6)	27 (5.8)	54 (11.6)	24 (5.2)
Severe or BG-confirmed symptomatic hypoglycemia[a], n (%)	23 (4.9)	24 (5.2)	36 (7.7)	39 (8.4)
Most frequent AEs occurring in ≥5% of patients in any treatment group (by MedDRA preferred term), n (%)[a]				
Nausea	34 (7.3)	62 (13.4)	70 (15.1)	32 (6.9)
Diarrhea	45 (9.7)	53 (11.4)	57 (12.3)	37 (7.9)
Nasopharyngitis	53 (11.4)	49 (10.6)	47 (10.1)	47 (10.1)
Vomiting	13 (2.8)	28 (6.0)	42 (9.0)	19 (4.1)
Headache	29 (6.2)	30 (6.5)	37 (8.0)	36 (7.7)
Decreased appetite	8 (1.7)	14 (3.0)	32 (6.9)	14 (3.0)
Upper respiratory tract infection	36 (7.7)	35 (7.5)	26 (5.6)	32 (6.9)
Hypertension	30 (6.4)	24 (5.2)	26 (5.6)	29 (6.2)
Back pain	24 (5.2)	25 (5.4)	25 (5.4)	29 (6.2)
Urinary tract infection	30 (6.4)	21 (4.5)	23 (4.9)	26 (5.6)
Arthralgia	22 (4.7)	14 (3.0)	21 (4.5)	30 (6.4)
Influenza	30 (6.4)	25 (5.4)	18 (3.9)	30 (6.4)
Diabetic retinopathy	27 (5.8)	24 (5.2)	16 (3.4)	27 (5.8)
Median (IQR) Kaplan-Meier estimated duration of gastrointestinal events, days				
Nausea	28.0 (3.0–105.0)	9.0 (4.0–41.0)	20.5 (4.0–61.5)	5.5 (1.5–25.0)
Diarrhea	4.0 (2.0–26.0)	3.0 (1.0–7.0)	9.0 (3.0–44.0)	5.5 (2.0–16.5)
Vomiting	2.0 (1.0–4.0)	2.0 (1.0–7.0)	2.0 (1.0–9.0)	1.0 (1.0–2.0)

607 Abbreviation: ADA, American Diabetes Association; AE, adverse event; BG, blood glucose; IQR, interquartile range; MedDRA,

608 Medical Dictionary for Regulatory Activities; SAE, serious adverse event.

609 [a] Hypoglycemic episodes were reported on a separate form to adverse events. Reported episodes were either severe (defined

610 according to the American Diabetes Association classification) or confirmed by a blood glucose value <56 mg/dL (3.1 mmol/L),

611 with symptoms consistent with hypoglycemia.

612 Preferred terms defined using MedDRA (version 20.1).

613 SI conversion factor: To convert glucose to mmol/L, multiply by 0.055494.

614 On treatment: The period where the patient is considered treated with trial product.

A

Assessed for eligibility N=2463

Excluded n=599
- Did not meet eligibility criteria n=523
- Other n=76

Randomized N=1864

Allocation

Oral semaglutide 3 mg	N=466
• Received allocated intervention	n=466

Oral semaglutide 7 mg	N=466
• Received allocated intervention	n=464
• Did not receive allocated intervention	n=2
• Randomized in error[a]	n=1
• Death before exposure	n=1

Oral semaglutide 14 mg	N=465
• Received allocated intervention	n=465

Sitagliptin 100 mg	N=467
• Received allocated intervention	n=466
• Did not receive allocated intervention	n=1
• Violated eligibility criteria before exposure[b]	n=1

Follow-up

Completed trial	n=433
• Completed treatment	n=388
• Completed treatment without rescue medication	n=243
Did not complete trial	n=33
• Lost to follow-up	n=9
• Withdrawal by patient	n=18
• Death	n=5
• Violated eligibility criteria[c]	n=1

Completed trial	n=436
• Completed treatment	n=396
• Completed treatment without rescue medication	n=301
Did not complete trial	n=30
• Lost to follow-up	n=7
• Withdrawal by patient	n=18
• Death	n=4
• Randomized in error	n=1

Completed trial	n=438
• Completed treatment	n=376
• Completed treatment without rescue medication	n=335
Did not complete trial	n=27
• Lost to follow-up	n=7
• Withdrawal by patient	n=17
• Death	n=1
• Adverse event	n=2

Completed trial	n=451
• Completed treatment	n=406
• Completed treatment without rescue medication	n=283
Did not complete trial	n=16
• Lost to follow-up	n=5
• Withdrawal by patient	n=8
• Death	n=3

Analysis

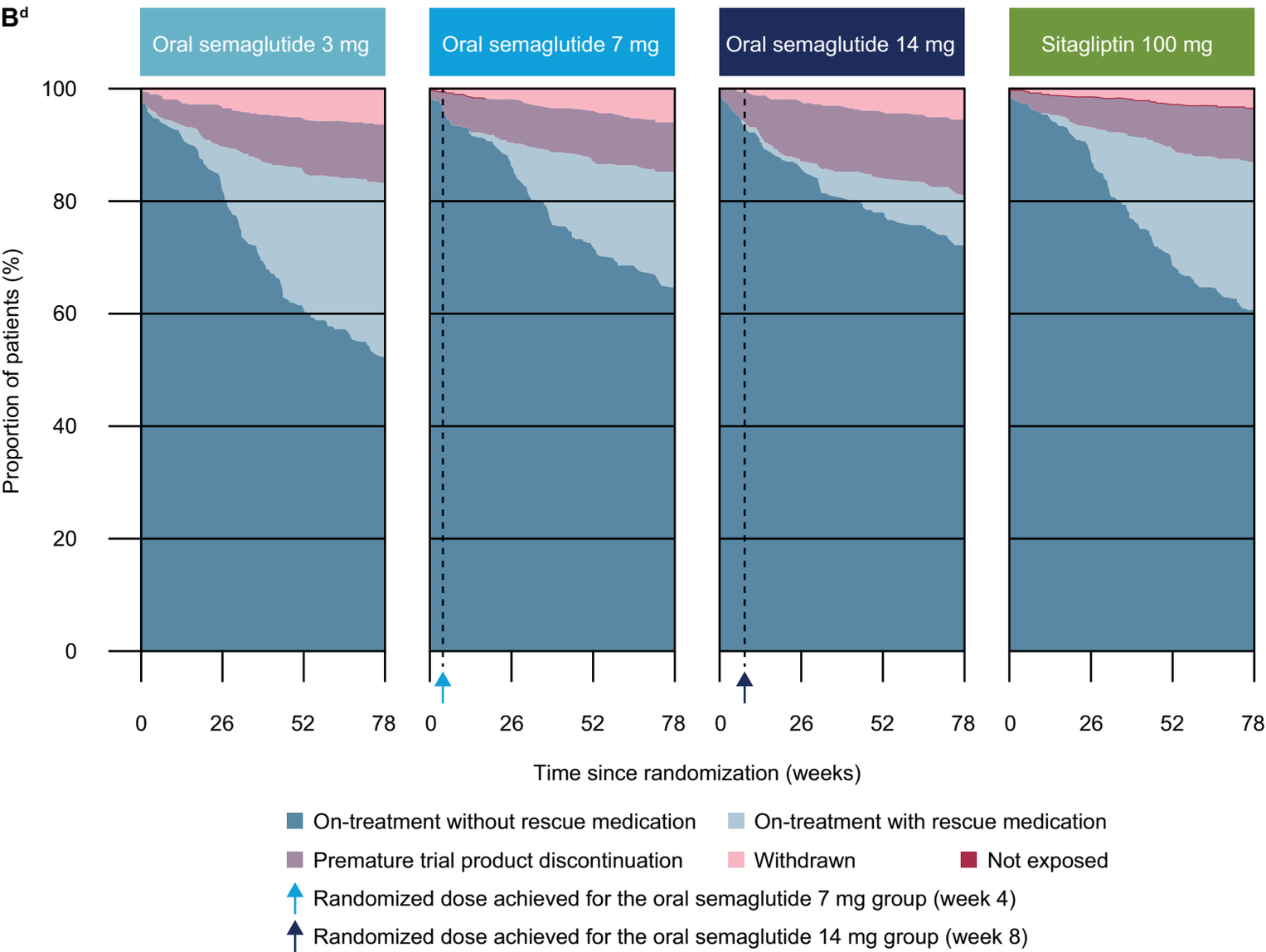
Included in efficacy analysis	n=466
Included in safety analysis	n=466

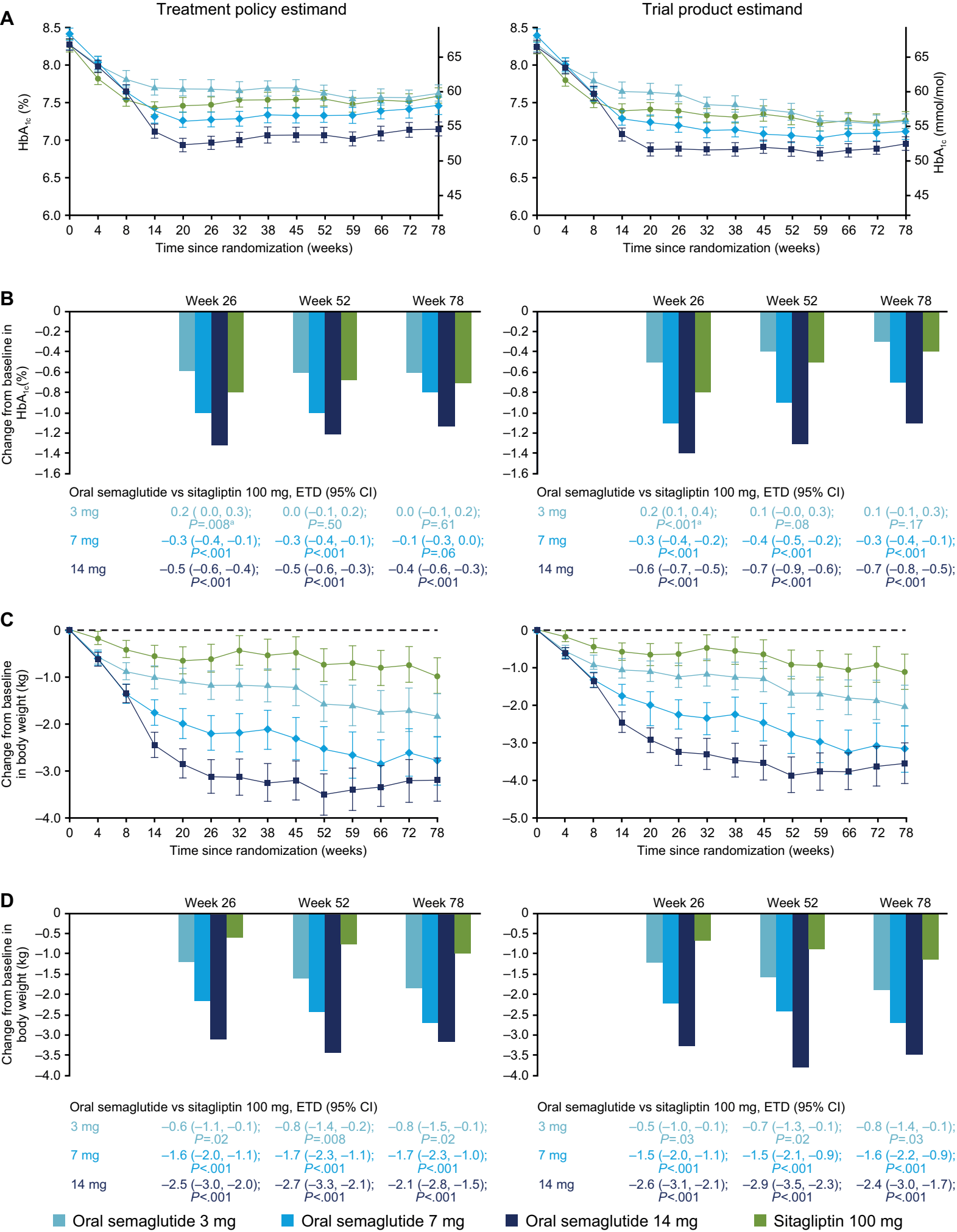
Included in efficacy analysis	n=465
• Excluded from analysis	n=1
• Randomized in error	n=1
Included in safety analysis	n=464
• Excluded from analysis	n=2
• Randomized in error[a]	n=1
• Death before exposure	n=1

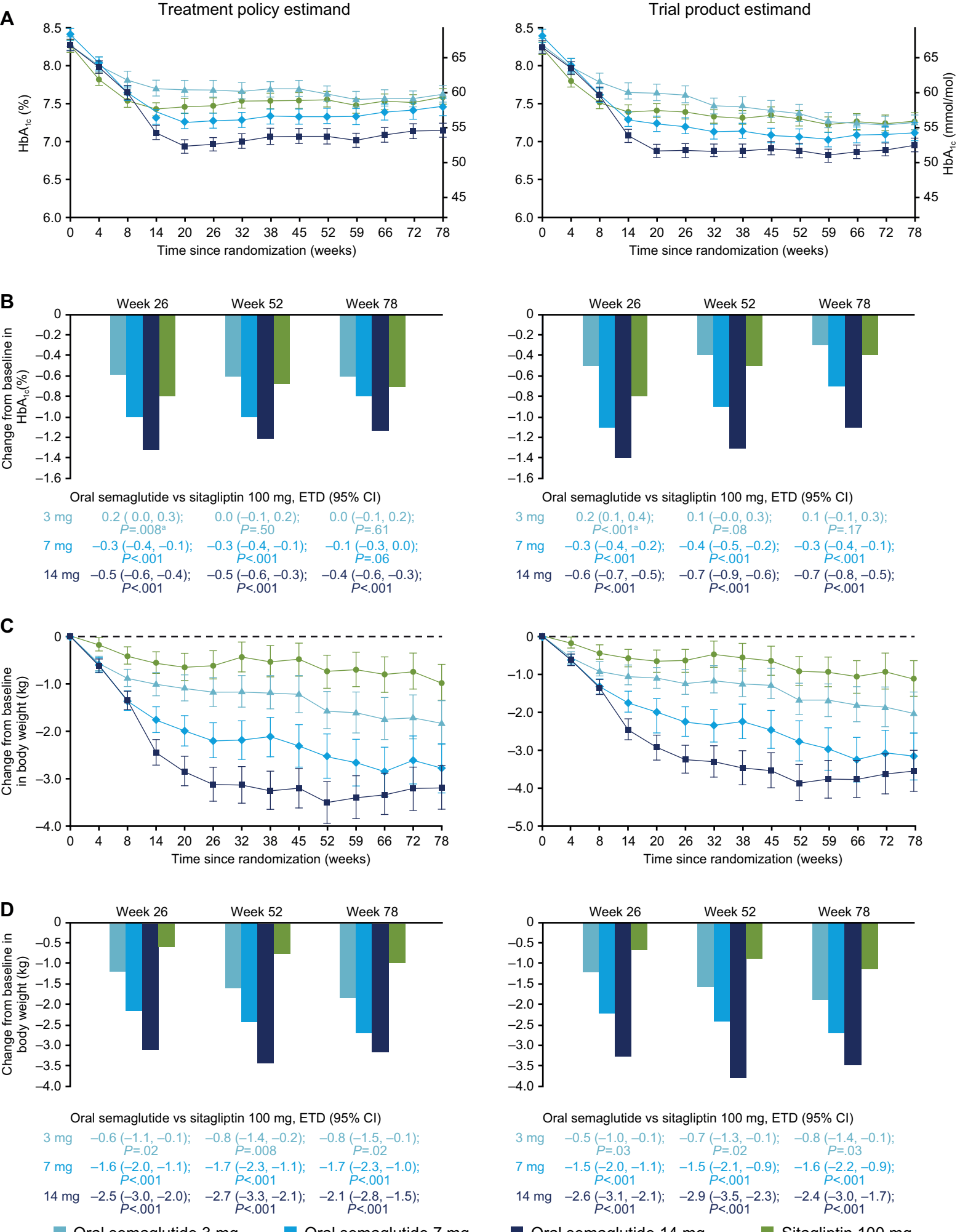
Included in efficacy analysis	n=465
Included in safety analysis	n=465

Included in efficacy analysis	n=467
Included in safety analysis	n=466
• Excluded from analysis	n=1
• Violated eligibility criteria before exposure[b]	n=1

B[d]




A
Treatment policy estimand
Trial product estimand
HbA1c (%)
HbA1c (mmol/mol)
Time since randomization (weeks)
B
Change from baseline in HbA1c (%)
Week 26
Week 52
Week 78
Oral semaglutide vs sitagliptin 100 mg, ETD (95% CI)
3 mg 0.2 (0.0, 0.3); P=.008a 0.0 (–0.1, 0.2); P=.50 0.0 (–0.1, 0.2); P=.61
7 mg –0.3 (–0.4, –0.1); P<.001 –0.3 (–0.4, –0.1); P<.001 –0.1 (–0.3, 0.0); P=.06
14 mg –0.5 (–0.6, –0.4); P<.001 –0.5 (–0.6, –0.3); P<.001 –0.4 (–0.6, –0.3); P<.001
Oral semaglutide vs sitagliptin 100 mg, ETD (95% CI)
3 mg 0.2 (0.1, 0.4); P<.001a 0.1 (–0.0, 0.3); P=.08 0.1 (–0.1, 0.3); P=.17
7 mg –0.3 (–0.4, –0.2); P<.001 –0.4 (–0.5, –0.2); P<.001 –0.3 (–0.4, –0.1); P<.001
14 mg –0.6 (–0.7, –0.5); P<.001 –0.7 (–0.9, –0.6); P<.001 –0.7 (–0.8, –0.5); P<.001
C
Change from baseline in body weight (kg)
Time since randomization (weeks)
D
Change from baseline in body weight (kg)
Week 26
Week 52
Week 78
Oral semaglutide vs sitagliptin 100 mg, ETD (95% CI)
3 mg –0.6 (–1.1, –0.1); P=.02 –0.8 (–1.4, –0.2); P=.008 –0.8 (–1.5, –0.1); P=.02
7 mg –1.6 (–2.0, –1.1); P<.001 –1.7 (–2.3, –1.1); P<.001 –1.7 (–2.3, –1.0); P<.001
14 mg –2.5 (–3.0, –2.0); P<.001 –2.7 (–3.3, –2.1); P<.001 –2.1 (–2.8, –1.5); P<.001
Oral semaglutide vs sitagliptin 100 mg, ETD (95% CI)
3 mg –0.5 (–1.0, –0.1); P=.03 –0.7 (–1.3, –0.1); P=.02 –0.8 (–1.4, –0.1); P=.03
7 mg –1.5 (–2.0, –1.1); P<.001 –1.5 (–2.1, –0.9); P<.001 –1.6 (–2.2, –0.9); P<.001
14 mg –2.6 (–3.1, –2.1); P<.001 –2.9 (–3.5, –2.3); P<.001 –2.4 (–3.0, –1.7); P<.001
Oral semaglutide 3 mg
Oral semaglutide 7 mg
Oral semaglutide 14 mg
Sitagliptin 100 mg


A
Treatment policy estimand
Trial product estimand
HbA1c (%)
HbA1c (mmol/mol)
Time since randomization (weeks)
B
Week 26
Week 52
Week 78
Change from baseline in HbA1c (%)
Oral semaglutide vs sitagliptin 100 mg, ETD (95% CI)
3 mg 0.2 (0.0, 0.3); P=.008a 0.0 (–0.1, 0.2); P=.50 0.0 (–0.1, 0.2); P=.61
7 mg –0.3 (–0.4, –0.1); P<.001 –0.3 (–0.4, –0.1); P<.001 –0.1 (–0.3, 0.0); P=.06
14 mg –0.5 (–0.6, –0.4); P<.001 –0.5 (–0.6, –0.3); P<.001 –0.4 (–0.6, –0.3); P<.001
3 mg 0.2 (0.1, 0.4); P<.001a 0.1 (–0.0, 0.3); P=.08 0.1 (–0.1, 0.3); P=.17
7 mg –0.3 (–0.4, –0.2); P<.001 –0.4 (–0.5, –0.2); P<.001 –0.3 (–0.4, –0.1); P<.001
14 mg –0.6 (–0.7, –0.5); P<.001 –0.7 (–0.9, –0.6); P<.001 –0.7 (–0.8, –0.5); P<.001
C
Change from baseline in body weight (kg)
Time since randomization (weeks)
D
Change from baseline in body weight (kg)
Oral semaglutide vs sitagliptin 100 mg, ETD (95% CI)
3 mg –0.6 (–1.1, –0.1); P=.02 –0.8 (–1.4, –0.2); P=.008 –0.8 (–1.5, –0.1); P=.02
7 mg –1.6 (–2.0, –1.1); P<.001 –1.7 (–2.3, –1.1); P<.001 –1.7 (–2.3, –1.0); P<.001
14 mg –2.5 (–3.0, –2.0); P<.001 –2.7 (–3.3, –2.1); P<.001 –2.1 (–2.8, –1.5); P<.001
3 mg –0.5 (–1.0, –0.1); P=.03 –0.7 (–1.3, –0.1); P=.02 –0.8 (–1.4, –0.1); P=.03
7 mg –1.5 (–2.0, –1.1); P<.001 –1.5 (–2.1, –0.9); P<.001 –1.6 (–2.2, –0.9); P<.001
14 mg –2.6 (–3.1, –2.1); P<.001 –2.9 (–3.5, –2.3); P<.001 –2.4 (–3.0, –1.7); P<.001
Oral semaglutide 3 mg
Oral semaglutide 7 mg
Oral semaglutide 14 mg
Sitagliptin 100 mg