Oral Semaglutide Versus Empagliflozin in Patients With Type 2 Diabetes Uncontrolled on Metformin: The PIONEER 2 Trial

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OBJECTIVE

Efficacy and safety of the glucagon-like peptide 1 (GLP-1) analog oral semaglutide and the sodium–glucose cotransporter 2 inhibitor empagliflozin were compared in patients with type 2 diabetes uncontrolled on metformin.

RESEARCH DESIGN AND METHODS

Patients were randomized to once-daily open-label treatment with oral semaglutide 14 mg ($n = 412$) or empagliflozin 25 mg ($n = 410$) in a 52-week trial. Key end points were change from baseline to week 26 in HbA_{1c} (primary) and body weight (confirmatory secondary). Two estimands addressed efficacy-related questions: treatment policy (regardless of trial product discontinuation or rescue medication) and trial product (on trial product without rescue medication) in all randomized patients.

RESULTS

Four-hundred (97.1%) patients in the oral semaglutide group and 387 (94.4%) in the empagliflozin group completed the trial. Oral semaglutide provided superior reductions in HbA_{1c} versus empagliflozin at week 26 (treatment policy –1.3 vs. –0.9% [–14 vs. –9 mmol/mol], estimated treatment difference [ETD] –0.4% [95% CI –0.6, –0.3%] [–5 mmol/mol (–6, –3 mmol/mol)]; $P < 0.0001$). The treatment difference in HbA_{1c} significantly favored oral semaglutide at week 26 for the trial product estimand (–1.4 vs. –0.9% [–15 vs. –9 mmol/mol], ETD –0.5% [95% CI –0.7, –0.4%] [–6 mmol/mol (–7, –5 mmol/mol)]; $P < 0.0001$) and at week 52 for both estimands ($P < 0.0001$). Superior weight loss was not confirmed at week 26 (treatment policy), but oral semaglutide was significantly better than empagliflozin at week 52 (trial product −4.7 vs. −3.8 kg; $P = 0.0114$). Gastrointestinal adverse events were more common with oral semaglutide.

CONCLUSIONS

Oral semaglutide was superior to empagliflozin in reducing HbA_{1c} but not body weight at 26 weeks in patients with type 2 diabetes uncontrolled on metformin. At week 52, HbA_{1c} and body weight (trial product estimand) were significantly reduced versus empagliflozin. Oral semaglutide was well tolerated within the established safety profile of GLP-1 receptor agonists.

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Many patients with type 2 diabetes fail to achieve or maintain adequate blood glucose control when treated with metformin monotherapy. Injectable glucagon-like peptide 1 receptor agonists (GLP-1RAs) and oral sodium–glucose cotransporter 2 (SGLT-2) inhibitors are recommended as second-line therapy because of their ability to lower glucose without increasing hypoglycemia risk, weight loss effect, and associated cardiovascular benefits (1,2).

Semaglutide is a human GLP-1 analog currently available as a once-weekly injection associated with reduced glycated hemoglobin (HbA_{1c}), weight loss, and fewer cardiovascular events in type 2 diabetes (3–9). Oral semaglutide is coformulated in a tablet with the absorption enhancer sodium *N*-(8-[2-hydroxylbenzoyl] amino) caprylate, which facilitates semaglutide absorption across the gastric mucosa (10). Oral semaglutide has demonstrated significantly greater reductions in HbA_{1c} and body weight compared with placebo in patients with type 2 diabetes uncontrolled with diet and exercise or oral antidiabetic medication, including in patients with moderate renal impairment (11–14). Significantly greater reductions in HbA_{1c} and body weight have also been shown with oral semaglutide, given as 7 or 14 mg/day or flexibly dosed, compared with sitagliptin in patients uncontrolled with oral antidiabetic drugs (15,16). Oral semaglutide also resulted in a noninferior reduction in HbA_{1c} and superior weight loss versus liraglutide in patients on metformin with or without an SGLT-2 inhibitor (13). Cardiovascular safety has been confirmed, with an indication of benefit, by a nonsignificant 21% risk reduction in major adverse cardiovascular events versus placebo (17).

Empagliflozin is a widely used oral SGLT-2 inhibitor shown to improve glycemic control and body weight (18–22) and associated with a reduced risk of cardiovascular and all-cause mortality in patients at high cardiovascular risk (23). The present phase 3a trial, PIONEER 2, is the first direct comparison of oral semaglutide with an SGLT-2 inhibitor, empagliflozin, in type 2 diabetes uncontrolled with metformin monotherapy.

RESEARCH DESIGN AND METHODS

Trial Design

This randomized, open-label, multinational, 52-week trial was conducted at 108 sites in 12 countries (Argentina, Brazil, Croatia, Greece, Hungary, Italy, Poland, Russia, Serbia, Spain, Thailand, U.S.). Patients were randomized (1:1) to once-daily oral semaglutide 14 mg or empagliflozin 25 mg for 52 weeks using an interactive web response system with a further 5 weeks of follow-up (Supplementary Fig. 1). An open-label trial design was used because manufacture of placebo tablets resembling empagliflozin was not feasible within a reasonable time frame. Oral semaglutide was initiated at 3 mg once daily, escalated to 7 mg at week 4, and 14 mg after week 8. Because food impairs absorption of oral semaglutide, patients were instructed to administer oral semaglutide in the morning in a fasted state with up to 120 mL of water at least 30 min before breakfast and any other oral medication. Empagliflozin was initiated at 10 mg once daily in the morning and escalated to 25 mg at week 8.

Additional antidiabetic medication was available for patients with persistent or unacceptable hyperglycemia on trial product and for patients who prematurely discontinued trial product and remained in the trial. Additional antidiabetic medication was defined as that initiated (or intensification of existing antidiabetic background medication by a dose increase of >20%) during the planned treatment period (i.e., from randomization to the planned end-of-treatment visit) either as add-on to trial product or initiated after premature discontinuation of trial product. The subset of additional antidiabetic medication (or intensification of existing antidiabetic background medication) used as add-on to trial product is defined as rescue medication. Short-term use (≤21 days) of antidiabetic medication (e.g., in connection with intercurrent illness) was not considered as additional antidiabetic medication (including rescue medication).

Rescue criteria were fasting plasma glucose >260 mg/dL (14.4 mmol/L) from week 8 to 13, >240 mg/dL (13.3 mmol/L) from week 14 to 25, and >200 mg/dL (11.1 mmol/L) (or HbA_{1c} >8.5% [69.4 mmol/mol]) from week 26 onward. Rescue medication was prescribed at the investigator's discretion (excluding GLP-1RAs, dipeptidyl peptidase 4 inhibitors, and amylin analogs in the oral semaglutide arm and SGLT-2 inhibitors in the empagliflozin arm). Patients who prematurely discontinued trial product remained in the trial and could receive any other antidiabetic medications at the investigator's discretion (excluding GLP-1RAs in the oral semaglutide arm before completion of the follow-up visit 5 weeks after the last date on trial product).

Two different questions related to the efficacy objectives were addressed through the definition of two estimands: treatment policy and trial product. Both estimands were defined based on interactions with regulatory agencies. The treatment policy estimand 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 on Harmonization (ICH) E9 (24). The estimand reflects the effect of initiating treatment with oral semaglutide compared with initiating treatment with empagliflozin, 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 empagliflozin without the confounding effect of rescue medication. The statistical analysis that was applied to estimate this estimand is similar to how many phase 3a diabetes trials have been evaluated, and results from such analyses are currently included in many product labels (prescribing information, U.S. and summary of product characteristics, European Union) for glucose-lowering drugs (e.g., Ozempic summary of product characteristics).

Trial product discontinuation and initiation of rescue medication are accounted for by the treatment policy strategy for the treatment policy estimand and by the hypothetical strategy for the trial product estimand as defined in draft ICH E9 (R1) (25). Further details on the use of estimands in this trial are provided in Supplementary Appendix 2, with additional background provided by Aroda et al. (26).

The trial protocol was approved by all relevant institutional review boards/independent ethics committees, and the

trial was conducted in accordance with ICH Good Clinical Practice guidelines and the Declaration of Helsinki. All patients provided written informed consent before any trial-related activity.

Patients

Eligible patients were adults with type 2 diabetes and an HbA_{1c} of 7.0–10.5% (53–91 mmol/mol) receiving a stable dose of metformin (≥1,500 mg or maximum tolerated). Key exclusion criteria (see Supplementary Table 1 for full list) were any medication for diabetes or obesity within the previous 90 days other than metformin or short-term (≤14 days) insulin, renal impairment with an estimated glomerular filtration rate <60 mL/min/1.73 m^2, proliferative retinopathy or maculopathy requiring acute treatment verified by fundus photography or dilated fundoscopy, and history of pancreatitis.

Trial End Points

The primary end point was change in HbA_{1c} from baseline to week 26. The confirmatory secondary end point was change in body weight (kg) from baseline to week 26.

Secondary end points included changes from baseline to week 52 in HbA_{1c} and body weight (kg) and changes from baseline to weeks 26 and 52 in fasting plasma glucose, self-measured blood glucose (SMBG) profile (7-point profile and mean postprandial increment over all meals), fasting C-peptide, fasting insulin, fasting proinsulin, fasting glucagon, HOMA of insulin resistance, HOMA of β-cell function, C-reactive protein, body weight (%), BMI, waist circumference, and fasting lipid profile. Other secondary end points were the proportion of patients achieving HbA_{1c} <7% (53 mmol/mol) or ≤6.5% (48 mmol/mol); weight loss of ≥5% or ≥10%; composite end point of HbA_{1c} <7% (53 mmol/mol) without severe or symptomatic hypoglycemia (blood glucose <56 mg/dL [<3.1 mmol/L]) and no weight gain; composite end point of an absolute reduction in HbA_{1c} of ≥1.0% (10.9 mmol/mol) and body weight loss of ≥3% (weeks 26 and 52); and changes from baseline to weeks 26 and 52 in the patient-reported outcomes, Short Form (SF) 36v2 Health Survey (Acute Version) (27) and Control of Eating Questionnaire (28). Further end points are listed in Supplementary Appendix 2, and the protocol is included as part of the Supplementary Data.

Safety end points included the number of treatment-emergent adverse events, incidence of American Diabetes Association (ADA)–classified (29) severe or confirmed symptomatic hypoglycemic episodes (blood glucose <56 mg/dL [<3.1 mmol/L]), and changes from baseline in heart rate, blood pressure, and other clinical and laboratory assessments. An independent external event adjudication committee (EAC) performed masked validation of predefined adverse events, including deaths, selected cardiovascular events, acute pancreatitis, malignant neoplasms, acute kidney injury, and lactic acidosis.

Statistical Analysis

The primary end point of change from baseline to week 26 in HbA_{1c} was tested for both noninferiority and superiority of oral semaglutide versus empagliflozin, with a sample size calculation to ensure a power of at least 90% for testing superiority. The confirmatory secondary end point of change from baseline to week 26 in body weight was tested for superiority of oral semaglutide versus empagliflozin. The confirmation of efficacy of oral semaglutide on change in HbA_{1c} and body weight from baseline to week 26 was based on a weighted Bonferroni closed testing strategy (30) to control the overall type I error for the hypotheses evaluated by the treatment policy estimand (Supplementary Fig. 2). Because of the potential for type I errors as a result of multiple comparisons, findings for analyses of additional secondary end points 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 confirmatory end points. Data collected at week 26, irrespective of premature discontinuation of trial product or initiation of rescue medication, were included in the statistical analysis. Imputation was done within groups defined by trial product and treatment status at week 26. Both the imputation and the analysis were based on ANCOVA models. The results were combined by use of Rubin's rule (31). Before testing for noninferiority, a value of 0.4% (the noninferiority margin) was added to imputed values at week 26 for the oral semaglutide treatment arm only (32). The trial product estimand was estimated by a mixed model for repeated measurements that used data collected before premature trial product discontinuation or initiation of rescue medication from all randomized patients.

Further details on the statistical analyses can be found in Supplementary Fig. 2. All analyses were performed using SAS 9.4M2 statistical software.

Data Availability

Data will be shared with bona fide researchers submitting a research proposal approved by the independent review board. Access request proposals can be found at http://novonordisk-trials.com. Data will be made available after research completion, approval of the product, and product use in the European Union and U.S. Individual participant data will be shared in data sets in a deidentified/anonymized format using a specialized SAS data platform.

RESULTS

Patients

A total of 1,122 patients were screened, with 822 randomized to oral semaglutide 14 mg once daily ($n = 412$) or empagliflozin 25 mg once daily ($n = 410$). Four-hundred (97.1%) patients in the oral semaglutide group and 387 (94.4%) in the empagliflozin group completed the trial (Supplementary Fig. 3). Baseline characteristics were well balanced between treatment groups (Table 1). Patients, of whom half (49.5%) were female, had a mean age of 58 years, baseline HbA_{1c} of 8.1% (65 mmol/mol), fasting plasma glucose of 173 mg/dL (9.6 mmol/L), average duration of diabetes of 7.4 years, and mean body weight of 91.6 kg.

Use of additional antidiabetic medication and rescue medication is shown in Supplementary Table 2. Through to week 26, 17 (4.1%) patients initiated additional antidiabetic medication in the oral semaglutide group; in 8 (1.9%) of these patients, it was rescue medication. In the empagliflozin group, 13 (3.2%) patients initiated additional antidiabetic medication through to week 26, with this being rescue medication in 5 (1.2%). Through to week 52, 52 (12.7%) patients initiated additional antidiabetic medication in the oral semaglutide group; in 31 (7.5%) of these patients, it was rescue medication. In the empagliflozin group, 56 (13.7%) patients initiated additional

Table 1—Baseline characteristics and demographics

	Oral semaglutide 14 mg	Empagliflozin 25 mg	Total
Patients, *n*	411	410	821
Age (years), mean (SD)	57 (10)	58 (10)	58 (10)
Female, *n* (%)	205 (49.9)	201 (49.0)	406 (49.5)
Race, *n* (%)			
White	355 (86.4)	353 (86.1)	708 (86.2)
Black or African American	26 (6.3)	33 (8.0)	59 (7.2)
Asian	28 (6.8)	21 (5.1)	49 (6.0)
Other	2 (0.5)	3 (0.7)	5 (0.6)
Ethnicity, *n* (%)			
Hispanic or Latino	91 (22.1)	108 (26.3)	199 (24.2)
Duration of diabetes (years), mean (SD)	7.2 (5.8)	7.7 (6.3)	7.4 (6.1)
Body weight (kg), mean (SD)	91.9 (20.5)	91.3 (20.1)	91.6 (20.3)
BMI (kg/m^2), mean (SD)	32.9 (6.3)	32.8 (5.9)	32.8 (6.1)
HbA_{1c}, mean (SD)			
%	8.1 (0.9)	8.1 (0.9)	8.1 (0.9)
mmol/mol	65 (10)	65 (10)	65 (10)
Fasting plasma glucose, mean (SD)			
mmol/L	9.5 (2.3)	9.7 (2.5)	9.6 (2.4)
mg/dL	171.5 (41.8)	174.0 (45.2)	172.8 (43.5)
Estimated glomerular filtration rate* (mL/min/1.73 m^2), mean (SD)	96 (15)	95 (15)	95 (15)

*Glomerular filtration rate was estimated by the Chronic Kidney Disease Epidemiology Collaboration equation.

antidiabetic medication, with this being rescue medication in 44 (10.7%). Sulfonylureas were the most commonly used additional antidiabetic and rescue medication. Disposition of patients throughout the trial is shown in Supplementary Fig 4.

Glycemic Control

Oral semaglutide 14 mg provided a superior reduction in HbA_{1c} compared with empagliflozin 25 mg at week 26 when evaluated by the treatment policy estimand (regardless of rescue medication use or trial product discontinuation) (–1.3% vs. –0.9% [–14 vs. –9 mmol/mol]; estimated treatment difference [ETD] –0.4% [95% CI –0.6, –0.3%] [–5 mmol/mol (–6, –3 mmol/mol)]; $P <$ 0.0001 for noninferiority and superiority) (Fig. 1). Results from sensitivity analyses supported the results of the confirmatory analysis (Supplementary Fig. 5). When evaluated by the trial product estimand (on trial product and without the use of rescue medication), the reduction in HbA_{1c} was significantly greater with oral semaglutide at week 26 (–1.4% vs. –0.9% [–15 vs. –9 mmol/mol], ETD –0.5% [–0.7, –0.4%] [–6 mmol/mol (–7, –5 mmol/mol)]; $P <$ 0.0001) (Fig. 1). Significantly greater reductions in HbA_{1c} with oral semaglutide compared with empagliflozin were also observed at week 52 (both estimands) (Fig. 1). More patients achieved the predefined HbA_{1c} targets with oral semaglutide than with empagliflozin, and the odds of doing so were significantly greater at weeks 26 and 52 (both estimands, all $P <$ 0.0001) (Fig. 1 and Table 2).

Fasting plasma glucose was reduced with both treatments, with no significant difference between groups (Table 2 and Supplementary Fig. 6). Oral semaglutide resulted in significantly greater reductions in mean 7-point SMBG profiles compared with empagliflozin at both weeks 26 and 52 (Table 2 and Supplementary Fig. 6) and significantly reduced mean postprandial increments, as averaged for all meals (excluding the treatment policy estimand evaluation at week 26) (Table 2).

Body Weight

Superiority of body weight reduction at week 26 with oral semaglutide over empagliflozin was not confirmed (treatment policy estimand −3.8 vs. −3.7 kg; ETD −0.1 kg [95% CI −0.7, 0.5 kg]; $P = 0.7593$). Results from sensitivity analyses supported the results of the confirmatory analysis (Supplementary Fig. 5). There was no difference between treatments using the trial product estimand (−4.2 vs. −3.8 kg; ETD −0.4 kg [−1.0, 0.1 kg]; $P = 0.1358$) (Fig. 1). A significantly greater reduction in body weight was achieved with oral semaglutide versus empagliflozin at week 52 when evaluated by the trial product estimand (−4.7 vs. −3.8 kg; ETD −0.9 kg [−1.6, −0.2 kg]; $P = 0.0114$) but not the treatment policy estimand (−3.8 vs. −3.6 kg; ETD −0.2 kg [−0.9, 0.5 kg]; $P = 0.6231$). Proportions of patients achieving ≥5% or ≥10% weight loss are shown in Fig. 1 and Table 2, respectively. Reductions in waist circumference were significantly greater with oral semaglutide than with empagliflozin at week 26 (both estimands) and at week 52 (trial product estimand) (Table 2).

Other Outcomes

More patients achieved the two composite end points ($HbA_{1c} <$7% [53 mmol/mol] without severe or symptomatic hypoglycemia and no weight gain and an absolute reduction in HbA_{1c} of ≥1.0% [10.9 mmol/mol] and body weight loss of ≥3%) with oral semaglutide versus empagliflozin, and the odds of doing so were significantly greater at both weeks 26 and 52 (Table 2). Reduction in C-reactive protein was significantly greater with oral semaglutide versus empagliflozin (Table 2). Other secondary end points are presented in Table 2 and Supplementary Table 3.

For the Control of Eating Questionnaire, the domains craving control (weeks 26 and 52) and craving for savory (week 52) were significantly improved in favor of oral semaglutide versus empagliflozin (treatment policy estimand). Both domains were significantly in favor of oral semaglutide at both weeks 26 and 52 for the trial product estimand. Patient-reported outcomes are summarized in Supplementary Fig. 7.

Safety

The overall number of adverse events and proportion of patients reporting adverse events were similar with oral semaglutide and empagliflozin, and most events were mild to moderate severity (Table 3). Fewer patients experienced serious adverse events in the oral semaglutide group. There was one death in the empagliflozin group (undetermined cause). The most frequent

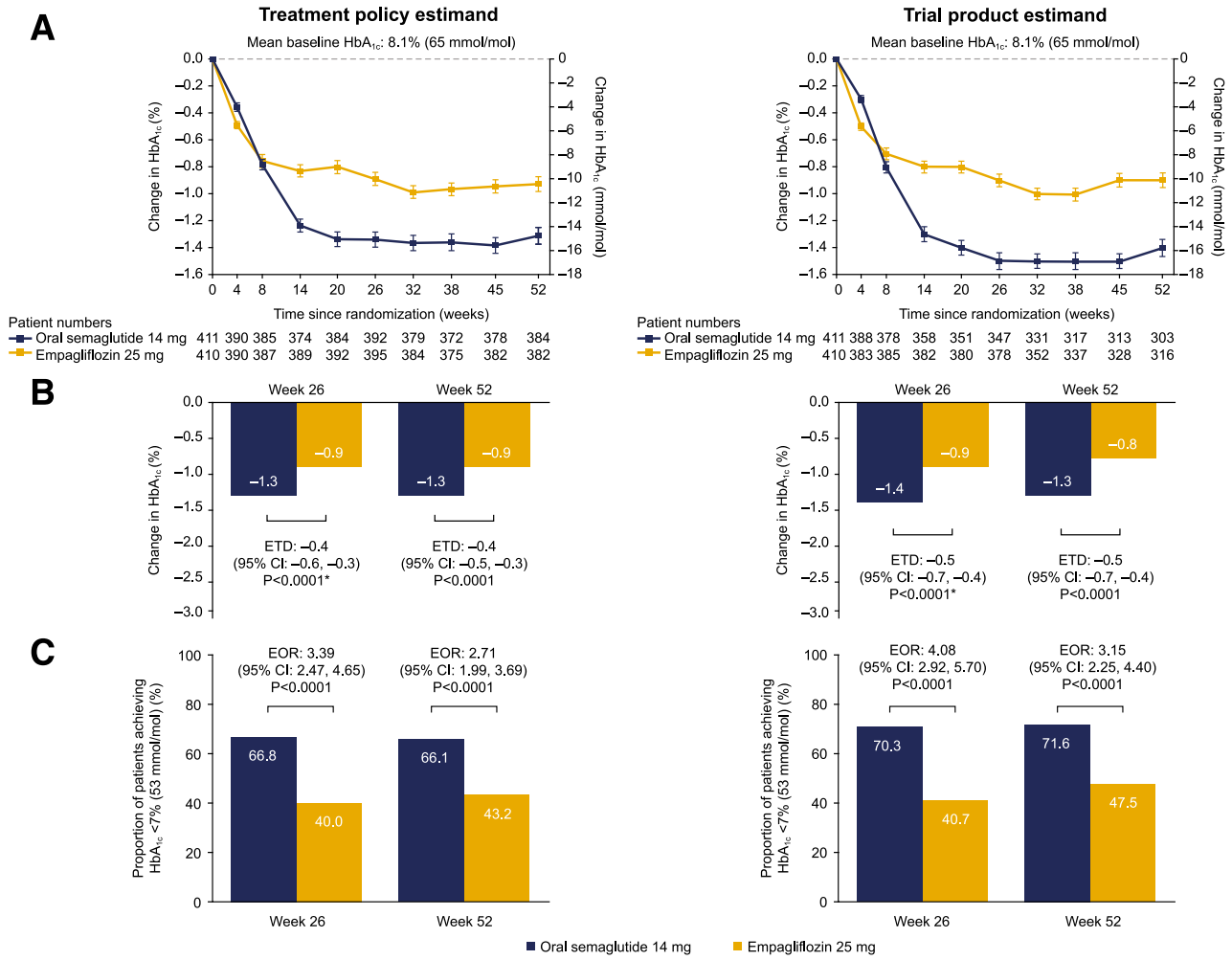

Figure 1—Glycemic control and body weight–related efficacy end points. *A*: Observed absolute change in HbA_{1c} over time. *B*: Estimated changes from baseline in HbA_{1c} at weeks 26 and 52. *C*: Observed proportions of patients achieving HbA_{1c} <7% (53 mmol/mol) at weeks 26 and 52. *D*: Observed absolute change in body weight over time. *E*: Estimated changes from baseline in body weight at weeks 26 and 52. *F*: Observed proportions of patients achieving body weight reduction ≥5% at weeks 26 and 52. Treatment policy estimand: Data irrespective of discontinuation of trial product and initiation of rescue medication were included. Trial product estimand: Data collected after discontinuation of trial product or initiation of rescue medication are excluded. *P* values are two-sided and unadjusted. *Superiority confirmed for oral semaglutide versus empagliflozin. Observed mean change (± SEM) from baseline (*A* and *D*), estimated mean changes from baseline at week 26 and 52 (*B* and *E*), and observed proportions of patients achieving target at weeks 26 and 52 (*C* and *F*). Patient numbers represent patients contributing to the means. EOR, estimated odds ratio.

adverse event with oral semaglutide was nausea, which was nonserious, usually mild to moderate severity and transient, and did not exceed a prevalence of 10% at any time (Table 3 and Supplementary Fig. 8). Female and male genital mycotic infections of mild to moderate severity occurred more frequently with empagliflozin than with oral semaglutide (8.5% and 6.7% vs. 2.0% and 0%, respectively) (Supplementary Table 4).

Adverse events resulting in trial product discontinuation were more frequent with oral semaglutide than with empagliflozin (10.7% vs. 4.4%) and were primarily related to gastrointestinal symptoms (8.0% vs. 0.7%) (Table 3). In both groups, premature discontinuations mainly occurred in the first 16 weeks of treatment.

Incidence of severe or confirmed symptomatic hypoglycemic episodes (<56 mg/dL [<3.1 mmol/L]) was low and similar in both groups (Table 3). Diabetic retinopathy–related adverse events were reported in 14 (3.4%) patients in the oral semaglutide group and in 5 (1.2%) in the empagliflozin group (in-trial period) (Supplementary Table 5). All such events were identified by routine eye examination as part of the trial protocol and were nonserious, of mild or moderate severity, and did not require treatment. EAC-confirmed malignant neoplasms were identified in seven (1.7%) patients in the oral semaglutide group and two (0.5%) in the empagliflozin group (in-trial period). There was no clustering of malignancies in any particular organ or system (Supplementary Table 6). Cardiovascular events occurred at a similar rate in both groups (EAC confirmed; oral semaglutide $n = 5$ [1.2%], empagliflozin $n = 6$ [1.5%]) (Supplementary Table 6). Other EAC-confirmed events and safety assessments are reported in Supplementary Tables 6 and 7.

CONCLUSIONS

Oral semaglutide is the first oral GLP-1RA to be investigated for the treatment of type 2 diabetes. In PIONEER 2, oral semaglutide was superior to empagliflozin, with meaningful reductions in HbA_{1c} at 26 weeks in patients with type 2 diabetes uncontrolled on metformin monotherapy. Furthermore, the difference between treatments remained significant at 52 weeks.

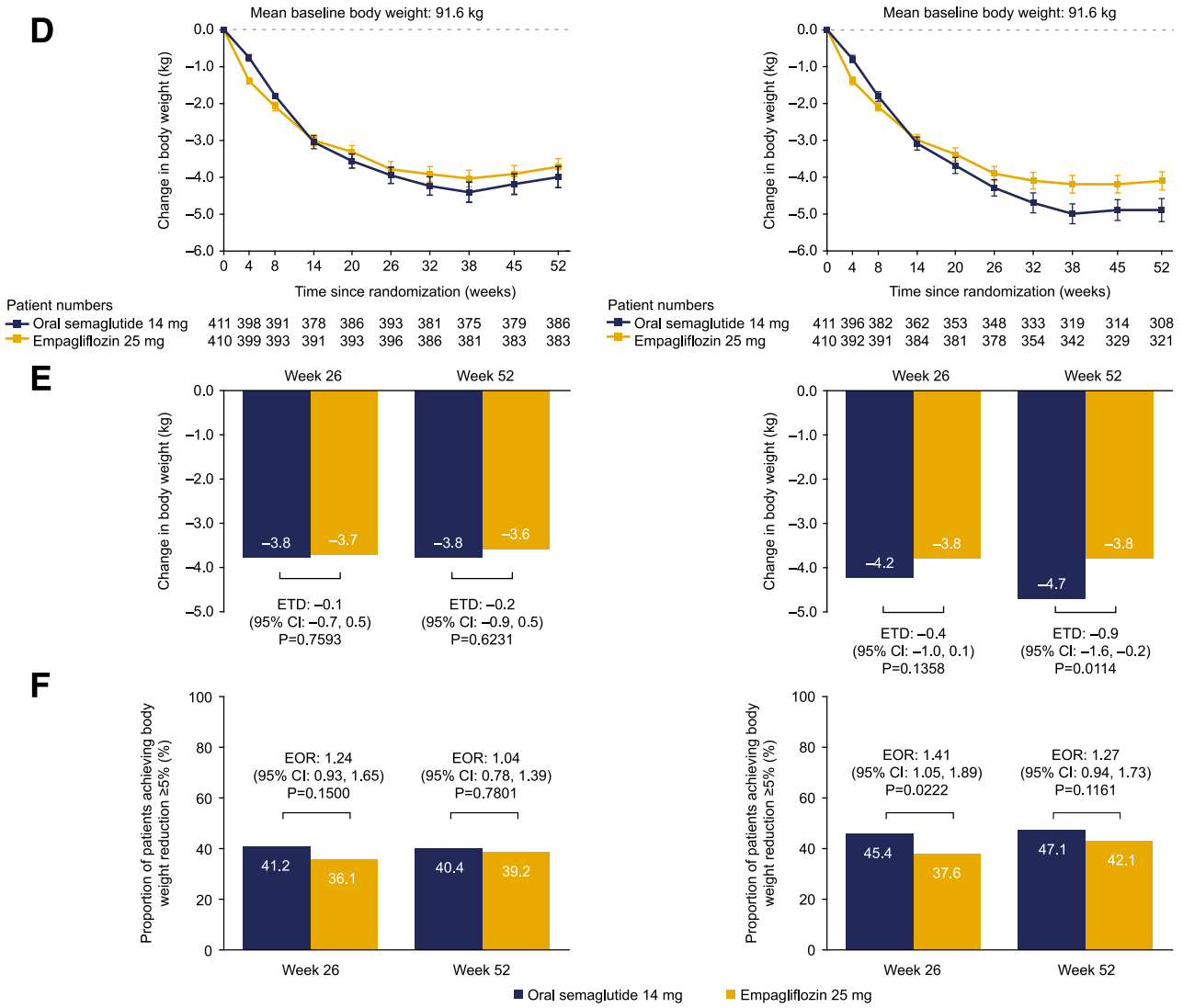

Figure 1—Continued

Attainment of ADA-recommended HbA_{1c} targets at 26 and 52 weeks was also significantly greater with oral semaglutide. Reductions in fasting plasma glucose were similar in both groups, suggesting differences in glycemic control may be mostly driven by the greater reduction in postprandial glucose with oral semaglutide.

Reductions in body weight occurred with both treatments, but superiority of oral semaglutide versus empagliflozin could not be confirmed at week 26. However, weight loss in the empagliflozin group stabilized around week 26, whereas in the oral semaglutide group, weight loss continued until around week 38 and was significantly greater at 52 weeks on the basis of the trial product estimand. This significantly greater weight loss at 52 weeks with oral semaglutide on the basis of the trial product estimand reflects the treatment effect without the confounding influence of rescue medication use and treatment discontinuations. Patients discontinuing oral semaglutide could not be switched to additional antidiabetic medication with a comparable weight-reducing effect, while patients on empagliflozin could be switched to GLP-1RAs.

The safety profile of oral semaglutide was consistent with previous trials (11–16). More patients prematurely discontinued treatment because of adverse events with oral semaglutide versus empagliflozin mainly as a result of gastrointestinal symptoms associated with dose escalation. The proportion of adverse events leading to discontinuation of oral semaglutide (10.7%) was similar to previous observations with injectable GLP-1RAs (6–11%) (4,33,34).

The use of subcutaneous semaglutide has previously been associated with a higher rate of diabetic retinopathy–related complications compared with placebo, which is consistent with the phenomenon of early worsening of preexisting diabetic retinopathy secondary to an initial, rapid improvement in glycemic control (6,35). The possible effect of subcutaneous semaglutide on diabetic eye disease is being further investigated in the ongoing FOCUS trial (NCT03811561) (36). In the current trial, diabetic retinopathy–related adverse events were more frequent with oral semaglutide compared with empagliflozin, although occurrence was low in both groups (3.4% vs. 1.2%). All events were nonserious, most were mild in severity, and none required treatment or led to trial product discontinuation. All were discovered during routine

Table 2—Selected secondary end points (treatment policy estimand and trial product estimand)[a]

	Treatment policy estimand				Trial product estimand			
	Week 26		Week 52		Week 26		Week 52	
	Oral semaglutide 14 mg	Empagliflozin 25 mg	Oral semaglutide 14 mg	Empagliflozin 25 mg	Oral semaglutide 14 mg	Empagliflozin 25 mg	Oral semaglutide 14 mg	Empagliflozin 25 mg
Patients, *n*	411	410	411	410	411	410	411	410
HbA_{1c} ≤6.5% (48 mmol/mol)								
Patients reaching end point, *n* (%)	186 (47.4)	68 (17.2)	182 (47.4)	83 (21.7)	181 (52.2)	68 (18.0)	164 (54.1)	74 (23.4)
Estimated OR (95% CI) oral semaglutide vs. empagliflozin	4.62 (3.28, 6.52); $P < 0.0001$		3.36 (2.43, 4.66); $P < 0.0001$		5.61 (3.93, 8.01); $P < 0.0001$		4.32 (3.05, 6.13); $P < 0.0001$	
Body weight reduction ≥10%								
Patients reaching end point, *n* (%)	49 (12.5)	27 (6.8)	58 (15.0)	30 (7.8)	49 (14.1)	27 (7.1)	56 (18.2)	28 (8.7)
Estimated OR (95% CI) oral semaglutide vs. empagliflozin	1.98 (1.21, 3.25); $P = 0.0066$		2.05 (1.28, 3.28); $P = 0.0028$		2.18 (1.33, 3.57); $P = 0.0021$		2.51 (1.57, 4.01); $P < 0.0001$	
HbA_{1c} <7% (53 mmol/mol) without hypoglycemia† and no weight gain								
Patients reaching end point, *n* (%)	237 (60.5)	141 (35.7)	214 (55.7)	149 (39.0)	222 (64.0)	139 (36.8)	191 (63.0)	139 (44.0)
Estimated OR (95% CI) oral semaglutide vs. empagliflozin	2.88 (2.12, 3.91); $P < 0.0001$		2.03 (1.50, 2.74); $P < 0.0001$		3.31 (2.40, 4.56); $P < 0.0001$		2.39 (1.74, 3.30); $P < 0.0001$	
HbA_{1c} reduction ≥1% (10.9 mmol/mol) and body weight loss ≥3%								
Patients reaching end point, *n* (%)	177 (45.2)	111 (28.1)	164 (42.7)	101 (26.4)	172 (49.6)	110 (29.1)	148 (48.8)	91 (28.8)
Estimated OR (95% CI) oral semaglutide vs. empagliflozin	2.10 (1.55, 2.85); $P < 0.0001$		2.10 (1.54, 2.87); $P < 0.0001$		2.41 (1.77, 3.29); $P < 0.0001$		2.33 (1.69, 3.21); $P < 0.0001$	
Waist circumference (cm)								
Estimated mean	104.8	105.5	105.1	105.7	104.5	105.6	104.4	105.6
Estimated mean change from baseline	−3.7	−3.0	−3.5	−2.9	−4.1	−3.0	−4.2	−2.9
ETD (95% CI) oral semaglutide vs. empagliflozin	−0.7 (–1.4, –0.0); $P = 0.0400$		−0.6 (–1.4, 0.2); $P = 0.1488$		−1.1 (–1.8, –0.4); $P = 0.0033$		−1.3 (–2.1, –0.4); $P = 0.0030$	
Fasting plasma glucose, mmol/L (mg/dL)								
Estimated mean	7.59 (136.8)	7.57 (136.5)	7.58 (136.6)	7.50 (135.1)	7.39 (133.2)	7.60 (137.0)	7.48 (134.7)	7.58 (136.7)
Estimated mean change from baseline	−1.99 (–35.9)	−2.01 (–36.3)	−2.01 (–36.2)	−2.09 (–37.6)	−2.19 (–39.5)	−1.99 (–35.8)	−2.11 (–38.1)	−2.00 (–36.1)
ETD (95% CI) oral semaglutide vs. empagliflozin	0.02 (–0.24, 0.28), 0.4 (–4.3, 5.0); $P = 0.8812$		0.08 (–0.20, 0.36), 1.4 (–3.6, 6.4); $P = 0.5759$		−0.21 (–0.44, 0.03), –3.7 (–8.0, 0.5); $P = 0.0874$		−0.11 (–0.37, 0.15), –2.0 (–6.6, 2.6); $P = 0.4016$	
Mean 7-point SMBG, mmol/L (mg/dL)								
Estimated mean	8.0 (143.7)	8.3 (148.8)	7.9 (142.4)	8.2 (147.4)	7.7 (138.8)	8.3 (148.7)	7.7 (138.5)	8.2 (147.1)
Estimated mean change from baseline	−2.2 (–39.8)	−1.9 (–34.7)	−2.3 (–41.1)	−2.0 (–36.1)	−2.4 (–44.0)	−1.9 (–34.0)	−2.5 (–44.3)	−2.0 (–35.7)
ETD (95% CI) oral semaglutide vs. empagliflozin	−0.3 (–0.5, –0.0), –5.0 (–9.5, –0.6); $P = 0.0267$		−0.3 (–0.5, –0.0), –5.1 (–9.7, –0.4); $P = 0.0328$		−0.6 (–0.8, –0.3), –10.0 (–13.8, –6.1); $P < 0.0001$		−0.5 (–0.7, –0.2), –8.7 (–12.9, –4.4); $P < 0.0001$	
7-point SMBG postprandial increment, mmol/L (mg/dL)								
Estimated mean	1.5 (27.5)	1.7 (30.0)	1.3 (23.2)	1.7 (30.7)	1.4 (25.1)	1.6 (29.1)	1.2 (22.5)	1.7 (30.2)
Estimated mean change from baseline	−0.5 (–8.7)	−0.3 (–6.2)	−0.7 (–13.0)	−0.3 (–5.5)	−0.6 (–11.4)	−0.4 (–7.3)	−0.8 (–14.0)	−0.3 (–6.3)
ETD (95% CI) oral semaglutide vs. empagliflozin	−0.1 (–0.4, 0.1), –2.5 (–6.6, 1.6); $P = 0.2388$		−0.4 (–0.6, –0.2), –7.5 (–11.5, –3.4); $P = 0.0003$		−0.2 (–0.4, –0.0), –4.1 (–7.9, –0.3); $P = 0.0356$		−0.4 (–0.6, –0.2), –7.7 (–11.5, –3.9); $P < 0.0001$	

Continued on p. 8

Table 2—Continued

	Treatment policy estimand				Trial product estimand			
	Week 26		Week 52		Week 26		Week 52	
	Oral semaglutide 14 mg	Empagliflozin 25 mg	Oral semaglutide 14 mg	Empagliflozin 25 mg	Oral semaglutide 14 mg	Empagliflozin 25 mg	Oral semaglutide 14 mg	Empagliflozin 25 mg
Fasting C-peptide (nmol/L)								
Estimated mean	0.958	0.798	0.959	0.827	0.964	0.799	0.964	0.805
Estimated ratio to baseline	1.08	0.90	1.09	0.94	1.09	0.91	1.09	0.91
Estimated treatment ratio (95% CI) oral semaglutide vs. empagliflozin	1.20 (1.15, 1.25); $P < 0.0001$		1.16 (1.11, 1.22); $P < 0.0001$		1.21 (1.15, 1.26); $P < 0.0001$		1.20 (1.14, 1.26); $P < 0.0001$	
Fasting insulin (pmol/L)								
Estimated mean	88	65	86	66	87	63	83	63
Estimated ratio to baseline	1.06	0.78	1.03	0.79	1.03	0.75	0.99	0.75
Estimated treatment ratio (95% CI) oral semaglutide vs. empagliflozin	1.35 (1.26, 1.46); $P < 0.0001$		1.31 (1.21, 1.41); $P < 0.0001$		1.37 (1.29, 1.46); $P < 0.0001$		1.32 (1.23, 1.41); $P < 0.0001$	
Fasting proinsulin (pmol/L)								
Estimated mean	18.3	17.1	18.7	17.9	17.3	16.8	17.6	17.0
Estimated mean change from baseline	0.72	0.68	0.74	0.71	0.68	0.66	0.69	0.67
ETD (95% CI) oral semaglutide vs. empagliflozin	1.07 (0.98, 1.17); $P = 0.1403$		1.05 (0.96, 1.14); $P = 0.3034$		1.03 (0.94, 1.12); $P = 0.5453$		1.04 (0.95, 1.14); $P = 0.4479$	
Fasting glucagon (pg/mL)								
Estimated mean	86	95	84	90	85	95	84	89
Estimated ratio to baseline	0.92	1.01	0.89	0.95	0.90	1.01	0.89	0.95
Estimated treatment ratio (95% CI) oral semaglutide vs. empagliflozin	0.91 (0.88, 0.94); $P < 0.0001$		0.94 (0.90, 0.97); $P = 0.0008$		0.89 (0.86, 0.92); $P < 0.0001$		0.94 (0.90, 0.97); $P = 0.0011$	
C-reactive protein (mg/L)								
Estimated mean	1.85	2.65	1.81	2.45	1.78	2.68	1.71	2.45
Estimated ratio to baseline	0.69	0.99	0.67	0.91	0.65	0.98	0.63	0.90
Estimated treatment ratio (95% CI) oral semaglutide vs. empagliflozin	0.70 (0.62, 0.79); $P < 0.0001$		0.74 (0.65, 0.84); $P < 0.0001$		0.66 (0.58, 0.75); $P < 0.0001$		0.70 (0.61, 0.80); $P < 0.0001$	

Treatment policy estimand: ANCOVA for continuous end points and logistic regression for binary end points, using data irrespective of discontinuation of trial product or initiation of rescue medication. Missing values were imputed by a pattern mixture model using multiple imputation. Patterns were defined by use of trial product and rescue medication. Trial product estimand: mixed model for repeated measurements for continuous end points and logistic regression for binary end points. Data collected after discontinuation of trial product or initiation of rescue medication are excluded. For binary end points, missing values were imputed from patients randomized to same trial product using sequential multiple imputation. *P* values are two-sided and unadjusted for the test of no difference. %, proportion of patients with nonmissing information; OR, odds ratio. [a]Additional end points are reported in Supplementary Table 4. †Severe or blood glucose–confirmed (plasma glucose <3.1 mmol/L [56 mg/dL]) symptomatic hypoglycemic episode.

Table 3—On-treatment adverse events

	Patients, *n* (%)	
	Oral semaglutide 14 mg (*n* = 410)	Empagliflozin 25 mg (*n* = 409)
Adverse events	289 (70.5)	283 (69.2)
Serious adverse events	27 (6.6)	37 (9.0)
Adverse event severity		
Mild	242 (59.0)	240 (58.7)
Moderate	140 (34.1)	118 (28.9)
Severe	24 (5.9)	23 (5.6)
Severe or blood glucose–confirmed symptomatic hypoglycemic episode*†‡	7 (1.7)	8 (2.0)
ADA-classified hypoglycemic episode*	45 (11.0)	39 (9.5)
Severe hypoglycemic episode*†	1 (0.2)	1 (0.2)
Most frequent adverse events ≥5% in either group (preferred term)		
Nausea	81 (19.8)	10 (2.4)
Diarrhea	38 (9.3)	13 (3.2)
Vomiting	30 (7.3)	7 (1.7)
Decreased appetite	21 (5.1)	2 (0.5)
Influenza	8 (2.0)	21 (5.1)
Adverse events resulting in premature trial drug discontinuation	44 (10.7)	18 (4.4)
Adverse events resulting in premature trial drug discontinuation (>1% for any system organ class or preferred term)		
Gastrointestinal disorders	33 (8.0)	3 (0.7)
Nausea	21 (5.1)	2 (0.5)
Vomiting	11 (2.7)	1 (0.2)
Abdominal pain	5 (1.2)	0
Infections and infestations	0	5 (1.2)
Deaths	0	1 (0.2)§

Safety end points were assessed using the safety analysis set (all patients exposed to one or more doses of trial product) and evaluated for both the on-treatment period (while on trial product) and the in-trial period (while in trial, regardless of discontinuation of trial product or use of rescue medication). *Hypoglycemic episodes were reported on a separate form from adverse events. †An episode that is severe, according to the ADA classification (requires assistance of another person to actively administer carbohydrate, glucagon, or other corrective action) (29). ‡Blood glucose confirmation of symptomatic hypoglycemia was based on a blood glucose value <56 mg/dL, with symptoms consistent with hypoglycemia. §One patient in the empagliflozin group died as a result of undetermined reasons after 268 days on trial drug.

end-of-treatment eye examination and were diagnosed as nonproliferative diabetic retinopathy. In a longer-term, 78-week, double-blind trial, no imbalance in the occurrence of diabetic retinopathy–related events were observed between oral semaglutide 3, 7, and 14 mg and sitagliptin (6.7%, 6.0%, 5.6%, and 7.7%, respectively) (15). Occurrence of diabetic retinopathy–related events was also similar with oral semaglutide and placebo (7.1% vs. 6.3%) in a double-blind trial that assessed cardiovascular outcomes in patients at high cardiovascular risk (17).

This trial provides a comparison of two increasingly used drug classes that are commonly added to metformin when glycemic control is not achieved. The principal limitation of the trial was the open-label design.

In conclusion, the oral GLP-1 analog oral semaglutide was superior to the SGLT-2 inhibitor empagliflozin for reduction in HbA_{1c}, but not body weight, at 26 weeks in patients with type 2 diabetes uncontrolled with metformin. Reductions in HbA_{1c} were significantly greater with oral semaglutide at 52 weeks. Assessed by the trial product estimand, oral semaglutide provided significant reductions in body weight at 52 weeks. Oral semaglutide was well tolerated, with a safety profile consistent with that of GLP-1RAs.

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