



PIONEER 1: Randomized Clinical Trial of the Efficacy and Safety of Oral Semaglutide Monotherapy in Comparison With Placebo in Patients With Type 2 Diabetes

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OBJECTIVE

This trial compared the efficacy and safety of the first oral glucagon-like peptide 1 (GLP-1) receptor agonist, oral semaglutide, as monotherapy with placebo in patients with type 2 diabetes managed by diet and exercise alone. Two estimands addressed two efficacy-related questions: 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.

RESEARCH DESIGN AND METHODS

This was a 26-week, phase 3a, randomized, double-blind, placebo-controlled, parallel-group trial conducted in 93 sites in nine countries. Adults with type 2 diabetes insufficiently controlled with diet and exercise were randomized (1:1:1:1) to once-daily oral semaglutide 3 mg, 7 mg, 14 mg, or placebo. The primary end point was change from baseline to week 26 in HbA_{1c}. The confirmatory secondary end point was change from baseline to week 26 in body weight.

RESULTS

In the 703 patients randomized (mean age 55 years, 50.8% male, and mean baseline HbA_{1c} 8.0% [64 mmol/mol]), oral semaglutide reduced HbA_{1c} (placebo-adjusted treatment differences at week 26: treatment policy estimand, -0.6% [3 mg], -0.9% [7 mg], and -1.1% [14 mg]; trial product estimand, -0.7% [3 mg], -1.2% [7 mg], and -1.4% [14 mg]; $P < 0.001$ for all) and body weight (treatment policy, -0.1 kg [3 mg], -0.9 kg [7 mg], and -2.3 kg [14 mg, $P < 0.001$]; trial product, -0.2 kg [3 mg], -1.0 kg [7 mg, $P = 0.01$], and -2.6 kg [14 mg, $P < 0.001$]). Mild-to-moderate transient gastrointestinal events were the most common adverse events with oral semaglutide. Trial product discontinuations occurred in 2.3–7.4% with oral semaglutide and 2.2% with placebo.

CONCLUSIONS

In patients with type 2 diabetes, oral semaglutide monotherapy demonstrated superior and clinically relevant improvements in HbA_{1c} (all doses) and body weight loss (14 mg dose) versus placebo, with a safety profile consistent with other GLP-1 receptor agonists.

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*A complete list of investigators in the Peptide Innovation for Early Diabetes Treatment 1 (PIONEER 1) trial is provided in the Supplementary Data online.

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Glucagon-like peptide 1 (GLP-1) receptor agonists are effective treatment options for achieving glycemic control in patients with type 2 diabetes but so far have only been available as subcutaneous injections (1,2). The GLP-1 analog semaglutide, administered subcutaneously once weekly, has been shown to effectively reduce glycosylated hemoglobin (HbA_{1c}) and induce body weight loss in patients with type 2 diabetes (3) and reduce the risk of cardiovascular events in those with established cardiovascular disease or high cardiovascular risk (4).

Peptide-based drugs, including GLP-1 receptor agonists, typically have very low bioavailability when administered orally due to extensive degradation by proteolytic enzymes and poor absorption across the gastrointestinal mucosa (5,6). Oral semaglutide is developed as a tablet, coformulated with the absorption enhancer sodium N-(8-[2-hydroxybenzoyl] amino) caprylate (SNAC) (7). SNAC exerts multiple actions to enhance absorption, including facilitating the passage of semaglutide across the gastric epithelium via a transcellular mechanism, as well as providing a localized increase in pH to protect semaglutide from proteolytic degradation (8). The pharmacokinetics of oral semaglutide have been established in healthy subjects and subjects with type 2 diabetes and support once-daily dosing (9). Based on the results of the dose-finding phase 2 trial (7), three doses of oral semaglutide (3, 7, and 14 mg) were selected for the phase 3 program. Here, we present the results of the first completed phase 3 trial with oral semaglutide, which assessed the efficacy and safety of oral semaglutide monotherapy in patients with type 2 diabetes managed only with diet and exercise.

RESEARCH DESIGN AND METHODS

The trial protocol was approved by relevant local independent ethics committees and institutional review boards at each site and conducted in accordance with the Declaration of Helsinki and International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) (10,11). All patients provided written, informed consent prior to commencement of trial-related activities.

Trial Design

This was a 26-week, randomized, double-blind, placebo-controlled, parallel-group

trial conducted at 93 sites across nine countries (Algeria, Bulgaria, Czech Republic, Japan, Mexico, Russia, Serbia, Turkey, and the U.S.) from September 2016 to December 2017. The trial was registered with ClinicalTrials.gov (identifier NCT02906930 [trial registered 15 September 2016 and initiated 20 September 2016]). Randomization of patients was stratified by Japanese and non-Japanese patients. Patients and investigators were blinded to treatment through the use of visually identical tablets and packaging for trial products and the use of a trial-specific interactive web/voice system that assigned treatment codes.

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 (12).

The treatment policy estimand evaluates the treatment effect for all randomized patients regardless of trial product discontinuation and use of rescue medication. This estimand reflects the intention-to-treat principle as defined in ICH E9 (R1) (13). The estimand reflects the effect of initiating treatment with oral semaglutide compared with initiating treatment with placebo, both potentially followed by 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 placebo 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 previously been evaluated, and results from such analyses are currently included in many product labels (prescribing information, U.S., and summary of product characteristics [SmPC], European Union) for glucose-lowering drugs (e.g., Ozempic SmPC) (14).

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) (13). Further details on the estimands can be found in Supplementary Appendix 2.

Patient Population

Adult patients with type 2 diabetes were eligible if they had HbA_{1c} in the range of 7.0–9.5% (53–80 mmol/mol) with management only by diet and exercise. Key exclusion criteria included treatment with any antidiabetes medication within 90 days before screening, proliferative retinopathy or maculopathy requiring acute treatment, personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2, estimated glomerular filtration rate <60 mL/min/1.73 m², or a history of pancreatitis. See Supplementary Table 1 for more details on eligibility criteria.

Drug Administration

Patients were randomized 1:1:1:1 to receive 3, 7, or 14 mg oral semaglutide or placebo. All patients randomized to oral semaglutide initiated treatment with 3 mg once daily with dose escalations every 4 weeks until the randomized maintenance dose was achieved. There was a 5-week follow-up period after the 26-week treatment period (Supplementary Fig. 1).

Since food intake can decrease the bioavailability of semaglutide administered in the oral formulation (15), patients were instructed to administer trial product in the morning in a fasting state, with up to half a glass of water (~120 mL or 4 fluid ounces), and wait at least 30 min before the first meal of the day and/or taking other oral medication.

Rescue medication criteria for persistent hyperglycemia were confirmed fasting blood glucose >240 mg/dL (13.3 mmol/L) from weeks 8–13 or >200 mg/dL (11.1 mmol/L) from week 14 onward. Rescue medication was prescribed at the investigator’s discretion according to American Diabetes Association and European Association for the Study of Diabetes guidelines (2) (excluding GLP-1 receptor agonists, dipeptidyl peptidase 4 inhibitors, and amylin analogs). Patients continued in the trial after receiving rescue medication and also if discontinuing trial product and receiving other glucose-lowering medications.

Study End Points and Assessments

The primary end point was change in HbA_{1c} from baseline to week 26. The confirmatory secondary end point was change from baseline to week 26 in body weight. Supportive secondary end points included changes in measures of glucose control (including fasting plasma glucose, C-peptide, insulin, proinsulin, glucagon, self-monitored blood glucose [SMBG] profile, and achievement of an HbA_{1c} target of <7% [53 mmol/mol] or ≤6.5% [48 mmol/mol]) and achievement of weight loss of at least 5% or 10%, as well as C-reactive protein and fasting lipid levels—all from baseline to week 26. Prespecified composite end points included the following: 1) HbA_{1c} <7% (53 mmol/mol) without severe (16) or blood glucose-confirmed (<56 mg/dL [3.1 mmol/L]) symptomatic hypoglycemia and no weight gain, and 2) at least an absolute reduction in HbA_{1c} of 1% (11 mmol/mol) and body weight loss of 3% or more. Blood samples were drawn at baseline and 4, 8, 14, 20, and 26 weeks and analyzed at a central laboratory to assess HbA_{1c} and fasting plasma glucose (all visits) and other efficacy parameters (baseline and week 26 only). Patients were provided with a blood glucose meter to perform a 7-point SMBG profile at baseline and week 26 and to confirm hypoglycemic symptoms.

Safety end points were number of adverse events and number of severe or blood glucose-confirmed symptomatic hypoglycemic episodes until week 31. Other safety measurements included changes in vital signs and laboratory variables. A treatment-blinded independent external adjudication committee (EAC) validated prespecified categories of adverse events (including deaths, cardiovascular events, malignant neoplasms, acute kidney injury, acute pancreatitis, and lactic acidosis).

Statistical Analysis

The primary end point and the confirmatory secondary end point were planned to be tested for superiority of oral semaglutide 3 mg, 7 mg, and 14 mg versus placebo, with a sample size calculation ($n = 704$) to ensure a power of at least 90% to jointly confirm HbA_{1c} superiority of oral semaglutide versus placebo at each dose level.

The confirmation of efficacy of oral semaglutide on change in HbA_{1c} and in

body weight both from baseline to week 26 was based on a weighted Bonferroni closed-testing strategy (17) to control the overall type 1 error for the hypotheses evaluated by the treatment policy estimand (see Supplementary Appendix 3 for details of statistical considerations). The treatment policy was controlled for multiplicity to claim superiority, and all other P values are descriptive.

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 and 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 rules (18).

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

Further details on the statistical analyses can be found in the Supplementary Appendix 3

All analyses were performed using SAS, version 9.4M2.

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 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

Patient Disposition and Baseline Characteristics

A total of 1,006 patients were screened and 703 patients were randomized (Supplementary Fig. 2). All randomized patients were exposed to trial product and included in the full and safety analysis sets. Forty randomized patients did

not complete the trial: 6 (3.4%) with oral semaglutide 3 mg, 14 (8.0%) with oral semaglutide 7 mg, 12 (6.9%) with oral semaglutide 14 mg, and 8 (4.5%) with placebo (Supplementary Fig. 2). Baseline demographics and disease characteristics were similar between treatment groups (Table 1). Approximately 50% of randomized patients were female, and mean age was 55 years, diabetes duration 3.5 years, BMI 31.8 kg/m², and HbA_{1c} 8.0% [64 mmol/mol].

In total, 46 (6.5%) patients received rescue medication, predominantly in the placebo group: 27 (15.2%) with placebo and 13 (7.4%), 4 (2.3%), and 2 (1.1%) with oral semaglutide 3, 7, and 14 mg, respectively (Supplementary Table 2). Additional glucose-lowering medication (rescue medication or the use of glucose-lowering medication for patients discontinuing trial product but remaining in the trial) was received by 16 (9.1%), 8 (4.6%), and 7 (4.0%) with oral semaglutide 3, 7, and 14 mg, respectively, and 35 (19.7%) with placebo (Supplementary Table 2).

Glycemic Control

All three doses of oral semaglutide resulted in clinically meaningful and superior reductions in HbA_{1c} compared with placebo for the treatment policy estimand (regardless of rescue medication use and trial product discontinuation) and statistically significant reductions for the trial product estimand (on treatment without the use of rescue medication) (Fig. 1). Placebo-adjusted estimated treatment differences at week 26 for oral semaglutide 3, 7, and 14 mg, respectively, were as follows ($P < 0.001$ for all): -0.6% (95% CI -0.8 to -0.4) (-6 mmol/mol [95% CI -9 to -4]), -0.9% (-1.1 to -0.6) (-9 mmol/mol [-12 to -7]), and -1.1% (-1.3 to -0.9) (-12 mmol/mol [-15 to -9]) for the treatment policy estimand and -0.7% (-0.9 to -0.5) (-7 mmol/mol [-10 to -5]), -1.2% (-1.5 to -1.0) (-14 mmol/mol [-16 to -11]), and -1.4% (-1.7 to -1.2) (-16 mmol/mol [-18 to -13]) for the trial product estimand.

The observed proportion of patients achieving the HbA_{1c} targets (<7.0% [53 mmol/mol] and ≤6.5% [48 mmol/mol]) were greater with oral semaglutide compared with placebo. The odds of achieving each target were statistically

Table 1—Baseline characteristics and demographics

	Oral semaglutide 3 mg (n = 175)	Oral semaglutide 7 mg (n = 175)	Oral semaglutide 14 mg (n = 175)	Placebo (n = 178)	Total (N = 703)
Men, n (%)	89 (50.9)	93 (53.1)	86 (49.1)	89 (50.0)	357 (50.8)
Age, years	55 ± 11	56 ± 11	54 ± 11	54 ± 11	55 ± 11
Race, n (%)					
White	135 (77.1)	131 (74.9)	130 (74.3)	132 (74.2)	528 (75.1)
Black or African American	6 (3.4)	11 (6.3)	10 (5.7)	10 (5.6)	37 (5.3)
Asian	31 (17.7)	30 (17.1)	29 (16.6)	31 (17.4)	121 (17.2)
Other	3 (1.7)	3 (1.7)	6 (3.4)	5 (2.8)	17 (2.4)
Hispanic or Latino ethnicity, n (%)	52 (29.7)	31 (17.7)	46 (26.3)	51 (28.7)	180 (25.6)
Diabetes duration, years	3.8 ± 5.3	3.6 ± 5.1	3.4 ± 4.4	3.4 ± 4.6	3.5 ± 4.9
Body weight, kg	86.9 ± 21.0	89.0 ± 21.8	88.1 ± 22.1	88.6 ± 23.4	88.1 ± 22.1
BMI, kg/m ²	31.8 ± 6.3	31.6 ± 6.4	31.7 ± 6.6	32.2 ± 6.9	31.8 ± 6.6
HbA _{1c} , %	7.9 ± 0.7	8.0 ± 0.6	8.0 ± 0.7	7.9 ± 0.7	8.0 ± 0.7
HbA _{1c} , mmol/mol	63 ± 8	64 ± 7	64 ± 8	63 ± 7	63 ± 8
Fasting plasma glucose, mg/dL	158 ± 42	162 ± 42	158 ± 39	160 ± 39	160 ± 41
Fasting plasma glucose, mmol/L	8.78 ± 2.35	8.98 ± 2.34	8.77 ± 2.17	8.88 ± 2.16	8.85 ± 2.25
Estimated glomerular filtration rate, mL/min/1.73 m ² *	99 ± 14	95 ± 16	97 ± 16	100 ± 15	98 ± 15

Data are means ± SD unless otherwise indicated. *Glomerular filtration rate was estimated by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula.

significantly greater with oral semaglutide than with placebo ($P < 0.001$ for all doses) (Table 2). Oral semaglutide also reduced fasting plasma glucose significantly more than placebo ($P < 0.001$ for the trial product estimand) (Table 2).

Body Weight

Oral semaglutide (14 mg only) provided superior reductions in body weight compared with placebo when evaluated by the treatment policy estimand. According to the trial product estimand, oral semaglutide (7 and 14 mg) provided statistically significant reductions in body weight compared with placebo (Fig. 1). Placebo-adjusted estimated treatment differences at week 26 for oral semaglutide 3, 7, and 14 mg, respectively, were -0.1 kg (95% CI -0.9 to 0.8) ($P = 0.87$), -0.9 kg (-1.9 to 0.1) ($P = 0.09$), and -2.3 kg (-3.1 to -1.5) ($P < 0.001$) for the treatment policy estimand and -0.2 kg (-1.0 to 0.6) ($P = 0.71$), -1.0 kg (-1.8 to -0.2) ($P = 0.01$), and -2.6 kg (-3.4 to -1.8) ($P < 0.001$) for the trial product estimand. Significantly more patients achieved body weight loss of at least 5% with oral semaglutide at 7 mg and 14 mg compared with placebo (Table 2).

Other Outcomes

The observed proportion of patients who achieved the triple composite end point of HbA_{1c} $< 7\%$ (53 mmol/mol) without

severe or blood glucose–confirmed symptomatic hypoglycemia or weight gain was higher with oral semaglutide (all doses) versus placebo (Table 2). The observed proportion of patients who achieved the composite end point of an HbA_{1c} reduction of 1% (11 mmol/mol) or more and body weight loss of 3% or more was also higher with oral semaglutide versus placebo (trial product estimand; Table 2). Results for fasting lipid levels and various parameters of glucose metabolism are included in Supplementary Table 3.

Safety

Overall, the incidence of adverse events and serious adverse events was similar for oral semaglutide compared with placebo. The most frequent adverse events were nausea and diarrhea (Table 3). Nausea was reported by a low proportion of patients across groups (5.1% to 16%) (Table 3 and Supplementary Fig. 3), and events were generally mild to moderate and transient. The majority of adverse events were mild to moderate in severity (Table 3). More patients prematurely discontinued trial product due to adverse events with oral semaglutide 7 and 14 mg, and these were predominantly gastrointestinal disorders (Table 3 and Supplementary Table 4). No deaths occurred while on trial product (Table 3 and Supplementary Table 5). One patient assigned to the oral semaglutide 14 mg group died due to cardiogenic

shock on trial day 138, 42 days after trial product discontinuation.

The proportion of subjects with at least one severe or blood glucose–confirmed symptomatic hypoglycemic episode event was low (5 [2.9%], 2 [1.1%], and 1 [0.6%] patients with oral semaglutide 3, 7, and 14 mg, respectively, and 1 [0.6%] with placebo) (Table 3), and only one severe hypoglycemic episode (oral semaglutide 7 mg) was reported. Diabetic retinopathy–related adverse events were also infrequent across groups (1 [0.6%], 6 [3.4%], and 2 [1.1%] patients with oral semaglutide 3, 7, and 14 mg, respectively, and 3 [1.7%] with placebo) (Supplementary Table 6).

There were significant increases in mean levels of lipase (13% to 34%) with oral semaglutide compared with placebo (Supplementary Table 7); increases greater than three times the upper limit of normal occurred in 1.7% to 3.4% with oral semaglutide and 1.7% with placebo. There were no instances of EAC-confirmed acute pancreatitis; the prevalence of other EAC-confirmed events is reported in Supplementary Table 7. At week 26, mean pulse rate increased significantly with oral semaglutide 14 mg (3 bpm; $P = 0.003$), but not with 3 or 7 mg, compared with placebo (Supplementary Table 7). There were no clinically relevant changes in blood pressure or other safety laboratory assessments.

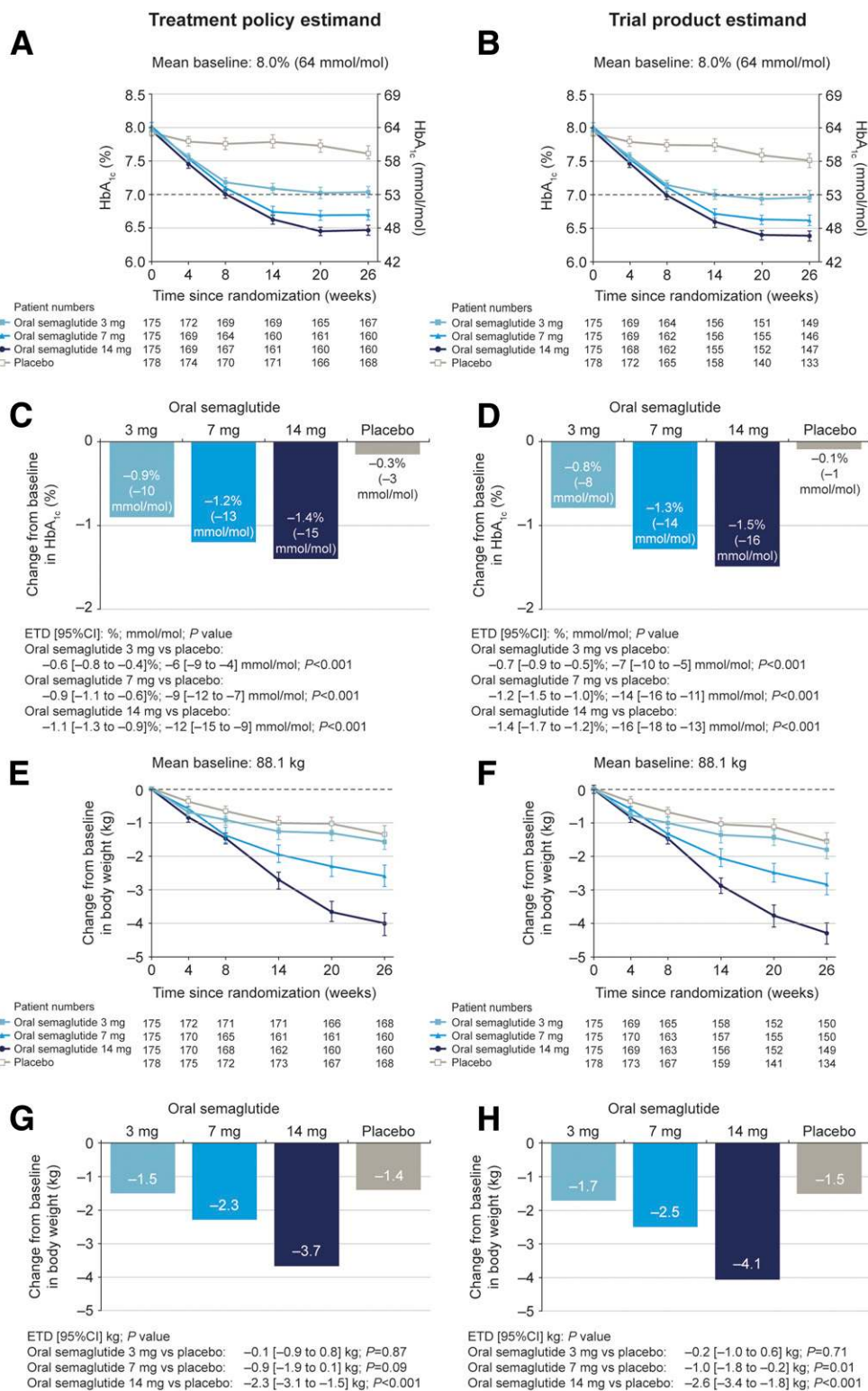


Figure 1—Change in HbA_{1c} (primary end point) and body weight (confirmatory secondary end point) from baseline to 26 weeks. Observed absolute mean values (\pm SEM) for HbA_{1c} by the treatment policy estimand (A) and the trial product estimand (B) and estimated mean change from baseline for HbA_{1c} by the treatment policy estimand (C) and the trial product estimand (D) at week 26. Observed change from baseline in body weight (\pm SEM) for the treatment policy estimand (E) and trial product estimand (F) and mean estimated change from baseline for the treatment policy estimand (G) and the trial product estimand (H). Data in the bar charts also show estimated treatment differences (ETDs) with 95% CIs. Treatment policy estimand (C and G): ANCOVA using data irrespective of discontinuation of trial product and 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 (D and H): MMRM. Data collected after discontinuation of trial product and initiation of rescue medication are excluded.

Table 2—Secondary end points at week 26

	Treatment policy estimand				Trial product estimand			
	Oral semaglutide 3 mg (n = 175)	Oral semaglutide 7 mg (n = 175)	Oral semaglutide 14 mg (n = 175)	Placebo (n = 178)	Oral semaglutide 3 mg (n = 175)	Oral semaglutide 7 mg (n = 175)	Oral semaglutide 14 mg (n = 175)	Placebo (n = 178)
% achieving HbA _{1c} <7% (53 mmol/mol)	55.1	68.8	76.9	31.0	59.1	71.9	80.3	33.8
OR (95% CI) vs. placebo	3.09 (1.91–4.99)	5.79 (3.50–9.59)	8.36 (4.86–14.41)	—	3.37 (2.05–5.55)	8.65 (5.04–14.83)	13.35 (7.49–23.83)	—
P value	<0.001	<0.001	<0.001	—	<0.001	<0.001	<0.001	—
% achieving HbA _{1c} ≤6.5% (48 mmol/mol)	35.9	47.5	63.8	17.9	38.9	50.0	68.0	21.1
OR (95% CI) vs. placebo	2.83 (1.66–4.83)	5.10 (2.97–8.76)	9.06 (5.20–15.78)	—	2.86 (1.65–4.96)	6.30 (3.60–11.02)	12.06 (6.75–21.55)	—
P value	<0.001	<0.001	<0.001	—	<0.001	<0.001	<0.001	—
% achieving body weight loss ≥5%	19.6	26.9	41.3	14.9	21.3	28.7	44.3	15.7
OR (95% CI) vs. placebo	1.30 (0.73–2.33)	2.05 (1.16–3.63)	3.74 (2.18–6.41)	—	1.27 (0.70–2.31)	1.92 (1.08–3.42)	4.17 (2.38–7.29)	—
P value	0.37	0.01	<0.001	—	0.43	0.03	<0.001	—
% achieving composite: HbA _{1c} <7% (53 mmol/mol) without hypoglycemia* and no weight gain	37.1	56.9	68.8	23.2	41.6	59.6	72.8	27.1
OR (95% CI) vs. placebo	1.98 (1.21–3.24)	4.49 (2.74–7.36)	7.13 (4.28–11.89)	—	2.20 (1.33–3.64)	5.29 (3.17–8.83)	10.08 (5.87–17.32)	—
P value	0.007	<0.001	<0.001	—	0.002	<0.001	<0.001	—
% achieving composite: HbA _{1c} reduction ≥1% (11 mmol/mol) and body weight loss ≥3%	18.0	36.9	50.6	10.7	20.1	39.0	54.4	11.3
OR (95% CI) vs. placebo	1.71 (0.90–3.26)	4.51 (2.47–8.22)	7.96 (4.40–14.42)	—	2.11 (1.07–4.13)	5.90 (3.12–11.17)	11.66 (6.15–22.11)	—
P value	0.10	<0.001	<0.001	—	0.03	<0.001	<0.001	—
Fasting plasma glucose, mg/dL								
Estimated mean	143.4	131.7	126.7	156.3	147.0	132.6	122.8	163.5
Mean change from baseline	–16.2	–27.9	–32.9	–3.2	–12.5	–27.0	–36.7	4.0
Estimated treatment difference vs. placebo (95% CI)	–12.9 (–21.4 to –4.5)	–24.6 (–35.1 to –14.2)	–29.6 (–38.3 to –21.0)	—	–16.5 (–24.2 to –8.8)	–30.9 (–38.7 to –23.2)	–40.7 (–48.5 to –33.0)	—
P value	0.003	<0.001	<0.001	—	<0.001	<0.001	<0.001	—
7-point SMBG mean, mg/dL								
Estimated mean	153.2	147.8	143.2	175.9	148.8	141.9	138.4	174.5
Mean change from baseline	–30.1	–35.5	–40.1	–7.5	–30.9	–37.8	–41.3	–5.2
Estimated treatment difference vs. placebo (95% CI)	–22.7 (–31.0 to –14.4)	–28.1 (–37.4 to –18.7)	–32.6 (–41.8 to –23.5)	—	–25.7 (–33.5 to –17.9)	–32.6 (–40.4 to –24.8)	–36.1 (–43.9 to –28.3)	—
P value	<0.001	<0.001	<0.001	—	<0.001	<0.001	<0.001	—

SI conversion factor: to convert glucose from mg/dL to mmol/L, multiply by 0.055494. The mean ± SD for the 7-point SMBG at baseline was 183.3 ± 42.2 mg/dL. Treatment policy estimand: ANCOVA for continuous end points and logistic regression for binary end points, using data irrespective of discontinuation of trial product and 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: MMRM for continuous end points and logistic regression for binary end points. Data collected after discontinuation of trial product and initiation of rescue medication were excluded. For binary end points, missing values were imputed from subjects randomized to the same trial product using sequential multiple imputation. P values less than 0.001 are reported as P < 0.001. P values between 0.001 and 0.01 are reported to the nearest thousandth, and P values greater than or equal to 0.01 are reported to the nearest hundredth. % achieving, proportion of patients achieving; OR, odds ratio. *Severe or blood glucose-confirmed (<56 mg/dL) symptomatic hypoglycemic episode.

Table 3—On-treatment adverse events

	Oral semaglutide 3 mg (<i>n</i> = 175)	Oral semaglutide 7 mg (<i>n</i> = 175)	Oral semaglutide 14 mg (<i>n</i> = 175)	Placebo (<i>n</i> = 178)
Any adverse event	101 (57.7)	93 (53.1)	99 (56.6)	99 (55.6)
Severity				
Severe	8 (4.6)	1 (0.6)	3 (1.7)	5 (2.8)
Moderate	40 (22.9)	29 (16.6)	34 (19.4)	47 (26.4)
Mild	89 (50.9)	84 (48.0)	81 (46.3)	81 (45.5)
Severe or blood glucose–confirmed symptomatic hypoglycemic episode*†‡	5 (2.9)	2 (1.1)	1 (0.6)	1 (0.6)
Severe hypoglycemic episodes*†	0	1 (0.6)	0	0
Most frequent adverse events >5% in any group (preferred term)				
Nausea	14 (8.0)	9 (5.1)	28 (16.0)	10 (5.6)
Diarrhea	15 (8.6)	9 (5.1)	9 (5.1)	4 (2.2)
Vomiting	5 (2.9)	8 (4.6)	12 (6.9)	4 (2.2)
Nasopharyngitis	10 (5.7)	11 (6.3)	3 (1.7)	6 (3.4)
Influenza	9 (5.1)	5 (2.9)	4 (2.3)	2 (1.1)
Headache	6 (3.4)	10 (5.7)	9 (5.1)	9 (5.1)
Decreased appetite	2 (1.1)	3 (1.7)	9 (5.1)	1 (0.6)
Serious adverse events	5 (2.9)	3 (1.7)	2 (1.1)	8 (4.5)
Adverse events leading to premature trial product discontinuation	4 (2.3)	7 (4.0)	13 (7.4)	4 (2.2)
Adverse events leading to premature trial product discontinuation (>3% in any system organ class)§				
Gastrointestinal disorders	3 (1.7)	4 (2.3)	9 (5.1)	1 (0.6)
Deaths	0	0	0	0

Data are *n* (%). SI conversion factor: to convert glucose to mmol/L, multiply by 0.055494. "On-treatment": the period when the patient is considered treated with trial product. *Hypoglycemic episodes were reported on a form separate from that used for adverse events. †Severe hypoglycemia was defined according to the American Diabetes Association classification (16) (requiring assistance of another person to actively administer carbohydrate or glucagon or take other corrective actions). ‡There was one case of severe nocturnal hypoglycemia, which occurred in a patient in the oral semaglutide 7 mg group. ‡Blood glucose confirmation of symptomatic hypoglycemia was based on a blood glucose value <56 mg/dL with symptoms consistent with hypoglycemia. §There were no more than *n* = 3 (1.7%) adverse events leading to premature trial product discontinuation by any one preferred term in any treatment group. ||One patient died (cardiogenic shock with onset 42 days after discontinuing treatment due to other adverse events [decreased appetite and weight loss]).

CONCLUSIONS

Oral semaglutide represents the first oral GLP-1 receptor agonist to be studied in phase 3 clinical trials for the treatment of type 2 diabetes. In the Peptide Innovation for Early Diabetes Treatment 1 (PIONEER 1) trial, the superiority of all three doses of oral semaglutide given once daily for 26 weeks in reducing HbA_{1c} was confirmed versus placebo. The highest dose of oral semaglutide studied (14 mg daily) resulted in a mean reduction of 1.5%, from a baseline HbA_{1c} of 8.0% (64 mmol/mol) to a final HbA_{1c} of 6.5% (47 mmol/mol), and a body weight reduction of 4.1 kg, with 80% of patients achieving an HbA_{1c} target of <7% (53 mmol/mol) (trial product estimand). These data are comparable with those observed with subcutaneous semaglutide in a similar population in the SUSTAIN 1 trial (19). Similar to the phase 2 trial of oral semaglutide (7), dose-dependent weight loss was observed, with a statistically significant effect of

oral semaglutide on body weight versus placebo seen at higher doses (trial product estimand). The findings from the current study are also consistent with the dose-dependent reductions from baseline in HbA_{1c} and body weight observed in the PIONEER 3 trial, which compared oral semaglutide with sitagliptin in adult patients with type 2 diabetes for up to 78 weeks (20). Notably, the patients included in PIONEER 3 had more advanced diabetes than those in PIONEER 1—diabetes was of longer duration at baseline (8.6 vs. 3.5 years, respectively) and uncontrolled with metformin alone or with sulfonylurea at trial entry (20).

The safety profile of oral semaglutide was generally consistent with that reported for subcutaneous semaglutide (19) and the GLP-1 receptor agonist class (21–25). As expected, the most frequent adverse events were gastrointestinal, in particular mild-to-moderate nausea. As fewer nausea events were observed with initiation of oral semaglutide at lower

doses in the phase 2 study (7), a dose escalation was used in the present trial to help mitigate adverse gastrointestinal effects. Consequently, the proportion of patients reporting gastrointestinal events and the number of trial product discontinuations due to adverse events were both low. Similarly, and consistent with the GLP-1 receptor agonist class, PIONEER 3 also identified gastrointestinal adverse events, including transient nausea, as the most common adverse events reported by patients using oral semaglutide (20).

The present trial has several considerations that may influence the interpretation and generalizability of the data. Our trial enrolled patients whose diabetes was being managed only with diet and exercise at trial entry, and the mean duration of diabetes was only 3.5 years. Also, oral semaglutide was given as first-line monotherapy, while metformin is usually recommended as first-line pharmacotherapy in the management of type 2 diabetes (1,2). However, the study

of oral semaglutide as monotherapy, as required by regulatory agencies, allows a clearer clinical interpretation of its efficacy and safety. Longer-duration trials are needed to determine the durability of the effect of oral semaglutide; such trials are part of the PIONEER program and include testing versus active comparators and also examining the efficacy and safety of oral semaglutide in combination with other glucose-lowering medications, including metformin. At present, the efficacy and safety of oral semaglutide compared with sitagliptin have been reported in patients with type 2 diabetes uncontrolled with metformin, alone or with sulfonylureas, in the PIONEER 3 trial, which demonstrated significantly greater HbA_{1c} reductions for the oral semaglutide 7 and 14 mg once-daily doses compared with sitagliptin (20).

The design of the present trial included estimands, as recommended by recent regulatory guidelines (13), to address different scientific questions of interest and to prespecify how intercurrent events and missing data were to be handled. The treatment policy estimand, which evaluates effect regardless of adherence to randomized treatment, may be relevant for understanding overall population-level effects, accounting for treatment effect, risks, adherence, and the addition of “rescue” medication. This is complemented by the trial product estimand, which here estimates treatment effect for those who remain on treatment without rescue medication, to support clinical decision-making by describing the anticipated treatment effect. A numerically greater HbA_{1c} reduction was observed with placebo for the treatment policy estimand compared with the trial product estimand, which is likely due to the inclusion of patients receiving rescue medication. However, in general, efficacy results were broadly consistent whether based on the treatment policy or trial product estimand, likely reflective of a high proportion of patients completing the trial with the vast majority completing on treatment (12).

Conclusion

PIONEER 1 demonstrates the efficacy and safety of the novel oral GLP-1 receptor agonist, semaglutide, in patients with type 2 diabetes. Oral semaglutide achieved clinically meaningful and superior glucose lowering (all dose levels) and

weight loss (14 mg dose) when used as monotherapy in patients with type 2 diabetes. Treatment with oral semaglutide was well tolerated, with a safety and tolerability profile consistent with the GLP-1 receptor agonist class. Ongoing additional studies in the PIONEER program will further define its effect when used in combination with other glucose-lowering therapies and in other populations (e.g., in those with high cardiovascular risk or renal impairment) of interest.

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References

- American Diabetes Association. 8. Pharmacologic approaches to glycemic treatment: *Standards of Medical Care in Diabetes—2018*. *Diabetes Care* 2018;41(Suppl. 1):S73–S85
- Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of hyperglycaemia in type 2 diabetes, 2015: a patient-centred approach. Update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetologia* 2015;58:429–442
- U.S. Food and Drug Administration. Ozempic—Highlights of prescribing information [Internet], 2017. Available from https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/209637bl.pdf. Accessed 14 November 2018
- Marso SP, Bain SC, Consoli A, et al.; SUSTAIN-6 Investigators. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med* 2016;375:1834–1844
- Graaf Cd, Donnelly D, Wootten D, et al. Glucagon-like peptide-1 and its class B G protein-coupled receptors: a long march to therapeutic successes. *Pharmacol Rev* 2016;68:954–1013
- Mahato RI, Narang AS, Thoma L, Miller DD. Emerging trends in oral delivery of peptide and protein drugs. *Crit Rev Ther Drug Carrier Syst* 2003;20:153–214
- Davies M, Pieber TR, Hartoft-Nielsen ML, Hansen OKH, Jabbour S, Rosenstock J. Effect of oral semaglutide compared with placebo and subcutaneous semaglutide on glycemic control in patients with type 2 diabetes: a randomized clinical trial. *JAMA* 2017;318:1460–1470
- Buckley ST, Bækdal TA, Vegge A, et al. Transcellular stomach absorption of a derivatized glucagon-like peptide-1 receptor agonist. *Sci Transl Med* 2018;10:ear7047

9. Granhall C, Donsmark M, Blicher TM, et al. Safety and pharmacokinetics of single and multiple ascending doses of the novel oral human GLP-1 analogue, oral semaglutide, in healthy subjects and subjects with type 2 diabetes. *Clin Pharmacokinet* 2019;58:781–794
10. World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. *JAMA* 2013;310:2191–2194
11. International Conference on Harmonisation. ICH Harmonised Tripartite Guideline. Guideline for Good Clinical Practice E6(R1), Step 4 [Internet], 1996. Available from https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R1_Guideline.pdf. Accessed 14 November 2018
12. Aroda VA, Saugstrup T, Buse JB, Donsmark M, Zacho J, Davies MJ. Incorporating and interpreting regulatory guidance on estimands in diabetes clinical trials: The PIONEER 1 randomized clinical trial as an example. *Diabetes Obes Metab*. 5 June 2019 [Epub ahead of print]. DOI:10.1111/dom.13804
13. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. Estimands and sensitivity analysis in clinical trials E9 (R1) [Internet], 2017. Available from http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E9/E9-R1EWG_Step2_Guideline_2017_0616.pdf. Accessed 14 November 2018
14. European Medicines Agency. Ozempic: Summary of Product Characteristics [Internet], 2018. Available from https://www.ema.europa.eu/documents/product-information/ozempic-epar-product-information_en.pdf. Accessed 14 November 2018
15. Bækdal TA, Borregaard J, Donsmark M, Breitschaft A, Søndergaard FL. Evaluation of the effects of water volume with dosing and post-dose fasting period on pharmacokinetics of oral semaglutide (Abstract) *Diabetes* 2017;66 (Suppl. 1):1179-P
16. Seaquist ER, Anderson J, Childs B, et al. Hypoglycemia and diabetes: a report of a workgroup of the American Diabetes Association and the Endocrine Society. *Diabetes Care* 2013;36:1384–1395
17. Bretz F, Posch M, Glimm E, Klinglmueller F, Maurer W, Rohmeyer K. Graphical approaches for multiple comparison procedures using weighted Bonferroni, Simes, or parametric tests. *Biom J* 2011;53:894–913
18. Little RJA, Rubin DB. *Statistical Analysis With Missing Data*. New York, NY, John Wiley and Sons, 1987
19. Sorli C, Harashima SI, Tsoukas GM, et al. Efficacy and safety of once-weekly semaglutide monotherapy versus placebo in patients with type 2 diabetes (SUSTAIN 1): a double-blind, randomised, placebo-controlled, parallel-group, multinational, multicentre phase 3a trial. *Lancet Diabetes Endocrinol* 2017;5:251–260
20. Rosenstock J, Allison D, Birkenfeld AL, et al.; PIONEER 3 Investigators. Effect of additional oral semaglutide vs sitagliptin on glycated hemoglobin in adults with type 2 diabetes uncontrolled with metformin alone or with sulfonylurea: the PIONEER 3 randomized clinical trial. *JAMA* 2019;321:1466–1480
21. Steinberg WM, Buse JB, Ghorbani MLM, Ørsted DD, Nauck MA; LEADER Steering Committee; LEADER Trial Investigators. Amylase, lipase, and acute pancreatitis in people with type 2 diabetes treated with liraglutide: results from the LEADER randomized trial. *Diabetes Care* 2017;40:966–972
22. Nauck MA, Frossard JL, Barkin JS, et al. Assessment of pancreas safety in the development program of once-weekly GLP-1 receptor agonist dulaglutide. *Diabetes Care* 2017;40:647–654
23. Lando HM, Alattar M, Dua AP. Elevated amylase and lipase levels in patients using glucagonlike peptide-1 receptor agonists or dipeptidyl-peptidase-4 inhibitors in the outpatient setting. *Endocr Pract* 2012;18:472–477
24. Chen YH, Huang CN, Cho YM, et al. Efficacy and safety of dulaglutide monotherapy compared with glimepiride in East-Asian patients with type 2 diabetes in a multicentre, double-blind, randomized, parallel-arm, active comparator, phase III trial. *Diabetes Obes Metab* 2018; 20:2121–2130
25. Htike ZZ, Zaccardi F, Papamargaritis D, Webb DR, Khunti K, Davies MJ. Efficacy and safety of glucagon-like peptide-1 receptor agonists in type 2 diabetes: a systematic review and mixed-treatment comparison analysis. *Diabetes Obes Metab* 2017;19:524–536