Efficacy, Safety, and Tolerability of Oral Semaglutide Versus Placebo Added to Insulin With or Without Metformin in Patients With Type 2 Diabetes: The PIONEER 8 Trial

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https://doi.org/10.2337/dc19-0898

OBJECTIVE

To investigate the efficacy, safety, and tolerability of oral semaglutide added to insulin with or without metformin.

RESEARCH DESIGN AND METHODS

Patients with type 2 diabetes uncontrolled on insulin with or without metformin were randomized to oral semaglutide 3 mg ($N = 184$), 7 mg ($N = 182$), or 14 mg ($N = 181$) or to placebo ($N = 184$) in a 52-week, double-blind trial. End points were change from baseline to week 26 in HbA_{1c} (primary) and body weight (confirmatory secondary). Two estimands were defined: treatment policy (effect regardless of trial product discontinuation or rescue medication) and trial product (effect assuming trial product continuation without rescue medication) in randomized patients.

RESULTS

Oral semaglutide was superior to placebo in reducing HbA_{1c} (estimated treatment difference [ETD] −0.5% [95% CI −0.7, −0.3%], −0.9% [−1.1, −0.7%], −1.2% [−1.4, −1.0%] for 3, 7, and 14 mg, respectively; $P < 0.001$) and body weight (ETD −0.9 kg [95% CI −1.8, −0.0 kg], −2.0 kg [−3.0, −1.0 kg], −3.3 kg [−4.2, 2.3 kg]; $P = 0.0392$ for 3 mg, $P \leq 0.0001$ for 7 and 14 mg) at week 26 (treatment policy estimand). Significantly greater dose-dependent HbA_{1c} and body weight reductions versus placebo were achieved with oral semaglutide at weeks 26 and 52 (both estimands). The most frequent adverse event with oral semaglutide was nausea (11.4–23.2% of patients vs. 7.1% with placebo; mostly mild to moderate).

CONCLUSIONS

Oral semaglutide was superior to placebo in reducing HbA_{1c} and body weight when added to insulin with or without metformin in patients with type 2 diabetes. The safety profile was consistent with other glucagon-like peptide 1 receptor agonists.

Glucagon-like peptide 1 receptor agonists (GLP-1RAs) reduce HbA_{1c} with a low risk of hypoglycemia and favorable effects on body weight (1,2). Furthermore, some GLP-1RAs provide cardiovascular benefits and are recommended by diabetes and cardiology guidelines for patients with concomitant cardiovascular disease (3,4). Combined with insulin, GLP-1RAs reduce HbA_{1c} and body weight from baseline without increasing hypoglycemia (5–9). Semaglutide is a GLP-1RA, and its

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Received 3 May 2019 and accepted 10 September 2019

Clinical trial reg. no. NCT03021187, clinicaltrials.gov

This article contains Supplementary Data online at http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc19-0898/-/DC1.

subcutaneous, once-weekly formulation improved glycemic control and reduced body weight from baseline when used alongside basal insulin in patients with type 2 diabetes (6).

An oral formulation of semaglutide has been developed and is the first oral GLP-1RA to enter phase 3 trials. As peptides have low oral bioavailability, oral semaglutide is coformulated with the absorption enhancer sodium N-(8-[2-hydroxybenzoyl] amino) caprylate, which facilitates semaglutide absorption across the gastric mucosa (10).

This article reports the findings of the Peptide Innovation for Early Diabetes Treatment 8 (PIONEER 8) trial, which investigated the efficacy, safety, and tolerability of oral semaglutide added onto insulin (basal, basal-bolus, or premixed) with or without metformin in patients with uncontrolled type 2 diabetes.

RESEARCH DESIGN AND METHODS

Trial Design

This randomized, double-blind, placebo-controlled, parallel-group trial was conducted at 111 sites in nine countries (Supplementary Appendix 1) between 2 February 2017 and 18 January 2018 (NCT03021187). There was a 2-week screening period, 52-week treatment period, and 5-week follow-up period (Supplementary Fig. 1*A*).

Patients were randomized 1:1:1:1 to once-daily oral semaglutide 3, 7, or 14 mg or placebo using an interactive web response system (Supplementary Appendix 2). Randomization was stratified by patients' country of origin (Japanese or non-Japanese) and background treatment (metformin or no metformin; basal, basal-bolus, or premixed insulin).

A 20% reduction in total daily insulin dosage was recommended at randomization and maintained to week 8 (Supplementary Fig. 1*B*) unless an increase was required to prevent acute metabolic deterioration. The treatment period was then split into two stages defined by restrictions in total daily insulin dosage. It could be altered during weeks 8–26, without exceeding the prerandomization dosage, and was freely adjustable at the investigator's discretion during weeks 26–52. Throughout the trial, the total daily insulin dosage could be reduced as needed. It was recommended that adjustments were made based on the lowest of three self-measured blood glucose (SMBG) values, preferably measured on 3 consecutive days prior to each phone contact/site visit, with the aim of obtaining a fasting plasma glucose (FPG) concentration of 4.0–5.5 mmol/L (71–99 mg/dL) and HbA_{1c} $<7.0\%$ (53 mmol/mol) (Supplementary Appendix 3). In brief, dosage was increased in increments of 2 units based on FPG values, starting at 2 units for 5.6–7.0 mmol/L (100–126 mg/dL) up to 8 units if >9.0 mmol/L (>162 mg/dL). For patients on basal-bolus insulin taken more than once daily, it was recommended to titrate each dose separately. For patients on basal-bolus insulin, recommendations were provided only for the basal component.

The trial protocol was approved by the institutional review board/independent ethics committee at each site, and the trial was conducted in accordance with International Council on Harmonization (ICH) Good Clinical Practice guidelines and the Declaration of Helsinki. All patients provided written informed consent.

Two different scientific questions related to the efficacy objectives were addressed through the definition of two estimands: the treatment policy estimand and the trial product estimand. Both estimands were defined based on interactions with regulatory agencies (11).

The treatment policy estimand addressed the question of 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 ICH E9 (12). This estimand reflects the effect of initiating treatment with oral semaglutide compared with initiating treatment with placebo, both potentially followed by either discontinuation of trial product and/or addition of, or switch to, another glucose-lowering drug.

The trial product estimand addressed the question of 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 that used in the majority of previously published phase 3a diabetes trials (13).

Trial product discontinuation and initiation of rescue medication were accounted for by the treatment policy strategy for the treatment policy estimand and by the hypothetical strategy for the trial product estimand as defined in draft ICH E9 (R1) (14). Further details are provided in Supplementary Appendix 4.

Patient Population

Adult patients with type 2 diabetes diagnosed $\geq$90 days before screening with baseline HbA_{1c} 7.0–9.5% (53–80 mmol/mol) were enrolled. Patients were required to be on a stable regimen of basal, basal-bolus (in any combination), or premixed insulin (including combinations of soluble insulin) at $\geq$10 units/day for $\geq$90 days before screening. If used, concomitant metformin was required to be at a stable dosage ($\geq$1,500 mg daily or the maximum tolerated dosage) for $\geq$90 days before screening. Aside from metformin, the insulin regimens described above, or short-term ($\leq$14 days) changes in insulin dosage for acute illness, use of any other glucose-lowering medication was not allowed in the 90 days before screening. Full eligibility criteria are provided in Supplementary Table 1.

Drug Administration

As the presence of food or liquid in the stomach impairs absorption of oral semaglutide (10), patients were instructed to administer trial product in the morning in a fasting state with $\leq$120 mL ($\leq$4 fl oz) water, then to wait at least 30 min before the first meal of the day or taking other oral medication. Tablets were not to be broken or chewed. These instructions were to ensure sufficient absorption of oral semaglutide. Patients randomized to oral semaglutide 3 mg were initiated and remained on the 3-mg dose. Those randomized to 7 and 14 mg began treatment at 3 mg, and the dose was escalated to 7 mg after 4 weeks and to 14 mg after a further 4 weeks until the randomized dose was achieved. Patients and investigators were blinded to all dose escalation steps.

Glucose-lowering rescue medication (either new glucose-lowering medication or intensification of existing medication) was available to patients taking trial product who had persistent or unacceptable hyperglycemia based on predefined FPG and HbA_{1c} rescue criteria

(two measures of FPG >11.1 mmol/L [>200 mg/dL] from week 16 onward and/or HbA_{1c} >8.5% [>69.4 mmol/mol] from week 26 onward). Intensification was defined as a >20% increase in the dose of existing medication from baseline, maintained for either two or more visits (for insulin) or ≥21 days (for other medications). Upon trial product discontinuation (either prematurely or at the end of the treatment period at week 52), patients had their total daily insulin dosage adjusted and/or switched to a suitable marketed product at the investigators' discretion. The use of GLP-1RAs was prohibited until after the follow-up visit, 5 weeks after the last dose of trial product. Patients continued in the trial after receiving rescue medication or prematurely discontinuing trial product.

Study End Points and Assessments

The primary end point was change in HbA_{1c}, and the confirmatory secondary end point was change in body weight, both from baseline to week 26.

Supportive secondary end points, assessed at weeks 26 and 52, were: changes from baseline in HbA_{1c} (week 52 only), body weight (week 52 only), total daily insulin dosage, FPG, SMBG 7-point profile (mean and mean postprandial increment), BMI, waist circumference, and fasting lipid profile; whether patients achieved HbA_{1c} <7.0% (53 mmol/mol) and ≤6.5% (48 mmol/mol), body weight loss ≥5% and ≥10%, and composites of HbA_{1c} <7.0% (53 mmol/mol) without hypoglycemia (treatment-emergent severe [defined according to the American Diabetes Association (ADA) classification] or blood glucose–confirmed [<3.1 mmol/L (56 mg/dL)]) symptomatic hypoglycemia and without body weight gain, and HbA_{1c} reduction ≥1.0% (10.9 mmol/mol) and body weight loss ≥3%. Changes from baseline to weeks 26 and 52 in the following patient-reported outcomes were also assessed: Short Form 36v2 Health Survey (Acute Version), Impact of Weight on Quality of Life-Lite Clinical Trial Version, and the Diabetes Treatment Satisfaction Questionnaires.

Safety end points included the number of treatment-emergent adverse events (AEs) during exposure to trial product, the number of severe or blood glucose–confirmed symptomatic hypoglycemic episodes (as defined above for the composite end point) and whether a patient experienced such episodes, and changes from baseline in laboratory assessments and vital signs.

Statistical Analysis

A sample size of 180 patients per treatment arm was calculated to provide 90% power to jointly confirm HbA_{1c} superiority of oral semaglutide over placebo at all dose levels at week 26.

Efficacy analyses were based on all randomized patients. The confirmation of efficacy of oral semaglutide on change in HbA_{1c} and body weight, both from baseline to week 26, was based on a weighted Bonferroni closed-testing strategy (15) (outlined in Supplementary Appendix 5) to control the overall type I error for the hypotheses evaluated by the treatment policy estimand.

The treatment policy estimand was estimated by a pattern mixture model using multiple imputation to handle missing week 26 data for both confirmatory end points. Data collected at week 26 from all randomized patients 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 (16).

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

Safety end points were assessed using the safety analysis set (all randomized patients exposed to one or more doses of trial product) and evaluated both on treatment (i.e., while receiving trial product regardless of rescue medication use) and in trial (i.e., while in the trial regardless of trial product discontinuation or rescue medication use).

All statistical analyses were performed using SAS version 9.4M2. Further details can be found in Supplementary Appendix 5.

RESULTS

Patients

Of the 1,038 patients screened, 731 were randomized (oral semaglutide 3 mg, $N = 184$; 7 mg, $N = 182$; 14 mg, $N = 181$; placebo, $N = 184$) and included in the efficacy analyses (Supplementary Fig. 2). All patients, except one (oral semaglutide 7 mg), were exposed to trial product and included in the safety analysis set.

Demographics and baseline disease characteristics are presented in Supplementary Table 2. Overall, 395 (54.0%) patients were male, 376 (51.4%) were white, 263 (36.0%) were Asian, and 49 (6.7%) were black or African American. Mean age was 61 years, mean HbA_{1c} was 8.2% (66 mmol/mol), mean body weight was 85.9 kg, and mean diabetes duration was 15.0 years.

Overall, 697 (95.3%) patients completed the trial, and trial product was discontinued prematurely by 24 (13.0%), 34 (18.7%), 37 (20.4%), and 22 (12.0%) patients for oral semaglutide 3, 7, and 14 mg and placebo, respectively. By week 26, 5 (2.7%), 2 (1.1%), 4 (2.2%), and 9 (4.9%) patients and by week 52, 54 (29.3%), 33 (18.1%), 31 (17.1%), and 67 (36.4%) patients had initiated rescue medication for oral semaglutide 3, 7, and 14 mg and placebo, respectively (Supplementary Table 3). The increased use of rescue medication from week 26 to 52 (in most cases, a >20% increase in total daily insulin dosage) reflects that insulin was freely adjustable during weeks 26–52 to reach an HbA_{1c} <7.0%.

Background metformin was used by 491 (67.2%) patients. The total number of patients on each insulin regimen at screening was 306 (41.9%), 284 (38.9%), and 129 (17.6%) for basal, basal-bolus, and premixed, respectively (Supplementary Table 2). Twelve patients were recorded to be on insulin regimens not defined in the protocol: Five were on regimens considered equivalent to those in the protocol and continued in the trial, and seven were randomized in error. Of these seven patients, one was never exposed to trial product, and treatment was discontinued for the remaining six upon discovery. For clinical reporting, these patients were assigned to the insulin regimen as originally assessed by the investigator.

At baseline, the overall mean (SD) total daily insulin dosage was 58 units (57 units). The mean total daily insulin dosage at baseline was slightly greater in the oral semaglutide 3- and 7-mg arms than in the 14-mg and placebo arms (61 and 63 units vs. 53 and 55 units, respectively) (Supplementary Table 2). A 20% reduction in total daily insulin dosage was recommended when initiating trial product. The

majority of patients (75.3% [$n = 546$]) had their insulin dosage reduced by 15–25%. For the remaining patients, the total daily insulin dosage was reduced by <15% for 8.4% ($n = 61$), by >25% for 3.4% ($n = 25$), and was unchanged for 12.4% ($n = 90$). There was no clear association between HbA_{1c} at screening and initial insulin dosage reduction.

Glycemic Control

For the treatment policy estimand, the estimated mean changes from baseline in HbA_{1c} at week 26 were –0.6% (–6 mmol/mol), –0.9% (–10 mmol/mol), –1.3% (–14 mmol/mol), and –0.1% (–1 mmol/mol) for oral semaglutide 3, 7, and 14 mg and placebo, respectively. Compared with placebo, HbA_{1c} reductions were superior for all doses of oral semaglutide, with estimated treatment differences (ETD) (95% CI) of –0.5% (–0.7, –0.3%) (–5 mmol/mol [–8, –3 mmol/mol]; $P < 0.0001$), –0.9% (–1.1, –0.7%) (–10 mmol/mol [–12, –7 mmol/mol]; $P < 0.0001$), and –1.2% (–1.4, –1.0%) (–13 mmol/mol [–15, –11 mmol/mol]; $P < 0.0001$) for the 3-, 7-, and 14-mg doses, respectively (Fig. 1). Sensitivity analyses were consistent with these findings (Supplementary Table 4 and Supplementary Fig. 3). In addition, there were statistically significantly greater HbA_{1c} reductions from baseline for all oral semaglutide doses versus placebo at week 26 for the trial product estimand and at week 52 for both estimands (Fig. 1). Furthermore, the observed proportions of patients achieving HbA_{1c} <7.0% (53 mmol/mol) and ≤6.5% (48 mmol/mol) were greater with oral semaglutide compared with placebo. The odds of achieving these targets were statistically significantly greater with oral semaglutide than with placebo (both estimands) (Table 1 and Supplementary Table 5).

At week 26, the total daily insulin dosage was reduced from baseline in all treatment arms (Fig. 1). By week 52, total daily insulin was reduced from baseline with oral semaglutide 7 and 14 mg and increased with oral semaglutide 3 mg and placebo. These changes from baseline were statistically significantly different with oral semaglutide versus placebo at week 26 and 52, except for the 3-mg dose at week 26 for the treatment policy estimand. As previously mentioned, many patients (mainly those on oral semaglutide 3 mg and placebo) increased their total daily insulin dosage from baseline by >20% during the freely adjustable insulin treatment period (weeks 26–52) (Supplementary Table 3). As this was considered rescue medication, this affected the results for this end point for the trial product estimand, where only data prior to initiation of rescue medication were used when estimating the results (Fig. 1).

Changes from baseline in FPG (Fig. 1) and 7-point SMBG means (Table 1) were statistically significantly greater with oral semaglutide than placebo at weeks 26 (except for FPG with 3 mg for the treatment policy estimand) and 52 for both estimands.

Body Weight

For the treatment policy estimand, the estimated mean body weight changes from baseline at week 26 were –1.4, –2.4, –3.7, and –0.4 kg for oral semaglutide 3, 7, and 14 mg and placebo, respectively. Compared with placebo, these body weight reductions were superior for all doses of oral semaglutide, with an ETD (95% CI) of –0.9 kg (–1.8, –0.0 kg; $P = 0.0392$), –2.0 kg (–3.0, –1.0 kg; $P = 0.0001$), and –3.3 kg (–4.2, –2.3 kg; $P < 0.0001$) for the 3-, 7-, and 14-mg doses, respectively (Fig. 2). Sensitivity analyses were consistent with these findings (Supplementary Table 4 and Supplementary Fig. 3). There were statistically significantly greater reductions in body weight from baseline with all oral semaglutide doses compared with placebo for the trial product estimand at week 26 and for both estimands at week 52 (Fig. 2 and Supplementary Table 5). Furthermore, the observed proportions of patients achieving body weight loss ≥5% were greater with oral semaglutide than with placebo. The odds of achieving this outcome were statistically significantly greater with oral semaglutide than with placebo (both estimands) (Fig. 2).

All oral semaglutide doses reduced BMI statistically significantly versus placebo at weeks 26 and 52 (both estimands) (Supplementary Table 5). Results for other body weight–related end points are presented in Supplementary Table 5.

Other Outcomes

The observed proportions of patients achieving HbA_{1c} <7.0% (53 mmol/mol) without hypoglycemia and without body weight gain were greater, and the odds of achieving the outcome statistically significantly greater, with oral semaglutide compared with placebo (both estimands) (Table 1). Oral semaglutide treatment tended to improve the fasting lipid profile from baseline. Reductions in total cholesterol were statistically significantly greater with all oral semaglutide doses compared with placebo for both estimands at weeks 26 and 52, except for the 3-mg dose at week 52 for the trial product estimand (Supplementary Table 5). Results for the patient-reported outcomes are presented in Supplementary Results 1 and Supplementary Figs. 4–6 and for the other supportive secondary end points in Supplementary Table 5.

Safety

Comparable proportions of patients experienced at least one AE while on treatment (Table 2). Gastrointestinal disorders occurred most frequently in the oral semaglutide 7- and 14-mg arms (3 mg, 39.1% [$n = 72$]; 7 mg, 44.8% [$n = 81$]; 14 mg, 50.3% [$n = 91$]), whereas infections and infestations were most common in the oral semaglutide 3-mg (39.7% [$n = 73$]) and placebo (43.5% [$n = 80$]) arms. The most frequently reported AEs were nausea with oral semaglutide (dose-dependently affecting 11.4–23.2% [$n = 21$–42] of patients) and nasopharyngitis with placebo (14.7% [$n = 27$] of patients) (Table 2). Of the nausea events, the majority were of mild or moderate severity and of short duration (Supplementary Fig. 7).

Serious AEs were reported by 13.6% ($n = 25$), 10.5% ($n = 19$), 6.6% ($n = 12$), and 9.2% ($n = 17$) of patients in the oral semaglutide 3-, 7-, and 14-mg and placebo arms, respectively (Table 2). Trial product was prematurely discontinued because of AEs by 7.1% ($n = 13$), 8.8% ($n = 16$), 13.3% ($n = 24$), and 2.7% ($n = 5$) of patients for oral semaglutide 3, 7, and 14 mg and placebo, respectively, with gastrointestinal disorders being the most frequent cause (Supplementary Table 6).

There was one pregnancy during the trial in a patient exposed to trial product (oral semaglutide 7 mg); treatment was discontinued, and the patient elected to have a termination.

Very few patients experienced severe hypoglycemic episodes (Table 2). The proportions of patients with a severe or blood glucose–confirmed symptomatic hypoglycemic episode were similar between patients receiving oral semaglutide and placebo (3 mg, 28.3% [$n = 52$];

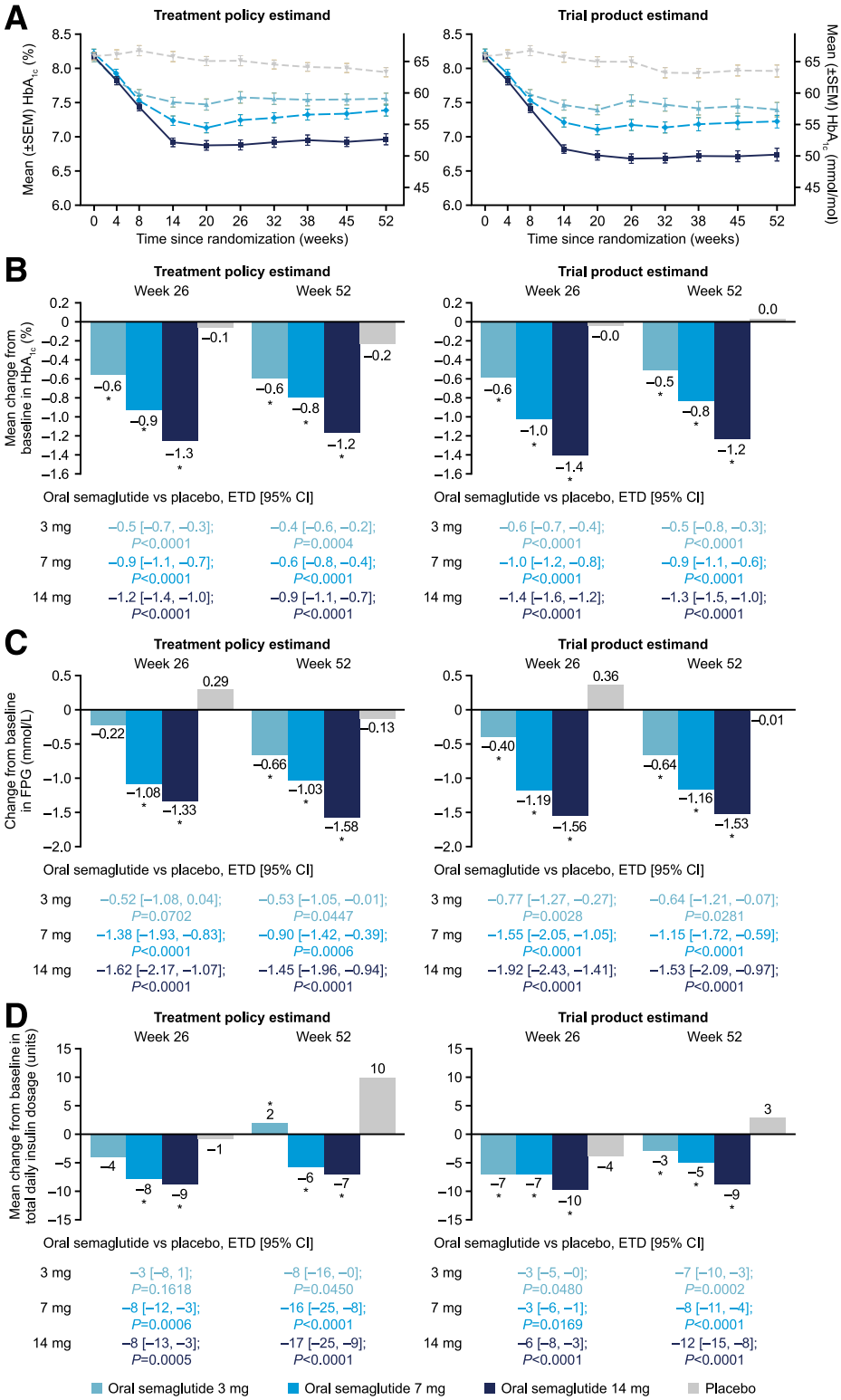

Figure 1—Glycemic control–related efficacy end points. *A*: Observed absolute HbA_{1c} over time. ▼, placebo; ▲, oral semaglutide 3 mg; ◆, oral semaglutide 7 mg; ■, oral semaglutide 14 mg. *B*: Estimated changes from baseline in HbA_{1c}. *C*: Estimated changes from baseline in FPG. *D*: Estimated changes from baseline in total daily insulin dosage. 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. Pattern was defined by randomized trial product and treatment status. 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 were excluded. For binary end points, missing values were imputed from patients randomized to the same trial product using sequential multiple imputation. *Statistically significant ETD versus placebo in favor of oral semaglutide. *P* values are unadjusted two-sided *P* values for the test of no difference.

Table 1—Key supportive secondary end points

	Treatment policy estimand				Trial product estimand			
	Oral semaglutide				Oral semaglutide			
	3 mg	7 mg	14 mg	Placebo	3 mg	7 mg	14 mg	Placebo
Patients, *n*	184	182	181	184	184	182	181	184
HbA_{1c} <7.0%								
Week 26								
Patients meeting end point, *n* (%)	50 (28.4)	74 (42.5)	101 (58.4)	12 (6.8)	50 (30.9)	70 (44.6)	96 (65.8)	11 (6.8)
EOR vs. placebo	5.61	12.37	22.52	—	6.35	14.21	31.84	—
95% CI	2.77, 11.37	6.12, 25.00	11.14, 45.51	—	3.10, 13.00	6.89, 29.29	15.35, 66.04	—
P value	<0.0001	<0.0001	<0.0001	—	<0.0001	<0.0001	<0.0001	—
Week 52								
Patients meeting end point, *n* (%)	50 (28.9)	67 (39.6)	91 (54.2)	16 (9.3)	37 (35.6)	53 (46.9)	72 (64.3)	10 (10.1)
EOR vs. placebo	4.02	7.21	12.96	—	4.59	7.90	16.00	—
95% CI	2.13, 7.58	3.84, 13.54	6.91, 24.32	—	2.22, 9.50	3.82, 16.36	7.77, 32.91	—
P value	<0.0001	<0.0001	<0.0001	—	<0.0001	<0.0001	<0.0001	—
Seven-point SMBG* (mmol/L), mean								
Week 26								
Estimated mean	8.9	8.4	8.1	9.7	8.8	8.2	7.7	9.7
Estimated change from baseline	−1.1	−1.7	−1.9	−0.3	−1.2	−1.7	−2.3	−0.3
ETD vs. placebo	−0.8	−1.4	−1.7	—	−0.9	−1.5	−2.1	—
95% CI	−1.3, −0.3	−1.8, −0.9	−2.1, −1.2	—	−1.4, −0.5	−1.9, −1.0	−2.5, −1.6	—
P value	0.0006	<0.0001	<0.0001	—	<0.0001	<0.0001	<0.0001	—
Week 52								
Estimated mean	8.5	8.4	8.0	9.2	8.5	8.3	7.9	9.3
Estimated change from baseline	−1.5	−1.6	−2.0	−0.8	−1.5	−1.7	−2.1	−0.7
ETD vs. placebo	−0.6	−0.8	−1.1	—	−0.8	−1.0	−1.4	—
95% CI	−1.2, −0.1	−1.3, −0.3	−1.7, −0.6	—	−1.3, −0.3	−1.5, −0.5	−1.8, −0.9	—
P value	0.0161	0.0035	<0.0001	—	0.0012	<0.0001	<0.0001	—

Proportions are observed proportions of patients with nonmissing information. *P* values are unadjusted two-sided *P* values for the test of no difference. 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. Pattern was defined by randomized trial product and treatment status. 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 were excluded. For binary end points, missing values were imputed from patients randomized to the same trial product using sequential multiple imputation. EOR, estimated odds ratio. *SMBG is reported as plasma-equivalent values of capillary whole-blood glucose.

7 mg, 26.0% [$n = 47$]; 14 mg, 26.5% [$n = 48$]; placebo, 29.3% [$n = 54$]) (Table 2). Across all treatment arms, the greatest number of hypoglycemic episodes occurred in patients on basal-bolus insulin.

Comparable proportions of patients experienced diabetic retinopathy–related AEs (Supplementary Table 7), all of which were mild or moderate in severity. Retinopathy events were identified during routine examination for 40 patients (10 per treatment arm), and 8 patients required treatment. The prevalence of external event adjudication committee (EAC)–confirmed cardiovascular events and acute kidney injury events during the trial was low and similar across treatment arms (Supplementary Table 8). Few patients had EAC-confirmed malignant neoplasms, and there were no EAC-confirmed events of acute pancreatitis.

There were three deaths during the trial, all of which occurred on treatment with oral semaglutide 14 mg (Supplementary Table 8). Of these patients, none reported severe or blood glucose–confirmed symptomatic hypoglycemic episodes during the trial. The EAC-confirmed cause of death was infection for one patient; cause of death was undetermined for the remaining two patients because their medical records were unavailable.

Compared with placebo, pulse rate increased for the oral semaglutide arms, with ETD of 2–4 beats/min at week 26 (all groups $P < 0.05$) and 1–2 beats/min at week 52 ($P < 0.05$ for oral semaglutide 14 mg only) while on treatment. There were no clinically relevant changes in laboratory safety parameters or other vital signs reported in any patients (Supplementary Table 9).

CONCLUSIONS

In this trial, oral semaglutide 3, 7, and 14 mg provided dose-dependent, statistically significant reductions in HbA_{1c} and body weight compared with placebo over 52 weeks in patients with type 2 diabetes inadequately controlled with insulin with or without metformin. Furthermore, oral semaglutide treatment enabled up to 54.2% of patients to achieve HbA_{1c} <7.0% (53 mmol/mol) at week 52 (treatment policy estimand). Better glycemic control was achieved with oral semaglutide 7 and 14 mg compared with placebo at weeks 26 and 52, despite lower total daily insulin dosages relative to baseline. These findings support the addition of GLP-1RAs as an effective treatment intensification strategy for patients who are unable to reach or maintain HbA_{1c} targets with insulin alone (17), as recommended in current treatment guidelines (3).

The HbA_{1c} and body weight reductions with oral semaglutide in this trial were similar to those reported in other PIONEER trials (13,18–20). Typical of a population on established insulin therapy, patients in PIONEER 8 were older and had

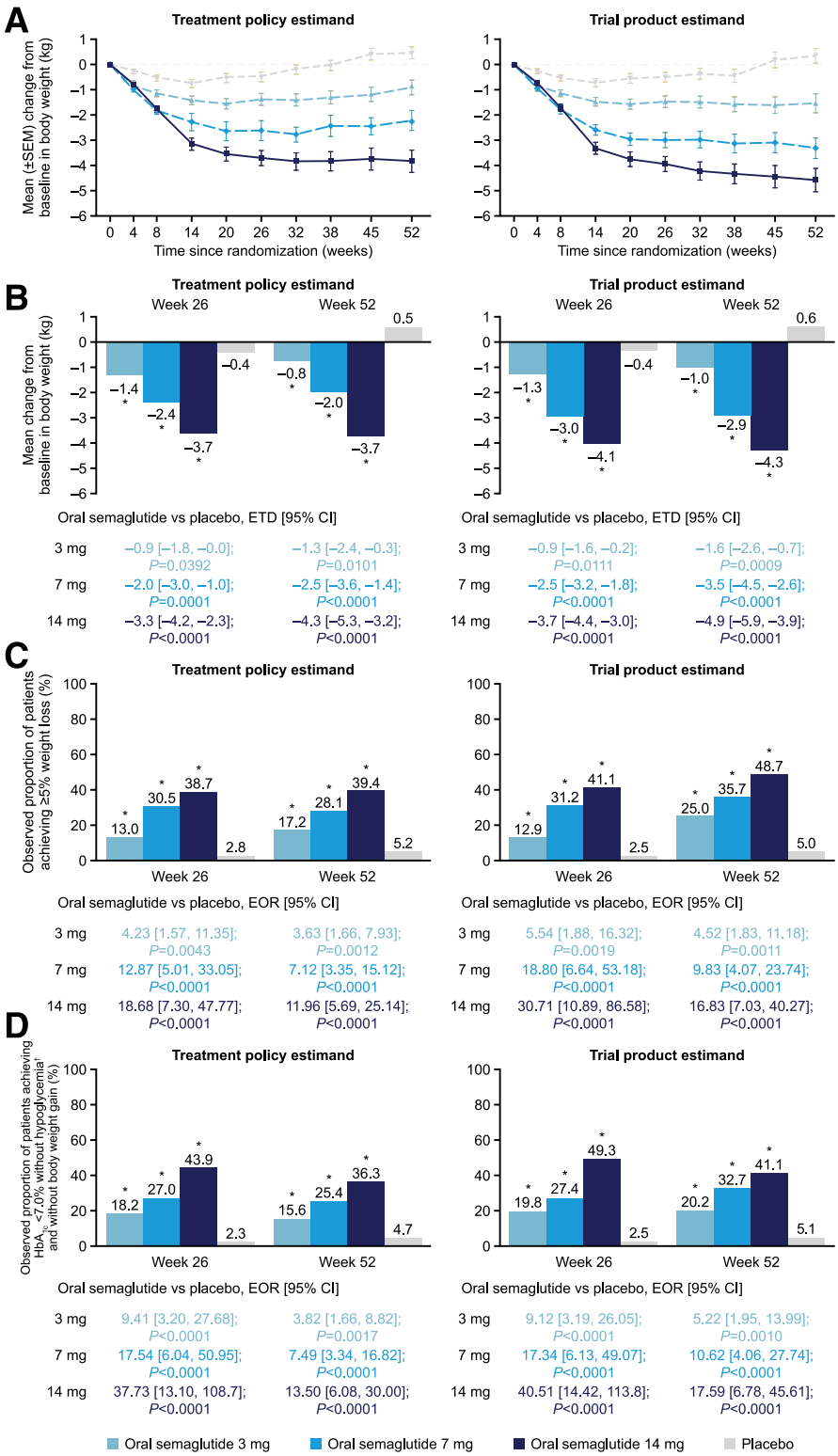

Figure 2—Body weight–related efficacy end points. *A*: Observed changes from baseline in body weight over time. ▼, placebo; ▲, oral semaglutide 3 mg; ◆, oral semaglutide 7 mg; ■, oral semaglutide 14 mg. *B*: Estimated changes from baseline in body weight. *C*: Observed proportions of patients achieving ≥5% weight loss. *D*: Observed proportions of patients achieving HbA_{1c} <7.0% without hypoglycemia and without body weight gain. 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. Pattern was defined by randomized trial product and treatment status. 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 were excluded. For binary end points, missing values were imputed from patients randomized to the same trial product using sequential multiple imputation. *Statistically significant ETD or estimated odds ratio (EOR) versus placebo in favor of oral semaglutide. *P* values are unadjusted two-sided *P* values for the test of no difference. †Severe or blood glucose–confirmed (<3.1 mmol/L [<56 mg/dL]) symptomatic hypoglycemic episode.

Table 2—On-treatment AEs and hypoglycemic episodes

	Oral semaglutide							
	3 mg (n = 184)		7 mg (n = 181)		14 mg (n = 181)		Placebo (n = 184)	
AE	n (%)	R	n (%)	R	n (%)	R	n (%)	R
Any AE	137 (74.5)	336	142 (78.5)	315	151 (83.4)	344	139 (75.5)	245
Most frequent AEs affecting ≥5% of patients in any treatment arm (by MedDRA preferred term)								
Nausea	21 (11.4)	12	30 (16.6)	19	42 (23.2)	37	13 (7.1)	10
Diarrhea	16 (8.7)	10	22 (12.2)	15	27 (14.9)	24	11 (6.0)	8
Decreased appetite	8 (4.3)	4	18 (9.9)	11	23 (12.7)	14	2 (1.1)	1
Vomiting	11 (6.0)	8	14 (7.7)	10	18 (9.9)	18	7 (3.8)	4
Nasopharyngitis	27 (14.7)	23	21 (11.6)	18	18 (9.9)	17	27 (14.7)	18
Upper respiratory tract infection	8 (4.3)	6	6 (3.3)	5	13 (7.2)	8	13 (7.1)	9
Constipation	8 (4.3)	4	15 (8.3)	9	12 (6.6)	8	5 (2.7)	3
Abdominal discomfort	7 (3.8)	4	11 (6.1)	7	10 (5.5)	6	3 (1.6)	2
Urinary tract infection	6 (3.3)	5	5 (2.8)	3	10 (5.5)	6	7 (3.8)	6
Hypertension	3 (1.6)	2	4 (2.2)	2	1 (0.6)	1	11 (6.0)	6
Serious AEs	25 (13.6)	23	19 (10.5)	15	12 (6.6)	14	17 (9.2)	13
AEs leading to premature trial product discontinuation	13 (7.1)	16	16 (8.8)	17	24 (13.3)	29	5 (2.7)	3
AEs leading to premature trial product discontinuation affecting ≥3% of patients in any treatment arm (by MedDRA system organ class)								
Gastrointestinal disorders	9 (4.9)	8	12 (6.6)	13	19 (10.5)	19	1 (0.5)	1
Death	0	0	0	0	3 (1.7)	2	0	0
Hypoglycemic episodes by classification and insulin regimen*	n/N (%)	R	n/N (%)	R	n/N (%)	R	n/N (%)	R
Severe or blood glucose–confirmed symptomatic†‡	52 (28.3)	105	47 (26.0)	102	48 (26.5)	86	54 (29.3)	82
Basal insulin	8 of 77 (10.4)	25	12 of 76 (15.8)	52	10 of 76 (13.2)	27	16 of 80 (20.0)	30
Basal-bolus insulin	36 of 71 (50.7)	206	29 of 73 (39.7)	168	31 of 70 (44.3)	155	27 of 72 (37.5)	155
Premixed insulin	8 of 36 (22.2)	92	6 of 32 (18.8)	62	7 of 35 (20.0)	76	11 of 32 (34.4)	52
Severe‡	5 (2.7)	3	1 (0.6)	1	2 (1.1)	1	1 (0.5)	1
Basal insulin	0	0	0	0	0	0	0	0
Basal-bolus insulin	4 of 71 (5.6)	6	1 of 73 (1.4)	1	1 of 70 (1.4)	1	0	0
Premixed insulin	1 of 36 (2.8)	3	0	0	1 of 35 (2.9)	4	1 of 32 (3.1)	3

Data are number and proportion of patients with at least one event or number and proportion of patients experiencing at least one hypoglycemic episode over number of patients on each insulin regimen, where applicable. On treatment: The period in which the patient was considered treated with trial product. MedDRA, Medical Dictionary for Regulatory Activities (version 20.1); R, observed rate of episodes per 100 years of exposure.
*Hypoglycemic episodes were reported on a separate form from AEs. †Severe hypoglycemia was defined according to the ADA classification (requires assistance of another person to actively administer carbohydrate, glucagon, or other corrective action). ‡Blood glucose confirmation of symptomatic hypoglycemia was based on a blood glucose value <3.1 mmol/L (56 mg/dL), with symptoms consistent with hypoglycemia.

more-advanced disease than those in these other trials (13,18–20). However, the similarities in the results, regardless of population differences, highlight the consistency of effect of oral semaglutide across the spectrum of care. Furthermore, these clinical benefits are consistent with results achieved with subcutaneous semaglutide in patients treated with insulin (6), suggesting that these individuals could benefit from semaglutide regardless of administration route.

Oral semaglutide may help to overcome some of the side effects associated with insulin use that contribute to therapeutic inertia in the initiation or intensification of an insulin regimen (21,22), such as weight gain (23). When added to insulin in the present trial, oral semaglutide resulted in significant body weight reductions versus placebo. Furthermore, the total daily insulin dosage was significantly reduced from baseline with oral semaglutide 7 and 14 mg versus placebo at weeks 26 and 52, suggesting an insulin-sparing effect at these doses.

Insulin use is also associated with an increased risk of hypoglycemia (24,25), which could be overcome by adding a GLP-1RA. Indeed, in a prior trial, the fixed combination of liraglutide and insulin degludec improved glycemic control compared with the equivalent dose of insulin alone, without increasing the hypoglycemia risk (26). Similarly, in our trial, despite the better glycemic control achieved with oral semaglutide, the proportions of patients with at least one severe or blood glucose–confirmed symptomatic hypoglycemic episode were similar across treatment arms. For all treatment arms, most of these episodes occurred in patients on basal-bolus insulin. This would be expected from a regimen with a prandial component, and an association between hypoglycemia and bolus insulin has previously been reported (27,28). Hypoglycemia is also associated with cardiovascular-related morbidity and mortality (29). In this trial, no association between severe or blood glucose–confirmed symptomatic hypoglycemic episodes and cardiovascular events was observed.

Consistent with other semaglutide trials (6,13,19,30), no unexpected safety issues were identified. Gastrointestinal

disorders, specifically nausea, were the most frequent AEs with oral semaglutide, which is consistent with other GLP-1RAs, and nausea is a known class effect of these agents (1). A dose escalation was used to help to mitigate the occurrence and severity of nausea, and the nausea events observed were mild or moderate and of short duration.

A strength of this trial was the inclusion of the consecutive insulin dosing stages (capped at baseline levels, then fully adjustable) during the treatment period. This allowed both the glucose-lowering effect of oral semaglutide to be determined in a controlled setting and data to be obtained longer term in a setting more reflective of clinical practice. However, the diversity of insulin types and regimens could have limited assessment of the interaction of oral semaglutide with specific regimens. In addition, titration of insulin dosage was performed at the discretion of individual investigators and was not enforced. While this was in line with the aim of the trial, it resulted in HbA_{1c} at week 52 being similar to baseline levels in patients receiving placebo. Had the insulin titration after week 26 been enforced, the comparison between oral semaglutide and placebo with regard to frequency of hypoglycemia and changes from baseline in insulin dosage could have been further strengthened. Furthermore, while the use of a placebo control allowed the evaluation of treatment effect, using an active comparator instead could have provided additional insight into the relative risks or benefits of oral semaglutide compared with other available approaches.

In summary, when added to insulin in the setting of inadequately controlled type 2 diabetes, oral semaglutide was superior to placebo at improving glycemic control and reducing body weight over 26 weeks, with significant differences also seen at 52 weeks, and with no increase in the risk of hypoglycemia. Furthermore, the overall safety profile was consistent with that of other GLP-1RAs.

Acknowledgments. Emisphere is acknowledged for providing a license to the Eligen Technology, the sodium N-(8-[2-hydroxybenzoyl] amino) caprylate component of oral semaglutide. The authors thank the patients, investigators, trial site staff, and Novo Nordisk employees involved in the trial. In addition, the authors thank Sophie Walton of Spirit Medical Communications Group Ltd. for medical writing and editorial assistance (funded by Novo Nordisk A/S) and Brian Bekker Hansen of Novo Nordisk for reviewing the manuscript.

Funding. J.B.B. is supported by grants from the ADA, National Institutes of Health (UL1-TR-002489, U01-DK-098246, UC4-DK-108612, U54-DK-118612), and Patient-Centered Outcomes Research Institute.

Duality of Interest. PIONEER 8 was funded by Novo Nordisk A/S, Denmark. B.Z. has served on scientific advisory boards of and received honoraria or consulting fees from AstraZeneca, Boehringer Ingelheim, Eli Lilly, Janssen, Merck, Sanofi, and Novo Nordisk. V.R.A. has received consulting fees from Adocia, AstraZeneca, BD, Novo Nordisk, Sanofi, and Zafgen and research grant support paid to her institution from AstraZeneca/Bristol-Myers Squibb, Calibra, Eisai, Fractyl, Janssen, Novo Nordisk, Sanofi, and Theracos, and her spouse is an employee of Merck Research Laboratories. J.B.B. has received consulting fees paid to his institution from Adocia, AstraZeneca, Dance Biopharm, Eli Lilly, MannKind, NovaTarg, Novo Nordisk, Senseonics, vTv Therapeutics, and Zafgen; has received research grant support from Novo Nordisk, Sanofi, and vTv Therapeutics; is a consultant to Cirius Therapeutics, CSL Behring, Neurimmune AG, and Whole Biome; and holds stock options in Mellitus Health, PhaseBio, Stability Health, and Whole Biome. B.C. has received research grant support from Amgen, Novo Nordisk, Pfizer, Sanofi, and Regeneron Pharmaceuticals and has served on scientific advisory boards of and received honoraria or consulting fees from Abbott, Akcea, Amgen, AstraZeneca, Genfit, Pierre Fabre, Eli Lilly, MSD, Merck & Co., Novo Nordisk, Regeneron Pharmaceuticals, and Sanofi. S.B.H. has received research grant support from AstraZeneca, Boehringer Ingelheim, Eli Lilly, Janssen, Novo Nordisk, and Sanofi and has served on scientific advisory boards of, provided consultation to, and received honoraria or consulting fees from Abbott, AstraZeneca, Eli Lilly, Janssen, Merck, Novo Nordisk, and Sanofi. E.A. has served on scientific advisory boards of and received honoraria or consulting fees from Alcon, Astellas Pharma, AstraZeneca, Eli Lilly, Kowa Pharmaceutical, Nippon Boehringer Ingelheim, Novo Nordisk, Sanofi, and Terumo Corporation; has received honoraria for lectures from Astellas Pharma, MSD, Novo Nordisk, Ono Pharmaceutical, and Sanofi; and received scholarship grants from Astellas Pharma, Daiichi Sankyo, Mitsubishi Tanabe Pharma, Nippon Boehringer Ingelheim, Novo Nordisk, Ono Pharmaceutical, Sanofi, Shionogi, Sumitomo Dainippon Pharma, and Takeda Pharmaceutical. S.T.H., K.B.P., and M.J.T.-J. are employees of Novo Nordisk, the sponsor of this trial. No other potential conflicts of interest relevant to this article were reported.

Author Contributions. B.Z. served as the global signatory investigator of the trial. B.Z., V.R.A., J.B.B., B.C., S.B.H., S.T.H., K.B.P., M.J.T.-J., and E.A. were involved in the acquisition, analysis, or interpretation of data and assisted with drafting and critical revision of the manuscript. S.T.H., K.P.J.B., and M.J.T.-J. designed the trial. M.J.T.-J. was responsible for the statistical analysis. B.Z. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Prior Presentation. Parts of this trial were presented in abstract form at the 79th Scientific Sessions of the American Diabetes Association, San Francisco, CA, 7–11 June 2019.

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