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Oral Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes


ABSTRACT

BACKGROUND
Establishing cardiovascular safety of new therapies for type 2 diabetes is important. Safety data are available for the subcutaneous form of the glucagon-like peptide-1 receptor agonist semaglutide but are needed for oral semaglutide.

METHODS
We assessed cardiovascular outcomes of once-daily oral semaglutide in an event-driven, randomized, double-blind, placebo-controlled trial involving patients at high cardiovascular risk (age of ≥50 years with established cardiovascular or chronic kidney disease, or age of ≥60 years with cardiovascular risk factors only). The primary outcome in a time-to-event analysis was the first occurrence of a major adverse cardiovascular event (death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke). The trial was designed to rule out 80% excess cardiovascular risk as compared with placebo (noninferiority margin of 1.8 for the upper boundary of the 95% confidence interval for the hazard ratio for the primary outcome).

RESULTS
A total of 3183 patients were randomly assigned to receive oral semaglutide or placebo. The mean age of the patients was 66 years; 2695 patients (84.7%) were 50 years of age or older and had cardiovascular or chronic kidney disease. The median time in the trial was 15.9 months. Major adverse cardiovascular events occurred in 61 of 1591 patients (3.8%) in the oral semaglutide group and 76 of 1592 (4.8%) in the placebo group (hazard ratio, 0.79; 95% confidence interval [CI], 0.57 to 1.11; P<0.001 for noninferiority). Results for components of the primary outcome were as follows: death from cardiovascular causes, 15 of 1591 patients (0.9%) in the oral semaglutide group and 30 of 1592 (1.9%) in the placebo group (hazard ratio, 0.49; 95% CI, 0.27 to 0.92); nonfatal myocardial infarction, 37 of 1591 patients (2.3%) and 31 of 1592 (1.9%), respectively (hazard ratio, 1.18; 95% CI, 0.73 to 1.90); and nonfatal stroke, 12 of 1591 patients (0.8%) and 16 of 1592 (1.0%), respectively (hazard ratio, 0.74; 95% CI, 0.35 to 1.57). Death from any cause occurred in 23 of 1591 patients (1.4%) in the oral semaglutide group and 45 of 1592 (2.8%) in the placebo group (hazard ratio, 0.51; 95% CI, 0.31 to 0.84). Gastrointestinal adverse events leading to discontinuation of oral semaglutide or placebo were more common with oral semaglutide.

CONCLUSIONS
In this trial involving patients with type 2 diabetes, the cardiovascular risk profile of oral semaglutide was not inferior to that of placebo. (Funded by Novo Nordisk; PIONEER 6 ClinicalTrials.gov number, NCT02692716.)
Cardiovascular disease is the primary cause of death in patients with type 2 diabetes, and the ruling out of an excess cardiovascular risk is a regulatory requirement for new glucose-lowering therapies. Glucagon-like peptide-1 (GLP-1) receptor agonists are well-established glucose-lowering medications for the treatment of type 2 diabetes and are associated with reductions in body weight and a low risk of hypoglycemia. These agents have shown cardiovascular safety (lixisenatide and exenatide) and, in several cases, benefit (liraglutide, albiglutide, semaglutide, and, most recently, dulaglutide). For example, in the Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes (SUSTAIN-6), patients who received a once-weekly subcutaneous injection of semaglutide had a 26% lower risk of the primary cardiovascular outcome than those who received placebo.

Recent diabetes and cardiology treatment guidelines recommend GLP-1 receptor agonists as a second-line treatment option for adults with type 2 diabetes.

All currently approved GLP-1 receptor agonists are administered subcutaneously. Oral semaglutide has been developed as a once-daily tablet, which may allay concerns about injections among some patients and clinicians and result in earlier initiation of GLP-1 receptor agonist therapy. As compared with once-weekly subcutaneous semaglutide, oral semaglutide has a different absorption profile. However, once the drug is absorbed, the pharmacokinetic properties and effects of semaglutide are similar, regardless of the route of administration. The present randomized, placebo-controlled, phase 3a trial, Peptide Innovation for Early Diabetes Treatment (PIONEER) 6, is a preapproval cardiovascular outcomes trial specifically designed to rule out an excess in cardiovascular risk with oral semaglutide among patients with type 2 diabetes.

**Methods**

**Trial Design and Oversight**

Detailed methods for this trial, which was conducted at 214 sites in 21 countries, have been published previously, and the protocol is available with the full text of this article at NEJM.org. The sponsor (Novo Nordisk) designed the trial and was responsible for the trial conduct, data collection, and data analysis. An independent data monitoring committee evaluated unblinded trial data.

All the authors had full access to the data, participated in drafting or critical revision of the manuscript, made the decision to submit the manuscript for publication, and vouch for the accuracy and completeness of the data and for the adherence of the trial to the protocol. The manuscript was drafted with support from a medical writer (funded by the sponsor), under the direction of the authors.

**Patients**

Patients were eligible to participate if they were 50 years of age or older and had established cardiovascular disease or chronic kidney disease, or if they were 60 years of age or older and had cardiovascular risk factors only. Key exclusion criteria were treatment with any GLP-1 receptor agonist, dipeptidyl peptidase 4 inhibitor, or pramlintide within 90 days before screening; New York Heart Association class 4 heart failure; planned coronary-artery, carotid-artery, or peripheral-artery revascularization; myocardial infarction, stroke, or hospitalization for unstable angina or transient ischemic attack within 60 days before screening; long-term or intermittent hemodialysis or peritoneal dialysis, or severe renal impairment (estimated glomerular filtration rate [GFR], <30 ml per minute per 1.73 m² of body-surface area); and proliferative retinopathy or maculopathy resulting in active treatment. The full eligibility criteria are provided in the Supplementary Appendix, available at NEJM.org.

**Procedures**

Patients were randomly assigned (in a 1:1 ratio) to receive once-daily oral semaglutide (target dose, 14 mg) or placebo (Fig. S1 in the Supplementary Appendix), both in addition to standard-of-care treatment, in a double-blind fashion. Randomization was stratified according to evidence of established cardiovascular disease or chronic kidney disease or the presence of cardiovascular risk factors only.

Patients were instructed to take oral semaglutide or placebo in the morning, with up to 120 ml of water, in a fasting state, and at least 30 minutes before eating, drinking, or taking any other oral medication. A dose-escalation schedule was used to decrease gastrointestinal side effects. Once the desired dose was reached, patients remained at the maximum 14-mg daily dose unless...
a reduction was warranted owing to problems with side effects. In such cases, investigators were encouraged to consider reescalating the dose once the symptoms had resolved or diminished. Investigators were encouraged to maintain and intensify patients’ existing glucose-lowering and cardiovascular medication, in accordance with local and international guidelines, in addition to semaglutide or placebo.

Follow-up appointments occurred every 6 to 7 weeks in person or by telephone. A full schedule of assessments is provided in the Supplementary Appendix.

OUTCOMES
The primary outcome was the time from randomization to the first occurrence of a major adverse cardiovascular event, a composite of death from cardiovascular causes (including undetermined causes of death), nonfatal myocardial infarction, or nonfatal stroke. Secondary cardiovascular outcomes included the time from randomization to the first occurrence of the following: an expanded composite outcome consisting of the primary outcome plus unstable angina resulting in hospitalization or heart failure resulting in hospitalization; a composite of death from any cause, nonfatal myocardial infarction, or nonfatal stroke; and the individual components of these composite outcomes. Additional efficacy outcomes included the change from baseline to the end of the treatment period in the glycated hemoglobin level, body weight, and lipid levels.

A select set of safety outcomes was investigated, encompassing adverse events leading to discontinuation of semaglutide or placebo, serious adverse events, and adverse events of special interest (including diabetic retinopathy assessed by scheduled eye examinations, and severe hypoglycemic episodes). Cardiovascular and other selected events were adjudicated by an independent, external event-adjudication committee whose members were unaware of the trial-group assignments.

STATISTICAL ANALYSIS
The statistical methods have been reported previously, and further information is provided in the Supplementary Appendix and below. Our trial was an event-driven trial designed to rule out an 80% excess in cardiovascular risk with oral semaglutide by assessment of noninferiority to placebo for the primary outcome (noninferiority margin of 1.8 for the upper boundary of the 95% confidence interval for the hazard ratio). The trial continued until accrual of at least 122 events, with no predefined minimum duration.

All analyses involved the full analysis set, which included all randomly assigned patients. The primary outcome encompassed events occurring between randomization and the final follow-up visit (aligned at 5 weeks after the last trial-wide assigned dose, except for patients who withdrew from the trial).

A stratified Cox proportional-hazards model was used for the primary outcome analysis, with trial group as a fixed factor. Conditional to confirmation of noninferiority, superiority testing was performed on the primary outcome. Analyses of all other outcomes were not controlled for multiple comparisons and should be interpreted as exploratory. Prespecified sensitivity and subgroup analyses explored the robustness of the primary outcome analysis. Secondary efficacy outcomes and adverse events were assessed by means of descriptive statistics.

RESULTS

PATIENTS
Between January and August 2017, a total of 3183 patients were randomly assigned to oral semaglutide (1591 patients) or placebo (1592 patients). The median time in the trial (including follow-up) was 15.9 months (range, 0.4 to 20.0), and approximately 75% of the patients received oral semaglutide or placebo for more than 1 year. In total, 3172 patients (99.7%) completed the trial; 1347 (84.7%) completed the trial regimen with oral semaglutide and 1435 (90.1%) with placebo (Fig. S2 in the Supplementary Appendix). Vital-status information was collected for the 11 patients who did not complete the trial, thus accounting for all patients who took part. Most patients (1106 of 1347, 82.1%) assigned to oral semaglutide who completed the trial regimen were receiving the 14-mg dose by the visit at the end of the treatment period (Fig. S3 in the Supplementary Appendix).

Baseline characteristics were similar in the two groups. Patients were predominantly male (2176 patients, 68.4%), and 2695 patients (84.7%) were 50 years of age or older and had established cardiovascular disease or chronic kidney disease (Table 1, and Tables S1 and S2 in the Supplementary Appendix). At baseline, the mean (±SD) body weight was 90.9±21.2 kg, the mean body-
mass index (the weight in kilograms divided by the square of the height in meters) 32.3±6.5, the mean glycated hemoglobin level 8.2±1.6% (66±18 mmol per mole), the mean age 66±7 years, and the mean duration of diabetes 14.9±8.5 years. The mean estimated GFR at baseline was 74±21 ml per minute per 1.73 m².

At baseline, most patients were taking metformin (2463 patients, 77.4%) or insulin (1930 patients, 60.6%); 1027 (32.3%) were taking sulfonylureas and 305 (9.6%) sodium–glucose co-transporter 2 (SGLT2) inhibitors (Table S3 in the Supplementary Appendix). In addition, 2988 patients (93.9%) were taking antihypertensive medication, 2712 (85.2%) lipid-lowering medication, and 2527 (79.4%) antithrombotic or antithrombolytic medication (Table S3 in the Supplementary Appendix). During the trial, more patients initiated or intensified glucose-lowering therapy in the placebo group than in the oral semaglutide group (Table S3 in the Supplementary Appendix), including greater use of SGLT2 inhibitors (111 patients [7.0%] vs. 50 [3.1%]).

**Table 1. Selected Baseline Demographic and Clinical Characteristics of the Patients.*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Oral Semaglutide (N = 1591)</th>
<th>Placebo (N = 1592)</th>
<th>Total (N = 3183)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age — yr</td>
<td>66±7</td>
<td>66±7</td>
<td>66±7</td>
</tr>
<tr>
<td>Female sex — no. (%)</td>
<td>507 (31.9)</td>
<td>500 (31.4)</td>
<td>1007 (31.6)</td>
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<tr>
<td>Body weight — kg</td>
<td>91.0±21.4</td>
<td>90.8±21.0</td>
<td>90.9±21.2</td>
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<tr>
<td>Body-mass index</td>
<td>32.3±6.6</td>
<td>32.3±6.4</td>
<td>32.3±6.5</td>
</tr>
<tr>
<td>Type 2 diabetes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration — yr</td>
<td>14.7±8.5</td>
<td>15.1±8.5</td>
<td>14.9±8.5</td>
</tr>
<tr>
<td>Glycated hemoglobin — %</td>
<td>8.2±1.6</td>
<td>8.2±1.6</td>
<td>8.2±1.6</td>
</tr>
<tr>
<td>Glycated hemoglobin — mmol/mol</td>
<td>66±17</td>
<td>66±18</td>
<td>66±18</td>
</tr>
<tr>
<td>Cardiovascular risk stratum — no. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age ≥50 yr and established CVD or chronic kidney disease</td>
<td>1350 (84.9)</td>
<td>1345 (84.5)</td>
<td>2695 (84.7)</td>
</tr>
<tr>
<td>Age ≥60 yr and cardiovascular risk factors only</td>
<td>241 (15.1)</td>
<td>247 (15.5)</td>
<td>488 (15.3)</td>
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<tr>
<td>Cardiovascular risk factors</td>
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<td></td>
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<tr>
<td>Blood pressure — mm Hg</td>
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<tr>
<td>Systolic</td>
<td>135±18</td>
<td>136±18</td>
<td>136±18</td>
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<tr>
<td>Diastolic</td>
<td>76±10</td>
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<td>76±10</td>
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<td>LDL cholesterol</td>
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<td>Geometric mean — mg/dl</td>
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<td>79</td>
<td>78</td>
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<tr>
<td>Coefficient of variation — %</td>
<td>44.9</td>
<td>41.2</td>
<td>43.1</td>
</tr>
<tr>
<td>Current smoker — no. (%)</td>
<td>184 (11.6)</td>
<td>165 (10.4)</td>
<td>349 (11.0)</td>
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<tr>
<td>Estimated GFR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean — ml/min/1.73 m²</td>
<td>74±21</td>
<td>74±21</td>
<td>74±21</td>
</tr>
<tr>
<td>Distribution — no. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥90 ml/min/1.73 m²</td>
<td>464 (29.2)</td>
<td>455 (28.6)</td>
<td>919 (28.9)</td>
</tr>
<tr>
<td>60 to &lt;90 ml/min/1.73 m²</td>
<td>686 (43.1)</td>
<td>703 (44.2)</td>
<td>1389 (43.6)</td>
</tr>
<tr>
<td>30 to &lt;60 ml/min/1.73 m²</td>
<td>418 (26.3)</td>
<td>409 (25.7)</td>
<td>827 (26.0)</td>
</tr>
<tr>
<td>&lt;30 ml/min/1.73 m²</td>
<td>16 (1.0)</td>
<td>13 (0.8)</td>
<td>29 (0.9)</td>
</tr>
<tr>
<td>Missing data</td>
<td>7 (0.4)</td>
<td>12 (0.8)</td>
<td>19 (0.6)</td>
</tr>
</tbody>
</table>

* Plus–minus values are means ±SD. Percentages may not total 100 because of rounding. To convert the values for low-density lipoprotein (LDL) cholesterol to millimoles per liter, multiply by 0.02586. CVD denotes cardiovascular disease, and GFR glomerular filtration rate. Further summary baseline data are provided in Bain et al.23

**CARDIOVASCULAR OUTCOMES**

The primary outcome occurred in 61 of 1591 patients (3.8%) receiving oral semaglutide and 76 of 1592 (4.8%) receiving placebo. Thus, non-inferiority was confirmed for oral semaglutide as compared with placebo, both added to stan-
standard-of-care treatment, with a point estimate corresponding to a 21% difference in risk (hazard ratio, 0.79; 95% confidence interval [CI], 0.57 to 1.11; P<0.001 for noninferiority; P=0.17 for superiority) (Fig. 1 and Table 2). Sensitivity analyses were consistent with the primary analysis (Fig. S4 in the Supplementary Appendix). The hazard ratio for the expanded outcome was similar to that for the primary outcome (with events in 83 of 1591 patients [5.2%] in the oral semaglutide group and 100 of 1592 [6.3%] in the placebo group; hazard ratio, 0.82; 95% CI, 0.61 to 1.10) (Table 2, and Fig. S5 in the Supplementary Appendix), as was the composite of death from any cause, nonfatal myocardial infarction, or nonfatal stroke (with events in 69 of 1591 patients [4.3%] and 89 of 1592 [5.6%], respectively; hazard ratio, 0.77; 95% CI, 0.56 to 1.05).

Among the individual components of the primary outcome, death from cardiovascular causes occurred in 15 of 1591 patients (0.9%) in the oral semaglutide group and 30 of 1592 (1.9%) in the placebo group (hazard ratio, 0.49; 95% CI, 0.27 to 0.92) (Fig. 1 and Table 2). First events of nonfatal myocardial infarction occurred in 37 of 1591 patients (2.3%) and 31 of 1592 (1.9%), respectively (hazard ratio, 1.18; 95% CI, 0.73 to 1.90). First events of nonfatal stroke occurred in 12 of 1591 patients (0.8%) and 16 of 1592 (1.0%), respectively (hazard ratio, 0.74; 95% CI, 0.35 to 1.57).

Death from any cause occurred in 23 of 1591 patients (1.4%) in the oral semaglutide group and 45 of 1592 (2.8%) in the placebo group (hazard ratio, 0.51; 95% CI, 0.31 to 0.84) (Table 2). First events of unstable angina resulting in hospitalization occurred in 11 of 1591 patients (0.7%) and 7 of 1592 (0.4%), respectively (hazard ratio, 1.56; 95% CI, 0.60 to 4.01). First events of heart failure resulting in hospitalization occurred in 21 of 1591 patients (1.3%) and 24 of 1592 (1.5%), respectively (hazard ratio, 0.86; 95% CI, 0.48 to 1.55). Results for the primary outcome were consistent within subgroups (Fig. S6 in the Supplementary Appendix).

Efficacy Outcomes

Glycated hemoglobin levels decreased more in the oral semaglutide group than in the placebo group (mean change from baseline to end of trial, –1.0 vs. –0.3 percentage points), as did body weight (mean change from baseline to end of trial, –4.2 kg vs. –0.8 kg) (Fig. 2, and Fig. S7 in the Supplementary Appendix). Systolic blood pressure decreased more in the oral semaglutide group than in the placebo group (Table S4 in the Supplementary Appendix), and levels of low-density lipoprotein cholesterol and triglycerides were modestly lower in the oral semaglutide group (Fig. S8 in the Supplementary Appendix).

Adverse Events and Safety

Serious adverse events occurred in 301 of 1591 patients (18.9%) in the oral semaglutide group and 358 of 1592 (22.5%) in the placebo group (Table 3). Serious adverse events were varied and involved several organ systems (Table S5 in the Supplementary Appendix).

More patients permanently discontinued oral semaglutide than placebo (184 of 1591 patients [11.6%] vs. 104 of 1592 [6.5%]) (Table 3, and Table S6 in the Supplementary Appendix). This difference was driven by gastrointestinal adverse events (in 108 of 1591 patients [6.8%] in the oral semaglutide group vs. in 26 of 1592 [1.6%] in the placebo group) (Table 3), primarily nausea (in 46 of 1591 patients [2.9%] vs. in 8 of 1592 [0.5%]), vomiting (in 24 of 1591 patients [1.5%] vs. in 4 of 1592 [0.3%]), and diarrhea (in 22 of 1591 patients [1.4%] vs. in 6 of 1592 [0.4%]), mostly nonserious. However, serious adverse events led to permanent discontinuation of oral semaglutide in 41 of 1591 patients (2.6%) and of placebo in 48 of 1592 patients (3.0%).

There were 68 deaths during the trial (in 23 of 1591 patients in the oral semaglutide group and in 45 of 1592 in the placebo group). The most frequent underlying causes of death were cardiovascular (in 10 of 23 deaths with oral semaglutide and in 23 of 45 deaths with placebo) (Table S7 in the Supplementary Appendix). There was no clustering of causes among deaths from noncardiovascular causes.

The percentage of patients with adverse events related to diabetic retinopathy during the trial (identified through a search of terms in the Medical Dictionary for Regulatory Activities, version 20.1) was 7.1% (113 of 1591 patients) with oral semaglutide and 6.3% (101 of 1592) with placebo (Table S8 in the Supplementary Appendix). Most cases were nonproliferative and were identified during routine examinations (111 of 120 cases [92.5%] with oral semaglutide and 94 of 110 [85.5%] with placebo); 174 of 230 cases (75.7%) resulted in no new treatment. In the placebo group, one serious retinopathy event and one
Figure 1. Cardiovascular Outcomes.

Shown are cumulative-incidence plots for the primary outcome (first major adverse cardiovascular events, representing a composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke) (Panel A), nonfatal myocardial infarction (Panel B), nonfatal stroke (Panel C), and death from cardiovascular causes (Panel D). Cumulative-incidence estimates are based on time from randomization to first event confirmed by the event-adjudication committee, with death from noncardiovascular causes (Panels A and D) or death from any cause modeled as competing risks. Data for patients were censored at the end of the in-trial observation period (from randomization to the final follow-up visit). Deaths from cardiovascular causes included deaths for which the cause was undetermined. The analysis for confirmation of noninferiority was controlled for multiple comparisons; P values and confidence intervals for other analyses have not been adjusted for multiple comparisons. The insets show the same data on an expanded y axis. CI denotes confidence interval.
event leading to discontinuation of placebo were reported.

Despite improved glycemic control with oral semaglutide, the percentage of patients with severe hypoglycemia was 1.4% (23 of 1591 patients), as compared with 0.8% (13 of 1592) with placebo. All severe hypoglycemic events occurred in patients receiving concomitant insulin or sulfonylureas at the time of the event.

No unexpected adverse events were reported, and there were no apparent imbalances in adjudicated adverse events between the two groups (Table 3, and Table S9 in the Supplementary Appendix). There was one confirmed case of acute pancreatitis with oral semaglutide and three cases with placebo. Malignant neoplasms were confirmed in 41 of 1591 patients (2.6%) in the oral semaglutide group and 48 of 1592 (3.0%) in the placebo group; in the oral semaglutide group, there was no evidence of clustering in any organ system. There was one case of medullary thyroid cancer in a patient receiving oral semaglutide who had preexisting thyroid nodules and an elevated calcitonin level at baseline.

The mean pulse rate was increased by 4 beats per minute with oral semaglutide and unchanged with placebo (Table S4 in the Supplementary Appendix). There were no clinically relevant changes in biochemical and hematologic variables.

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The trial was designed to randomly assign approximately three times as many patients as were enrolled in our trial. Consequently, fewer events were observed in our trial (in 137 of 3183 patients) than in SUSTAIN-6 (in 254 of 3297), the LEADER trial (in 1302 of 9340), or the Harmony Outcomes trial (in 766 of 9463). However, the hazard ratios were similar in the present trial and SUSTAIN-6, which may suggest that the cardiovascular effect of semaglutide is independent of the route of administration.

Generally, the results were consistent across the components of the primary outcome and the other cardiovascular outcomes (e.g., hospitalization for heart failure). Thus, oral semaglutide has a cardiovascular safety profile similar to that of the subcutaneous form, as shown in SUSTAIN-6.

No treatment interactions were evident in

Figure 2. Efficacy Outcomes (In-Trial Observation Period).

The curves show the observed change from baseline in the glycated hemoglobin level (Panel A) and body weight (Panel B). Data are for the full analysis set during the in-trial observation period, which was from randomization to the last visit (end of treatment). The end of treatment occurred when the required number of first major adverse cardiovascular events was exceeded. The individual patients’ in-trial observation period ranged from 2 to 87 weeks, with a median duration of 69 weeks. Bars indicate standard errors.

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**Figure 2. Efficacy Outcomes (In-Trial Observation Period).**

The curves show the observed change from baseline in the glycated hemoglobin level (Panel A) and body weight (Panel B). Data are for the full analysis set during the in-trial observation period, which was from randomization to the last visit (end of treatment). The end of treatment occurred when the required number of first major adverse cardiovascular events was exceeded. The individual patients’ in-trial observation period ranged from 2 to 87 weeks, with a median duration of 69 weeks. Bars indicate standard errors.
subgroup analyses, including in patients with established cardiovascular disease or chronic kidney disease as compared with those with cardiovascular risk factors only. These data should be interpreted with caution owing to low patient numbers and wide confidence intervals.

More patients received treatment with an SGLT2 inhibitor after randomization in the placebo group than in the oral semaglutide group. These drugs have been shown to reduce cardiovascular risk,\textsuperscript{24-26} which could have potentially affected the treatment difference for the primary outcome. However, few patients initiated SGLT2 inhibitors in the current trial (and they used these drugs over a shorter duration than in trials showing the aforementioned reduction in cardiovascular risk), which makes an influence on the primary outcome unlikely in our view.

Oral semaglutide reduced glycated hemoglobin levels and body weight in the present trial, which is consistent with the phase 3a efficacy and safety trial PIONEER 3\textsuperscript{27} and with data for subcutaneous semaglutide in SUSTAIN-6.\textsuperscript{26} In our trial, oral semaglutide was associated with glycemic benefits despite instructions to intensify glucose-lowering therapy in all patients as needed and despite more patients in the placebo group receiving additional glucose-lowering medications.

No unexpected adverse events were identified with oral semaglutide. More patients permanently discontinued oral semaglutide than placebo, mostly due to gastrointestinal events, as observed with all GLP-1 receptor agonists (including subcutaneous semaglutide). Fewer serious adverse events and deaths occurred in the oral semaglutide group than in the placebo group. The difference between the two groups in the number of deaths was largely accounted for by deaths from cardiovascular causes (10 of 23 deaths in the oral semaglutide group vs. 23 of 45 in the placebo group), although there were also more deaths from noncardiovascular causes in the placebo group (8 of 23 deaths vs. 15 of 45).

In SUSTAIN-6, subcutaneous semaglutide was

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**Table 3. Adverse Events (during the Treatment Period unless Specified).\textsuperscript{*}\footnote{Adverse events were summarized descriptively for both the treatment period (from the date of the first dose to the date of the last dose plus 38 days or the final follow-up visit [whichever occurred first]) and the in-trial observation period (from randomization to the final follow-up visit). Further adverse events of special interest are shown in Table S9 in the Supplementary Appendix.} **

<table>
<thead>
<tr>
<th>Event</th>
<th>Oral Semaglutide (N=1591)</th>
<th>Placebo (N=1592)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse event leading to permanent discontinuation of oral semaglutide or placebo</td>
<td>184 (11.6)</td>
<td>104 (6.5)</td>
</tr>
<tr>
<td>According to system organ class\textsuperscript{†}</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>108 (6.8)</td>
<td>26 (1.6)</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>19 (1.2)</td>
<td>7 (0.4)</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>17 (1.1)</td>
<td>13 (0.8)</td>
</tr>
<tr>
<td>Serious adverse event</td>
<td>301 (18.9)</td>
<td>358 (22.5)</td>
</tr>
<tr>
<td>Leading to permanent discontinuation of oral semaglutide or placebo</td>
<td>41 (2.6)</td>
<td>48 (3.0)</td>
</tr>
<tr>
<td>Adverse events of special interest</td>
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<td></td>
</tr>
<tr>
<td>Acute kidney injury\textsuperscript{‡}</td>
<td>32 (2.0)</td>
<td>37 (2.3)</td>
</tr>
<tr>
<td>Acute pancreatitis\textsuperscript{‡}</td>
<td>1 (0.1)</td>
<td>3 (0.2)</td>
</tr>
<tr>
<td>Retinopathy or related complications\textsuperscript{$\ddagger$}</td>
<td>113 (7.1)</td>
<td>101 (6.3)</td>
</tr>
<tr>
<td>Severe hypoglycemia\textsuperscript{$\S$}</td>
<td>23 (1.4)</td>
<td>13 (0.8)</td>
</tr>
<tr>
<td>Malignant neoplasms\textsuperscript{$\S\ddagger$}</td>
<td>41 (2.6)</td>
<td>48 (3.0)</td>
</tr>
</tbody>
</table>

\textsuperscript{*} Shown are events with an incidence of at least 1% in either trial group.

\textsuperscript{†} Shown are events confirmed by the event-adjudication committee.

\textsuperscript{$\ddagger$} These events were identified through a search of terms in the Medical Dictionary for Regulatory Activities, version 20.1.

\textsuperscript{$\S$} Data are for the in-trial observation period.

\textsuperscript{$\S\ddagger$} Malignant thyroid neoplasms were excluded. Such neoplasms occurred in two patients receiving oral semaglutide: one patient had medullary thyroid cancer and one had a recurrence of a previous thyroid cancer.
associated with a higher risk of diabetic retinopathy complications than placebo. 26 Most events occurred early in that trial, possibly attributable to the magnitude and rapidity of the reduction in glycated hemoglobin levels in patients with preexisting diabetic retinopathy. 28 Given that result, patients with proliferative retinopathy or maculopathy resulting in active treatment were excluded from our trial. We observed no apparent imbalance between the trial groups in adverse-event reporting of diabetic retinopathy; almost all cases were nonproliferative and did not result in additional treatment during the trial. A long-term trial to investigate the effects of semaglutide on the development and progression of diabetic retinopathy is ongoing (ClinicalTrials.gov number, NCT03811561).

Our event-driven, double-blind trial was powered to investigate whether there was an excess cardiovascular risk with oral semaglutide. A high completion rate (99.7%), a high percentage of patients who continued to receive oral semaglutide (>80%), and full vital status known at trial end for all randomly assigned patients indicate high validity for the conduct of the trial and the results.

In conclusion, the present trial showed non-inferiority of oral semaglutide to placebo (hazard ratio, 0.79; 95% CI, 0.57 to 1.11), ruling out an 80% excess cardiovascular risk. Gastrointestinal adverse events were the major reason for discontinuation of oral semaglutide.

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