ORIGINAL ARTICLE

Oral Semaglutide and Cardiovascular Outcomes in High-Risk Type 2 Diabetes

D.K. McGuire,[1,2] N. Marx,[3] S.L. Mulvagh,[4] J.E. Deanfield,[5] S.E. Inzucchi,[6] R. Pop-Busui,[7] J.F.E. Mann,[8,9] S.S. Emerson,[10] N.R. Poulter,[11] M.D.M. Engelmann,[12] M.S. Ripa,[12] G.K. Hovingh,[12] K. Brown-Frandsen,[12] S.C. Bain,[13] M.A. Cavender,[14] M. Gislum,[12] J.-P. David,[12] and J.B. Buse,[14] for the SOUL Study Group*

ABSTRACT

BACKGROUND

The cardiovascular safety of oral semaglutide, a glucagon-like peptide 1 receptor agonist, has been established in persons with type 2 diabetes and high cardiovascular risk. An assessment of the cardiovascular efficacy of oral semaglutide in persons with type 2 diabetes and atherosclerotic cardiovascular disease, chronic kidney disease, or both is needed.

METHODS

In this double-blind, placebo-controlled, event-driven, superiority trial, we randomly assigned participants who were 50 years of age or older, had type 2 diabetes with a glycated hemoglobin level of 6.5 to 10.0%, and had known atherosclerotic cardiovascular disease, chronic kidney disease, or both to receive either once-daily oral semaglutide (maximal dose, 14 mg) or placebo, in addition to standard care. The primary outcome was major adverse cardiovascular events (a composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke), assessed in a time-to-first-event analysis. The confirmatory secondary outcomes included major kidney disease events (a five-point composite outcome).

RESULTS

Among the 9650 participants who had undergone randomization, the mean (±SD) follow-up was 47.5±10.9 months, and the median follow-up was 49.5 months. A primary-outcome event occurred in 579 of the 4825 participants (12.0%; incidence, 3.1 events per 100 person-years) in the oral semaglutide group, as compared with 668 of the 4825 participants (13.8%; incidence, 3.7 events per 100 person-years) in the placebo group (hazard ratio, 0.86; 95% confidence interval, 0.77 to 0.96; P=0.006). The results for the confirmatory secondary outcomes did not differ significantly between the two groups. The incidence of serious adverse events was 47.9% in the oral semaglutide group and 50.3% in the placebo group; the incidence of gastrointestinal disorders was 5.0% and 4.4%, respectively.

CONCLUSIONS

Among persons with type 2 diabetes and atherosclerotic cardiovascular disease, chronic kidney disease, or both, the use of oral semaglutide was associated with a significantly lower risk of major adverse cardiovascular events than placebo, without an increase in the incidence of serious adverse events. (Funded by Novo Nordisk; SOUL ClinicalTrials.gov number, NCT03914326.)

The authors' full names, academic degrees, and affiliations are listed at the end of the article. Dr. McGuire can be contacted at darren.mcguire@utsouthwestern.edu or at University of Texas Southwestern Medical Center, 5323 Harry Hines Blvd., Dallas, TX 75390-8860.

*Members of the SOUL Study Group are listed in the Supplementary Appendix, available at NEJM.org.

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Approximately 828 million adults worldwide are affected by diabetes,[1] with type 2 diabetes accounting for more than 90% of cases.[2] Type 2 diabetes is associated with a high risk of cardiovascular disease.[3,4] Trials designed to assess cardiovascular outcomes in persons with type 2 diabetes have shown that certain glucagon-like peptide 1 (GLP-1) receptor agonists and certain sodium–glucose cotransporter 2 (SGLT2) inhibitors reduce the risk of major adverse cardiovascular events.[5-7]

Semaglutide is a long-acting GLP-1 receptor agonist. For the injectable formulation of semaglutide, cardiovascular efficacy has been established in persons with type 2 diabetes and cardiovascular disease or a high risk of cardiovascular disease, as well as in those with type 2 diabetes and chronic kidney disease.[5,8,9] For the oral formulation of semaglutide, cardiovascular safety has been established in persons with type 2 diabetes and high cardiovascular risk,[10] but an assessment of cardiovascular efficacy is needed. The Semaglutide Cardiovascular Outcomes Trial (SOUL) was designed to assess the cardiovascular efficacy of oral semaglutide in persons with type 2 diabetes and established atherosclerotic cardiovascular disease, chronic kidney disease, or both.

Methods

Trial Design and Oversight

We conducted an international, double-blind, randomized, placebo-controlled, event-driven, superiority phase 3b trial. The trial design has been described previously[11] and is summarized in Figure S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org.

The trial was overseen by an academic-led steering committee (a list of members is provided in the Supplementary Appendix) in partnership with the trial sponsor, Novo Nordisk, which managed trial operations. The trial steering committee provided overall leadership, oversaw the design and conduct of the trial and the analysis of the data, and was responsible for reporting the results. Data analysis was conducted by the sponsor, and the analyses of the primary and confirmatory secondary outcomes were independently verified by Statogen Consulting. All the authors had access to summary results from the analyzed data set, contributed to the writing of the manuscript, and made the decision to submit the manuscript for publication. Medical writing and editorial support was funded by the sponsor. All the authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol, available at NEJM.org.

Trial Participants

Persons were eligible for inclusion in the trial if they were 50 years of age or older and had type 2 diabetes, a glycated hemoglobin level of 6.5 to 10.0%, and at least one of the following conditions: coronary artery disease, cerebrovascular disease, symptomatic peripheral artery disease, or chronic kidney disease (defined by an estimated glomerular filtration rate [eGFR] of <60 ml per minute per 1.73 m^2).[11] Persons who had end-stage kidney disease or had received long-term kidney-replacement therapy were excluded. The full inclusion and exclusion criteria are provided in the Supplementary Appendix. All the participants provided written informed consent.

Trial Procedures

After completion of a screening visit, participants were randomly assigned in a 1:1 ratio to receive once-daily oral semaglutide or matching placebo, in addition to standard care. The dose-escalation regimen for oral semaglutide is described in Figure S1; the dose was started at 3 mg and was escalated to 7 mg and then 14 mg. The 14-mg dose was to be maintained until the end of treatment, with dose reductions, extensions of dose-escalation intervals, and treatment pauses allowed if needed to mitigate treatment-associated adverse events. Treatment was to be continued until the end of the trial, when the target number of primary-outcome events had occurred. Standard care consisted of glucose-lowering and cardiovascular risk–reducing therapies administered in accordance with local guidelines.

Participants were instructed to take the semaglutide or placebo tablet in the morning, in a fasting state, with up to 120 ml of water and to wait at least 30 minutes before taking food, drink, or other oral medications. Trial visits occurred at 4, 8, and 13 weeks after randomization and approximately every 13 weeks thereafter. Details regarding the visit schedule and assessments have been described previously.[11] The trial observation period was defined as the time from randomization until the end-of-trial visit or the participant's death,

the date of last contact, or the date of participant withdrawal.

TRIAL OUTCOMES

The primary outcome was major adverse cardiovascular events (a three-point composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke), assessed in an analysis of the time from randomization to the first event. The confirmatory secondary outcomes were three time-to-first-event outcomes tested in hierarchical order: major kidney disease events (a five-point composite of death from cardiovascular causes, death from kidney-related causes, a persistent reduction from baseline in the eGFR of ≥50% as measured with the Chronic Kidney Disease Epidemiology Collaboration method,[12] a persistent eGFR of <15 ml per minute per 1.73 m^2, or the initiation of long-term kidney-replacement therapy with either dialysis or transplantation); death from cardiovascular causes; and major adverse limb events (a two-point composite of hospitalization for acute limb ischemia or hospitalization for chronic limb ischemia).

Supportive secondary outcomes included time-to-first-event outcomes such as heart failure events (a three-point composite of death from cardiovascular causes, an urgent visit for heart failure, or hospitalization for heart failure), death from any cause, fatal or nonfatal myocardial infarction, fatal or nonfatal stroke, and severe hypoglycemic episodes. Measures of metabolism and inflammation were assessed; the change from baseline to week 104 for each of these measures was a prespecified secondary outcome. Adverse events and serious adverse events were reported. Details regarding the efficacy and safety outcomes are provided in the Supplementary Appendix. Potential cardiovascular and kidney-related outcome events and selected adverse events were assessed by means of central adjudication, which was performed with the use of standard outcome definitions by an external adjudication committee whose members were unaware of the randomized group assignments.[13]

STATISTICAL ANALYSIS

For this event-driven trial, we estimated that a sample of 9642 participants would provide the trial with 90% power to detect a 17% lower risk of a primary-outcome event in the oral semaglutide group than in the placebo group at an overall one-sided significance level of 0.025. The sample-size estimate was based on the following assumptions: a primary-outcome event occurring in 3.5% of the participants per year in the placebo group, a trial duration of 5 years 5 weeks, and withdrawal or loss to follow-up occurring in 1% of the participants in each group.[11] One interim analysis for superiority was prespecified to occur when two thirds of the total planned number of primary-outcome events had accrued. The target number of primary-outcome events was at least 1225.

Efficacy analyses were performed in the intention-to-treat population, which included all the individual participants who had undergone randomization, regardless of adherence to oral semaglutide or placebo or changes to background medications. Data from the participants who withdrew from the trial, died, or were lost to follow-up were censored at the time of withdrawal, death, or last contact, respectively.

For the time-to-first-event outcomes, hazard ratios and 95% confidence intervals were calculated with the use of a Cox proportional-hazards model with randomized group assignment as a fixed factor. For the primary outcome, the hazard ratio, 95% confidence interval, and P value were adjusted on the basis of the group sequential design with the use of likelihood-ratio ordering.[14] If superiority with respect to the primary outcome was established for oral semaglutide, the confirmatory secondary outcomes were to be evaluated in hierarchical order; a significant effect of oral semaglutide had to be shown at each step before the next outcome could be tested for significance. To account for the results from the prespecified interim analysis and to preserve the studywise one-sided type 1 error at 2.5%, the nominal significance level was calculated with the Lan–DeMets alpha-spending function for the primary and confirmatory secondary outcomes.[15] Although the statistical analysis plan specified that one-sided P values would be used for hypothesis testing, two-sided P values are reported here.

To investigate the effect of the assumption of independent censoring of data for participants who were withdrawn or lost to follow-up, a two-way tipping-point analysis and analyses with multiple imputation of event times for participants who were withdrawn or lost to follow-up were performed as sensitivity analyses. Consistency of

the treatment effect with respect to the primary outcome was explored in analyses of subgroups defined according to information obtained at baseline (age, sex, race, ethnic group, region, body-mass index, glycated hemoglobin level, medical history, eGFR, and medication use). The trial was not powered to compare the treatment effect across subgroups. Confidence intervals for supportive secondary outcomes were not adjusted for multiplicity and therefore cannot be used for hypothesis testing. Details regarding the interim analysis and the analyses of secondary outcomes are provided in the Supplementary Appendix. All statistical analyses were performed with SAS software, version 9.4 TS1M5 (SAS Institute).

RESULTS

PARTICIPANTS

From June 2019 through March 2021, a total of 9650 persons underwent randomization at 444 sites in 33 countries, with 4825 participants randomly assigned to each trial group (Table 1). The mean (±SD) age of the participants was 66.1±7.6 years, and 28.9% were women. Most participants had a history of cardiovascular disease (coronary artery disease in 70.7%, heart failure in 23.1%, cerebrovascular disease in 21.2%, and peripheral artery disease in 15.7%), and 42.4% had a history of chronic kidney disease. In both trial groups, 26.9% of the participants were receiving SGLT2 inhibitors at baseline. A full description of participant characteristics and medications used at baseline is provided in Table S1, and the representativeness of the trial population is summarized in Table S2.

The disposition of the participants is shown in Figure S2. The mean follow-up was 47.5±10.9 months, the median follow-up was 49.5 months (interquartile range, 44.0 to 54.9), and 9495 participants (98.4%) completed the trial, having died or attended the end-of-trial visit. Vital status was available for 99.5% of the participants. Participants received oral semaglutide or placebo for 87.4% of the total possible duration (86.5% in the oral semaglutide group and 88.4% in the placebo group). Treatment with an open-label GLP-1 receptor agonist during the trial (a protocol violation) was initiated in 172 participants (3.6%) in the oral semaglutide group and in 253 participants (5.2%) in the placebo group. The distribution of participants who were receiving the 3-mg, 7-mg, and 14-mg doses of oral semaglutide or placebo over time is summarized in Figure S3A. Premature permanent discontinuation of oral semaglutide or placebo occurred in 1309 participants (27.1%) in the oral semaglutide group and in 1373 participants (28.5%) in the placebo group (Fig. S3B).

PRIMARY AND CONFIRMATORY SECONDARY OUTCOMES

A primary-outcome event occurred in 579 of the 4825 participants (12.0%; incidence, 3.1 events per 100 person-years) in the oral semaglutide group, as compared with 668 of the 4825 participants (13.8%; incidence, 3.7 events per 100 person-years) in the placebo group (hazard ratio, 0.86; 95% confidence interval [CI], 0.77 to 0.96; P=0.006), results that showed the superiority of oral semaglutide over placebo (Fig. 1A and Table 2). In a prespecified analysis of primary-outcome events occurring through week 156 (3 years), the absolute risk reduction (difference in risk between the oral semaglutide group and the placebo group) was 2.0 percentage points, and the number needed to treat to prevent one event in this population was 50 persons (95% CI, 31 to 125). The effect of oral semaglutide with respect to the primary outcome was consistent across prespecified sensitivity analyses (Table S3) and appeared to be consistent across most analyses of prespecified subgroups, including those defined according to age, sex, body-mass index, a history of cardiovascular or kidney disease, eGFR, and medication use at baseline (Fig. S4).

A total of 301 participants (6.2%) in the oral semaglutide group and 320 participants (6.6%) in the placebo group died from cardiovascular causes (hazard ratio, 0.93; 95% CI, 0.80 to 1.09) (Fig. 1B). Nonfatal myocardial infarction occurred in 191 participants (4.0%) in the oral semaglutide group and in 253 participants (5.2%) in the placebo group (hazard ratio, 0.74; 95% CI, 0.61 to 0.89) (Fig. 1C), and nonfatal stroke occurred in 144 (3.0%) and 161 (3.3%), respectively (hazard ratio, 0.88; 95% CI, 0.70 to 1.11) (Fig. 1D).

For the first confirmatory secondary outcome in the hierarchy (major kidney disease events), an event occurred in 403 participants (8.4%; incidence, 2.1 events per 100 person-years) in the oral semaglutide group, as compared with 435 participants (9.0%; incidence, 2.3 events per 100 person-years) in the placebo group (hazard ratio, 0.91; 95% CI, 0.80 to 1.05; P=0.19) (Fig. 1E).

Table 1. Characteristics of the Participants at Baseline.*

Characteristic	Oral Semaglutide (N=4825)	Placebo (N=4825)
Age — yr	66.1±7.6	66.1±7.5
Female sex — no. (%)	1376 (28.5)	1414 (29.3)
Race or ethnic group — no. (%)†		
White	3327 (69.0)	3321 (68.8)
Black	124 (2.6)	128 (2.7)
Asian	1134 (23.5)	1121 (23.2)
American Indian or Alaska Native	7 (0.1)	12 (0.2)
Native Hawaiian or Pacific Islander	4 (<0.1)	5 (0.1)
Other	185 (3.8)	192 (4.0)
Not reported	44 (0.9)	46 (1.0)
Hispanic or Latino ethnic group — no. (%)†	674 (14.0)	706 (14.6)
Body weight — kg	87.5±19.1	88.3±19.6
Body-mass index‡	31.0±5.7	31.2±5.9
Glycated hemoglobin level — mmol/mol	63.6±12.6	63.5±12.3
Glycated hemoglobin level — %	8.0±1.2	8.0±1.1
Median duration of diabetes (IQR) — yr	14.7 (9.0–20.8)	14.6 (8.9–20.8)
History of cardiovascular or kidney disease — no. (%)§		
Cardiovascular disease only	2730 (56.6)	2738 (56.7)
Chronic kidney disease only	632 (13.1)	609 (12.6)
Both cardiovascular and chronic kidney disease	1303 (27.0)	1317 (27.3)
Hypertension — no. (%)	4378 (90.7)	4381 (90.8)
Current smoking — no. (%)	545 (11.3)	584 (12.1)
Systolic blood pressure — mm Hg	134.6±16.3	134.7±16.4
Diastolic blood pressure — mm Hg	76.6±10.1	76.7±10.1
Pulse — beats/min	72.8±11.1	72.9±11.4
Median high-sensitivity C-reactive protein level (IQR) — mg/liter	2.0 (0.9–4.3)	2.0 (0.9–4.5)
eGFR — ml/min/1.73 m^2¶	74.0±22.6	73.6±22.6

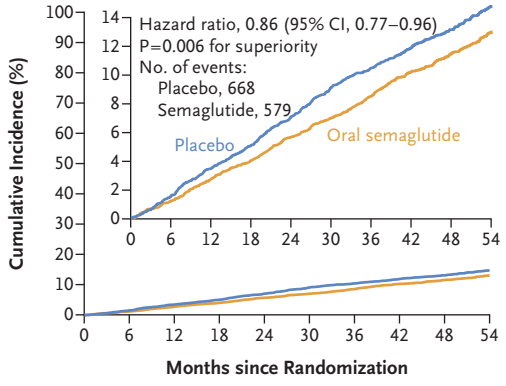
* Plus–minus values are means ±SD. Percentages may not total 100 because of rounding. A full description of participant characteristics and medications used at baseline is provided in Table S1. The abbreviation eGFR denotes estimated glomerular filtration rate, and IQR interquartile range.
† Race and ethnic group were reported by the participant.
‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.
§ For 3.3% of the participants, whether only one criterion or two criteria were fulfilled was unknown. Chronic kidney disease was defined by an eGFR of less than 60 ml per minute per 1.73 m^2; the most recent eGFR available in the medical record was used if it had been obtained within the previous 6 months.
¶ The eGFR was measured at randomization with the use of the Chronic Kidney Disease Epidemiology Collaboration method.[12]

Among the five components of this composite outcome, death from cardiovascular causes accounted for 71.2% of the events, whereas 28.8% were kidney-related events. The remaining two confirmatory secondary outcomes in the hierarchy were not tested for significance: death from cardiovascular causes (hazard ratio, 0.93; 95% CI, 0.80 to 1.09) (Fig. 1B) and major adverse limb events (hazard ratio, 0.71; 95% CI, 0.52 to 0.96) (Fig. 1F).

SUPPORTIVE SECONDARY OUTCOMES

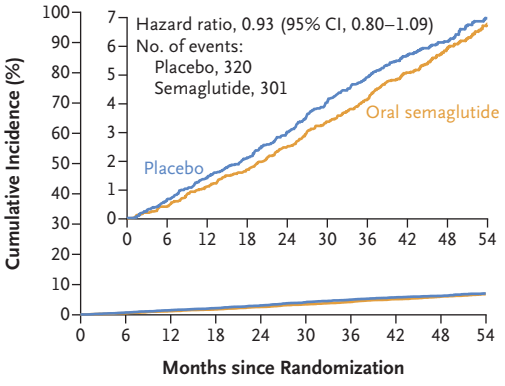
The results for additional efficacy outcomes are summarized in Table 2. The hazard ratio (oral

A Major Adverse Cardiovascular Events



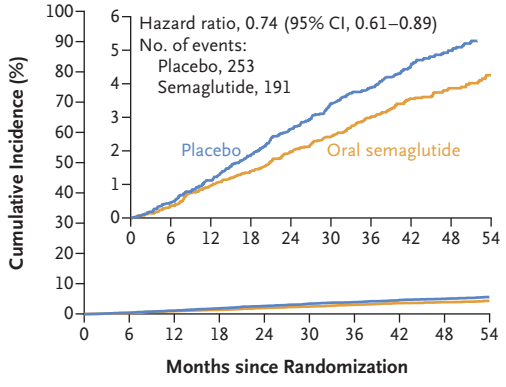
No. at Risk										
Placebo	4825	4718	4583	4455	4322	4194	4101	3727	2517	1346
Oral semaglutide	4825	4743	4635	4542	4438	4346	4239	3831	2555	1346

B Death from Cardiovascular Causes



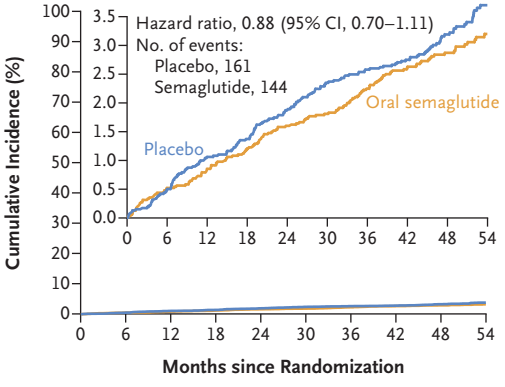
No. at Risk										
Placebo	4825	4760	4680	4594	4511	4427	4355	3991	2721	1460
Oral semaglutide	4825	4781	4712	4648	4583	4509	4436	4040	2727	1460

C Nonfatal Myocardial Infarction



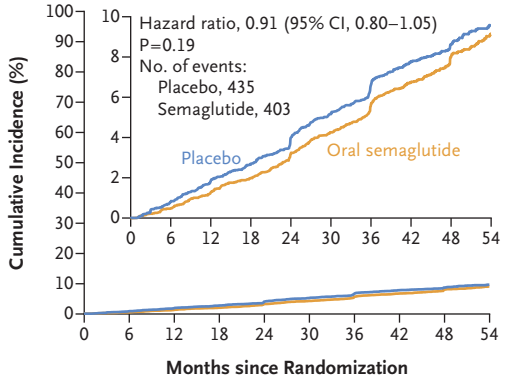
No. at Risk										
Placebo	4825	4739	4631	4511	4395	4284	4197	3821	2595	1390
Oral semaglutide	4825	4766	4672	4593	4505	4416	4322	3922	2638	1394

D Nonfatal Stroke



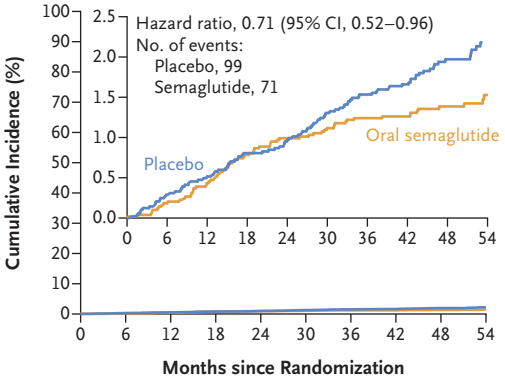
No. at Risk										
Placebo	4825	4739	4631	4533	4432	4330	4254	3890	2636	1412
Oral semaglutide	4825	4758	4675	4595	4513	4434	4346	3943	2640	1408

E Major Kidney Disease Events



No. at Risk										
Placebo	4825	4753	4661	4570	4469	4378	4282	3911	2658	1429
Oral semaglutide	4825	4778	4704	4636	4551	4469	4372	3973	2681	1430

F Major Adverse Limb Events



No. at Risk										
Placebo	4825	4746	4655	4459	4470	4376	4296	3940	2678	1436
Oral semaglutide	4825	4772	4691	4612	4540	4463	4388	3999	2696	1439

Figure 1 (facing page). Time-to-First-Event Efficacy Outcomes.

Cumulative-incidence plots are shown for the primary outcome: major adverse cardiovascular events (Panel A), a three-point composite of death from cardiovascular causes (Panel B), nonfatal myocardial infarction (Panel C), or nonfatal stroke (Panel D). Cumulative-incidence plots are also shown for the confirmatory secondary outcomes, which were tested in hierarchical order: major kidney disease events (Panel E), death from cardiovascular causes (Panel B), and major adverse limb events (Panel F). The major kidney disease events outcome is a five-point composite of death from cardiovascular causes, death from kidney-related causes, a persistent reduction from baseline in the estimated glomerular filtration rate (eGFR) of 50% or more as measured with the Chronic Kidney Disease Epidemiology Collaboration method, a persistent eGFR of less than 15 ml per minute per 1.73 m^2, or the initiation of long-term kidney-replacement therapy with either dialysis or transplantation. The major adverse limb events outcome is a two-point composite of hospitalization for acute limb ischemia or hospitalization for chronic limb ischemia. Two-sided P values are shown. Because the results for the first confirmatory secondary outcome were not significant, the results for the two subsequent confirmatory secondary outcomes in the testing hierarchy are reported as point estimates and 95% confidence intervals. The x axis is truncated at 54 months because of the limited number of participants in the trial after that time point. The insets show the same data on an enlarged y axis.

semaglutide vs. placebo) for heart failure events was 0.90 (95% CI, 0.79 to 1.03); for death from any cause, 0.91 (95% CI, 0.80 to 1.02); for fatal or nonfatal myocardial infarction, 0.73 (95% CI, 0.61 to 0.88); and for fatal or nonfatal stroke, 0.95 (95% CI, 0.76 to 1.17).

The change from baseline to week 104 in the mean glycated hemoglobin level was −0.71 percentage points with oral semaglutide and −0.15 percentage points with placebo (estimated difference, −0.56 percentage points; 95% CI, −0.61 to −0.52) (Fig. 2A); the trial population was also receiving standard care that could include glycemia treatment. The change from baseline to week 104 in the mean body weight was −4.22 kg with oral semaglutide and −1.27 kg with placebo (estimated difference, −2.95 kg; 95% CI, −3.18 to −2.73) (Fig. 2B). The high-sensitivity C-reactive protein level was lower in the oral semaglutide group than in the placebo group at baseline, and the difference persisted over time (geometric mean level at week 104, 1.56 vs. 2.01 mg per liter) (Fig. 2C).

A total of 88 episodes of severe hypoglycemia occurred in the oral semaglutide group, and 121 episodes occurred in the placebo group (mean ratio, 0.73; 95% CI, 0.50 to 1.07). These episodes occurred in 76 participants (1.6%) and 84 participants (1.7%), respectively; in an analysis of the time to the first episode, the hazard ratio was 0.90 (95% CI, 0.66 to 1.22).

SAFETY OUTCOMES

Serious adverse events were reported in 2312 participants (47.9%) in the oral semaglutide group and in 2427 participants (50.3%) in the placebo group (P=0.02). The most common serious adverse events were cardiac disorders (occurring in 861 [17.8%] and 954 [19.8%], respectively) and infections or infestations (occurring in 726 [15.0%] and 797 [16.5%]). Gastrointestinal disorders were more common with oral semaglutide than with placebo (occurring in 239 [5.0%] and 210 [4.4%], respectively). The difference between the trial groups in the incidence of gallbladder disorders, retinal disorders, or malignant neoplasms ranged from 0.4 to 0.8 percentage points (22 to 38 events). Acute pancreatitis occurred in 0.4% of the participants in both groups.

Adverse events that led to permanent discontinuation of oral semaglutide or placebo occurred in 749 participants (15.5%) in the oral semaglutide group and in 559 participants (11.6%) in the placebo group. Such events were mainly gastrointestinal disorders (in 310 [6.4%] and 98 [2.0%], respectively), as well as infections or infestations (in 63 [1.3%] and 96 [2.0%]). Additional adverse events that led to permanent discontinuation of the trial regimen were specified as other (in 6.6% and 7.9%) and as unintentional (in 2.9% and 4.0%). Death from noncardiovascular causes occurred in 227 participants (4.7%) receiving oral semaglutide and in 257 participants (5.3%) receiving placebo. A summary of safety events is shown in Table S4.

DISCUSSION

Oral semaglutide was associated with a significantly lower risk of major adverse cardiovascular events than placebo, with a hazard ratio of 0.86 (corresponding to a relative risk reduction of 14%), among persons with type 2 diabetes and atherosclerotic cardiovascular disease, chronic kidney disease, or both. These results show a cardiovas-

Table 2. Primary and Secondary Efficacy Outcomes.*

Outcome	Oral Semaglutide (N=4825)		Placebo (N=4825)		Hazard Ratio (95% CI)	P Value†
	no. of participants with event (%)	*no. of events per 100 person-yr*	*no. of participants with event (%)*	*no. of events per 100 person-yr*		
Primary outcome						
Major adverse cardiovascular events, three-point composite‡	579 (12.0)	3.1	668 (13.8)	3.7	0.86 (0.77–0.96)	0.006
Confirmatory secondary outcomes						
Major kidney disease events, five-point composite§	403 (8.4)	2.1	435 (9.0)	2.3	0.91 (0.80–1.05)	0.19
Death from cardiovascular causes	301 (6.2)	1.6	320 (6.6)	1.7	0.93 (0.80–1.09)	—
Major adverse limb events, two-point composite¶	71 (1.5)	0.4	99 (2.1)	0.5	0.71 (0.52–0.96)	—
Supportive secondary outcomes						
Major adverse cardiovascular events, five-point composite‖	670 (13.9)	3.6	777 (16.1)	4.3	0.84 (0.76–0.93)	—
Nonfatal myocardial infarction	191 (4.0)	1.0	253 (5.2)	1.4	0.74 (0.61–0.89)	—
Fatal or nonfatal myocardial infarction	200 (4.1)	1.1	268 (5.6)	1.4	0.73 (0.61–0.88)	—
Nonfatal stroke	144 (3.0)	0.8	161 (3.3)	0.9	0.88 (0.70–1.11)	—
Fatal or nonfatal stroke	164 (3.4)	0.9	171 (3.5)	0.9	0.95 (0.76–1.17)	—
Coronary revascularization	200 (4.1)	1.1	263 (5.5)	1.4	0.75 (0.62–0.90)	—
Hospitalization for unstable angina pectoris	74 (1.5)	0.4	80 (1.7)	0.4	0.92 (0.67–1.26)	—
Death from any cause	528 (10.9)	2.8	577 (12.0)	3.0	0.91 (0.80–1.02)	—
Death from noncardiovascular causes	227 (4.7)	1.2	257 (5.3)	1.4	0.87 (0.73–1.04)	—
Heart failure events, three-point composite**	405 (8.4)	2.1	443 (9.2)	2.4	0.90 (0.79–1.03)	—
Heart failure	146 (3.0)	0.8	167 (3.5)	0.9	0.86 (0.69–1.08)	—
Major kidney disease events, four-point composite††	112 (2.3)	0.6	129 (2.7)	0.7	0.86 (0.66–1.10)	—
Death from kidney-related causes	1 (<0.1)	<0.1	7 (0.1)	<0.1	0.14 (0.01–0.79)	—
Severe hypoglycemic episode	76 (1.6)	0.5	84 (1.7)	0.6	0.90 (0.66–1.22)	—

* Time-to-first-event outcomes are shown for the intention-to-treat population (all the individual participants who had undergone randomization) during the trial observation period. All the outcomes were analyzed with the use of a Cox proportional-hazards model with randomized group assignment as a categorical fixed factor. Confidence intervals for supportive secondary outcomes were not adjusted for multiplicity and therefore cannot be used for hypothesis testing. Data from participants without events of interest were censored at the end of their trial observation period.

† Two-sided P values are shown. After accounting for the results from the interim analysis, the nominal two-sided significance level for the primary outcome was 0.04561. The nominal two-sided significance level for the first confirmatory secondary outcome was 0.04433.

‡ As the primary outcome, the major adverse cardiovascular events outcome is a three-point composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke.

§ As the first confirmatory secondary outcome, the major kidney disease events outcome is a five-point composite of death from cardiovascular causes, death from kidney-related causes, a persistent reduction from baseline in the eGFR of 50% or more as measured with the Chronic Kidney Disease Epidemiology Collaboration method, a persistent eGFR of less than 15 ml per minute per 1.73 m^2, or the initiation of long-term kidney-replacement therapy with either dialysis or transplantation.

¶ The major adverse limb events outcome is a two-point composite of hospitalization for acute limb ischemia or hospitalization for chronic limb ischemia.

‖ As a supportive secondary outcome, the major adverse cardiovascular events outcome is a five-point composite of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, or hospitalization for unstable angina.

** The heart failure events outcome is a three-point composite of death from cardiovascular causes, an urgent visit for heart failure, or hospitalization for heart failure.

†† As a supportive secondary outcome, the major kidney disease events outcome is a four-point composite of death from kidney-related causes, a persistent reduction from baseline in the eGFR of 50% or more as measured with the Chronic Kidney Disease Epidemiology Collaboration method, a persistent eGFR of less than 15 ml per minute per 1.73 m^2, or the initiation of long-term kidney-replacement therapy with either dialysis or transplantation.

cular benefit of oral semaglutide and are consistent with results reported for injectable semaglutide and other GLP-1 receptor agonists with established cardiovascular efficacy.[8,9]

Among the three components of the primary outcome, nonfatal myocardial infarction had the largest difference in risk between the oral semaglutide group and the placebo group. This finding contrasts with results from PIONEER 6, a noninferiority trial investigating the use of oral semaglutide in persons with type 2 diabetes and high cardiovascular risk, in which a reduction in the risk of death from cardiovascular causes was the dominant beneficial effect.[10] Of note, the mean duration of follow-up and the sample size in SOUL (47.5 months and 9650 participants, respectively) were approximately three times those in PIONEER 6 (15.8 months and 3183 participants). Overall, the reduction in the risk of a primary-outcome event in SOUL is in keeping with observations in other trials assessing cardiovascular outcomes associated with GLP-1 receptor agonists.[5,7]

The results for all three confirmatory secondary outcomes were directionally consistent with the results for the primary outcome, but a significant effect was not observed for the first outcome in the hierarchy (major kidney disease events), and thus statistical testing was stopped at the second step. Among the five components of the first confirmatory secondary outcome, death from cardiovascular causes accounted for 71.2% of the events. The results for this composite outcome in SOUL (hazard ratio, 0.91; 95% CI, 0.80 to 1.05; P=0.19) differed from those seen in FLOW (hazard ratio, 0.76; 95% CI, 0.66 to 0.88; P=0.0003), a trial investigating injectable semaglutide administered once weekly at a dose of 1.0 mg in persons with type 2 diabetes and chronic kidney disease.[9]

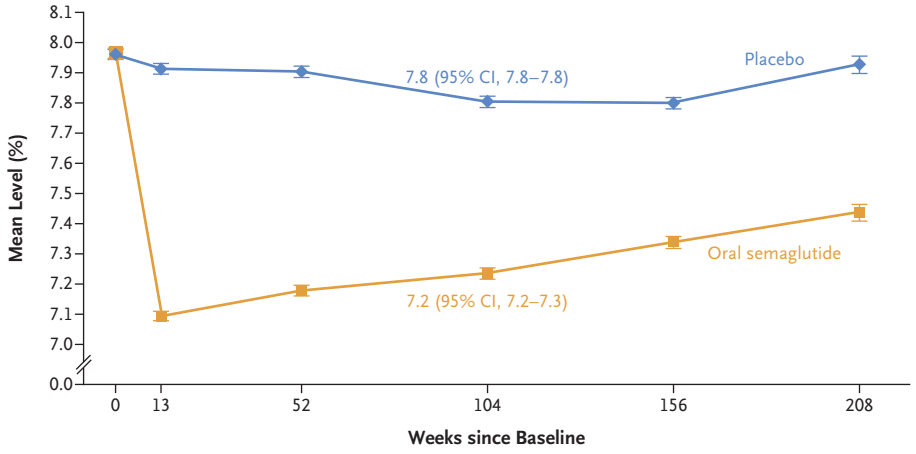
The difference between these two trials in the risk of major kidney disease events may be due to chance, or it could be related to population characteristics (baseline eGFR, 47.0 ml per minute per 1.73 m^2 in FLOW vs. 73.8 ml per minute per 1.73 m^2 in SOUL). In addition, the difference in bioavailability between subcutaneous semaglutide administered once weekly at a dose of 1 mg (89%) and oral semaglutide administered once daily at a dose of 14 mg (0.4 to 1%) may be a factor.[16,17] However, the option to have an efficacious oral GLP-1 receptor agonist is relevant to patients' preference for oral over injectable diabetes medication[18] and aims to alleviate concerns about injections among patients and clinicians.[19]

The overall safety profile of oral semaglutide in SOUL was consistent with that seen in previous trials of semaglutide,[20] and no new safety signals were observed. The incidence of serious adverse events was lower among participants receiving oral semaglutide than among those receiving placebo, a difference that was mostly due to the higher incidence of cardiac disorders and infections or infestations in the placebo group. The incidence of adverse events that led to discontinuation of oral semaglutide or placebo was higher among participants receiving oral semaglutide, a difference that was largely due to gastrointestinal symptoms. Gastrointestinal events are known to occur with GLP-1 receptor agonists, particularly during treatment initiation and dose escalation.[21]

The strengths of this trial include its large sample size and long follow-up duration. The effect of oral semaglutide with respect to cardiovascular outcomes appeared to be consistent across age-based subgroups and consistent with the effect observed in trials of injectable semaglutide, although direct comparisons cannot be made outside the context of a comparative-effectiveness trial. The effect of oral semaglutide with respect to the primary outcome appeared to be larger among participants with glycated hemoglobin levels higher than 8% than among those with lower glycated hemoglobin levels and also appeared to be larger among participants in certain regions (particularly Asia). It should be noted that the trial was not powered to compare the treatment effect across subgroups, and the effect appeared to be consistent across all other subgroups. Furthermore, the cardioprotective effect of oral semaglutide was seen in a population with high concomitant use of cardiovascular protective drugs, including SGLT2 inhibitors.

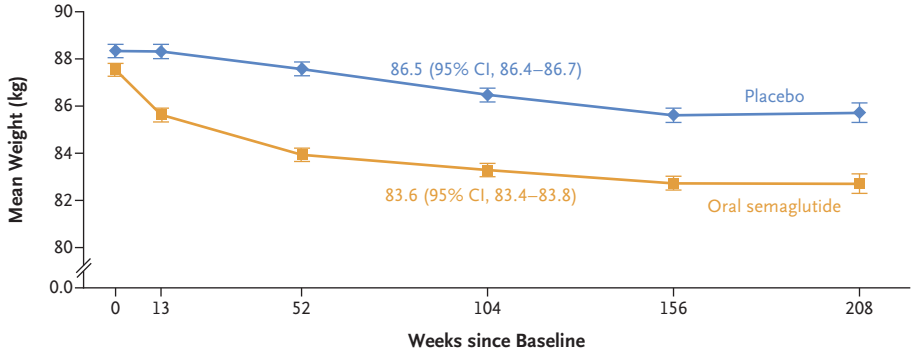
Among limitations of this trial was the inclusion criterion of a history of cardiovascular disease, chronic kidney disease, or both, which was designed to enrich the trial population for assessing the effect of oral semaglutide. Although this inclusion criterion resulted in a trial population that was not representative of the global population with type 2 diabetes, approximately 32% of persons with type 2 diabetes have cardiovascular disease,[22] and an estimated 25 to 40%

A Glycated Hemoglobin Level



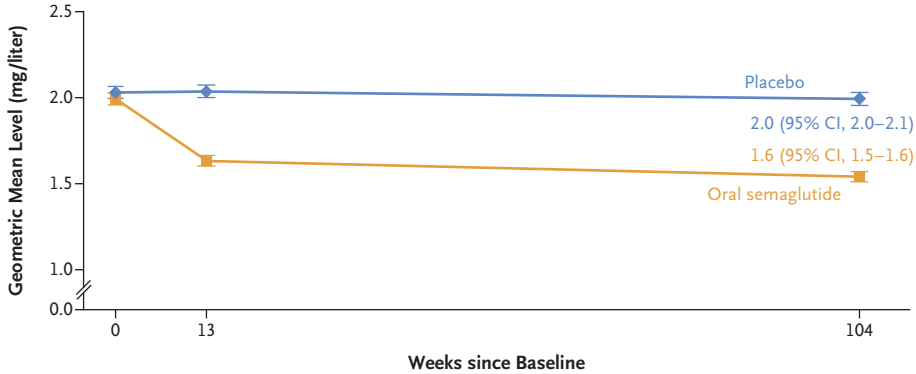
No. at Risk						
Placebo	4749	4497	4355	4065	3837	2057
Oral semaglutide	4736	4525	4386	4144	3985	2155

B Body Weight



No. at Risk						
Placebo	4820	4322	4350	4159	3897	2100
Oral semaglutide	4819	4336	4371	4255	4022	2183

C High-Sensitivity C-Reactive Protein Level



No. at Risk				
Placebo	4791	4546		4119
Oral semaglutide	4786	4583		4200

Figure 2 (facing page). Measures of Metabolism and Inflammation.

Shown are the observed mean glycated hemoglobin level (Panel A), mean body weight (Panel B), and geometric mean high-sensitivity C-reactive protein level (Panel C) for the intention-to-treat population (all the individual participants who had undergone randomization) during the trial observation period. The change from baseline to week 104 for each of these measures was a prespecified secondary outcome. I bars indicate standard errors.

have chronic kidney disease.[23] In addition, as seen in other trials assessing cardiovascular outcomes, the trial population was not fully representative of the overall global population in terms of demographic characteristics, particularly because only 28.9% of enrolled participants were women and only 2.6% identified as Black (Table S1); 9.5% of the participants enrolled in the United States identified as Black. Type 2 diabetes is more likely to affect Black persons than White persons, and the risk of cardiovascular disease and the associated mortality are higher among women than men.[24,25] Finally, the effects of oral semaglutide with respect to kidney-related outcomes could not be clarified.

In this randomized, placebo-controlled trial involving persons with type 2 diabetes and atherosclerotic cardiovascular disease, chronic kidney disease, or both, daily oral semaglutide was superior to placebo in reducing the risk of major adverse cardiovascular events.

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AUTHOR INFORMATION

Darren K. McGuire, M.D., M.H.Sc.,[1,2] Nikolaus Marx, M.D.,[3] Sharon L. Mulvagh, M.D.,[4] John E. Deanfield, M.D.,[5] Silvio E. Inzucchi, M.D.,[6] Rodica Pop-Busui, M.D., Ph.D.,[7] Johannes F.E. Mann, M.D.,[8,9] Scott S. Emerson, M.D., Ph.D.,[10] Neil R. Poulter, F.Med.Sci.,[11] Mads D.M. Engelmann, M.D., Ph.D.,[12] Maria Sejersten Ripa, M.D., M.D.Sc.,[12] G. Kees Hovingh, M.D., Ph.D.,[12] Kirstine Brown-Frandsen, M.D.,[12] Stephen C. Bain, M.D.,[13] Matthew A. Cavender, M.D., M.P.H.,[14] Mette Gislum, M.Sc.,[12] Jens-Peter David, Ph.D.,[12] and John B. Buse, M.D., Ph.D.[14]

[1] University of Texas Southwestern Medical Center, Dallas; [2] Parkland Health System, Dallas; [3] Clinic for Cardiology, Angiology, and Intensive Care Medicine, Rheinisch-Westfälische Technische Hochschule Aachen University, University Hospital Aachen, Aachen, Germany; [4] Department of Medicine, Division of Cardiology, Dalhousie University, Halifax, NS, Canada; [5] Institute of Cardiovascular Sciences, University College London, London; [6] Section of Endocrinology, Yale University School of Medicine, New Haven, CT; [7] Division of Endocrinology, Diabetes, and Clinical Nutrition, Oregon Health and Science University, Portland; [8] Kuratorium für Heimdialyse Kidney Center, Munich, Germany; [9] Friedrich Alexander University of Erlangen, Erlangen, Germany; [10] Department of Biostatistics, University of Washington, Seattle; [11] Imperial Clinical Trials Unit, Imperial College London, London; [12] Novo Nordisk, Søborg, Denmark; [13] Swansea University Medical School, Swansea, United Kingdom; [14] University of North Carolina School of Medicine, Chapel Hill.

REFERENCES

1. NCD Risk Factor Collaboration (NCD-RisC). Worldwide trends in diabetes prevalence and treatment from 1990 to 2022: a pooled analysis of 1108 population-representative studies with 141 million participants. Lancet 2024;404:2077-93.

2. Magliano DJ, Boyko EJ. IDF diabetes atlas. 10th ed. Brussels: International Diabetes Federation, 2021.

3. Rawshani A, Rawshani A, Franzén S, et al. Risk factors, mortality, and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med 2018;379:633-44.

4. American Diabetes Association Professional Practice Committee. Cardiovascular disease and risk management: standards of care in diabetes — 2024. Diabetes Care 2024;47:Suppl 1:S179-S218.

5. Sattar N, Lee MMY, Kristensen SL, et al. Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of randomised trials. Lancet Diabetes Endocrinol 2021;9:653-62.

6. McGuire DK, Shih WJ, Cosentino F, et al. Association of SGLT2 inhibitors with cardiovascular and kidney outcomes in patients with type 2 diabetes: a meta-analysis. JAMA Cardiol 2021;6:148-58.

7. Badve SV, Bilal A, Lee MMY, et al. Effects of GLP-1 receptor agonists on kidney and cardiovascular disease outcomes: a meta-analysis of randomised controlled trials. Lancet Diabetes Endocrinol 2025;13:15-28.

8. Marso SP, Bain SC, Consoli A, et al. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med 2016;375:1834-44.

9. Perkovic V, Tuttle KR, Rossing P, et al. Effects of semaglutide on chronic kidney disease in patients with type 2 diabetes. N Engl J Med 2024;391:109-21.

10. Husain M, Birkenfeld AL, Donsmark M, et al. Oral semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med 2019;381:841-51.

11. McGuire DK, Busui RP, Deanfield J, et al. Effects of oral semaglutide on cardiovascular outcomes in individuals with type 2 diabetes and established atherosclerotic cardiovascular disease and/or chronic kidney disease: design and baseline characteristics of SOUL, a randomized trial. Diabetes Obes Metab 2023;25:1932-41.

12. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med 2009;150:604-12.

13. Hicks KA, Mahaffey KW, Mehran R, et al. 2017 Cardiovascular and stroke end-

point definitions for clinical trials. Circulation 2018;137:961-72.
14. Wassmer G, Brannath W. Group sequential and confirmatory adaptive designs in clinical trials. Berlin: Springer Nature, 2016.
15. Glimm E, Maurer W, Bretz F. Hierarchical testing of multiple endpoints in group-sequential trials. Stat Med 2010;29:219-28.
16. Novo Nordisk. Rybelsus (semaglutide) tablets, for oral use: highlights of prescribing information. 2024 (https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/213051s018lbl.pdf).
17. Overgaard RV, Delff PH, Petri KCC, Anderson TW, Flint A, Ingwersen SH. Population pharmacokinetics of semaglutide for type 2 diabetes. Diabetes Ther 2019;10:649-62.
18. Dibonaventura MD, Wagner J-S, Girman CJ, et al. Multinational Internet-based survey of patient preference for newer oral or injectable type 2 diabetes medication. Patient Prefer Adherence 2010;4:397-406.
19. Cooke CE, Lee HY, Tong YP, Haines ST. Persistence with injectable antidiabetic agents in members with type 2 diabetes in a commercial managed care organization. Curr Med Res Opin 2010;26:231-8.
20. Aroda VR, Erhan U, Jelnes P, et al. Safety and tolerability of semaglutide across the SUSTAIN and PIONEER phase IIIa clinical trial programmes. Diabetes Obes Metab 2023;25:1385-97.
21. Gorgojo-Martínez JJ, Mezquita-Raya P, Carretero-Gómez J, et al. Clinical recommendations to manage gastrointestinal adverse events in patients treated with GLP-1 receptor agonists: a multidisciplinary expert consensus. J Clin Med 2022;12:145.
22. Einarson TR, Acs A, Ludwig C, Panton UH. Prevalence of cardiovascular disease in type 2 diabetes: a systematic literature review of scientific evidence from across the world in 2007–2017. Cardiovasc Diabetol 2018;17:83.
23. de Boer IH, Khunti K, Sadusky T, et al. Diabetes management in chronic kidney disease: a consensus report by the American Diabetes Association (ADA) and Kidney Disease: Improving Global Outcomes (KDIGO). Diabetes Care 2022;45:3075-90.
24. Kautzky-Willer A, Leutner M, Harreiter J. Sex differences in type 2 diabetes. Diabetologia 2023;66:986-1002.
25. Bancks MP, Kershaw K, Carson AP, Gordon-Larsen P, Schreiner PJ, Carnethon MR. Association of modifiable risk factors in young adulthood with racial disparity in incident type 2 diabetes during middle adulthood. JAMA 2017;318:2457-65.