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

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ABSTRACT

BACKGROUND

Oral semaglutide, a glucagon-like peptide-1 receptor agonist, has proven cardiovascular safety in people with type 2 diabetes at high cardiovascular risk. The SOUL trial assessed cardiovascular effects with oral semaglutide in people with type 2 diabetes and atherosclerotic cardiovascular and/or chronic kidney disease.

METHODS

In this double-blind, placebo-controlled, event-driven, superiority trial, participants aged ≥50 years, with a glycated hemoglobin level 6.5–10.0%, and known atherosclerotic cardiovascular and/or chronic kidney disease, were randomized to once-daily oral semaglutide (14 mg) or placebo in addition to standards of care. The primary outcome was time to first major adverse cardiovascular event (death from cardiovascular cause, nonfatal myocardial infarction, or nonfatal stroke).

RESULTS

For the 9650 randomized participants, mean (±SD) follow-up was 47.5±10.9 months (median 49.5 months). The incidence of the primary outcome was significantly lower in the semaglutide group (579/4825 participants, 12.0%, rate 3.1 per 100 person-years) compared with placebo (668/4825 participants, 13.8%, rate 3.7 per 100 person-years); hazard ratio, 0.86; 95% confidence interval (CI), 0.77–0.96; P=0.006. There were no significant differences in key secondary outcomes, including a major kidney disease events composite. Serious adverse events were less common with semaglutide (47.9%) than with placebo (50.3%), P=0.02. There was a higher incidence of gastrointestinal disorders with oral semaglutide (5.0% versus 4.4%).

CONCLUSIONS

Oral semaglutide significantly reduced cardiovascular events in people with type 2 diabetes and atherosclerotic cardiovascular and/or chronic kidney disease without an increase in serious adverse events. (Funded by Novo Nordisk; SOUL, ClinicalTrials.gov number NCT03914326.)

Globally, approximately 828 million adults are affected by diabetes,[1] with type 2 accounting for over 90% of cases.[2] Type 2 diabetes is associated with high risk for cardiovascular disease.[3,4] Trials designed to assess cardiovascular outcomes in type 2 diabetes have demonstrated that certain glucagon-like peptide-1 receptor agonists (GLP-1 RAs) and certain sodium-glucose cotransporter-2 inhibitors (SGLT2is) reduce the risk of major adverse cardiovascular events.[5-7]

Semaglutide is a long-acting GLP-1 RA and its injectable formulation has been shown to reduce cardiovascular risk in people with type 2 diabetes with or at high risk for cardiovascular disease, as well as in those with type 2 diabetes and chronic kidney disease.[5,8,9] The oral formulation of semaglutide has proven cardiovascular safety,[10] but whether it reduces cardiovascular outcomes remains unknown.

The Semaglutide cardiOvascular oUtcomes triaL (SOUL; NCT03914326) was designed to assess the cardiovascular efficacy of oral semaglutide in people with type 2 diabetes with established atherosclerotic cardiovascular disease and/or chronic kidney disease.

METHODS

Trial Design and Oversight

The design of this international, double-blind, randomized, placebo-controlled, event-driven, superiority phase 3b trial has been described previously[11] and is summarized in **Figure S1** in the Supplementary Appendix.

The trial was overseen by an academic-led steering committee (see Supplementary Appendix) in partnership with the trial sponsor, Novo Nordisk, which managed trial operations. The trial steering committee provided overall leadership, oversaw trial design, conduct, and analysis, and was responsible for reporting results. Analyses were conducted by the sponsor, with those of the primary and confirmatory secondary outcomes independently verified by Statogen Consulting (Research Triangle Park, NC, USA). All authors contributed to the writing of this report, with editorial assistance provided by Ashfield MedComms (an Inizio company) who developed the first draft,

funded by the sponsor. The authors had access to summary results from the analyzed dataset, made the decision to submit the manuscript for publication, and vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol.

Participants

Full inclusion and exclusion criteria are listed in the Supplementary Appendix. In brief, participants were male or female, aged ≥50 years, with type 2 diabetes, glycated hemoglobin A_{1c} level 6.5–10.0% and at least one of the following conditions: coronary artery disease, cerebrovascular disease, symptomatic peripheral artery disease, and/or chronic kidney disease (defined as eGFR <60 ml/min/1.73 m^2; excluding those with end-stage kidney disease or on chronic kidney replacement therapy).[11]

Trial Procedures

Following written informed consent, a screening visit was completed. Participants were randomized 1:1 to once-daily treatment with oral semaglutide or matching placebo (with a dose escalation regimen described in **Fig. S1)**, in addition to standard-of-care glucose-lowering and cardiovascular risk-reducing therapies according to local guidelines. Participants were instructed to take the tablet in the morning in a fasting state with ≤120 ml of water and to wait ≥30 minutes before taking food, drink, or other oral medications. Trial visits occurred at 4, 8, and 13 weeks post-randomization, and approximately every 13 weeks thereafter. Details on visit schedule and assessments have been described previously.[11]

Trial Outcomes

The primary outcome was time from randomization to first major cardiovascular event (a 3-point composite of death from cardiovascular cause, nonfatal myocardial infarction, or nonfatal stroke). Three confirmatory secondary outcomes were tested in hierarchical order: (1) time to first

occurrence of a 5-point major kidney disease events composite consisting of: death from cardiovascular cause, death from kidney cause, persistent ≥50% reduction from baseline in eGFR (The Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] method[12]), persistent eGFR <15 ml/min/1.73 m^2, or initiation of chronic kidney replacement therapy (dialysis/transplantation); (2) time to death from cardiovascular cause; and (3) time to first occurrence of major adverse limb event, a composite consisting of hospitalization for acute or chronic limb ischemia. Outcome definitions, additional supportive secondary outcomes, and safety assessments are detailed in the Supplementary Appendix. Potential cardiovascular and kidney outcome events and selected adverse events underwent central adjudication by a blinded external adjudication committee, using standard cardiovascular outcome definitions.[13]

Statistical Analysis

SOUL was an event-driven trial, designed to provide 90% power to detect a 17% relative reduction in the hazard for the primary outcome for oral semaglutide compared with placebo at an overall one-sided significance level of 0.025. Assuming an annual event rate of 3.5% for the primary outcome in the placebo group, a trial duration of 5 years and 5 weeks, and a withdrawal or loss-to-follow-up rate of 1% in both groups, an estimate of 9642 participants should be randomized.[11] One interim analysis for superiority was prespecified to occur when two-thirds of the total planned number of primary outcome events had accrued.

Efficacy analyses followed the intention-to-treat principle and included all unique randomized participants, irrespective of adherence to study drug or changes to background medications. Data from participants who withdrew from the trial, died, or were lost to follow-up were censored at time of withdrawal, death, or last contact, respectively.

For time-to-event outcomes, hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated using a Cox proportional hazards model with randomization treatment as fixed factor. For the primary outcome, the HR, 95% CI, and P value were adjusted for the group sequential design

using likelihood-ratio ordering.[14] If superiority for the primary outcome was established, the confirmatory secondary outcomes were to be evaluated in the hierarchical order, where statistical significance was required at each step to test the next hypothesis. To account for 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[15] for the primary and confirmatory secondary outcomes (see Supplementary Appendix). Although the statistical analysis plan specified that one-sided P values would be used for hypothesis testing, results are reported here with two-sided P values.

Confidence intervals for supportive secondary outcomes were not adjusted for multiplicity, and therefore cannot be interpreted as hypothesis tests.

For details on interim analysis and secondary outcomes, see Supplementary Appendix. All statistical analyses were performed with SAS software, version 9.4 TS1M5 (SAS Institute, Cary, NC, USA).

RESULTS

Trial Participants

Overall, 9650 individuals were randomized (4825 per arm) at 444 sites across 33 countries between June 2019 and March 2021. The mean (±SD) age of participants was 66.1±7.6 years, and 28.9% were women (**Table 1**). Most participants had a history of cardiovascular disease (70.7% coronary artery disease, 23.1% heart failure, 21.2% cerebrovascular disease, 15.7% peripheral artery disease) and 42.4% had a history of chronic kidney disease. Concomitant use of SGLT2is at baseline was 26.9% in each arm. The full baseline characteristics and concomitant medications are presented in **Table S1** and representativeness of SOUL participants is summarized in **Table S2**.

Participant disposition is shown in **Figure S2**. Mean follow-up was 47.5±10.9 months (median 49.5 months, interquartile range 44.0–54.9), and 9495 (98.4%) participants completed the trial (having died or attended end-of-trial visit). Vital status was available for 99.5% of participants.

Participants received the trial product for 87.4% of the potential treatment time (86.5% oral semaglutide, 88.4% placebo). Treatment with an open-label GLP-1 RA during the trial (a protocol violation) was initiated in 172 (3.6%) and 253 (5.2%) participants in the oral semaglutide and placebo group, respectively. Proportions of participants receiving the 3, 7, or 14 mg doses over time are summarized in **Figure S3A.** Permanent premature treatment discontinuation occurred in 1309 (27.1%) and 1373 (28.5%) participants receiving oral semaglutide and placebo, respectively (**Fig. S3B**).

Primary and Confirmatory Secondary Outcomes

Primary outcome events occurred in 579/4825 participants (12.0%; incidence rate 3.1 per 100 person-years) in the oral semaglutide group and 668/4825 (13.8%; incidence rate 3.7) in the placebo group (HR, 0.86; 95% CI, 0.77–0.96; P=0.006 demonstrating superiority of oral semaglutide over placebo; **Fig. 1A** and **Table 2**). The absolute risk reduction at week 156 (3 years) was 2%, and the number of people needed to be treated over 3 years to prevent one primary outcome event was 50 (95% CI, 31–125) in this population (**Table S3**). Results of the primary outcome were consistent across prespecified sensitivity analyses (**Table S3**) and generally consistent across prespecified subgroups, including age, sex, BMI, cardiovascular/kidney disease, eGFR, and concomitant medication, except for region and glycated hemoglobin (**Fig. S4**).

Death from cardiovascular cause occurred in 301 participants (6.2%) receiving oral semaglutide and 320 (6.6%) receiving placebo (HR, 0.93; 95% CI, 0.80–1.09; **Fig. 1B**); nonfatal myocardial infarction in 191 (4.0%) and 253 (5.2%) participants (HR, 0.74; 95% CI, 0.61–0.89; **Fig. 1C**), and nonfatal stroke in 144 (3.0%) and 161 (3.3%) participants, respectively (HR, 0.88; 95% CI, 0.70–1.11; **Fig. 1D**).

Events of the 5-point major kidney disease events composite, the first confirmatory secondary outcome, occurred in 403 participants (8.4%; incidence rate 2.1 per 100 person-years) in the oral semaglutide group and in 435 (9.0%; incidence rate 2.3) in the placebo group (HR, 0.91; 95%

CI, 0.80–1.05; P=0.19; **Fig. 1E**). Within this composite outcome, 71.2% events comprised death from cardiovascular cause, while kidney-related events represented 28.8%. The remaining two confirmatory outcomes in the hierarchy were not statistically tested (death from cardiovascular cause [HR, 0.93; 95% CI, 0.80–1.09; **Fig. 1B**] and major adverse limb event composite [HR, 0.71; 95% CI, 0.52–0.96; **Fig. 1F**]).

Supporting Secondary Outcomes

The results for additional efficacy outcomes are summarized in **Table 2**. HR for the heart failure composite outcome was 0.90 (95% CI, 0.79 to 1.03); for death from any cause 0.91 (95% CI, 0.80 to 1.02), all fatal/nonfatal myocardial infarction 0.73 (95% CI, 0.61 to 0.88), and all fatal/nonfatal stroke 0.95 (95% CI, 0.76 to 1.17).

Levels of glycated hemoglobin decreased from baseline to 104 weeks by a mean –0.71 and –0.15 percentage points with oral semaglutide and placebo, respectively (estimated treatment difference, –0.56; 95% CI, –0.61 to –0.52; **Fig. 2A**) when added to standard of care glycemia treatment. Body weight changed from baseline to week 104 by –4.22 kg with oral semaglutide and –1.27 kg with placebo (estimated treatment difference, –2.95; 95% CI, –3.18 to –2.73; **Fig. 2B**). High-sensitivity C-reactive protein levels were lower with oral semaglutide compared with placebo and remained different over time (geometric mean at week 104, 1.56 and 2.01; **Fig. 2C**).

There were 88 severe hypoglycemic episodes with oral semaglutide and 121 with placebo (mean ratio, 0.73; 95% CI, 0.50–1.07). These episodes occurred in 76 (1.6%) and 84 (1.7%) participants, respectively, with HR for time to first episode of 0.90 (95% CI, 0.66–1.22; **Table 2**).

Safety Outcomes

Serious adverse events were reported less frequently in the oral semaglutide (2312 participants; 47.9%) than the placebo group (2427 participants; 50.3%); P=0.02. Most common were cardiac

disorders (861 [17.8%] and 954 [19.8%], respectively) and infections/infestations (726 [15.0%] and 797 [16.5%], respectively). The frequency of gallbladder disorders, retinal disorders, and malignant neoplasms was slightly higher with oral semaglutide than with placebo (between-arm differences of 0.4–0.8 percentage points, or 22–38 events); acute pancreatitis occurred at the same rate in both arms (0.4%).

Adverse events leading to permanent treatment discontinuation were more common for oral semaglutide (749 [15.5%]) than placebo (559 [11.6%]), comprising mainly gastrointestinal disorders in both arms (310 [6.4%] and 98 [2.0%], respectively). Additionally, the placebo group had 96 cases (2.0%) of infections/infestations leading to treatment discontinuation (versus 63 [1.3%] with oral semaglutide). The other most common reasons for discontinuation were 'other' (6.6% for oral semaglutide, 7.9% for placebo) and unintentional treatment discontinuation (2.9% and 4.0%, respectively). Death from non-cardiovascular cause occurred in 227 (4.7%) participants receiving oral semaglutide and 257 (5.3%) participants receiving placebo. The safety summary is shown in **Table S4**.

DISCUSSION

Oral semaglutide decreased the hazard of major cardiovascular events, with 14% relative risk reduction (2% absolute risk reduction over 3 years) compared to placebo in people with type 2 diabetes and atherosclerotic cardiovascular and/or chronic kidney disease. This study establishes the cardiovascular efficacy of oral semaglutide, with results consistent with injectable semaglutide and other GLP-1 RAs with proven cardiovascular benefit.[8,9]

Of the events within the primary outcome, the largest difference was the reduced risk in nonfatal myocardial infarction. This is in contrast with PIONEER 6 (non-inferiority trial of oral semaglutide in people with type 2 diabetes at high cardiovascular risk), where reduction in death from cardiovascular cause was the dominant beneficial effect.[10] Of note, the mean duration of follow-up and sample size in SOUL (47.5 months, 9650 participants) were three-fold larger than in

PIONEER 6 (15.8 months, 3183 participants). On the whole, the risk reduction in primary outcome events in SOUL is in keeping with observations across all other cardiovascular outcomes trials with GLP-1 RAs.[5,7]

All three confirmatory secondary outcomes were directionally consistent with the primary outcome, but a significant effect was not observed and the statistical testing stopped at the second step of the hierarchy. The finding of a non-significant effect with oral semaglutide on the 5-point major kidney disease events composite in SOUL (with death from cardiovascular cause being dominant, 71.2%) was different than that in the FLOW trial (SOUL: HR, 0.91; 95% CI, 0.80–1.05, P=0.19; FLOW: HR, 0.76; 95% CI, 0.66–0.88, P=0.0003).[9] In FLOW, weekly injectable semaglutide 1.0 mg was investigated in people with type 2 diabetes and chronic kidney disease.[9] The difference in the major kidney disease events outcome may be due to chance, or could potentially be related to population characteristics (FLOW participants had a mean baseline eGFR 47.0 ml/min/1.73m^2,[9] versus 73.8 ml/min/1.73m^2 in SOUL participants). Additionally, the difference in bioavailability between once-weekly subcutaneous semaglutide 1 mg (89%) and once-daily oral semaglutide 14 mg (0.4–1%) may be a factor.[16,17] However, the option to have an efficacious oral GLP-1A will be 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 with semaglutide,[20] and no new safety signals were observed. The incidence of serious adverse events was lower in participants receiving oral semaglutide than those receiving placebo, mostly due to the higher rate of cardiovascular events and infections in the placebo group. More oral semaglutide-treated participants permanently discontinued treatment due to adverse events compared with placebo, largely due to gastrointestinal symptoms. Gastrointestinal events are known to occur with GLP-1 RAs, 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 on cardiovascular outcomes was consistent across age and other

subgroups in this trial, as well as with trials with injectable semaglutide, although direct comparisons cannot be inferred without a comparative effectiveness trial. While the effect of oral semaglutide on the primary outcome appeared larger in participants with glycated hemoglobin >8% and in certain regions (particularly Asia), it should be noted that the subgroup analyses were not powered, and the effect was generally consistent across all other subgroups. Furthermore, the cardioprotective effect of oral semaglutide was on top of a high concomitant use of cardiovascular protective drugs, including SGLT2is.

Limitations of this study include the inclusion criterion of a pre-existing history of cardiovascular disease and/or chronic kidney disease, which was designed to enrich the study population for assessing the effect of oral semaglutide. While this is not representative of all people with type 2 diabetes, approximately 32% of the global population with type 2 diabetes do have cardiovascular disease,[22] and it is estimated that 25–40% have chronic kidney disease.[23] Additionally, similar to other cardiovascular outcomes trials, the trial population demographics were not fully representative of the global population, particularly because only 28.9% and 2.6% of enrolled participants were women or identified as Black, respectively (see Table S1). With regard to the latter group, 9.5% of the patients enrolled in the United States identified as Black/African American. Type 2 diabetes affects Black/African American people more than White people, with women having a greater relative risk of cardiovascular disease and associated mortality than men.[24,25] Lastly, the potential kidney benefits of oral semaglutide could not be clarified.

In conclusion, in this randomized, placebo-controlled trial involving people with type 2 diabetes and atherosclerotic cardiovascular disease and/or impaired kidney function, daily oral semaglutide was superior to placebo in reducing the hazard of major cardiovascular events.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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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;404:2077-2093.
2. Magliano DJ, Boyko EJ, IDF Diabetes Atlas 10th edition scientific committee. IDF Diabetes Atlas 10th edition. 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;379:633–644.
4. American Diabetes Association Professional Practice Committee. 10. Cardiovascular Disease and Risk Management: Standards of Care in Diabetes-2024. Diabetes Care. 2024;47: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;9:653–662.
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;6:148–158.
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(1):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;375:1834–1844.
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;391:109–121.
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;381:841–851.
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;25:1932–1941.
12. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009;150:604–612.
13. Hicks KA, Mahaffey KW, Mehran R, et al. 2017 cardiovascular and stroke endpoint definitions for clinical trials. Circulation. 2018;137:961–972.
14. Wassmer G, Brannath W. Group sequential and confirmatory adaptive designs in clinical trials: Springer Nature; 2016.
15. Glimm E, Maurer W, Bretz F. Hierarchical testing of multiple endpoints in group-sequential trials. Stat Med. 2010;29:219–228.
16. Novo Nordisk. RYBELSUS (semaglutide) tablets, for oral use. Highlights of prescribing information. 2024. (Accessed 13 Dec 2024 at 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;10:649–662.
18. Dibonaventura MD, Wagner JS, 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;26:231–238.

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;25:1385–1397.
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;45:3075–3090.
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;318:2457–2465.

FIGURE LEGENDS

Figure 1. Time-to-Event Primary and Secondary Outcomes.

Shown are cumulative incidence plots of the primary and keys secondary outcomes. Panel A shows the primary cardiovascular composite outcome (death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke). Panel B shows the first confirmatory secondary outcome of 5-point major kidney disease events composite (consisting of death from cardiovascular cause, death from kidney cause, persistent ≥50% reduction from baseline in eGFR, persistent eGFR <15 ml/min/1.73 m^2, or initiation of chronic kidney replacement therapy [dialysis/transplantation]). Panel C shows the cumulative incidence of the second confirmatory secondary endpoint (death from cardiovascular causes), which is also a component of the primary outcome. Panel D shows the third secondary confirmatory outcome of major adverse limb events (acute and chronic limb ischemia hospitalizations). Panels E and F show the remaining components of the primary outcome: nonfatal myocardial infarction and nonfatal stroke, respectively. The definitions of all endpoints are provided in the Supplementary Appendix.

Two-sided P values are shown. Because the between-group difference in the major kidney disease events composite outcome did not meet the required P value for hierarchical testing, results for the two subsequent confirmatory outcomes in the testing hierarchy are reported as point estimates and 95% CIs. The x-axis is truncated at 54 months because of the limited number of participants in the trial after 54 months. The insets show the same data on an enlarged y-axis.

CI, confidence interval; eGFR, estimated glomerular filtration rate.

Figure 2. Outcomes by Measures of Metabolism and Inflammation.

The curves show the observed means from baseline in the glycated hemoglobin level (Panel A), body weight (Panel B), and observed geometric means of high-sensitivity C-reactive protein levels (panel C). Data are for the full analysis set during the in-trial observation period. Bars indicate standard errors. Mean values (95% confidence intervals) are shown for the prespecified timepoint of 104 weeks.

CI, confidence interval.

TABLES

Table 1. Baseline Characteristics (abridged).

	Oral semaglutide (N = 4825)	**Placebo** (N = 4825)
Age — years	66.1 (7.6)	66.1 (7.5)
Female sex — n (%)	1376 (28.5)	1414 (29.3)
Race — n (%)		
White	3327 (69.0)	3321 (68.8)
Black or African American	124 (2.6)	128 (2.7)
Asian	1134 (23.5)	1121 (23.2)
Hispanic/Latino ethnicity — n (%)	674 (14.0)	706 (14.6)
Body weight — kg	87.5 (19.1)	88.3 (19.6)
Body mass index — kg/m^2	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)
Duration of diabetes — years, median (IQR)	14.7 (9.0–20.8)	14.6 (8.9–20.8)
History of cardiovascular/kidney disease — n (%)		
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 — n (%)	4378 (90.7)	4381 (90.8)
Current smoking — n (%)	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)
High-sensitivity CRP — mg/l, median (IQR)	2.0 (0.9–4.3)	2.0 (0.9–4.5)

eGFR — ml/min/1.73 m^2 (CKD-EPI method[12])†	74.0 (22.6)	73.6 (22.6)

Data are mean±SD unless otherwise stated. The full demographics and baseline characteristics are shown in Table S1.

*Defined as eGFR <60 ml/min/1.73 m^2 based on medical records using the latest available ≤6 months old assessment.

†Measured at randomization.

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; CKD-EPI, The Chronic Kidney Disease Epidemiology Collaboration; CRP, C-reactive protein; DPP-4, dipeptidyl peptidase-4; eGFR, estimated glomerular filtration rate; GIP, gastric inhibitory polypeptide; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HDL, high-density lipoprotein; IQR, interquartile range; LDL, low-density lipoprotein; SD, standard deviation; SGLT2, sodium-glucose co-transporter-2.

Table 2. Primary and Secondary Time-to-Event Efficacy Outcomes

Event	Oral semaglutide (N = 4825)		Placebo (N = 4825)		Hazard Ratio (95% CI)	Two-sided P value
	N (%)	Rate	*N (%)*	Rate		
Primary outcome:						
3-point cardiovascular composite	579 (12.0)	3.1	668 (13.8)	3.7	0.86 (0.77–0.96)	0.006[*]
Confirmatory secondary outcomes:						
5-point major kidney disease events composite	403 (8.4)	2.1	435 (9.0)	2.3	0.91 (0.80–1.05)	0.19[†]
Death from cardiovascular cause	301 (6.2)	1.6	320 (6.6)	1.7	0.93 (0.80–1.09)	–
Major adverse limb event composite	71 (1.5)	0.4	99 (2.1)	0.5	0.71 (0.52–0.96)	–
Supportive secondary outcomes:						
5-point cardiovascular 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/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/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)	–
All-cause death	528 (10.9)	2.8	577 (12.0)	3.0	0.91 (0.80–1.02)	–
Non-cardiovascular death	227 (4.7)	1.2	257 (5.3)	1.4	0.87 (0.73–1.04)	–
Heart failure 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)	–
4-point major kidney disease events composite	112 (2.3)	0.6	129 (2.7)	0.7	0.86 (0.66–1.10)	–
Death from kidney cause	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)	–

[*]The two-sided significance level for the primary endpoint after accounting for the interim analysis was 0.04561.

[†]The nominal two-sided significance level for the 5-point major kidney disease events composite was 0.04433.

Rate shows incidence rate per 100 person-years. Dashes represent outcomes for which a P value is not available (not formally tested). Data are for the full analysis population during the in-trial observation period (from randomization to the end-of-trial visit). All end points were analyzed with the use of a Cox proportional hazards model with treatment as a categorical fixed factor. Supportive secondary outcomes were not adjusted for multiplicity. Data from patients without events of interest were censored at the end of their in-trial period. For definitions of composite outcomes, please see the Supplementary Appendix.

eGFR, estimated glomerular filtration rate; N, number of participants.