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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

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Abstract

Aim: To describe the design of the SOUL trial (Semaglutide cardiOvascular oUtcomes triaL) and the baseline clinical data of its participants.

Materials and methods: In SOUL, the effects of oral semaglutide, the first oral glucagon-like peptide-1 receptor agonist, on the risk of cardiovascular (CV) events in individuals with type 2 diabetes and established atherosclerotic CV disease (ASCVD) and/or chronic kidney disease (CKD) will be assessed. SOUL is a randomized, double-blind, parallel-group, placebo-controlled CV outcomes trial comparing oral semaglutide (14 mg once daily) with placebo, both in addition to standard of care, in individuals aged ≥50 years with type 2 diabetes and evidence of ASCVD (coronary artery disease [CAD], cerebrovascular disease, symptomatic peripheral arterial disease [PAD]) and/or CKD (estimated glomerular filtration rate <60 mL/min/1.73 m^2). The primary outcome is time from randomization to first occurrence of a major adverse CV event (MACE; a composite of CV death, nonfatal myocardial infarction or nonfatal stroke). This event-driven trial will continue until 1225 first adjudication-confirmed MACEs have occurred. Enrolment has been completed.

Results: Overall, 9650 participants were enrolled between June 17, 2019 and March 24, 2021 (men 71.1%, White ethnicity 68.9%, mean age 66.1 years, diabetes duration 15.4 years, body mass index 31.1 kg/m^2, glycated haemoglobin 63.5 mmol/mol [8.0%]). The most frequently used antihyperglycaemic medications at baseline were metformin (75.7%), insulin and insulin analogues (50.5%), sulphonylureas (29.1%),

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sodium-glucose cotransporter-2 inhibitors (26.7%) and dipeptidyl peptidase-4 inhibitors (23.0%). At randomization, 70.7% of participants had CAD, 42.3% had CKD, 21.1% had cerebrovascular disease and 15.7% had symptomatic PAD (categories not mutually exclusive). Prevalent heart failure was reported in 23.0% of participants.
Conclusion: SOUL will provide evidence regarding the CV effects of oral semaglutide in individuals with type 2 diabetes and established ASCVD and/or CKD.

KEYWORDS
cardiovascular disease, GLP-1, randomized trial, semaglutide, type 2 diabetes

1 | INTRODUCTION

Cardiovascular (CV) disease (CVD) is a common cause of morbidity and mortality in individuals with type 2 diabetes.[1,2] People with type 2 diabetes have a higher risk of coronary artery disease (CAD), heart failure (HF), stroke, peripheral arterial disease (PAD) and atrial fibrillation when compared to those without type 2 diabetes.[2,3] Clinical intervention trials evaluating the effectiveness of more versus less intensive glucose control have failed to demonstrate convincing benefits for CV outcomes in type 2 diabetes.[4] However, results from trials designed specifically to assess CV safety/efficacy of antihyperglycaemic medications in type 2 diabetes have proven that some, but not all agents among the glucagon-like peptide-1 receptor agonist (GLP-1RA) and sodium-glucose cotransporter-2 (SGLT2) inhibitor classes lower CVD risk. Importantly, among those with proven CV efficacy, these effects have been observed to be largely independent of glucose-lowering effects.[5,6]

Semaglutide is a long-acting GLP-1 analogue widely approved to improve glycaemic control in individuals with type 2 diabetes that can be administered either subcutaneously once weekly or orally once daily.[7,8] Results from the Semaglutide Unabated Sustainability in Treatment of Type 2 Diabetes (SUSTAIN) 6 trial (NCT01720446), a randomized trial of injectable semaglutide versus placebo in individuals with type 2 diabetes with or at high atherosclerotic CVD (ASCVD) risk, demonstrated a significant 26% relative reduction and a 2.3% absolute reduction in the risk of the major adverse CV event (MACE) composite of CV death, nonfatal myocardial infarction (MI) and nonfatal stroke for injectable semaglutide compared with placebo.[9]

This reduced risk was driven by a significant decrease (39%) in the incidence of nonfatal stroke and a nonsignificant decrease (26%) in nonfatal MI with injectable semaglutide versus placebo, although there was no significant difference in the incidence of CV death between treatment groups. Results from the PIONEER 6 (Peptide InnOvatioN for Early diabEtes tReatment; NCT02692716) dedicated CV safety trial, conducted with oral semaglutide in patients with type 2 diabetes with high CVD risk, demonstrated a 21% decrease in the incidence of MACE and a significant 53% reduction in the incidence of CV death with oral semaglutide versus placebo.[10] As both of these trials were primarily designed to demonstrate CV safety with limited numbers of outcome events to analyse, whether the differential estimates of effect on CV death between the trials is a true finding or is attributable to play of chance remains unclear. Based on the results from the SUSTAIN 6 trial[9] and complemented by subsequent data from the oral semaglutide registration programme, including the results from PIONEER 6,[10] injectable (but not oral) semaglutide was granted a US Food and Drug Administration (FDA) product label indication to reduce the risk for CV death, MI and stroke in individuals with type 2 diabetes and established CVD, similar to the product labelling for two other injectable GLP-1RAs, liraglutide and dulaglutide.[11-13] While PIONEER 6 successfully demonstrated CV safety, it was not powered to formally assess the CV efficacy of oral semaglutide and therefore the Semaglutide cardiOvascular oUtcomes triaL (SOUL; NCT03914326) was designed specifically for this purpose.

Indeed, SOUL was designed to assess the effect of oral semaglutide versus placebo on the primary composite outcome of time to the first event of CV death, nonfatal MI or nonfatal stroke (MACE) in individuals with type 2 diabetes and established ASCVD and/or chronic kidney disease (CKD). Additionally, in SOUL, the effect of oral semaglutide on several secondary outcomes will be assessed, including expanded CV composites, the progression of CKD, symptomatic PAD and HF outcomes. In this paper, the design of the SOUL trial and the baseline characteristics of the enrolled trial population are described.

2 | MATERIALS AND METHODS

2.1 | Trial design and oversight

SOUL is a randomized, double-blind, parallel-group, placebo-controlled CV outcomes trial comparing oral semaglutide (14 mg once daily) with placebo, both in addition to standard of care, in individuals with type 2 diabetes with established ASCVD and/or CKD and was conducted in compliance with the International Conference for Harmonization Good Clinical Practice guidelines, applicable regulatory requirements and in accordance with the Declaration of Helsinki. Review and approval by independent ethics committees and institutional review boards was mandated prior to the commencement of the trial at each site. In the clinical trial application, regulatory authorities were provided with protocol amendments, reports on serious adverse events (SAEs) and the clinical trial report, according to national requirements. All participants provided written informed consent prior to any trial-related activity. An independent data monitoring committee provided

intermittent unblinded reviews of accumulating data and had the mandate to give guidance on trial continuation, modification or termination.

2.2 | Participants

Eligible individuals were men or women, aged ≥50 years, diagnosed with type 2 diabetes according to the American Diabetes Association criteria/definition,[14] with a glycated haemoglobin (HbA_{1c}) level ranging between 47 and 86 mmol/mol (6.5%-10.0%) and had at least one of the following conditions:

1. CAD, defined as at least one of: prior MI; prior coronary revascularization procedure; ≥50% stenosis in ≥1 coronary artery documented by cardiac catheterization or computed tomography (CT) coronary angiography; and/or CAD with ischaemia documented by stress test with any imaging modality;
2. Cerebrovascular disease, defined as at least one of: prior stroke; prior carotid artery revascularization procedure; ≥50% stenosis in carotid artery documented by invasive angiography, magnetic resonance angiography, CT angiography or Doppler ultrasonography;
3. Symptomatic PAD, defined as at least one of: intermittent claudication with an ankle-brachial index <0.85 at rest; intermittent claudication with a ≥50% stenosis in ≥1 peripheral artery documented by invasive angiography, magnetic resonance angiography, CT angiography, or Doppler ultrasonography; prior peripheral artery revascularization procedure (excluding carotid); and/or lower extremity amputation at or above the ankle due to atherosclerotic disease;
4. CKD, defined as an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2.

Key exclusion criteria included: MI, stroke, or hospitalization for unstable angina, or transient ischaemic attack within 60 days prior to screening; planned coronary, carotid or peripheral artery revascularization; New York Heart Association class IV HF; treatment with any GLP-1RA within 30 days prior to screening; end-stage kidney disease requiring chronic or intermittent haemodialysis or peritoneal dialysis; history of major surgical procedures involving the stomach that may affect drug absorption; uncontrolled and potentially unstable diabetic retinopathy or maculopathy (documented by a retinal examination required within 90 days before screening or in the period between screening and randomization). Other exclusion criteria are detailed in the Appendix, Section 1.

Following informed consent, a screening visit was completed, during which participant demographics were recorded, a retinal examination (if not done within the past 90 days) and urine pregnancy test (for women of child-bearing potential) performed, and HbA_{1c} level assessed. Medical history, smoking status, concomitant medications and concomitant illnesses were recorded at randomization (visit 0), along with a physical examination.

2.3 | Trial treatment and procedures

Eligible participants were randomized in a 1:1 ratio to once-daily treatment with either oral semaglutide or matching placebo (Figure 1). Randomization was performed using an interactive web response system on the same day as the screening visit or up to 3 weeks afterwards. Blinding of investigational product was maintained through using visually identical oral semaglutide and placebo tablets, regardless of dose level, in identical packaging. Oral semaglutide is a co-formulation of semaglutide and the absorption enhancer sodium N-(8-[2-hydroxylbenzoyl] amino) caprylate (SNAC); the placebo did not contain SNAC.

To mitigate the potential for adverse gastrointestinal symptoms of active study drug, participants in both arms followed a blinded dose-escalation regimen, receiving 3 mg oral semaglutide/placebo once daily for 4 weeks, followed by 7 mg oral semaglutide/placebo once daily for 4 weeks and then 14 mg oral semaglutide/placebo once daily for the remainder of the trial (Figure 1). Dose reductions, extensions of dose escalation intervals and treatment pauses were permitted if treatment with the trial product was associated with unacceptable adverse events (AEs) or due to other circumstances. Participants were instructed to take the tablet in the morning in a fasting state with up to 120 mL of water and to wait at least 30 minutes before any further food or drink or taking other oral medications.

The trial design and visit schedule are presented in Figure 1 and Table S1. Trial visits occurred at weeks 4, 8 and 13 following randomization and approximately every 13 weeks thereafter. A variety of assessments and procedures were performed at different intervals (Table S1), including: body weight; blood sampling to assess HbA_{1c}, creatinine, high-sensitivity C-reactive protein, liver parameters (at randomization only) and lipid profiles; cognitive testing; collection of reports for SAEs, reports of AEs of special interest or AEs requiring event adjudication or additional data collection, AEs leading to discontinuation of trial treatment, and AEs related to coronavirus disease (COVID-19) infections (irrespective of seriousness); and pregnancies. In addition to the retinal examination required prior to, or as part of, the screening procedures, retinal examinations were performed at week 52 and yearly thereafter, and at the end of treatment visit. Blood samples were taken and stored for future analyses among participants who signed an additional informed consent form for a biobank repository, whole blood was collected at randomization for genetic analyses, and serum samples were collected for repository storage at randomization, week 13 and at 2 years for future biomarker analyses to be determined. Future research using the biobank samples will aim to find out more about type 2 diabetes, heart disease or other related diseases, and to further our understanding of oral semaglutide, with specific analyses to be determined henceforth.

Investigators, in collaboration with treating clinicians, were responsible for making every effort that participants were treated according to the local and regional recommended standard of care for glycaemic management and CV and kidney disease risk management. Investigators received recommendations from the trial leadership team for the management of glycaemic control and CV risk factors

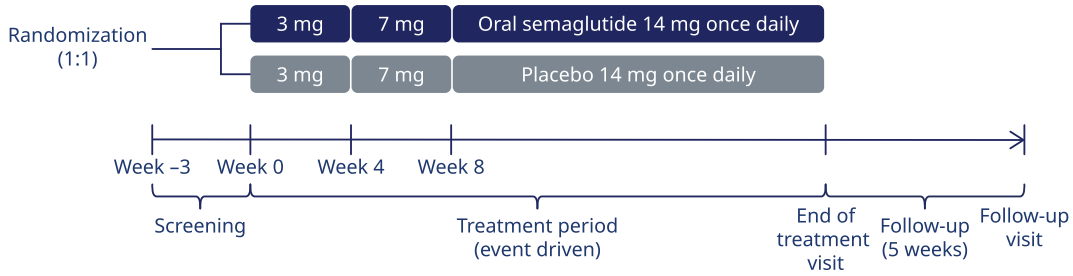

FIGURE 1 SOUL (Semaglutide cardiOvascular oUtcomes triaL) in individuals with type 2 diabetes trial design

(including blood pressure, lipids (low-density lipoprotein [LDL] cholesterol), antiplatelet/anticoagulant therapy), and healthy lifestyle in a written guidance document that was updated as appropriate during the trial conduct (see Appendix, Section 2). With the primary purpose of the trial being to assess CV safety and efficacy of oral semaglutide and not glycaemic control per se, both arms were to be treated to standard of care glycaemic control targets using open-label medical therapy. Use of other GLP-1RAs was not permitted, but for those with prevailing indications, the use of SGLT2 inhibitors was encouraged. This trial was funded, designed, initiated and conducted by Novo Nordisk (Søborg, Denmark).

2.4 | Data and resource availability

Data are available upon reasonable request. Data will be shared with bona fide researchers submitting a research proposal approved by the independent review board. Access request proposals can be found at novonordisk-trials.com.

2.5 | Trial outcomes

Potential CV and kidney outcome events, along with selected AEs, underwent central adjudication by a masked external event adjudication committee, as summarized in Table S2 and using standard CV outcome definitions for adjudication, as endorsed by the FDA.[11]

Primary and confirmatory secondary outcomes are summarized in Table 1. The primary trial outcome is time from randomization (week 0) to first occurrence of adjudication-confirmed MACE (a composite outcome consisting of CV death, nonfatal MI or nonfatal stroke). Confirmatory secondary outcomes in hierarchical order for analyses include time from randomization to:

1. The first occurrence of an adjudication-confirmed composite outcome comprising CV death, kidney-related death, persistent ≥50% reduction from baseline in eGFR (CKD Epidemiology Collaboration [CKD-EPI]), persistent eGFR (CKD-EPI) <15 mL/min/1.73 m^2 or initiation of chronic kidney replacement therapy (dialysis or kidney transplantation). For the eGFR components of the composite endpoint, "persistent" is defined as two consecutive central laboratory assessments that meet criteria, at least 4 weeks apart;
2. Occurrence of CV death;
3. First occurrence of major adverse limb events, a composite outcome consisting of hospitalization for acute or chronic limb ischaemia.

TABLE 1 Primary and confirmatory secondary outcomes

Outcome title	Timeframe
Primary outcome	
Time to first occurrence of MACE, a composite outcome consisting of:	From randomization (week 0) to end of trial (up to 61 months or more[a])
• CV death	
• Nonfatal MI	
• Nonfatal stroke	
Confirmatory secondary outcomes	
Time to first occurrence of a composite outcome consisting of:	From randomization (week 0) to end of trial (up to 61 months or more[a])
• CV death	
• Kidney-related death	
• Persistent ≥50% reduction in eGFR (CKD-EPI)[b]	
• Persistent eGFR (CKD-EPI) <15 mL/min/1.73 m^2	
• Initiation of chronic kidney replacement therapy (dialysis or kidney transplantation)	
Time to occurrence of CV death	From randomization (week 0) to end of trial (up to 61 months or more[a])
Time to first occurrence of major adverse limb events, a composite outcome consisting of:	From randomization (week 0) to end of trial (up to 61 months or more[a])
• Acute limb ischaemia hospitalization	
• Chronic limb ischaemia hospitalization	

Abbreviations: CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; CV, cardiovascular; eGFR, estimated glomerular filtration rate; MACE, major adverse cardiovascular event; MI, myocardial infarction.
[a]Trial is event-driven.
[b]Compared with baseline.

TABLE 2 Patient demographics and baseline characteristics

	Total randomized population (N = 9650)
Age, years	66.1 (7.6)
Male, n (%)	6860 (71.1)
Race, n (%)	
White	6648 (68.9)
Black/African American	252 (2.6)
Asian	2255 (23.4)
Other	405 (4.2)
Not reported	90 (0.9)
Ethnicity, n (%)	
Hispanic/Latino	1380 (14.3)
Body weight, kg	87.9 (19.3)
Body mass index, kg/m^2	31.1 (5.8)
HbA_{1c}, mmol/mol	63.5 (12.5)
HbA_{1c}, %	8.0 (1.1)
Duration of diabetes, years	15.4 (8.8)
CVD status, n (%)	
CAD, n (%)	6821 (70.7)
Prior MI, n (%)	3861 (40.0)
Prior coronary revascularization, n (%)	5198 (53.9)
Coronary artery stenosis ≥50%, n (%)	4100 (42.5)
Cerebrovascular disease, n (%)	2040 (21.1)
Stroke, n (%)	1487 (15.4)
Ischaemic	1184 (12.3)
Haemorrhagic	86 (0.9)
Carotid artery stenosis ≥50%, n (%)	651 (6.7)
Carotid arterial revascularization, n (%)	285 (3.0)
PAD, n (%)	1513 (15.7)
HF, n (%)	2215 (23.0)
CKD, n (%)	4082 (42.3)
Hypertension, n (%)	8755 (90.7)
Current smoking, n (%)	1128 (11.7)
Vital signs	
Systolic blood pressure, mmHg	134.6 (16.3)
Diastolic blood pressure, mmHg	76.7 (10.1)
Pulse, beats/min	73 (11.0)
Cholesterol, mg/dL	
Total cholesterol, geometric mean (CoV)	150.5 (26.0)
LDL cholesterol, geometric mean (CoV)	70.7 (47.8)
HDL cholesterol, geometric mean (CoV)	41.1 (25.7)
Triglycerides, median (IQR)	157 (112; 223)
hsCRP, mg/L, median (IQR)	1.96 (0.89; 4.37)
eGFR, mL/min/1.73 m^2	
ESKD (<15 mL/min/1.73 m^2), n (%)	11 (0.1)
≥15 to <30 mL/min/1.73 m^2, n (%)	227 (2.4)
≥30 to <45 mL/min/1.73 m^2, n (%)	949 (9.8)
≥45 to <60 mL/min/1.73 m^2, n (%)	1629 (16.9)
≥60 to <90 mL/min/1.73 m^2, n (%)	3748 (38.8)
≥90 mL/min/1.73 m^2, n (%)	3000 (31.1)

Note: Data are mean (SD) unless otherwise stated. CKD was defined as eGFR <60 mL/min/1.73 m^2. As the trial is ongoing, data may be subject to minor changes until database lock.

Abbreviations: CAD, coronary artery disease; CKD, chronic kidney disease; CoV, coefficient of variation; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; HbA1c, glycated haemoglobin; HDL, high-density lipoprotein; HF, heart failure; hsCRP, high-sensitivity C-reactive protein; IQR, interquartile range; LDL, low-density lipoprotein; MI, myocardial infarction; PAD, peripheral arterial disease; SD, standard deviation.

Additional supportive secondary outcomes and exploratory outcomes are listed in Table S3. Of note, while any method of eGFR calculation in clinical use was accepted to determine trial eligibility, for the confirmatory endpoint, eGFR was calculated using the 2009 CKD-EPI formula that included a term for race.[15] However, after the recruitment of SOUL trial participants was completed, a new CKD-EPI formula without race as a factor has been recommended,[16] and consequently a supplementary analysis using this new CKD-EPI formula without race has been prespecified to evaluate the impact of the updated formula on the results.

Because there is some evidence to suggest that GLP-1RAs may slow progression of cognitive decline,[17,18] baseline and subsequent cognitive assessments were completed using the Montreal Cognitive Assessment,[19] and in countries with English or Spanish as the primary language (Argentina, Canada, Colombia, Mexico, Spain, the UK, the United States), the Platform for Research Online to Investigate Cognition and Genetics in Aging (PROTECT) Cognitive Test Battery was assessed.[20,21]

2.6 | Trial duration and follow-up

SOUL is an event-driven trial designed to continue until 1225 first adjudication-confirmed primary outcomes have occurred. With an assumed MACE rate in the placebo arm of 3.5% per year, and a recruitment period of approximately 18 months, the expected trial duration for an enrolled participant is approximately 3.5 to 5 years, including the follow-up period (5 weeks after end of treatment). Participants could discontinue the trial product at any time during the trial but were expected to continue adhering to the trial schedule otherwise. For participants interrupting the investigational product during the trial, treatment with the trial product could be resumed at the discretion of the investigator at any time.

2.7 | Sample size

Based on a 1:1 randomization ratio and assuming an annualized placebo MACE rate of 3.5%, a true hazard ratio of 0.83, it was

TABLE 3 Baseline antihyperglycaemic and cardiovascular medications by cardiorenal diagnosis

	All (N = 9650)	Presence of CAD (n = 6821)	Presence of CBVD (n = 2040)	Presence of PAD (n = 1513)	Presence of CKD (n = 4082)
Antihyperglycaemic agents (%)					
Metformin	75.7	77.8	76.7	74.0	64.4
Sulphonylureas	29.1	28.9	29.5	26.5	28.0
SGLT2 inhibitors	26.7	29.4	22.6	23.6	22.4
GLP-1RAs	0	0	0	0	0
DPP-4 inhibitors	23.0	21.9	21.7	19.1	26.1
Pioglitazone	4.1	3.3	4.1	2.8	4.9
α-Glucosidase inhibitors	2.0	1.8	1.9	1.3	2.4
Insulin and analogues	50.5	49.9	49.6	60.4	57.4
Long-acting insulin	38.9	38.8	39.5	51.2	43.5
Short-acting insulin	25.2	25.5	24.6	33.8	30.2
Premix insulin	5.0	4.6	3.7	3.8	5.8
Other	1.3	1.3	1.3	1.0	1.7
CV medications (%)					
ACE inhibitor/ARB/ARNI	80.0	80.4	81.2	82.8	81.4
Beta-blocker	63.8	75.1	56.9	60.7	58.1
Calcium channel blocker	36.5	33.8	44.1	40.7	41.9
Diuretic	41.4	40.8	43.5	44.7	50.4
Thiazides/thiazide-like diuretics	24.3	21.7	27.3	25.4	28.5
Loop diuretics	15.9	17.3	15.3	18.1	21.6
Mineralocorticoid antagonists	9.1	10.7	9.2	9.9	10.3
LDL cholesterol-lowering medication	88.2	91.6	86.8	86.7	84.9
Statin	85.5	89.3	84.5	84.3	81.2
Ezetimibe	9.3	11.1	7.30	9.5	8.0
PCSK-9 inhibitor	1.0	1.0	1.0	1.0	1.0
Fibrate	7.8	7.3	5.9	8.8	9.3
Antiplatelet medication	76.3	86.1	79.2	81.3	62.8
Acetylsalicylic acid	66.8	76.6	62.7	68.9	54.6
P2Y12 inhibitor	25.0	30.3	29.3	26.6	17.3
Others	1.8	1.4	2.4	8.3	1.7
Anticoagulant medication	9.4	10.2	12.7	12.6	10.8
DOAC	5.9	6.5	7.8	7.1	6.7
Vitamin K antagonist	3.1	3.4	4.5	4.3	3.7

Note: As the trial is ongoing, data may be subject to minor changes until database lock.

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; CAD, coronary artery disease; CBVD, cerebrovascular disease; CKD, chronic kidney disease; CV, cardiovascular; DDP-4, dipeptidyl peptidase-4; DOAC, direct oral anticoagulant; GLP-1RA, glucagon-like peptide-1 receptor agonist; LDL, low-density lipoprotein; PAD, peripheral arterial disease; PCSK-9, proprotein convertase subtilisin/kexin type 9; P2Y12, purinergic receptor type Y subtype 12; SGLT2, sodium-glucose co-transporter 2.

determined that a total of 1225 first MACEs are required to confirm superiority for the primary outcome with 90% power using a one-sided type I error rate of 0.025. It was determined that 9642 participants would be needed for randomization, guided by the following assumptions: (a) uniform recruitment occurs in 18 months; (b) annual loss to follow-up incidence (see Appendix, Section 3 for definition) in both treatment groups of 1%; and (c) trial duration of 5 years and 5 weeks. The trial uses a group sequential design and interim testing with one planned interim analysis, with results to be reviewed by an independent data monitoring committee using group sequential stopping boundaries as guidance. To ensure type I error rate control in relation to the interim testing, the Lan-DeMets α-spending function approximating the O'Brien-Fleming stopping boundaries is used.

2.8 | Statistical methods

A Cox proportional hazards model will be used for the primary analysis, with treatment group as a fixed factor together with the two-sided 95% confidence interval and one-sided fixed design *P* value for hypothesis testing. Outcomes are analysed according to the intention-to-treat principle evaluating the effect of the randomized treatment intervention, irrespective of adherence and changes to background medication. Participants who either withdraw or are lost to follow-up during the trial will be censored at the time of withdrawal or time of last contact, respectively. If superiority for the primary outcome is established, sensitivity analyses will be performed to investigate the impact of independent censoring of participants who withdraw from the trial or are lost to follow-up. In addition, superiority of oral semaglutide versus placebo will be tested for the confirmatory secondary outcomes adjusted to account for the group sequential design via a hierarchical testing scheme in the order of (a) the primary composite CKD outcome, (b) CV death, and (c) major adverse limb events.

All statistical analyses will be performed using intention-to-treat methods on the full analysis set, which will include all unique randomized participants.

3 | RESULTS

3.1 | Clinical characteristics

Between June 17, 2019 and March 24, 2021, 9650 individuals were randomized to either oral semaglutide 14 mg once daily or placebo. The trial enrolled participants at 444 sites in 33 countries in Africa, Asia, Europe, Latin and North America, and the Middle East. Participant demographics and baseline characteristics are presented in Table 2. Most participants were male (71.1%) and White (68.9%), with a mean age of 66.1 years and mean body mass index of 31.1 kg/m^2. The mean duration of diabetes was 15.4 years, and the mean HbA_{1c} level was 63.5 mmol/mol (8.0%). The majority of participants reported a history of hypertension (90.7%) and were treated with at least one antihypertensive medication. Almost one-third (29.1%) of participants had an eGFR <60 mL/min/1.73 m^2 at baseline. The most frequently used antihyperglycaemic medications and CV medications at baseline are summarized in Table 3, overall and stratified by qualifying comorbidities for trial eligibility.

Most participants had a history of CAD (70.7%), while 21.1% had cerebrovascular disease, 15.7% had symptomatic PAD, and 42.3% had CKD, with diagnoses not being mutually exclusive (Table 2). Overall, 49.9% of participants were included, with only a single cardiorenal syndrome diagnosis (CAD 29.3%, cerebrovascular disease 5.4%, symptomatic PAD 2.3%, CKD 12.9%). A total of 23% of participants had a prior diagnosis of HF, with some, but not all, patients with HF classified categorically as having preserved or reduced ejection fraction; aetiology not being further classified and ejection fraction per se was not captured. As the trial is ongoing, data may be subject to minor changes until database lock.

4 | DISCUSSION

The CV safety and efficacy of GLP-1RAs in individuals with type 2 diabetes with or at high CV risk have been demonstrated in at least nine CV outcomes trials thus far,[9,10,22-28] and are supported by results of a meta-analysis of these trials with a combined total of 60 080 participants.[5] The results from these trials have confirmed that the GLP-1RA class, as a group, has beneficial effects on CV, mortality and kidney outcomes in individuals with type 2 diabetes with or at high risk for CVD.

The results from the SOUL trial will add to the evidence base for the safety and CV efficacy of GLP-1RAs, specifically evaluating safety and efficacy of the first oral GLP-1RA.[29] If the trial outcome is favourable, the availability of an oral GLP-1RA with proven CV efficacy may help overcome any hesitancy from patients and clinicians alike, in using this category of antihyperglycaemic medication, previously only available in injectable formulations. Indeed, a previous survey conducted with 113 physicians and 1096 patients has shown delays in treatment prescribing and uptitration of GLP-1RAs, despite poor glycaemic control, predominantly due to the injectable mode of administration, lack of convenience and perceived increased injection burden.[30]

Baseline characteristics of the SOUL trial participants are broadly in line with those of prior CV outcome trials that assessed GLP-1RAs, but there are some differences in participant mix compared with those prior trials that are worth noting.[5] SOUL includes a slightly larger proportion of men (71.1% compared with 54%-69%) and a larger proportion of non-White participants (30.1% vs. 13.0%-30.0%). The proportion of participants enrolled in the SOUL trial with HF at baseline is higher (23.0%) than the proportion included in previous CV outcomes trials of GLP-1RAs (10.0%-14.8%).[31-33] This is an even more representative population of participants with type 2 diabetes than in prior trials as HF is highly prevalent among patients meeting SOUL trial eligibility criteria. However, importantly, this higher HF prevalence will yield increased statistical power for subanalyses exploring the effect of oral semaglutide among patients with prevalent HF for the primary outcome and also for HF-related outcomes.

Participants in SOUL had CV risk factors beyond HbA_{1c} well controlled on average at baseline. Most individuals had a history of hypertension, and were receiving at least one antihypertensive agent, with mean blood pressure 135/77 mmHg. Most participants (~88%) were also on LDL cholesterol-lowering agents, and LDL cholesterol levels were moderately to well controlled on average. Participants with proliferative diabetic retinopathy were excluded from SOUL based on observations of early worsening phenomenon of retinopathy observed in SUSTAIN 6 with injectable semaglutide.[9] To further assess this issue, the long-term effects of injectable semaglutide on the development and progression of diabetic retinopathy in patients with type 2 diabetes is being evaluated in a dedicated retinopathy trial (FOCUS; NCT03811561).[34] The CV and kidney effects of injectable semaglutide are also being evaluated in two ongoing trials that have completed enrolment: the semaglutide effects on heart disease and stroke in patients with overweight or obesity without diabetes (SELECT;

NCT03574597)[35] and the semaglutide renal outcomes trial of patients with type 2 diabetes and chronic kidney disease (FLOW; NCT03819153).[36]

In contrast to earlier GLP-1RA CV outcome trials, a sizable proportion of participants (26.7%) in SOUL were treated at baseline with SGLT2 inhibitors, while this ranged from <1% to 15% in earlier trials.[9,23,37,38] This higher use of SGLT2 inhibitors in SOUL reflects the evolutionary positioning of SGLT2 inhibitors in contemporary clinical guidelines and society recommendations for treating individuals with type 2 diabetes and established ASCVD, HF and/or CKD.[3,39,40] Moreover, it is fully anticipated that the use of SGLT2 inhibitors will increase among participants during the trial. This should provide the most robust opportunity to date to analyse outcomes stratified by concomitant use of another antihyperglycaemic therapy with proven CV and CKD benefits, although, still with limitations that SGLT2 inhibitor use is not randomized. This is the basis of a prespecified statistical analysis plan for exploratory analyses stratified by concomitant SGLT2 inhibitor use. The use of sulphonylureas was in general less frequent in SOUL (29.1%) compared with prior CV outcomes trials of GLP-1RAs that ranged from 25% in AMPLITUDE-O (Effect of Efpeglenatide on Cardiovascular Outcomes; NCT03496298) to 51% in LEADER (Liraglutide Effect and Action in Diabetes: Evaluation of cardiovascular outcome Results; NCT01179048),[23,27,37,38] again reflecting evolutions of, and changes in, contemporary clinical guidelines and society recommendations.

In summary, SOUL is a randomized, double-blind, placebo-controlled trial assessing the CV safety of oral semaglutide, the first oral GLP-1RA, in individuals with type 2 diabetes and established ASCVD and/or CKD. Data generated from this trial are expected to provide practising clinicians with more information as to the optimal utilization of antihyperglycaemic agents in type 2 diabetes, in an effort to reduce the risk of CV and kidney disease events.

AUTHOR CONTRIBUTIONS

Darren K. McGuire, Rodica P. Busui, John Deanfield, Silvio E. Inzucchi, Johannes F. E. Mann, Nikolaus Marx, Sharon L. Mulvagh, Neil Poulter, Mads D. M. Engelmann, G. Kees Hovingh, Maria Sejersten Ripa, Mette Gislum, Kirstine Brown-Frandsen and John B. Buse designed the trial, conducted the trial/performed data collection, and analysed the data. Darren K. McGuire drafted and all authors revised the manuscript and approved the final version. Darren K. McGuire is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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CONFLICT OF INTEREST STATEMENT

Darren K. McGuire reports honoraria for trial leadership from Boehringer Ingelheim, Sanofi, Merck & Co, Pfizer, AstraZeneca, Novo Nordisk, Esperion, Lilly USA, Lexicon and CSL Behring; and honoraria for consultancy from Lilly USA, Boehringer Ingelheim, Merck & Co, Novo Nordisk, Applied Therapeutics, Metavant, Sanofi, Afimmune, CSL Behring, Bayer and GSK. Rodica P. Busui served as an Associate Editor for *Diabetes*; serves as an Associate Editor for *Diabetes Care*; has received grant support from AstraZeneca; conducts research for, and receives personal compensation from, Boehringer Ingelheim/Lilly Alliance; reports honoraria for trial leadership from Novo Nordisk; and is a paid consultant for Averitas Pharma, Nevro, Roche and Regenacy. John Deanfield has received honoraria and/or consulting fees from Amgen, Boehringer Ingelheim, Merck, Pfizer, Aegerion, Novartis, Sanofi, Takeda, Novo Nordisk and Bayer; and has received research grant funding from the British Heart Foundation. Silvio E. Inzucchi has served on clinical trial committees and advisory boards for Boehringer Ingelheim, AstraZeneca and Novo Nordisk; has been a consultant to Merck, Pfizer, Lexicon, Bayer, vTv Therapeutics, Esperion and Abbott; and has delivered lectures supported by Boehringer Ingelheim and AstraZeneca. Johannes F. E. Mann reports speaker/consultancy fees from AstraZeneca, Bayer Healthcare, Boehringer Ingelheim, Idorsia, Lexicon, MEDICE, Novartis, Novo Nordisk, Sanofi and Vifor-Fresenius Pharma. Nikolaus Marx has received support for clinical trial leadership from Boehringer Ingelheim and Novo Nordisk; served as a consultant to Boehringer Ingelheim, Merck, Novo Nordisk, AstraZeneca and Bristol-Myers Squibb; received grant support from Boehringer Ingelheim, Merck and Novo Nordisk; served as a speaker for Boehringer Ingelheim, Merck, Novo Nordisk, Lilly, Bristol-Myers Squibb and AstraZeneca; and is supported by the *Deutsche Forschungsgemeinschaft* (German Research Foundation; TRR 219; Project-ID 322900939 [M03, M05]). Sharon L. Mulvagh has received consultancy fees from Novo Nordisk; consultancy fees and research grant support from Lantheus Medical Imaging; and received funding from the Heart and Stroke Canada Foundation and the Canadian Institute of Health Research. Neil Poulter reports speaker fees from Servier and Novo Nordisk. Mads D. M. Engelmann, G. Kees Hovingh, Maria Sejersten Ripa, Mette Gislum and Kirstine Brown-Frandsen are employees of Novo Nordisk A/S and hold company stocks. G. Kees Hovingh is a part-time employee of the Amsterdam University Medical Center. John B. Buse's contracted consulting fees and travel support for contracted activities are paid to the University of North Carolina by ADOCIA, Novo Nordisk, Senseonics and vTv Therapeutics; as well as grant support from Dexcom, NovaTarg, Novo Nordisk, Sanofi, Tolerion and vTv Therapeutics; he has received personal compensation for consultation (<$10 000 annually each) from Alkahest, Anji, AstraZeneca, Bayer, Boehringer Ingelheim, Carmot Therapeutics, CeQur, Cirius Therapeutics Inc, Dasman Diabetes Institute (Kuwait), Eli Lilly, Fortress Biotech, GentiBio, Glycadia, Glyscend, Janssen,

Mediflix, Medscape, Mellitus Health, Pendulum Therapeutics, Praetego, Stability Health and Valo; in lieu of payment for consultation, he has received stock/options in Glyscend, Mellitus Health, Pendulum Therapeutics, PhaseBio, Praetego and Stability Health.

PEER REVIEW

The peer review history for this article is available at https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/dom.15058.

DATA AVAILABILITY STATEMENT

Data are available upon reasonable request. Data will be shared with bona fide researchers submitting a research proposal approved by the independent review board.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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