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ORIGINAL ARTICLE

The rationale, design and baseline data of FLOW, a kidney outcomes trial with once-weekly semaglutide in people with type 2 diabetes and chronic kidney disease

Peter Rossing[1,2], Florian M.M. Baeres[3], George Bakris[4], Heidrun Bosch-Traberg[3], Mette Gislum[3], Stephen C.L. Gough[3], Thomas Idorn[3], Jack Lawson[3], Kenneth W. Mahaffey[5], Johannes F.E. Mann[6], Henriette Mersebach[3], Vlado Perkovic[7], Katherine Tuttle[8], Richard Pratley[9], and on behalf of the FLOW Steering Committee and FLOW Trial Investigators

[1]Complication Research, Steno Diabetes Center Copenhagen, Herlev, Denmark, [2]Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark, [3]Novo Nordisk A/S, Søborg, Denmark, [4]Department of Medicine, AHA Comprehensive Hypertension Center, University of Chicago Medicine, Chicago, IL, USA, [5]Department of Medicine, Stanford Center for Clinical Research, Stanford School of Medicine, Palo Alto, CA, USA, [6]Outpatients Clinic, KfH Kidney Center, München, Germany, [7]Faculty of Medicine and Health, University of New South Wales, Sydney, NSW, Australia, [8]Division of Nephrology, University of Washington/Providence Health Care, Spokane, WA, USA and [9]Translational Research Institute, AdventHealth, Orlando, FL, USA

Correspondence to: Peter Rossing; E-mail: peter.rossing@regionh.dk

ABSTRACT

Background. Chronic kidney disease (CKD) is a common complication of type 2 diabetes (T2D). Glucagon-like peptide-1 receptor agonists (GLP-1RAs) improve glycaemic control and lower body weight in people with T2D, and some reduce the risk of cardiovascular (CV) events in those with high CV risk. GLP-1RAs might also have kidney-protective effects. We report the design and baseline data for FLOW (NCT03819153), a trial investigating the effects of semaglutide, a once-weekly (OW) GLP-1RA, on kidney outcomes in participants with CKD and T2D.

Methods. FLOW is a randomised, double-blind, parallel-group, multinational, phase 3b trial. Participants with T2D, estimated glomerular filtration rate (eGFR) ≥50–≤75 ml/min/1.73 m^2 and urine albumin: creatinine ratio (UACR) >300–<5000 mg/g or eGFR ≥25–<50 ml/min/1.73 m^2 and UACR >100–<5000 mg/g were randomised 1:1 to OW semaglutide 1.0 mg or matched placebo, with renin–angiotensin–aldosterone system blockade (unless not tolerated/contraindicated). The composite primary endpoint is time to first kidney failure (persistent eGFR <15 ml/min/1.73 m^2 or initiation of chronic kidney replacement therapy), persistent ≥50% reduction in eGFR or death from kidney or CV causes.

Results. Enrolled participants ($N = 3534$) had a baseline mean age of 66.6 years [standard deviation (SD) 9.0], haemoglobin A_{1c} of 7.8% (SD 1.3), diabetes duration of 17.4 years (SD 9.3), eGFR of 47.0 ml/min/1.73 m^2 (SD 15.2) and median UACR of 568 mg/g (range 2–11 852). According to Kidney Disease: Improving Global Outcomes guidelines categorisation, 68.2% were at very high risk for CKD progression.

Conclusion. FLOW will evaluate the effect of semaglutide on kidney outcomes in participants with CKD and T2D, and is expected to be completed in late 2024.

Keywords: albuminuria, cardiovascular disease, diabetic kidney disease, glomerular filtration rate, glucagon-like peptide-1 receptor agonist

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GRAPHICAL ABSTRACT

The rationale, design and baseline data of FLOW, a kidney outcomes trial with once-weekly semaglutide in people with type 2 diabetes and chronic kidney disease

Background

Evidence has emerged of potential kidney-protective effects of GLP-1RAs in people with T2D. FLOW is a dedicated kidney outcomes trial to assess semaglutide in a population with CKD and T2D at high risk of kidney disease progression.

Methods

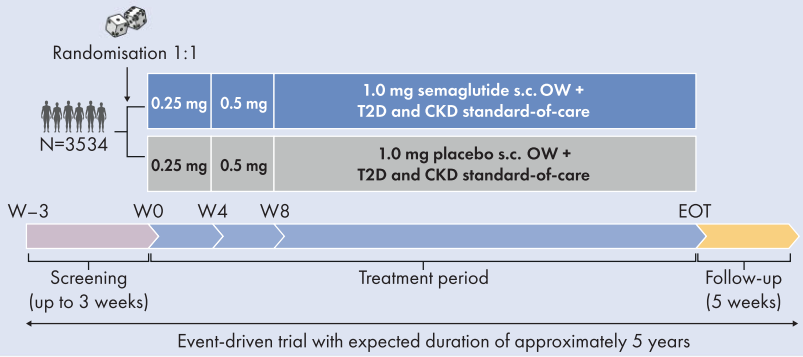
Participants:

- Adults with T2D
- eGFR ≥50 to ≤75 ml/min/1.73 m² and UACR >300 to <5000 mg/g OR
- eGFR ≥25 to <50 ml/min/1.73 m² and UACR >100 to <5000 mg/g

Composite primary endpoint:

Time to first occurrence of:

- Kidney failure (persistent eGFR <15 ml/min/1.73 m² or initiation of CKRT);
- Persistent ≥50% reduction in eGFR; or
- Death from kidney or CV causes



Baseline characteristics

68.2% at very high risk for CKD progression according to KDIGO categorisation, eGFR of 47.0 (15) ml/min/1.73 m²; median UACR of 568 (range: 2–11 852) mg/g

Advanced type 2 diabetes:
Mean age 66.6 years
Mean diabetes duration 17.4 years
Mean HbA_{1c} 7.8%

15.5% receiving SGLT-2is

CKD, chronic kidney disease; CKRT, chronic kidney replacement therapy; CV, cardiovascular; eGFR, estimated glomerular filtration rate; EOT, end of treatment; GLP-1RA, glucagon-like peptide-1 receptor agonist; HbA_{1c}, glycosylated haemoglobin; KDIGO, Kidney Disease: Improving Global Outcomes; OW, once weekly; s.c., subcutaneous; SGLT-2i, sodium-glucose cotransporter-2 inhibitor; T2D, type 2 diabetes; UACR, urine albumin-to-creatinine ratio; W, week.

Conclusion

FLOW will evaluate the effect of semaglutide on kidney outcomes in participants with CKD and T2D, and is expected to complete in late 2024.

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KEY LEARNING POINTS

What is already known about this subject?

- Evidence has emerged of the potential kidney-protective effects of glucagon-like peptide-1 receptor agonists (GLP-1RAs) in people with type 2 diabetes (T2D).
- To date, data have mostly been derived from cardiovascular (CV) outcome or glycaemic control trials featuring populations not selected for chronic kidney disease (CKD) and/or with kidney disease events as secondary outcomes.
- Reduction of CKD progression by GLP-1RAs is yet to be confirmed and requires dedicated trials of kidney outcomes with GLP-1RAs.

What this study adds?

- FLOW (NCT03819153) is a dedicated kidney outcomes trial to assess semaglutide, a once-weekly GLP-1RA, in a population with CKD and T2D at high risk of kidney disease progression.
- The trial is designed to assess whether treatment with once-weekly subcutaneous semaglutide delays the progression of kidney disease and lowers the risk of kidney failure, as well as kidney and CV disease mortality, compared with placebo in people with CKD and T2D.
- Baseline data from the FLOW trial, which is ongoing, show that enrolled participants are nearly all classified as high or very high risk for CKD progression according to Kidney Disease: Improving Global Outcomes guidelines categorisation, which assesses risk based on estimated glomerular filtration rate and urine albumin:creatinine ratio.

What impact this may have on practice or policy?

- The FLOW trial will provide evidence on the effects of semaglutide on kidney outcomes, potentially expanding treatment options for patients with T2D to slow the progression of CKD and reduce kidney failure.

INTRODUCTION

Chronic kidney disease (CKD) is associated with increased morbidity and mortality, including an increased risk of both kidney failure and cardiovascular (CV) events [1]. CKD is a common complication of type 2 diabetes (T2D), affecting ≈40% of those with T2D, and the risk increases with diabetes duration [1]. The presence of CKD causes average healthcare costs to increase by almost 50% compared with costs for those with diabetes alone [2].

Clinical practice guidelines recommend multifactorial interventions to reduce the risk of CKD developing or progressing in people with T2D [3]. Recommendations include optimising blood glucose levels towards an individualised target, lowering blood pressure, moderating dietary protein intake and weight loss. Guidelines on CKD and diabetes management, such as the 2022 Kidney Disease: Improving Global Outcomes (KDIGO) guidelines for patients with CKD and the 2022 American Diabetes Association (ADA) standards-of-care (SoC) guidelines for patients with T2D recommend treatment with renin–angiotensin–aldosterone system (RAAS) blocking agents and sodium–glucose co-transporter 2 inhibitors (SGLT2is) in most patients [3, 4]. Both guidelines also recommend a non-steroidal mineralocorticoid receptor antagonist (finerenone) for patients with CKD at increased risk for CV events, or CKD progression, or unable to use SGLT2is [4, 5]. The 2022 KDIGO guidelines recommend long-acting glucagon-like peptide-1 receptor agonists (GLP-1RAs) with proven CV benefits as the preferred second-line treatment for glucose lowering and CV event risk reduction in individuals either with CV disease (CVD) or at high risk of CVD who are not achieving individualised glycaemic targets despite the use of metformin and an SGLT2i or who are unable to use those medications [3]. For patients with confirmed atherosclerotic CVD or at high risk of CV events, the 2022 ADA SoC guidelines recommend either a GLP-1RA or an SGLT2i with proven CV benefits [4].

GLP-1RAs are an effective treatment for glycaemic control and weight reduction in people with T2D and have a good safety and tolerability profile (generally transient gastrointestinal adverse events being most common), including in those with CKD [3, 4]. Some GLP-1RAs [albiglutide, efpeglenatide, dulaglutide, liraglutide and once-weekly (OW) semaglutide] reduce the risk of major adverse CV events (MACE) in people with T2D with established CVD or at high risk of CVD [6–10]. Meta-analyses of CV outcomes trials (CVOTs), which included >40 000 participants, suggest potential kidney-protective effects of GLP-1RAs, with some (liraglutide, dulaglutide, semaglutide and efpeglenatide) associated with reductions in secondary composite kidney outcomes (macroalbuminuria, substantial loss of kidney function, kidney failure and death due to kidney disease; Fig. 1) [11, 12]. However, these benefits were driven by a lower risk of persistent macroalbuminuria [6, 10, 13].

Despite improvements in kidney outcomes with available pharmacotherapies, the risk of kidney failure in people with CKD and T2D remains high [14, 15]. Given the promising preliminary findings with GLP-1RAs, further exploration of this drug class as agents to improve kidney outcomes in people with CKD and T2D is a priority. FLOW (NCT03819153) is a dedicated kidney outcomes trial designed to determine the kidney-protective effects of semaglutide in participants with CKD and T2D, as well as assessing the effect on CVD mortality. Here we describe the study design and report the baseline characteristics of the FLOW population.

MATERIALS AND METHODS

Overall trial design and treatment

FLOW is a randomised, double-blind, parallel-group, multinational, phase 3b trial comparing semaglutide with matched placebo. Both arms received the SoC when the trial began (2019), including RAAS blockade for delaying the progression of CKD in participants with CKD and T2D.

An overview of the FLOW trial design is shown in Fig. 2. Participants were randomly assigned 1:1, using a central interactive web response system, to receive OW subcutaneous (s.c.) injections of semaglutide 1.0 mg or visually identical placebo, in addition to the maximum labelled or tolerated dose of a RAAS blocking agent (unless contraindicated or not tolerated). SGLT2i use is permitted, and randomisation was stratified by use at baseline. Participants, investigators and all trial personnel (except the independent data monitoring committee) are blinded to treatment assignment. An 8-week dose escalation regimen was employed at the start of treatment, with dose escalation (as tolerated) from 0.25 mg/week for 4 weeks to 0.5 mg for 4 weeks, followed by a maintenance dose of 1.0 mg/week throughout the remainder of the treatment period. Participants were trained in handling the pen injector when dispensed for the first time and instructed to inject the trial product s.c. OW in the abdomen or thigh. Training was repeated at week 4, week 26 and yearly. If a participant experiences unacceptable adverse events (AEs), extensions of dose escalation intervals, dose reductions and treatment pauses are allowed at the discretion of the investigator. Optimisation of glucose-lowering, CKD and CVD SoC medications, in accordance with local practice guidelines, is permitted throughout the trial. A specific guidance document on the management of CKD and CVD in T2D was provided to support the trial investigators.

FLOW is an event-driven trial with an expected duration of ≈5 years; participants are anticipated to receive trial medication for 3–5 years depending on recruitment time.

The trial is being conducted in accordance with the International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use Good Clinical Practice guidelines and the Declaration of Helsinki. The trial protocol is approved by the institutional review board and ethics committee at each participating centre. All participants provided written informed consent before any trial-related activity. The trial is sponsored by Novo Nordisk.

During the coronavirus disease 2019 (COVID-19) pandemic, protocol amends were made and local guidance adjusted to ensure no undue risk of COVID-19 exposure for participants and staff and to maintain data integrity, recruitment and retention. Face-to-face site visits could be replaced with

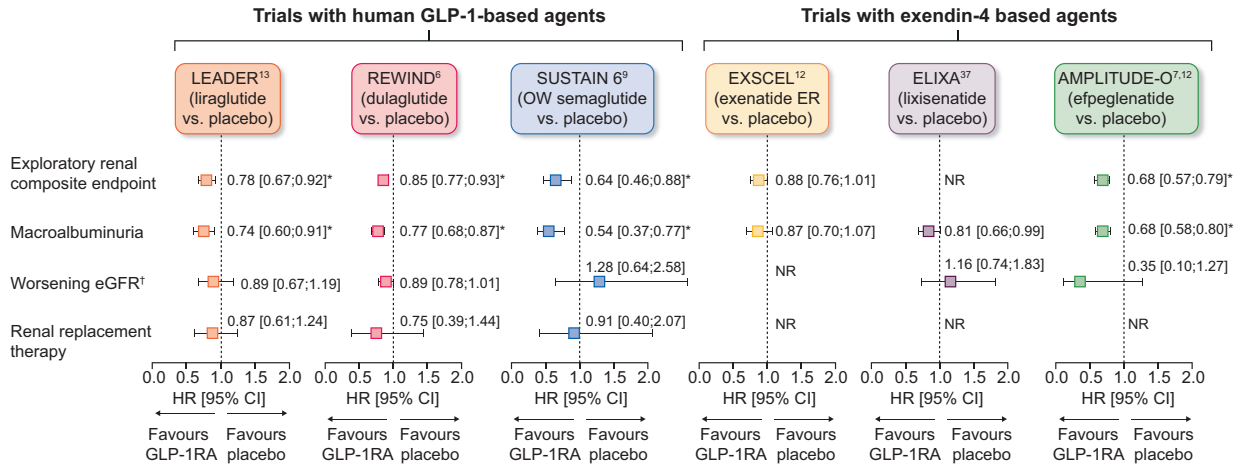

Figure 1: Results of exploratory kidney analyses from GLP-1RA CV outcomes trials. *$P < .05$. †Defined as doubling of serum creatinine in LEADER, SUSTAIN 6 and ELIXA and sustained eGFR decline of ≥30% in REWIND. Direct comparisons not possible due to differing study designs. Secondary kidney composite endpoints were new-onset persistent macroalbuminuria/very high albuminuria, persistent doubling of the serum creatinine or end-stage kidney disease in LEADER; first occurrence of new macroalbuminuria/very high albuminuria (UACR >33.9 mg/mmol), a sustained decline in eGFR of ≥30% or chronic KRT in REWIND; new or worsening nephropathy (defined as persistent macroalbuminuria/very high albuminuria, persistent doubling of serum creatinine and a creatinine clearance of <45 ml/min/1.73 m^2 or the need for continuous KRT) in SUSTAIN 6; a 40% decline in eGFR, KRT, kidney death or incident macroalbuminuria/very high albuminuria in EXSCEL; and incident macroalbuminuria (UACR >33.9 mg/mmol) plus an increase in UACR of ≥30% from baseline, sustained decrease in eGFR of ≥40% for ≥30 days, renal replacement therapy for ≥90 days and sustained eGFR <15 ml/min/1.73 m^2 for ≥30 days in AMPLITUDE-O [6, 7, 10, 13, 38, 43]. exenatide ER, exenatide extended release; KRT, kidney replacement therapy; NR, not reported.

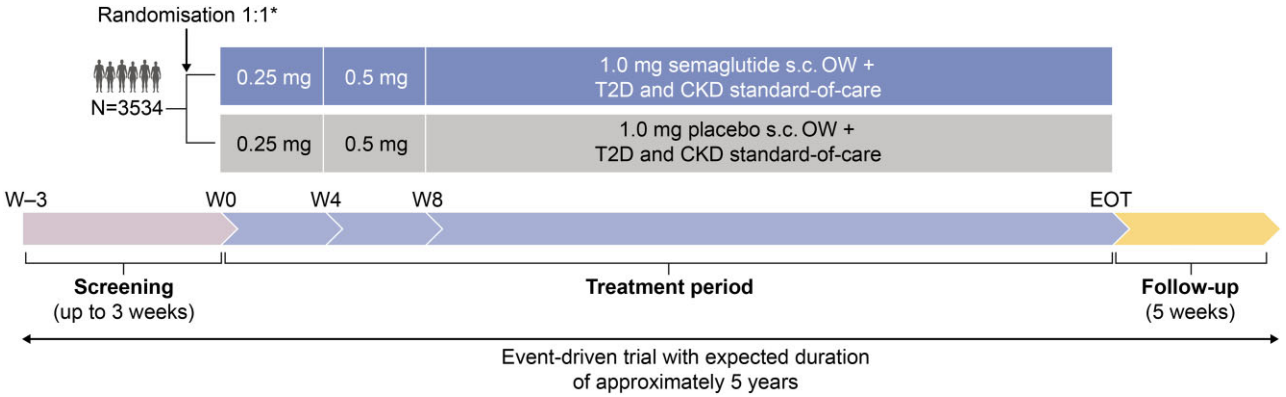

Figure 2: FLOW trial design. *Stratified by SGLT-2i use (yes/no). EOT, end of treatment; N, number of participants; W, week.

phone and home visits, remote monitoring and alternative trial drug dispensing and co-participation in COVID-19 trials was permitted. Guidance documents were issued to trial sites and along with local support from global expert panel members. Data on COVID events, vaccination and co-occurrence with study outcomes were added to the data collection.

FLOW includes sites in Ukraine and Russia, which are being monitored continuously to ensure the safety of investigators, site staff and subjects in these countries, as well as protocol compliance, trial product supply, data integrity and trial oversight. No protocol adjustments have been required, due to the built-in flexibility of the protocol.

Population

Participants were enrolled from 418 trial locations across 28 countries (Fig. 3 and Supplementary Table 1). Adults (≥18 years or ≥20 years in Japan) with pre-existing CKD with high albuminuria, low estimated glomerular filtration rate (eGFR), T2D, haemoglobin A_{1c} (HbA_{1c}) ≤10% (<86 mmol/mol) and on stable treatment with the maximum labelled or tolerated dose of a RAAS blocking agent (unless contraindicated or not tolerated) were eligible for enrolment. Key inclusion and exclusion criteria are shown in Table 1; eligibility criteria were designed to select a broad population with both CKD and T2D and at high risk for progression of CKD.

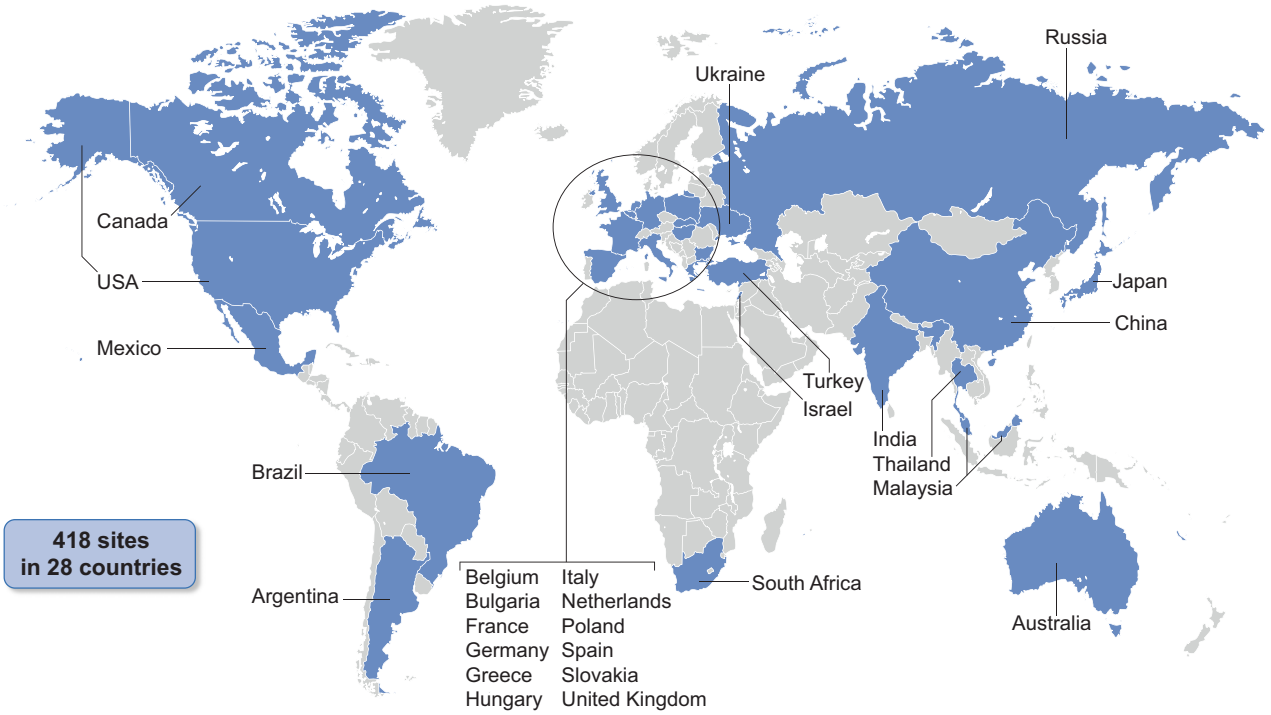

Figure 3: Map of trial site locations.

Table 1: Inclusion and exclusion criteria for the FLOW trial.

Inclusion criteria	Exclusion criteria
• Informed consent • Male or female • Age ≥18 years (except for Japan where participants must be ≥20 years) • Diagnosis of T2D • HbA_{1c} ≤10% (≤86 mmol/mol) • Renal impairment, defined as either: eGFR[a] ≥50 and ≤75 ml/min/1.73 m^2 and UACR >300 and <5000 mg/g[b,c] or eGFR[a] ≥25 and <50 ml/min/1.73 m^2 and UACR >100 and <5000 mg/g[b] • Stable treatment with maximum labelled or tolerated dose of a RAAS blocking agent[d]	• Known or suspected hypersensitivity to trial product(s) or related products • Pregnancy, breastfeeding or intention to become pregnant; child-bearing potential and not using a highly effective contraceptive method • Participation in any clinical trial of an approved or non-approved investigational medicinal product within 30 days before screening • Any disorder which, in the investigator's opinion, might jeopardise a subject's safety or compliance with the protocol • Congenital or hereditary kidney diseases[e] or autoimmune kidney diseases[f] • MI, stroke, hospitalisation for unstable angina or TIA within 60 days prior to the day of screening; NYHA class IV; or planned coronary, carotid or peripheral artery revascularisation • Use of any GLP-1RA within 30 days prior to screening • Personal or first-degree relative(s) with a history of MEN2 or MTC • Chronic or intermittent haemodialysis or peritoneal dialysis within ≤90 days • Uncontrolled and potentially unstable diabetic retinopathy or maculopathy[g] • Presence or history of malignant neoplasm within 5 years prior to the day of screening[h] • Prior solid organ transplant or awaiting solid organ transplant • Combination use of ACE inhibitor and ARB

[a]Based on the CKD-EPI formula.
[b]Measurements taken ≤90 days before screening with subject in usual health condition.
[c]Number of participants with eGFR ≥60 ml/min/1.73 m^2 capped at 20% of randomised participants.
[d]ACE inhibitor or ARB, unless such treatment is contraindicated or not tolerated.
[e]Including PKD.
[f]Including glomerulonephritis or congenital urinary tract malformations.
[g]Verified by a fundus examination performed within the past 90 days prior to screening or in the period between screening and randomisation; eye examination performed by a suitably qualified healthcare provider (e.g. optometrist or ophthalmologist).
[h]Basal and squamous cell skin cancer and any carcinoma *in situ* were allowed.
ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; MEN2, multiple endocrine neoplasia type 2; MI, myocardial infarction; MTC, medullary thyroid carcinoma; NYHA, New York Heart Association; PKD, polycystic kidney disease; TIA, transient ischaemic attack.

Table 2: FLOW trial endpoints.

Study endpoints	Time frame
Primary endpoint	
Time to first occurrence of a composite endpoint consisting of • Onset of kidney failure, defined as initiation of chronic kidney replacement therapy (dialysis or kidney transplantation) or persistent eGFR <15 ml/min/1.73 m^2 for at least 4 weeks • Death from kidney failure • CV death • Onset of persistent ≥50% reduction in eGFR (CKD-EPI) versus baseline	Randomisation to EOT
Confirmatory secondary endpoints	
Annual rate of change in eGFR (CKD-EPI) (total eGFR slope)	Randomisation to EOT
Time to first occurrence of a composite CV MACE endpoint consisting of: • Non-fatal myocardial infarction • Non-fatal stroke • CV death	Randomisation to EOT
Time to occurrence of all-cause death	Randomisation to EOT
Supportive secondary endpoints	
Time to occurrence of each of the individual components of the primary composite endpoint and of the confirmatory secondary MACE endpoint	Randomisation to EOT
Time to first occurrence of MALE, a composite endpoint consisting of: • Acute limb ischaemia hospitalisation • Chronic limb ischaemia hospitalisation	Randomisation to EOT
Annual rate of change in eGFR (CKD-EPI) (chronic eGFR slope)	Week 12 to EOT
Change in eGFR (CKD-EPI)	Randomisation to week 12
Change in eGFR (cystatin C CKD-EPI)	Randomisation to year 3
Relative change in UACR	Randomisation to year 3
Change in body weight	Randomisation to year 3
Change in HbA_{1c}	Randomisation to year 3
Change in systolic blood pressure	Randomisation to year 3
Change in diastolic blood pressure	Randomisation to year 3
Number of severe hypoglycaemic episodes	Randomisation to EOT
Exploratory endpoints	
Change in EQ-5D-5L index score	Randomisation to year 3
Change in EQ-5D-5L visual analogue scale score	Randomisation to year 3

Randomisation = week 0; end of trial = a period expected to be ≥61 months for the individual participant; persistent = two consecutive central laboratory assessments that meet criteria, at least 4 weeks apart. Events including deaths, those leading to kidney replacement therapy, acute coronary syndrome, stroke or transient ischaemic attack, and MALE are reviewed by an independent external EAC in a blinded manner.
EOT, end of trial; EQ-5D-5L, EuroQol five-dimension, five-level questionnaire; MALE, major adverse limb events.

The number of participants with eGFR ≥60 ml/min/1.73 m^2 at randomisation was capped at 20% to ensure the predominance of participants with moderate–severe CKD. Laboratory-based inclusion and exclusion criteria were based on historical values recorded within 90 days of the screening visit, values recorded at an optional pre-screening visit or central laboratory values recorded at screening. Baseline data for eGFR and urine albumin:creatinine ratio (UACR) came from central laboratory assessments only.

Outcome measures

All primary, confirmatory secondary and supportive secondary endpoints (Table 2) are assessed from randomisation to the end of the trial. The composite primary endpoint is time to first occurrence of kidney failure [persistent eGFR <15 ml/min/1.73 m^2 using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula or initiation of chronic kidney replacement therapy (dialysis or kidney transplantation)], persistent ≥50% reduction in eGFR (CKD-EPI) when compared with baseline, or death due to kidney or CV causes. For the eGFR components of the primary endpoint, persistent is defined as two consecutive central laboratory assessments at least 4 weeks apart that meet the criteria. Confirmatory secondary endpoints are annual rate of change of eGFR (total eGFR slope), time to first occurrence of three-point MACE (comprising non-fatal myocardial infarction, non-fatal stroke or death from CV causes) and time to occurrence of all-cause death. Additional secondary and exploratory endpoints compare the effect of semaglutide versus placebo on a range of CV, CKD, clinical and metabolic outcomes, as well as health outcomes and quality of life (Table 2).

Statistical considerations

FLOW is an event-driven trial; *a priori* a minimum of 3508 participants were expected to be randomised to provide 90% power, using a one-sided type I error rate of 0.025, to detect the likelihood of semaglutide 1.0 mg versus placebo reaching a 20% relative risk reduction [corresponding to a hazard ratio (HR) of 0.8] for the primary endpoint. Assuming a true HR of 0.8, a total of 854 primary endpoint events are required and the trial will be complete when this number of primary endpoints is collected.

The trial uses a group sequential design. Interim testing evaluating the primary endpoint for superiority will be

performed based on a locked snapshot of the study database at the time-point of interim testing. Interim testing will be performed by an external statistician independent of trial conduct. An independent data monitoring committee (DMC) will evaluate unblinded interim testing using group sequential stopping boundaries as guidance; to ensure type I error rate control, the alpha spending function developed by Lan and DeMets will be used to provide stopping boundaries. Stopping the trial for superiority is allowed if a stopping boundary is crossed and the DMC makes the decision to recommend early trial termination.

The primary efficacy estimand for all endpoints is based on the intention-to-treat principle, evaluating the effect of the randomised treatment intervention, irrespective of adherence and changes to background medication.

The treatment effect will be expressed as an HR with corresponding 95% confidence interval (CI) and will be estimated using a stratified Cox proportional hazards model with treatment (semaglutide, placebo) as a fixed factor together with the two-sided 95% CI and one-sided *P*-value for hypothesis testing; stratification is by use of SGLT2is (yes/no) at baseline. If superiority is confirmed for the primary endpoint, then superiority will be tested for the confirmatory secondary endpoints adjusted to account for the group sequential design through a hierarchical testing strategy:

1. Annual rate of change in eGFR (total eGFR slope)
2. Time to first occurrence of MACE
3. Time to occurrence of all-cause death.

Since the recruitment of FLOW trial participants, a new CKD-EPI formula without race as a factor has been recommended; a pre-specified supplementary analysis has now been added to evaluate the impact of the updated formula on the results [16].

Study oversight

FLOW was designed and organised by the sponsor in collaboration with regulatory agencies, a steering committee and a global expert panel. The steering committee provides academic and scientific leadership and ensures that conduct of this study conforms to protocols, while the global expert panel provides scientific, medical and operational input at a country level. The independent DMC reviews safety and efficacy data as defined in the protocols and makes recommendations for additions or adjustments. Planned interim testing for superiority will also be performed by the DMC. An external, independent and blinded events adjudication committee (EAC) is in charge of adjudicating predefined events. The management structure of the trial and relationships between the trial committees can be found in Supplementary Fig. S1.

RESULTS

A total of 3534 participants have been enrolled and randomised to treatment. Baseline and demographic characteristics for the overall population are shown in Table 3 and Supplementary Table 1. Participants had a mean age of 66.6 years (SD 9.0), 69.7% were male and 65.7% were white. The mean HbA_{1c} was 7.8% (SD 1.3) or 61.5 mmol/mol (SD 14.1) and a high proportion of participants (68.6%) had a baseline HbA_{1c} >7%. The mean baseline diabetes duration was 17.4 years (SD 9.3), body mass index was 32.0 kg/m^2 (SD 6.3) and systolic and diastolic blood pressure were 138.6 mmHg (SD 15.8) and 76.4 mmHg (SD 10.0), respectively.

Regarding kidney function, the mean baseline eGFR was 47.0 ml/min/1.73 m^2 (SD 15.2) and the median UACR was 568 mg/g (range 2–11 852); baseline laboratory assessments may differ slightly from eligibility criteria required at screening (see the Population section of the Methods where this is described). Macroalbuminuria (UACR ≥300 mg/g) was evident in 68.4% of participants. According to KDIGO categories [3], the majority of participants (68.2%) were classified as very high risk for CKD progression (Fig. 4).

Many participants had comorbidities such as neuropathy and retinopathy (43.0% and 44.9%, respectively) at baseline. A medical history of CVD was also common (52.0%) and 19.1% of participants had previous heart failure. The most frequently used glucose-lowering medications at baseline were insulin (61.5%) and metformin (51.6%), and 15.5% of participants were receiving SGLT2is. Participants were required to be on RAAS blockade unless treatment was contraindicated or not tolerated; overall, 95.3% were receiving RAAS inhibitors at baseline. Most participants were also receiving lipid-lowering medication (79.2%) (Table 3).

DISCUSSION

Despite the availability of established and newer pharmacotherapies to delay CKD progression in people with T2D, the risk of progression and the associated morbidity and mortality remains substantial [14, 15]. With a projected global increase in diabetes prevalence from an estimated 537 million in 2021 to 780 million by 2045 [1], there is a clear need for additional treatment options to help mitigate the residual risk in those individuals with concomitant CKD.

Secondary analyses, primarily of CVOTs, suggest a potential kidney-protective effect of GLP-1RAs in people with T2D and at risk of CVD [6, 9–12, 17–28]. Given the relatively low proportion of participants with CKD at baseline (≈20–25%), the variability in the severity of CKD exhibited by participants and the nature of secondary endpoints in CVOTs, available data can only be considered hypothesis generating. Improved albuminuria is the most consistent kidney outcome with GLP-1RAs to date, although this might largely be due to the relatively low occurrence of kidney events and the relatively low prevalence of existing CKD in CVOT populations selected for CV risk. GLP-1RA-associated preservation of eGFR in participants with T2D and CKD has also been demonstrated in CVOTs and non-CVOTs [17, 20, 29]. Trials that are both specifically designed and statistically powered are needed to clearly define the effects of GLP-1RAs on clinically meaningful kidney outcomes.

FLOW is a dedicated kidney outcomes trial designed to assess the kidney-protective effects of semaglutide, a GLP-1RA, and its potential to improve treatment options in people with CKD and T2D. The composite endpoint components selected

Table 3: Baseline characteristics and demographics.

Characteristics	Values
Total randomised population, *N*	3534
Age (years)	66.6 (9.0)
Male, *n* (%)	2464 (69.7)
Race, *n* (%)	
White	2323 (65.7)
Black or African American	160 (4.5)
Asian	846 (23.9)
American Indian or Alaska Native	25 (0.7)
Hawaiian or other Pacific Islander	5 (0.1)
Other	96 (2.7)
Not reported	79 (2.2)
Ethnicity, *n* (%)	
Hispanic or Latino	556 (15.7)
Not Hispanic or Latino	2833 (80.2)
Not reported	145 (4.1)
Region, *n* (%)	
Europe	962 (27.2)
Asia	913 (25.8)
North America	865 (24.5)
South America	252 (7.1)
Africa	101 (2.9)
Other	441 (12.5)
Systolic BP (mmHg)	138.6 (15.8)
Diastolic BP (mmHg)	76.4 (10.0)
Pulse (bpm)	73.1 (11.3)
Body mass index (kg/m^2)	32.0 (6.3)
Body weight (kg)	89.6 (20.5)
HbA_{1c} (%)	7.8 (1.3)
HbA_{1c} (mmol)	61.5 (14.1)
HbA_{1c} >7%, *n* (%)	2424 (68.6)
T2D duration, years	17.4 (9.3)
eGFR (ml/min/1.73 m^2)[a]	47.0 (15.2)
eGFR <60 ml/min/1.73 m^2, *n* (%)	2814 (79.6)
UACR (mg/g), median (range)	568 (2–11 852)
Macroalbuminuria (UACR ≥300 mg/g), *n* (%)	2419 (68.4)
Diabetic neuropathy, *n* (%)[b]	1521 (43.0)
Diabetic retinopathy in worst eye, *n* (%)[c]	1585 (44.9)
Mild non-proliferative	943 (26.7)
Moderate–severe non-proliferative	436 (12.3)
Proliferative	204 (5.8)
Diabetic macular oedema in worst eye, *n* (%)[c]	240 (6.8)
Previous cardiovascular disease[c]	1838 (52.0)
Previous MI	513 (14.5)
Previous stroke	367 (10.4)
Heart failure	675 (19.1)
Very high CKD progression risk (KDIGO criteria), *n* (%)[d]	2413 (68.2)
Oral anti-diabetes drugs at baseline, *n* (%)	
Metformin[e]	1825 (51.6)
Sulphonylurea	879 (24.9)
DPP-4i	898 (25.4)
SGLT2i	548 (15.5)
Thiazolidinedione	147 (4.2)
Alpha-glucosidase inhibitors	109 (3.1)
Insulin at baseline, *n* (%)	2172 (61.5)
Long acting	1616 (45.7)
Short acting	1293 (36.6)
Premixed	224 (6.3)
RAAS inhibitors, *n* (%)	3368 (95.3)
Cardiovascular medications, *n* (%)	3511 (99.3)
Beta blockers	1823 (51.6)
ACE inhibitors	1242 (35.1)
Angiotensin receptor blockers	2127 (60.2)
Calcium channel blockers	1992 (56.4)
Angiotensin receptor–neprilysin inhibitor	24 (0.68)

Table 3: Continued.

Characteristics	Values
Lipid-lowering drugs, *n* (%)	2799 (79.2)
Statins	2655 (75.1)
Bile acid sequestrants	1 (0.03)
Fibrates	302 (8.5)
Ezetimibe	248 (7.0)
PCSK-9 inhibitors	9 (0.3)
Eicosapentaenoic acid ethyl ester	22 (0.6)
Omega-3-acid ethyl ester	12 (0.3)
Other omega 3-triglycerides	64 (1.8)

All values are mean (SD) unless stated otherwise.
As the trial is ongoing, data may be subject to minor changes until database lock.
[a]eGFR was estimated using the CKD-EPI equation.
[b]Based on medical history.
[c]Based on eye examination at baseline, verified by a fundus examination performed within the past 90 days prior to screening or in the period between screening and randomisation; eye examination performed by a suitably qualified healthcare provider (e.g. optometrist or ophthalmologist).
[d]Defined as (i) UACR (mg/g) <30 and eGFR (mL/min/1.73 m^2) ≤15 to <30, (ii) UACR (mg/g) ≤30 to <300 and eGFR (mL/min/1.73 m^2) ≤30 to <45, (iii) UACR (mg/g) ≤30 to <300 and eGFR (mL/min/1.73 m^2) ≤15 to <30, (iv) UACR (mg/g) ≤300 and eGFR (mL/min/1.73 m^2) ≤45 to <60, (v) UACR (mg/g) ≤300 and eGFR (mL/min/1.73 m^2) ≤30 to <45 or (vi) UACR (mg/g) ≤300 and eGFR (mL/min/1.73 m^2): ≤15 to <30.
[e]Relatively low proportion of patients due to metformin being contraindicated in participants with a low eGFR.
ACE, angiotensin-converting enzyme; BP, blood pressure; bpm, beats per minute; DPP-4i, dipeptidyl peptidase-4 inhibitor; MI, myocardial infarction; n, number of participants; PCSK-9, proprotein convertase subtilisin/kexin type 9.

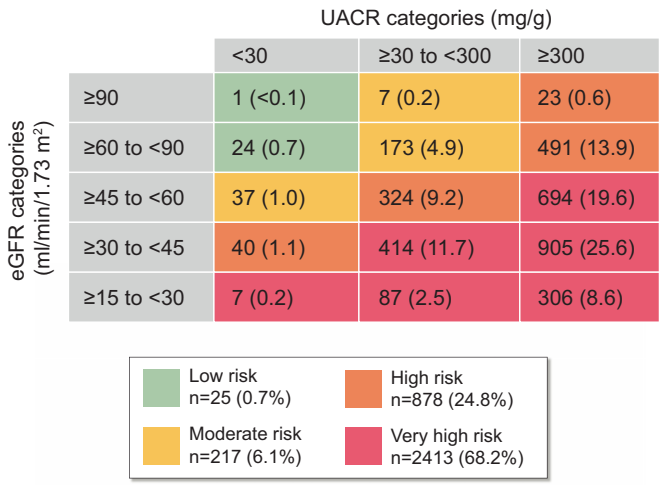

Figure 4: KDIGO risk categories among FLOW participants. Data are *n* (%) for each category. To facilitate recruitment to the FLOW trial and increase generalisability of the outcomes by reflecting typical clinical practice, eligibility in terms of laboratory results could be based on historical values. Adapted from the KDIGO Diabetes Work Group, 2020 [3].

for FLOW are widely recognised by health authorities and regulatory bodies as robust measures for the assessment of kidney protection [30]. CV death is included in the composite endpoint, alongside death from kidney failure, because of the multiple pathways and risk factors that are common to these two conditions and the resulting competing risks [31].

To facilitate recruitment to the FLOW trial and increase generalisability of the outcomes by reflecting typical clinical practice, eligibility in terms of laboratory results could be based on historical values. However, baseline data were based on central laboratory-derived values, resulting in data from a small number of participants not fulfilling all inclusion criteria at this specific visit. Permitting use of the broad spectrum of concomitant glucose-lowering medications inherent in a SoC approach, as well as treatments for comorbidities and CKD/CV risk factors (including SGLT2is), enables a pragmatic approach to treatment comparisons and for secondary analyses of treatment combinations depending on patient characteristics/baseline therapy. There is substantial overlap between the FLOW population and the populations studied in the dedicated kidney outcome studies with SGLT2is (CREDENCE, DAPA-CKD and EMPA-KIDNEY) [15, 30, 32], which have led to recommendations for the use of SGLT2i for patients with T2D and CKD [3]. Similarly, FLOW will allow for a rigorous evaluation of the potential of semaglutide for the management of CKD in T2D.

The significant CKD burden of the FLOW trial population is reflected in the baseline data showing that 68.2% of participants classified according to KDIGO guidelines criteria are at very high risk of CKD progression. A high proportion of participants had HbA_{1c} >7%, coupled with a mean diabetes duration of 17.4 years, reflecting a population with a substantial diabetes burden. As such, participants in the FLOW trial represent a population that is likely to benefit from additional treatment options that go beyond glycaemic control to address metabolic risk and comorbidities [3].

Two ongoing CVOTs with secondary kidney outcomes, SOUL (oral semaglutide in participants with T2D and CVD or CKD; NCT03914326) and SELECT (s.c. semaglutide 2.4 mg in participants with obesity and established CVD; NCT03574597), will also provide insights on the effect of semaglutide in kidney disease [33, 34].

The mechanism of action for GLP-1RAs in the kidney is not yet fully elucidated, although several hypotheses have been proposed. Mediation analyses of SUSTAIN 6 (semaglutide), REWIND (dulaglutide) and LEADER (liraglutide) CVOTs suggest that indirect effects such as improved glycaemic control, weight loss and reduced blood pressure cannot fully account for the kidney-protective effects and indicate that other factors also play a role [6, 35–37]. Potential direct

effects include reduced inflammation, oxidative stress or haemodynamic effects [38–40]. Indeed, reductions in oxidative stress and inflammation have been demonstrated with semaglutide in murine studies showing antioxidative activity and suppression of inflammatory cytokines specifically in the kidney [40, 41]. Evidence for a direct mechanism is limited and will be more thoroughly examined in the mechanistic REMODEL trial (NCT04865770). REMODEL will utilise magnetic resonance imaging to assess kidney oxygenation, inflammation and global kidney perfusion; kidney biopsies to evaluate gene expression via single-nucleus RNA sequencing and morphometric parameters; and blood and urinalysis to assess biomarkers of kidney function and kidney damage [42].

Existing data from CVOTs and real-world evidence suggest that GLP-1RAs have the potential to slow the progression of CKD in people with T2D at high risk of CV events [6, 9–11, 17–28], although no dedicated kidney outcomes trials in populations with CKD and T2D have yet been conducted. The FLOW trial is fully recruited with a population of participants with a T2D mean baseline eGFR of 47.0 ml/min/1.73 m^2, a median UACR of 568 mg/g and a mean baseline HbA_{1c} of 7.8%. FLOW is the first dedicated kidney outcomes trial with a GLP-1RA that includes people with T2D at high or very high risk for CKD progression and is specifically designed to provide evidence on the effects of semaglutide on kidney outcomes. We anticipate that FLOW will complete in late 2024.

SUPPLEMENTARY DATA

Supplementary data are available at *ndt* online.

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AUTHORS' CONTRIBUTIONS

All authors were involved in the conceptualisation of the article and its development and critical revision and have read and agreed to the published version. M.G. provided data analysis.

DATA AVAILABILITY STATEMENT

The data sets analysed during the current study are available from the corresponding author upon reasonable request.

CONFLICT OF INTEREST STATEMENT

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