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CLINICAL STUDY DESIGN

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# Rationale, design and baseline characteristics of the effect of canagliflozin in patients with type 2 diabetes and microalbuminuria in the Japanese population: The CANPIONE study

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## Abstract

**Aim:** To evaluate the effect of canagliflozin, a sodium-glucose co-transporter-2 (SGLT2) inhibitor, on albuminuria and the decline of estimated glomerular filtration rate (eGFR) in participants with type 2 diabetes and microalbuminuria.

**Methods:** The CANPIONE study is a multicentre, randomized, parallel-group and open-labelled study consisting of a unique 24-week preintervention period, during which the rate of eGFR decline before intervention is estimated, followed by a 52-week intervention and a 4-week washout period. Participants with a geometric mean urinary albumin-to-creatinine ratio (UACR) of 50 and higher and less than 300 mg/g in two consecutive first-morning voids at two different time points, and an eGFR of 45 ml/min/1.73m$^2$ or higher, are randomly assigned to receive canagliflozin 100 mg daily or to continue guideline-recommended treatment, except for SGLT2 inhibitors. The first primary outcome is the change in UACR, and the second primary outcome is the change in eGFR slope.

**Results:** A total of 258 participants were screened and 98 were randomized at 21 sites in Japan from August 2018 to May 2021. The mean baseline age was 61.4 years and 25.8% were female. The mean HbA1c was 7.9%, mean eGFR was 74.1 ml/min/1.73m$^2$ and median UACR was 104.2 mg/g.

**Conclusions:** The CANPIONE study will determine whether the SGLT2 inhibitor canagliflozin can reduce albuminuria and slow eGFR decline in participants with type 2 diabetes and microalbuminuria.

**KEYWORDS**
canagliflozin, CANPIONE study, diabetic kidney disease, eGFR slope, SGLT2 inhibitor, urinary albumin-to-creatinine ratio

## 1 | INTRODUCTION

Diabetic kidney disease (DKD) has received growing attention as a global public health problem because of the increased incidence of end-stage kidney disease (ESKD).[1,2] Sodium-glucose co-transporter-2 (SGLT2) inhibitors have been shown to have effects beyond glucose lowering that include benefits on DKD. The initial effect of SGLT2 inhibition is manifested by a dip in estimated glomerular filtration rate (eGFR), primarily reflecting reduction of glomerular hyperfiltration through normalization of tubuloglomerular feedback, followed by stabilization of eGFR during prolonged treatment.[3,4] The Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) trial,[5] the first large trial of SGLT2 inhibitors dedicated to evaluate kidney outcomes, has shown that canagliflozin, relative to placebo, slows the progression of eGFR decline and reduces the risk of ESKD in participants with established DKD. The DAPA-CKD trial showed that dapagliflozin reduced the risk of ESKD and prolonged survival in patients with chronic kidney disease (CKD). These benefits were consistent in patients with and without type 2 diabetes.[6,7] In the CREDENCE trial, almost all participants had macroalbuminuria at baseline, and therefore it remains unclear as to whether the benefit on kidney and cardiovascular outcomes shown in the CREDENCE trial can be extended to individuals with type 2 diabetes and microalbuminuria.

The effect of CANagliflozin in type 2 diabetic PatIents with micrOalbuminuria in JapaNEse population (CANPIONE) study is uniquely designed to test the effect of canagliflozin on the first primary outcome, the longitudinal profile of change in urinary albumin-to-creatinine ratio (UACR) from baseline to the intervention period (weeks 4-52), and the second primary outcome, change in eGFR slope

(calculated by subtracting the individual preintervention slope from the chronic slope [weeks 4-52] during the intervention period). The novelty of the study protocol is to evaluate change in eGFR slope by taking into account both the preintervention and chronic slopes at the individual participant level. Because the individual preintervention slope represents a participant-specific natural course of eGFR decline before intervention, this method allows precise evaluation of the treatment effect on individual DKD progression and might provide a clue for evaluating the individual treatment efficacy in the personalized medicine for DKD.

## 2 | METHODS

### 2.1 | Study design

The CANPIONE study is a multicentre, randomized, open-label and parallel-group study. It is designed to assess the effect of canagliflozin (100 mg once daily) compared with treatment with drugs other than SGLT2 inhibitors on the early stage of DKD in adults with type 2 diabetes. Figure 1 shows the overall study design. The study protocol and informed consent form were reviewed and approved by the local Institutional Review Board (IRB) at each study centre or Central IRB at Okayama University Hospital, and thereafter by the Okayama University Certified Review Board on 22 January 2019, in accordance with the Clinical Trial Act.

### 2.2 | Participant inclusion and exclusion criteria

Individuals with type 2 diabetes who periodically come to the outpatient clinics are screened for eligibility and recruited at each study site. Participants in the CANPIONE study are Japanese men and women aged 20 to 75 years with type 2 diabetes who have inadequate glycaemic control (HbA1c ≥ 7.0% [≥53 mmol/mol] and <11.0% [<97 mmol/mol]), and are in the early stages of DKD (eGFR ≥ 45 ml/min/1.73m$^2$ at visit 1 and geometric mean UACR ≥ 50 and <300 mg/g in two consecutive first-morning voids at both visits 2 and 3). Enrolment of participants with an HbA1c of 6.5% or higher (≥48 mmol/mol) and less than 7.0% (<53 mmol/mol) commenced on 25 November 2019 based on findings from the CREDENCE trial showing that canagliflozin was effective and safe in patients with HbA1c levels down to 6.5% or higher (≥48 mmol/mol).[8] All participants are required to provide informed consent, and be willing and able to adhere to the study protocol requirements. The detailed inclusion and exclusion criteria are listed in Table 1. The eGFR and UACR range of inclusion criteria are shown on the Kidney Disease: Improving Global Outcome (KDIGO) heatmap[9] (Figure 2).

### 2.3 | Screening and preintervention period (24 weeks)

Participants are tested at visits 1, 2 and 3 for the inclusion and exclusion criteria. All antidiabetic medications are continued as before during the preintervention period of 24 weeks (Figure 1). Every 8 weeks, the measurements, including UACR and serum creatinine (eGFR), are performed. Participants who do not qualify based on inclusion or exclusion criteria can be re-enrolled twice after appropriate changes to clinical management.

### 2.4 | Randomization and intervention period (52 weeks)

The eligible participants are randomly assigned to canagliflozin or control in a 1:1 ratio by permuted blocks as per site design via a central

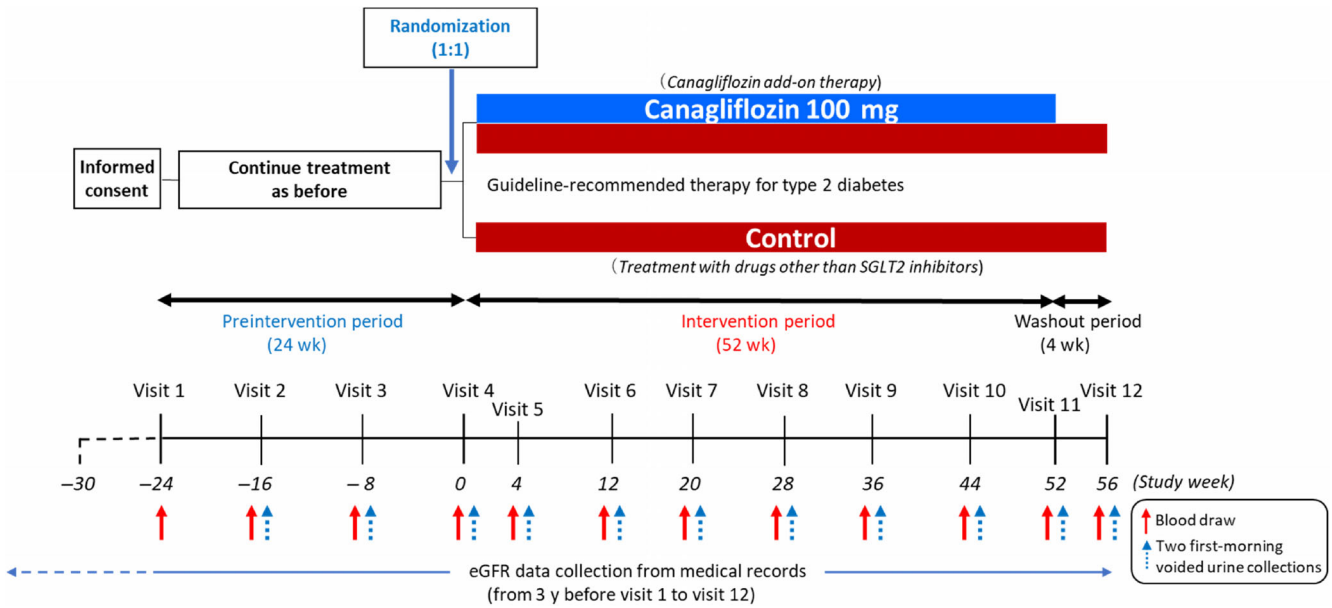


**FIGURE 1** The CANPIONE study design. eGFR, estimated glomerular filtration rate; SGLT2, sodium-glucose co-transporter-2

**TABLE 1** Participant inclusion and exclusion criteria

| |
|---|
| Inclusion criteria |
| 1. Man or woman with a diagnosis of type 2 diabetes |
| 2. Age ≥ 20 to < 75 y at the time of informed consent |
| 3. HbA1c[a] ≥ 6.5% and < 11.0% at visit 1 |
| 4. Geometric mean of two first-morning voided UACR[a] ≥ 50 and < 300 mg/g at visit 2 and visit 3 |
| 5. eGFR[a] ≥ 45 ml/min/1.73 $m^2$ at visit 1 |
| 6. All participants are required to have signed an informed consent document indicating that they understood the purpose of and procedures required for the study and are willing to participate in the study |
| Exclusion criteria |
| 1. Use of SGLT2 inhibitor ≤ 12 wk prior to informed consent |
| 2. Known allergies or hypersensitivity to canagliflozin or other SGLT2 inhibitors |
| 3. History of severe diabetic ketosis (including ketoacidosis), diabetic coma or precoma |
| 4. Severe infection, pre- or post-surgery (i.e. requiring general anaesthesia), or severe trauma at visit 1 or visit 3 |
| 5. Urinary tract infection or genital infection at visit1 or visit 3 |
| 6. Underlying renal disease other than diabetic kidney disease at visit1 or visit 3 |
| 7. New York Heart Association Class IV heart failure at visit1 or visit 3 |
| 8. Severe hypertension (systolic blood pressure ≥ 180 mmHg and/or diastolic blood pressure ≥ 110 mmHg) at visit1 or visit 3 |
| 9. History of arteriosclerosis obliterans and/or foot ulcer and/or limb amputation |
| 10. Pregnant, possibly pregnant, breastfeeding or planning to become pregnant during the study |
| 11. Presence of malignant neoplasms at visit 1 or visit 3, or treatment for malignant neoplasms within the last 5 y at the time of informed consent |
| 12. Severe liver disease at visit1 or visit 3 |
| 13. Treatment with systemic steroids at visit1 or visit 3 |
| 14. Treatment with NSAIDs at visit1 or visit 3 |
| 15. Reduction in eGFR[a] ≥ 30% from visit 1 to visit 3 |
| 16. Any condition that, in the opinion of the investigator, would compromise the participant's well-being or ability to perform the study requirements |

Abbreviations: eGFR, estimated glomerular filtration rate; NSAIDs, non-steroidal anti-inflammatory drugs; SGLT2, sodium-glucose co-transporter-2; UACR, urinary albumin-to-creatinine ratio.
[a]Provided by the central laboratory.

electronic data capture system. Because the CANPIONE study is a modest-sized randomized controlled trial (RCT), stratifying participants by multiple covariates may result in ineffective randomization for other factors. In addition, all of the participating physicians are board-certified diabetologists or other physicians with equivalent experiences and knowledge in diabetes care, and hence the clinical management of diabetes, which is potentially related to the baseline characteristics of the participants, is basically performed according to the treatment guideline. We therefore decided to stratify only by site, and not by other covariates. Participants assigned to canagliflozin treatment take a canagliflozin 100 mg tablet once daily before or after the first meal of the day until completion of the intervention period or premature treatment discontinuation. Participants assigned to the control group receive treatment with drugs other than SGLT2 inhibitors. In both groups, glycaemic management is performed in line with the latest version of the treatment guideline from the Japan Diabetes Society at the discretion of the responsible investigator.[14] Participants are instructed to attend the clinic at prespecified times over the duration of the study. The prohibited medications and the restricted concomitant medications during the study are listed in Table S1. Participants who prematurely discontinue study medication (but who do not withdraw consent) are encouraged to continue the rest of all visits for follow-up as originally planned. Postrandomization follow-up is scheduled for every 4 to 8 weeks until week 52 (Figure 1). Each follow-up visit includes collection of information about adverse events, concomitant therapies and study drug adherence. In addition, vital signs are recorded, and blood and two first-morning voided urines are collected for laboratory measurements.

## 2.5 | Washout period (4 weeks)

Participants assigned to canagliflozin treatment finish canagliflozin treatment just before the washout period. Other background medications are continued in both groups (Figure 1).

## 2.6 | Outcomes

The CANPIONE study has two primary outcomes that are tested in a hierarchical close testing procedure (Table 2). The first primary outcome is the longitudinal profile of change in log-transformed UACR from baseline to the intervention period (weeks 4-52). The second primary outcome is the change in eGFR slope, represented by the change from the 'preintervention slope' to the 'chronic slope' during the intervention period (weeks 4-52). UACR assessment at each time point will be based on values obtained from duplicate first-morning voided urines and analysed by a central laboratory. The within-individual change in eGFR slope will be calculated by individually subtracting the preintervention slope from the chronic slope. Serum creatinine will be measured by the central laboratory and eGFR will be calculated by using the Japanese equation for eGFR (eGFR [ml/min/1.73$m^2$] $= 194 \times \text{serum creatinine}^{-1.094} \times \text{age}^{-0.287} \times 0.739$ [if female]) established by the Japanese Society of Nephrology.[15] In addition to the centrally measured and calculated eGFR values, eGFR values measured at each study site during the period from 3 years prior to the first visit (visit 1) to the last visit (visit 12) of the study will also be collected to evaluate the preintervention eGFR slope, including the period before initiation of the

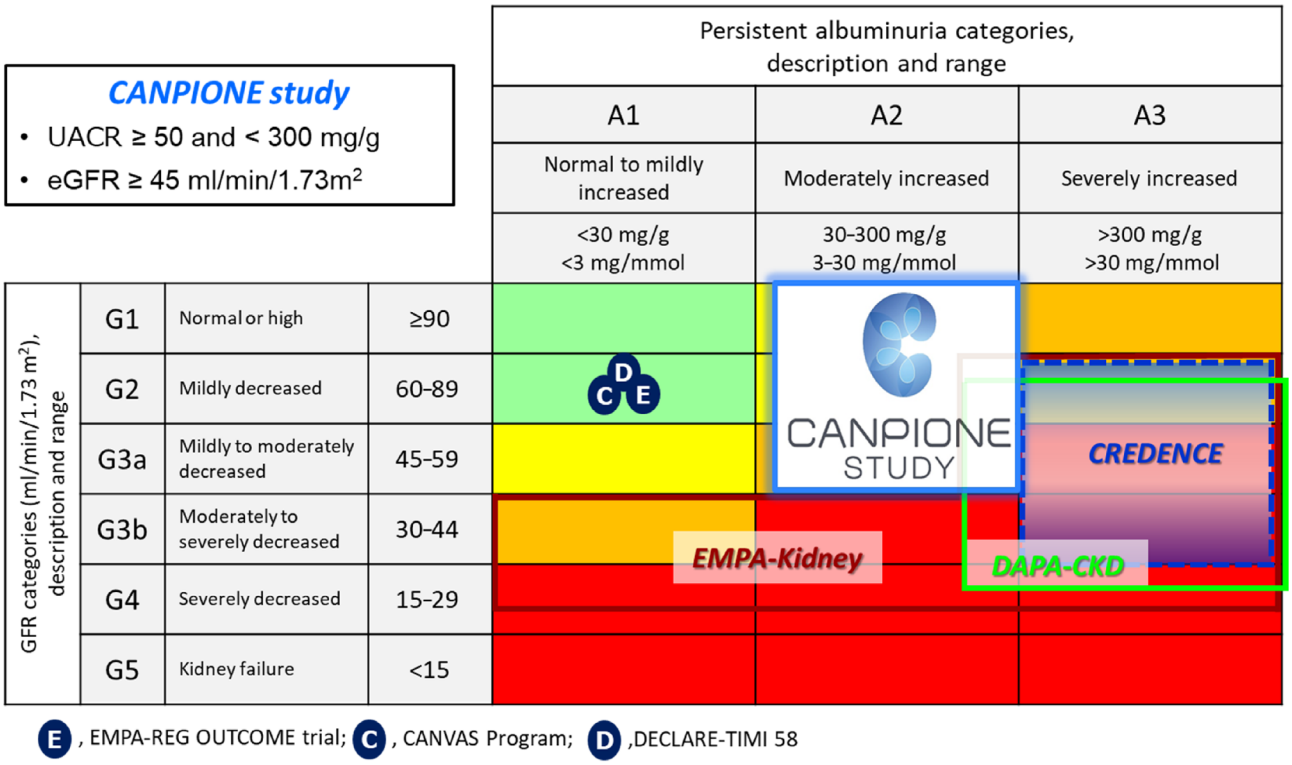


**FIGURE 2** The estimated glomerular filtration rate (eGFR) and urinary albumin-to-creatinine ratio (UACR) range of the inclusion criteria in the CANPIONE study and the Kidney Disease: Improving Global Outcome (KDIGO) heatmap. The eGFR and UACR range of the inclusion criteria in the CANPIONE study are shown on the KDIGO heatmap (prognosis of chronic kidney disease [CKD] by GFR and albuminuria category). Adapted from Ref.[9] with permission from KDIGO. The circled letters E, C and D stand for the EMPA-REG OUTCOME trial, CANVAS Program and DECLARE-TIMI 58 trial, respectively, and are placed based on the mean baseline eGFR (74, 76.5 and 86.1 ml/min/1.73m$^2$, respectively) and median baseline UACR levels (17.7, 12.3 and 13.1 mg/g, respectively).[10-12] The areas surrounded by the blue dotted line, green line and brown line indicate the eGFR and UACR range of the inclusion criteria in CREDENCE,[5] DAPA-CKD[6] and EMPA-KIDNEY,[13] respectively

study. Secondary outcomes and exploratory outcomes are listed in Tables 2 and S2.

## 2.7 | Statistical considerations

### 2.7.1 | Sample size calculation

The sample size was mainly calculated for the first primary outcome to keep the power of the two-sample *t*-test at least 80% with the significance level of 5% (two-sided), and it was initially planned to include 300 participants (150 in each group) to detect a group difference in log-transformed UACR of −0.36 with a common standard deviation (SD) of 1.1. For the second primary outcome, this study would maintain sufficient power when we assumed a group difference of 2.0 with a common SD of 4.0 or 4.5.

Because there was no appropriate Japanese clinical result that could be used as a reference for reliable sample size designing, a sample size re-estimation was preplanned to conduct before the study enrolment deadline. Moreover, the spread of the coronavirus disease 2019 (COVID-19) infection hampered participant recruitment and completion of enrolment before the planned deadline. For deciding the necessity of a half-year extension of the study enrolment deadline, which was the maximum allowable term, we conducted sample size re-estimation.[16-18]

In our study, only the data managers could access all the information about randomized assignment, although participants and clinicians were not masked to group allocation at the individual study site level. The sample size re-estimation was performed by blinded statisticians from an independent third-party contract research organization (CRO) who were unaware of treatment assignment to avoid the risk of a type 1 error. For the re-estimation, the current latest measurements of log-transformed UACR during the intervention period were used to calculate the pooled variance. The initially assumed group difference of −0.36 was maintained and the sample size was re-estimated under the conditions of power: 80% and 50% with the significance level of 5% (two-sided). The CRO made a recommendation based on predefined decision criteria. That is, to prevent inflation of type 1 error, the criteria included always continuing participant enrolment at the time of sample size re-estimation, even if sufficient power may have already been secured. The CRO only informed whether there was a need for a half-year extension of the study enrolment deadline and did not inform the re-estimated sample size itself. Because only a few participants had completed the intervention period at the time of re-estimation, the final results of the first primary outcome were hardly predictable. The details of sample size re-

**TABLE 2** Primary and secondary outcomes of the CANPIONE study

| |
|---|
| First primary outcome<br>Longitudinal profile of change in UACR from baseline to the intervention period (weeks 4-52) |
| Second primary outcome<br>Change in eGFR slope (calculated by individually subtracting the preintervention slope from the chronic slope [weeks 4-52] during the intervention period) |
| Secondary outcomes |
| 1. Important secondary outcome: change in eGFR from baseline to the end of the washout period |
| 2. The rate of progression to macroalbuminuria (defined as a UACR ≥ 300 mg/g on at least two consecutive visits in the intervention period [weeks 4-52] accompanied by a UACR value increase of ≥ 30% from baseline) |
| 3. The rate of remission to normoalbuminuria (defined as a UACR < 30 mg/g on at least two consecutive visits in the intervention period [weeks 4-52] accompanied by at least a 30% decrease in albuminuria from baseline) |
| 4. Change in eGFR from week 52 to the end of the washout period |
| 5. Chronic eGFR slope (weeks 4-52) |
| 6. Change in UACR at each visit in the intervention period from baseline |
| 7. Change in UACR stratified by the use of angiotensin-converting enzyme inhibitors/angiotensin-receptor blockers |
| 8. Changes in HbA1c, body mass index and blood pressure |
| 9. Incidence rate of cardiovascular events (cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, hospitalization for heart failure, hospitalization for unstable angina and coronary revascularization [percutaneous coronary intervention or coronary artery bypass graft]) |

Abbreviations: eGFR, estimated glomerular filtration rate; UACR, urinary albumin-to-creatinine ratio.

**TABLE 3** Baseline characteristics of randomized participants

| Characteristic | Total ($n = 97$)[a] |
|---|---|
| Gender, *n* (%) | |
| Male | 72 (74.2) |
| Female | 25 (25.8) |
| Age, y | 61.4 ± 10.2 |
| Duration of diabetes, y | 15.1 ± 9.0 |
| Body mass index, kg/m$^2$ | 27.6 ± 4.5 |
| Waist circumference, cm | 96.1 ± 10.3[b] |
| Blood pressure, mmHg | |
| Systolic | 136.6 ± 16.6 |
| Diastolic | 77.5 ± 10.8 |
| HbA1c, % | 7.9 ± 1.2 |
| Total cholesterol, mg/dl | 189.0 ± 30.0 |
| Triglycerides, mg/dl | 178.2 ± 113.8 |
| HDL-C, mg/dl | 50.9 ± 12.8 |
| LDL-C, mg/dl | 111.1 ± 25.2 |
| eGFR, ml/min/1.73m$^2$ | 74.1 ± 19.7 |
| Median UACR, mg/g | 104.2 |
| Current smoker, *n* (%) | 35 (36.1) |
| Hypertension, *n* (%) | 77 (79.4) |
| Heart failure, *n* (%) | 0 (0) |
| Drug therapy, *n* (%) | |
| Insulin | 42 (43.3) |
| Sulphonylurea | 25 (25.8) |
| Metformin | 61 (62.9) |
| DPP-4 inhibitors | 51 (52.6) |
| GLP-1 receptor agonists | 17 (17.5) |
| RAAS inhibitors | 63 (64.9) |
| Calcium channel blockers | 51 (52.6) |
| Diuretics | 5 (5.2) |
| Statins | 43 (44.3) |

*Note*: Data are mean ± standard deviation unless otherwise indicated.
Abbreviations: DPP-4, dipeptidyl peptidase-4; eGFR, estimated glomerular filtration rate; GLP-1, glucagon-like peptide-1; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; RAAS, renin angiotensin aldosterone system; UACR, urinary albumin-to-creatinine ratio (geometric mean in visits 2, 3 and 4).
[a]One randomized participant died because of cerebral haemorrhage before baseline data collection.
[b]The baseline waist circumference was missing for one participant.

estimation were documented in advance in the interim analysis plan for sample size re-estimation.

The data cut-off for the re-estimation was performed on 22 June 2021 including 69 randomized participants' data. As a result, the extension of the study enrolment deadline was adopted according to the recommendation by the CRO, and the sample size was revised to 110 (55 for each group) based on the feasibility of participant enrolment by the extended deadline. We acknowledge the decrease in statistical power; however, the first primary analysis will be performed using a mixed model for repeated measurements (MMRM) taking into account all postrandomization UACR values for the first primary outcome. This ensures that the original power, which was based on a two-sample *t*-test, is maintained.

### 2.7.2 | Assessment of primary outcomes

The primary analyses will be performed using the full analysis set. To avoid the statistical multiplicity issue of two primary outcome results, these will be interpreted by a hierarchical closed testing procedure. Briefly, the first primary outcome will be analysed without adjusting the significance level, and only if it is significant will the second primary outcome be analysed as well. The first primary analysis was initially a two-sample *t*-test of change in log-transformed UACR from baseline to week 52 in the intervention period between treatment groups, but was subsequently modified to the MMRM analysis to increase statistical power because the spread of COVID-19 infection impacted the recruitment of participants, and the validity of this

approach was reported.[19] As the second primary analysis, MMRM analysis will be applied for estimating the difference of individual preintervention and chronic (weeks 4-52) eGFR slopes, and comparing between the treatment groups. If the number of eGFR measurements during the preintervention period is determined not to be sufficient to estimate the preintervention eGFR slope, then eGFR values from medical records at each study site will also be used to establish reliable preintervention eGFR slopes after the validation of linearity and compatibility between eGFR values measured at the central laboratory and each study site. The other secondary analyses and sensitivity analyses will be conducted. The data will be analysed by the CRO under the supervision of the biostatistics office of the academic research organization (ARO). The details of the statistical final analysis will be described in the statistical analysis plan.

### 2.8 | Study oversight and organization

The CANPIONE study is sponsored by Mitsubishi Tanabe Pharma Corporation, Osaka, Japan. There is no input from the sponsor organization into the design, conduct, analysis or reporting of the study. The management of the study will be provided by the ARO in collaboration with the CRO. The ARO is located at the Center for Innovative Clinical Medicine, Okayama University Hospital, Okayama, Japan. The CANPIONE study is overseen by a fully independent Data and Safety Monitoring Board (DSMB) consisting of three academic members. The DSMB reviews safety data and overall study conduct throughout the study.

## 3 | RESULTS/STUDY STATUS

During the participant enrolment period of 34 months (August 2018 to May 2021), a total of 258 participants were screened and 98 underwent randomization at 21 sites in Japan. Of the 160 participants who did not meet the inclusion criteria and were not randomized, 73.8% were excluded because of out-of-range geometric mean UACR values, 15.0% as a result of HbA1c levels and 1.3% because of eGFR values during the preintervention period. Baseline characteristics of the CANPIONE study are shown in Table 3 (one randomized participant died because of cerebral haemorrhage before baseline data collection). The mean age of the enrolled participants at baseline was 61.4 years and 25.8% were female. Participants had a mean duration of type 2 diabetes of 15.1 years. Baseline mean HbA1c was 7.9% (63 mmol/mol), mean eGFR was 74.1 ml/min/1.73m$^2$ and median UACR was 104.2 mg/g.

This report follows the latest version of protocol (version 6.1) amended on 22 June 2021. Any protocol amendments will be updated in the Japan Registry of Clinical Trials (jRCT).

## 4 | DISCUSSION

The CANPIONE study has a unique study design consisting of 24 weeks of preintervention followed by 52 weeks of intervention, then a 4-week washout to evaluate two primary outcomes, changes in UACR and eGFR slope, for assessment of the protective role of canagliflozin on DKD with microalbuminuria. In the CANPIONE study, the change in UACR was chosen as the first primary outcome because albuminuria has long been known as a key predictor for the progression of DKD,[20,21] and importantly, the early change in albuminuria has recently been shown to be a valid surrogate endpoint for ESKD.[22]

A recent post hoc analysis of the ALTITUDE trial[23] evaluated the utility of a new method for patient enrolment in clinical trials. The study showed that using less strict albuminuria inclusion criteria for participants who based on historical data met the trial inclusion criteria, resulted in fewer screen failures and increased clinical trial efficiency. Consideration of using less strict albuminuria inclusion criteria is relevant for large clinical trials recruiting patients at the risk of progression to clinical kidney endpoints such as kidney failure. However, in the CANPIONE study, with albuminuria change as the primary endpoint, we use rather strict inclusion criteria for albuminuria consisting of geometric mean of two first-morning voided UACR at two different time points (8 weeks apart) to accurately assess the effect of canagliflozin (Table 1).

Although a decline in eGFR of 30% or 40% over 2 to 3 years is an established surrogate endpoint in clinical trials with CKD,[24] application of this endpoint is limited at earlier stages of CKD with higher eGFR[25] because it still necessitates a large sample size and long duration of follow-up to achieve proper statistical power. In addition to the early change in albuminuria, the eGFR slope has also been proposed as a valid surrogate endpoint in clinical trials for the early stage of CKD.[26] It has been shown that the changes in UACR and eGFR in combination provide a stronger association for future major kidney events than either change alone in participants with type 2 diabetes.[27] Therefore, in the CANPIONE study, the change in eGFR slope is chosen as the second primary outcome to complement and reinforce the first primary outcome. Previous trials that evaluated the effect of interventions on eGFR slope assessed the effect from a baseline cross-sectional measurement. By contrast, the CANPIONE study will first determine the preintervention eGFR slope followed by an assessment of the eGFR slope during intervention (chronic slope). The characterization of the preintervention eGFR slope is a novel design feature and allows for a more accurate assessment of the change in eGFR slope (before and during canagliflozin treatment) at an individual participant level.

For the assessment of drugs with initial acute eGFR decline, the use of total slope is preferred over chronic slope to prevent a type 1 error (i.e. falsely concluding benefit)[28]; however, the use of total slope requires a larger sample size and longer follow-up period if the acute effect is large and the rate of eGFR decline is slow. In fact, in participants of the CANVAS Program with microalbuminuria,[29] the mean difference in initial eGFR decline for canagliflozin versus placebo (−2.50 ml/min/1.73m$^2$) is comparatively greater than the mean difference in annual eGFR decline during the prolonged treatment period (0.99 ml/min/1.73m$^2$), suggesting that it will take at least 2 years for canagliflozin treatment to compensate for the initial eGFR decline. One of the approaches to overcome this issue would be to use the chronic

eGFR slope calculated from the first postrandomization eGFR value in combination with eGFR values at baseline and after withdrawal of canagliflozin treatment, and showing initial acute eGFR decline is reversible.[30] A more unique and better approach would be to use the preintervention slope in addition to the chronic slope. In current trials, we only use the baseline eGFR and albuminuria values assuming that there is an equal allocation of patients with a high or low risk of progression to active and control treatment. In addition, high-risk patients are selected for kidney outcome trials on the basis of lower eGFR and higher albuminuria. However, a majority of these patients do not always progress to ESKD, as shown in patients with a stable pretrial eGFR slope in the SONAR trial.[31] Because the individual eGFR slope has a strong relation with ESKD,[32] the individual preintervention slope will be a better indicator for high risk selection. Currently, trial outcome is based on group averages for ESKD/doubling serum creatinine. In the CANPIONE study, we determine the difference in eGFR slope between the preintervention eGFR slope and the chronic eGFR slope during the trial, and compare this difference in eGFR slope between canagliflozin and placebo treatment. This provides an accurate assessment of the effect of canagliflozin versus placebo and enhances the power of the study, particularly in early DKD stage studies where hard endpoints take a long time to manifest.

Because the establishment of a stabilized preintervention slope requires prospective eGFR measurements while changing the treatment as infrequently as possible, a half-year preintervention represents the maximum allowable period. Therefore, in the CANPIONE study, eGFR values in medical records during the period from 3 years prior to the first visit to the last visit of the study will also be utilized to establish a reliable preintervention eGFR slope. Together with the unique and novel study design to evaluate the pharmacological effects of canagliflozin, the current primary and secondary outcomes would enable comprehensive assessment and understanding of the renoprotective effects of canagliflozin in participants with early-stage DKD over the limited duration of the study. The current study design might also provide important clues for the future direction of clinical trials in the early stages of DKD.

In the clinical course of DKD, persistent microalbuminuria is a hallmark of disease progression and is associated with accelerated kidney function decline. This is illustrated by the CANVAS trial, which shows that the mean annual eGFR decline in patients with microalbuminuria was 2-fold higher compared with patients with normoalbuminuria ($-1.14$ vs. $-0.47$ ml/min/1.73m$^2$).[33] The CREDENCE trial showed the benefit of canagliflozin in slowing the decline in eGFR in patients with type 2 diabetes and macroalbuminuric CKD. It is noteworthy that the mean annual eGFR decline of the chronic slope was $-1.85$ ml/min/1.73m$^2$ in the canagliflozin group of the CREDENCE trial,[5] which is approximately equivalent to that of the placebo group with microalbuminuria ($-1.88$ ml/min/1.73 m$^2$ per year) in the EMPA-REG OUTCOME trial,[34] suggesting that canagliflozin can slow the progression of kidney function decline to a level equivalent to that of microalbuminuria patients. The CANPIONE study will assess whether canagliflozin can further slow eGFR decline in patients with microalbuminuria to a level observed in patients with normoalbuminuria.

In summary, the evidence from large trials for canagliflozin and other SGLT2 inhibitors indicate potential benefits of SGLT2 inhibitors on kidney outcomes in patients with type 2 diabetes. The CANPIONE study is uniquely designed and dedicated to assess kidney outcomes for the comprehensive understanding of beneficial effects of canagliflozin in participants with type 2 diabetes and microalbuminuria by evaluating the change in albuminuria and change in individual eGFR slope.

## AUTHOR CONTRIBUTIONS

S. Miyamoto contributed to the conception, design and conduct of the study and wrote the first draft of the manuscript. HJLH, DdZ and KS contributed to the conception, design and conduct of the study and critical revision of the manuscript for important intellectual content. NM contributed to the statistical analysis. MY contributed to the design, statistical analysis and critical revision of the manuscript for important intellectual content. The other authors contributed to data collection. All authors reviewed and approved the manuscript.

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## CONFLICT OF INTEREST

S. Miyamoto reports honoraria for speaking from Daiichi Sankyo, Mitsubishi Tanabe and Taisho. HJLH has served as a consultant for AbbVie, AstraZeneca, Bayer, Boehringer Ingelheim, Chinook, CSL Pharma, Gilead, Janssen, Merck, Mundi Pharma, Mitsubishi Tanabe, Novo Nordisk and Retrophin. He has received research support from AbbVie, AstraZeneca, Boehringer Ingelheim and Janssen. DdZ has served as a member of advisory boards and/or as a speaker for Bayer, Boehringer Ingelheim, Fresenius, Mitsubishi Tanabe and Travere; as a member of Steering Committees and/or speaker for AbbVie and Janssen; and as a member of Data Safety and Monitoring Committees for Bayer. MT reports honoraria for speaking from Kissei, Medtronic, Terumo, Abbott, MSD, Eli Lilly, Novartis, Takeda, Sumitomo Dainippon, Sanofi, Novo Nordisk, Daiich Sankyo, Mitsubishi Tanabe, Ono, Boehringer Ingelheim, AstraZeneca and Astellas; and research grants from LifeScan Japan, Mitsubishi Tanabe, Daiich Sankyo, Novo Nordisk, Sanofi, Takeda, Eli Lilly and MSD. DS reports honoraria for speaking from MSD, Eli Lilly Japan and Nippon Boehringer Ingelheim.

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## DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.;

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## SUPPORTING INFORMATION

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