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

Satoshi Miyamoto MD | Hiddo J. L. Heerspink PhD | Dick de Zeeuw MD | Masao Toyoda MD | Daisuke Suzuki MD | Takashi Hatanaka MD | Tohru Nakamura MD | Shinji Kamei MD | Satoshi Murao MD | Kazuyuki Hida MD | Shinichiro Ando MD | Hiroaki Akai MD | Yasushi Takahashi MD | Daisuke Koya MD | Munehiro Kitada MD | Hisashi Sugano MD | Tomokazu Nunoue MD | Akihiko Nakamura MD | Motofumi Sasaki MD | Tatsuaki Nakatou MD | Kei Fujimoto MD | Daiji Kawanami MD | Takashi Wada MD | Nobuyuki Miyatake MD | Michihiro Yoshida PhD | Kenichi Shikata MD | the CANPIONE study Investigators

1Center for Innovative Clinical Medicine, Okayama University Hospital, Okayama, Japan
2Department of Clinical Pharmacy and Pharmacology, University of Groningen, University Medical Center Groningen, Groningen, the Netherlands
3Division of Nephrology, Endocrinology and Metabolism, Department of Internal Medicine, Tokai University School of Medicine, Isehara, Japan
4Suzuki Diabetics Clinic, Atsugi, Japan
5Department of Diabetes and Endocrinology, National Hospital Organization Fukuyama Medical Center, Fukuyama, Japan
6Diabetes Internal Medicine, Sumitomo Besshi Hospital, Nihama, Japan
7Department of Diabetic Medicine, Kurashiki Central Hospital, Kurashiki, Japan
8Department of Diabetes and Endocrinology, Takamatsu Hospital, Takamatsu, Japan
9Department of Diabetology and Metabolism, National Hospital Organization Okayama Medical Center, Okayama, Japan
10Department of Internal Medicine Diabetic Center, Okayama City Hospital, Okayama, Japan
11Division of Diabetes and Metabolism, Faculty of Medicine, Tohoku Medical and Pharmaceutical University, Sendai, Japan
12Department of Diabetes, Ochiai General Hospital, Maniwa, Japan
13Department of Diabetology and Endocrinology, Kanazawa Medical University, Uchinada, Japan
14Division of Anticipatory Molecular Food Science and Technology, Medical Research Institute, Kanazawa Medical University, Uchinada, Japan
15Omi Medical Center, Kusatsu, Japan
16Department of Diabetes and Endocrinology, Kochi Health Sciences Center, Kochi, Japan
17Nunoue Clinic, Tsuyama, Japan
18Internal Medicine, Osafune Clinic, Setouchi, Japan
19Department of Diabetes and Endocrinology, Matsue City Hospital, Matsue, Japan

Trial registration numbers: jRCTs061180047 and UMIN000029905

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

© 2022 The Authors. Diabetes, Obesity and Metabolism published by John Wiley & Sons Ltd.
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/1.73m² 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/1.73m² 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). 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. The Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) trial, 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 patients 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. 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/1.73m² 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). 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 (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
Participants

Participant inclusion and exclusion criteria

≥

In addition to the centrally measured experiences and knowledge in diabetes care, and hence the clinical board-certified diabetologists or other physicians with equivalent for other factors. In addition, all of the participating physicians are participants by multiple covariates may result in ineffective randomization of 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. 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/1.73m²] = 194 × serum creatinine⁻¹.₀₉₄ × age⁻₀.₂₈₇ × 0.₇₃₉ [if female]] established by the Japanese Society of Nephrology. 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
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 $\log_2(0.36)$ 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. 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 $\log_2(0.36)$ 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-
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 estimation was maintained.
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/1.73m² 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, and importantly, the early change in albuminuria has recently been shown to be a valid surrogate endpoint for ESKD. A recent post hoc analysis of the ALTITUDE trial 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, application of this endpoint is limited at earlier stages of CKD with higher eGFR 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. 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. 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); 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, the mean difference in initial eGFR decline for canagliflozin versus placebo (>2.50 ml/min/1.73m²) is comparatively greater than the mean difference in annual eGFR decline during the prolonged treatment period (0.99 ml/min/1.73m²), 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. 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. Because the individual eGFR slope has a strong relation with ESKD, 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/1.73m²). The CRE-DENCE 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/1.73m² in the canagliflozin group of the CRE-DENCE trial, which is approximately equivalent to that of the placebo group with microalbuminuria (−1.88 ml/min/1.73 m² per year) in the EMPA-REG OUTCOME trial, 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.

**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, Mundipharma, 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 Traver; 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, Daiichi 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.
T. Nakamura reports a manuscript fee from Takeda. KH reports honoraria for speaking from Takeda and Eli Lilly; and research grants from Eli Lilly, AstraZeneca, Mitsubishi Tanabe, Sanofi and Boehringer Ingelheim. 

HA reports honoraria for speaking from Eli Lilly, MSD, Arkay, Sumitomo Dainippon, Ono, Kracie, Astellas, Kowa, Becton Dickinson, Kyowa Hakko Kirin, LifeScan Japan, Sanofi, Takeda, Taisho, Chugai, Novo Nordisk, Boehringer Ingelheim, Mitsubishi Tanabe, Daiichi Sankyo, Novartis, Sanwa Chemistry, Kissei, Abbot and Kowa; and research grants from Boehringer Ingelheim, Kyowa Hakko Kirin, Ono, Eli Lilly, Takeda, Sanofi, and Taisho. D. Koya reports honoraria for speaking from MSD, Astellas, AstraZeneca, Mitsubishi Tanabe, Eli Lilly, Boehringer Ingelheim, Novo Nordisk and Sumitomo Dainippon; and research grants from Mitsubishi Tanabe and AstraZeneca. D. Koya and MK belong to the endowed department sponsored by Boehringer Ingelheim, Mitsubishi Tanabe, Ono and Taisho Toyama. MK reports research grants from Mitsubishi Tanabe, AstraZeneca, Sanwa Kagaku Kenkyusho and Kyowa Kirin. AN reports honoraria for speaking from Mitsubishi Tanabe, Fukuda Denshi, Astellas, Chugai, Novartis, MSD, Takeda, Kissei, Kyowa Hakko Kirin, Sanofi, Bristol-Myers, Kowa, Sanwa Kagaku Kenkyusho and Ono. T. Nakatou reports honoraria for speaking from Eli Lilly, Novo Nordisk and Sumitomo Dainippon. KF reports honoraria for speaking from Sanofi, Merck Sharpe & Dohme, Taisho, Eli Lilly, Terumo, Arkay, Astellas, AstraZeneca, Boehringer Ingelheim, Mitsubishi Tanabe, Ono, Novo Nordisk, Kissei, Sumitomo Dainippon, Kowa, Takeda, Daiichi Sankyo, Chugai, Abbott, Otsuka and Kyowa Hakko Kirin. D. Kawanami reports honoraria for speaking from Novo Nordisk, Sanofi, Boehringer Ingelheim, Kyowa Kirin, Sumitomo Dainippon, Ono, Kowa, Taisho, Mitsubishi Tanabe, Daiichi Sankyo, MSD, Kowa, AstraZeneca, Teijin and Takeda; and research grants from Novo Nordisk, Mitsubishi Tanabe, Daiichi Sankyo, Terumo, Nipro, Eli Lilly, Boehringer Ingelheim, Kyowa Kirin, Sumitomo Dainippon, Taisho, Teijin and Takeda. TW reports a consulting fee from Mitsubishi Tanabe; honoraria for speaking from Astellas, Bayer, Chugai, Kowa, Kyowa Kirin, Mitsubishi Tanabe, Miyarisan, MSD, Boehringer Ingelheim, Ono, Sanofi, Sanwa Chemistry and Sysmex; and research grants from Astellas, Bayer, Chugai, Eli Lilly, Kissei, Kowa, Kyowa Kirin, Mitsubishi Tanabe, Asahi Kasei, Mochida, Takeda, Otsuka, Sanofi, Terumo, Torii and Fuji Yukihin. NM reports honorarium for speaking from Sumitomo Dainippon. MY has received stock dividends from Takeda. KS reports honoraria for speaking from MSD, Eli Lilly, Boehringer Ingelheim, Novo Nordisk, Mitsubishi Tanabe and Kyowa Hakko Kirin; research support from Takeda, MSD, Kyowa Hakko Kirin and Mitsubishi Tanabe; and a consulting fee from Daiichi Sankyo. TH, SK, S. Murao, SA, YT, HS, T. Nunoue and MS have no conflicts of interest to declare.

DATA AVAILABILITY STATEMENT

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

ORCID
Satoshi Miyamoto https://orcid.org/0000-0002-9056-6395
Hiddo J. L. Heerspink https://orcid.org/0000-0002-3126-3730
Munehiro Kitada https://orcid.org/0000-0002-3854-1385

REFERENCES

1. World Health Organization. Global report on diabetes. https://www.who.int/publications/i/item/9789241565257. Accessed January 21, 2022.
2. Adler AI, Stevens RJ, Manley SE, et al. Development and progression of nephropathy in type 2 diabetes: the United Kingdom Prospective Diabetes Study (UKPDS 64). Kidney Int. 2003;63(1):225-232.
3. Anders HJ, Davis JM, Thraru K. Nephron protection in diabetic kidney disease. N Engl J Med. 2016;375(21):2096-2098.
4. Cherney DZ, Perkins BA, Soleymanlou N, et al. Renal hemodynamic effect of sodium-glucose co-transporter 2 inhibition in patients with type 1 diabetes mellitus. Circulation. 2014;129(5):587-597.
5. Perkovic V, Jardine MJ, Neal B, et al. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. N Engl J Med. 2019;380(24):2295-2306.
6. Heerspink HJL, Stefansson BV, Correa-Rotter R, et al. Dapagliflozin in patients with chronic kidney disease. N Engl J Med. 2020;383(15):1436-1446.
7. Wheeler DC, Stefansson BV, Jongs N, et al. Effects of dapagliflozin on major adverse kidney and cardiovascular events in patients with diabetic and non-diabetic chronic kidney disease: a prespecified analysis from the DAPA-CKD trial. Lancet Diabetes Endocrinol. 2021;9(1):22-31.
8. Cannon CP, Perkovic V, Agarwal R, et al. Evaluating the effects of canagliflozin on cardiovascular and renal events in patients with type 2 diabetes mellitus and chronic kidney disease according to baseline HbA1c, including those with HbA1c <7%; results from the CREDENCE trial. Circulation. 2020;141(5):407-410.
9. Chapter 1: Definition and classification of CKD. Kidney Int Suppl. 2013;3(1):19-62.
10. Zinman B, Inzucchi SE, Lachin JM, et al. Rationale, design, and baseline characteristics of a randomized, placebo-controlled cardiovascular outcome trial of empagliflozin (EMPA-REG OUTCOME). Cardiovasc Diabetol. 2014;13:102.
11. Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. N Engl J Med. 2017;377(7):644-657.
12. Raz I, Mosenzon O, Bonaca MP, et al. DECLARE-TIMI 58: participants' baseline characteristics. Diabetes Obes Metab. 2018;20(5):1102-1110.
13. Harrington WG, Preiss D, Haynes R, et al. The potential for improving cardio-renal outcomes by sodium-glucose co-transporter-2 inhibition in people with chronic kidney disease: a rationale for the EMPA-KIDNEY study. Clin Kidney J. 2018;11(6):749-761.
14. Araki E, Goto A, Kondo T, et al. Japanese clinical practice guideline for diabetes 2019. Diabetol Int. 2020;11(3):165-223.
15. Matsuo S, Imai E, Horio M, et al. Revised equations for estimated GFR from serum creatinine in Japan. Am J Kidney Dis. 2020;56(3):956-992.
16. Gould AL, Shih WJ. Sample size re-estimation without unblinding for monitoring clinical trials that do not have pre-specified sample size re-estimation procedures. Stat Med. 2012;31(28):3019-3031.
17. Gould AL. Interim analyses for monitoring clinical trials that do not have pre-specified sample size re-estimation procedures. Stat Med. 2012;31(28):3019-3031.
18. Rudofsky H, Andersen AR, Smidt UM, Christiansen JS, Oxenboll B, Svendsen PA. Diabetic nephropathy and arterial hypertension. The effect of antihypertensive treatment. Diabetes. 1983;32(Suppl 2):83-87.
22. Heerspink HJL, Greene T, Tighiouart H, et al. Change in albuminuria as a surrogate endpoint for progression of kidney disease: a meta-analysis of treatment effects in randomised clinical trials. Lancet Diabetes Endocrinol. 2019;7(2):128-139.

23. Waijer SW, Provenzano M, Mulder S, et al. Impact of random variation in albuminuria and estimated glomerular filtration rate on patient enrolment and duration of clinical trials in nephrology. Diabetes Obes Metab. 2022;24:983-990.

24. Levey AS, Inker LA, Matsushita K, et al. GFR decline as an end point for clinical trials in CKD: a scientific workshop sponsored by the National Kidney Foundation and the US Food and Drug Administration. Am J Kidney Dis. 2014;64(6):821-835.

25. Oshima M, Toyama T, Haneda M, et al. Estimated glomerular filtration rate decline and risk of end-stage renal disease in type 2 diabetes. PLoS One. 2018;13(8):e0201535.

26. Inker LA, Heerspink HJL, Tighiouart H, et al. GFR slope as a surrogate end point for kidney disease progression in clinical trials: a meta-analysis of treatment effects of randomized controlled trials. J Am Soc Nephrol. 2019;30(9):1735-1745.

27. Ohkuma T, Jun M, Chalmers J, et al. Combination of changes in estimated GFR and albuminuria and the risk of major clinical outcomes. Clin J Am Soc Nephrol. 2019;14(6):862-872.

28. Holtkamp F, Gudmundsdottir H, Maciulaitis R, Benda N, Thomson A, Vetter T. Change in albuminuria and estimated GFR as end points for clinical trials in early stages of CKD: a perspective from European regulators. Am J Kidney Dis. 2020;75(1):6-8.

29. Perkovic V, de Zeeuw D, Mahaffey KW, et al. Canagliflozin and renal outcomes in type 2 diabetes: results from the CANVAS Program randomised clinical trials. Lancet Diabetes Endocrinol. 2018;6(9):691-704.

30. Levey AS, Gansevoort RT, Coresh J, et al. Change in albuminuria and GFR as end points for clinical trials in early stages of CKD: a scientific workshop sponsored by the National Kidney Foundation in collaboration with the US Food and Drug Administration and European Medicines Agency. Am J Kidney Dis. 2020;75(1):84-104.

31. Waijer SW, de Vries ST, Busch R, et al. Large between-patient variability in eGFR decline before clinical trial enrollment and impact on atrasentan’s efficacy: a post hoc analysis from the SONAR trial. J Am Soc Nephrol. 2021;32(11):2731-2734.

32. Oshima M, Jun M, Ohkuma T, et al. The relationship between eGFR slope and subsequent risk of vascular outcomes and all-cause mortality in type 2 diabetes: the ADVANCE-ON study. Diabetologia. 2019;62(11):1988-1997.

33. Neuen BL, Ohkuma T, Neal B, et al. Effect of canagliflozin on renal and cardiovascular outcomes across different levels of albuminuria: data from the CANVAS program. J Am Soc Nephrol. 2019;30(11):2229-2242.

34. Wanner C, Heerspink HJL, Zinman B, et al. Empagliflozin and kidney function decline in patients with type 2 diabetes: a slope analysis from the EMPA-REG OUTCOME trial. J Am Soc Nephrol. 2018;29(11):2755-2769.

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher’s website.

How to cite this article: Miyamoto S, Heerspink HJL, de Zeeuw D, et al. 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. Diabetes Obes Metab. 2022;24(8):1429-1438. doi:10.1111/dom.14731