Effect of canagliflozin on the decline of estimated glomerular filtration rate in chronic kidney disease patients with type 2 diabetes mellitus: A multicenter, randomized, double-blind, placebo-controlled, parallel-group, phase III study in Japan

Takashi Wada1, Kazumi Mori-Anai2*, Akiko Takahashi2, Takahiro Matsui3, Masaya Inagaki2, Mitsutaka Iida4, Ken Maruyama2, Hidetaka Tsuda2

1Department of Nephrology and Laboratory Medicine, Faculty of Medicine, Institute of Medical, Pharmaceutical and Health Sciences, Graduate School of Medical Sciences, Kanazawa University, Kanazawa, Japan, 2Ikuyaku. Integrated Value Development Division, Mitsubishi Tanabe Pharma Corporation, Tokyo, Japan, 3Ikuyaku. Integrated Value Development Division, Mitsubishi Tanabe Pharma Corporation, Osaka, Japan, and 4Quality & Vigilance Division, Mitsubishi Tanabe Pharma Corporation, Tokyo, Japan

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*Correspondence
Kazumi Mori-Anai
Tel: +81-3-6748-7738
Fax: +81-3-6685-3024
E-mail address: mori.kazumi@ma.mt-pharma.co.jp

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ABSTRACT
Aims/Introduction: The Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) trial has shown the effects of canagliflozin on preventing clinically important kidney outcomes in patients with type 2 diabetes mellitus and chronic kidney disease; however, not many Japanese patients were included in the trial. The present study evaluated the efficacy and safety of canagliflozin in Japanese chronic kidney disease patients with type 2 diabetes mellitus.

Materials and Methods: In this multicenter, randomized, double-blind, placebo-controlled, parallel-group, phase III study, chronic kidney disease patients with type 2 diabetes mellitus were randomly assigned to receive either 100 mg canagliflozin or a matching placebo once daily for 104 weeks. The primary efficacy end-point was the incidence of a 30% decline in estimated glomerular filtration rate.

Results: Overall, 308 patients were randomized to the canagliflozin (n = 154) and placebo (n = 154) groups. The incidence of a 30% decline in estimated glomerular filtration rate at week 104 was 18.2% and 29.5%, respectively, and the point estimate of the intergroup difference (placebo – canagliflozin) was 11.3% (95% confidence interval 1.2–21.5, P = 0.029), which was significant. The overall incidence of adverse events was similar in the two groups.

Conclusions: This study suggests that canagliflozin safely reduces the risk of end-stage renal disease in Japanese chronic kidney disease patients with type 2 diabetes mellitus.

INTRODUCTION
Chronic kidney disease (CKD) is associated with a risk of progression to end-stage renal disease (ESRD) requiring renal replacement therapy and an independent risk factor for cardiovascular (CV) diseases. The number of patients with CKD in Japan is estimated as 13.3 million; the prevalence rates of treated ESRD and dialysis are the second-highest in the world, and diabetic nephropathy is the most common underlying disease among patients initiating hemodialysis. In Japan, very few patients can undergo kidney transplantation, and
dialysis poses a heavy burden. Thus, treatments should be developed to improve the prognosis and quality of life of CKD patients with diabetes, especially in Japan.

The sodium–glucose cotransporter 2 inhibitor, canagliflozin, reportedly reduced the risk of renal and CV events in the Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) trial. In this trial, canagliflozin suppressed the primary composite end-point (comprising ESRD, doubling of serum creatinine [DoSC], renal death or CV death) in patients with type 2 diabetes mellitus and albuminuric CKD. The CREDENCE trial was a multinational study, and its subanalysis also showed the efficacy of canagliflozin for East and Southeast Asian subpopulations. However, just 110 Japanese patients were included in the CREDENCE trial; this sample size was insufficient to analyze the effect of canagliflozin on the prevention of renal and CV events in Japanese patients.

Conventional clinical trials using hard end-points, such as renal death and DoSC, are difficult to implement, because they require a long observation period and a large sample size. In fact, a few randomized controlled trials with regulatory approval have been carried out with these true end-points in nephrology. To address the clinical trial issues in nephrology, an international working group sponsored by the National Kidney Foundation and the United States Food and Drug Administration discussed the feasibility of using surrogate end-points, and concluded that a decline in estimated glomerular filtration rate (eGFR) of 30–40% over 2–3 years is an acceptable surrogate end-point of ESRD, although a study design needs to be devised on a case-by-case basis for interventions with acute effects on eGFR. A subsequent study has shown that these end-points are associated with the risk of ESRD in Japanese patients with reduced eGFR, confirming the validity of these surrogate end-points in clinical studies.

We carried out a phase III study to evaluate the renal efficacy and safety of canagliflozin in Japanese CKD patients with type 2 diabetes mellitus, with reference to the results of the CREDENCE trial. Although canagliflozin exerts an acute decline in eGFR, the impact of this effect on the incidence of a 30% decline in eGFR was limited in previous studies. Therefore, we set the primary end-point at a 30% decline in eGFR over 2 years.

MATERIALS AND METHODS

Study design

The present multicenter, randomized, double-blind, placebo-controlled, parallel-group, phase III study evaluated the renal efficacy and safety of canagliflozin in Japanese CKD patients with type 2 diabetes mellitus. The study period comprised screening (up to 4 weeks), run-in (2 weeks), treatment (104 weeks) and follow-up (4 weeks) periods. The primary end-point was the incidence of a 30% decline in eGFR at week 104.

The present study was carried out according to the ethical principles of the Declaration of Helsinki, the Pharmaceutical and Medical Device Act and the Good Clinical Practice guidelines. The protocol was approved by the institutional review board, and informed consent was obtained from all patients. The study was registered at ClinicalTrials.gov (NCT03436693).

Patients

Japanese CKD patients with type 2 diabetes mellitus were recruited using the main inclusion and exclusion criteria, which were similar to those for the CREDENCE trial. In brief, the inclusion criteria were patients aged ≥30 years, with a glycated hemoglobin (HbA1c) level of ≥6.5% and ≤12.0%, eGFR (as calculated by the equation for estimating Japanese GFR) of ≥30 and <90 mL/min/1.73 m², and a median urinary albumin-to-creatinine ratio (UACR) of ≥300 and ≤5,000 mg/g creatinine. All patients were required to receive an angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker at the maximum approved dose for at least 5 weeks before the screening period. Patients with type 1 diabetes mellitus, non-diabetic renal disease, a history of nephrectomy or renal transplantation, or a history of hemodialysis therapy were excluded (Table S1).

Treatment protocols

Patients were stratified by eGFR categories (30–<45, 45–<60 and 60–<90 mL/min/1.73 m²), and were randomly assigned in a double-blind fashion (1:1) to receive either 100 mg canagliflozin or matching placebo once daily. The patients received the placebo once daily during the run-in period and 100 mg canagliflozin or the matching placebo, taken orally before or after breakfast, once daily during the 104-week treatment period. Diet and exercise therapies continued unchanged from ≥12 weeks before the first day of the treatment period to the end of the study. Creatinine, HbA1c, blood glucose and other general laboratory values were examined at a contract clinical laboratory (LSI Medience Corporation, Tokyo, Japan).

End-points

The primary efficacy end-point was the incidence of a 30% decline in eGFR at week 104; the percentage of patients whose eGFR at the end of the treatment period decreased by ≥30% compared with the baseline, as defined the mean of the values during the first days of the run-in and treatment periods. Secondary efficacy end-points included the incidence of a 40% decline in eGFR and the following end-points used in the CREDENCE trial: a composite end-point of ESRD, DoSC, renal death or CV death (the primary end-point of the CREDENCE trial); a composite of CV death or hospitalization for heart failure (HHF); a composite of CV death, non-fatal myocardial infarction, or non-fatal stroke; HHF; a composite renal end-point comprising ESRD, DoSC or renal death; CV death; all-cause mortality (ACM); and a composite CV end-point comprising CV death, non-fatal myocardial infarction, non-fatal stroke, HHF or unstable angina. Furthermore, changes in eGFR...
from the baseline and those in UACR, systolic blood pressure, diastolic blood pressure, HbA1c and bodyweight from the first day of the treatment period were analyzed at each evaluation time point. The incidence of 30% and 40% declines in eGFR at week 104 was also calculated from data obtained in the CRE- DENCE trial to verify the robustness of the present results.

Safety evaluation included the assessment of adverse events (AEs), laboratory tests, resting standard 12-lead electrocardio-gram and vital signs. Considering the results of clinical studies on canagliflozin carried out so far, the following were defined as AEs of special interest: lower-limb amputation (including lower-limb events), volume depletion, fracture, osmotic diure-sis, kidney-related AEs, diabetic ketoacidosis, acute pancreatitis, urinary tract infection, upper urinary tract infection, female genital infection, male genital infection, hypoglycemia and malignancy.

Statistical analysis
Based on the data of the CREDENCE trial and the CKD Japan Cohort study, we assumed that the incidence of a 30% decline in eGFR in the placebo group would be 20% and that the relative risk reduction with canagliflozin would be 20%, as noted in the CREDENCE trial when this study was planned. We assumed the incidence of a 30% decline in eGFR in the canagliflozin group would be 16%. The sample size was set at 150 patients per group for a total of 300 patients to ensure that the point estimate of the intergroup difference (placebo group – canagliflozin group) exceeds 0 with a probability of ≥80% in the incidence of a 30% decline in eGFR.

The full analysis set was defined as the efficacy analysis set comprising all randomized patients, excluding those who were not in stage III of diabetic nephropathy, those who never received canagliflozin or a matching placebo and those with no data on efficacy end-points after randomization. The safety analysis set comprised all randomized patients, excluding those who never received the investigational product and those for whom no post-randomization safety data were available.

The incidence of a 30% decline in eGFR was calculated using the multiple imputation method to complement missing data assuming that the data missing is due to missing at random. The point estimate of the difference in incidence between groups (placebo – canagliflozin) was calculated, and the 95% confidence interval (CI) of the intergroup difference was then calculated using the Farrington–Manning method. The P-value was calculated as a post-hoc analysis. The same analysis was carried out for the incidence of a 40% decline in eGFR. The event-related end-points, including the composite end-point of ESRD, DoSC, renal death or CV death, a composite of CV death or hospitalization for heart failure, were analyzed using the stratified Cox proportional hazards regression model according to the treatment group and the eGFR categories at the run-in period. Hazard ratios (HRs), 95% CI and P-values were estimated for the canagliflozin versus placebo groups. All tests applied a two-sided significance level of 5%.

Time courses of other end-points, such as eGFR, UACR, systolic and diastolic blood pressure, HbA1c, and bodyweight, were evaluated using a mixed model for repeated measures with the following covariates: treatment group, evaluation time point, interaction between treatment group and evaluation time point, eGFR categories during the run-in period, the values of each analysis item on the first day of the treatment period, and interaction between the values of each analysis item on the first day of the treatment period and evaluation time point. UACR was log-transformed for the analysis, because the distribution of UACR data was highly skewed.

For AEs, the number and rate of patients with AEs and incidence per 1,000 patient-years were calculated for each treatment group.

All analyses were carried out at a contract analysis organization (Takumi Information Technology Co., Ltd., Tokyo, Japan) using SAS (Version 9.4; SAS Institute, Cary, NC, USA).

RESULTS
The present study was carried out between 15 February 2018 and 21 January 2021 at 89 sites in Japan. Of the 627 patients who provided their consent, 308 underwent randomization to receive either canagliflozin (154 patients) or the placebo (154 patients; Figure S1), and were included in the full analysis set and safety analysis set. The baseline demographic and clinical characteristics of the patients were well-balanced between the two groups (Table 1). The mean age was 62.5 years, 79.2% of the patients were men and the mean baseline eGFR was 55.7 mL/min/1.73 m². The median UACR was 683 mg/g creatinine, and the mean HbA1c was 7.76%. Of these patients, 251 completed the 104-week treatment period.

The incidence of a 30% decline in eGFR at week 104 was 18.2% (95% CI, 11.7–24.8) in the canagliflozin group and 29.5% (95% CI, 21.9–37.2) in the placebo group. The point estimate of the intergroup difference (placebo – canagliflozin) was 11.3% (95% CI 1.2–21.5, P = 0.029), which exceeded 0, and was significant (Table 2).

The incidence of a 40% decline in eGFR at week 104 was 10.1% (95% CI 5.0–15.3) in the canagliflozin group and 13.9% (95% CI 8.0–19.9) in the placebo group, and the point estimate of the intergroup difference was 3.8% (95% CI −4.1 to 11.7, P = 0.343), which exceeded 0 (Table S4).

In the canagliflozin group, the eGFR decreased rapidly in the early treatment phase (up to week 4), followed by a gradual decrease (Figure 1a). In the placebo group, a linear decrease in eGFR was observed throughout the treatment period. The change from baseline to week 104 (least square mean ± standard error) was −10.39 ± 0.83 mL/min/1.73 m² in the canagliflozin group and −11.49 ± 0.83 mL/min/1.73 m² in the placebo group. The difference between the treatment groups was 1.09 mL/min/1.73 m² (95% CI −1.21 to 3.40, P = 0.351).

UACR in the canagliflozin group decreased from the beginning of treatment, and was consistently lower than that in the placebo group until the end of the study (Figure 1b). The
geometric mean change in UACR at week 104 from baseline was −38.8% (95% CI −47.5 to −28.6) in the canagliflozin group and 17.8% (95% CI 1.0–37.3) in the placebo group. The geometric mean of UACR was 48.0% lower (95% CI 35.4–58.2, P < 0.001) in the canagliflozin group than in the placebo group at week 104.

The event rate of the composite end-point of ESRD, DoSC, or renal death was numerically lower in the canagliflozin group than in the placebo group (HR 0.60; 95% CI 0.23–0.81, P = 0.029). Additionally, there was a trend toward a reduction in the risk of events in the canagliflozin group for the following end-point: a composite renal end-point comprising ESRD, DoSC or renal death; a composite of CV death or HHF; and HHF (Table 3). By contrast, the event rate for the following events was numerically higher in the canagliflozin group: CV death; ACM; a composite of CV death, non-fatal myocardial infarction or non-fatal stroke; and a composite of CV death, non-fatal myocardial infarction, non-fatal stroke, HHF or unstable angina (Table 3).

Systolic blood pressure and bodyweight were significantly lower in the canagliflozin group than in the placebo group throughout the study period (Figure S2a,d). The intergroup difference at week 104 in systolic blood pressure was −4.17 mmHg (95% CI −7.59 to −0.75, P = 0.017), and that in bodyweight was −0.81 kg (95% CI −1.60 to −0.02, P = 0.043). Diastolic blood pressure and HbA1c were numerically lower in the canagliflozin group than in the placebo group throughout the study period (Figure S2b,c). The intergroup difference in diastolic blood pressure was −1.40 mmHg (95% CI −3.41 to 0.62, P = 0.174) and that in HbA1c was −0.23% (95% CI −0.46 to 0.00, P = 0.055) at week 104.

The incidence of AEs was 92.9% (143/154 patients) in the canagliflozin group and 90.9% (140/154 patients) in the placebo group, and the incidence of serious AEs was 27.9% (43/154 patients) in the canagliflozin group and 21.4% (33/154 patients) in the placebo group (Table 4). There was not much of a difference in the incidences of AEs of special interest between the two groups (Table 4). No lower-limb amputations were
reported in either group, and the incidence of fractures was 2.6% (4/154 patients) in the canagliflozin group and 5.8% (9/154 patients) in the placebo group. There were no clinically significant changes in laboratory values, resting standard 12-lead electrocardiograms or vital sign data. Overall, these findings were consistent with those observed in the CREDENCE trial.

The results of the present study were compared with those of the CREDENCE trial. The proportion of men was slightly higher, and the BMI, UACR and HbA1c values were numerically lower in the present study than in the CREDENCE trial; however, there were no major differences in the patients’ backgrounds between the two studies (Tables 1 and S2). In the CREDENCE trial, the incidence of a 30% decline in eGFR at week 104 was 21.5% (95% CI 19.6–23.5) in the canagliflozin group and 26.7% (95% CI 24.6–28.8) in the placebo group, and the point estimate of the intergroup difference was 5.2% (95% CI 2.3–8.0, \( P < 0.001 \)), which exceeded 0 and was significant (Table S3). These data are consistent with those of the present study.

Figure 1 | Effects of canagliflozin on renal-related outcomes over time in Japanese chronic kidney disease patients with type 2 diabetes mellitus. (a) Changes in estimated glomerular filtration rate from the mean of the values at the first days of the run-in and treatment period, and (b) urinary albumin (mg)-to-creatinine (g) ratio (UACR) from the first day of the treatment period. Data are presented as least square (LS) mean ± standard error (SE) in (a), and as the geometric mean with 95% confidence interval (CI) in (b).
study. The point estimate of the difference in the incidence of a 40% decline in eGFR between the groups was >0 in both the CREDENCE trial and the present study, which was significantly different in the CREDENCE trial (Table S4).

**DISCUSSION**

We carried out a phase III study using a 30% decline in eGFR over 2 years as the primary end-point to evaluate the renal efficacy and safety of canagliflozin in Japanese CKD patients with type 2 diabetes mellitus. To our knowledge, the present study is the first clinical trial in Japan with the primary end-point of the incidence of a 30% decline in eGFR. The results suggest that canagliflozin benefits Japanese CKD patients with type 2 diabetes mellitus.

In the CREDENCE trial, canagliflozin reduced the risk of renal events\(^5\). The post-hoc analysis of the CREDENCE trial data carried out in the present study showed a significantly lower incidence of a 30% decline in eGFR at week 104 in the canagliflozin group compared with the placebo group. Similarly, the incidence of a 30% decline in eGFR at week 104 was significantly lower in the canagliflozin group than in the placebo group in the present study. In the present study, the point estimate of the intergroup difference in the incidence of a 40% decline in eGFR was numerically lower in the canagliflozin group than in the placebo group. Thus, canagliflozin might reduce the risk of ESRD in Japanese CKD patients with type 2 diabetes mellitus.

Similar to the CREDENCE trial, we investigated the effect of canagliflozin on the risk of renal and CV events. The present data show that canagliflozin tends to reduce the risk of the primary end-point of the CREDENCE trial (a composite of ESRD, DoSC and renal or CV death). However, no numerical reduction was noted in the occurrence of four outcomes (CV death; ACM; a composite of CV death, non-fatal myocardial infarction or non-fatal stroke; and a composite of CV death, non-fatal myocardial infarction, non-fatal stroke, HHF or unstable

angina) in the canagliflozin group compared with that in the placebo group. In terms of the three CV-related components of these outcomes (CV death, ACM and non-fatal myocardial infarction), the incidences were numerically higher in the canagliflozin group, but the total numbers of events were small even if both groups were added. Our data further show that the incidence rates per 1,000 patient-years in the placebo group for CV death, ACM and non-fatal myocardial infarction were 3.47, 3.47 and 3.48, respectively, which were lower than those noted in the CREDENCE trial (24.4, 35.0 and 15.5, respectively)\(^13\). These low incidence rates might make it difficult to properly evaluate the effect of canagliflozin on the risk of these individual components and some composite outcomes. Furthermore, CV death, ACM and non-fatal myocardial infarction were considered to have no reasonable causal relationship with canagliflozin. One of the three CV deaths in the canagliflozin group occurred on the second day of the treatment period, and one non-CV death of the four ACM events in the canagliflozin group was a completed suicide. Additionally, the analysis of East and Southeast Asians in the CREDENCE trial showed the reduced risk of these outcomes as in the overall population\(^6\), which was inconsistent with the results of the present study. Hence, canagliflozin might not increase the risk of CV outcomes.

In the CREDENCE trial, canagliflozin decreased eGFR more than the placebo in the early treatment stage. The initial decline in eGFR induced by sodium–glucose cotransporter 2 inhibitors might be because of the suppression of afferent arteriolar dilatation through tubuloglomerular feedback, possibly leading to renal protection\(^14\). The time course of eGFR in the present study was similar to that in the CREDENCE trial for both the canagliflozin and placebo groups, with an initial decline observed only in the canagliflozin group. Furthermore, the decrease in eGFR at week 104 from baseline was numerically different in the CREDENCE trial (Table S4).

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**Table 3** | Effects of canagliflozin on renal and cardiovascular outcomes in Japanese chronic kidney disease patients with type 2 diabetes mellitus

| Event                                      | Canagliflozin | Placebo | Hazard ratio (95% CI) | P-value |
|---------------------------------------------|---------------|---------|-----------------------|---------|
| ESRD, DoSC, renal death or CV death         | 7/154 (4.5)   | 11/154 (7.1) | 24.29 (38.66) | 0.60 (0.23–1.55) | 0.293 |
| CV death or HHF                             | 4/154 (2.6)   | 4/154 (2.6)   | 13.86 (13.90) | 0.96 (0.24–3.86) | 0.958 |
| CV death, MI or stroke                      | 9/154 (5.8)   | 3/154 (1.9)    | 31.27 (10.48) | 2.95 (0.80–10.89) | 0.105 |
| HHF                                         | 1/154 (0.6)   | 3/154 (1.9)    | 3.46 (10.43)  | 0.34 (0.03–3.23) | 0.345 |
| ESRD, DoSC or renal death                   | 4/154 (2.6)   | 10/154 (6.5)   | 13.88 (35.15) | 0.38 (0.12–1.22) | 0.103 |
| CV death                                    | 3/154 (1.9)   | 1/154 (0.6)    | 10.38 (3.47)  | 2.76 (0.29–26.6) | 0.379 |
| ACM                                         | 4/154 (2.6)   | 1/154 (0.6)    | 13.84 (3.47)  | 3.77 (0.42–37.6) | 0.235 |
| CV death, MI, stroke, HHF or unstable angina| 10/154 (6.5)  | 7/154 (4.5)    | 34.78 (24.54) | 1.42 (0.54–3.72) | 0.481 |

*ACM, all-cause mortality; CI, confidence interval; CV, cardiovascular; DoSC, doubling of serum creatinine; ESRD, end-stage renal disease; HHF, hospitalization for heart failure; MI, myocardial infarction.*
with the CREDENCE trial results, the UACR in our study was lower in the canagliflozin group than in the placebo group throughout the treatment period. Thus, the efficacy data of canagliflozin in this study are consistent with those of the CRE- DENCE trial.

The incidences of AEs and serious AEs were comparable between the canagliflozin and placebo groups in the present study. Overall, the incidence rates of AEs of special interest were nearly identical between the two groups. An increased risk of lower-limb amputation and fracture was reported in the canagliflozin group compared with the placebo group. Overall, no safety concerns were identified for canagliflozin treatment in the present study.

The present study had some limitations. First, the sample size was small and might have limited the scope for some secondary end-points. Second, we included patients with an HbA1c level of ≥6.5% and ≤12.0%, eGFR of ≥30 and <90 mL/min/1.73 m², and a median UACR of ≥300 and ≤5,000 mg/g creatinine. Hence, whether the findings can be generalized to patients with different nephropathy statuses remains obscure.

In conclusion, the efficacy and safety of canagliflozin are consistent between the present study and the CRE- DENCE trial, suggesting that canagliflozin safely reduces the risk of ESRD in Japanese CKD patients with type 2 diabetes mellitus.

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### Table 4 | Effects of canagliflozin on safety outcomes in Japanese chronic kidney disease patients with type 2 diabetes mellitus

| AEs                                      | Total n (%) | AEs related to study drug | Serious AEs | AEs leading to discontinuation of study drug | AEs related to study drug leading to discontinuation of study drug | AEs leading to death | AEs related to study drug leading to death |
|------------------------------------------|-------------|---------------------------|-------------|---------------------------------------------|---------------------------------------------------------------------|---------------------|-------------------------------------------|
| AEs                                      |       |                           |             |                                             |                                                                     |                     |                                           |
| Amputation                                | 0 (0)       | 0                         | 4 (2.6)     |                                             |                                                                     |                     |                                           |
| Volume depletion                         | 4 (2.6)     | 8 (5.2)                   | 9 (5.8)     |                                             |                                                                     |                     |                                           |
| Fracture                                  | 4 (2.6)     | 9 (5.8)                   | 2 (1.3)     |                                             |                                                                     |                     |                                           |
| Osmotic diuresis                         | 4 (2.6)     | 2 (1.3)                   | 6 (3.9)     |                                             |                                                                     |                     |                                           |
| Renal-related AEs                        | 6 (3.9)     | 6 (3.9)                   | 20.75       |                                             |                                                                     |                     |                                           |
| Diabetic ketoacidosis                    | 4 (2.6)     | 3 (1.9)                   | 13.84       |                                             |                                                                     |                     |                                           |
| Acute pancreatitis                       | 1 (0.6)     | 0                         | 3.46        |                                             |                                                                     |                     |                                           |
| Urinary tract infection                  | 4 (2.6)     | 6 (3.9)                   | 13.84       |                                             |                                                                     |                     |                                           |
| Upper urinary tract infection            | 2 (1.3)     | 2 (1.3)                   | 6.92        |                                             |                                                                     |                     |                                           |
| Female mycotic genital infection         | 0 (0)       | 1 (4.0)                   | –           |                                             |                                                                     |                     |                                           |
| Male mycotic genital infection           | 1 (0.9)     | 0                         | 4.74        |                                             |                                                                     |                     |                                           |
| Hypoglycemia                             | 43 (27.9)   | 43 (27.9)                 | 148.74      |                                             |                                                                     |                     |                                           |
| Malignancy                               | 7 (4.5)     | 7 (4.5)                   | 24.21       |                                             |                                                                     |                     |                                           |

Adverse event (AE) terms reported by investigators were coded using the Medical Dictionary for Regulatory Activities version 20.1.
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DISCLOSURE
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Animal studies: N/A.

DATA AVAILABILITY STATEMENT
The deidentified datasets generated and/or analyzed during the current study, protocols, annotated case report form, dataset specifications, and clinical study report may be available from Mitsubishi Tanabe Pharma Corporation upon reasonable request from qualified researchers at https://vivli.org. For the Mitsubishi Tanabe Pharma Corporation criteria on data sharing, see https://vivli.org/ourmember/mitsubishi-tanabe-pharma/.

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SUPPORTING INFORMATION

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

Figure S1 | Patient flow diagram.

Figure S2 | Effects of canagliflozin on changes in (a) systolic blood pressure, (b) diastolic blood pressure, (c) glycohemoglobin (HbA1c) and (d) bodyweight from the first day of the treatment period in Japanese chronic kidney disease patients with type 2 diabetes mellitus.

Table S1 | Inclusion and exclusion criteria.

Table S2 | Key baseline demographic characteristics of patients in the Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) trial.

Table S3 | Incidence of 30% decline in estimated glomerular filtration rate at week 104 in the Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) trial.

Table S4 | Incidence of 40% decline in estimated glomerular filtration rate at week 104 in a Japanese phase III study and the Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) trial.

Table S5 | Institutions and principal investigators.