Effects of Canagliflozin in Patients With Baseline eGFR <30 mL/min/1.73 m^2: Subgroup Analysis of the Randomized CREDENCE Trial

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Abstract

Background and objectives: The CREDENCE trial demonstrated that the sodium glucose co-transporter 2 (SGLT2) inhibitor canagliflozin reduced the risk of kidney failure and cardiovascular events in participants with type 2 diabetes mellitus and chronic kidney disease. Little is known about use of SGLT2 inhibitors in patients with estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2. CREDENCE participants had type 2 diabetes mellitus, urinary albumin:creatinine ratio >300-5000 mg/g, and eGFR 30-<90 mL/min/1.73 m^2 at screening. This post hoc analysis evaluated participants with eGFR <30 mL/min/1.73 m^2 at randomization.

Design, setting, participants, and measurements: Effects of eGFR slope through Week 130 were analyzed using a piecewise, linear mixed effects model. Efficacy was analyzed in the intention-to-treat population, based on Cox proportional hazard models and safety was analyzed in the on-treatment population. At randomization (an average of 29 days after screening), 174/4401 (4%) participants had an eGFR <30 mL/min/1.73 m^2 (mean [standard deviation] eGFR: 26 [3] mL/min/1.73 m^2).

Results: From Weeks 3 to 130, there was a 66% difference in the mean rate of eGFR decline with canagliflozin versus placebo (mean slopes: –1.30 vs –3.83 mL/min/1.73 m^2/year; difference: –2.54 mL/min/1.73 m^2/year; 95% confidence interval [CI]: 0.90-4.17). Effects of canagliflozin on kidney, cardiovascular, and mortality outcomes were consistent for those with eGFR <30 and ≥30 mL/min/1.73 m^2 (all *P* interaction >0.20). The estimate for kidney failure in participants with eGFR <30 mL/min/1.73 m^2 (hazard ratio [HR]: 0.67; 95% CI: 0.35-1.27) was similar to those with eGFR ≥30 mL/min/1.73 m^2 (HR: 0.70; 95% CI: 0.54-0.91; *P* interaction=0.80). There was no imbalance in the rate of kidney-related adverse events or acute kidney injury (AKI) associated with canagliflozin between participants with eGFR <30 and ≥30 mL/min/1.73 m^2 (all *P* interaction >0.12).

Conclusions: This post hoc analysis suggests that canagliflozin slowed progression of kidney disease, without increasing AKI, even in participants with eGFR <30 mL/min/1.73 m^2.

Key words: chronic kidney disease, diabetes, diabetic nephropathy, Canagliflozin

Introduction

Diabetes is the leading cause of kidney failure; approximately 1 in 4 adults with diabetes will develop chronic albuminuria and/or persistent declines in estimated glomerular filtration rate (eGFR) (1). Despite the risk of kidney failure in people with type 2 diabetes, treatment options to slow nephropathy progression are limited (2, 3). Sodium glucose co-transporter 2 (SGLT2) inhibitors, which were originally developed to aid in the control of blood glucose levels in people with type 2 diabetes, have been shown to reduce the risk of cardiovascular events, including major adverse cardiovascular events (myocardial infarction, stroke, or cardiovascular death) and hospitalization for heart failure, in patients with type 2 diabetes and high cardiovascular risk in cardiovascular outcomes trials (4). Results from these trials also suggested that SGLT2 inhibition slows progression to kidney failure, but the low risk of kidney disease of these study cohorts led to a small number of kidney-related events across trials (4). Until recently, there were limited data regarding the use of SGLT2 inhibitors in patients with compromised kidney function, and there were few treatment options for this patient population with low eGFR and high risk for developing kidney failure.

The Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) study was a dedicated kidney outcomes trial that demonstrated that the SGLT2 inhibitor canagliflozin significantly reduces the risk of kidney failure and cardiovascular events in participants with type 2 diabetes and chronic kidney disease (5, 6). Based on data from the CREDENCE trial, the US Food and Drug Administration approved canagliflozin for reducing the risk of kidney failure, doubling of serum creatinine, cardiovascular death, and hospitalization for heart failure in adults with type 2 diabetes and diabetic nephropathy with albuminuria (7). The US prescribing information for canagliflozin was also updated to allow continuation of canagliflozin 100 mg in patients already receiving therapy whose eGFR falls below 30 mL/min/1.73 m^2 with a urinary albumin:creatinine ratio

(UACR) >300 mg/g until initiation of dialysis or kidney transplantation, reflecting the form of the CREDENCE trial intervention (7, 8). Despite this, the potential kidney and cardiovascular benefits of canagliflozin in patients with advanced CKD (eGFR below 30 mL/min/1.73 m^2) have not been reported. This manuscript describes the efficacy and safety of canagliflozin in a post hoc subgroup analysis of CREDENCE trial participants with eGFR <30 mL/min/1.73 m^2 at randomization.

Methods

Study design

CREDENCE (ClinicalTrials.gov Identifier: NCT02065791) was a randomized, double-blind, placebo-controlled, multicenter, international trial, the details of which have been published previously (5, 6). This post hoc analysis examined efficacy and safety outcomes in patients with eGFR <30 mL/min/1.73 m^2 at randomization. While participants were enrolled in the study based on eGFR of 30 to <90 mL/min/1.73 m^2 at screening, some patients had eGFR values change by the time of randomization, such that the recorded eGFR measurement was below 30 mL/min/1.73 m^2 by the time of randomization assessment.

Study participants

Eligible participants were ≥30 years of age with type 2 diabetes, glycated hemoglobin (HbA1c) of 6.5% to 12.0%, screening eGFR of 30 to <90 mL/min/1.73 m^2, UACR of >300 to 5,000 mg/g (>33.9 to 565.6 mg/mmol), and were receiving treatment with a stable maximum labeled or tolerated dose of an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker for ≥4 weeks prior to randomization. Exclusion criteria included non-diabetic kidney disease, type 1 diabetes mellitus, and prior treatment of kidney disease with immunosuppression or a history of kidney replacement therapy.

Randomization and study treatment

Participants were randomized to receive oral canagliflozin 100 mg daily or matching placebo. The protocol stipulated that study treatment be continued until the commencement of dialysis, receipt of a kidney transplant, occurrence of diabetic ketoacidosis, pregnancy, receipt of disallowed therapy or study conclusion (5, 6). Background treatment intensification for glycemic management and cardiovascular protection according to practice guidelines was recommended.

Outcomes

This post hoc analysis assessed the following intermediate outcomes: change from baseline in HbA1c, systolic blood pressure (BP), UACR, and eGFR. In addition, eGFR change was assessed and measured as the acute change in eGFR from baseline to Week 3,[6] the annualized chronic change in eGFR from Week 3 until the end of treatment, and the total annualized change in eGFR from baseline to Week 130.

Efficacy analyses were the same as those identified in the primary study and included the effects of canagliflozin on the primary composite outcome of kidney failure, doubling of serum creatinine, or kidney or cardiovascular death (5, 6). Other efficacy outcomes included the effects of canagliflozin on cardiovascular death; the composite of cardiovascular death or hospitalization for heart failure; the composite of cardiovascular death, myocardial infarction, or stroke; hospitalization for heart failure; the composite of kidney failure, doubling of serum creatinine, or kidney death; kidney failure; and the composite of dialysis, kidney transplantation, or kidney death. Safety analyses included assessments of adverse events.

Statistical analysis

Changes in HbA1c and systolic BP over time were analyzed using a mixed effects model for repeated measures, which included data up to Week 182, assuming an unstructured

covariance and adjusting for baseline value, treatment, trial visit, and interactions of treatment by visit and baseline value by visit. Due to the highly skewed distribution of UACR data, UACR was log-transformed and the geometric mean of post-baseline UACR was estimated using a similar model. The geometric mean ratio was used to calculate the reduction in post-randomization UACR for canagliflozin compared to placebo.

On-treatment eGFR slope was estimated using a piecewise, linear mixed effects model with a knot at Week 3, including the fixed effects of treatment, randomization eGFR, continuous time, and a linear spline in follow-up time, with a knot at Week 3, with interactions of treatment with the time spline terms. The model also included random intercepts, initial slopes (prior to Week 3), and long-term slopes (after Week 3) to account for variation in trajectories across participants. When the full model failed to converge, a simplified model with a single random slope was used. The effects of canagliflozin on mean total slope through Week 130 were computed as a weighted combination of the estimated effects on the initial and long-term slopes.

Kidney, cardiovascular, and mortality outcomes were analyzed in the intention-to-treat population, based on Cox proportional hazard models in participants with randomization eGFR <30 and ≥30 mL/min/1.73 m^2. Safety outcomes were analyzed in all treated participants through 30 days after the last dose (on-treatment). The interaction of treatment effects between participants with randomization eGFR <30 and ≥30 mL/min/1.73 m^2 was tested by adding eGFR category as a covariable and an interaction term of treatment by eGFR categories to the Cox model. Hazard ratios (HRs) and 95% confidence intervals (CIs) for canagliflozin versus placebo were estimated. Due to the post hoc nature of this analysis, only nominal *P* values were reported.

Data availability

Data from this study will be made available in the public domain via the Yale University Open Data Access Project (http://yoda.yale.edu/) once the product and relevant indication studied have been approved by regulators in the United States and European Union and the study has been completed for 18 months.

Ethics

Local institutional ethics committees approved the trial protocols at each site. All participants provided written informed consent. The trial was conducted according to the principles outlined in the Declaration of Helsinki.

Results

Patients

A total of 4401 participants were randomized to canagliflozin or placebo in the CREDENCE trial, with a median follow-up duration of 2.62 (interquartile range, 2.11–3.09) years.

At the time of screening when eligibility for the trial based on eGFR was assessed, all participants had an eGFR between 30 and <90 mL/min/1.73 m^2. However, by the time of randomization (an average of 29 days later), 174 (4%) participants had an eGFR <30 mL/min/1.73 m^2 but were still eligible for the trial as per the study protocol. The mean (standard deviation) eGFR for these 174 participants was 35 (7) mL/min/1.73 m^2 at screening and 26 (3) mL/min/1.73 m^2 at randomization. The distribution of eGFR values among participants with randomization eGFR <30 mL/min/1.73 m^2 is shown in Supplementary Figure 1. Median (interquartile range) time between screening and randomization measurement was comparable for patients with eGFR <30 and ≥30 mL/min/1.73 m^2 (29 [24-36] and 29 [23-36] days, respectively), with no notable differences between treatment groups.

Most patients (>88%) had their randomization assessment between 3 and 8 weeks after screening. However, a higher proportion of patients with eGFR <30 mL/min/1.73 m^2 had randomization measurements >8 weeks after screening compared with patients with eGFR ≥30 mL/min/1.73 m^2 (13/174 [7%] vs 156/4226 [4%], *P* interaction =0.01) (Supplementary Table 1).

Baseline characteristics for participants within the subgroup with eGFR <30 mL/min/1.73 m^2 were balanced between the groups randomized to canagliflozin and placebo (Table 1).

In the overall trial, 25% of patients in the canagliflozin group and 30% of patients in the placebo group discontinued treatment for any reason, and a total of 12% and 13% of patients in the canagliflozin and placebo groups, respectively, discontinued for an adverse event. There were no differences in effects of canagliflozin versus placebo on discontinuation between patients with eGFR <30 and ≥30 mL/min/1.73 m^2 (*P* interaction >0.15; Figure 1).

Intermediate Outcomes

In the 174 patients with eGFR <30 mL/min/1.73 m^2, there was no difference between the effect of canagliflozin and placebo on HbA1c over the course of the study (difference in least squares mean change: –0.27%; 95% CI: –0.63, +0.09). The effect of canagliflozin on systolic BP in patients with randomization eGFR <30 mL/min/1.73 m^2 did not clearly differ compared to placebo over the course of the study (difference in least squares mean change: –2.66 mmHg; 95% CI: –6.18, 0.86). In contrast, the geometric mean for UACR was 33% lower (95% CI: –49, –10) during the study in patients treated with canagliflozin than those in the placebo group (Figure 2A). No differences in the effects of canagliflozin on HbA1c, systolic BP, and UACR were observed between patients with eGFR <30 and ≥30 mL/min/1.73 m^2 (*P* for heterogeneity = 0.86, 0.66, and 1.0, respectively).

Mean eGFR in participants with eGFR <30 mL/min/1.73 m^2 over the course of the study is depicted in Figure 2B. The mean annual decline in eGFR from baseline to Week 130 was slower in patients treated with canagliflozin compared with placebo (mean slopes of +0.03 vs –1.88 mL/min/1.73 m^2/year, respectively; placebo-subtracted difference: 1.91 mL/min/1.73 m^2/year; 95% CI: 0.18, 3.64). The mean acute change in eGFR from baseline to Week 3 was 3.26 mL/min/1.73 m^2 with canagliflozin and 4.14 mL/min/1.73 m^2 with placebo (placebo-subtracted difference: –0.88 mL/min/1.73 m^2; 95% CI: –3.16, 1.39). From Week 3 to the last measurement, there was a 66% difference in the mean rate of eGFR decline with canagliflozin compared with placebo (mean slopes of –1.30 vs –3.83 mL/min/1.73 m^2/year, respectively; placebo-subtracted difference: 2.54 mL/min/1.73 m^2/year; 95% CI: 0.90, 4.17).

Kidney, Cardiovascular, and Mortality Outcomes

Despite a limited number of events in the subset of 174 participants with eGFR <30 mL/min/1.73 m^2, the point estimates for the effects of canagliflozin on most kidney, cardiovascular, and mortality outcomes were generally consistent with those seen in patients with eGFR ≥30 mL/min/1.73 m^2 (all *P* interaction >0.20; Figure 3). Treatment with canagliflozin reduced the risk of kidney failure in participants with eGFR ≥30 mL/min/1.73 m^2 (HR: 0.70; 95% CI: 0.54, 0.91) and the effects were consistent in participants with eGFR <30 mL/min/1.73 m^2 (HR: 0.67; 95% CI: 0.35, 1.27; *P* interaction = 0.80).

Safety

Within the subgroup of patients with eGFR <30 mL/min/1.73 m^2, those treated with canagliflozin had similar rates of adverse events, serious adverse events, hyperkalemia, and hypoglycemia compared to those treated with placebo. There was also no imbalance in the rate of kidney-related adverse events or acute kidney injury events with canagliflozin compared with placebo in this subgroup. In addition, there was no evidence of heterogeneity in the occurrence of adverse events between patients with eGFR <30 and ≥30 mL/min/1.73

m^2 (all *P* interaction >0.12; Figure 4). The incidence of serious adverse events during on- and off-treatment periods are shown in Supplementary Table 2. Among patients with eGFR <30 mL/min/1.73 m^2, the number of participants with a fracture (4 in each group) or amputation (3 with canagliflozin and 1 with placebo) was low between groups.

Discussion

In this post hoc analysis of participants in the CREDENCE trial with eGFR <30 mL/min/1.73 m^2 at randomization, treatment with canagliflozin reduced albuminuria and the rate of eGFR decline compared with placebo. The effects of canagliflozin on kidney, cardiovascular, and mortality outcomes in participants with eGFR <30 mL/min/1.73 m^2 appeared to be consistent with those seen in participants with eGFR ≥30 mL/min/1.73 m^2 at randomization. There was no detectable increase in harmful effects, including kidney-related adverse events and acute kidney injury, with canagliflozin compared with placebo in participants with eGFR <30 mL/min/1.73 m^2. These results support the use and continuation of SGLT2 inhibitor treatment even in patients with eGFR <30 mL/min/1.73 m^2 until the commencement of maintenance dialysis or receipt of a kidney transplant, and clinicians should consider this when discussing treatment options for patients with low eGFR.

Canagliflozin slowed the rate of eGFR decline in this subgroup of patients with eGFR <30 mL/min/1.73 m^2. Unlike the overall population, there was no detectable initial acute drop in eGFR with canagliflozin in this subgroup, which is consistent with results of a subgroup analysis of patients with stage 3b and 4 chronic kidney disease from another SGLT2 inhibitor study (9). There is no clear evidence that a reduction in intraglomerular pressure occurs at this stage of nephropathy with these agents (10), although recent data demonstrate that blood pressure reduction is similar in this advanced stage to that observed in early stages of nephropathy (11). Other factors such as blood pressure reduction may have also contributed

to the slowing of chronic kidney disease. In addition, the requirement that the screening eGFR had to exceed 30 mL/min/1.73 m^2 suggests that some of the randomization eGFR values that were less than 30 mL/min/1.73 m^2 probably resulted from random variation in patients whose typical eGFR was greater than 30 mL/min/1.73 m^2. Thus, an additional consideration is reversion to the mean since this cohort did have eGFR values just above 30 mL/min/1.73 m^2 at screening and below 30 mL/min/1.73 m^2 at randomization. Furthermore, most participants had eGFR levels between 20 and 30 mL/min/1.73 m^2, so these results may not be generalizable to people with even lower eGFR levels.

Studies in animal models demonstrate that SGLT2 inhibition results in sympathetic inhibition of kidney nerve function and this may account for the glucose independent effect of SGLT2 inhibition on blood pressure (12). Therefore, the 3 to 4 mmHg reduction in blood pressure that results from SGLT2 inhibition may contribute in some part to renoprotection similar to what was observed in the captopril trial, where a 4 mmHg difference in blood pressure contributed to slowed progression of diabetic nephropathy (13). The aforementioned denervation hypothesis is also consistent with results from the Dapagliflozin and Prevention of Adverse-Outcomes in Heart Failure (DAPA HF) trial, which demonstrated that the SGLT2 inhibitor dapagliflozin was beneficial in people without diabetes (14). The denervation hypothesis also aligns with the beneficial effects of canagliflozin observed in the subset of patients with eGFR <30 mL/min/1.73 m^2, in whom some kidney and cardiovascular benefits are seen and are glucose-independent. Additionally, the heterogeneity of effects on HbA1c, but not on other efficacy outcomes between eGFR subgroups (30 to <45, 45 to <60, and 60 to <90 mL/min/1.73 m^2) further supports a glucose-independent mechanism of kidney and cardiovascular protection (8). While other potential mechanisms for renoprotection are actively being studied (11, 15-17), it is clear that the albuminuria reduction seen in this

subgroup was similar to the overall population and this is a well-accepted surrogate for renoprotection (18).

The conclusions that can be drawn from this non-prespecified subgroup, post hoc analysis should be interpreted cautiously due to the limited statistical precision to robustly assess these outcomes due to the small sample size of this participant group.

The recently terminated Dapagliflozin And Prevention of Adverse outcomes in Chronic Kidney Disease (DAPA-CKD) trial (19) and ongoing Effects of Dapagliflozin in Non-diabetic Patients With Proteinuria (DIAMOND) trial (20) recruited participants with eGFR down to 25 mL/min/1.73 m^2 while The Study of Heart and Kidney Protection With Empagliflozin (EMPA-Kidney) trial (21) includes those with an eGFR down to 20 mL/min/1.73 m^2. Once available, data from these trials will provide additional insight into the effect of SGLT2 inhibitors in people with lower initial eGFR levels. Until these data are made available, the consistent benefit of canagliflozin in the overall CREDENCE population and in patients with eGFR <30 mL/min/1.73 m^2 at randomization, suggest that there is no reason to discontinue treatment until the commencement of maintenance dialysis or receipt of a kidney transplant, as stipulated in the CREDENCE protocol. While there may be similar renoprotective effects in people with eGFR below 30 mL/min/1.73 m^2, we would not recommend initiating treatment with SGLT2 inhibitor in eGFR <30 mL/min/1.73 m^2 until results of the other pending results are available.

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Supplementary Materials Table of Contents

Supplementary Table 1. Time Between Screening and Randomization Measurements

eGFR, estimated glomerular filtration rate.

Supplementary Table 2. Serious Adverse Events During On- and Off-treatment

SAE, serious adverse event; eGFR, estimated glomerular filtration rate; SD, standard deviation.

*2 patients with eGFR <30 mL/min/1.73 m^2 in the canagliflozin arm stopped the drug due to a fatal SAE.

†10 and 8 patients with eGFR ≥30 mL/min/1.73 m^2 in the canagliflozin and placebo arms, respectively, stopped the drug due to a fatal SAE.

Supplementary Figure 1. Distribution of eGFR at randomization in participants with randomization eGFR <30 mL/min/1.73 m^2.

eGFR, estimated glomerular filtration rate.

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Table 1. Baseline Characteristics of Participants With Randomization eGFR <30 mL/min/1.73 m^2

Characteristic*	Canagliflozin (n = 84)	Placebo (n = 90)	Total (N = 174)
Age, y	64 (10)	66 (9)	65 (10)
Male, n (%)	54 (64)	52 (58)	106 (61)
Race, n (%)			
White	55 (65)	59 (66)	114 (66)
Black	7 (8)	2 (2)	9 (5)
Asian	14 (17)	11 (12)	25 (14)
Other†	8 (10)	18 (20)	26 (15)
Current smoker, n (%)	9 (11)	14 (16)	23 (13)
History of hypertension, n (%)	82 (98)	89 (99)	171 (98)
History of heart failure, n (%)	9 (11)	14 (16)	23 (13)
Duration of diabetes, y	17.5 (9.9)	16.6 (9.3)	17.0 (9.6)
History of cardiovascular disease, n (%)	41 (49)	45 (50)	86 (49)
History of amputation, n (%)	10 (12)	2 (2)	12 (7)
Body mass index, kg/m^2	32 (7)	31 (6)	32 (6)
Systolic BP, mmHg	138 (16)	139 (17)	139 (16)

Diastolic BP, mmHg	75 (9)	76 (11)	76 (10)
HbA1c, %	8.2 (1.3)	8.0 (1.1)	8.1 (1.2)
eGFR, mL/min/1.73 m^2	26 (3)	27 (3)	26 (3)
UACR, mg/g, median (IQR)	1056 (459-2525)	1153 (483-2253)	1064 (464-2376)

BP, blood pressure; eGFR, estimated glomerular filtration rate; UACR, urinary albumin:creatinine ratio; IQR, interquartile range; SD, standard deviation.

*Data are mean (SD) unless otherwise indicated.

†Other includes American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, multiple, other, unknown, and not reported.

Figure Legends

Figure 1. Reason for discontinuation of treatment.

HR, hazard ratio; CI, confidence interval; eGFR, estimated glomerular filtration rate.

*Other reasons include poor adherence, safety or tolerability, disallowed therapy, protocol violation, site closure, and other.

Figure 2. Effects of canagliflozin over time in participants with randomization eGFR <30 mL/min/1.73 m^2 on A) UACR* and B) eGFR.[†] Baseline levels of UACR (median) and eGFR (mean) are shown below the legend.

UACR, urinary albumin:creatinine ratio; eGFR, estimated glomerular filtration rate; CI, confidence interval; SE, standard error.

*Data are geometric mean ratio (95% CI).

[†]Data are mean (±SE).

Figure 3. Effects of canagliflozin on kidney, cardiovascular, and mortality outcomes in participants with randomization eGFR <30 versus ≥30 mL/min/1.73 m^2.

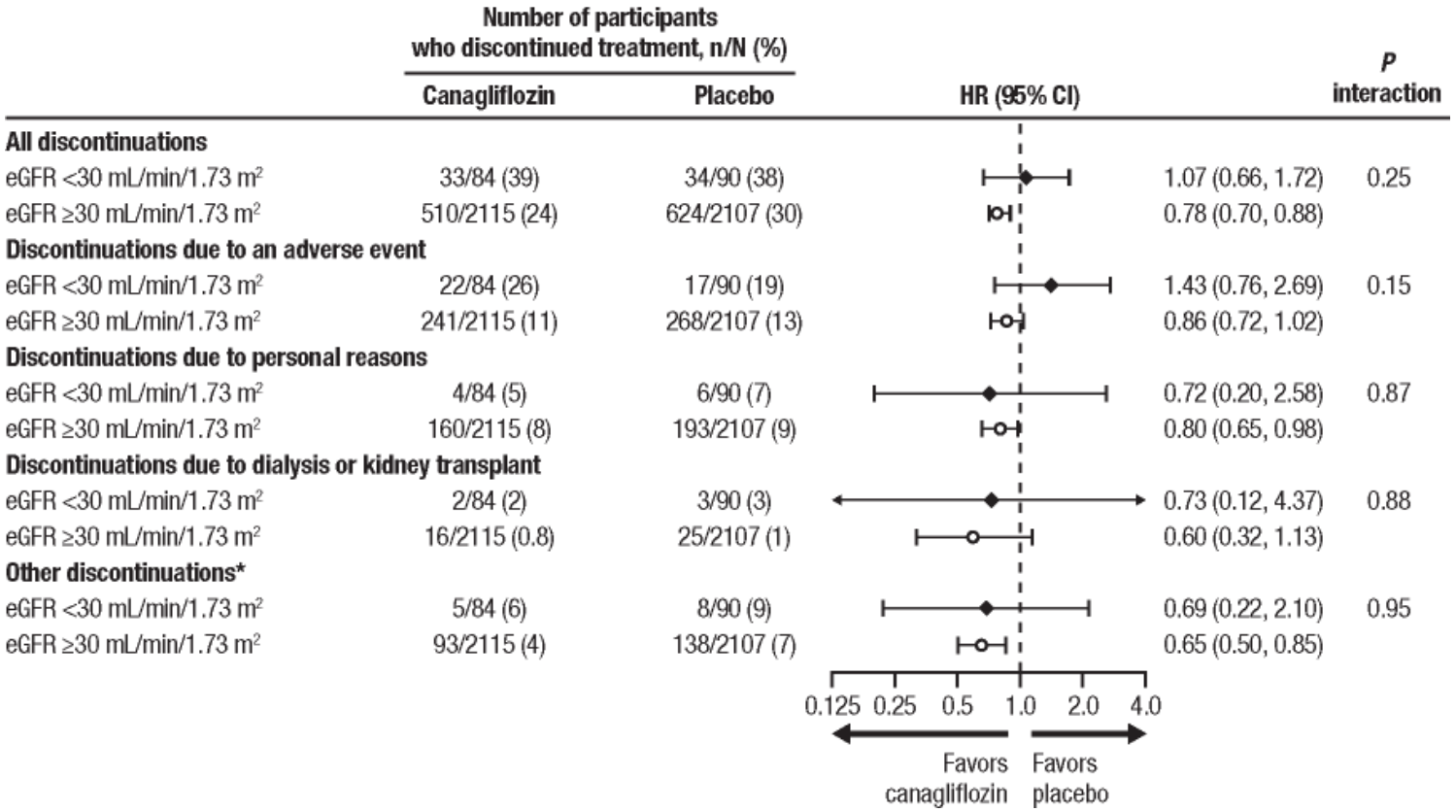
eGFR, estimated glomerular filtration rate; HR, hazard ratio; CI, confidence interval.

Figure 4. Effects of canagliflozin on safety outcomes in participants with randomization eGFR <30 versus ≥30 mL/min/1.73 m^2.

eGFR, estimated glomerular filtration rate; HR, hazard ratio; CI, confidence interval; AE, adverse event.

Figures

Figure 1. Reason for discontinuation of treatment.



HR, hazard ratio; CI, confidence interval; eGFR, estimated glomerular filtration rate.

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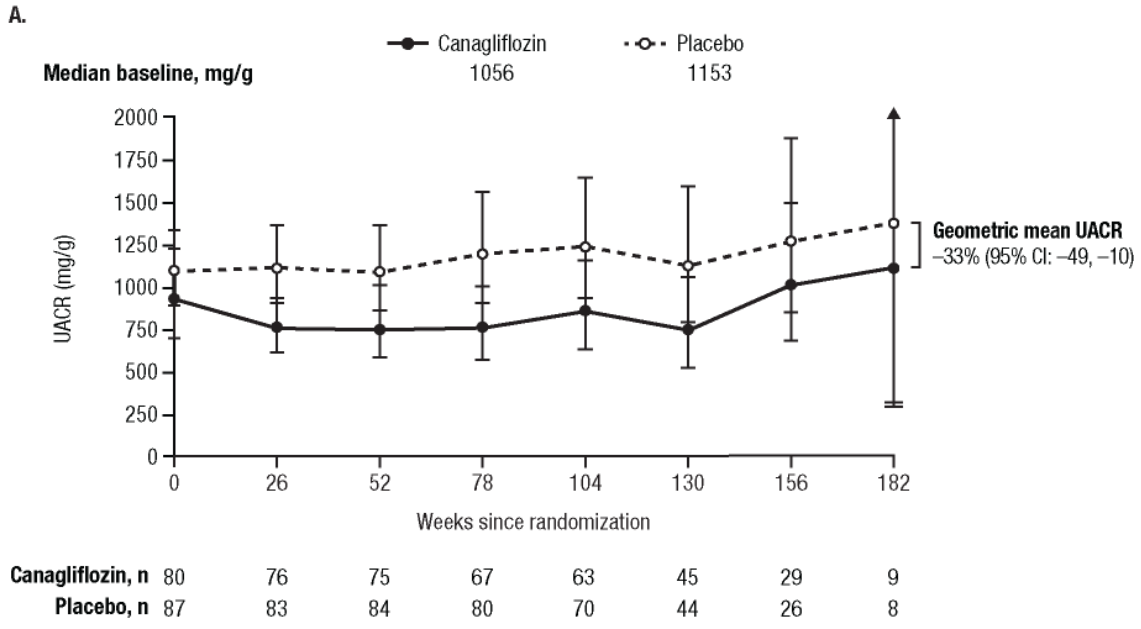

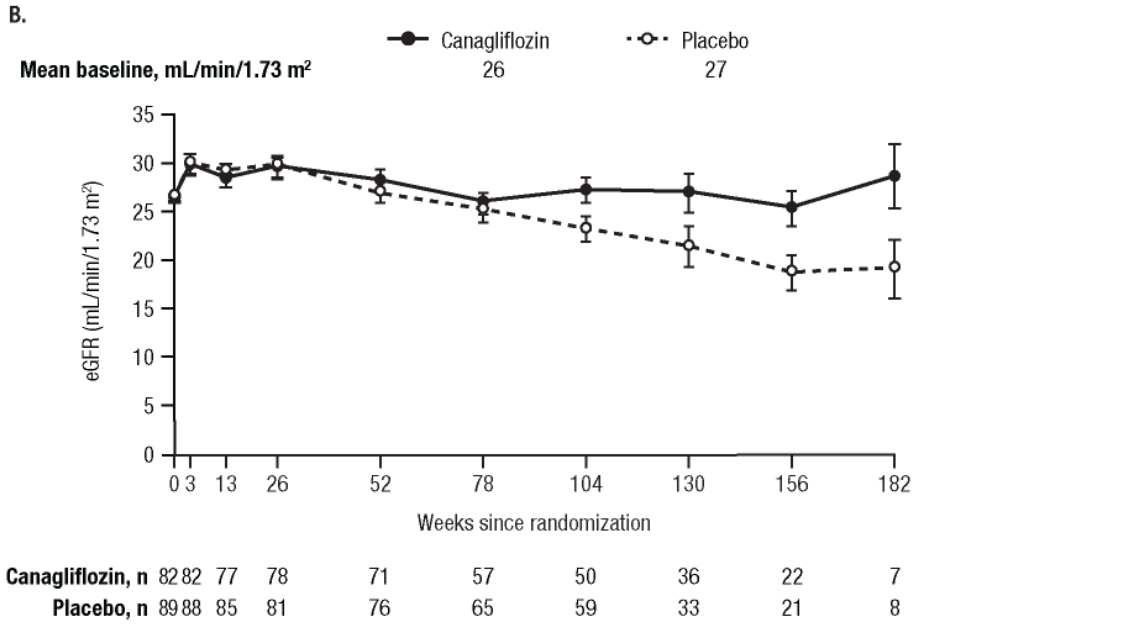

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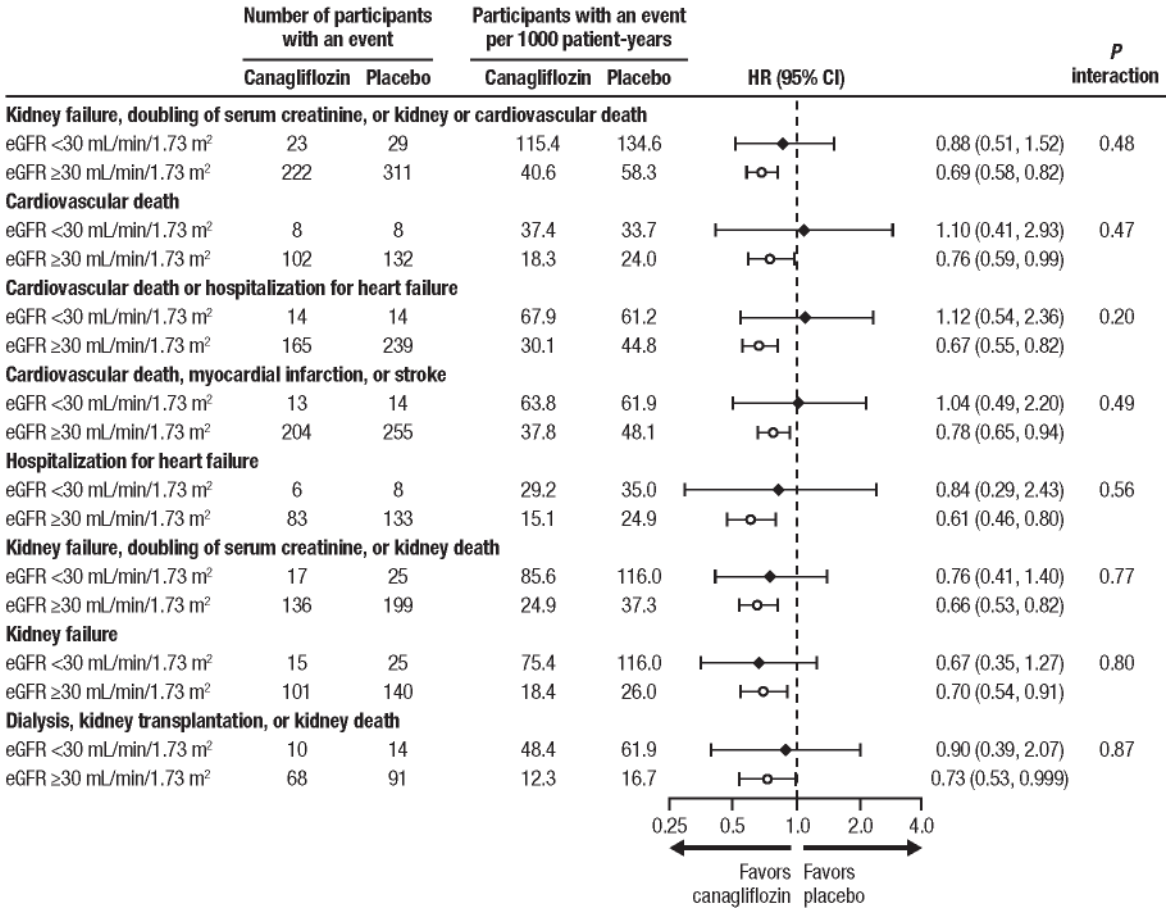
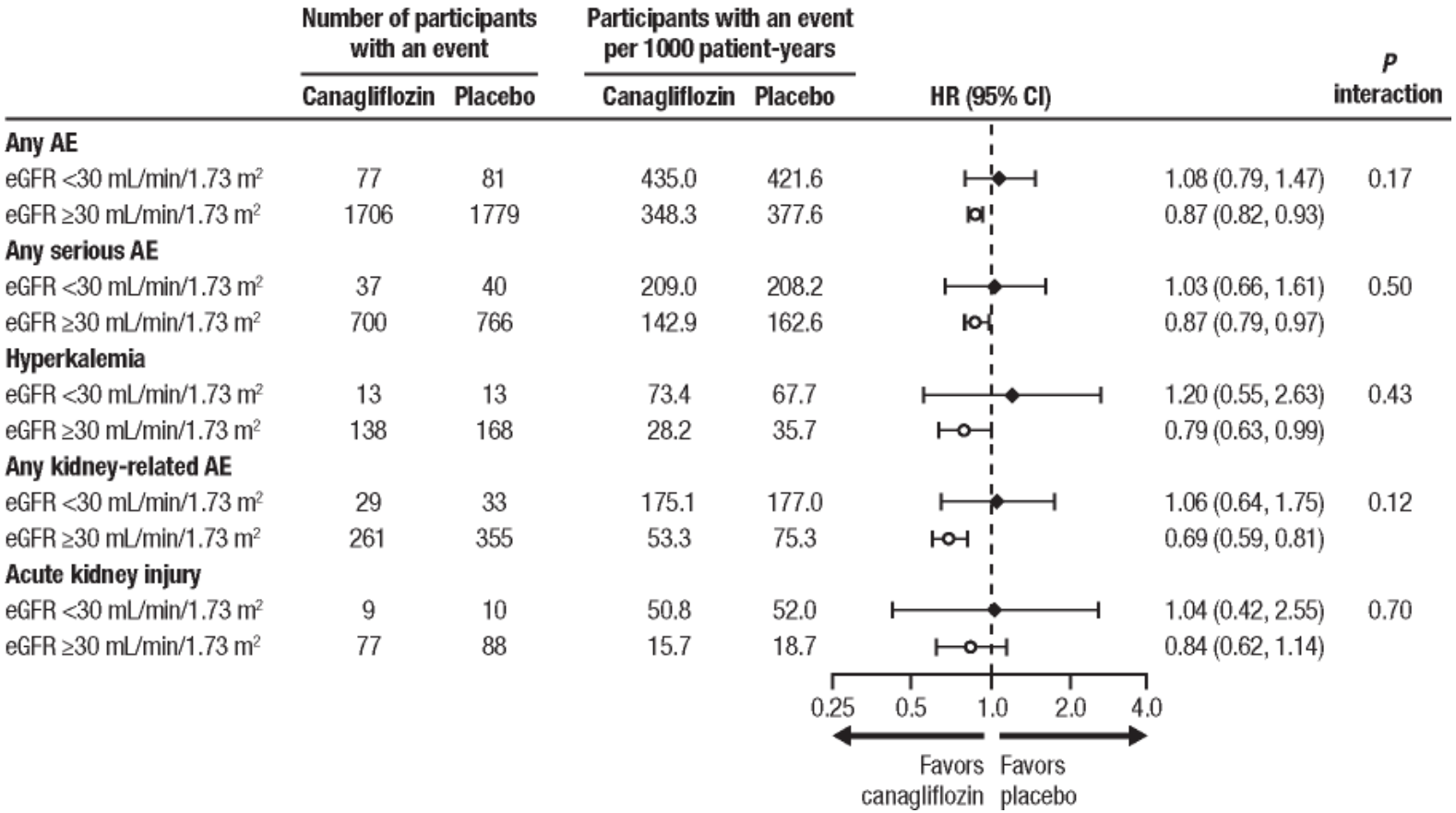


eGFR, estimated glomerular filtration rate; HR, hazard ratio; CI, confidence interval.

Figure 4. Effects of canagliflozin on safety outcomes in participants with randomization eGFR <30 versus ≥30 mL/min/1.73 m².



eGFR, estimated glomerular filtration rate; HR, hazard ratio; CI, confidence interval; AE, adverse event.

Supplementary Materials

Supplementary Table 1. Time Between Screening and Randomization Measurements

	Canagliflozin	Placebo	Total
All			
Participants, n	2201	2199	4400
<3 weeks, n (%)	161 (7)	161 (7)	322 (7)
3 to 8 weeks, n (%)	1959 (89)	1950 (89)	3909 (89)
>8 weeks, n (%)	81 (4)	88 (4)	169 (4)
Randomization eGFR <30 mL/min/1.73 m^2			
Participants, n	84	90	174
<3 weeks, n (%)	4 (5)	3 (3)	7 (4)
3 to 8 weeks, n (%)	74 (88)	80 (89)	154 (89)
>8 weeks, n (%)	6 (7)	7 (8)	13 (7)
Randomization eGFR ≥30 mL/min/1.73 m^2			
Participants, n	2117	2109	4226
<3 weeks, n (%)	157 (7)	158 (7)	315 (7)
3 to 8 weeks, n (%)	1885 (89)	1870 (89)	3755 (89)
>8 weeks, n (%)	75 (4)	81 (4)	156 (4)

eGFR, estimated glomerular filtration rate.

Supplementary Table 2. Serious Adverse Events During On- and Off-treatment

	Patients who continued the drug		Patients who discontinued the drug for reasons other than adverse event	
	Canagliflozin	**Placebo**	**Canagliflozin**	**Placebo**
On-treatment (until post-30 days after the last date of study drug)				
Patients with any SAE, n/N (%)				
Randomization eGFR <30 mL/min/1.73 m^2	16/51 (31)	22/56 (39)	5/11 (45)	8/17 (47)
Randomization eGFR ≥30 mL/min/1.73 m^2	466/1605 (29)	474/1483 (32)	89/269 (33)	115/356 (32)
Patients with a SAE per 1000 patient-years				
Randomization eGFR <30 mL/min/1.73 m^2	119.6	152.6	294.9	325.0
Randomization eGFR ≥30 mL/min/1.73 m^2	110.8	123.4	255.5	241.3
SAE episodes, n				
Randomization eGFR <30 mL/min/1.73 m^2	40	45	8	18
Randomization eGFR ≥30 mL/min/1.73 m^2	875	936	185	272
Days to the last date of drug, mean (SD)				

Randomization eGFR <30 mL/min/1.73 m^2	957.9 (228.1)	940.2 (246.0)	563.0 (370.2)	528.8 (316.1)
Randomization eGFR ≥30 mL/min/1.73 m^2	957.0 (236.3)	946.1 (235.5)	472.9 (313.8)	489.0 (313.3)
Off-treatment (after 30 days post the last date of study drug)				
Patients with any SAE, n/N (%)				
Randomization eGFR <30 mL/min/1.73 m^2	2/51 (4)*	0	3/11 (27)	4/17 (24)
Randomization eGFR ≥30 mL/min/1.73 m^2	10/1605 (0.6)†	8/1483 (0.5)†	59/269 (22)	96/356 (27)
Patients with a SAE per 1000 patient-years				
Randomization eGFR <30 mL/min/1.73 m^2	1002.1	0	259.7	189.0
Randomization eGFR ≥30 mL/min/1.73 m^2	528.8	429.7	157.4	197.6
SAE episodes, n				
Randomization eGFR <30 mL/min/1.73 m^2	5	0	8	5
Randomization eGFR ≥30 mL/min/1.73 m^2	28	12	180	266
Days after the last date of drug, mean (SD)				
Randomization eGFR <30 mL/min/1.73 m^2	14.3 (45.1)	3.8 (5.7)	383.5 (312.5)	454.6 (308.1)

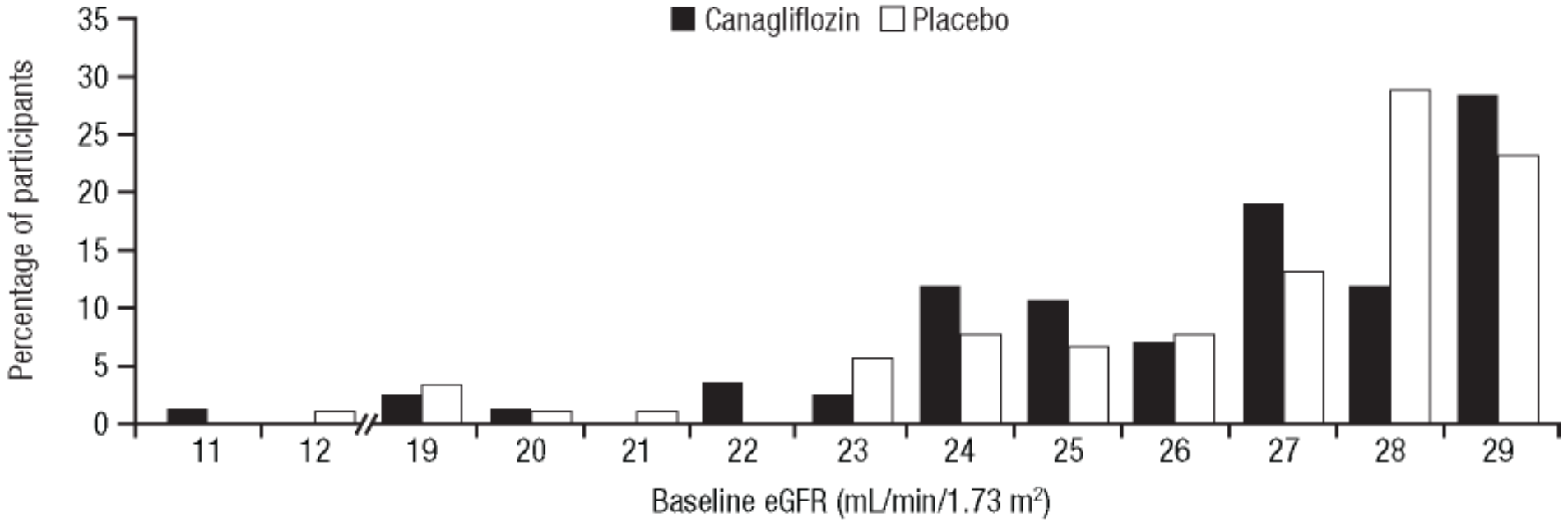
Randomization eGFR ≥30 mL/min/1.73 m^2	4.3 (12.9)	4.6 (16.5)	508.9 (313.8)	498.5 (338.4)
Total (on- and off-treatment)				
Patients with any SAE, n/N (%)				
Randomization eGFR <30 mL/min/1.73 m^2	17/51 (33)	22/56 (39)	6/11 (55)	9/17 (53)
Randomization eGFR ≥30 mL/min/1.73 m^2	468/1605 (29)	476/1483 (32)	117/269 (43)	157/356 (44)
Patients with a SAE per 1000 patient-years				
Randomization eGFR <30 mL/min/1.73 m^2	125.4	152.2	210.7	196.8
Randomization eGFR ≥30 mL/min/1.73 m^2	110.9	123.4	162.0	163.3
SAE episodes, n				
Randomization eGFR <30 mL/min/1.73 m^2	45	45	16	23
Randomization eGFR ≥30 mL/min/1.73 m^2	903	948	366	539
Days during follow-up, mean (SD)				
Randomization eGFR <30 mL/min/1.73 m^2	971.2 (213.7)	943.1 (246.8)	945.5 (396.7)	982.5 (215.5)
Randomization eGFR ≥30 mL/min/1.73 m^2	960.3 (235.1)	949.7 (234.9)	980.8 (259.1)	986.5 (257.8)

SAE, serious adverse event; eGFR, estimated glomerular filtration rate; SD, standard deviation.

*2 patients with eGFR <30 mL/min/1.73 m^2 in the canagliflozin arm stopped the drug due to a fatal SAE.

†10 and 8 patients with eGFR ≥30 mL/min/1.73 m^2 in the canagliflozin and placebo arms, respectively, stopped the drug due to a fatal SAE.

Supplementary Figure 1. Distribution of eGFR at randomization in participants with randomization eGFR <30 mL/min/1.73 m^2.



eGFR, estimated glomerular filtration rate.