





Efficacy of luseogliflozin for renal function preservation in patients with type 2 diabetes mellitus and impaired renal function: A randomized open-label clinical trial (RESOLUTION study)

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Keywords

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ABSTRACT

Introduction: The renoprotective effects of luseogliflozin, a sodium-glucose cotransporter 2 inhibitor, in patients with renal dysfunction are unexamined. We evaluated the efficacy of luseogliflozin in slowing renal function decline among patients with type 2 diabetes mellitus and moderate to severe renal dysfunction.

Materials and Methods: In a multicenter, randomized, open-label, controlled clinical trial, patients with type 2 diabetes mellitus and an estimated glomerular filtration rate based on serum creatinine (eGFR_{creat}) of 15–45 mL/min/1.73 m² were randomized into luseogliflozin or control groups. The primary endpoint was the change in eGFR_{creat} from baseline to 104 weeks. Secondary endpoints included eGFR_{creat} and eGFR_{creat} slope changes from 4 to 104 weeks (chronic eGFR_{creat} slope).

Results: Among 152 participants, eGFR_{creat} change from baseline to 104 weeks did not significantly differ between groups. The luseogliflozin group showed a significant decrease in eGFR_{creat} from 2 to 12 weeks compared to the control group; the largest decline occurred at 4 weeks (initial eGFR decline). There were no differences between groups thereafter. The chronic eGFR_{creat} slope was less negative in the luseogliflozin group compared to the control group (not significant). Conversely, subgroup analysis indicated that the difference in chronic eGFR_{creat} slope between groups was significantly

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greater (with a less negative or even positive slope observed in the luseogliflozin group compared to the control group) among patients with eGFR_{creat} <30 mL/min/1.73 m², urinary albumin/creatinine ratio <30 mg/g creatinine, systolic blood pressure <130 mmHg, or females.

Conclusions: Although the primary endpoint did not reach statistical significance, luseogliflozin may provide renoprotective benefits in patients with type 2 diabetes mellitus and moderate-to-severe renal impairment, potentially by slowing eGFR_{creat} decline post-initial decline.

INTRODUCTION

Diabetic nephropathy occurs in 20–40% of patients with diabetes mellitus (DM)¹. Diabetic kidney disease (DKD) encompasses typical diabetic nephropathy and atypical diabetes-related kidney disease, the latter of which is associated with glomerular filtration rate (GFR) decline without overt albuminuria². DKD is the leading cause of end-stage renal disease (ESRD)³, and patients with DKD are at a high risk of cardiovascular disease (CVD)⁴.

GFR measurements are essential for diagnosing and staging chronic kidney diseases (CKD), including DKD⁵. The GFR is typically expressed as the estimated GFR (eGFR) based on serum creatinine (Cre) levels. Assessing the magnitude of change in GFR through long-term observation is necessary to evaluate the effectiveness of treatments aimed at slowing GFR decline. Additionally, assessing the rate of decline, or GFR slope, over a specific timeframe is crucial for predicting future changes in renal function^{6,7}. Previous reports have shown that steeper negative GFR slopes are associated with an increased risk of ESRD, CVD, and all-cause mortality^{8,9}.

Large placebo-controlled trials have demonstrated that sodium-glucose cotransporter 2 inhibitors (SGLT2is) offer significant benefits in reducing the risk of cardiorenal disease progression, including atherosclerotic disease, heart failure, and CKD, in patients with type 2 diabetes mellitus. Notably, the CREDENCE trial¹⁰, which targeted patients with diabetic nephropathy, along with the DAPA-CKD^{11,12}, and EMPA-KIDNEY^{13–16} trials, which targeted patients with CKD with or without type 2 diabetes mellitus, demonstrated that canagliflozin, dapagliflozin, and empagliflozin significantly reduced the risk of renal composite outcomes and improved the GFR slope compared to placebo, independent of glucose control. Therefore, SGLT2is have been recommended for patients with eGFR ≥20 mL/min/1.73 m² who have type 2 diabetes mellitus with CKD¹⁷, and the renoprotective benefits of these medications are considered a class effect. However, the renoprotective effects of SGLT2is in patients with severe renal dysfunction, including an eGFR of 15–20 mL/min/1.73 m², have not been examined. Among SGLT2is, luseogliflozin exhibits similar pharmacokinetics across patients with varying levels of renal function, including those with moderate-to-severe

renal impairment¹⁸. Consequently, it may be unnecessary to consider dose reductions or an increased risk of adverse events due to heightened drug exposure, regardless of the degree of renal dysfunction. Nevertheless, the efficacy and safety of luseogliflozin in slowing renal function decline in patients with type 2 diabetes mellitus and CKD, particularly those with moderate-to-severe renal dysfunction, have not been adequately investigated.

MATERIALS AND METHODS

Study design

The Renal Efficacy Study of LUseogliflozin in patients with Type 2 diabetes mellitus and impaired renal function (RESOLUTION study) was a multicenter, open-label, randomized-controlled trial conducted across 22 medical institutions (Table S1) in Japan. Participants were enrolled between August 2020 and September 2022. All study procedures were conducted in accordance with the Declaration of Helsinki, the Clinical Trials Act, and other current legal regulations in Japan. The Kanazawa Medical University Clinical Research Review Board approved the study protocol (approval number: T013; July 17, 2020). This study was registered with the Japan Registry of Clinical Trials (jRCT) (registration number: jRCTs041200039). Written informed consent was obtained from all enrolled individuals meeting the eligibility criteria before the intervention. Data collection, management, monitoring, audits, and statistical analyses were outsourced to third-party entities (Soiken Inc., Osaka, Japan; EviPRO Co., Ltd., Tokyo, Japan) to avoid bias and ensure quality.

Subjects

The main inclusion criteria were as follows: (1) type 2 diabetes mellitus diagnosis, (2) a GFR estimated by serum creatinine (eGFR_{creat}) of 15–45 mL/min/1.73 m² at the latest visit (within 12 weeks) before providing consent, and (3) aged ≥20 years at the time of providing consent. Full inclusion and exclusion criteria are listed in Table S2.

Randomization, study intervention, and observation

Eligible patients who provided consent were randomly assigned to the luseogliflozin or control groups at an approximate 1:1

ratio using a minimization procedure to balance allocation factors (age < 70 or ≥ 70 years; eGFR_{creat} <30 or ≥ 30 mL/min/1.73 m²; and urinary albumin creatinine ratio (UACR) <300 or ≥ 300 mg/g-Cre). Patients in the luseogliflozin group received luseogliflozin at an initial dose of 2.5 mg daily. If glycemic control was insufficient, a dose increase to 5.0 mg daily was permitted with careful follow-up. Patients assigned to the control group did not receive luseogliflozin but continued their current treatment at the time of consent. All patients were subsequently observed for 104 weeks. The detailed observation schedules/items and intervention provisions, including prohibited/restricted agents and rescue therapy, are presented in Tables S3 and S4, respectively.

Outcomes

The primary endpoint was the change in eGFR_{creat} from baseline to week 104. Secondary endpoints included change in eGFR_{creat} from weeks 4 to 104, similar outcomes using GFR estimated by serum cystatin C (eGFR_{cys}), other renal, hepatic, and metabolic biomarkers, and frequency of adverse events. Prespecified exploratory endpoints included eGFR slopes¹⁹ between baseline and week 104 (total slope) and weeks 4 and 104 (chronic slope), and their subgroup analyses. The comprehensive list of outcomes is shown in Table S5.

Sample size

The eGFR slope in patients with stage G3b or G4 CKD was -2.6 ± 10 mL/min/1.73 m²/year in the Chronic Kidney Disease-Japan Cohort (CKD-JAC)²⁰, whereas that after luseogliflozin initiation in patients with similar CKD stages was -0.2 mL/min/1.73 m²/year based on the stratified analysis of clinical trials²¹ and postmarketing surveillance²². Therefore, we assumed that the changes in eGFR_{creat} from baseline to week 104 would be -5.2 ± 10 mL/min/1.73 m² and -0.4 mL/min/1.73 m² in the control and luseogliflozin groups, respectively. Consequently, the minimum sample size required to achieve a significance level of 0.05 from a two-sided test with a statistical power of 85% was determined to be 79 cases per group (158 cases for two groups). We estimated the dropout rate to be 20%; hence, the planned number of participants was set to 100 cases per group (200 cases per group).

Statistical analysis

All tests were two-sided, and statistical significance was set at P -value <0.05. Multiplicity was not adjusted for any of the endpoints. A statistical analysis plan was developed before the database lock. All statistical analyses were outsourced to third-party entities (EviPRO Co., Ltd.) to avoid bias and ensure quality. All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

Three analysis sets were defined in this study. The full analysis set (FAS) included all patients registered and assigned to either of the study treatment groups. Patients with severe protocol violations were excluded from the FAS. The per-protocol

set (PPS) excluded patients with a protocol violation. The safety analysis set included all registered patients who received at least one dose of the study intervention. Primary endpoint analyses were performed using data from the FAS and PPS, whereas secondary endpoint analyses were performed using FAS data. A safety analysis was performed using the safety analysis set.

Patient characteristics at baseline were reported as frequencies and proportions for categorical data and as summary statistics (number of patients, mean, standard deviation, minimum, first quartile, median, third quartile, and maximum) for continuous data.

The primary endpoint, change eGFR_{creat} from baseline to week 104, was analyzed through analysis of covariance, with the allocation factors as covariates. Summary statistics for the measurements and changes at each time point were calculated, and one- and two-sample t -tests were performed for within-group and between-group comparisons, respectively.

Summary statistics (number of patients and proportion) were calculated for secondary endpoints involving proportions, and the chi-squared test and Fisher's exact test were performed for between-group comparisons. Summary statistics for measurements and changes at each time point were calculated for secondary endpoints involving continuous variables, and one- and two-sample t -tests were performed for within-group and between-group comparisons, respectively. Wilcoxon signed-rank tests for within-group changes and rank-sum tests for between-group comparisons were performed if the values deviated from the normal distribution.

Regarding exploratory endpoints, the eGFR slope was calculated according to the CANPIONE study¹⁹. Briefly, the eGFR slope was estimated using a piecewise linear mixed-effects model (with knots at week 4), assuming that data were missing at random. Two phases of eGFR slopes (total [weeks 0–104] and chronic [weeks 4–104]) were estimated for each group, along with differences in the slope between the groups at each phase, changes in eGFR slopes, and their 95% confidence intervals (CIs). The model utilized an unstructured covariance structure, with patients as random effects and treatment group, time, interaction between the treatment group and time, and allocation factors as fixed effects. Compound symmetry was used if the results did not converge.

RESULTS

Baseline participant characteristics

The study population flowchart is shown in Figure 1. In total, 3,010 patients were evaluated for eligibility, and 152 were enrolled and randomized into the luseogliflozin (76 patients) or control group (76 patients). One patient in the luseogliflozin group was excluded due to dropout before the initiation of the study intervention, resulting in a safety analysis set constituting 75 and 76 patients in the luseogliflozin and control groups, respectively. After the initiation of the study intervention, one patient in the luseogliflozin group was excluded owing to a prohibited agent violation, and five in the control group were

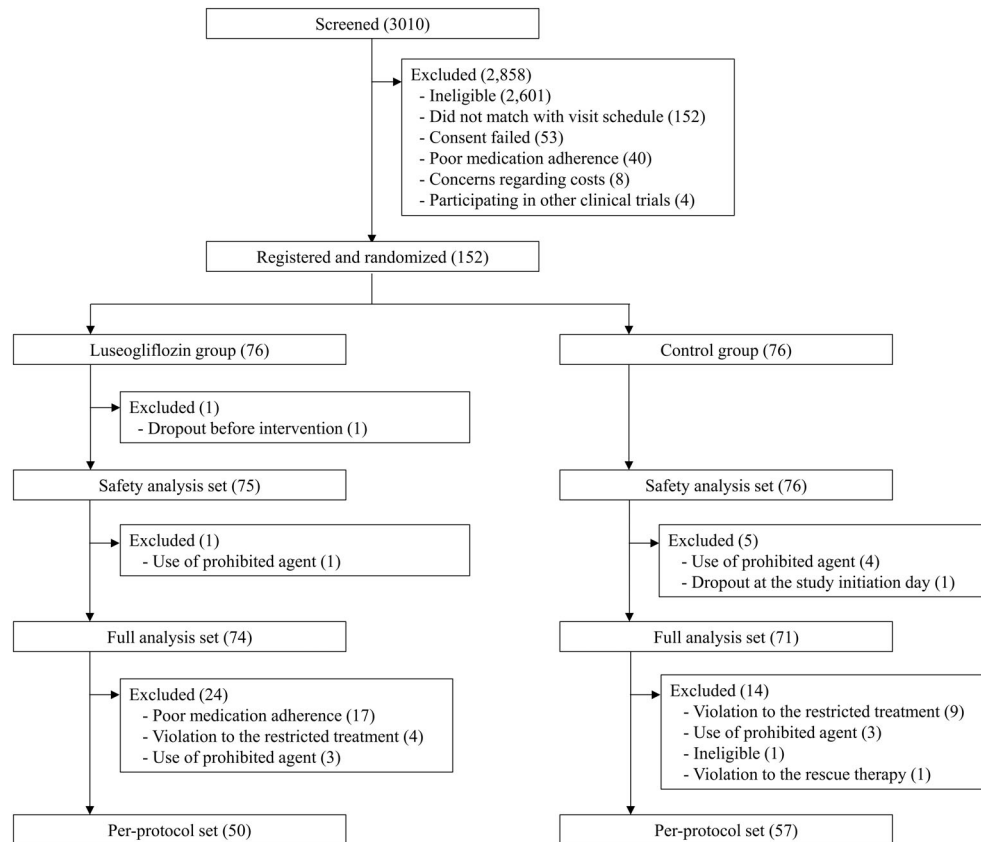


Figure 1 | Study flowchart of patient enrolment and analysis.

excluded owing to a prohibited agent violation (four patients) and dropout on the initiation day of the study intervention, resulting in a FAS constituting 74 and 71 patients in the luseogliflozin and control groups, respectively. Twenty-four and 14 patients were excluded from the PPS in the luseogliflozin and control groups, respectively, resulting in a PPS constituting 50 and 57 patients, respectively.

Baseline patient characteristics are presented in Table 1. The baseline characteristics were well balanced between the groups, except for systolic blood pressure (SBP) ($P = 0.004$), hepatic disease comorbidities ($P = 0.034$), and diabetic retinopathy ($P = 0.045$). Baseline medication use, including the use of anti-diabetic and antihypertensive agents, showed no between-group differences.

Changes in eGFR and eGFR slope

The primary endpoint was the change in eGFR_{creat} from baseline to 104 weeks. eGFR_{creat} significantly decreased from baseline to 104 weeks in both the luseogliflozin and control groups, and there was no significant difference in the change between the groups (Figure 2a). At other observation points, eGFR_{creat} significantly decreased in the luseogliflozin group throughout

the observation period, with the largest decline occurring at 4 weeks (initial eGFR decline). In contrast, the control group exhibited a significant decrease from baseline at weeks 38, 52, 76, and 88. Notably, the luseogliflozin group showed a significant decrease in eGFR_{creat} compared to the control group during weeks 2–12.

The change in eGFR_{creat} from week 4 was analyzed as a prespecified secondary endpoint, with a significant decrease in eGFR_{creat} from week 4 to weeks 38, 52, 76, 88, and 104 in the control group. In contrast, no significant changes were observed in the luseogliflozin group during the observation period. Consequently, the control group exhibited a significant decrease in eGFR_{creat} compared to the luseogliflozin group at weeks 38 and 76 (Figure 2b).

The total eGFR_{creat} slope was numerically less negative in the luseogliflozin group than in the control group, without statistical significance ($P = 0.69$; Figure 2a). Additionally, the chronic eGFR_{creat} slope was numerically less negative in the luseogliflozin group than in the control group, without statistical significance ($P = 0.22$; Figure 2b).

Sensitivity analyses of eGFR_{creat} using PPS and eGFR_{cys} using FAS showed similar tendencies (Figures S1 and S2).

Table 1 | Demographic and clinical characteristics of the patients at baseline

Characteristics	Luseogliflozin group (n = 74)	Control group (n = 71)	Total (n = 145)
Age (year)	71.4 ± 9.1	71.8 ± 7.8	71.6 ± 8.5
Sex			
Male	49 (66.2)	49 (69.0)	98 (67.6)
Female	25 (33.8)	22 (31.0)	47 (32.4)
Height (cm)	161.6 ± 8.6	161.5 ± 10.1	161.5 ± 9.3
Weight (kg)	66.7 ± 12.2	66.1 ± 13.0	66.4 ± 12.6
BMI (kg/m ²)	25.5 ± 4.1	25.3 ± 4.1	25.4 ± 4.1
Duration of diabetes (years)	17.7 ± 10.9 (67)	19.0 ± 11.3 (62)	18.3 ± 11.1 (129)
HbA1c (%)	7.3 ± 1.1	7.1 ± 0.9	7.2 ± 1.0
UACR (mg/g-Cre)			
UACR <30 mg/g-Cre	13 (17.8)/73	13 (18.8)/69	26 (18.3)/142
30 ≤ UACR <300 mg/g-Cre	26 (35.6)/73	31 (44.9)/69	57 (40.1)/142
300 mg/g-Cre ≤ UACR	34 (46.6)/73	25 (36.2)/69	59 (41.5)/142
eGFR _{creat} (mL/min/1.73 m ²)			
eGFR _{creat} <15 mL/min/1.73 m ²	1 (1.4)	0 (0.0)	1 (0.7)
15 ≤ eGFR _{creat} < 30 mL/min/1.73 m ²	12 (16.2)	15 (21.1)	27 (18.6)
30 ≤ eGFR _{creat} < 45 mL/min/1.73 m ²	49 (66.2)	44 (62.0)	93 (64.1)
45 mL/min/1.73 m ² ≤ eGFR _{creat}	12 (16.2)	12 (16.9)	24 (16.6)
Blood pressure			
Systolic blood pressure (mmHg)	138.1 ± 15.7	130.4 ± 15.8	134.4 ± 16.2
Diastolic blood pressure (mmHg)	74.1 ± 11.1	71.8 ± 12.7	73.0 ± 11.9
History			
Cardiocerebrovascular disease	17 (23.0)	17 (23.9)	34 (23.4)
Comorbidity			
Macrovascular disease	22 (29.7)	17 (23.9)	39 (26.9)
Cerebrovascular disease	5 (6.8)	5 (7.0)	10 (6.9)
Coronary artery disease	16 (21.6)	10 (14.1)	26 (17.9)
Peripheral artery disease	4 (5.4)	5 (7.0)	9 (6.2)
Microvascular disease	66 (89.2)	62 (87.3)	128 (88.3)
Diabetic nephropathy			
Stage 2	21 (28.4)	27 (38.0)	48 (33.1)
Stage 3	26 (35.1)	16 (22.5)	42 (29.0)
Stage 4	15 (20.3)	15 (21.1)	30 (20.7)
Diabetic retinopathy			
Simple diabetic retinopathy	18 (24.3)	13 (18.6)/70	31 (21.5)/144
Preproliferative diabetic retinopathy	5 (6.8)	10 (14.3)/70	15 (10.4)/144
Proliferative diabetic retinopathy	12 (16.2)	3 (4.3)/70	15 (10.4)/144
Diabetic neuropathy	21 (28.4)	20 (28.2)	41 (28.3)
Hepatic disease	9 (12.2)	2 (2.8)	11 (7.6)
Hypertension	68 (91.9)	68 (95.8)	136 (93.8)
Dyslipidemia	61 (82.4)	56 (78.9)	117 (80.7)
Concomitant medication use			
Anti-diabetic agent	70 (94.6)	67 (94.4)	137 (94.5)
Sulfonylurea	9 (12.2)	7 (9.9)	16 (11.0)
Alpha-glucosidase inhibitor	13 (17.6)	11 (15.5)	24 (16.6)
Biguanide	18 (24.3)	18 (25.4)	36 (24.8)
Glinide	16 (21.6)	17 (23.9)	33 (22.8)
Thiazolidine	3 (4.1)	4 (5.6)	7 (4.8)
Dipeptidyl-peptidase 4 inhibitor	44 (59.5)	42 (59.2)	86 (59.3)
Oral GLP-1 receptor agonist	2 (2.7)	1 (1.4)	3 (2.1)
Human GLP-1 analog injectable	2 (2.7)	6 (8.5)	8 (5.5)
Long-acting GLP-1 receptor agonist	7 (9.5)	11 (15.5)	18 (12.4)
Insulin	22 (29.7)	20 (28.2)	42 (29.0)
Others	0 (0.0)	0 (0.0)	0 (0.0)

Table 1. (Continued)

Characteristics	Luseogliflozin group (n = 74)	Control group (n = 71)	Total (n = 145)
Antihypertensive	66 (89.2)	60 (84.5)	126 (86.9)
Diuretic	12 (16.2)	6 (8.5)	18 (12.4)
Potassium-sparing diuretic	5 (6.8)	4 (5.6)	9 (6.2)
Calcium antagonist	52 (70.3)	41 (57.7)	93 (64.1)
Angiotensin receptor antagonist	51 (68.9)	47 (66.2)	98 (67.6)
Angiotensin-converting enzyme inhibitor	1 (1.4)	3 (4.2)	4 (2.8)
Alpha1 antagonist	3 (4.1)	2 (2.8)	5 (3.4)
Alpha/beta-antagonist	6 (8.1)	2 (2.8)	8 (5.5)
Beta-antagonist	7 (9.5)	7 (9.9)	14 (9.7)
Transdermal beta1 antagonist	0 (0.0)	1 (1.4)	1 (0.7)
Direct renin inhibitor	1 (1.4)	0 (0.0)	1 (0.7)
Angiotensin receptor neprilysin inhibitor	1 (1.4)	0 (0.0)	1 (0.7)
Loop diuretic	0 (0.0)	3 (4.2)	3 (2.1)
Long-acting loop diuretic	2 (2.7)	1 (1.4)	3 (2.1)
Nonthiazide antihypertensive	1 (1.4)	1 (1.4)	2 (1.4)
Mineralocorticoid receptor antagonist	3 (4.1)	2 (2.8)	5 (3.4)
Others	0 (0.0)	0 (0.0)	0 (0.0)
Dyslipidemia therapeutic agent	53 (71.6)	51 (71.8)	104 (71.7)
Vitamin D	4 (5.4)	0 (0.0)	4 (2.8)

Data are presented as the mean \pm SD for continuous variables and as the number of patients (%) for categorical variables. In cases where the number of patients with data differed from the number of patients in each group, the number of patients with data is shown after the data in parentheses. BMI, body mass index; eGFR, glomerular filtration rate estimated using serum creatinine; GLP-1, glucagon-like peptide 1; UACR, urinary albumin/creatinine ratio.

In a prespecified exploratory subgroup analysis, the adjusted between-group difference in the chronic eGFR_{creat} slope was significantly greater, showing a less negative or even positive slope, in the luseogliflozin group compared to the control group, among patients with the baseline levels of eGFR_{creat} <30 mL/min/1.73 m², UACR <30 mg/g-Cr, SBP <130 mmHg, or females (Figure 3).

The proportion of patients whose eGFR_{creat} decreased by \geq 30% from baseline did not differ between the groups throughout the observation period (Figure S3A). The proportion of patients whose eGFR_{creat} decreased by \geq 20% from baseline was significantly larger in the luseogliflozin group (eight patients [11.3%]) than in the control group (one patient [1.4%]; $P = 0.033$) only at week 4, with no significant between-group differences at other observation points (Figure S3B). The proportion of patients whose eGFR_{creat} was <10 mL/min/1.73 m² (Figure S3C) and the incidence of dialysis (Figure S3D) did not show significant between-group differences throughout the observation period.

Changes in UACR

UACR significantly decreased from baseline to weeks 26 and 52 in the luseogliflozin group, showing a significant decrease in the luseogliflozin group compared to the control group at weeks 52 ($P = 0.016$) and 64 ($P = 0.049$; Figure S4).

Changes in clinical laboratory tests and BMI

HbA1c levels in the luseogliflozin group significantly decreased from baseline to weeks 8 and 12. However, no significant between-group differences were observed throughout the observation period (Figure 4a). Body mass index (BMI) in the luseogliflozin group significantly decreased from baseline throughout the observation period and was significantly lower than that in the control group (Figure 4b). SBP (at weeks 4, 8, 12, 26, and 104), diastolic blood pressure (at weeks 12 and 76), aspartate aminotransferase (at weeks 64 and 76), gamma-glutamyl transpeptidase (γ GTP) (at weeks 8 and 76), and uric acid (at weeks 38 and 88) significantly decreased in the luseogliflozin group compared to the control group (Figure 4c–h).

The percent change from baseline significantly increased for total ketone bodies (at weeks 52 and 104), 3-hydroxybutyric acid (3OHBA) (at weeks 52 and 104), and acetoacetic acid (AcAc) (at week 52) in the luseogliflozin group. However, no significant differences were observed between the groups (Figure S5A–C). A post-hoc analysis demonstrated a significant positive correlation between the chronic eGFR_{creat} slope and the percent change from baseline to week 104 in total ketone bodies (correlation coefficient (95% CI): 0.27 (0.02, 0.49), $P = 0.035$) and 3OHBA (0.27 (0.02, 0.49), $P = 0.036$) in the luseogliflozin group. AcAc did not show a significant

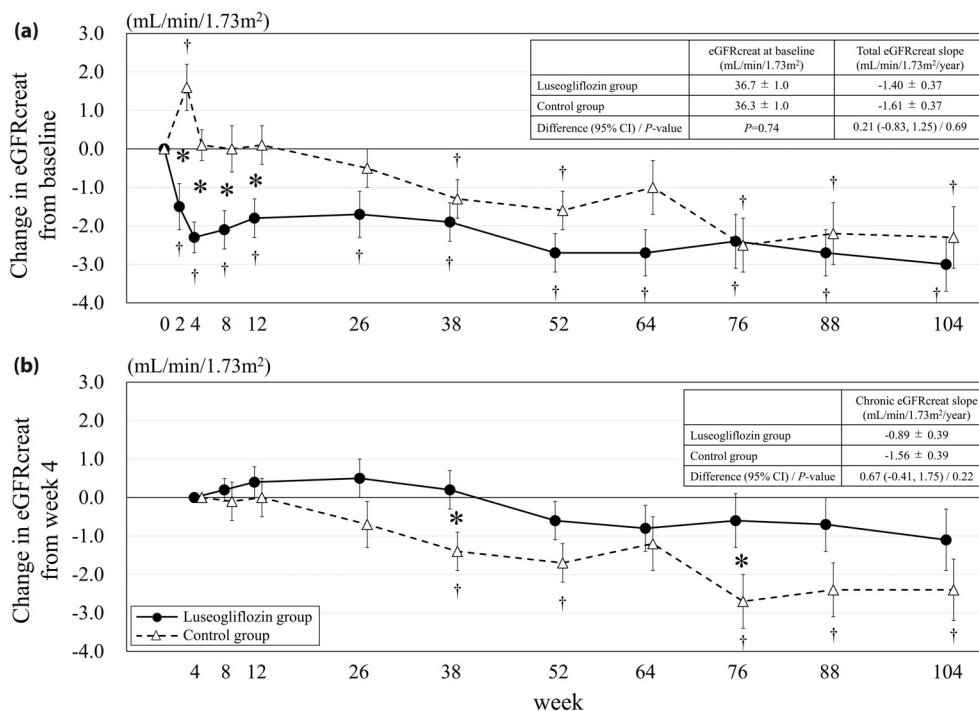


Figure 2 | Change in eGFR_{crea} and eGFR_{crea} slope. Data are presented as mean ± standard error. One-sample *t*-tests were used for within-group comparisons. Two-sample *t*-tests were used for between-group comparisons. †Represents *P* < 0.05 for the within-group comparison. eGFR_{crea}, glomerular filtration rate estimated by serum creatinine. **P* < 0.05, between-group comparison of changes. The eGFR_{crea} slope was estimated using a piecewise linear mixed-effects model (with knots at week 4), assuming that data were missing at random. It was performed with an unstructured covariance structure, with patients as random effects and treatment group, time, interaction between the treatment group and time, and allocation factors as fixed effects. Compound symmetry was used if the results did not converge.

correlation with the chronic eGFR_{crea} slope (correlation coefficient (95% CI): 0.23 (-0.03, 0.45), *P* = 0.08; Table S6).

Safety

During the study period, two patients (2.7%) died in the luseogliflozin group (one due to disseminated intravascular coagulation after percutaneous coronary intervention for myocardial infarction and another due to alcoholic cirrhosis), and one (1.3%) died in the control group (due to myocardial infarction; Table S7). However, none of these deaths were judged to have been caused by the intervention. Adverse events occurred in 54 patients (72.0%) in the luseogliflozin group and 54 (71.1%) in the control group, whereas serious adverse events occurred in 22 patients (29.3%) in the luseogliflozin group and 21 (27.6%) in the control group. Frequent adverse events were hypertension (11 [14.7%] and 13 [17.1%] patients in the luseogliflozin and control groups, respectively), edema (7 [9.3%] and 4 [5.3%] patients, respectively), and hyperglycemia (7 [9.3%] and 9 [11.8%] patients, respectively), with no difference in the frequency of adverse events between groups.

DISCUSSION

This is the first study to investigate whether luseogliflozin has an effect on the preservation of renal function in patients with

type 2 diabetes mellitus and moderate-to-severe renal dysfunction. The change in eGFR_{crea} from baseline to 104 weeks, as the primary endpoint, did not significantly differ between the groups. In the luseogliflozin group, an initial decline in eGFR was observed, with the largest decrease occurring 4 weeks following the intervention. However, the subsequent chronic eGFR slope was less negative than that of the control group, although this difference was not statistically significant.

The results of three large randomized controlled trials: CREDENCE¹⁰, DAPA-CKD¹¹, and EMPA-KIDNEY trials¹³, clearly demonstrated that SGLT2is provide significant benefits for renal composite outcomes. This served as the primary endpoint compared to placebo in patients with DKD or CKD, regardless of the presence of type 2 diabetes mellitus. Regarding renal function decline progression, the eGFR slope after the initial eGFR decline was less negative in the SGLT2i group compared to the placebo group in the three trials (-1.85 ± 0.13 vs -4.59 ± 0.14 mL/min/1.73 m²/year in CREDENCE¹⁰; -1.67 ± 0.11 vs -3.59 ± 0.11 mL/min/1.73 m²/year in DAPA-CKD¹¹; and -1.37 ± 0.08 vs -2.75 ± 0.08 mL/min/1.73 m²/year in EMPA-KIDNEY¹³), indicating long-term preservation of renal function. In the present study, involving patients with type 2 diabetes mellitus and moderate-to-severe renal dysfunction, the trend was consistent

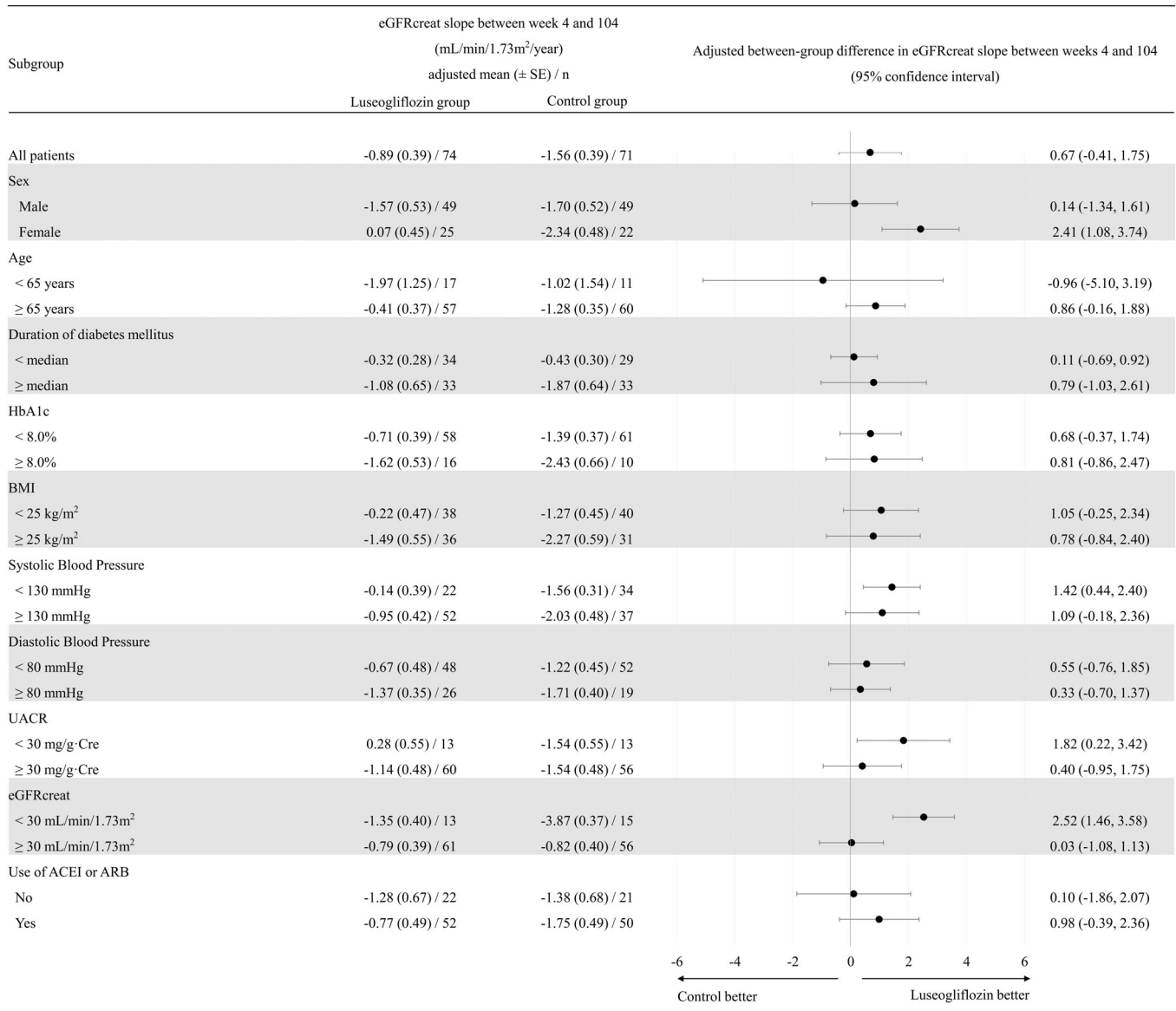


Figure 3 | Subgroup analysis of eGFR_{crea} slope. Data are presented as the adjusted mean ± standard error or adjusted between-group difference (95% confidence interval). The eGFR_{crea} slope was estimated using a piecewise linear mixed-effects model (with knots at week 4), assuming that data were missing at random. It was performed with an unstructured covariance structure, with patients as random effects and treatment group, time, interaction between the treatment group and time, and allocation factors as fixed effects. Compound symmetry was used if the results did not converge. eGFR_{crea}, glomerular filtration rate estimated by serum creatinine.

with the results of the aforementioned trials. The chronic eGFR_{crea} slope after the initial decline was numerically less negative in the luseogliflozin group compared to the control group (-0.89 ± 0.39 vs -1.56 ± 0.39 mL/min/1.73 m²/year, respectively), although this difference was not statistically significant. A possible reason for the lack of statistically significant between-group differences in the chronic eGFR_{crea} slope or the mean change in eGFR_{crea} from weeks 4–104 might be that the rate of eGFR_{crea} decline in the control group was

lower than that observed in the three trials^{10,11,13}. On the other hand, a previous systematic review indicated that the normal decline rate in healthy adults without hypertension ranges from -0.37 to -1.07 mL/min/1.73 m²/year²³. While comparing data before and after the intervention was not possible, the chronic eGFR_{crea} slope after luseogliflozin intervention was nearly equivalent to that in healthy adults without hypertension. This suggests that luseogliflozin may have a renoprotective effect; however, further long-term studies are

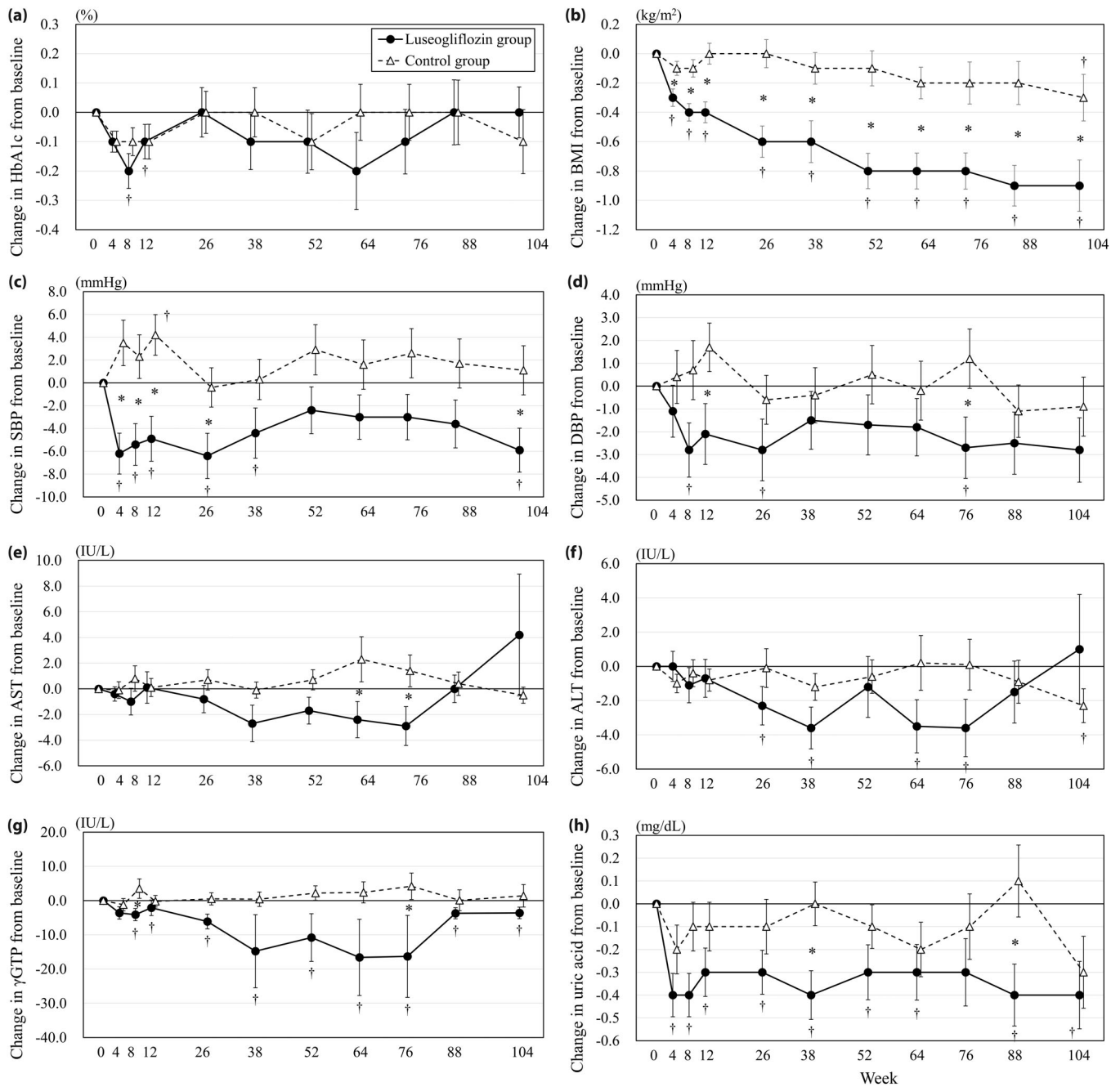


Figure 4 | Change in laboratory test values. Data are presented as mean ± standard error. One-sample *t*-tests were used for within-group comparisons. Two-sample *t*-tests were used for between-group comparisons. †Represents *P* < 0.05 for the within-group comparison. **P* < 0.05, between-group comparison of changes. ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; DBP, diastolic blood pressure; HbA1c, hemoglobin A1c; SBP, systolic blood pressure; γ-GTP, gamma-glutamyl transpeptidase.

necessary to evaluate its impact on the preservation of renal function.

In the three aforementioned trials, the benefit of SGLT2is on eGFR slope alleviation was demonstrated across the range of eGFR^{13,24,25}, albuminuria^{13,24}, SBP²⁴, and sex²⁴. Notably, in the

EMPA-KIDNEY¹³ trial, it was observed that the higher the baseline UACR or eGFR value, the more pronounced the effect of empagliflozin in improving chronic eGFR slope. In the present study, stratified analysis showed that the chronic eGFR-creatinine slope in the luseogliflozin group was significantly less

negative, or even positive, compared to the control group in patients with baseline eGFR_{creat} <30 mL/min/1.73 m² or UACR <30 mg/g-Cre. Conversely, in patients with baseline eGFR_{creat} ≥30 mL/min/1.73 m² or UACR ≥30 mg/g-Cre, luseogliflozin did not demonstrate a significant improvement in the chronic eGFR_{creat} slope. The discrepancies in these findings from the stratified analyses of eGFR_{creat} slopes may be attributed to the differences in chronic eGFR slopes observed in the control groups of these studies. Regarding the population with UACR ≥30 mg/g-Cre, the chronic eGFR slope in the control group was -1.69 ± 0.14 and -4.11 ± 0.11 mL/min/1.73 m²/year in patients with $30 \leq \text{UACR} \leq 300$ mg/g-Cre and UACR >300 mg/g-Cre, respectively, and regarding the population with eGFR ≥30 mL/min/1.73 m², it was -2.50 ± 0.12 mL/min/1.73 m²/year in patients with $30 \leq \text{eGFR} < 45$ mL/min/1.73 m² in the EMPA-KIDNEY trial. In contrast, this study demonstrated chronic eGFR_{creat} slopes of -1.54 ± 0.48 and -0.82 ± 0.40 mL/min/1.73 m²/year in patients with UACR ≥30 mg/g-Cre and eGFR_{creat} ≥30 mL/min/1.73 m², respectively. Thus, the lesser decline in eGFR in the control group of this study compared to that of the EMPA-KIDNEY trial may have contributed to the smaller difference between the groups. On the other hand, the chronic eGFR slope in the control group was -0.89 ± 0.16 mL/min/1.73 m²/year in patients with UACR <30 mg/g-Cre, and -2.50 ± 0.12 mL/min/1.73 m²/year in patients with eGFR <30 mL/min/1.73 m² in the EMPA-KIDNEY trial. In contrast, this study showed chronic eGFR_{creat} slopes of -1.54 ± 0.55 and -3.87 ± 0.37 mL/min/1.73 m²/year for patients with UACR <30 mg/g-Cre and eGFR_{creat} <30 mL/min/1.73 m², respectively. Thus, the more substantial decline in eGFR observed in the control group of this study compared to that of the EMPA-KIDNEY trial may have resulted in a significant difference between the groups. In addition, the subgroups with baseline levels of SBP <130 mmHg or females showed that the chronic eGFR_{creat} slope was significantly less negative or even positive in the luseogliflozin group compared to the control group. However, the reason for the discrepancy in findings between this study and the three previously mentioned trials remains unclear.

Recent cohort studies conducted in several countries, including the United States²⁶ and Japan²⁷, revealed a decrease in albuminuria prevalence owing to advancements in diabetes treatment among patients with DKD. Conversely, the prevalence of reduced GFR has increased over the past 20 years. Additionally, the aging population of patients with diabetes contributes to renal function decline. In this study, the mean age of participants was 71 years, and the stratified analysis indicated that luseogliflozin significantly improved the eGFR_{creat} slope compared to current treatments in the groups with eGFR_{creat} <30 mL/min/1.73 m² or UACR <30 mg/g-Cre. Furthermore, luseogliflozin did not increase further renal function decline to eGFR_{creat} <10 mL/min/1.73 m². These findings may be meaningful for the treatment of elderly patients with DKD who experience severe renal function decline without

albuminuria, a trend that has been increasingly observed in clinical practice in recent years.

No significant difference was observed in the change in HbA1c levels between the two groups, which may be attributed to the open-label nature of the trial. Specifically, some patients in the luseogliflozin group reduced the dose of other antidiabetic agents including insulin at the start of treatment to avoid hypoglycemia or excessive hypoglycemia. Additionally, the efficacy of luseogliflozin in reducing glucose levels may diminish based on the degree of renal impairment, particularly regarding its pharmacodynamic profile¹⁸, as well as other SGLT2is. In contrast, BMI significantly decreased during the observational period. Furthermore, other metabolic parameters such as SBP, hepatic and biliary enzymes, and serum uric acid values tended to decrease in the luseogliflozin group, similar to previous reports^{28–31}. Serum ketone bodies significantly increased from baseline to weeks 52 and 104 in the luseogliflozin group in the within-group comparison. Interestingly, a post-hoc analysis demonstrated a significant positive correlation between the chronic eGFR_{creat} slope and the percentage change in total ketone bodies and 3OHBA in the luseogliflozin group. Since basic research has demonstrated that ketone bodies increased by SGLT2is have a renoprotective effect^{32–34}, the increase in ketone bodies in this study might partially contribute to kidney function preservation.

Regarding safety, the addition of luseogliflozin did not increase the incidence of ESRD (dialysis incidence or progression to an eGFR_{creat} <10 mL/min/1.73 m²). The proportion of patients whose eGFR_{creat} decreased by ≥20–30% from baseline did not differ between the groups, except for the initial decline observed at week 4. These results demonstrate the safety of luseogliflozin even in patients with moderate-to-severe renal dysfunction.

This study had several potential limitations. First, this was an open-label study that lacked blinding for patients and physicians, which may have introduced bias. However, we believe that the open-label design did not significantly affect the results because the study employed objectively measurable endpoints, including eGFR. Second, this study was conducted exclusively in Japan, and all participants were Japanese, potentially limiting the generalizability of these findings to other countries or patients of different ethnicities. Third, the study did not achieve the target sample size of 200 patients, and only 152 patients were enrolled. One possible reason for the small sample size is the increased use of SGLT2is in Japan. Many physicians in the study reported difficulties in screening eligible candidates, as many had already been treated with SGLT2is. Additionally, our study was conducted during the COVID-19 pandemic, which affected participant enrollment. The insufficient sample size may have affected the results of the study. Fourth, several baseline patients' characteristics, including SBP, hepatic disease comorbidities, and diabetic retinopathy, were not well-balanced between the groups. Although this was a randomized-controlled trial, because of the target number of cases, we set only three

allocation factors (age, eGFR_{creat}, and UACR), and other factors could not be controlled. The possibility that the unbalance in the patients' background between the groups might affect the results in this study. We could not judge whether the reason for the lack of a significant between-group difference in the primary endpoint was the insufficient power, the unbalance in the patients' background, or that luseogliflozin did not have renoprotective benefits in patients with type 2 diabetes mellitus and moderate-to-severe renal impairment. Further study with a larger, sufficient sample size, with well-controlled patients' backgrounds may be required.

In conclusion, although the primary endpoint did not reach statistical significance, luseogliflozin may provide renoprotective benefits for patients with type 2 diabetes mellitus and moderate-to-severe renal impairment, potentially by slowing the rate of eGFR decline following the initial decline, without increasing further renal function decline to eGFR_{creat} <10 mL/min/1.73 m² and dialysis incidence.

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Approval of the research protocol: The protocol of this study was approved (approval number: T013) by the Kanazawa Medical University Clinical Research Review Board.

Informed Consent: Written informed consent was obtained prior to intervention from all enrolled individuals who met the eligibility criteria.

Approval date of Registry and the Registration No. of the study/trial: August 24, 2020, jRCTs041200039.

Animal Studies: N/A.

DATA AVAILABILITY STATEMENT

The datasets generated and/or analyzed during the current study are not publicly available because of the lack of a statement in the study protocol enabling data sharing with a third party after the end of the study, informed consent documents, and a lack of approval for data sharing by the ethics review board.

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SUPPORTING INFORMATION

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

Data S1. Supporting Information.

Figure S1. Changes in eGFR_{creat} using the PPS.

Figure S2. Changes in eGFR_{cys} using the FAS.

Figure S3. Proportion of patients whose eGFR_{creat} decreased by $\geq 30\%$, $\geq 20\%$, became < 10 mL/min/1.73 m², and incidence of dialysis

Figure S4. Change in UACR.

Figure S5. Percentage change in ketone bodies.

Table S1. Participation in medical institutions.

Table S2. Eligibility criteria.

Table S3. Observational schedule and items.

Table S4. Study intervention provisions.

Table S5. Study outcomes.

Table S6. Correlation between the chronic eGFR_{creat} slope and percent change in ketone bodies.

Table S7. Adverse events.