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ORIGINAL RESEARCH

Impact of Reduced Renal Function on the Glucose-Lowering Effects of Luseogliflozin, a Selective SGLT2 Inhibitor, Assessed by Continuous Glucose Monitoring in Japanese Patients with Type 2 Diabetes Mellitus

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ABSTRACT

Introduction: We investigated the impact of reduced renal function on 24-h glucose variability in Japanese patients with type 2 diabetes mellitus (T2DM) treated with luseogliflozin.

Methods: In this double-blind, placebo-controlled, crossover study, 37 Japanese patients with T2DM [glycated hemoglobin (HbA1c) 7.0–10.0%] and estimated glomerular filtration rate (eGFR) ≥45 mL/min/1.73 m^2 were randomized into two groups in which patients first received luseogliflozin then placebo, or vice versa, for 7 days each. Twenty-four-hour glucose variability was measured on day 7 in each period and was compared among patients divided into three groups according to their baseline eGFR (mL/min/1.73 m^2): normal (≥90; $n = 13$; normal group), normal-to-mildly reduced renal function (≥75 to <90; $n = 12$; normal–mild group), and mild-to-moderately reduced renal function (<75; $n = 9$; mild–moderate group).

Results: The mean [95% confidence interval (CI)] placebo-subtracted 24-h cumulative urinary glucose excretion (g) was 82.1 (72.7, 91.5), 82.5 (73.4, 91.5), and 62.2 (51.2, 73.3); the placebo-subtracted 24-h mean glucose concentration (mg/dL) was −24.39 (−32.53, −16.26), −28.28 (−39.35, −17.22), and −11.53 (−23.93, 0.86); and the placebo-subtracted peak postprandial glucose (mg/dL) was −26.9 (−46.9, −6.9), −38.1 (−59.6, −16.6), and 1.5 (−25.5, 28.4) in the normal, normal–mild, and mild–moderate groups, respectively. The mean lowest glucose concentrations (placebo vs. luseogliflozin, mg/dL) decreased to similar levels in the normal (115.4 vs. 93.4), normal–mild (121.0 vs. 97.9), and mild–moderate (104.0 vs. 91.1) groups.

Conclusion: This post hoc subanalysis revealed that although mild-to-moderately reduced renal function attenuated the glucose-lowering effects of luseogliflozin on peak postprandial

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glucose, it did not attenuate the effects of luseogliflozin on fasting glucose. These findings may explain the smaller increase in urinary glucose excretion in these patients relative to patients with normal renal function or normal-to-moderately reduced renal function. Further studies may be needed to examine these findings in large populations of patients with T2DM and reduced renal function.
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Keywords: Continuous glucose monitoring; Endocrinology; Estimated glomerular filtration rate; Glucose variability; Luseogliflozin; Renal function; SGLT2 inhibitor; Type 2 diabetes mellitus

INTRODUCTION

Sodium–glucose cotransporter 2 (SGLT2) inhibitors are newly approved drugs that ameliorate hyperglycemia without increasing the risk of hypoglycemia or body weight gain compared with other glucose-lowering drugs [1–3]. Accordingly, they are included as one of the treatment options for combination therapy of type 2 diabetes mellitus (T2DM) in the current American Diabetes Association/European Association for the Study of Diabetes treatment recommendations [4].

Because the amount of glucose filtered through the glomerulus and urinary glucose excretion (UGE) are correlated with renal function [5], it is important to investigate the relationship between renal function/renal impairment and the efficacy of SGLT2 inhibitors. Indeed, it has been reported that the pharmacodynamics of SGLT2 inhibitors in diabetic subjects with renal impairment are consistent with the observation of reduced efficacy in these patients [6], and that some SGLT2 inhibitors are contraindicated in patients with chronic kidney disease, or their daily dose might need to be reduced [6].

Luseogliflozin is a highly selective and potent SGLT2 inhibitor [7, 8] approved for use as monotherapy or in combination with other antidiabetic drugs based on the results of the clinical trial program [9–11]. In a pharmacokinetic/pharmacodynamic study involving Japanese patients with T2DM, a single dose of luseogliflozin significantly increased 24-h UGE and significantly decreased fasting blood glucose and 2-h postprandial plasma glucose in patients with normal renal function, mildly reduced renal function, or moderately reduced renal function, but not in patients with severely reduced renal function [12]. Similar findings have been reported for other SGLT2 inhibitors in pharmacokinetic/pharmacodynamic studies and longer term studies [6].

To our knowledge, however, no studies have investigated the relationship between reduced renal function and daily glucose variability in patients treated with a SGLT2 inhibitor. Therefore, to investigate the potential impact of reduced renal function on 24-h glucose variability in patients treated with an SGLT2 inhibitor, we performed a subanalysis of our previously reported study in which patients were treated with luseogliflozin or placebo for 7 days in a crossover manner, with 24-h continuous glucose monitoring (CGM) starting on day 7 of treatment [13].

METHODS

Ethics Statement

As previously described [13], the study was conducted in accordance with the ethical

standards of the Helsinki Declaration of 1975, as revised in 2013, the Japanese Pharmaceutical Affairs Law, Good Clinical Practice, and institutional and national recommendations on clinical trials. The study protocol was approved by the Institutional Review Board of each institute. Written informed consent was obtained from all patients before enrolment. This study was registered with the Japan Pharmaceutical Information Center (identifier: JapicCTI-142548).

Study Design

In this double-blind, placebo-controlled, crossover study, 37 Japanese patients with T2DM inadequately controlled with diet and exercise (HbA1c 7.0–10.0%) whose estimated glomerular filtration rate (eGFR) was ≥45 mL/min/1.73 m^2 were randomized into two groups in which patients first received luseogliflozin then placebo, or vice versa, for 7 days each. Each treatment period was separated by a washout period of 7–14 days. Patients were hospitalized on day 7 and consumed a standardized meal (536 kcal, with approximately 20% protein, 25% fat, and 55% carbohydrate) at breakfast, lunch, and dinner. Twenty-four-hour CGM was started on day 7. Because the data for one patient who left a relatively large amount of the standardized meal at breakfast and two patients who did not complete the 24-h CGM were excluded from this subanalysis, 34 patients were divided into three groups according to their baseline eGFR: normal (≥90 mL/min/1.73 m^2; $n = 13$), normal-to-mildly reduced renal function (≥75 to <90 mL/min/1.73 m^2; $n = 12$), or mild-to-moderately reduced renal function (<75 mL/min/1.73 m^2; $n = 9$). We chose the cutoff value of 75 mL/min/1.73 m^2 because this represents an intermediate value in stage 2 chronic kidney disease (defined as eGFR of ≥60 to <90 mL/min/1.73 m^2) and provided similar numbers of patients in each group. To evaluate the difference between groups of patients in the difference between luseogliflozin and placebo, one-way analysis of variance (ANOVA) were used to analyze the normally distributed variables, and Kruskal–Wallis test were used to analyze the non-normally distributed variables.

Data Analysis

The primary endpoints of the original study were indices derived from CGM. Other efficacy endpoints were pharmacodynamic variables, including serum insulin concentrations, plasma glucagon concentrations, and urinary glucose concentrations (pooled urine and 24-h urine samples). The following variables were calculated using the CGM data: 24-h mean glucose, area under the curve (AUC), peak blood glucose concentration, time to peak blood glucose concentration, and blood glucose concentration in preprandial or fasting periods. The glucose concentration–time curves were analyzed for the following periods: 0–24 h, after breakfast (0–5 h), after lunch (5–11 h), after dinner (11–15 h), and the sleeping period (15–24 h). Pharmacodynamic variables included the AUC and the maximum concentration (C_{max}) for serum insulin and plasma glucagon. Cumulative UGE was also calculated.

All statistical analyses were performed using SAS software (version 9.2; SAS Institute Inc., Cary, NC, USA). Mixed-effects models were used to analyze normally distributed variables, after visual inspection of the histogram for each variable. The mixed-effects models included treatment, sequence and period as fixed effects, and patient as a random effect. The

least-squares mean differences between luseogliflozin and placebo with 95% confidence intervals (95% CI) were estimated for each variable in the mixed-effects models. Non-normally distributed variables were analyzed using Wilcoxon signed-rank test and the median and the interquartile range of differences between luseogliflozin and placebo were calculated.

To evaluate the difference between groups in the difference between luseogliflozin and placebo, ANOVA were used to analyze the normally distributed variables, and Kruskal–Wallis test were used to analyze the non-normally distributed variables.

RESULTS

The demographic and baseline characteristics of the patients of each group are shown in Table 1. Although glucose-related variables tended to be lower in the mild–moderate group, there were no significant differences between groups.

The variations in 24-h glucose concentrations measured by CGM and the UGE rates on day 7 of treatment with luseogliflozin and placebo are shown in Fig. 1. The 24-h glucose variables derived from CGM are shown in Table 2 and the pharmacodynamic variables are shown in Table 3.

Although glucose variability was consistently lower with luseogliflozin than with placebo in the normal and normal–mild groups, glucose variability was not consistently lower with luseogliflozin than with placebo in the mild–moderate group, because of the smaller change in postprandial glucose concentrations in this group.

The mean 24-h glucose was lower with luseogliflozin than with placebo in all three groups. However, the placebo-subtracted change in the mean 24-h glucose was smaller in the mild–moderate group than in the normal and normal–mild groups. The placebo-subtracted change in mean 24-h glucose was therefore significantly different between groups ($P = 0.023$, ANOVA).

The $AUC_{0–24\ h}$ for glycemic variability was smaller with luseogliflozin than with placebo in all three groups. However, the placebo-subtracted change in the $AUC_{0–24\ h}$ for glycemic variability was smaller in the mild–moderate group than in the normal and normal–mild groups. The placebo-subtracted change in the $AUC_{0–24\ h}$ for glycemic variability was significantly different between groups ($P = 0.023$, ANOVA). The AUCs for glycemic variability after each meal (i.e., $AUC_{0–5\ h}$, $AUC_{5–11\ h}$, and $AUC_{11–15\ h}$) and during the sleeping period ($AUC_{15–24\ h}$) were also smaller with luseogliflozin than with placebo in all three groups. The placebo-subtracted AUCs for glycemic variability were significantly different between groups at breakfast and lunch ($P = 0.006$ and $P = 0.026$, respectively, ANOVA).

The peak glucose concentrations throughout the day and after each meal were significantly lower with luseogliflozin than with placebo in the normal and normal–mild groups, but not in the mild–moderate group. The placebo-subtracted difference in the peak glucose concentration was significantly different between groups after breakfast ($P = 0.047$, ANOVA), but not at the other measurement times.

The fasting glucose concentrations (i.e., glucose concentration measured before each meal and in the sleeping period) were consistently lower with luseogliflozin than with placebo in all three groups. Furthermore, the placebo-subtracted changes in the fasting

Table 1 Patient characteristics at baseline

Characteristics	Mild–moderate group	Normal–mild group	Normal group	*P* value[a]
n	9	12	13	
Age (years)	64.0 ± 7.7	62.8 ± 9.3	57.9 ± 7.8	0.194
Body weight (kg)	62.86 ± 13.91	67.93 ± 15.99	65.32 ± 11.88	0.713
BMI (kg/m^2)	25.25 ± 4.36	24.73 ± 3.81	24.16 ± 3.13	0.794
Disease duration (years)	6.1 ± 3.4	8.1 ± 4.9	7.2 ± 4.1	0.576
HbA1c (%)	7.43 ± 0.68	7.90 ± 0.77	7.90 ± 0.77	0.290
FPG (mg/dL)	148.8 ± 29.5	165.5 ± 27.4	158.8 ± 20.4	0.344
Glycosylated albumin (%)	21.18 ± 4.92	23.16 ± 3.16	21.08 ± 2.98	0.308
Serum insulin (μU/mL)	8.528 ± 3.284	8.349 ± 5.563	7.779 ± 4.430	0.921
Plasma glucagon (pg/mL)	84.4 ± 12.9	90.8 ± 40.7	82.8 ± 27.7	0.795
eGFR (mL/min/1.73 m^2)	66.2 ± 5.5	82.7 ± 3.9	100.5 ± 8.4	<0.001
SBP (mmHg)	120.3 ± 14.7	133.1 ± 13.1	122.4 ± 11.6	0.058
DBP (mmHg)	75.3 ± 11.3	79.8 ± 9.4	74.4 ± 6.3	0.294
Urinary albumin corrected for urinary creatinine (mg/g Cr)	47.79 ± 52.29	30.47 ± 27.16	11.35 ± 9.80	0.040

Data are mean ± standard deviation. The differences between groups were analyzed by one-way ANOVA
Glucose: 1 mg/dL = 0.0556 mmol/L
Insulin: 1 μU/mL = 6.945 pmol/L
Glucagon: 1 pg/mL = 1 ng/L
BMI body mass index, *DBP* diastolic blood pressure, *eGFR* estimated glomerular filtration rate, *FPG* fasting plasma glucose, *HbA1c* hemoglobin A1c, *SBP* systolic blood pressure
[a] Between-group difference

glucose concentrations were not significantly different between groups.

The lowest glucose concentration from 0 to 24 h was lower with luseogliflozin than with placebo in all groups. The placebo-subtracted change in the lowest glucose concentration was not significantly different between groups.

Luseogliflozin significantly increased the cumulative UGE compared with placebo in all of the periods in all three groups (all $P < 0.05$). However, the placebo-subtracted changes in the cumulative UGE were smaller in the mild–moderate group than in the normal and normal–mild groups, and these differences were statistically significant between groups for all measurement times except after dinner (throughout the day: $P = 0.007$; after breakfast: $P = 0.037$; after lunch: $P = 0.007$; after dinner: $P = 0.198$; sleeping period: $P = 0.050$, ANOVA).

The serum insulin and plasma glucagon levels on day 7 in each treatment period are shown in Fig. 2. The serum insulin concentrations were consistently lower throughout the day with luseogliflozin than with placebo. The AUCs for serum insulin after each meal, during the sleeping period, and from 0 to 24 h were also smaller with luseogliflozin than with placebo in all three groups. The plasma glucagon concentrations were higher throughout the 24-h measurement period with

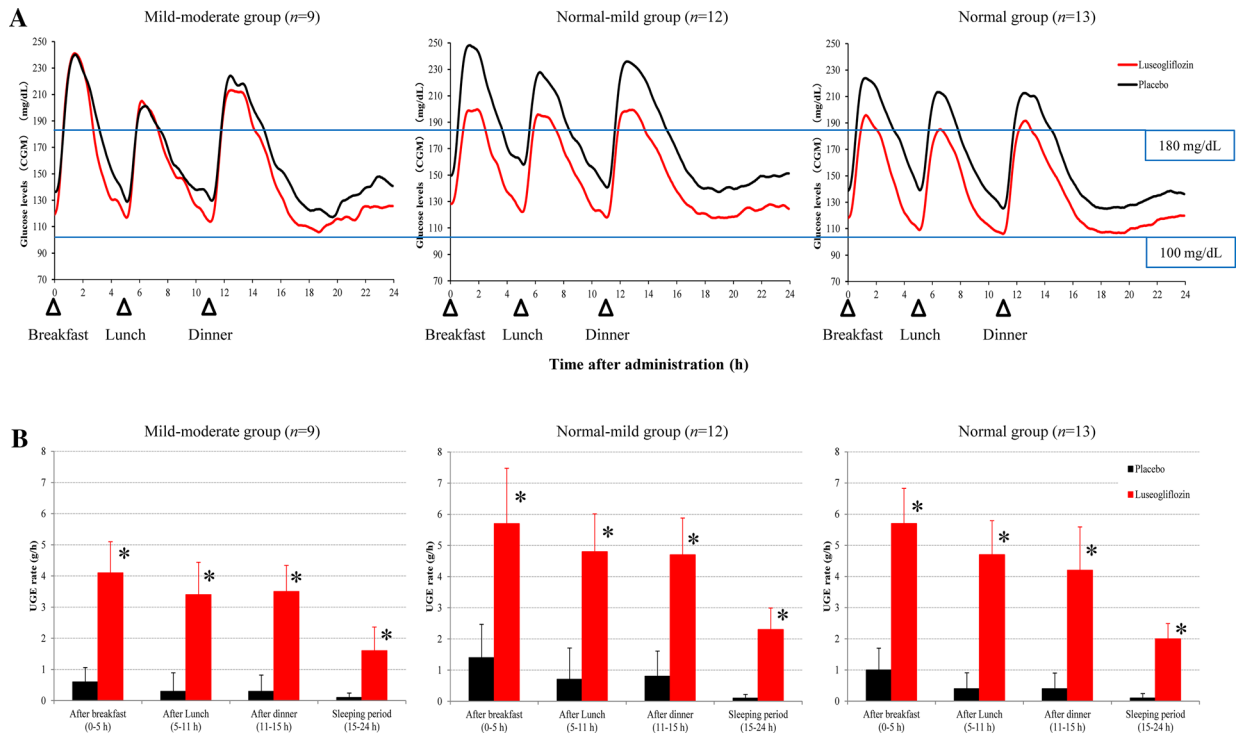

Fig. 1 **a** Twenty-four-hour glucose concentrations measured by continuous glucose monitoring (1 mg/dL = 0.0556 mmol/L). Values are presented as the mean (*error bars* were omitted for clarity). **b** Urinary glucose excretion rate. Values are as the mean + standard deviation. $^{*}P < 0.05$ for luseogliflozin vs. placebo

luseogliflozin than with placebo, and the AUCs for plasma glucagon were higher with luseogliflozin than with placebo in almost all period in all groups. The placebo-subtracted differences in serum insulin- and plasma glucose-related variables were not significantly different between groups.

DISCUSSION

In this post hoc subanalysis, we investigated the impact of renal function decline on the glucose-lowering effects of luseogliflozin, including 24-h glucose variability, as well as pharmacodynamic variables. For the purpose of this subanalysis, we divided the patients into three groups based on their baseline eGFR: normal renal function, normal-to-mildly reduced renal function, and mild-to-moderately reduced renal function.

There were no significant differences in the demographic and baseline characteristics of between groups of patients, with the exceptions of eGFR and urinary albumin corrected for urinary creatinine.

We noted some differences in the variables derived from 24-h CGM among the three groups of patients. Although luseogliflozin decreased the fasting glucose concentrations (i.e., before each meal and in the sleeping period) in all three groups, it did not significantly reduce the postprandial glucose concentrations relative to placebo in the mild–moderate group. Furthermore, consistent with our original findings [13], luseogliflozin significantly increased the cumulative UGE

Table 2 Glucose variables derived from 24-h continuous glucose monitoring

Variables	Mild-moderate group ($n = 9$)			Normal–mild group ($n = 12$)		
	Placebo	Luseogliflozin	Difference (vs. placebo)	Placebo	Luseogliflozin	Difference (vs. placebo)
Normally distributed variables						
24-h mean glucose concentration (mg/dL)	162.06 (124.55, 199.57)	150.52 (113.01, 188.03)	−11.53 (−23.93, 0.86)	177.47 (159.93, 195.02)	149.19 (131.64, 166.74)	−28.28* (−39.35, −17.22)
SD over 24 h (mg/dL)	38.25 (27.11, 49.39)	42.42 (31.28, 53.57)	4.18 (−4.42, 12.78)	37.63 (31.39, 43.86)	32.85 (26.61, 39.08)	−4.78 (−10.79, 1.24)
AUC for glycemic variability (mg/dL h)						
Throughout the day (0–24 h)	3878.2 (2979.6, 4776.9)	3602.7 (2704.1, 4501.4)	−275.5 (−572.1, 21.2)	4247.5 (3826.9, 4668.1)	3570.5 (3149.9, 3991.1)	−677.0* (−942.3, −411.7)
After breakfast (0–5 h)	925.0 (710.4, 1139.5)	869.6 (655.1, 1084.2)	−55.3 (−137.7, 27.0)	1000.3 (894.2, 1106.4)	806.7 (700.6, 912.8)	−193.6* (−256.3, −130.9)
After lunch (5–11 h)	965.8 (684.5, 1247.1)	929.4 (648.1, 1210.7)	−36.4 (−123.9, 51.0)	1095.6 (957.3, 1233.9)	938.7 (800.3, 1077.0)	−157.0* (−254.4, −59.6)
After dinner (11–15 h)	772.6 (579.1, 966.1)	738.1 (544.6, 931.6)	−34.5 (−131.7, 62.8)	828.8 (739.9, 917.7)	702.6 (613.7, 791.5)	−126.2* (−190.8, −61.5)
Sleeping period (15–24 h)	1214.9 (990.4, 1439.3)	1065.6 (841.2, 1290.1)	−149.3* (−251.7, −46.8)	1322.8 (1208.2, 1437.5)	1122.5 (1007.8, 1237.2)	−200.3* (−282.6, −118.1)
Peak glucose concentration (mg/dL)						
Throughout the day (0–24 h)	251.2 (198.5, 303.8)	252.6 (200.0, 305.2)	1.5 (−25.5, 28.4)	256.0 (231.5, 280.6)	217.9 (193.4, 242.5)	−38.1* (−59.6, −16.6)
After breakfast (0–5 h)	245.3 (197.3, 293.4)	245.2 (197.2, 293.3)	−0.1 (−23.2, 23.0)	254.1 (230.1, 278.1)	208.6 (184.6, 232.6)	−45.5* (−69.4, −21.7)
After lunch (5–11 h)	209.3 (162.6, 255.9)	207.4 (160.8, 254.1)	−1.8 (−17.7, 14.1)	230.4 (201.6, 259.3)	199.8 (170.9, 228.7)	−30.7* (−54.2, −7.2)

Table 2 continued

Variables	Mild-moderate group ($n = 9$)			Normal–mild group ($n = 12$)		
	Placebo	Luseogliflozin	Difference (vs. placebo)	Placebo	Luseogliflozin	Difference (vs. placebo)
After dinner (11–15 h)	227.8 (176.9, 278.8)	221.0 (170.1, 272.0)	−6.8 (−38.2, 24.6)	240.3 (215.2, 265.5)	205.2 (180.1, 230.3)	−35.1* (−54.5, −15.8)
Lowest glucose concentration (mg/dL)	104.0 (82.4, 125.7)	91.1 (69.5, 112.7)	−12.9 (−32.8, 7.0)	121.0 (108.1, 133.9)	97.9 (85.0, 110.8)	−23.1* (−34.1, −12.1)
Time to peak glucose concentration (h)						
After breakfast	1.73 (1.23, 2.23)	1.60 (1.10, 2.10)	−0.13 (−0.90, 0.64)	1.71 (1.42, 1.99)	1.68 (1.40, 1.97)	−0.02 (−0.41, 0.36)
After lunch	1.41 (1.12, 1.70)	1.24 (0.95, 1.53)	−0.17 (−0.47, 0.13)	1.49 (1.18, 1.79)	1.55 (1.24, 1.85)	0.06 (−0.38, 0.50)
After dinner	1.66 (1.34, 1.99)	1.68 (1.35, 2.01)	0.02 (−0.44, 0.48)	1.71 (1.43, 1.99)	1.59 (1.31, 1.87)	−0.12 (−0.48, 0.24)
Glucose concentration in the preprandial or fasting period (mg/dL)						
Before breakfast (0 h)	136.1 (111.5, 160.6)	118.8 (94.3, 143.3)	−17.3 (−35.2, 0.7)	147.2 (133.7, 160.6)	128.9 (115.4, 142.4)	−18.3* (−30.6, −6.0)
Before lunch (5 h)	129.7 (86.7, 172.7)	117.1 (74.0, 160.1)	−12.7 (−36.4, 11.0)	158.9 (139.1, 178.8)	122.5 (102.7, 142.4)	−36.4* (−51.0, −21.9)
Before dinner (11 h)	130.0 (92.8, 167.2)	113.2 (76.0, 150.4)	−16.8 (−39.1, 5.5)	138.9 (123.5, 154.3)	117.8 (102.4, 133.3)	−21.1* (−35.5, −6.7)
Sleeping period (18 h)	122.6 (99.6, 145.5)	107.7 (84.8, 130.6)	−14.9 (−32.7, 2.9)	139.5 (125.0, 154.0)	120.5 (106.0, 135.0)	−19.0* (−29.3, −8.7)
Mean amplitude of glycemic excursions (mg/dL)	93.93 (70.72, 117.14)	104.71 (81.50, 127.92)	10.78 (−11.84, 33.40)	95.08 (79.65, 110.51)	83.05 (67.61, 98.48)	−12.03 (−32.21, 8.14)
Non-normally distributed variables						
Proportion of time over 24 h with glucose levels in the following ranges						
≥181 mg/dL (%)	19.1 (7.3, 50.3)	18.1 (3.5, 39.2)	−5.2 (−11.1, 2.4)	44.3 (21.7, 55.0)	28.0 (7.5, 33.5)	−19.4* (−26.0, −12.2)

Table 2 continued

Variables	Mild-moderate group ($n = 9$)			Normal–mild group ($n = 12$)		
	Placebo	Luseogliflozin	Difference (vs. placebo)	Placebo	Luseogliflozin	Difference (vs. placebo)
≥70 to ≤180 mg/dL (%)	80.9 (49.7, 92.7)	81.9 (60.8, 91.3)	5.2 (−2.4, 11.1)	55.7 (45.0, 78.3)	72.1 (66.5, 91.7)	19.4* (11.3, 26.0)
<70 mg/dL (%)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)
AUC for glucose levels ≥181 mg/dL (mg/dL h)	102 (23, 494)	157 (4, 373)	−19 (−100, 67)	389 (135, 760)	150 (17, 218)	−185* (−437, −63)
AOC for glucose levels <70 mg/dL (mg/dL h)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)
M value	7.6 (3.5, 24.0)	8.6 (3.4, 17.3)	−1.4 (−4.7, 2.7)	21.6 (9.4, 34.6)	11.3 (4.1, 13.7)	−10.6* (−16.4, −3.9)

Variables	Normal group ($n = 13$)			*P* value (between-group difference)
	Placebo	Luseogliflozin	Difference (vs. placebo)	
Normally distributed variables				
24-h mean glucose concentration (mg/dL)	162.47 (146.03, 178.91)	138.08 (121.63, 154.52)	−24.39* (−32.53, −16.26)	0.059
SD over 24 h (mg/dL)	34.87 (27.55, 42.20)	31.94 (24.61, 39.27)	−2.93 (−9.61, 3.74)	0.156
AUC for glycemic variability (mg/dL h)				
Throughout the day (0–24 h)	3888.3 (3494.5, 4282.1)	3304.2 (2910.4, 3698.1)	−584.0* (−779.1, −388.9)	0.058
After breakfast (0–5 h)	933.4 (826.8, 1039.9)	768.8 (662.2, 875.3)	−164.6* (−216.9, −112.3)	0.009
After lunch (5–11 h)	1009.5 (898.3, 1120.8)	849.5 (738.2, 960.8)	−160.0* (−232.5, −87.5)	0.057
After dinner (11–15 h)	751.5 (667.6, 835.3)	656.6 (572.8, 740.4)	−94.9* (−140.1, −49.6)	0.140
Sleeping period (15–24 h)	1193.9 (1079.2, 1308.6)	1029.4 (914.6, 1144.1)	−164.5* (−243.1, −85.9)	0.599
Peak glucose concentration (mg/dL)				
Throughout the day (0–24 h)	237.9 (212.3, 263.5)	211.0 (185.4, 236.5)	−26.9* (−46.9, −6.9)	0.033
After breakfast (0–5 h)	232.2 (206.5, 257.9)	204.6 (178.9, 230.3)	−27.6* (−48.6, −6.6)	0.020
After lunch (5–11 h)	217.2 (190.1, 244.4)	190.8 (163.6, 217.9)	−26.4* (−47.7, −5.2)	0.109

Table 2 continued

Variables	Normal group (n = 13)			P value (between-group difference)
	Placebo	Luseogliflozin	Difference (vs. placebo)	
After dinner (11–15 h)	219.6 (193.2, 246.1)	196.0 (169.5, 222.4)	−23.7* (−41.8, −5.6)	0.174
Lowest glucose concentration (mg/dL)	115.4 (103.2, 127.6)	93.4 (81.2, 105.5)	−22.0* (−32.7, −11.4)	0.342
Time to peak glucose concentration (h)				
After breakfast	1.46 (1.10, 1.82)	1.45 (1.09, 1.81)	−0.01 (−0.34, 0.32)	0.917
After lunch	1.48 (1.23, 1.73)	1.50 (1.26, 1.75)	0.03 (−0.24, 0.29)	0.734
After dinner	1.74 (1.46, 2.01)	1.37 (1.10, 1.65)	−0.36* (−0.64, −0.09)	0.336
Glucose concentration in the preprandial or fasting period (mg/dL)				
Before breakfast (0 h)	138.1 (125.5, 150.7)	118.8 (106.2, 131.3)	−19.3* (−25.5, −13.2)	0.918
Before lunch (5 h)	140.4 (123.3, 157.5)	109.5 (92.4, 126.6)	−30.9* (−44.2, −17.6)	0.070
Before dinner (11 h)	125.1 (112.5, 137.6)	106.2 (93.6, 118.8)	−18.9* (−31.0, −6.8)	0.835
Sleeping period (18 h)	125.0 (111.6, 138.5)	107.5 (94.1, 120.9)	−17.5* (−28.7, −6.4)	0.784
Mean amplitude of glycemic excursions (mg/dL)	88.03 (68.24, 107.82)	84.91 (65.13, 104.70)	−3.11 (−21.59, 15.36)	0.285
Non-normally distributed variables				
Proportion of time over 24 h with glucose levels in the following ranges				
≥181 mg/dL (%)	22.6 (16.7, 47.6)	10.4 (1.7, 21.5)	−13.9* (−20.1, −6.3)	0.079
≥70 to ≤180 mg/dL (%)	77.4 (52.4, 83.3)	84.4 (78.5, 98.3)	13.2* (3.5, 20.1)	0.077
<70 mg/dL (%)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0.856
AUC for glucose levels ≥181 mg/dL (mg/dL h)	74 (38, 462)	37 (1, 136)	−74* (−279, −7)	0.108
AOC for glucose levels <70 mg/dL (mg/dL h)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0.856

Table 2 continued

Variables	Normal group (n = 13)			P value (between-group difference)
	Placebo	Luseogliflozin	Difference (vs. placebo)	
M value	7.8 (6.2, 26.5)	5.6 (3.1, 9.0)	−5.4* (−10.7, −2.1)	0.077

Values are derived from 24-h continuous glucose monitoring. Normally distributed variables are presented as the least-squares mean (95% confidence interval) and the differences between luseogliflozin and placebo were analyzed using a mixed-effects model, which included treatment, sequence and period as fixed effects and patients as a random effect. Non-normally distributed variables are presented as the median (interquartile range), and the differences between luseogliflozin and placebo were determined using Wilcoxon signed-rank test. To evaluate the difference between groups in the difference between luseogliflozin and placebo, ANOVA were used to analyze the normally distributed variables, and Kruskal–Wallis test were used to analyze the non-normally distributed variables. Data are shown for the pharmacodynamic analysis set

Glucose : 1 mg/dL = 0.0556 mmol/L

AOC area over the curve, *AUC* area under the curve, *SD* standard deviation around the mean glucose concentration

* $P < 0.05$ for luseogliflozin vs. placebo

Table 3 Pharmacodynamic variables

Variables	Mild–moderate group ($n = 9$)			Normal–mild group ($n = 12$)		
	Placebo	Luseogliflozin	Difference (vs. placebo)	Placebo	Luseogliflozin	Difference (vs. placebo)
Normally distributed variables						
Cumulative UGE (g)						
Throughout the day (0–24 h)	6.3 (−5.5, 18.0)	68.5 (56.8, 80.2)	62.2* (51.2, 73.3)	15.2 (2.8, 27.5)	97.6 (85.3, 110.0)	82.5* (73.4, 91.5)
After breakfast (0–5 h)	2.9 (−0.2, 6.0)	20.7 (17.6, 23.8)	17.8* (15.2, 20.3)	6.9 (2.3, 11.4)	28.6 (24.0, 33.1)	21.7* (17.6, 25.7)
After lunch (5–11 h)	1.5 (−2.5, 5.6)	20.2 (16.2, 24.3)	18.7* (15.9, 21.5)	4.4 (0.1, 8.7)	29.0 (24.7, 33.3)	24.7* (21.5, 27.8)
After dinner (11–15 h)	1.3 (−1.0, 3.5)	14.0 (11.7, 16.2)	12.7* (11.1, 14.3)	3.4 (0.8, 6.0)	18.9 (16.3, 21.5)	15.5* (12.9, 18.0)
Sleeping period (15–24 h)	0.5 (−3.3, 4.3)	14.1 (10.3, 17.9)	13.6* (8.3, 18.9)	0.7 (−2.1, 3.6)	20.6 (17.7, 23.4)	19.8* (15.9, 23.7)
Non-normally distributed variables						
AUC for serum insulin (μU/mL h)						
Throughout the day (0–24 h)	476 (410, 859)	473 (393, 641)	−64 (−152, −35)	429 (306, 622)	340 (263, 451)	−71* (−187, −32)
After breakfast (0–5 h)	159 (122, 330)	143 (109, 190)	-16 (−86, −10)	115 (88, 198)	101 (67, 142)	−19* (−38, −12)
After lunch (5–11 h)	150 (99, 208)	118 (107, 137)	−19 (−31, 19)	119 (80, 167)	84 (63, 135)	−21* (−38, −8.3)
After dinner (11–15 h)	97 (91, 135)	93 (72, 114)	−19 (−27, −16)	91 (55, 124)	77 (47, 82)	-20* (−42, −11)
Sleeping period (15–24 h)	125 (94, 195)	115 (83, 148)	−24 (−29, 4)	105 (74, 135)	86 (65, 110)	−15 (−58, 5)
C_{max} for serum insulin (μU/mL)						
Throughout the day (0–24 h)	47.8 (36.9, 109)	47.6 (31.2, 54.0)	−5.7 (−36.0, −0.2)	34.5 (30.3, 64.0)	30.7 (20.6, 48.4)	−6.0* (−12.7, −2.7)
After breakfast (0–5 h)	47.8 (36.9, 109)	47.6 (31.2, 54.0)	−3.9 (−36.0, −0.2)	33.9 (24.9, 60.4)	29.6 (19.1, 45.1)	−5.6* (−9.9, −3.4)
After lunch (5–11 h)	36.0 (30.0, 57.2)	34.7 (27.1, 38.5)	−4.1 (−6.5, −1.8)	33.3 (20.6, 48.4)	22.0 (16.2, 36.2)	−5.4* (−12.2, −1.4)
After dinner (11–15 h)	35.9 (30.2, 44.9)	29.3 (28.0, 35.9)	−7.7* (−10.5, −3.0)	29.7 (17.7, 42.9)	23.4 (15.9, 28.8)	−4.2* (−13.7, −2.2)
Sleeping period (15–24 h)	20.9 (17.9, 29.0)	20.1 (14.1, 22.0)	−1.9 (−5.5, 1.1)	15.5 (12.3, 24.1)	14.0 (10.0, 17.6)	−1.8 (−10.6, 0.3)

Table 3 continued

Variables	Mild–moderate group ($n = 9$)			Normal–mild group ($n = 12$)		
	Placebo	Luseogliflozin	Difference (vs. placebo)	Placebo	Luseogliflozin	Difference (vs. placebo)
AUC for plasma glucagon (pg/mL h)						
Throughout the day (0–24 h)	2020 (1880, 2350)	2340 (2100, 2630)	270 (40, 450)	2050 (1870, 2350)	2200 (2020, 2550)	115 (−35, 290)
After breakfast (0–5 h)	492 (391, 506)	478 (465, 536)	51 (−8, 91)	458 (404, 546)	480 (449, 546)	20 (−42, 60)
After lunch (5–11 h)	521 (442, 643)	609 (559, 745)	117 (44, 138)	529 (468, 609)	607 (529, 660)	52* (6, 109)
After dinner (11–15 h)	357 (329, 390)	391 (353, 424)	52 (20, 68)	364 (329, 394)	354 (337, 422)	14 (−30, 40)
Sleeping period (15–24 h)	765 (716, 783)	873 (779, 954)	77* (40, 184)	752 (684, 826)	761 (707, 937)	68* (−7, 118)
C_{max} for plasma glucagon (pg/mL)						
Throughout the day (0–24 h)	105 (101, 126)	118 (108, 136)	19 (4, 24)	114 (103, 129)	116 (104, 127)	−2 (−17, 10)
After breakfast (0–5 h)	105 (92, 120)	106 (99, 131)	13 (5, 14)	114 (92, 129)	116 (98, 127)	6 (−18, 10)
After lunch (5–11 h)	103 (92, 119)	118 (108, 136)	16 (−9, 41)	94 (88, 112)	106 (101, 125)	14 (−9, 16)
After dinner (11–15 h)	103 (101, 126)	118 (105, 136)	12 (4, 19)	101 (93, 108)	106 (97, 119)	2 (−3, 15)
Sleeping period (15–24 h)	88 (87, 95)	99 (91, 118)	4 (−2, 23)	87 (80, 101)	87 (83, 110)	8 (−4, 18)

Variables	Normal group ($n = 13$)			P value (between-group difference)
	Placebo	Luseogliflozin	Difference (vs. placebo)	
Normally distributed variables				
Cumulative UGE (g)				
Throughout the day (0–24 h)	9.5 (1.0, 18.0)	91.6 (83.1, 100.1)	82.1* (72.7, 91.5)	0.007
After breakfast (0–5 h)	4.8 (1.9, 7.7)	28.6 (25.7, 31.5)	23.8* (21.0, 26.6)	0.037
After lunch (5–11 h)	2.4 (−0.7, 5.5)	28.1 (25.0, 31.2)	25.8* (22.6, 29.0)	0.007
After dinner (11–15 h)	1.6 (−0.7, 4.0)	17.0 (14.6, 19.3)	15.3* (12.6, 18.1)	0.198
Sleeping period (15–24 h)	0.5 (−1.4, 2.4)	17.9 (16.0, 19.8)	17.4* (14.7, 20.1)	0.050
Non-normally distributed variables				

Table 3 continued

Variables	Normal group ($n = 13$)			*P* value (between-group difference)
	Placebo	Luseogliflozin	Difference (vs. placebo)	
AUC for serum insulin (μU/mL h)				
Throughout the day (0–24 h)	382 (276, 633)	323 (232, 484)	−78* (−122, −44)	0.911
After breakfast (0–5 h)	117 (69, 193)	94 (63, 126)	−28* (−55, −18)	0.822
After lunch (5–11 h)	104 (79, 171)	84 (71, 152)	−21* (−45, −13)	0.550
After dinner (11–15 h)	77 (50, 125)	70 (45, 102)	−10* (−15, −4)	0.144
Sleeping period (15–24 h)	83 (69, 136)	75 (60, 116)	−8 (−22, 3)	0.592
C_{max} for serum insulin (μU/mL)				
Throughout the day (0–24 h)	37.7 (25.6, 61.8)	31.9 (21.8, 37.7)	−7.7* (−12.2, −2.9)	0.995
After breakfast (0–5 h)	37.7 (20.3, 61.8)	31.9 (18.0, 37.7)	−5.8* (−12.2, −2.1)	0.920
After lunch (5–11 h)	28.7 (18.0, 43.6)	20.9 (16.7, 36.4)	−7.5* (−10.6, −2.7)	0.707
After dinner (11–15 h)	28.1 (16.8, 39.5)	25.6 (15.6, 30.0)	−3.4* (−10.3, −1.7)	0.572
Sleeping period (15–24 h)	12.9 (11.6, 21.4)	13.2 (9.8, 20.0)	0.1 (−3.1, 1.2)	0.424
AUC for plasma glucagon (pg/mL h)				
Throughout the day (0–24 h)	2000 (1800, 2170)	2070 (1800, 2530)	50 (0, 150)	0.426
After breakfast (0–5 h)	434 (403, 530)	450 (351, 572)	−22 (−62, 49)	0.292
After lunch (5–11 h)	483 (446, 531)	511 (456, 640)	32 (−24, 73)	0.411
After dinner (11–15 h)	340 (298, 373)	349 (298, 398)	9 (−9, 52)	0.339
Sleeping period (15–24 h)	720 (626, 738)	770 (644, 878)	49 (27, 90)	0.477
C_{max} for plasma glucagon (pg/mL)				
Throughout the day (0–24 h)	100 (95, 119)	98 (91, 140)	1 (−12, 16)	0.433
After breakfast (0–5 h)	100 (92, 118)	98 (83, 126)	−10 (−19, 14)	0.278

Table 3 continued

Variables	Normal group ($n = 13$)			P value (between-group difference)
	Placebo	Luseogliflozin	Difference (vs. placebo)	
After lunch (5–11 h)	92 (79, 102)	97 (83, 129)	7 (−2, 19)	0.737
After dinner (11–15 h)	90 (84, 107)	96 (80, 120)	4 (−6, 11)	0.640
Sleeping period (15–24 h)	83 (82, 93)	94 (74, 103)	2 (0, 14)	0.847

Laboratory tests were performed using blood samples obtained over 24-h. Normally distributed variables are presented as the least-squares mean (95% confidence interval) and the differences between luseogliflozin and placebo were analyzed using a mixed-effects model, which included treatment, sequence and period as fixed effects and patients as a random effect. Non-normally distributed variables are presented as the median (interquartile range), and the differences between luseogliflozin and placebo were determined using Wilcoxon signed-rank test. To evaluate the difference between groups in the difference between luseogliflozin and placebo, ANOVA were used to analyze the normally distributed variables, and Kruskal–Wallis test were used to analyze the non-normally distributed variables. Data are shown for the pharmacodynamic analysis set

Glucose: 1 g = 0.00556 mol

AUC area under the curve, C_{max} maximum concentration, *UGE* urinary glucose excretion

* $P < 0.05$ for luseogliflozin vs. placebo

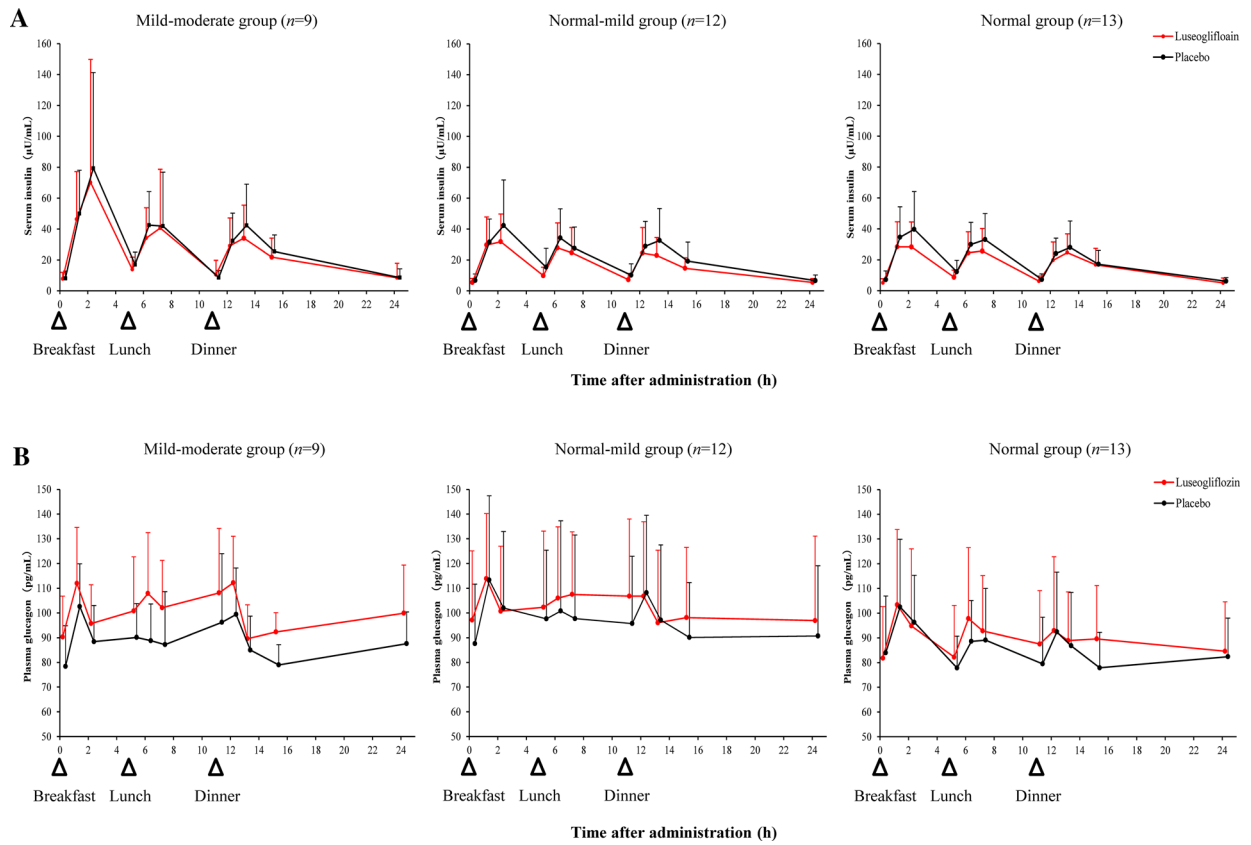

Fig. 2 **a** Twenty-four-hour serum insulin levels after 7 days of once-daily administration of 2.5 mg luseogliflozin or placebo. Values are means + standard deviation. **b** Twenty-four-hour plasma glucagon levels after 7 days of once-daily administration of 2.5 mg luseogliflozin or placebo. Values are mean + standard deviation

compared with placebo in each of the three groups. However, the placebo-subtracted change in UGE was slightly smaller in the mild–moderate group than in the other two groups. This result is consistent with those of a previous study showing that UGE is attenuated in patients with renal impairment, owing to a reduction in glucose filtered through the glomeruli [12]. It seems feasible that luseogliflozin could not suppress the sharp glucose fluctuations in the postprandial periods in the mild–moderate group owing to the reduced amount of glucose that can be filtered through the glomerulus in individuals with reduced renal function. In normal conditions, the kidney can filter about 180 g of glucose per day, and this amount is likely to be reduced in individuals with reduced renal function. In fasting conditions (i.e., before each meal and overnight), the amount of glucose filtered through the kidney is likely to be relatively stable and manageable in all patients, albeit at a lower level in patients with reduced renal function than in patients with normal renal function. However, in patients with reduced renal function, the kidney is less able to respond to sudden increases in glucose concentrations, especially after a meal, limiting the impact of SGLT2 inhibitors on UGE. Nevertheless, the placebo-subtracted change in fasting glucose was smaller in the mild–moderate group than in the other

groups, probably because of the lower baseline value in this group, being closer to the renal threshold for glucose reabsorption in the kidney [14]. The fasting glucose concentrations with luseogliflozin were similar between groups, which might be related to the renal threshold for glucose and the low risk of hypoglycemia in patients treated with SGLT2 inhibitors.

Luseogliflozin also decreased insulin concentrations and decreased the AUC of insulin in all of the groups. It is possible that these changes were driven by the reductions in circulating glucose concentrations. These findings suggest that luseogliflozin may reduce insulin secretion in patients with normal renal function or mildly reduced renal function. It is also notable that luseogliflozin increased plasma glucagon concentrations throughout the day in all three groups. This effect of luseogliflozin may be due to enhanced gluconeogenesis to prevent excessive reductions in circulating glucose, especially in fasting conditions.

Several pharmacokinetic/pharmacodynamic studies have demonstrated that the effects of SGLT2 inhibitors on UGE and plasma glucose concentrations are attenuated by reduced renal function, especially severely reduced renal function or chronic kidney disease [6, 15–18], consistent with our findings using 24-h CGM. Our results provide further insight into the impact of reduced renal function on the glucose-lowering effects of SGLT2 inhibitors, and that co-administration of a SGLT2 inhibitor with another antidiabetic drug, which improves postprandial glucose, might be useful for the patients with reduced renal function if improvements in glucose concentrations are not observed with monotherapy. It is particularly notable that the effects of luseogliflozin on postprandial glucose concentrations were attenuated in individuals with mild–moderate reductions in renal function relative to the other groups, but the reduction in fasting blood glucose was essentially unaffected by reduced renal function. Therefore, the reduced efficacy of SGLT2 inhibitors on overall glycemic control (i.e., HbA1c) is likely to be driven by the smaller reductions in postprandial glucose fluctuations, a major contributor to overall glycemic variability.

It is also important to consider that reduced renal function may increase systemic exposure to luseogliflozin, as has been demonstrated for dapagliflozin [19]. An increase in exposure may increase the risk of unwanted side effects, and dose adjustments may be necessary in individuals with moderate-to-severely reduced renal function, although this possibility must be evaluated in longer term studies of patients with moderate-to-severely reduced renal function.

Some limitations of this study warrant mention. In particular, because these subanalyses were conducted in a post hoc exploratory manner, the number of patients differed between groups. Accordingly, it will be necessary to conduct prospective studies of larger numbers of patients to examine the impact of reduced renal function on the glucose-lowering effects of luseogliflozin and the implications, if any, on the clinical use of luseogliflozin. In addition, we did not enroll patients with moderate-to-severely reduced renal function. Considering that the changes in glucose-related variables were lower in the mild–moderate group than in the normal and normal–moderate groups, it is possible that moderate-to-severely reduced renal function will attenuate the clinical efficacy of luseogliflozin by reducing UGE and affecting glucose variability. Indeed, in a 24-week randomized, placebo-controlled trial of

Japanese patients with T2DM, ipragliflozin significantly improved glycemic control in patients with mildly reduced renal function but not in patients with moderately reduced renal function [20]. However, it was reported that canagliflozin significantly reduced HbA1c, body weight, and blood pressure among patients with stage 3 chronic kidney disease (defined as eGFR $\geq$30 to <60 mL/min/1.73 m^2) [21]. Therefore, it will be necessary to evaluate the efficacy of luseogliflozin in patients with moderate-to-severely reduced renal function and in patients with mildly reduced renal function. Finally, patients were only administered luseogliflozin and placebo for 7 days each. Therefore, longer studies are required to examine the clinical relevance of the present results in terms of the changes in HbA1c.

CONCLUSIONS

The results of this post hoc subanalysis indicate that the effects of luseogliflozin on lowering postprandial glucose are attenuated in patients with mild-to-moderately reduced renal function (eGFR <75 mL/min/1.73 m^2). Nevertheless, the improvements in fasting glucose concentrations measured before each meal and during the sleeping period and the reductions in insulin concentrations in patients with mild-to-moderately reduced renal function were similar to those in patients with normal renal function or patients with normal-to-mildly reduced renal function. These findings suggest that luseogliflozin improves fasting glucose concentrations, at least, without increasing the burden on pancreatic β-cells in patients with mild-to-moderately reduced renal function. Furthermore, the results suggest that luseogliflozin can be used in combination with other oral antidiabetic agents, which improve postprandial glucose, in patients with reduced renal function.

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Compliance with Ethics Guidelines. The study was conducted in accordance with the ethical standards of the Helsinki Declaration of 1975, as revised in 2013, the Japanese

Pharmaceutical Affairs Law, Good Clinical Practice, and institutional and national recommendations on clinical trials. The study protocol was approved by the Institutional Review Board of each institute. Written informed consent was obtained from all patients before enrolment. This study was registered with the Japan Pharmaceutical Information Center (identifier: JapicCTI-142548).

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