Luseogliflozin, an SGLT2 Inhibitor, in Japanese Patients With Mild/Moderate Hepatic Impairment: A Pharmacokinetic Study

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Abstract
This open-label, parallel-group study evaluated the effect of mild and moderate hepatic impairment on the pharmacokinetics of a single dose of luseogliflozin in Japanese subjects. Thirteen subjects with hepatic impairment (mild, n = 8; moderate, n = 5) and 6 healthy subjects received a single 5-mg dose of luseogliflozin. Serial blood sampling over 72 hours and 24-hour urine collection were done for pharmacokinetic analysis of luseogliflozin and its metabolites and to measure pharmacokinetic and pharmacodynamic parameters, respectively. Demographic characteristics were similar at baseline for both groups. Geometric mean ratios of maximum plasma concentration (Cmax) and area under the plasma concentration–time curve from time zero to infinity (AUCinf [90%CI]) of unchanged luseogliflozin were 1.02 (0.790–1.32) and 0.774 (0.580–1.03), respectively, on comparing patients with hepatic impairment with healthy subjects, and 0.939 (0.752–1.17) and 1.00 (0.780–1.28), respectively, in subjects with mild and moderate hepatic impairment. Although mean plasma concentrations of metabolites were slightly higher in patients with hepatic impairment versus healthy subjects, their time-course plasma concentrations were very low compared with those of unchanged luseogliflozin. Single-dose luseogliflozin 5 mg was well tolerated by study participants, indicating luseogliflozin dose adjustment is not necessary in patients with mild and moderate hepatic impairment.

Keywords
luseogliflozin, SGLT2 inhibitor, hepatic impairment, pharmacokinetics, diabetes

The prevalence of type 2 diabetes is higher in patients who have liver diseases, such as nonalcoholic fatty liver disease, alcoholic liver disease, and cirrhosis. Most patients with cirrhosis have diabetes or impaired glucose tolerance.¹

In addition, increased insulin resistance is frequently associated with chronic liver diseases such as hepatitis C virus (HCV)–associated cirrhosis.² Furthermore, a possible association between the use of exogenous insulin or sulfonylureas and the incidence of hepatocellular carcinoma in hepatitis C–positive patients with diabetes mellitus, particularly in noncirrhotic patients, has been reported.³ These findings indicate that caution should be exercised when selecting antidiabetic agents in patients with type 2 diabetes mellitus coexistent with chronic liver diseases.⁴

Luseogliflozin is a highly selective sodium-glucose cotransporter 2 (SGLT2) inhibitor.⁵ The half-maximal inhibitory concentrations (IC₅₀) of luseogliflozin against human SGLT1 and SGLT2 are 2900 and 2.26 nmol/L, respectively. Therefore, luseogliflozin specifically inhibits the activity of SGLT2, with a resultant hypoglycemic effect based on the promotion of urinary glucose excretion (UGE) by the inhibition...
of glucose reabsorption in the renal proximal tubule, as demonstrated in different animal models.\(^6\) Because this mechanism is not insulin dependent, there is a minimal risk of hypoglycemia and weight gain.

In clinical studies, luseogliflozin showed a favorable pharmacokinetic profile in healthy Japanese subjects. Its peak plasma level (C\text{max}) and area under the concentration–time curve (AUC) increased in a dose-dependent manner, and no interaction with food was observed. The mean time to C\text{max} (T\text{max}) ranged from 0.667 to 2.25 hours. The mean plasma half-life of luseogliflozin (T\text{1/2}) after multiple dosing for 7 days ranged from 9.14 to 10.7 hours, and no detectable accumulation of luseogliflozin was observed.\(^7\) In patients with type 2 diabetes, 2 double-blind, placebo-controlled, 12-week dose-ranging studies have been conducted using daily oral doses of 0.5, 2.5, and 5 mg or 1, 2.5, 5, and 10 mg of luseogliflozin, respectively.\(^8,9\) Luseogliflozin reduced levels of glycated hemoglobin (HbA\text{1c}) significantly compared with placebo. Although the dose-response to luseogliflozin was apparent at lower doses, doses of 2.5 mg or greater showed comparable efficacy. In those studies, luseogliflozin treatment was generally well tolerated.

It has been hypothesized that luseogliflozin is mainly metabolized by multiple hepatic enzymes including cytochrome P450 (CYP) isoforms: CYP3A4, CYP3A5, CYP4A11, CYP4F2, CYP4F3B, and UDP-glucuronosyltransferase 1A1 (UGT1A1).\(^9\) As luseogliflozin has a minimal inhibitory effect on CYP,\(^11\) drug interactions because of luseogliflozin-induced CYP inhibition are unlikely. In clinical studies conducted so far, the pharmacokinetics of luseogliflozin have been evaluated mainly in healthy adult or elderly subjects as well as patients with type 2 diabetes and renal impairment.\(^5-14\) However, the pharmacokinetics of luseogliflozin in a special population, such as patients with hepatic impairment, has not been evaluated.

The primary objectives of this study were to evaluate the influence of mild to moderate hepatic impairment on the pharmacokinetics and safety of a single dose of luseogliflozin when compared with healthy subjects. The secondary objective was to evaluate the influence of hepatic function on the amount of UGE, which is a pharmacodynamic parameter for the estimation of treatment efficacy with luseogliflozin in patients with type 2 diabetes mellitus.

**Methods**

**Study Design**

An open-label, parallel-group single-dose study for luseogliflozin was conducted at 5 sites in Japan (AMC Nishiumeda Clinic, Osaka; Japan Community Health Care Organization, Osaka Hospital, Osaka; Kurume Clinical Pharmacology Clinic, Fukuoka; Keikokai Medical Corp., P-One Clinic, Tokyo; and Kitasato University East Hospital, Kanagawa). At the end of a 28-day screening period, subjects were admitted to the study sites 2 days before the administration of luseogliflozin and discharged after completion of the end-of-study evaluation, scheduled 72 hours after dosing. Total hospitalization period was 5 nights. Eligible subjects received a single dose of luseogliflozin 5 mg orally before breakfast with 150 mL of water. Luseogliflozin 5 mg used in this study was considered a maximum clinical dose based on the results of previous clinical studies.\(^8,9\)

**Subjects**

In the hepatic impairment group, patients of either sex aged 20–75 years diagnosed with hepatic cirrhosis and categorized as class A (mild, 5–6 points) or class B (moderate, 7–9 points) per the Child-Pugh classification\(^15,16\) were considered eligible for inclusion in the study. Key exclusion criteria included ascites refractory to treatment, hepatic encephalopathy, class C (severe, 10–15 points) hepatic impairment per the Child-Pugh classification, patients receiving medications for the treatment of type 2 diabetes mellitus, estimated glomerular filtration rate (eGFR) < 45 mL/min/1.73 m\(^2\) at screening, and patients receiving/having received interferon treatment within 24 weeks before screening.

For the group with healthy subjects, male or female subjects 20 years of age or older with their background demographic characteristics (age, sex, and body weight) matched closely to the patients with hepatic impairment were included.

All subjects provided written informed consent to participate in the study. The protocol was approved by the institutional review boards at the respective study centers (AMC Nishiumeda Clinic, Japan Community Health Care Organization Osaka Hospital, Kurume Clinical Pharmacology Clinic, Keikokai Medical Corp., P-One Clinic, and Kitasato University East Hospital). This study was conducted in compliance with the Good Clinical Practice guidelines and the principles of the Declaration of Helsinki.

**Meals**

All subjects received identical meals on days -1 and 1. The total daily calorie was approximately 1800 kcal, consisting of 70% carbohydrates, 20% protein, and 10% fat for all subjects.

On day 1, after overnight fasting, breakfast was served approximately 1 minute after dosing, lunch was served 4 hours after dosing, and dinner was served 12 hours after dosing. On day -1 breakfast was completed within 15 minutes before blood sampling.
Pharmacokinetic Assessments

Blood samples (5 mL) collected in tubes containing sodium heparin were centrifuged immediately after collection at the clinical facility (4°C, 3000 rpm, for 15 minutes) at predose and 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 24, 48, and 72-hours postdose to record plasma concentrations of luseogliflozin and its metabolites (M1, M2, M3, and M17). The 24-hour urine sample was pooled at 4°C, and a 6-mL sample for pharmacokinetic assessment was aliquoted and stored at -70°C until analysis to determine urinary concentrations of unchanged luseogliflozin and its metabolites on days -1 (-24 to 0 hours before administration), 1, 2, and 3 (0-24, 24-48, and 48-72 hours after administration). To determine the concentrations of luseogliflozin and its metabolites, plasma and urinary samples were analyzed at the Nishiwaki Laboratory, JCL Bioassay Corporation using validated high-performance liquid chromatography–tandem mass spectrometry (LC-MS/MS) assays that were conducted after subjecting the samples to solid-phase extraction.

Bioanalytical Method

As previously described,9 for the determination of luseogliflozin, the plasma (150-μL) or urine (50-μL) samples were spiked with luseogliflozin-d5 as an internal standard (IS). Luseogliflozin and the IS were extracted from matrices using an OASIS HLB solid-phase extraction cartridge (30 mg/1 cc, Waters, Milford, Massachusetts). After the eluate was evaporated, the reconstituted sample was injected into an LC-MS/MS system. Chromatographic separation was performed on an Inertsil ODS-3 analytical column (2.1 mm i.d. × 50 mm, 5 μm; GL Sciences, Tokyo, Japan) with 1 mM ammonium acetate and acetonitrile as the mobile phase under a gradient condition at a flow rate of 0.25 mL/min. An API4000 triple quadrupole mass spectrometer with a TurboIonSpray interface in a negative ionization mode was used for MS determination. MRM transitions were m/z 419 → 225 or 295 for M1, m/z 405 → 315 for M2, m/z 449 → 104 for M3, m/z 463 → 315 for M17, m/z 424 → 225 or 300 for M1-d5, m/z 410 → 320 for M2-d5, m/z 454 → 104 for M3-d5, and m/z 468 → 320 for M17-d5. The LLOQ for all metabolites in plasma and urine was 0.1 and 1 ng/mL, respectively. Within- and between-day variability for all metabolites was ±7.4% for plasma and ±8.7% for urine.

Pharmacokinetic parameters, including the observed maximum plasma concentration (Cmax), time to Cmax (tmax), and area under the plasma concentration–time curve from time zero to infinity (AUCinf), were derived by noncompartmental analysis based on plasma concentrations of unchanged luseogliflozin and its metabolites.

Pharmacodynamic Assessments

To measure UGE, 24-hour pooled urine samples were collected on days -1, 1, 2, and 3. Urine samples were maintained at 4°C during sample collection. Urinary glucose concentrations were determined using the Glucoroder-NX (A&TCorp., Yokohama, Japan) at the Mitsubishi Chemical Medience Corporation (Tokyo, Japan).

Safety

Safety assessments included recording of adverse events (AEs), vital signs (body temperature, blood pressure, and pulse rate), physical examination, electrocardiogram (ECG), and routine clinical laboratory testing including liver function tests (alanine transaminase, aspartate transaminase, gamma glutamyl transpeptidase, alkaline phosphatase, lactate dehydrogenase, total protein), renal function tests (creatinine, blood urea nitrogen, uric acid, cystatin C), and blood glucose.

Statistical Analysis

Statistical analyses were performed with SAS System Release 9.2 (SAS Institute, Tokyo, Japan). Pharmacokinetic parameters and urinary excretion
Table 1. Subject Demographics and Baseline Characteristics by Hepatic Function

|               | Normal Hepatic Function | Mild Hepatic Impairment | Moderate Hepatic Impairment |
|---------------|-------------------------|-------------------------|-----------------------------|
| n             | 6                       | 8                       | 5                           |
| Male/female   | 5/1                     | 7/1                     | 4/1                         |
| Age, years    |                         |                         |                             |
| Mean ± SD     | 48.2 ± 9.3              | 57.4 ± 12.2             | 54.8 ± 12.5                 |
| Range         | 40–65                   | 43–75                   | 44–72                       |
| Body weight, kg|                        |                         |                             |
| Mean ± SD     | 65.63 ± 12.4            | 62.84 ± 12.44           | 68.26 ± 9.28                |
| Range         | 49.0–79.3               | 44.7–79.7               | 60.5–82.4                   |
| BMI, kg/m²    |                         |                         |                             |
| Mean ± SD     | 23.67 ± 3.10            | 23.22 ± 3.20            | 23.98 ± 1.49                |
| Range         | 20.3–28.0               | 18.2–27.0               | 22.3–25.8                   |
| Fasting plasma glucose, mg/dL |             |                         |                             |
| Mean ± SD     | 97.0 ± 5.5              | 104.8 ± 17.7            | 99.2 ± 8.1                  |
| Range         | 89–105                  | 91–145                  | 88–107                      |
| Total bilirubin, mg/dL |             |                         |                             |
| Mean ± SD     | 0.78 ± 0.40             | 0.99 ± 0.35             | 1.96 ± 0.74                 |
| Range         | 0.6–1.6                 | 0.5–1.6                 | 1.0–2.7                     |
| Albumin, g/dL |                         |                         |                             |
| Mean ± SD     | 4.32 ± 0.10             | 3.78 ± 0.38             | 3.08 ± 0.18                 |
| Range         | 4.2–4.4                 | 3.3–4.5                 | 2.8–3.2                     |
| Prothrombin time, % |             |                         |                             |
| Mean ± SD     | 101 ± 0                 | 92.5 ± 6.0              | 74.6 ± 8.8                  |
| Range         | 101–101                 | 85–101                  | 66–85                       |
| Ascites       |                         |                         |                             |
| None          | 7                       | 3                       |
| Mild          | 1                       | 2                       |
| Serological test for hepatitis, |       |                         |                             |
| HCV antibody positive | 0            | 4                       | 3                           |
| HBs antigen positive | 0            | 1                       | 0                           |
| None          | 6                       | 3                       | 2                           |

SD, standard deviation; BMI, body mass index; HCV, hepatitis C virus; HBs, hepatitis B surface antigen.

Results

Subject Demographics

In total, 25 subjects (15 patients with hepatic impairment and 10 healthy adult subjects) were screened. Of these, 19 received the study drug (13 patients with hepatic impairment and 6 healthy adult subjects) and completed the study. Data from all patients who enrolled in the study were included in the statistical analyses. Both groups were balanced with regard to baseline and demographic characteristics (age, sex, weight, and body mass index). Total bilirubin was higher in the group of subjects with hepatic impairment compared with healthy subjects. Prothrombin time (%) and albumin were lower in the group of patients with hepatic impairment (Table 1).

Plasma Concentrations of Luseogliflozin and Its Metabolites

The time course of the plasma concentration of luseogliflozin in healthy subjects and patients with mild...
hepatic impairment were similar (Figure 1). In the group of patients with moderate hepatic impairment, the time-course change in the plasma concentration of luseogliflozin was relatively low for 0.5 to 4 hours after the dose; thereafter, plasma concentration changes were similar to those in the other 2 groups.

The time-course plasma concentrations of individual metabolites were very low compared with the plasma concentration of luseogliflozin. The mean plasma concentration of M1 in healthy subjects was higher than that in patients with mild and moderate hepatic impairment, whereas the mean plasma concentration of M2, M3, and M17 in patients with mild hepatic impairment was higher than that in the healthy subjects and in patients with moderate hepatic impairment.

The $C_{\text{max}}$ (mean $\pm$ SD) of luseogliflozin in patients with moderate hepatic impairment was 170 $\pm$ 28.4 ng/mL, which was relatively lower than the $C_{\text{max}}$ in patients with mild hepatic impairment (228 $\pm$ 54.9 ng/mL) and in healthy subjects (228 $\pm$ 80.6 ng/mL). Other pharmacokinetic parameters, including AUC, were similar across the groups (Table 2).

With regard to luseogliflozin metabolites, the $C_{\text{max}}$ and AUC of each metabolite were much lower than those of unchanged luseogliflozin. The mean $C_{\text{max}}$ and AUC of M1 in patients with mild and moderate hepatic impairment were lower than their values in healthy subjects, whereas the mean $C_{\text{max}}$ of the other metabolites (M2, M3, and M17) in patients with mild hepatic impairment was higher than that in healthy subjects or patients with moderate hepatic impairment.

For luseogliflozin, the GMRs of the $C_{\text{max}}$, with the 90% CIs (patients with hepatic impairment/healthy subjects) were 1.02 (0.790–1.32) and 0.774 (0.580–1.03) and those of the AUC$_{\text{inf}}$ were 0.939 (0.752–1.17) and 1.00 (0.780–1.28) in subjects with mild and moderate hepatic impairment, respectively. The $C_{\text{max}}$ in the group of patients with moderate hepatic impairment was 23% lower than that for the group of healthy subjects.

Scatterplots of the $C_{\text{max}}$ and AUC$_{\text{inf}}$ of unchanged luseogliflozin and Child-Pugh classification factors (total bilirubin, albumin, and prothrombin time) indicated the absence of any meaningful correlation between the parameters of hepatic function and the $C_{\text{max}}$ and AUC$_{\text{inf}}$ of luseogliflozin (Figure 2).

**Urinary Excretion Rates of Luseogliflozin and Its Metabolites**

The cumulative urinary excretion rates (mean $\pm$ SD) of unchanged luseogliflozin for 0 to 72 hours were 3.90% $\pm$ 0.41%, 3.33% $\pm$ 1.42%, and 5.45% $\pm$ 1.33% of the dose in the groups of healthy subjects, patients with mild hepatic impairment, and patients with moderate hepatic impairment, respectively. Moreover, the urinary excretion and cumulative urinary excretion rates of metabolites (M1, M2, M3, and M17) as well as their time-course changes were similar for the study groups.

**Pharmacodynamic Parameters**

Luseogliflozin increased the 24-hour UGE both in patients with hepatic impairment and in healthy subjects. The mean change $\pm$ SD from baseline in 24-hour UGE for patients with mild hepatic impairment, patients with moderate hepatic impairment, and healthy subjects were 38.8 $\pm$ 19.0, 50.3 $\pm$ 13.1, and 55.2 $\pm$ 8.5 g/day, respectively.
Table 2. Pharmacokinetic Parameters of Luseogliflozin and Metabolites by Hepatic Function Group

| Analyte  | Parameter | Normal Hepatic Function | Mild Hepatic Impairment | Moderate Hepatic Impairment |
|----------|-----------|-------------------------|-------------------------|-----------------------------|
|          | (n = 6)   | (n = 8)                  | (n = 5)                 |
| Luseogliflozin | C<sub>max</sub> (ng/mL) | 228 ± 80.6             | 228 ± 54.9             | 170 ± 28.4                   |
|           | AUC<sub>inf</sub> (ng·h/mL) | 1800 ± 427             | 1720 ± 523             | 1780 ± 260                   |
|           | T<sub>max</sub> (h) | 1.17 ± 1.4             | 0.50 ± 0               | 0.50 ± 0                     |
|           | T<sub>1/2</sub> (h) | 11.0 ± 1.17            | 10.9 ± 1.14            | 12.9 ± 1.85                  |
|           | CL/F (L/h) | 2.89 ± 0.589           | 3.12 ± 0.839           | 2.86 ± 0.393                 |
| M1       | C<sub>max</sub> (ng/mL) | 0.634 ± 0.322          | 0.315 ± 0.1            | 0.276 ± 0.121                |
|           | AUC<sub>inf</sub> (ng·h/mL) | 13.5 ± 7.47            | 5.47 ± 3.22            | 7.79 ± 2.60*                 |
|           | T<sub>max</sub> (h) | 2.83 ± 2.56            | 2.44 ± 1.24            | 4.40 ± 2.63                  |
|           | T<sub>1/2</sub> (h) | 14.4 ± 1.76            | 15.4 ± 6.05            | 18.3 ± 2.46*                 |
| M2       | C<sub>max</sub> (ng/mL) | 8.11 ± 3.35            | 9.46 ± 2.61            | 6.95 ± 2.16                  |
|           | AUC<sub>inf</sub> (ng·h/mL) | 233 ± 79.5             | 285 ± 113              | 271 ± 65.1                   |
|           | T<sub>max</sub> (h) | 5.42 ± 5.16            | 4.50 ± 3.30            | 10.8 ± 2.68                  |
|           | T<sub>1/2</sub> (h) | 13.5 ± 1.72            | 14.0 ± 2.52            | 18.0 ± 4.46                  |
| M3       | C<sub>max</sub> (ng/mL) | 1.77 ± 0.735           | 2.36 ± 1.61            | 1.28 ± 0.254                 |
|           | AUC<sub>inf</sub> (ng·h/mL) | 21.5 ± 5.65            | 34.3 ± 18.0            | 27.3 ± 4.70                  |
|           | T<sub>max</sub> (h) | 2.08 ± 2.91            | 1.19 ± 0.651           | 1.70 ± 0.671                 |
|           | T<sub>1/2</sub> (h) | 8.81 ± 0.737           | 9.98 ± 1.44            | 13.3 ± 3.49                  |
| M17      | C<sub>max</sub> (ng/mL) | 5.86 ± 2.18            | 9.01 ± 4.77            | 5.32 ± 1.93                  |
|           | AUC<sub>inf</sub> (ng·h/mL) | 131 ± 45.4             | 214 ± 105              | 146 ± 38.5                   |
|           | T<sub>max</sub> (h) | 5.83 ± 3.25            | 5.94 ± 3.05            | 7.4 ± 3.29                   |
|           | T<sub>1/2</sub> (h) | 11.0 ± 1.39            | 11.4 ± 2.07            | 13.8 ± 2.33                  |

Mean ± SD. \( a_n = 4. \)

Safety

There were no serious AEs reported, and none of the subjects experienced hypoglycemia in this study. An AE (nasopharyngitis) was observed in a subject in the mild hepatic impairment group and was mild in severity and reversible. A causal relationship with the study drug was ruled out. No AE was reported for patients with moderate hepatic impairment or for healthy subjects. No clinically relevant changes were observed in clinical laboratory tests and vital signs.

In 12-lead ECG findings, 1 patient with moderate hepatic impairment had QTcF values that exceeded 480 milliseconds after dosing with luseogliflozin, and was attributable to a high QTcF value at baseline (476
milliseconds). No other study participants experienced QTcF changes of more than 30 milliseconds from their baseline recording.

**Discussion**

In general, hepatic disease, in particular cirrhosis, results in numerous pathophysiologic changes in the liver and may influence the pharmacokinetic parameters such as $C_{\text{max}}$ and/or AUC.

In clinical pharmacologic studies of other SGLT2 inhibitors, systemic drug exposure in patients with moderate and/or severe hepatic impairment was found to have increased significantly. The GMRs of the $C_{\text{max}}$ and AUC$_{\text{inf}}$ of dapagliflozin, ipragliflozin, and empagliflozin were 140%, 127%, and 123% and 136%, 125%, and 147%, respectively, in patients with moderate hepatic impairment compared with healthy subjects.

The increase in dapagliflozin and ipragliflozin exposure was hypothesized as being attributable to a decrease in UGT activity, which contributes to the metabolism of those drugs, whereas the observed increases in empagliflozin exposure were attributed to decreases in hepatic clearance of unchanged drug or a reduction in glucuronidation in the liver and eventual excretion via bile.

In this study, changes in luseogliflozin exposure in patients with mild and moderate hepatic impairment were minimal. The $C_{\text{max}}$ of luseogliflozin was approximately 23% lower in the moderate hepatic impairment group compared with the group of healthy subjects; however, the AUC was similar for both groups.

This study could not conclusively determine why the AUC did not change in patients with impaired hepatic function; however, the clearance of luseogliflozin was relatively low (circa 3 L/h) when compared with other SGLT2 inhibitors. Moreover, luseogliflozin is hypothesized to be metabolized in the kidneys and the small intestine. Therefore, the AUC of luseogliflozin is not affected despite hepatic blood flow changes determined by the level of hepatic impairment. The slight reduction in the $C_{\text{max}}$ in the moderate hepatic impairment group can be explained by the increase in volume of distribution because of edema and/or ascites and delayed absorption of luseogliflozin because of portal hypertensive gastroenteropathy in this patient group.

Luseogliflozin is believed to be mainly metabolized by several metabolic enzymes in the liver. The primary metabolic pathways of luseogliflozin in humans are estimated as: (1) $O$-deethylation (M2) and subsequent glucuronidation (M12), (2) $\omega$-hydroxylation at the ethoxy group (M3) followed by oxidation to form the corresponding carboxylic acid metabolite (M17), and (3) direct glucuronidation (M8). In humans, it is likely that the CYP3A4/5 is primarily involved in the metabolism of unchanged luseogliflozin to M2. CYP4A11, -4F2, and -4F3B are primarily involved in the metabolism of unchanged luseogliflozin to M3; UGT1A1, -1A8, and -1A9 are primarily involved in the metabolism of M2 to a glucuronide conjugate of M2 (M12); and alcohol and aldehyde dehydrogenases are involved in the metabolism of M3 to M17.

The plasma concentration of 4 metabolites was measured in this study. M2 and M17 are the major metabolites of luseogliflozin. M1 and M3 are considered the active metabolites from their chemical structures. No major differences in exposure were observed for M3 and the major metabolites M2 and M17, irrespective of the severity of impairment in hepatic function. Although slight differences were observed for M1, these were not considered clinically relevant, as M1 is not a major metabolite of luseogliflozin.

The cumulative urinary excretion rates of unchanged luseogliflozin were slightly higher in the moderate hepatic impairment group than those of other groups. This might be explained by some of the subjects in the moderate hepatic impairment group showing relatively high eGFR. In this study, the effects of severe hepatic impairment on the safety and pharmacokinetics of luseogliflozin were not studied because of challenges in enrolling these patients in Japan. To estimate the influences of severe hepatic impairment on the pharmacokinetics of luseogliflozin, further analysis using individual parameters of the Child-Pugh classification were conducted. There was no obvious proportionality between the parameters of impaired hepatic function and a greater exposure to luseogliflozin, especially in AUC, which represents pharmacological effects. This could be because luseogliflozin is metabolized or eliminated by multiple pathways.

To date, clinical pharmacologic studies in special populations, such as patients with renal or hepatic impairment, are rarely conducted in Japan. In general, such studies are usually conducted in Eastern Europe or in the United States.

In Japan, infection with HCV is the most prevalent cause of cirrhosis of the liver, accounting for approximately 60% of all cirrhosis cases, and is followed by hepatitis B virus infection (13.9%), alcohol (13.6%), primary biliary cirrhosis (2.4%), and autoimmune hepatitis (1.9%). This prevalence is different from that in the United States or the United Kingdom. Although a limited number of subjects were enrolled in this study, more than 50% of patients were hepatitis C antibody test positive. Their demographic characteristics were similar to typical Japanese population with cirrhosis.

In this study, a single dose of 5 mg luseogliflozin was well tolerated in subjects with normal hepatic function as well as in patients with mild or moderate hepatic impairment.
impaired. Only 1 AE (nasopharyngitis) was observed, and it was mild in intensity, and no safety-related concerns were identified in the clinical laboratory tests or on evaluation of vital signs or ECG.

Twenty-four-hour UGE is a good, short-term biomarker for pharmacodynamic evaluation of SGLT2 inhibitors. SGLT2 inhibitors can significantly increase the UGE, even in healthy subjects with normal glucose levels. In this study, although the baseline blood glucose levels were comparable between the groups, the 24-hour UGE was slightly lower in the mild hepatic impairment group than in the moderate hepatic impairment and normal hepatic function groups. A possible reason for this could be that 1 subject in the mild hepatic impairment group showed a slight increase in UGE (6.7 g), although the pharmacokinetic parameters such as Cmax and AUCinf were similar to those of the other subjects. Therefore, the cause of this slight increase in UGE is unclear. The mean UGE in the mild hepatic impairment group, with the exception of this subject, was 43.3 g, which was comparable with that of the patients with moderate hepatic impairment and healthy subjects.

There are some limitations in this study. Patients with type 2 diabetes on antihyperglycemic medication were excluded for the purpose of comparing UGE with healthy subjects. In addition, patients with hepatic impairment who had comorbidities such as ascites refractory to treatment and hepatic encephalopathy were excluded from this study. Although a single dose of luseogliflozin 5 mg was well tolerated in patients with mild or moderate hepatic impairment, the long-term safety and efficacy of luseogliflozin in this population has not been established, and further investigation is necessary.

Conclusion
A single dose of luseogliflozin 5 mg was well tolerated in patients with mild or moderate hepatic impairment. The pharmacokinetics and pharmacodynamics of a single dose of luseogliflozin 5 mg in patients with mild or moderate hepatic impairment were considered to be not remarkably different from those in healthy subjects; therefore, we report that dose adjustment of luseogliflozin is not required in patients with mild or moderate hepatic impairment.

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Declaration of Conflicting Interests
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