# Efficacy and Safety of Luseogliflozin in Patient with Type 2 Diabetes Complicated by Hepatic Dysfunction

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**Research**

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# Abstract

Background: Improvements in glycemic control and hepatic function are clinically important goals in the treatment of patients with type 2 diabetes mellitus complicated by hepatic dysfunction. The favorable effects of the sodium-glucose co-transporter inhibitor luseogliflozin on hepatic dysfunction were anticipated for humans. Nevertheless, few clinical studies have confirmed its real-world efficacy on hepatic dysfunction. This trial was conducted to assess the safety and efficacy of luseogliflozin in patients with type 2 diabetes mellitus complicated by hepatic dysfunction.

Methods: This prospective, single-site, single-arm, open-label trial included 55 subjects. Subjects were administered with luseogliflozin and observed for 52 weeks. The primary endpoints were the change and percent change in aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transpeptidase (γ-GTP), and hemoglobin A1c (HbA1c) from baseline to week 52. The secondary endpoints included body weight, body mass index (BMI), waist circumference, blood pressure, fasting plasma glucose (FPG), homeostatic model assessment beta (HOMA-β), homeostatic model assessment of insulin resistance (HOMA-IR), ferritin, Mac-2 binding protein (M2-BP), fatty liver index (FLI), fibrosis-4 (FIB-4) index, type IV collagen 7S domain, nonalcoholic fatty liver disease (NAFLD) fibrosis score, high-sensitivity C-reactive protein (hs-CRP), and interleukin-6 (IL-6).

Results: AST, ALT, γ-GTP, and HbA1c significantly decreased from baseline to week 52. Body weight, BMI, waist circumference, and FPG also significantly decreased. HOMA-IR significantly decreased but HOMA-β was unchanged. FLI, ferritin, M2-BP, and NAFLD fibrosis scores significantly decreased whereas the FIB-4 index and type IV collagen 7S domain did not significantly change. The hs-CRP and IL-6 levels did not significantly change.

Conclusion: Luseogliflozin administration in T2DM patients with hepatic dysfunction was well tolerated, improved hepatic function, reduced liver fat, and attenuated liver injury and fibrosis. The present study might help establish a therapeutic approach for T2DM patients with hepatic dysfunction induced by SGLT2 inhibitors.

Trial registration: This study was registered under the University Hospital Medical Information Network Clinical Trial Registry (UMIN-CTR) (No. UMIN000025808) and the Japan Registry of Clinical Trials (No. jRCTs021180017).


# Background

Previous studies have associated type 2 diabetes mellitus (T2DM) with hepatic dysfunction. The association between T2DM and hepatic dysfunction is classified as follows [1, 2]: (1) hepatic dysfunction caused by T2DM (nonalcoholic fatty liver disease (NAFLD), nonalcoholic steatohepatitis (NASH), diabetic hepatopathy, or glycogenic hepatopathy exacerbated by T2DM); (2) T2DM caused by hepatic dysfunction (hepatic diabetes); and (3) hepatic dysfunction simultaneous with T2DM (chronic autoimmune hepatitis and autoimmune hepatic dysfunction). The prevalence of NAFLD in T2DM patients was as high as 50–

70% [3, 4]. Hepatic dysfunction was a major cause of death in T2DM patients [5–7]. Therefore, improvements in glycemic control and hepatic function are clinically important goals in the treatment of patients with T2DM complicated by hepatic dysfunction.

Novel oral hypoglycemic agents known as sodium glucose co-transporter 2 (SGLT2) inhibitors have been recently launched. They are widely used in T2DM treatment. SGLT2 inhibitors block renal glucose reabsorption, promote urinary glucose excretion, and lower plasma glucose levels in an insulin-independent manner. Hence, there is a reduced risk of induction of hypoglycemia associated with them. The safety of SGLT2 inhibitors in combination with other hypoglycemic agents has been confirmed [8]. Moreover, SGLT2 inhibitors confer cardiovascular protection [9, 10], reduce body weight [11], lower mean 24-h glucose levels [12], decrease blood pressure [13], and improve blood lipid factors [14].

Luseogliflozin is a type of SGLT2 inhibitor. It improved NASH in an animal T2DM model [15]. Its favorable effects on hepatic dysfunction were anticipated for humans. Nevertheless, few clinical studies have confirmed its real-world efficacy on hepatic dysfunction. Therefore, the aim of this study was to evaluate luseogliflozin safety and efficacy in patients with T2DM complicated by hepatic dysfunction.

## Methods

# Study design

A single-center, single-arm, open-label, prospective interventional trial was conducted from November 2016 to September 2020. It was registered at the University Hospital Medical Information Network Clinical Trial Registry (UMIN-CTR) which is a nonprofit organization in Japan that meets the requirements of the International Committee of Medical Journal Editors (No. UMIN000025808) and the Japan Registry of Clinical Trials (No. jRCTs021180017). The study protocol was approved by the Institutional Review Board of Seino Internal Medical Clinic in November 2016 according to the Ethical Guidelines for Medical and Health Research Involving Human Subjects issued by the Ministry of Health, Labour and Welfare in Japan. As the Clinical Trials Act was dispensed, the study protocol was reinspected and approved by the Fukushima Medical University Certified Review Board and certification was procured from the Minister of Health, Labour and Welfare in Japan in March 2019. The study was conducted in accordance with the Declaration of Helsinki, the Ethical Guidelines for Medical and Health Research Involving Human Subjects issued by the Ministry of Health, Labour and Welfare in Japan, the Clinical Trials Act, and other current legal regulations in Japan. Written informed consent was obtained from all participants after the study was fully explained to them. To minimize bias, data management and statistical analyses were conducted by third-party entities (DOT World Co. Ltd., Tokyo, Japan; Soiken Inc., Tokyo, Japan).

# Patient population

T2DM patients with hepatic dysfunction were included in the present trial. Patient inclusion criteria were as follows: (1) men and women ≥ 20 y and ≤ 80 y at the time of trial participation consent; (2) poor glycemic control despite diet and exercise therapy or treatment with hypoglycemic agents for ≥ 12 wks;

(3) HbA1c ≥ 6.5% and < 9.5%; (4) BMI ≥ 20 kg/$m^2$; (5) provision of written informed consent; and (6) hepatic dysfunction (ALT ≥ 31 IU/L). Patient exclusion criteria were as follows: (1) type 1 diabetes mellitus; (2) history of severe ketosis, diabetic coma, or precoma; (3) severe pre- or post-surgical infection or serious trauma; (4) severe renal dysfunction (estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 $m^2$); (5) history of stroke, myocardial infarction, or other serious cardiovascular complications requiring hospitalization ≤ 6 mo prior to giving trial participation consent; (6) existing use of SGLT2 inhibitor; (7) pregnancy, breastfeeding, possible pregnancy, or intention to become pregnant; (8) history of hypersensitivity to luseogliflozin or any of its components; and (9) any conditions deemed inappropriate by the physicians for trial participation.

# Study intervention

As this study was a single-arm trial, randomization was not conducted. The subjects furnished informed consent and then began to consume 2.5 mg oral luseogliflozin once daily either before or after breakfast. The study intervention was conducted for 52 wks and the subjects were observed at baseline (week 0) and at weeks 12, 24, and 52. All enrolled subjects were prohibited from using any SGLT2 inhibitor other than luseogliflozin during the trial. Moreover, enrolled subjects were not permitted to change the type, usage, or dose of any other therapeutic agents such as antiplatelet, antihypertensive, or antidyslipidemia drugs. They were not allowed to alter the type or degree of diet and exercise therapy during the study, provided that these treatments were safely regulated.

# Study outcomes

The primary endpoints comprised the change and percent change in aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transpeptidase (γ-GTP), and hemoglobin A1c (HbA1c) level from baseline to week 52. The secondary endpoints were as follows: (1) changes in AST, ALT, γ-GTP, and HbA1c levels from baseline to weeks 12 and 24; (2) changes in fasting plasma glucose (FPG) level, homeostatic model assessment beta (HOMA-β), homeostatic model assessment of insulin resistance (HOMA-IR), body weight, body mass index (BMI), waist circumference, blood pressure, NAFLD fibrosis score, fibrosis-4 (FIB-4) index, and fatty liver index (FLI) from baseline to weeks 12, 24, and 52; (3) changes in type IV collagen 7S domain, ferritin, Mac-2 binding protein (M2-BP), and high-sensitivity C-reactive protein (hs-CRP)) level from baseline to weeks 24 and 52; and (4) change in interleukin-6 (IL-6) level from baseline to week 52.

# Sample size calculation and statistical analysis

The target number of enrolled subjects was 50 and was based on the possible number of subjects who could give their consent following daily medical examinations at the Seino Internal Medical Clinic.

The primary and secondary endpoints were evaluated on the Full Analysis Set (FAS) which includes all subjects assigned to a study intervention. However, subjects who did not receive the study agent were excluded from the FAS. Subjects for whom no data related to the efficacy endpoints could be obtained after study agent initiation were also excluded from the FAS. The Per-Protocol Set (PPS) excluded

subjects from the FAS if they presented with substantial protocol violations such as eligible criteria nonconformance, use of prohibited drugs, and poor adherence to the study agent. The safety analysis included all treated patients. All two-sided tests were performed and $P < 0.05$ was considered as statistically significant. Summary statistics (number of subjects, mean, standard deviation, minima, median, and maxima) and changes from baseline were calculated for continuous data. A one-sample *t*-test was conducted to identify the change from baseline. Frequencies and proportions were calculated for the categorical data. SAS version 9.4 (SAS, Cary, NC, USA) was used to perform all statistical analyses.

## Results

# Baseline characteristics of the study participants

Between April 2017 and September 2018, 55 subjects were enrolled in this study and received the intervention (luseogliflozin administration). One subject discontinued the visit to the institution during the study. Five subjects discontinued luseogliflozin use because of adverse events during the study. Hence, 55 subjects were included in both the safety analysis set and the FAS (Fig. 1) and 49 subjects completed the study intervention. The baseline characteristics of the subjects are summarized in Table 1.

Table 1
Baseline characteristics of subjects

| **Characteristics** | **mean ± standard deviation or *n* (%)** |
|---|---|
| Age (y) | 52.7 ± 11.4 |
| Gender (male/female) | 38 (69.1) / 17 (30.9) |
| Height (cm) | 165.6 ± 8.3 |
| Body weight (kg) | 80.4 ± 14.9 |
| BMI (kg/m$^2$) | 29.2 ± 4.0 |
| Waist circumstance (cm) | 98.5 ± 9.9 |
| Duration of diabetes mellitus | 8.8 ± 6.4 |
| Drinking habit | 36 (65.5) |
| Smoking habit | 24 (43.6) |
| Cerebrovascular complications | 3 (5.5) |
| Diabetic complications | 20 (36.4) |
| Diabetic nephropathy | 14 (25.5) |
| Diabetic neuropathy | 4 (7.3) |
| Diabetic retinopathy | 5 (9.1) |
| Hypertension | 30 (54.5) |
| Dyslipidemia | 29 (52.7) |
| Antidiabetic agents | |
| Sulfonylurea | 11 (20.0) |
| Biguanide | 49 (89.1) |
| α-Glucosidase inhibitor | 6 (10.9) |
| Glinide | 1 (1.8) |
| Thiazolidinedione | 1 (1.8) |
| DPP-4 inhibitor | 30 (54.5) |
| SGLT2 inhibitor | 0 (0) |
| GLP-1 receptor agonist | 1 (1.8) |

Data are presented as mean ± standard deviation or *n* (%) among 55 subjects in the full analysis set. BMI, body mass index; DPP-4, dipeptidyl peptidase-4; SGLT2, sodium-glucose transport protein 2; GLP-1, glucagon-like peptide-1.

| Characteristics | mean ± standard deviation or *n* (%) |
|---|---|
| Insulin | 1 (1.8) |
| Combination agent | 13 (23.6) |
| Antihypertensive agent | 26 (47.3) |
| Antithrombotic agent | 2 (3.6) |
| Lipid-lowering agent | 22 (40.0) |
| Antihyperuricemic agent | 4 (7.3) |
| Other concomitant agents | 36 (65.5) |

Data are presented as mean ± standard deviation or *n* (%) among 55 subjects in the full analysis set. BMI, body mass index; DPP-4, dipeptidyl peptidase-4; SGLT2, sodium-glucose transport protein 2; GLP-1, glucagon-like peptide-1.

# Primary endpoints

The primary endpoints of this study were the change and percent change in AST, ALT, γ-GTP, and HbA1c levels from baseline to week 52. The AST, ALT, γ-GTP, and HbA1c significantly decreased from baseline to week 52. The AST levels were 40.2 ± 16.4 IU/L and 28.0 ± 13.6 IU/L at baseline and week 52, respectively, and the change from baseline to week 52 was − 12.2 ± 13.0 IU/L ($P < 0.0001$). The ALT levels were 73.0 ± 39.6 IU/L and 46.3 ± 32.3 IU/L at baseline and week 52, respectively, and the change from baseline to week 52 was − 25.2 ± 23.9 IU/L ($P < 0.0001$). The γ-GTP levels were 78.2 ± 38.8 and 54.6 ± 28.2 IU/L at baseline and week 52, respectively, and the change from baseline to week 52 was − 21.4 ± 22.1 IU/L ($P < 0.0001$). The HbA1c levels were 7.5% ± 0.5% and 7.0 ± 0.6% at baseline and week 52, respectively, and the change from baseline to week 52 was − 0.6% ± 0.5% ($P < 0.0001$) (Table 2). The AST, ALT, γ-GTP, and HbA1c levels significantly decreased from baseline to weeks 12 and 24. The changes in AST level from baseline were − 8.9 ± 11.1 IU/L ($P < 0.0001$) and − 10.5 ± 13.9 IU/L ($P < 0.0001$) at weeks 12 and 24, respectively. The changes in ALT level from baseline were − 17.5 ± 19.4 IU/L ($P < 0.0001$) and − 21.0 ± 26.0 IU/L ($P < 0.0001$) at weeks 12 and 24, respectively. The changes in γ-GTP level from baseline were − 12.5 ± 19.1 IU/L ($P < 0.0001$) and − 12.8 ± 26.7 IU/L ($P = 0.0012$) at weeks 12 and 24, respectively. The changes in HbA1c level from baseline were − 0.5% ± 0.4% ($P < 0.0001$) and − 0.5% ± 0.5% ($P < 0.0001$) at weeks 12 and 24, respectively.

Table 2
Primary endpoints

| Endpoint | Week | | Measurement | Change | | | Percent change | | |
|---|---|---|---|---|---|---|---|---|---|
| | | *n* | mean ± SD | *n* | mean ± SD | *p* value | *n* | mean ± SD | *p* value |
| AST (IU/L) | 0 | 55 | 40.2 ± 16.4 | | | | | | |
| | 12 | 54 | 30.9 ± 10.5 | 54 | -8.9 ± 11.1 | < 0.0001 | 54 | -17.5 ± 23.6 | < 0.0001 |
| | 24 | 52 | 29.4 ± 12.3 | 52 | -10.5 ± 13.9 | < 0.0001 | 52 | -19.7 ± 34.3 | 0.0001 |
| | 52 | 50 | 28.0 ± 13.6 | 50 | -12.2 ± 13.0 | < 0.0001 | 50 | -26.1 ± 24.8 | < 0.0001 |
| ALT (IU/L) | 0 | 55 | 73.0 ± 39.6 | | | | | | |
| | 12 | 54 | 54.1 ± 28.6 | 54 | -17.5 ± 19.4 | < 0.0001 | 54 | -19.4 ± 25.3 | < 0.0001 |
| | 24 | 52 | 49.7 ± 30.0 | 52 | -21.0 ± 26.0 | < 0.0001 | 52 | -22.5 ± 36.8 | < 0.0001 |
| | 52 | 50 | 46.3 ± 32.3 | 50 | -25.2 ± 23.9 | < 0.0001 | 50 | -31.1 ± 30.1 | < 0.0001 |
| γ-GTP (IU/L) | 0 | 55 | 78.2 ± 38.8 | | | | | | |
| | 12 | 54 | 63.4 ± 29.7 | 54 | -12.5 ± 19.1 | < 0.0001 | 54 | -14.1 ± 20.2 | < 0.0001 |
| | 24 | 52 | 62.8 ± 36.1 | 52 | -12.8 ± 26.7 | 0.0012 | 52 | -15.5 ± 27.0 | 0.0001 |
| | 52 | 50 | 54.6 ± 28.2 | 50 | -21.4 ± 22.1 | < 0.0001 | 50 | -26.0 ± 24.5 | < 0.0001 |
| HbA1c (%) | 0 | 55 | 7.5 ± 0.5 | | | | | | |
| | 12 | 54 | 7.0 ± 0.5 | 54 | -0.5 ± 0.4 | < 0.0001 | 54 | -7.0 ± 4.9 | < 0.0001 |
| | 24 | 52 | 7.0 ± 0.5 | 52 | -0.5 ± 0.5 | < 0.0001 | 52 | -7.0 ± 6.3 | < 0.0001 |
| | 52 | 50 | 7.0 ± 0.6 | 50 | -0.6 ± 0.5 | < 0.0001 | 50 | -7.8 ± 6.3 | < 0.0001 |

Data are presented as *n* and mean ± standard deviation. AST, aspartate aminotransferase; ALT, alanine aminotransferase; γ-GTP, gamma-glutamyl transpeptidase; HbA1c, hemoglobin A1c

# Vital signs

Body weight, BMI, and waist circumstance significantly decreased from baseline to weeks 12, 24, and 52. The body weights were 80.4 ± 14.9 kg, 77.5 ± 14.0 kg, 78.0 ± 14.0 kg, and 77.6 ± 14.2 kg at baseline and weeks 12, 24, and 52, respectively. The changes in body weight from baseline were − 1.9 ± 1.3 kg ($P$< 0.0001), -2.6 ± 1.8 kg ($P$< 0.0001), and − 3.1 ± 2.5 kg ($P$< 0.0001) at weeks 12, 24, and 52, respectively. The BMI were 29.2 ± 4.0 kg/$m^2$, 28.3 ± 4.0 kg/$m^2$, 28.3 ± 3.8 kg/$m^2$, and 28.0 ± 3.8 kg/$m^2$ at baseline and weeks 12, 24, and 52, respectively. The changes in BMI from baseline were − 0.7 ± 0.5 kg/$m^2$ ($P$< 0.0001), -0.9 ± 0.7 kg/$m^2$ ($P$< 0.0001), and − 1.1 ± 0.9 kg/$m^2$ ($P$< 0.0001) at weeks 12, 24, and 52, respectively. The waist circumferences were 98.5 ± 9.9 cm, 97.0 ± 10.2 cm, 97.2 ± 9.9 cm, and 96.7 ± 10.3 cm at baseline and weeks 12, 24, and 52, respectively. The changes in waist circumference from baseline were − 1.6 ± 3.0 cm ($P$= 0.0003), -1.6 ± 3.2 cm ($P$= 0.0006), and − 2.4 ± 3.2 cm ($P$< 0.0001) at weeks 12, 24, and 52, respectively (Table 3). In contrast, the systolic blood pressure significantly decreased only from baseline (131.9 ± 11.9 mm Hg) to week 12 (127.4 ± 11.6 mm Hg). The change in systolic blood pressure from baseline was − 4.4 ± 13.0 mmHg ($P$= 0.0172) and significant decreases disappeared after week 24. No significant changes were observed for diastolic blood pressure or pulse.

Table 3
Vital signs

| Endpoint | Week | Measurement | | Change | | | Percent change | | |
|---|---|---|---|---|---|---|---|---|---|
| | | *n* | mean ± SD | *n* | mean ± SD | *p* value | *n* | mean ± SD | *p* value |
| Body weight (kg) | 0 | 55 | 80.4 ± 14.9 | | | | | | |
| | 12 | 53 | 77.5 ± 14.0 | 53 | -1.9 ± 1.3 | < 0.0001 | 53 | -2.4 ± 1.7 | < 0.0001 |
| | 24 | 52 | 78.0 ± 14.0 | 52 | -2.6 ± 1.8 | < 0.0001 | 52 | -3.1 ± 2.0 | < 0.0001 |
| | 52 | 50 | 77.6 ± 14.2 | 50 | -3.1 ± 2.5 | < 0.0001 | 50 | -3.8 ± 2.9 | < 0.0001 |
| BMI ($kg/m^2$) | 0 | 55 | 29.2 ± 4.0 | | | | | | |
| | 12 | 53 | 28.3 ± 4.0 | 53 | -0.7 ± 0.5 | < 0.0001 | 53 | -2.4 ± 1.7 | < 0.0001 |
| | 24 | 52 | 28.3 ± 3.8 | 52 | -0.9 ± 0.7 | < 0.0001 | 52 | -3.1 ± 2.0 | < 0.0001 |
| | 52 | 50 | 28.0 ± 3.8 | 50 | -1.1 ± 0.9 | < 0.0001 | 50 | -3.8 ± 2.9 | < 0.0001 |
| Waist circumstance (cm) | 0 | 55 | 98.5 ± 9.9 | | | | | | |
| | 12 | 53 | 97.0 ± 10.2 | 53 | -1.6 ± 3.0 | 0.0003 | 53 | -1.6 ± 3.1 | 0.0004 |
| | 24 | 52 | 97.2 ± 9.9 | 52 | -1.6 ± 3.2 | 0.0006 | 52 | -1.6 ± 3.1 | 0.0005 |
| | 52 | 47 | 96.7 ± 10.3 | 47 | -2.4 ± 3.2 | < 0.0001 | 47 | -2.4 ± 3.2 | < 0.0001 |
| Systolic blood pressure (mm Hg) | 0 | 55 | 131.9 ± 11.9 | | | | | | |
| | 12 | 53 | 127.4 ± 11.6 | 53 | -4.4 ± 13.0 | 0.0172 | 53 | -2.9 ± 9.8 | 0.0383 |
| | 24 | 52 | 130.5 ± 11.2 | 52 | -1.0 ± 13.2 | 0.6019 | 52 | -0.2 ± 10.0 | 0.8753 |
| | 52 | 50 | 129.8 ± 12.5 | 50 | -1.9 ± 14.6 | 0.3565 | 50 | -0.9 ± 10.7 | 0.5373 |

Data are presented as *n* and mean ± standard deviation. BMI, body mass index

| Endpoint | Week | Measurement | | Change | | | Percent change | | |
|---|---|---|---|---|---|---|---|---|---|
| | | *n* | mean ± SD | *n* | mean ± SD | *p* value | *n* | mean ± SD | *p* value |
| Diastolic blood pressure (mm Hg) | 0 | 55 | 81.3 ± 9.5 | | | | | | |
| | 12 | 53 | 79.2 ± 8.8 | 53 | -2.1 ± 9.4 | 0.1178 | 53 | -1.8 ± 11.9 | 0.2869 |
| | 24 | 52 | 78.7 ± 8.7 | 52 | -2.4 ± 9.4 | 0.0731 | 52 | -2.2 ± 12.1 | 0.2077 |
| | 52 | 50 | 79.8 ± 8.5 | 50 | -1.4 ± 10.2 | 0.3223 | 50 | -0.81 ± 13.0 | 0.6629 |
| Pulse | 0 | 53 | 75.0 ± 10.7 | | | | | | |
| | 12 | 52 | 74.3 ± 11.8 | 50 | -0.3 ± 9.7 | 0.8163 | 50 | 0.15 ± 13.0 | 0.9371 |
| | 24 | 52 | 73.7 ± 11.6 | 50 | -1.3 ± 8.6 | 0.2809 | 50 | -1.35 ± 11.4 | 0.4096 |
| | 52 | 48 | 73.8 ± 12.0 | 46 | -0.8 ± 8.1 | 0.4930 | 46 | -0.77 ± 10.6 | 0.6219 |

Data are presented as *n* and mean ± standard deviation. BMI, body mass index

# Glucose metabolism

The fasting plasma glucose levels significantly decreased from baseline to weeks 12, 24, and 52 (148.8 ± 20.7 mg/dL, 131.3 ± 17.7 mg/dL, 133.2 ± 23.5 mg/dL, and 130.4 ± 19.8 mg/dL at baseline and weeks 12, 24, and 52, respectively. The changes in fasting plasma glucose level from baseline were − 17.9 ± 15.5 mg/dL ($P < 0.0001$), -16.8 ± 20.2 mg/dL ($P < 0.0001$), and − 18.8 ± 19.5 mg/dL ($P < 0.0001$) at weeks 12, 24, and 52, respectively. Plasma insulin and HOMA-IR significantly decreased from baseline to weeks 12, 24, and 52. The plasma insulin levels were 12.8 ± 7.0 μU/mL, 10.9 ± 5.7 μU/mL, 11.0 ± 5.8 μU/mL, and 11.1 ± 6.9 μU/mL at baseline and weeks 12, 24, and 52, respectively. The changes in plasma insulin level from baseline were − 2.0 ± 4.6 μU/mL ($P = 0.0026$), -2.0 ± 5.0 μU/mL ($P = 0.0065$), and − 1.7 ± 5.4 μU/mL ($P = 0.0323$) at weeks 12, 24, and 52, respectively. The HOMA-IR were 4.8 ± 2.7, 3.6 ± 2.1, 3.7 ± 2.2, and 3.6 ± 2.4 at baseline and weeks 12, 24, and 52, respectively. The changes in HOMA-IR from baseline were − 1.2 ± 1.7 ($P < 0.0001$), -1.2 ± 1.8 ($P < 0.0001$), and − 1.1 ± 2.2 ($P = 0.0007$) at weeks 12, 24, and 52, respectively. HOMA-β did not significantly change (Table 4).

Table 4
Other efficacy endpoints

| Endpoint | Week | Measurement | | Change | | | Percent Change | | |
|---|---|---|---|---|---|---|---|---|---|
| | | *n* | mean ± SD | *n* | mean ± SD | *p* value | *n* | mean ± SD | *p* value |
| Fasting plasma glucose (mg/dL) | 0 | 55 | 148.8 ± 20.7 | | | | | | |
| | 12 | 54 | 131.3 ± 17.7 | 54 | -17.9 ± 15.5 | < 0.0001 | 54 | -11.4 ± 9.7 | < 0.0001 |
| | 24 | 52 | 133.2 ± 23.5 | 52 | -16.8 ± 20.2 | < 0.0001 | 52 | -10.8 ± 12.9 | < 0.0001 |
| | 52 | 50 | 130.4 ± 19.8 | 50 | -18.8 ± 19.5 | < 0.0001 | 50 | -12.0 ± 12.6 | < 0.0001 |
| Plasma insulin (μU/mL) | 0 | 55 | 12.8 ± 7.0 | | | | | | |
| | 12 | 53 | 10.9 ± 5.7 | 53 | -2.0 ± 4.6 | 0.0026 | 53 | -11.5 ± 28.1 | 0.0043 |
| | 24 | 52 | 11.0 ± 5.8 | 52 | -2.0 ± 5.0 | 0.0065 | 52 | -10.1 ± 31.0 | 0.0230 |
| | 52 | 49 | 11.1 ± 6.9 | 49 | -1.7 ± 5.4 | 0.0323 | 49 | -8.9 ± 41.4 | 0.1396 |
| HOMA-β (%) | 0 | 55 | 55.6 ± 30.1 | | | | | | |
| | 12 | 53 | 59.3 ± 28.3 | 53 | 3.8 ± 25.3 | 0.2802 | 53 | 14.9 ± 47.2 | 0.0258 |
| | 24 | 52 | 61.0 ± 32.1 | 52 | 5.7 ± 29.4 | 0.1710 | 52 | 18.9 ± 54.9 | 0.0166 |
| | 52 | 49 | 61.5 ± 35.3 | 49 | 6.8 ± 26.0 | 0.0714 | 49 | 19.5 ± 55.4 | 0.0175 |
| HOMA-IR | 0 | 55 | 4.8 ± 2.7 | | | | | | |
| | 12 | 53 | 3.6 ± 2.1 | 53 | -1.2 ± 1.7 | < 0.0001 | 53 | -21.9 ± 24.7 | < 0.0001 |
| | 24 | 52 | 3.7 ± 2.2 | 52 | -1.2 ± 1.8 | < 0.0001 | 52 | -20.0 ± 28.6 | < 0.0001 |
| | 52 | 49 | 3.6 ± 2.4 | 49 | -1.1 ± 2.2 | 0.0007 | 49 | -18.7 ± 41.3 | 0.0027 |

Data are presented as *n* and mean ± standard deviation. HOMA-β, homeostatic model assessment beta; HOMA-IR, homeostatic model assessment of insulin resistance; FIB-4, fibrosis-4; FLI, fatty liver index; M2-BP, Mac-2 binding protein; hs-CRP, high-sensitivity C-reactive protein; IL-6, interleukin-6

| Endpoint | Week | Measurement | | Change | | | Percent Change | | |
|---|---|---|---|---|---|---|---|---|---|
| | | *n* | mean ± SD | *n* | mean ± SD | *p* value | *n* | mean ± SD | *p* value |
| Ferritin (ng/mL) | 0 | 55 | 191.4 ± 144.9 | | | | | | |
| | 24 | 52 | 123.9 ± 113.2 | 52 | -64.6 ± 73.1 | < 0.0001 | 52 | -36.4 ± 25.1 | < 0.0001 |
| | 52 | 49 | 113.6 ± 97.9 | 49 | -76.9 ± 74.2 | < 0.0001 | 49 | -40.1 ± 24.0 | < 0.0001 |
| M2-BP | 0 | 55 | 0.74 ± 0.30 | | | | | | |
| | 24 | 52 | 0.68 ± 0.27 | 52 | -0.06 ± 0.18 | 0.0187 | 52 | -5.5 ± 20.5 | 0.0581 |
| | 52 | 48 | 0.65 ± 0.25 | 48 | -0.08 ± 0.18 | 0.0027 | 48 | -8.3 ± 22.1 | 0.0121 |
| NAFLD fibrosis score | 0 | 55 | 4.1 ± 0.6 | | | | | | |
| | 12 | 54 | 4.0 ± 0.8 | 54 | -0.2 ± 0.5 | 0.0225 | 54 | -3.8 ± 12.3 | 0.0292 |
| | 24 | 52 | 3.9 ± 0.6 | 52 | -0.5 ± 0.4 | 0.0005 | 52 | -4.4 ± 9.6 | 0.0019 |
| | 52 | 50 | 4.0 ± 0.7 | 50 | -0.1 ± 0.6 | 0.1178 | 50 | -2.9 ± 14.6 | 0.1732 |
| FIB-4 index | 0 | 55 | 3.1 ± 1.8 | | | | | | |
| | 12 | 54 | 3.1 ± 1.5 | 54 | -0.1 ± 0.9 | 0.6897 | 54 | 3.1 ± 25.0 | 0.3728 |
| | 24 | 51 | 3.0 ± 1.4 | 51 | -0.1 ± 0.8 | 0.3621 | 51 | 2.0 ± 21.6 | 0.5123 |
| | 52 | 47 | 3.2 ± 1.6 | 47 | 0.2 ± 0.9 | 0.0774 | 47 | 12.4 ± 25.8 | 0.0020 |
| FLI | 0 | 55 | 73.3 ± 16.7 | | | | | | |
| | 12 | 53 | 64.2 ± 22.9 | 53 | -8.9 ± 13.6 | < 0.0001 | 53 | -13.6 ± 18.6 | < 0.0001 |
| | 24 | 52 | 65.8 ± 22.1 | 52 | -7.5 ± 10.3 | < 0.0001 | 52 | -11.8 ± 16.0 | < 0.0001 |

Data are presented as *n* and mean ± standard deviation. HOMA-β, homeostatic model assessment beta; HOMA-IR, homeostatic model assessment of insulin resistance; FIB-4, fibrosis-4; FLI, fatty liver index; M2-BP, Mac-2 binding protein; hs-CRP, high-sensitivity C-reactive protein; IL-6, interleukin-6

| Endpoint | Week | | Measurement | Change | | | Percent Change | | |
|---|---|---|---|---|---|---|---|---|---|
| | | *n* | mean ± SD | *n* | mean ± SD | *p* value | *n* | mean ± SD | *p* value |
| | 52 | 47 | 60.8 ± 24.8 | 47 | -12.5 ± 12.0 | < 0.0001 | 47 | -20.1 ± 19.6 | < 0.0001 |
| Type IV collagen 7S domain (ng/mL) | 0 | 55 | 4.6 ± 1.2 | | | | | | |
| | 24 | 52 | 4.6 ± 0.8 | 52 | 0.0 ± 1.0 | 0.8387 | 52 | 4.8 ± 23.2 | 0.1423 |
| | 52 | 49 | 4.6 ± 0.7 | 49 | 0.1 ± 1.0 | 0.4492 | 49 | 6.3 ± 24.5 | 0.0768 |
| hs-CRP (mg/dL) | 0 | 55 | 0.11 ± 0.13 | | | | | | |
| | 24 | 52 | 0.09 ± 0.10 | 52 | -0.02 ± 0.10 | 0.1222 | 52 | 10.7 ± 96.3 | 0.4259 |
| | 52 | 49 | 0.08 ± 0.11 | 49 | -0.03 ± 0.13 | 0.0968 | 49 | 7.8 ± 150.7 | 0.7172 |
| IL-6 (pg/mL) | 0 | 55 | 2.1 ± 2.7 | | | | | | |
| | 52 | 49 | 1.6 ± 1.2 | 49 | -0.3 ± 1.1 | 0.0847 | 49 | -4.6 ± 38.7 | 0.4062 |

Data are presented as *n* and mean ± standard deviation. HOMA-β, homeostatic model assessment beta; HOMA-IR, homeostatic model assessment of insulin resistance; FIB-4, fibrosis-4; FLI, fatty liver index; M2-BP, Mac-2 binding protein; hs-CRP, high-sensitivity C-reactive protein; IL-6, interleukin-6

# Hepatic function biomarkers

FLI is a surrogate liver fat marker and significantly decreased from baseline to weeks 24 and 52. The FLI values were 73.3 ± 16.7, 64.2 ± 22.9, 65.8 ± 22.1, and 60.8 ± 24.8 at baseline and weeks 12, 24, and 52, respectively. The changes in FLI from baseline were − 8.9 ± 13.6 ($P$< 0.0001), -7.5 ± 10.3 ($P$< 0.0001), and − 12.5 ± 12.0 ($P$< 0.0001) at weeks 12, 24, and 52, respectively. Ferritin is a hepatic impairment biomarker. Its levels significantly decreased from baseline to weeks 24 and 52. The ferritin levels were 191.4 ± 144.9 ng/mL, 123.9 ± 113.2 ng/mL, and 113.6 ± 97.9 ng/mL at baseline and weeks 24 and 52, respectively. The changes in ferritin level from baseline were − 64.6 ± 73.1 ng/mL ($P$< 0.0001) and − 76.9 ± 74.2 ng/mL ($P$< 0.0001) at weeks 24 and 52, respectively. The hepatic fibrosis biomarker level M2-BP decreased from baseline to weeks 24 and 52. The M2-BP levels were 0.74 ± 0.30, 0.68 ± 0.27, and 0.65 ± 0.25 at baseline and weeks 24 and 52, respectively. The changes in M2-BP level from baseline were − 0.06 ± 0.18 ($P$= 0.0187) and − 0.08 ± 0.18 ($P$= 0.0027) at weeks 24 and 52, respectively. The NAFLD fibrosis score significantly decreased from baseline to weeks 12 and 24. The NAFLD fibrosis scores were

4.1 ± 0.6, 4.0 ± 0.8 and 3.9 ± 0.6 at baseline and weeks 12 and 24, respectively. The changes in NAFLD fibrosis score from baseline were − 0.2 ± 0.5 ($P$ = 0.0225) and − 0.5 ± 0.4 ($P$ = 0.0005) at weeks 12 and 24, respectively. However, there was no significant change in NAFLD fibrosis score by week 52. The FIB-4 index and the type IV collagen 7S domain did not significantly change from baseline (Table 4).

# Inflammation biomarkers

The hs-CRP and IL-6 levels did not significantly change from baseline (Table 4).

# Safety outcomes

Twenty-four adverse events were reported in eighteen out of fifty-five subjects (32.7%) (Table 5). The most common adverse events were genital infection and dry skin (six subjects each; 10.9%). Four serious adverse events (facial paresis, venous thrombosis, Báker's cyst, and gastric cancer) were reported during the study. Nevertheless, none of them was considered to be related to luseogliflozin administration. No hypoglycemia or severe hypoglycemia was reported during the study.

Table 5
Adverse events

| Adverse event | Frequency |
|---|---|
| Death | 0 (0) |
| Any adverse events | 18 (32.7) |
| Serious adverse event | 4 (7.3) |
| Genital infection | 6 (10.9) |
| Dry skin | 6 (10.9) |
| Balanitis | 1 (1.8) |
| Dehydration | 1 (1.8) |
| Skin rash | 1 (1.8) |
| Constipation | 1 (1.8) |
| Genital itching | 1 (1.8) |
| Facial paresis | 1 (1.8) |
| Arthritis | 1 (1.8) |
| Disc herniation (Low back pain) | 1 (1.8) |
| Venous thrombosis | 1 (1.8) |
| Pulled muscle | 1 (1.8) |
| Baker cyst | 1 (1.8) |
| Gastric cancer | 1 (1.8) |
| Data are presented as *n* (%). | |

# Discussion

The purpose of this study was to assess the safety and efficacy of the SGLT2 inhibitor luseogliflozin in T2DM patients with hepatic dysfunction. We observed improvement in glycemic control and the hepatic function biomarkers AST, ALT, and γ-GTP. Moreover, FLI (a surrogate liver fat marker), ferritin (a hepatic impairment biomarker), M2-BP, and the NAFLD fibrosis score (hepatic fibrosis biomarkers) were significantly improved in response to luseogliflozin administration.

Several previous studies in T2DM patients showed that luseogliflozin administration decreased hepatic function biomarkers [8, 14, 16]. A recent single-arm LEAD trial in T2DM patients with NAFLD demonstrated a significant decrease in hepatic function biomarkers [17]. The results of the present study

were consistent with those of previous reports. The present study confirmed that luseogliflozin improved hepatic function in T2DM patients with hepatic dysfunction and ALT levels > 31 IU/L at enrolment.

Additionally, this study revealed improvement in the hepatic fibrosis biomarkers M2-BP and NAFLD fibrosis score following luseogliflozin administration in T2DM patients with hepatic dysfunction. The LEAD trial showed decrease in the AST, ALT, γ-GTP, and ferritin levels in T2DM patients with NAFLD. However, the hepatic fibrosis markers FIB4 index, NAFLD fibrosis score, type IV collagen 7S, and M2BP were unchanged [17]. Hence, luseogliflozin may only be able to ameliorate mild to moderate hepatic dysfunction but not established NAFLD.

The beneficial effects of SGLT2 inhibitors on body weight and composition have been reported [18–21]. The present study demonstrated significant reduction in body weight, BMI, and waist circumstance after luseogliflozin administration. The surrogate liver fat marker FLI significantly decreased in the present study. This finding was consistent with that reported by previous studies which demonstrated decrease in liver fat following SGLT2 inhibitor treatment [22–24] and might explain the hepatic function improvement observed here.

This trial also disclosed that that plasma insulin levels and HOMA-IR were significantly decreased by luseogliflozin administration. This finding was consistent with earlier reports of reductions in HOMA-IR (insulin resistance improvement) by SGLT2 inhibitors [25, 26]. In contrast, HOMA-β did not significantly improve in the present study. SGLT2 inhibitors apparently improved pancreatic β-cell function in animal models [27]. However, no study has evaluated the effects of SGLT2 inhibitors on pancreatic β-cell function in humans. A Korean clinical study in Korea showed that a group responding well to SGLT2 inhibitors presented with relatively higher HOMA than the group responding poorly to SGLT2 inhibitors. Nevertheless, the HOMA-β level was not associated with SGLT2 inhibitor responsiveness [28]. The results of this study suggested that SGLT2 inhibitors improved insulin resistance but not insulin secretion in the pancreatic β-cells of T2DM patients.

Here, luseogliflozin administration did not improve inflammation because it did not lower the hs-CRP or IL-6 levels. It has been previously reported that SGLT2 inhibitors suppress inflammation in animal models [29, 30]. However, only a few human trials reported an association between SGLT2 inhibitors and inflammation [31, 32]. Further studies are needed to assess the efficacy of SGLT2 inhibitors in attenuation of inflammation.

No serious adverse events associated with luseogliflozin were detected in the present study. Genital infection and dry skin were the most commonly observed adverse reactions here but they are well-known side effects of SGLT2 inhibitors. There were no remarkable occurrences of any unknown side effects. No hypoglycemia was recorded during this trial. It was reported earlier that SGLT2 inhibitors lowered plasma glucose in an insulin-independent manner and posed a low risk of inducing hypoglycemia [33]. Moreover, recent large-scale clinical trials demonstrated that SGLT2 inhibitors prevented mortality, macrovascular complications, and renal impairment progression associated with T2DM [9, 10]. Overall, SGLT2 inhibitors are well tolerated in T2DM patients with hepatic dysfunction.

The study protocol described the enrolment of 50 subjects. Nevertheless, it was feasible for the Seino Internal Medical Clinic to support the enrolment of 55 subjects. The over-registration was reported to the Fukushima Medical University Certified Review Board and approved by them. The last five subjects were excluded and the results of the present study were re-analyzed with only 50 participants. Once again, all primary endpoints (ALT, AST, γ-GTP, and HbA1c) showed significant improvements. Therefore, over-registration by five patients did not influence the outcome of this trial and all 55 subjects were included in the FAS and analyzed.

This study had several limitations. First, there were relatively few enrolled subjects in this trial and it was conducted in only one clinical institution (Seino Internal Medical Clinic) in Japan. Second, it was a single-arm trial. Third, the eligibility criterion hepatic dysfunction was defined only by the ALT level at enrolment. Therefore, the participants in this trial had mild to moderate hepatic dysfunction. These constraints may limit the generalizability of this study and large-scale, multicenter, randomized controlled trials are required to validate its findings.

# Conclusion

Luseogliflozin administration was tolerated in T2DM patients with hepatic dysfunction. It improved hepatic function, reduced liver fat, and attenuated liver injury and fibrosis. The results of this trial might facilitate the establishment of a treatment strategy for T2DM patients with hepatic dysfunction caused by SGLT2 inhibitors.

# Abbreviations

ALT alanine aminotransferase

AST aspartate aminotransferase

BMI body mass index

eGFR estimated glomerular filtration rate

FAS full analysis set

FIB-4 Fibrosis-4

FLI fatty liver index

FPG fasting plasma glucose

γ-GTP gamma-glutamyl transpeptidase

HbA1c hemoglobin A1c

HOMA-β homeostatic model assessment beta

HOMA-IR homeostasis model assessment of insulin resistance

hs-CRP high-sensitivity C-reactive protein

IL-6 interleukin-6

M2-BP Mac-2-binding protein

NAFLD nonalcoholic fatty liver disease

NASH nonalcoholic steatohepatitis

PPS per protocol set

SGLT2 sodium glucose co-transporter 2

T2DM type 2 diabetes mellitus

# Declarations

*Ethics approval and consent to participate*

The study protocol was initially approved by the Institutional Review Board of the Seino Internal Medical Clinic in November 2016 according to the Ethical Guidelines for Medical and Health Research Involving Human Subjects issued by the Ministry of Health, Labour and Welfare in Japan. As the Clinical Trials Act was dispensed, the study protocol was reinspected and approved by the Fukushima Medical University Certified Review Board which obtained certification from the Minister of Health, Labour and Welfare in Japan in March 2019. The study was conducted in accordance with the Declaration of Helsinki, the Ethical Guidelines for Medical and Health Research Involving Human Subjects issued by the Ministry of Health, Labour and Welfare in Japan, the Clinical Trials Act, and other current legal regulations in Japan. Written informed consent was obtained from all participants after full explanation of the study.

*Consent for publication*

As this manuscript does not contain any individual personal data, consent for publication was not required or applicable.

*Availability of data and materials*

The datasets generated and/or analyzed during the current study are not publicly available as there is no third-party data sharing statement in the study protocol. Furthermore, we did not secure approval for sharing the informed consent documents from the Institutional Review Board of the Seino Internal Medical Clinic or the Fukushima Medical University Certified Review Board.

*Competing interests*

HS received lecture fees from Shionogi Co. Ltd., Mitsubishi Tanabe Pharma Co., Astellas Pharma Inc., Novartis Pharma K.K., Eli Lilly and Co., Ono Pharmaceutical Co. Ltd., MSD K.K., and Sanofi K.K.

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*Author contributions*

HS conceived and designed the study. HS enrolled the subjects, acquired the data, and drafted and revised the manuscript. HS met the International Committee of Medical Journal Editors (ICMJE) criteria for authorship of this article and assumed full responsibility for its overall integrity.

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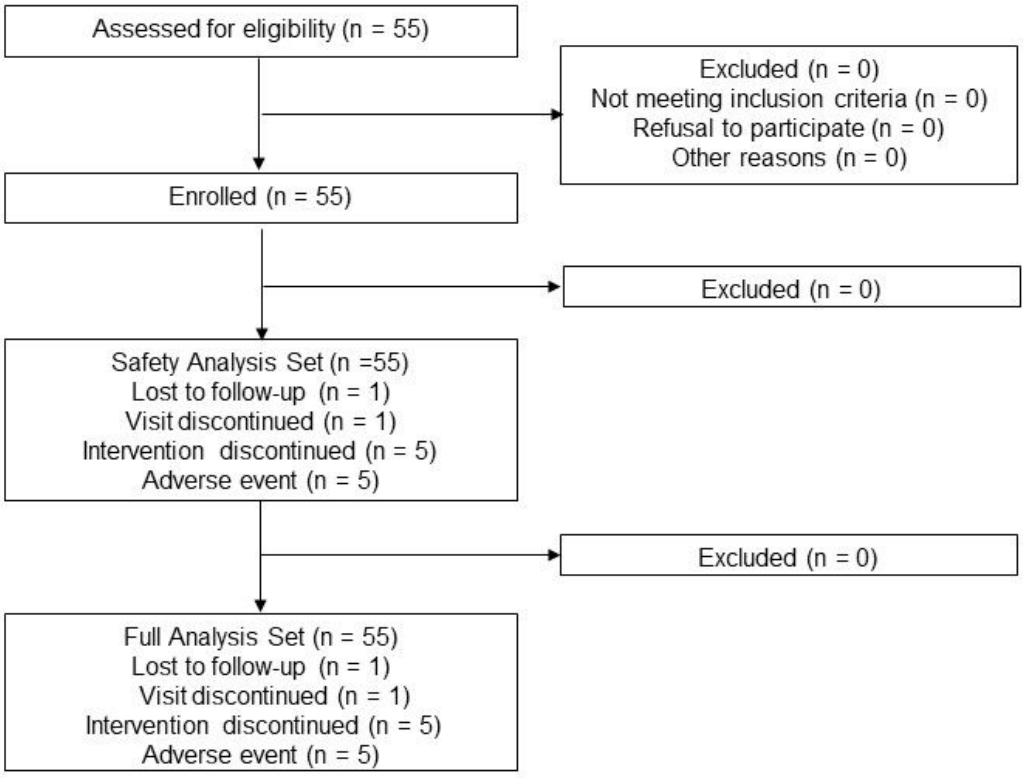
# Figures

Fig. 1




## Figure 1

Flowchart depicting study participant enrolment, allocation, and analysis 55 eligible subjects were enrolled in this study. All 55 subjects were included and analyzed in the Safety Analysis Set and Full Analysis Set in this study.