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CLINICAL TRIAL

Sodium-glucose cotransporter-2 inhibitor luseogliflozin added to glucagon-like peptide 1 receptor agonist liraglutide improves glycemic control with bodyweight and fat mass reductions in Japanese patients with type 2 diabetes: A 52-week, open-label, single-arm study

Yutaka Seino[1,2], Daisuke Yabe[2], Takashi Sasaki[3], Atsushi Fukatsu[4], Hisae Imazeki[5], Hidekazu Ochiai[5]*, Soichi Sakai[5]

[1]Kansai Electric Power Hospital, Osaka, [2]Kansai Electric Power Medical Research Institute, Kobe, [3]Institute of Clinical Medicine and Research, The Jikei University School of Medicine, Chiba, [4]Yachiyo Hospital, Aichi, and [5]Taisho Pharmaceutical Co., Ltd., Tokyo, Japan

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***Correspondence**
Hidekazu Ochiai
Tel.: +81-3-3985-1111
Fax: +81-3-3985-0650
E-mail address:
h-ochiai@so.taisho.co.jp

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ABSTRACT

Aims/Introduction: The aim of the present study was to evaluate the safety and efficacy of luseogliflozin added to liraglutide monotherapy in Japanese individuals with type 2 diabetes.

Materials and Methods: This 52-week, multicenter, open-label, single-arm clinical study enrolled Japanese patients who had inadequate glycemic control with diet/exercise and liraglutide monotherapy. Major efficacy end-points included the changes from baseline in glycated hemoglobin, fasting plasma glucose and bodyweight. Body composition was also assessed in individuals who had access to bioelectrical impedance analysis. Safety assessments included adverse events, clinical laboratory tests, vital signs and 12-lead electrocardiograms.

Results: Of 76 patients who received luseogliflozin, 62 completed the study. The changes from baseline in glycated hemoglobin, fasting plasma glucose, and bodyweight (mean ± SE) were −0.68 ± 0.10%, −32.1 ± 3.6 mg/dL and −2.71 ± 0.24 kg at week 52, respectively (all, $P < 0.001$ vs baseline). Luseogliflozin was associated with greater reductions in fat mass than lean mass at all measuring points ($n = 22$): fat vs lean mass changes (mean ± SE) at week 52 were −2.49 ± 0.45 kg ($P < 0.001$ vs baseline) and −0.44 ± 0.26 kg ($P = 0.107$ vs baseline), respectively. Insulin secretion and Matsuda Index were also improved at weeks 12 and 52 compared with baseline. Adverse events and adverse drug reactions occurred in 65.8 and 27.6% of patients, respectively. The overall safety profile, including frequency of hypoglycemia, was found to be consistent with those of previous studies and there were no new safety concerns.

Conclusions: Luseogliflozin added to liraglutide was well tolerated, and improved glycemic control with bodyweight and fat mass reductions in Japanese type 2 diabetes patients.

INTRODUCTION

Management of type 2 diabetes often involves the use of various antidiabetic drugs, either as monotherapy or combination therapy. In addition to glycated hemoglobin (HbA1c)-lowering

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effects, glycemic control and bodyweight effects should be taken into account when selecting antidiabetic drugs. The reasons are because severe hypoglycemia owing to intensive glucose-lowering intervention can be associated with an increased risk of vascular complications[1,2], and obesity/overweight leads to lifestyle-related disease and earlier death[3]. Recently, glucagon-like peptide 1 (GLP-1) receptor agonists (GLP-1RAs) and sodium-glucose cotransporter-2 (SGLT2) inhibitors have gained increased attention because they exert HbA1c-lowering effects and promote substantial bodyweight reduction, with limited risk of hypoglycemia. GLP-1RAs (e.g., liraglutide) reduce bodyweight by suppressing appetite, and improve pre- and post-prandial glucose levels by enhancing insulin secretion and suppressing glucagon secretion glucose-dependently[4], whereas SGLT2 inhibitors (e.g., luseogliflozin) show similar effects by enhancing urinary glucose excretion[5]. Because of their distinct mechanisms that exert glycemic effects and reductions in bodyweight, co-administration of GLP-1RAs and SGLT2 inhibitors might be effective for the management of overweight or obese type 2 diabetes patients. At present, there is only one clinical trial focusing on this combination therapy in Caucasian type 2 diabetes patients[6]. Thus, the safety and efficacy of this combination therapy are still largely unknown and need to be evaluated in other ethnic groups, such as Asians, in whom type 2 diabetes phenotypically differs from that of Caucasians[7].

In the current study, the efficacy and safety of luseogliflozin added on to liraglutide was evaluated in Japanese individuals with type 2 diabetes inadequately controlled by diet/exercise and liraglutide.

METHODS

The present study was carried out in compliance with the Declaration of Helsinki, Good Clinical Practice and the International Conference on Harmonisation guidelines. The study protocol was reviewed and approved by the institutional review boards at all participating medical institutions, and written informed consent was obtained from all enrolled individuals.

Study design

This was a 52-week, multicenter, open-label, single-arm clinical study (Japan Pharmaceutical Information Center: JapicCTI-142583), which was designed according to the Japanese guidelines for the clinical evaluation of oral antidiabetic drugs and long-term treatment[8,9]. All individuals received luseogliflozin (2.5 mg, orally) once daily before breakfast in addition to a once-daily injection of liraglutide. The luseogliflozin dose could be increased to 5 mg at weeks 28, 32, 36 or 40 if HbA1c was ≥7.4% at the corresponding visit, and if there were no safety concerns (Figure S1). This study was carried out between June 2014 and January 2016, and was performed at 12 medical institutions in Japan (Table S1). In the current study, individuals receiving GLP-1RAs other than liraglutide were not recruited, because at the time the study was initiated, liraglutide was the only GLP-1RA approved as monotherapy for type 2 diabetes in Japan.

Participants

Japanese type 2 diabetes patients were eligible if they satisfied the following criteria: diet therapy and prescription of a fixed dose of liraglutide monotherapy within the approved range in Japan for ≥12 weeks before starting luseogliflozin; age ≥20 years; HbA1c of 7.0–10.5%; and a maximum change in HbA1c of 1.0% during the 4-week observation period. Major exclusion criteria are shown in the Supporting Information. Other antidiabetic drugs were prohibited from the start of the screening period until the end of the study. Hypolipidemic, antihypertensive and diuretic drugs were permitted, provided that they were prescribed at a constant dose throughout the study. Diet and exercise at registration were continued throughout the study, except in the case of adverse events (AEs).

Clinical evaluations

The major efficacy end-points were changes from baseline (week 0) to week 52 in HbA1c, fasting plasma glucose (FPG), bodyweight and waist circumference. Meal tolerance tests (MTTs) were also carried out at weeks 0, 12 and 52, and plasma glucose, insulin, glucagon and serum C-peptide immunoreactivity levels were measured. The MTT procedure is summarized in the Supporting Information. The insulin secretory rate (ISR) was estimated by deconvolution from the C-peptide immunoreactivity concentration[10], using Phoenix® WinNonlin® version 6.2 (Certara, Princeton, NJ, USA). Whole-body insulin sensitivity was evaluated using the Matsuda Index[11]. All laboratory tests were analyzed at a central laboratory (LSI Medience Corporation, Tokyo, Japan). Vital signs, 12-lead electrocardiography, bodyweight and waist circumference were recorded at each institution. Body composition was assessed at weeks 0, 4, 12, 24 and 52 as an exploratory end-point by bioelectrical impedance analysis (BIA) using an Inbody S10 (Inbody Co, Ltd., Seoul, Korea) in individuals who were recruited and monitored at two medical institutions with an available device (Table S1).

Safety was assessed in terms of the nature and frequency of AEs, including changes in laboratory values, vital signs and 12-lead electrocardiography findings. AEs, including hypoglycemia, were judged by the investigators. When an AE was observed, its description, severity, seriousness, causal relationship to the study drug and other pertinent information were recorded.

Statistical analysis

Safety and efficacy analyses were carried out in the same data-set, which comprised all individuals who received the study drug at least once and who underwent post-administration examinations/observations (n = 76). BIA was carried out in all individuals with available data at baseline and at the relevant visit (n = 22).

Basic statistics of each efficacy or safety end-point were calculated at each measuring point through to week 52, and changes from baseline to each visit were evaluated using a one-sample *t*-test (missing or incomplete data were not imputed). Individuals who received luseogliflozin at a dose of 2.5 or 5 mg were included in the analyses. The significance level was set at 5% (two-sided) with 95% confidence intervals (two-sided). ISR was plotted against plasma glucose at weeks 0, 12 and 52. Regression coefficients were calculated with *P*-values. AEs and adverse drug reactions were classified according to the system organ class and preferred term defined by MedDRA/J version 19.0 and their frequencies during the 52-week treatment period were tabulated. All statistical analyses were carried out using SAS® version 9.2 (SAS Inc., Cary, North Carolina, USA).

RESULTS

Demographics

Of the 76 individuals who received luseogliflozin, 62 completed the 52-week treatment period (Figure 1). Patient demographics and baseline characteristics are shown in Table 1. There was no change in the liraglutide dose during the study. The starting dose of luseogliflozin was 2.5 mg, and was increased to 5 mg in 40 individuals (52.6%) without subsequent reduction in dose for the remainder of the study.

HbA1c, FPG and bodyweight

HbA1c decreased significantly from baseline to week 2, and this reduction was maintained through to week 52 (Figure S2). The mean ± SE change in HbA1c from baseline to week 52 was −0.68 ± 0.10% ($P < 0.001$). FPG and bodyweight also decreased significantly from week 2 onwards, and these reductions were maintained through to week 52 (Figure S2). The mean ± SE changes in FPG and bodyweight from baseline to week 52 were −32.1 ± 3.6 mg/dL and −2.71 ± 0.24 kg, respectively (both $P < 0.001$). The proportion of individuals achieving bodyweight reduction ≥5% at week 52 was 33.9%. We analyzed the changes in bodyweight in two subgroups of individuals based on baseline BMI. The mean ± SD change in bodyweight from baseline to week 52 was similar in both groups: −2.59 ± 1.38 kg in the lower BMI group ($n = 26$, <25 kg/m^2) and −2.79 ± 2.17 kg in the higher BMI group ($n = 36$, ≥25 kg/m^2). Furthermore, the proportion of individuals with reductions in both HbA1c and bodyweight was 80.0% at week 12 and 72.6% at week 52 (Figure S3). Other efficacy variables are shown in Table 2.

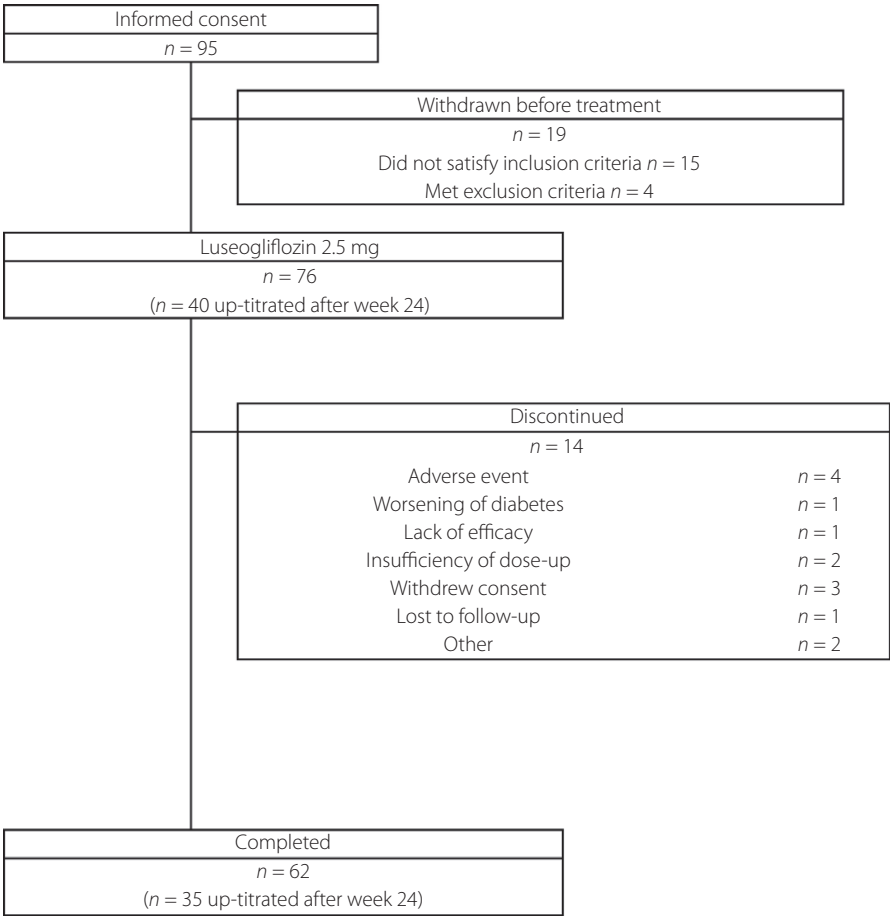

Figure 1 | Patient disposition.

Table 1 | Patient demographics and baseline characteristics

Characteristic	All patients	BIA set
n	76	22
Sex, male	47 (61.8)	12 (54.5)
Age (years)	58.4 ± 10.2	56.2 ± 10.1
Bodyweight (kg)	70.93 ± 16.40	66.93 ± 14.63
BMI (kg/m^2)	26.53 ± 4.67	25.70 ± 3.93
Waist circumference (cm)	92.88 ± 12.11	90.61 ± 12.03
Body component		
Fat mass (kg)	–	21.68 ± 7.91
Lean mass (kg)	–	45.25 ± 9.85
Duration of diabetes (years)	10.4 ± 6.8	15.5 ± 8.1
HbA1c (%)	8.52 ± 1.08	8.86 ± 1.08
FPG (mg/dL)	183.7 ± 35.9	189.1 ± 31.1
PPG, 2-h (mg/dL)	292.9 ± 68.1	–
Fasting plasma CPR (ng/mL)	1.92 ± 0.94	–
eGFR (mL/min/1.73 m^2)	84.2 ± 18.5	87.3 ± 20.6
Luseogliflozin dose		
Dosing up 5 mg	40 (52.6)	17 (77.3)
Liraglutide dose		
0.6 mg/day	10 (13.2)	1 (4.5)
0.9 mg/day	66 (86.8)	21 (95.5)

Values are shown as the mean ± SD or *n* (%). BIA, bioelectrical impedance analysis; BMI, body mass index; CPR, C-peptide immunoreactivity; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin; PPG, postprandial plasma glucose.

Meal tolerance test

Luseogliflozin was associated with significant reductions in postprandial plasma glucose at each time-point (0.5, 1 and 2 h) from baseline to week 12, and these reductions were maintained to week 52 (Figure S4). The mean ± SE change in 2-h postprandial plasma glucose from baseline to week 52 was −56.5 ± 5.4 mg/dL ($P < 0.001$). Luseogliflozin added to liraglutide had little effect on postprandial insulin, but led to increased postprandial glucagon at week 52 (Figure S4). To evaluate the effect of β-cell function (i.e., β-cell glucose sensitivity), we plotted the plasma glucose concentration vs ISR (Figure S5) and used a linear regression model for analysis. A correlation between both parameters was observed at all time-points ($P = 0.0001$; baseline, $P < 0.0001$; week 12 and 52). The slope of the regression line increased over time from baseline (Table S2). These results show that insulin secretion (which corresponds to the plasma glucose concentration) was improved with luseogliflozin + liraglutide combination therapy. The Matsuda Index, which is indicative of whole-body insulin sensitivity, increased significantly from baseline to weeks 12 and 52 (Table 2).

Body composition

Changes in body composition were assessed in 24 individuals at two medical institutions in which BIA devices were available. Two individuals were excluded from the analyses owing to incorrect baseline measurements. The mean ± SE change in bodyweight from baseline to week 52 was −2.92 ± 0.40 kg ($P < 0.001$) in this subgroup, which was generally similar to that of the overall study population (Table S3). Fat mass decreased significantly between weeks 4 and 52, and the magnitude of these changes increased over time (Figure 2). Slight decreases in lean mass were observed at all visits, although these decreases were not statistically significant or time-dependent. Waist circumference decreased significantly from baseline to each visit (Table 2). In addition, the changes in bodyweight and waist circumference from baseline to week 52 were positively correlated with the change in fat mass (Figure S6).

Safety

Overall, 65.8% of individuals experienced at least one AE, and 27.6% experienced at least one adverse drug reaction (Table 3). AEs observed in ≥5% of individuals are shown in Table 3. The most frequent AE was nasopharyngitis (34.2%). Most of the AEs were mild in severity, and no deaths occurred during the treatment period. Four serious AEs were reported in one patient each. Two of them (acute myocardial infarction and brain stem infarction) were deemed by the investigators to be probably related to luseogliflozin.

Hypoglycemia occurred in five individuals (6.6%); all of these events were mild in severity and did not require the assistance of another person. The rate of hypoglycemia by patient-year method was 0.31 events/patient-year. Pollakiuria occurred in 9.2% of individuals, but did not lead to study discontinuation in any patient. There were four AEs related to skin disorders, but all of these events were rated as mild in severity and resolved with or without appropriate interventions. Although gastrointestinal disorders, which are common AEs associated with liraglutide, occurred in 13.2% of individuals, all cases were mild or moderate in severity. The most frequently reported gastrointestinal AE was vomiting (3.9%).

There were no reported cases of pancreatitis or suspected pancreatic dysfunction. The mean amylase concentration increased significantly from baseline, whereas the mean lipase concentration did not change significantly from baseline at week 52 (Table S4). The changes in amylase and lipase concentrations were within the reference ranges.

There were no AEs associated with ketosis or ketoacidosis. The fasting acetoacetic acid and β-hydroxybutyric acid concentrations increased significantly from baseline to week 24, but thereafter the value remained constant until week 52. In addition, the concentrations of blood ketone bodies at 2 h after the meal were within the reference range.

Regarding laboratory tests, hematocrit and blood urea nitrogen levels increased significantly from baseline, although the values remained roughly constant from week 12 onwards. Aspartate aminotransferase, alanine aminotransferase and γ-glutamyl transferase decreased significantly from baseline to week 52. Furthermore, significant increases in adiponectin and high-density lipoprotein cholesterol were observed from baseline to week 52. A slight reduction in triglycerides was observed, but it was not statistically significant at week 52. Systolic blood

Table 2 | Changes in efficacy values over time

	Baseline (n = 76)	Week 12 (n = 75)	Week 24 (n = 70)	Week 36 (n = 69)	Week 52 (n = 62)
HbA1c (%)	8.52 ± 1.08	7.94 ± 0.95 −0.54 (−0.67, −0.41)*	7.88 ± 0.93 −0.58 (−0.74, −0.43)*	7.83 ± 0.98 −0.68 (−0.86, −0.50)*	7.74 ± 0.91 −0.68 (−0.87, −0.49)*
FPG (mg/dL)	183.7 ± 35.9	159.7 ± 28.2 −23.8 (−29.8, −17.8)*	154.8 ± 29.5 −28.8 (−34.9, −22.7)*	149.2 ± 25.0 −35.0 (−42.5, −27.4)*	150.1 ± 25.8 −32.1 (−39.3, −24.8)*
2-h PPG (mg/dL)	292.9 ± 68.1	236.0 ± 57.4 −56.7 (−66.9, −46.6)*‡	–	–	229.3 ± 53.8 −56.5 (−67.3, −45.7)*
PPG, $AUC_{0–2\ h}$ (mg·h/dL)	558 ± 97.2	481 ± 78.4 −77.0 (−91.8, −62.3)*‡	–	–	470 ± 74.4 −80.5 (−96.7, −64.3)*
Glycated albumin (%)	23.47 ± 4.39	20.37 ± 3.58 −3.06 (−3.56, −2.56)*	20.41 ± 3.72 −2.83 (−3.40, −2.26)*	20.44 ± 4.09 −2.85 (−3.44, −2.26)*	20.31 ± 3.90 −2.57 (−3.24, −1.89)*
Bodyweight (kg)	70.93 ± 16.40	69.47 ± 16.46 −1.65 (−1.95, −1.35)*	68.91 ± 16.79 −2.52 (−2.91, −2.12)*	68.49 ± 16.76 −2.86 (−3.31, −2.41)*	68.64 ± 17.01 −2.71 (−3.18, −2.23)*
Change in bodyweight (%)	0.00 ± 0.00	−2.45 ± 1.92 −2.45 (−2.89, −2.00)*	−3.65 ± 2.42 −3.65 (−4.23, −3.08)*	−4.20 ± 2.84 −4.20 (−4.89, −3.52)*	−3.95 ± 2.63 −3.95 (−4.62, −3.28)*
Waist circumference (cm)	92.88 ± 12.11	91.45 ± 12.42 −1.39 (−1.94, −0.85)*	90.20 ± 12.62 −2.63 (−3.28, −1.98)*	89.85 ± 12.57 −3.09 (−3.85, −2.34)*	90.15 ± 12.84 −2.86 (−3.65, −2.07)*
Fasting insulin (μU/mL)	12.237 ± 9.031	10.287 ± 7.733 −1.926 (−2.958, −0.894)*	10.003 ± 7.727 −2.469 (−3.471, −1.468)*	10.368 ± 8.346 −2.161 (−3.209, −1.113)*	9.251 ± 7.735 −3.490 (−4.483, −2.496)*
2-h insulin (μU/mL)	50.065 ± 47.390	42.358 ± 35.112 −8.407 (−12.951, −3.863)*‡	–	–	44.051 ± 38.282 −9.020 (−15.66, −2.38)**
Insulin, $AUC_{0–2\ h}$ (μU h/mL)	68.5 ± 58.4	63.5 ± 49.2 −5.81 (−10.2, −1.41)**‡	–	–	67.5 ± 61.0 −4.59 (−9.44, 0.269)
Serum CPR (ng/mL)	1.92 ± 0.94	1.81 ± 0.91 −0.09 (−0.21, 0.03)	1.81 ± 0.94 −0.08 (−0.22, 0.06)	1.73 ± 0.86 −0.17 (−0.30, −0.05)**	1.70 ± 0.88 −0.19 (−0.31, −0.07)**
2-h serum CPR (ng/mL)	5.04 ± 2.34	5.27 ± 2.56 0.23 (−0.21, 0.66)‡	–	–	5.20 ± 2.45 0.15 (−0.23, 0.52)
Serum CPR, $AUC_{0–2\ h}$ (ng h/mL)	6.87 ± 3.17	7.27 ± 3.39 0.384 (−0.0543, 0.823)‡	–	–	7.09 ± 3.51 0.202 (−0.147, 0.551)
Fasting glucagon (pg/dL)	94.0 ± 26.3	98.5 ± 26.1 4.8 (−0.3, 9.9)	99.2 ± 23.6 5.7 (0.5, 10.9)**	98.3 ± 22.0 4.4 (−0.9, 9.7)†	104.5 ± 32.4 11.1 (5.4, 16.8)*
2-h glucagon (pg/mL)	92.4 ± 23.4	93.9 ± 21.4 1.7 (−2.6, 6.0)‡	–	–	98.5 ± 22.8 7.4 (3.0, 11.8)**
Glucagon, $AUC_{0–2\ h}$ (pg h/mL)	203 ± 51.3	207 ± 50.9 4.52 (−4.71, 13.7)‡	–	–	224 ± 57.3 23.3 (14.0, 32.6)*

Table 2 (*Continued*)

	Baseline (n = 76)	Week 12 (n = 75)	Week 24 (n = 70)	Week 36 (n = 69)	Week 52 (n = 62)
Intact proinsulin (pmol/L)	12.05 ± 12.22	9.40 ± 9.38 −2.60 (−4.07, −1.12)**	8.23 ± 7.92 −3.93 (−5.47, −2.39)*	8.26 ± 9.58 −3.90 (−5.39, −2.40)*	8.85 ± 11.17 −3.39 (−4.80, −1.98)*
Matsuda index	3.41 ± 2.33	4.61 ± 3.55 1.26 (0.85, 1.66)*‡	–	–	5.32 ± 4.44 1.94 (1.23, 2.65)*
HOMA-R	5.46 ± 3.89	4.10 ± 3.28 −1.34 (−1.86, −0.83)*	3.79 ± 2.92 −1.76 (−2.25, −1.27)*	3.79 ± 3.05 −1.80 (−2.34, −1.25)*	3.41 ± 2.88 −2.19 (−2.73, −1.65)*
HOMA-β (%)	40.8 ± 36.6	40.9 ± 33.1 0.1 (−4.4, 4.5)	43.7 ± 37.3 1.8 (−2.9, 6.5)	47.5 ± 42.9 5.5 (0.2, 10.9)**	42.2 ± 40.0 −1.4 (−6.8, 3.9)

Values are shown as the mean ± SD (upper) and as the mean (95% confidence interval) change from baseline (lower). *P < 0.001 vs baseline (one-sample t-test); **P < 0.05 vs baseline (one-sample t-test). †n = 68; ‡n = 74. AUC, area under the concentration–time curve; CPR, C-peptide immunoreactivity; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin; HOMA-β, homeostasis model assessment of β-cell function; HOMA-R, homeostasis model assessment of insulin resistance; PPG, postprandial plasma glucose.

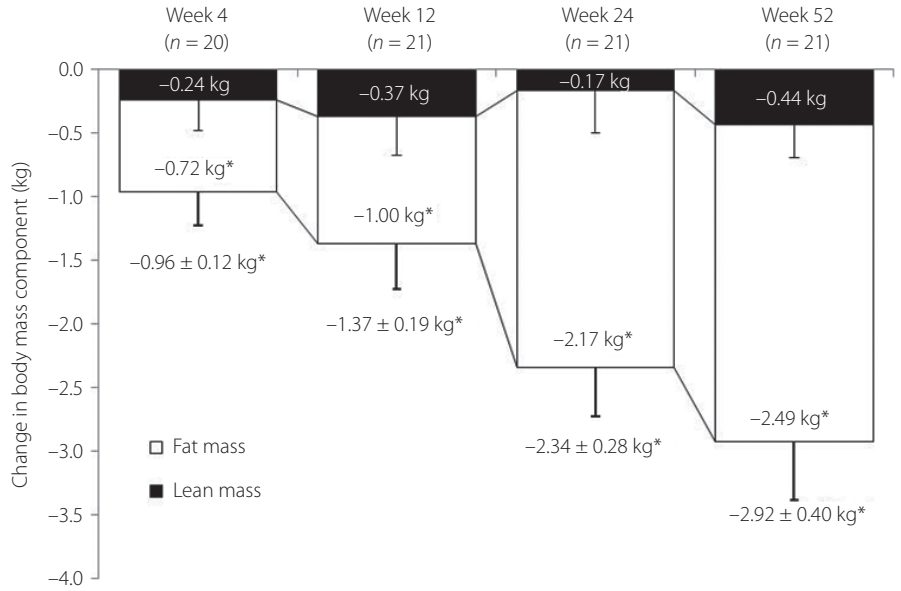

Figure 2 | Changes in fat mass and lean mass as contributors to the change in bodyweight from baseline to weeks 4, 12, 24 and 52. Values are shown as the mean change ± SE. The mean changes ± SE in bodyweight at each point are also shown. *P < 0.05 versus baseline (one-sample t-test).

pressure, diastolic blood pressure and pulse rate decreased significantly from baseline to week 52. There were no clinically abnormal 12-lead electrocardiography findings. The changes in safety-related variables are shown in Table S4.

DISCUSSION

The present study showed that luseogliflozin improves glycemic control in type 2 diabetes patients with inadequate glycemic control on diet/exercise and liraglutide monotherapy. In the current combination therapy study, we observed reductions in HbA1c and FPG (HbA1c −0.68%, FPG −32.1 mg/dL) similar to the results of previous 52-week luseogliflozin + oral antidiabetic drug studies (HbA1c −0.68 to −0.52%, FPG, −21.4 to −17.8 mg/dL)[12]. These results suggest that luseogliflozin add-on therapy is an option to achieve better glycemic control in type 2 diabetes patients inadequately controlled by liraglutide monotherapy. Fasting plasma insulin level and postprandial plasma glucose were decreased at every measuring point, and the slope of regression lines for the ISR and Matsuda Index increased over time. A preclinical study found that luseogliflozin had protective effects on pancreatic β-cells[13]. These results suggest that glucose-stimulated insulin secretory capacity is recovered by the attenuation of glucotoxicity and improvement of insulin resistance. This is supported by the finding that the frequency of hypoglycemia was not remarkably increased despite the greater decrease in FPG.

Table 3 | Summary of adverse events

	Luseogliflozin (n = 76)
Any AE	50 (65.8)
Any ADR	21 (27.6)
Any serious AEs	4 (5.3)
AEs leading to discontinuation	5 (6.6)
Common AEs (AEs in ≥5% of individuals)	
Nasopharyngitis	26 (34.2)
Pollakiuria	7 (9.2)
Hypoglycemia	4 (5.3)
AEs of special interest	
Hypoglycemia	5 (6.6)
Hypoglycemia	4 (5.3)
Hypoglycemia unawareness	1 (1.3)
Urinary tract infections	2 (2.6)
Cystitis	1 (1.3)
Urinary tract infection	1 (1.3)
Genital infections	3 (3.9)
Vulvovaginal candidiasis	2 (2.6)
Prostatitis	1 (1.3)
Pollakiuria	7 (9.2)
AEs related to volume depletion	5 (6.6)
Thirst	3 (3.9)
Dehydration	1 (1.3)
Blood urea increased	1 (1.3)
Skin disorders	4 (5.3)
Eczema	2 (2.6)
Rash	1 (1.3)
Dermatitis contact	1 (1.3)
Gastrointestinal disorders	10 (13.2)
Vomiting	3 (3.9)
Diarrhea	2 (2.6)
Abdominal pain lower	2 (2.6)
Abdominal pain	1 (1.3)
Constipation	1 (1.3)
Enterocolitis	1 (1.3)
Gastric ulcer	1 (1.3)
Large intestine polyp	1 (1.3)

Data are shown as n (%). ADR, adverse drug reaction; AE, adverse event.

Luseogliflozin added to liraglutide significantly reduced bodyweight over a period of 52 weeks (−2.71 kg at week 52), similar to the results of a luseogliflozin monotherapy study (−2.68 kg at week 52)[14], indicating that luseogliflozin caused a similar bodyweight reduction despite the ≥12-week liraglutide pretreatment before luseogliflozin administration. The extent of the weight loss effects of luseogliflozin and liraglutide have been reported to depend on baseline BMI[15–17]. However, in the present study, similar changes in bodyweight were observed in both the high- and low-BMI groups (≥25 and <25 kg/m^2, respectively). Although the mechanism underlying this phenomenon is not clear at present, it might involve a combination of suppression of appetite by liraglutide and calorie loss through glycosuria induced by luseogliflozin.

There were some safety concerns regarding the weight loss induced by SGLT2 inhibitors, such as fluid loss by osmotic diuresis, and sarcopenia,[18] which is an emerging problem among aging societies, such as Japan, a country that has increasing numbers of elderly type 2 diabetes patients[19]. In the present study, the reduction of fat mass was more than fivefold greater than that of lean body mass at week 52. BIA analyses showed that luseogliflozin was associated with greater reductions in fat mass than lean body mass, including water and muscle. These results indicate that the reduction in fat mass was the main contributor to the reduction in bodyweight during luseogliflozin treatment. In clinical studies comprising mainly Caucasians (mean baseline BMI >30 kg/m^2), dapagliflozin and canagliflozin treatment were reported to result in weight loss, two-thirds of which was attributable to a reduction in fat mass. In general, Japanese tend to have lower BMIs than those of Caucasians. Importantly, fat mass reduction in Japanese patients contributed to bodyweight reduction (the weight loss ratio of fat to lean mass was 5:1), similar to studies in Caucasians, although these previous studies used the dual-energy X-ray absorptiometry method rather than the BIA method used in the present study[20,21]. This might be a result characteristic of the combination of luseogliflozin and liraglutide. However, as this difference could be related to differences in race or even in the measuring method itself, further study is required. Finally, in the present study, the change in fat mass correlated with the change in waist circumference. Considering that waist circumference is a predictor of visceral fat mass[22], these results suggest that visceral fat mass decreased during the treatment period.

A slight reduction in lean mass and an increase in hematocrit and blood urea nitrogen were observed over time until week 12, suggesting that luseogliflozin was associated with mild fluid loss in the early treatment period, as reported in a previous study[14]. In addition, the change in blood ketone bodies was similar to that of previous studies[12,14,23]. Thus, there were no serious safety concerns identified regarding fluid loss or blood ketone bodies throughout our 52-week study.

The frequency of hypoglycemia in the present study (6.6% or 0.31 events/patient-year) was not markedly higher than that associated with 52-week luseogliflozin monotherapy (2.3%) or liraglutide monotherapy (minor hypoglycemic episodes: 0.19 events/patient-year, symptoms-only hypoglycemic episodes: 0.51 events/patient-year)[14,16]. None of the episodes of hypoglycemia required assistance or led to treatment discontinuation. Luseogliflozin did not influence the frequency of AEs associated with liraglutide (i.e., gastrointestinal-related AEs and pancreatitis). Our study identified no additional safety concerns associated with luseogliflozin added to liraglutide.

The present study had some limitations. First, this was an open-label, single-arm study with a relatively small sample size; therefore, further investigation is necessary to adequately evaluate this combination therapy. Second, the maximum dose of

liraglutide in Japan is half that used overseas. Therefore, our results are not generalizable to patient populations with different dosing guidelines. Third, the individuals who participated in the BIA analysis were not selected at random, but for practical reasons, which might have introduced bias. Further studies will be required to confirm these results.

In conclusion, luseogliflozin added to liraglutide is well tolerated, significantly improves glycemic control and leads to reductions in bodyweight (especially fat mass). This combination therapy could be an attractive treatment option for overweight or obese Japanese individuals with type 2 diabetes.

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DISCLOSURE

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Figure S1| Study design. HbA1c, glycated hemoglobin.
Figure S2| Time-courses for changes in (a) glycated hemoglobin (HbA1c), (b) fasting plasma glucose (FPB) and (c) bodyweight from baseline to each visit. Values are shown as the mean ± SE in the graphs. Mean values ± SD are also provided in the tables below each graph. $^{*}P < 0.001$ versus baseline (one-sample *t*-test).
Figure S3| Scatterplots for change in glycated hemoglobin (HbA1c) versus change in bodyweight from baseline to week 12 (upper) and week 52 (lower). The *n* (%) for each quartile are shown.
Figure S4| Changes in the meal tolerance test parameters of (a) plasma glucose, (b) serum insulin, (c) serum C-peptide immunoreactivity and (d) plasma glucagon from baseline to weeks 12 and 52. Values are shown as the mean ± SE. $^{\dagger}P < 0.05$ at weeks 12 and 52 versus baseline (one-sample *t*-test). $^{\ddagger}P < 0.05$ at week 52 versus baseline (one-sample *t*-test).
Figure S5| Scatterplot for plasma glucose concentration versus insulin secretion rate at baseline, week 12 and week 52.
Figure S6| Scatterplots for change in fat mass versus change in bodyweight (upper) and change in fat mass versus change in waist circumference (lower) from baseline to week 52. Data are shown for all patients who completed the 52-week treatment period in whom fat mass was measured by bioelectrical impedance analysis ($n = 21$).
Table S1| Study sites and principal investigators.
Table S2| Linear regression analysis of the relationship between insulin secretory rate and plasma glucose concentration.
Table S3| Changes in efficacy values over time in the bioelectrical impedance analysis subset group.
Table S4| Changes in laboratory test values and vital signs over time.
Data S1| Supplementary methods.