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CLINICAL TRIAL

Efficacy and safety of luseogliflozin added to various oral antidiabetic drugs in Japanese patients with type 2 diabetes mellitus

Yutaka Seino[1], Nobuya Inagaki[2], Masakazu Haneda[3], Kohei Kaku[4], Takashi Sasaki[5†], Atsushi Fukatsu[6], Michito Ubukata[7], Soichi Sakai[7]*, Yoshishige Samukawa[7]

[1]Kansai Electric Power Hospital, Osaka, [2]Kyoto University Graduate School of Medicine, Kyoto, [3]Asahikawa Medical University, Hokkaido, [4]Kawasaki Medical School, Department of Internal Medicine, Okayama, [5]Division of Diabetes and Endocrinology, The Jikei University Graduate School of Medical Research, [7]Taisho Pharmaceutical Co., Ltd., Tokyo, and [6]Yachiyo Hospital, Aichi, Japan

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***Correspondence**
Soichi Sakai
Tel.: +81-3-3985-1307
Fax: +81-3-3985-0650
E-mail address: so-sakai@so.taisho.co.jp

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ABSTRACT

Introduction: Two studies were carried out to investigate the efficacy and safety of luseogliflozin added to existing oral antidiabetic drugs (OADs) in Japanese type 2 diabetic patients inadequately controlled with OAD monotherapy.

Materials and Methods: In the trial involving add-on to sulfonylureas (study 03-1), patients were randomly assigned to receive luseogliflozin 2.5 mg or a placebo for a 24-week double-blind period, followed by a 28-week open-label period. In the open-label trial involving add-on to other OADs; that is, biguanides, dipeptidyl peptidase-4 inhibitors, thiazolidinediones, glinides and α-glucosidase inhibitors (study 03-2), patients received luseogliflozin for 52 weeks.

Results: In study 03-1, luseogliflozin significantly decreased glycated hemoglobin at the end of the 24-week double-blind period compared with the placebo (–0.88%, $P < 0.001$), and glycated hemoglobin reduction from baseline at week 52 was –0.63%. In study 03-2, luseogliflozin added to other OADs significantly decreased glycated hemoglobin from baseline at week 52 (–0.52 to –0.68%, $P < 0.001$ for all OADs). Bodyweight reduction was observed in all add-on therapies, even with agents associated with weight gain, such as sulfonylureas and thiazolidinediones. Most adverse events were mild in severity. When added to a sulfonylurea, incidences of hypoglycemia during the double-blind period were 8.7% and 4.2% for luseogliflozin and placebo, respectively, but no major hypoglycemic episodes occurred. The frequency and incidences of adverse events of special interest for sodium glucose cotransporter 2 inhibitors and adverse events associated with combined OADs were acceptable.

Conclusions: Add-on therapies of luseogliflozin to existing OADs improved glycemic control, reduced bodyweight and were well tolerated in Japanese type 2 diabetic patients. These trials were registered with the Japan Pharmaceutical Information Center (add on to sulfonylurea: JapicCTI-111507; add on to other OADs: JapicCTI-111508).

INTRODUCTION

Type 2 diabetes mellitus is one of the most prevalent chronic diseases globally. Although basic management of type 2 diabetes mellitus initially involves diet and exercise therapies, eventually patients often require treatment with oral antidiabetic drugs (OADs). For patients with insufficient glycemic control while receiving conventional OAD monotherapy, combination therapy with another OAD having a different mechanism of action, glucagon-like peptide-1 analog, or insulin might be required[1]. As many patients fail to achieve glycemic goals

†Present address: Division of Translational and Molecular Medicine, Institute of Clinical Medicine and Research, The Jikei University School of Medicine, Chiba, Japan.
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despite treatment with multiple drugs, a new class of antidiabetic agent is needed.

Inhibition of sodium glucose cotransporter 2 (SGLT2) increases urinary glucose excretion (UGE) and reduces plasma glucose levels by suppressing reabsorption of glucose at the renal proximal tubules[2–4]. As the mechanism of action of SGLT2 inhibitors is markedly different from that of other OADs, this makes its combined use with any other OADs possible and thereby provides the additional glucose-lowering effect. Indeed, the efficacy of SGLT2 inhibitors added to metformin has been evaluated by several clinical trials in Europe and the USA[5–7], where metformin is usually used as the first-line drug for treating type 2 diabetes mellitus. In Japanese clinical settings, in contrast, various different initial combination therapies are possible, as the choice of OADs is tailored to the condition of the patients, thus clinical trials investigating the combination therapies with the numerous existing OADs are required.

Sulfonylurea (SU) is frequently used for many diabetic patients, as insulin hyposecretion is regarded as the main pathogenetic mechanism for the development of type 2 diabetes mellitus in the Japanese population[8], so SGLT2 inhibitors are very likely to be added to SU therapy in Japan. Combination therapy of SGLT2 inhibitor with SU, however, could possibly increase the frequency or enhance the intensity of hypoglycemia, a typical side-effect of SU, such as the serious hypoglycemia seen when dipeptidyl peptidase-4 inhibitors (DPP4i) are co-administered with SU[9]. Furthermore, evaluations of whether combining SGLT2 inhibitors with OADs other than SU increases the risk of the major side-effects of these drugs (e.g. weight gain, edema, lactic acidosis, gastrointestinal disorders) are also required, along with assessments of whether the risk of the prevalent adverse drug reactions of SGLT2 inhibitors increases when added to other OADs.

Luseogliflozin is a novel and selective SGLT2 inhibitor. In our 24-week, double-blind, randomized, placebo-controlled trial, luseogliflozin monotherapy was associated with marked improvements in glycemic control and was well tolerated in Japanese patients with type 2 diabetes mellitus[10]. Thus, we carried out two 52-week trials to evaluate the efficacy and safety of luseogliflozin as add-on therapy to every existing OAD that is available in Japanese clinical settings, which are the SUs, biguanides (BGs), DPP4i, thiazolidinediones (TZDs), glinides and α-glucosidase inhibitors (α-GIs).

In the trial involving add-on to SU (study 03-1), luseogliflozin 2.5 mg or a placebo was administered during a 24-week double-blind period, followed by administration of luseogliflozin for a 28-week open-label period (52 weeks in total). In the trial involving add-on to OADs other than SU (study 03-2), luseogliflozin was administered to all patients during a 52-week open-label treatment period.

MATERIALS AND METHODS

These two studies were carried out in compliance with the Declaration of Helsinki, Good Clinical Practice (GCP) and the International Conference on Harmonization (ICH) guidelines. The study protocols were reviewed and approved by the institutional review boards of all participating medical institutions, and written informed consent was obtained from all subjects participating in the studies. The equivalent National Glycohemoglobin Standardization Program value (%) of glycated hemoglobin (HbA1c) was calculated using the Japan Diabetes Society-assigned value[11]. These studies were registered beforehand at the Japan Pharmaceutical Information Center (add on to SU: JapicCTI-111507; add on to other OADs: JapicCTI-111508). The list of study sites and principle investigators are included in the supporting information (Tables S1 and S2).

Study Design

Aimed at investigating the efficacy and safety of luseogliflozin added to other OADs, two studies were carried out where luseogliflozin was given as an add-on to SU (study 03-1) or to other OADs (BG, DPP4i, TZD, glinide, α-GI; study 03-2). These studies were designed by referring to the Japanese guidelines for the clinical evaluation of OADs and long-term treatment[12,13].

Both studies enrolled Japanese patients with type 2 diabetes mellitus in whom plasma glucose control was inadequate on diet and exercise therapies, and treatment with a single OAD (SU: glimepiride, BG: metformin, DPP4i: sitagliptin, vildagliptin or alogliptin, TZD: pioglitazone, glinide: mitiglinide or nateglinide, α-GI: voglibose or miglitol). Study 03-1 (add-on to SU) was a multicenter, placebo-controlled, randomized, double-blind, parallel-group comparative study. Study participants were randomized at a ratio of 2:1 to receive either luseogliflozin 2.5 mg or a placebo (i.e. glimepiride alone) before breakfast once daily. All participants that completed the 4-week observation period and 24-week double-blind treatment period proceeded to the 28-week open-label treatment period and received luseogliflozin. Study 03-2 (add-on to other OADs) was a multicenter, open-label, uncontrolled study in which all participants received luseogliflozin 2.5 mg before breakfast once daily for 52 weeks. In both studies, for patients whose HbA1c was ≥7.4% at both weeks 16 and 20, the dose of luseogliflozin was allowed to be increased to 5 mg. Both studies were carried out from May 2011 to October 2012; 46 medical institutions participated in study 03-1 (add-on to SU) and 68 medical institutions participated in study 03-2 (add-on to other OADs).

Patients

Of the type 2 diabetic patients who had received regular diet therapy and treatment with a single OAD at a fixed dose from over 8 weeks before the observation period, those aged ≥20 years in whom HbA1c was 6.9–10.5% and its change was within 1.0% during the 4-week observation period were selected as study participants. Major exclusion criteria were: the presence of diabetes other than type 2; endocrine disorders other than diabetes that might affect plasma glucose; implementation of diabetic treatment within 8 weeks before the initiation of the

observation period; history of nephrectomy or renal transplantation; renal disorder requiring active treatment; estimated glomerular filtration rate (eGFR) of <45 mL/min/1.73 m^2 during the observation period; urinary tract or genital infection; the presence of obvious dysuria; elevation of aspartate aminotransferase or alanine aminotransferase to ≥2.5-fold the upper limit of normal; blood pressure >170/100 mmHg; change in antihypertensive agent during the observation period; diabetic microangiopathy; and severe heart disease. Use of an insulin product and an antidiabetic agent other than those coadministered in the study was prohibited. Use of a hypolipidemic agent, an antihypertensive agent or a diuretic agent was permitted as long as the dose was kept constant throughout the study period.

Clinical Evaluations

Major efficacy end-points were the changes from baseline (week 0) in HbA1c, fasting plasma glucose (FPG) and bodyweight. The safety end-points were the nature and frequency of adverse events (AEs), including changes in laboratory values, vital signs and 12-lead electrocardiogram (ECG) findings. During the study period, participants visited medical institutions at weeks 0, 2 and 4, and every 4 weeks thereafter until week 52 to undergo medical examination, laboratory tests (hematology, blood chemistry and urinalysis), physical examinations (blood pressure, pulse rate and body temperature) and 12-lead ECG examination. When an AE was observed, its description, severity, seriousness, causal relationship to the study drug and other pertinent information were recorded. All laboratory tests were analyzed at a central laboratory.

Statistical Analyses

Efficacy and safety assessments were carried out in all participants who received the study drug at least once and underwent examination/observation for the post-administration assessment.

Basic statistics of each efficacy end-point were calculated at each evaluation point in both studies. In study 03-1 (add-on to SU), differences between the luseogliflozin group and placebo group in changes in efficacy end-points at the end of the 24-week double-blind treatment period were evaluated. For the evaluation of HbA1c and FPG, analysis of covariance was carried out using the value at the start of the double-blind treatment period as the covariate, and for the evaluation of other efficacy end-points, two-sample *t*-test was applied. When data were missing or deemed unacceptable at week 24 (the end of the double-blind treatment period), the last observation carried forward method was applied. In addition, for each type of coadministered OAD, within-group mean changes from baseline (week 0) for individual efficacy end-points were evaluated by the one-sample *t*-test (missing or unacceptable data were not complemented). In both analyses, significance level was set at 5% (two-sided) and confidence coefficient was set at 95% (two-sided).

Adverse events observed were coded using the Japanese version of the Medical Dictionary for Regulatory Activities, version 15.0, and their frequencies during the 52-week treatment period were tabulated by the type of coadministered OAD. In study 03-1, incidence rates of AEs in the luseogliflozin group and placebo group during the 24-week double-blind treatment period were also tabulated.

Basic statistics of laboratory values, vital signs and 12-lead ECG findings by the type of coadministered antidiabetic agent at each evaluation point through week 52 were calculated.

RESULTS

Demographics

A total of 222 patients were randomized to either the placebo or luseogliflozin group in study 03-1, and 59–117 patients were administered luseogliflozin in each OAD group in study 03-2 (Figure 1). The mean age of each OAD group in study 03-2 (add-on to other OADs) was 57.7–60.8 years, and the percentages of male participants were 58.1–69.5%, whereas the mean HbA1c values at baseline were similar across all groups (7.84–8.00%; Table 1). Similarly, no differences were seen between the luseogliflozin group and placebo group in study 03-1 (add-on to SU).

Efficacy

Efficacy of Luseogliflozin Add-On to SU (Study 03-1)

Luseogliflozin significantly reduced HbA1c from baseline compared with the placebo, with the difference being –0.88% ($P < 0.001$) at week 24 (the end of the double-blind period; Figure 2). Similarly, the differences in the change in FPG and bodyweight compared with the placebo at week 24 were –34.2 mg/dL and –1.51 kg, respectively, where both differences were statistically significant ($P < 0.001$ for both end-points; Figure S1). After 52 weeks of luseogliflozin treatment, HbA1c, FPG and bodyweight were significantly lower than baseline, with the mean change being –0.63%, –22.4 mg/dL and –2.23 kg, respectively.

Efficacy of Luseogliflozin Add-On to Other OADs (Study 03-2)

Luseogliflozin lowered HbA1c when it was added to any of the OADs (Figure 2). Significant lowering of HbA1c was maintained from week 2 through to week 52 when compared with baseline in all the OAD groups, with the mean change in HbA1c from baseline at week 52 being –0.61, –0.52, –0.60, –0.59, and –0.68% for the BG, DPP4i, TZD, Glinide and α-GI groups, respectively ($P < 0.001$ for all groups). Similarly, the decrease in FPG and bodyweight from baseline at week 52 in each OAD group was –21.4 to –17.8 mg/dL and –2.88 to –1.96 kg, respectively, with luseogliflozin significantly lowering the FPG and bodyweight in all these groups ($P < 0.001$ for all groups; Figure S1).

Safety

Safety During the 24-Week Double-Blind Period (Study 03-1)

The incidence of AEs and adverse drug reactions (ADRs) during 24 weeks of treatment with luseogliflozin add-on to SU

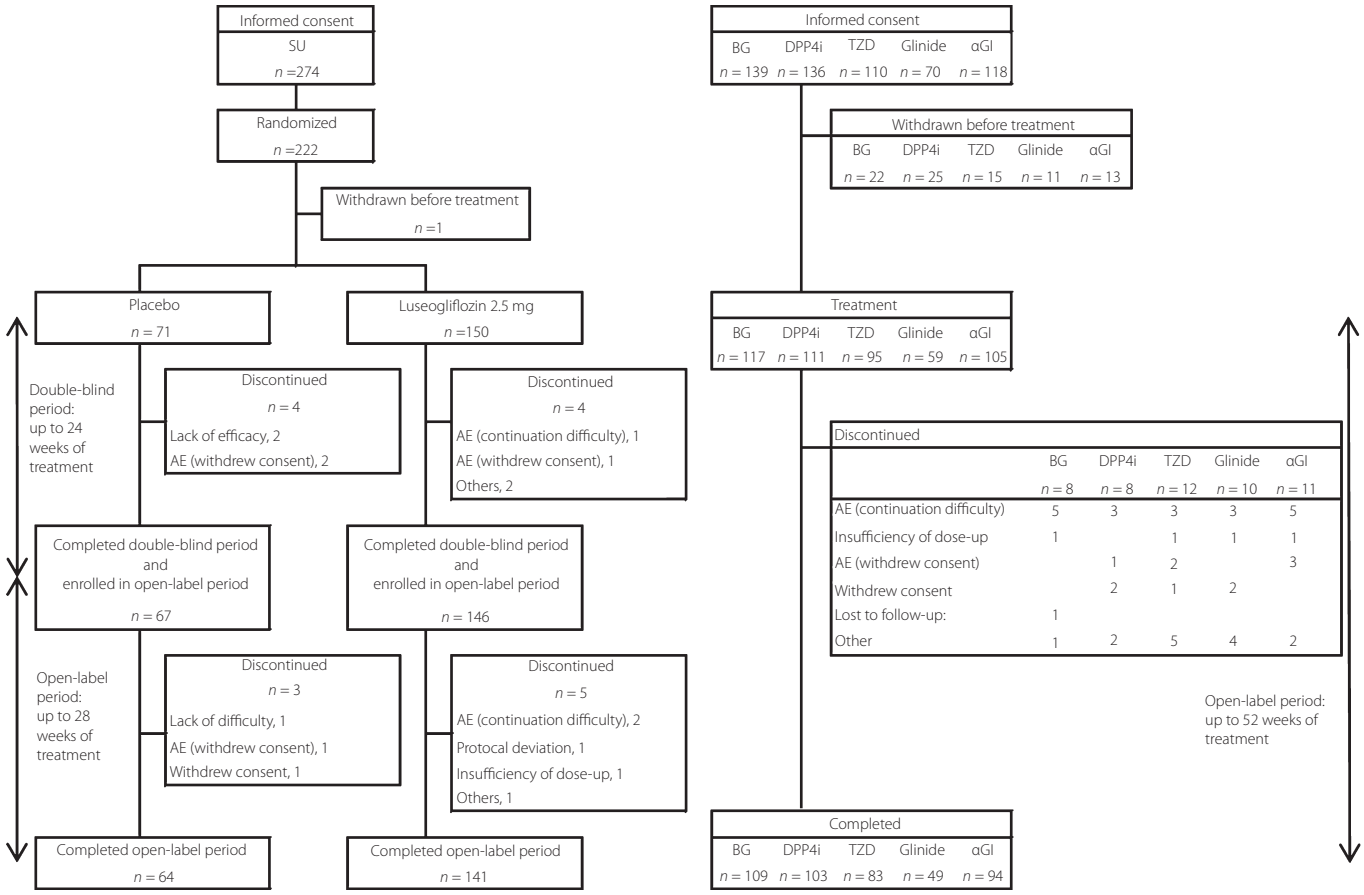

Figure 1 | Patient disposition. AE, adverse event; BG, biguanide; DPP4i, dipeptidyl peptidase-4 inhibitor; SU, sulfonylurea; TZD, thiazolidinedione; α-GI, α-glucosidase inhibitor.

(59.3% and 17.3%) was similar to that of the placebo group (64.8% and 15.5%). Serious AEs (SAEs) were observed in five participants in the luseogliflozin group, but none of these events were considered to be drug-related. Adverse events that led to discontinuation occurred in two participants each in the luseogliflozin group and the placebo group. However, none of these AEs in the luseogliflozin group were considered to be drug-related.

Safety at Week 52 of Treatment (Study 03-1, 03-2)

The incidence of AEs was 71.2–84.2% when luseogliflozin was added to each of the OADs for 52 weeks, whereas ADRs occurred in 12.4–25.4% of patients (Table 2). Common AEs (AEs with an incidence ≥5% in any of the OAD groups) were constipation, nasopharyngitis, pharyngitis, upper respiratory tract infection, contusion, albumin urine present, β2 microglobulin urine increased, C-reactive protein increased, blood urine present, white blood cells urine positive, blood ketone body increased, urine ketone body present, hypoglycemia and back pain. Most of the AEs were of mild severity, and SAEs were observed in 3–11 participants in each OAD group. There was one participant who died in the SU co-administration group (Study 03-1) as a result of acute myocardial infarction that was considered not to be drug-related. A total of five serious ADRs were observed in the studies; these were myocardial infarction (SU), angina unstable (α-GI), acute myocardial infarction (α-GI), prostatitis (TZD) and drug eruption (glinide). Adverse events led to discontinuation in four to eight participants in each OAD group.

Hypoglycemia

The incidence of hypoglycemia in Study 03-1 was 8.7% when luseogliflozin was added to SU for 24 weeks, which was higher than the placebo group (4.2%; Table S3). Meanwhile, the incidence of hypoglycemia was 10.7% over 52 weeks of add-on therapy, where no obvious increase with long-term administration was observed. The incidence of hypoglycemia in participants who received a high dose of SU (≥3 mg) was 8.3% (2/24) compared with 8.7% (11/126) in those who received a low dose (<3 mg). There were no hypoglycemic events that were serious or severe enough to require the assistance of another person. All hypoglycemia recovered rapidly with either food or oral glucose intake, and no participants discontinued because of hypoglycemia.

Table 1 | Demographic and baseline characteristics of patients

	Study 03-1		Study 03-2				
	SU		BG	DPP4i	TZD	Glinide	α-GI
	Placebo $n = 71$	Luseogliflozin $n = 150$	$n = 117$	$n = 111$	$n = 95$	$n = 59$	$n = 105$
Age (years)	59.9 ± 10.5	61.2 ± 8.4	57.7 ± 10.6	58.9 ± 10.8	60.8 ± 11.0	60.1 ± 13.1	60.4 ± 11.1
Sex (male)	48 (67.6%)	112 (74.7%)	68 (58.1%)	75 (67.6%)	66 (69.5%)	38 (64.4%)	70 (66.7%)
Weight (kg)	65.34 ± 10.57	66.39 ± 11.48	69.40 ± 13.07	67.62 ± 14.45	71.67 ± 13.40	66.38 ± 12.71	66.19 ± 12.90
BMI (kg/m^2)	24.66 ± 3.31	24.78 ± 3.63	26.05 ± 3.54	25.25 ± 3.89	26.88 ± 4.35	25.37 ± 4.18	25.12 ± 3.79
HbA1c (%)	8.01 ± 0.73	8.07 ± 0.85	7.84 ± 0.71	7.88 ± 0.78	7.95 ± 0.92	8.00 ± 0.88	7.85 ± 0.77
FPG (mg/dL)	148.2 ± 28.3	151.1 ± 32.7	143.8 ± 24.8	152.1 ± 30.7	141.7 ± 29.9	146.9 ± 31.2	148.0 ± 27.0
Diabetes duration (years)	7.9 ± 6.6	7.4 ± 5.6	5.8 ± 4.4	6.2 ± 5.7	7.1 ± 5.6	6.6 ± 5.6	6.6 ± 6.0
eGFR (mL/min/1.73 m^2)	84.3 ± 16.3	81.5 ± 17.3	85.9 ± 20.6	82.5 ± 17.2	80.1 ± 14.1	84.5 ± 19.9	80.2 ± 15.9

α-GI, α-glucosidase inhibitor; BG, biguanide; BMI, body mass index; DPP4i, dipeptidyl peptidase-4 inhibitor; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; HbA1c, hemoglobin A1c; HOMA-β, homeostasis model assessment of β-cell function; SD, standard deviation; SU, sulfonylurea; TZD, thiazolidinedione. Data represent mean ± standard deviation or *n* (%).

The incidence of hypoglycemia in the other OAD groups in Study 03-2 was 0.9–3.4% (Table 2). Cases of hypoglycemia in these OAD groups were mild in severity, and no cases of hypoglycemia that were serious or severe enough to require the assistance of another person were observed. One participant in the α-GI co-administration group discontinued because of hypoglycemia.

Urinary Tract and Genital Infections

The incidences of urinary tract infections and genital infections in each of the OAD groups over 52 weeks were 0–5.3% and 0–2.1%, respectively (Table 2). Most of these infections were mild in severity, although prostatitis reported in one participant in the TZD co-administration group was serious. All the infections resolved spontaneously or with antibiotic treatment, and no participants discontinued as a result of an infection.

Pollakiuria and Volume Depletion

The incidences of AEs related to pollakiuria or volume depletion in each of the OAD groups over 52 weeks were 0.9–3.4% and 0–1.8%, respectively (Table 2). All these AEs were mild, except for one moderate case of hypotension in the BG co-administration group, and no SAEs were observed. One participant in the TZD co-administration group discontinued because of mild pollakiuria and dehydration. Hematocrit and blood urea nitrogen were seen to be higher than baseline in all the OAD groups (Table 3).

Adverse Events Associated With Each OAD

Edema, a known side-effect of TZDs, did not occur in the TZD co-administration group. Similarly, lactic acidosis, a side-effect of BGs, was also not observed in the present study. While gastrointestinal symptoms, such as constipation, diarrhea, vomiting and gastritis, are known side-effects of α-GI and BG, most of these gastrointestinal AEs were mild in severity in these groups.

Laboratory Tests and Vital Signs

Mild elevation in urinary β2 microglobulin was observed in all the OAD groups, although the level of increase did not suggest tubular impairment, as urinary N-acetyl-D-glucosaminidase was not elevated (Table 3). In addition, marked changes in the eGFR were not observed in any of the OAD groups. In all the groups, blood ketone bodies were elevated, whereas aspartate aminotransferase, alanine aminotransferase, γ-glutamyl transpeptidase and triglyceride levels were decreased compared with baseline. Although low-density lipoprotein levels were slightly increased, the low-density lipoprotein/high-density lipoprotein ratio decreased as a result of an increase in high-density lipoprotein cholesterol levels in all the groups. Adiponectin levels were increased in all the groups. Decreases were seen in both the systolic blood pressure and diastolic blood pressure across all the groups compared with baseline, especially obvious in the TZD co-administration group.

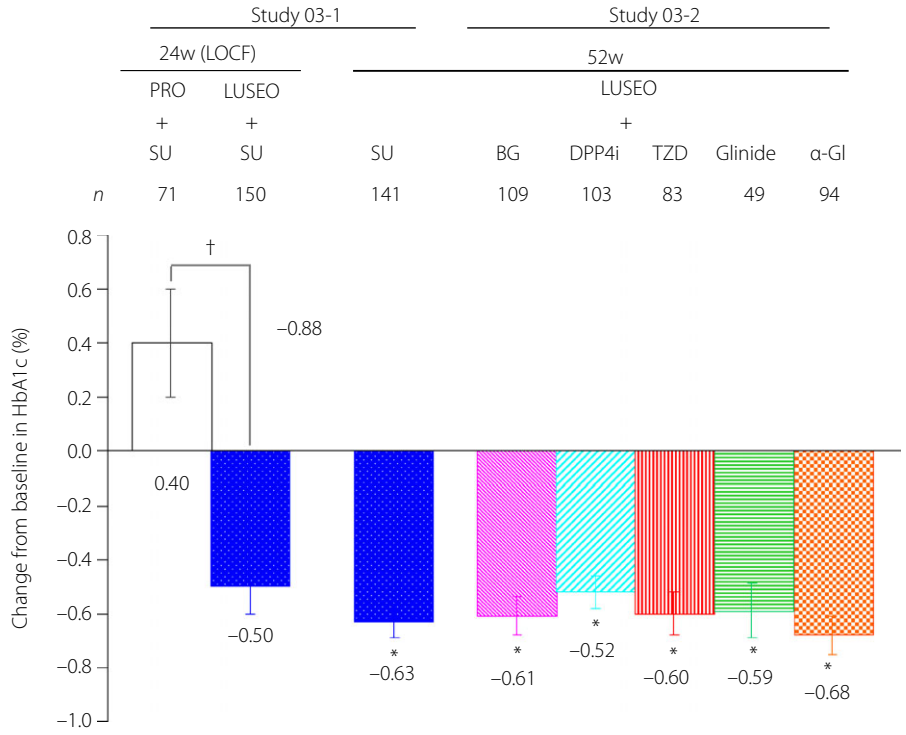

Figure 2 | Changes in glycated hemoglobin (HbA1c) at week 24 for the luseogliflozin and placebo groups in study 03-1, and at week 52 for each oral antidiabetic drug (OAD) group in studies 03-1 and 03-2. Data at week 24 represent mean ± 95% confidence interval, and data at week 52 are mean ± standard error. Differences in least squares (LS) mean change with luseogliflozin relative to placebo at week 24 (LS mean [95% confidence interval], last observation carried forward [LOCF]) was –0.88 [–1.0 to –0.7]%. †$P < 0.001$ *vs* placebo. *$P < 0.001$ *vs* baseline. BG, biguanide; DPP4i, dipeptidyl peptidase-4 inhibitor; LUSEO, luseogliflozin; PBO, placebo; SU, sulfonylurea; TZD, thiazolidinedione; α-GI, α-glucosidase inhibitor.

DISCUSSION

The present study found that add-on of luseogliflozin, a SGLT2 inhibitor, to OADs with different mechanisms of action (SUs, BGs, DPP4i, TZDs, glinides, α-GIs) improved glycemic control as shown by reductions in HbA1c and FPG, and these improvements remained stable throughout 52 weeks of treatment. Thus, luseogliflozin can be a new therapeutic option not only as monotherapy, but also as add-on therapy in patients with type 2 diabetes mellitus inadequately controlled with another OAD.

In the treatment of diabetes, bodyweight, blood pressure and serum lipids also need to be managed in addition to glycemic control[1]. Significant and sustained weight loss with luseogliflozin was observed in all OAD groups. Luseogliflozin in combination with OADs was also associated with decreases in systolic and diastolic blood pressure, increase in adiponectin and improvement in serum lipids (high-density lipoprotein cholesterol and triglyceride). Thus, luseogliflozin is considered to have beneficial effects on these parameters in addition to its glucose-lowering effect independent of the background therapies. This is particularly important, because traditional therapies for type 2 diabetes mellitus result in either weight gain or no changes in weight[1], therefore the added benefit of weight loss with luseogliflozin could be clinically meaningful.

It is expected that luseogliflozin will have the potential to ameliorate weight gain and edema, the major side-effects of other OADs. Some of the existing OADs (SU and TZD) are known to be associated with weight gain[14,15], and this poses a clinical problem as the number of therapeutic options are limited by their side-effects. The finding that luseogliflozin reduced bodyweight even as add-on to SU and TZD, which cause weight gain, is noteworthy, and luseogliflozin will benefit those patients who are receiving these OADs. Furthermore, TZD has been reported to have side-effects, such as edema, which is induced by increased reabsorption of sodium in the renal tubules through peroxisome proliferator-activated receptor-γ[16]. A greater decrease in blood pressure in patients who received the luseogliflozin-TZD combination than those in other OAD groups was observed in the present study. As the reduction in blood pressure was considered to be related to the putative diuretic effect of luseogliflozin, it might partially contribute to the additional decrease in blood pressure in patients with fluid retention caused by TZD.

The incidence of hypoglycemia with luseogliflozin-SU combination therapy was higher than those with SU monotherapy, and it was also higher than those observed in our previous study on luseogliflozin monotherapy (2.3%)[17]. However, there were no major hypoglycemic episodes, and most events were

Table 2 | Summary of adverse events

	Study 03-1	Study 03-2				
	SU	BG	DPP4i	TZD	Glinide	α-GI
n	150	117	111	95	59	105
Any AE	122 (81.3)	92 (78.6)	82 (73.9)	80 (84.2)	42 (71.2)	79 (75.2)
Any ADR	32 (21.3)	23 (19.7)	21 (18.9)	20 (21.1)	15 (25.4)	13 (12.4)
Death	1 (0.7)	0	0	0	0	0
Other serious AEs	9 (6.0)	11 (9.4)	4 (3.6)	7 (7.4)	3 (5.1)	7 (6.7)
AEs leading to discontinuation	4 (2.7)	5 (4.3)	5 (4.5)	5 (5.3)	4 (6.8)	8 (7.6)
Common AEs (AEs with an incidence ≥5% in any of the OAD groups)						
Constipation	8 (5.3)	8 (6.8)	1 (0.9)	5 (5.3)	0	2 (1.9)
Nasopharyngitis	47 (31.3)	38 (32.5)	31 (27.9)	34 (35.8)	15 (25.4)	36 (34.3)
Pharyngitis	8 (5.3)	4 (3.4)	1 (0.9)	7 (7.4)	0	2 (1.9)
Upper respiratory tract infection	8 (5.3)	10 (8.5)	5 (4.5)	3 (3.2)	2 (3.4)	5 (4.8)
Contusion	3 (2.0)	2 (1.7)	5 (4.5)	6 (6.3)	0	2 (1.9)
Albumin urine present	1 (0.7)	1 (0.9)	6 (5.4)	3 (3.2)	2 (3.4)	1 (1.0)
β2 microglobulin urine increased	8 (5.3)	4 (3.4)	9 (8.1)	6 (6.3)	2 (3.4)	4 (3.8)
C-reactive protein increased	14 (9.3)	10 (8.5)	11 (9.9)	16 (16.8)	4 (6.8)	5 (4.8)
Blood urine present	1 (0.7)	2 (1.7)	4 (3.6)	7 (7.4)	1 (1.7)	1 (1.0)
White blood cells urine positive	2 (1.3)	5 (4.3)	4 (3.6)	7 (7.4)	2 (3.4)	0
Blood ketone body increased	1 (0.7)	3 (2.6)	2 (1.8)	5 (5.3)	6 (10.2)	1 (1.0)
Urine ketone body present	1 (0.7)	3 (2.6)	2 (1.8)	3 (3.2)	4 (6.8)	1 (1.0)
Hypoglycemia	16 (10.7)	3 (2.6)	1 (0.9)	3 (3.2)	2 (3.4)	3 (2.9)
Back pain	5 (3.3)	2 (1.7)	4 (3.6)	6 (6.3)	1 (1.7)	3 (2.9)
Special interest AEs						
Hypoglycemia	16 (10.7)	3 (2.6)	1 (0.9)	3 (3.2)	2 (3.4)	3 (2.9)
Urinary tract infections†	0	4 (3.4)	3 (2.7)	5 (5.3)	2 (3.4)	1 (1.0)
Male	0	1 (1.5)	0	1 (1.5)	0	0
Female	0	3 (6.1)	3 (2.9)	4 (8.3)	2 (6.1)	1 (9.5)
Genital infections‡	2 (1.3)	2 (1.7)	2 (1.8)	2 (2.1)	1 (1.7)	0
Male	0	1 (1.5)	1 (1.3)	1 (1.5)	0	0
Female	2 (5.3)	1 (2.0)	1 (2.8)	1 (3.4)	1 (4.8)	0
Pollakiuria	4 (2.7)	2 (1.7)	1 (0.9)	3 (3.2)	2 (3.4)	2 (1.9)
AEs related to volume depletion§	1 (0.7)	2 (1.7)	2 (1.8)	1 (1.1)	0	1 (1.0)

α-GI, α-glucosidase inhibitor; ADR, adverse drug reaction; AE, adverse event; BG, biguanide; DPP4i, dipeptidyl peptidase-4 inhibitor; OAD, oral antidiabetic drug; SAE, serious adverse event; SU, sulfonylurea; TZD, thiazolidinedione. Data represent *n* (%). †Includes cystitis, pyelonephritis, urinary tract infection and cystitis bacterial. ‡Includes genital candidiasis, vulvitis, vulvovaginal candidiasis, vaginitis bacterial and prostatitis. §Includes thirst, blood pressure decreased, blood potassium increased, blood urea increased, blood uric acid increased, dehydration, hypotension and orthostatic hypotension.

mild in severity. No hypoglycemic events required assistance or led to discontinuation, and all events recovered with feeding. No prolonged hypoglycemia was reported. It should be taken into account that the mechanism of action of SUs, which is to directly stimulate insulin secretion from pancreatic β-cells, is associated with the highest risk of hypoglycemia among the OADs, thus the risk of hypoglycemia might naturally increase when luseogliflozin is added to SUs. In addition, because the doses of SU were not to be changed throughout the present study, the risk of hypoglycemia in real-life clinical settings where changes in SU doses could occur needs to be further investigated. Meanwhile, the incidence rates of hypoglycemia in add-on therapy to the other OADs were similar to those of luseogliflozin monotherapy[10]. All events were mild in severity, showing low risks of hypoglycemia in those patients.

Urinary tract and genital infections observed in patients treated with luseogliflozin add-on to other OADs were mild and recovered with appropriate treatments. A higher incidence of polyuria and signs indicating volume depletion, such as small increases in hematocrit, were observed, although only one patient who experienced polyuria and thirst discontinued. These results suggest that combination therapy with other OADs did not exacerbate AEs expected from the pharmacological action of luseogliflozin, such as urinary tract and genital infections, polyuria and volume depletion, although further investigations are required to confirm these findings.

Table 3 | Changes in laboratory test values at week 52

	Study 03-1		Study 03-2									
	SU		BG		DPP4i		TZD		Glinide		α-GI	
	n	Mean ± SD	*n*	Mean ± SD	*n*	Mean ± SD	*n*	Mean ± SD	*n*	Mean ± SD	*n*	Mean ± SD
Hematocrit (%)												
BL	150	42.02 ± 3.76	117	41.57 ± 3.21	111	41.60 ± 3.97	95	40.62 ± 4.15	59	40.99 ± 3.76	105	41.48 ± 3.74
Week 52	140	43.99 ± 4.01	109	43.83 ± 3.72	103	43.67 ± 4.12	83	42.74 ± 4.17	49	43.31 ± 3.91	94	43.98 ± 4.06
Change from BL	2.03 (1.7, 2.4)		2.24 (1.8, 2.7)		1.86 (1.5, 2.2)		2.11 (1.7, 2.5)		2.70 (2.1, 3.3)		2.67 (2.2, 3.1)	
BUN (mg/dL)												
BL	150	14.9 ± 3.9	117	14.3 ± 3.8	111	15.0 ± 4.1	95	15.1 ± 4.0	59	14.5 ± 4.2	105	14.1 ± 4.2
Week 52	141	17.3 ± 4.6	109	16.6 ± 4.2	103	16.2 ± 3.8	83	16.6 ± 4.4	49	16.5 ± 4.5	94	16.4 ± 5.1
Change from BL	2.4 (2, 3)		2.4 (2, 3)		1.2 (1, 2)		1.5 (1, 2)		2.1 (1, 3)		2.4 (2, 3)	
NAG (U/L)												
BL	150	10.10 ± 8.60	117	9.79 ± 7.25	111	9.94 ± 9.45	95	10.97 ± 8.85	59	9.19 ± 5.92	105	9.95 ± 7.99
Week 52	141	9.48 ± 7.53	109	9.88 ± 7.20	103	8.32 ± 5.50	83	10.33 ± 5.99	49	7.72 ± 5.37	94	9.71 ± 8.18
Change from BL	−0.45 (−1.7, 0.8)		0.00 (−1.4, 1.4)		−1.47 (−3.2, 0.3)		−0.71 (−2.3, 0.9)		−1.24 (−3.1, 0.7)		−0.27 (−2.2, 1.7)	
β2-microglobulin (μg/L)												
BL	150	194.8 ± 226.2	117	175.5 ± 244.9	111	143.4 ± 145.8	95	173.5 ± 184.2	59	167.1 ± 187.8	105	250.7 ± 870.2
Week 52	141	265.8 ± 457.4	109	199.1 ± 356.3	103	154.6 ± 128.6	83	287.1 ± 667.2	49	187.7 ± 306.7	94	227.4 ± 372.6
Change from BL	73.1 (7, 139)		35.1 (−1, 71)		19.7 (−6, 46)		112.1 (−17, 241)		16.3 (−65, 97)		−31.1 (−189, 127)	
eGFR (mL/min/1.73 m^2)												
BL	150	81.5 ± 17.3	117	85.9 ± 20.6	111	82.5 ± 17.2	95	80.1 ± 14.1	59	84.5 ± 19.9	105	80.2 ± 15.9
Week 52	141	80.7 ± 17.9	109	86.0 ± 20.1	103	82.8 ± 18.2	83	80.4 ± 14.2	49	83.6 ± 21.1	94	79.7 ± 16.2
Change from BL	−0.24 (−1.7, 1.2)		−0.74 (−2.3, 0.9)		−0.19 (−1.8, 1.5)		0.41 (−1.2, 2.0)		−0.65 (−3.2, 1.9)		−0.62 (−2.1, 0.9)	
AST (IU/L)												
BL	150	24.6 ± 8.1	117	25.5 ± 9.7	111	26.0 ± 10.2	95	26.2 ± 8.9	59	24.3 ± 10.3	105	24.6 ± 9.0
Week 52	141	23.7 ± 7.2	109	22.3 ± 6.4	103	24.2 ± 6.8	83	24.0 ± 9.8	49	22.0 ± 6.1	94	23.3 ± 5.8
Change from BL	−1.1 (−2, 0)		−3.0 (−5, −1)		−2.0 (−4, −1)		−1.9 (−4, 0)		−2.2 (−4, 0)		−1.6 (−3, 0)	
ALT (IU/L)												
BL	150	25.6 ± 13.0	117	30.5 ± 20.3	111	26.9 ± 16.5	95	25.0 ± 13.8	59	26.5 ± 16.1	105	29.8 ± 17.7
Week 52	141	21.8 ± 8.4	109	22.6 ± 13.0	103	23.6 ± 12.5	83	19.9 ± 8.1	49	20.4 ± 11.0	94	23.9 ± 10.3
Change from BL	−4.1 (−6, −2)		−7.2 (−10, −4)		−4.1 (−6, −2)		−4.8 (−7, −3)		−5.9 (−9, −3)		−5.6 (−8, −3)	
γ-GTP (IU/L)												
BL	150	46.5 ± 35.9	117	42.4 ± 36.7	111	46.2 ± 38.4	95	37.1 ± 31.9	59	43.7 ± 64.8	105	43.2 ± 37.1
Week 52	141	37.7 ± 29.5	109	34.2 ± 38.1	103	42.7 ± 37.1	83	33.7 ± 41.2	49	40.1 ± 78.4	94	34.5 ± 32.0
Change from BL	−9.6 (−13, −6)		−7.5 (−13, −2)		−5.5 (−9, −2)		−4.1 (−9, 1)		−5.5 (−11, 0)		−9.3 (−13, −6)	
Triglyceride (mg/dL)												
BL	150	145.1 ± 93.9	117	156.4 ± 122.3	111	134.5 ± 104.4	95	123.8 ± 84.1	59	147.8 ± 98.2	105	138.3 ± 118.3
Week 52	141	137.6 ± 115.7	109	128.8 ± 87.0	103	117.0 ± 84.6	83	115.9 ± 72.6	49	125.5 ± 81.4	94	113.8 ± 116.4
Change from BL	−10.1 (−23, 3)		−27.8 (−52, −4)		−21.6 (−36, −7)		−12.2 (−26, 1)		−24.2 (−42, −6)		−26.2 (−42, −10)	

Table 3 | (*Continued*)

	Study 03-1		Study 03-2									
	SU		BG		DPP4i		TZD		Glinide		α-GI	
	n	Mean ± SD	*n*	Mean ± SD	*n*	Mean ± SD	*n*	Mean ± SD	*n*	Mean ± SD	*n*	Mean ± SD
LDL-C (mg/dL)												
BL	150	118.7 ± 26.2	117	113.9 ± 26.4	111	116.7 ± 29.3	95	112.6 ± 29.2	59	115.5 ± 25.4	105	115.0 ± 27.7
Week 52	141	121.4 ± 26.0	109	117.2 ± 26.4	103	117.7 ± 27.7	83	112.5 ± 24.6	49	121.0 ± 22.9	94	119.4 ± 28.5
Change from BL	2.6 (–1, 6)		4.9 (1, 9)		0.5 (–4, 5)		0.5 (–4, 5)		5.7 (–1, 12)		4.8 (0, 9)	
HDL-C (mg/dL)												
BL	150	56.5 ± 14.2	117	54.6 ± 13.3	111	57.9 ± 16.1	95	61.5 ± 15.6	59	56.0 ± 16.6	105	53.7 ± 14.2
Week 52	141	61.2 ± 16.5	109	59.9 ± 15.3	103	63.2 ± 16.0	83	67.7 ± 20.2	49	59.1 ± 15.1	94	60.8 ± 15.8
Change from BL	4.8 (4, 6)		4.9 (3, 7)		5.8 (4, 7)		6.3 (4, 8)		3.4 (1, 6)		6.5 (5, 8)	
LDL/HDL ratio												
BL	150	2.242 ± 0.744	117	2.210 ± 0.746	111	2.125 ± 0.645	95	2.006 ± 0.960	59	2.189 ± 0.668	105	2.265 ± 0.755
Week 52	141	2.144 ± 0.779	109	2.078 ± 0.676	103	1.972 ± 0.650	83	1.850 ± 0.839	49	2.176 ± 0.668	94	2.072 ± 0.658
Change from BL	–0.106 (–0.19, –0.02)		–0.089 (–0.17, –0.01)		–0.164 (–0.25, –0.08)		–0.158 (–0.24, –0.07)		–0.014 (–0.14, 0.11)		–0.153 (–0.24, –0.06)	
Adiponectin (μg/mL)												
BL	150	6.74 ± 3.21	117	6.06 ± 2.63	111	7.25 ± 4.53	95	15.24 ± 9.92	59	7.11 ± 3.35	105	7.19 ± 3.72
Week 52	141	7.43 ± 3.75	109	6.83 ± 3.26	103	7.36 ± 3.44	83	17.27 ± 12.98	49	7.90 ± 3.40	94	8.25 ± 4.46
Change from BL	0.75 (0.5, 1.0)		0.83 (0.6, 1.1)		0.72 (0.5, 1.0)		2.00 (1.0, 3.0)		0.67 (0.3, 1.1)		1.03 (0.7, 1.4)	
Acetoacetic acid (μmol/L)												
BL	150	36.3 ± 27.3	117	33.6 ± 26.4	111	35.3 ± 23.8	95	41.0 ± 36.9	59	35.8 ± 25.6	105	32.6 ± 24.2
Week 52	141	65.2 ± 49.2	109	59.3 ± 70.6	103	56.6 ± 42.1	83	52.9 ± 43.5	49	63.2 ± 64.0	94	55.6 ± 47.5
Change from BL	29.0 (21, 37)		25.4 (13, 37)		22.2 (14, 30)		10.2 (–1, 21)		27.4 (11, 44)		22.9 (13, 33)	
β-hydroxybutyric acid (μmol/L)												
BL	150	78.8 ± 69.5	117	74.1 ± 79.6	111	75.9 ± 68.4	95	96.2 ± 109.5	59	81.6 ± 74.6	105	72.7 ± 79.4
Week 52	141	151.5 ± 143.8	109	140.5 ± 244.5	103	129.3 ± 132.3	83	140.2 ± 194.0	49	160.4 ± 170.1	94	136.5 ± 158.7
Change from BL	73.2 (49, 97)		65.3 (24, 106)		56.3 (30, 82)		39.4 (–6, 85)		79.8 (36, 123)		64.2 (32, 96)	
SBP (mmHg)												
BL	150	128.9 ± 15.2	117	126.5 ± 13.8	111	126.4 ± 13.4	95	132.3 ± 15.5	59	127.8 ± 15.6	105	128.5 ± 15.4
Week 52	141	124.7 ± 15.0	109	122.4 ± 13.4	103	123.0 ± 13.0	83	124.7 ± 13.1	49	123.7 ± 14.4	94	122.7 ± 14.6
Change from BL	–4.4 (–7, –2)		–4.1 (–7, –2)		–3.2 (–6, –1)		–8.3 (–11, –6)		–4.8 (–9, –1)		–6.3 (–9, –4)	
DBP (mmHg)												
BL	150	75.1 ± 8.6	117	76.3 ± 10.4	111	74.9 ± 9.6	95	76.1 ± 10.7	59	73.5 ± 10.3	105	76.2 ± 10.8
Week 52	141	73.7 ± 9.2	109	75.1 ± 9.9	103	73.9 ± 9.8	83	71.7 ± 10.0	49	71.1 ± 9.9	94	72.5 ± 8.8
Change from BL	–1.7 (–3, 0)		–1.1 (–3, 1)		–0.8 (–3, 1)		–4.5 (–6, –3)		–3.2 (–5, –1)		–3.9 (–6, –2)	

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BG, biguanide; BUN, blood urea nitrogen; CI, confidence interval; DBP, diastolic blood pressure; DPP4i, dipeptidyl peptidase-4 inhibitor; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; NAG, N-acetyl-D-glucosaminidase; SBP, systolic blood pressure; SU, sulfonylurea; TZD, thiazolidinedione; α-GI, α-glucosidase inhibitor; γ-GTP, γ-glutamyl transpeptidase. Values at baseline (BL) and week 52 represent mean ± standard deviation (SD), and changes from BL represent mean (95% confidence interval).

Meanwhile, edema and lactic acidosis, which are known respective side-effects of TZDs and BGs[1], did not occur in the present study. The frequencies of gastrointestinal AEs in patients receiving α-GIs or BGs were not particularly high, and most events were mild. Above all, AEs related to known side-effects of combined OADs were tolerable for patients in this study, although more long-term and large-scale investigations in patient populations covering a broader background are required.

The present study had some potential limitations. First, because no control group was included in study 03-2 and after 24 weeks of treatment in study 03-1, it is unclear whether the rate of AEs was greater than the background rate or whether changes in any of the parameters might be due to the effects of the season or other conditions. Second, the duration and sample size was insufficient to enable assessment of the risk of rare adverse events. Third, the present study only evaluated the efficacy and safety of combining luseogliflozin with OADs, and did not include insulin and GLP-1 analogs.

Luseogliflozin improved glycemic control in combination with other OADs with different mechanisms of action. With regard to safety, the incidence of hypoglycemia was slightly higher when luseogliflozin was added to SU, although no major hypoglycemia occurred. In add-on therapy with other OADs, there was no increase in the frequency and severity of AEs. In conclusion, luseogliflozin used as add-on therapy to other OADs provided additional glycemic control and was generally well tolerated.

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SUPPORTING INFORMATION

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

Figure S1 | Changes in (a) fasting plasma glucose (FPG) and (b) bodyweight at week 24 for the luseogliflozin and placebo groups in study 03-1, and at week 52 for each oral antidiabetic drug (OAD) group in studies 03-1 and 03-2. Data at week 24 represent mean ± 95% confidence interval, and data at week 52 are mean ± standard error. Differences in least squares mean change with luseogliflozin relative to placebo at week 24 (least squares mean [95% confidence interval], last observation carried forward [LOCF]) were –34.2 mg/dL [–41 to –27 mg/dL] and –1.51 kg [–2.0 to –1.0 kg] for the FPG and bodyweight, respectively. $^{\dagger}P < 0.001$ vs placebo. $^{*}P < 0.001$ vs baseline. BG, biguanide; DPP4i, dipeptidyl peptidase-4 inhibitor; LUSEO, luseogliflozin; PBO, placebo; SE, standard error; SU, sulfonylurea; TZD, thiazolidinedione; α-GI, α-glucosidase inhibitor.
Table S1 | The list of study sites and principle investigators (study 03-1: Add-on to sulfonylurea).
Table S2 | The list of study sites and principle investigators (study 03-2: Add-on to other oral antidiabetic drugs).
Table S3 | Details of hypoglycemia during the double-blind period in study 03-1.