

Efficacy and safety of luseogliflozin in Caucasian patients with type 2 diabetes: results from a phase III, randomized, placebo-controlled, clinical trial

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ABSTRACT

Introduction Most data demonstrating the efficacy and safety of luseogliflozin (luseo) in people with type 2 diabetes mellitus (T2DM) originate from the Japanese population. This study evaluated luseo versus placebo (PCB) as add-on to metformin in a Caucasian population with inadequately controlled T2DM.

Research design and methods This was a multicenter, randomized, double-blind, PCB-controlled, parallel-group study. Patients aged 18–75 years with inadequately controlled T2DM (glycated hemoglobin (HbA1c) $\geq 7\%$ to $\leq 10\%$ (≥ 53 to ≤ 86 mmol/mol)) despite a diet and exercise program and on a stable metformin regimen were eligible. Patients were randomized to one of three luseo groups (2.5, 5.0 and 10.0 mg) or PCB for 12 weeks (W12). The primary endpoint was change in HbA1c expressed as least-square means from baseline (W0) to W12.

Results A total of 328 patients were randomized: PCB (n=83) and luseo 2.5 mg (n=80), 5.0 mg (n=86), and 10.0 mg (n=79). Mean age (\pm SD) was 58.5 ± 8.8 years; 64.6% were women; body mass index was 31.5 ± 3.4 kg/m²; and HbA1c was 8.54 ± 0.70 . At W12, mean reductions in HbA1c from W0 were -0.98% , -1.09% , -1.18% , and -0.73% in the luseo 2.5, 5.0 and 10.0 mg, and PCB groups, respectively, all of which were statistically significant. Compared with PCB, HbA1c levels were significantly decreased by 0.25% (p=0.045), 0.36% (p=0.006), and 0.45% (p=0.001) in the luseo 2.5, 5.0, and 10.0 mg groups, respectively. In all luseo dose groups, reductions in body weight were statistically significant compared with PCB. Data from the safety analysis were consistent with the known luseo safety profile.

Conclusions All doses of luseo as add-on to metformin in Caucasian patients with uncontrolled T2DM demonstrated significant efficacy in decreasing HbA1c after W12 of treatment.

Trial registration number ISRCTN39549850.

INTRODUCTION

According to latest estimates from the International Diabetes Federation, the global prevalence of diabetes in individuals aged 20–79 years old was 10.5% (536.6 million people) in 2021 and is expected to reach 783.2 million, representing 12.2% of the world's adult

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Luseogliflozin (luseo) is a highly selective sodium–glucose cotransporter-2 (SGLT-2) inhibitor for reducing blood glucose levels in patients with type 2 diabetes. Currently, most of the data demonstrating the efficacy and safety of luseo originate from studies conducted in Japanese populations.

WHAT THIS STUDY ADDS

⇒ The current study provides evidence that the blood glucose-lowering benefits of luseo are also observed in Caucasian patients with uncontrolled type 2 diabetes.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Therapeutic targeting of SGLT-2 represents a valuable option in the management of patients with type 2 diabetes. Current evidence supports the addition of luseo to treatment protocols in a wide range of patients.

population by 2045.^{1,2} Type 2 diabetes mellitus accounts for most of the projected increase, which reflects not only the growth and demographics of an aging population but also high rates of obesity and increasingly sedentary lifestyles. Treatment of diabetes is aimed mainly at reducing the level of hyperglycemia and therefore at alleviating symptoms and minimizing the risk of long-term complications with the overall aim of enabling people with diabetes to achieve a quality of life and life expectancy similar to that of the general population.³ Data from the United Kingdom Prospective Diabetes Study and many subsequent studies have established that intensive glucose control from the time of diagnosis is associated with significant reductions in the risk of microvascular disease, including retinopathy, neuropathy and nephropathy⁴; risk reductions for myocardial infarction and

death from any cause were also observed with extended post-trial follow-up.^{5–7} These findings have led guidelines to advocate early more intensive glucose-lowering therapy.⁸ While blood glucose targets should be individualized, a reasonable glycated hemoglobin (HbA1c) level for most adults is 7% or less (53 mmol/mol).⁹ Many patients, however, still do not reach their glycemic targets with estimates of the proportion achieving an HbA1c of $\leq 7.0\%$ ranging from 50% to 55%.^{10–12} Recent data from the Russian Federal Diabetes Register suggest that only around half of patients (52%) with a diagnosis of type 2 diabetes are achieving this goal.¹³ The search for novel glucose-lowering agents with alternative mechanisms of action to existing treatments therefore remains a priority.

Recent attention has focused on the kidney as a potential therapeutic target, particularly as renal glucose reabsorption is increased in type 2 diabetes.¹⁴ The orally administered sodium–glucose cotransporter-2 (SGLT-2) inhibitors are a novel therapeutic class, which act by inhibiting SGLT-2-mediated renal glucose reabsorption in the proximal renal tubule. With this mechanism of action, the SGLT-2 inhibitors promote excretion of excess glucose in the urine, thereby lowering blood glucose.^{15–17}

Loss of glucose in the urine also means loss of calories, and weight loss is observed with administration of these agents.¹⁷ Importantly, the mechanism of action of the SGLT-2 inhibitors is not dependent on functioning beta cells or insulin, and they are therefore also an option for those with advanced type 2 diabetes, particularly if glycemic control is inadequate with existing oral glucose-lowering agents.

Luseogliflozin (luseo) (Lusefi, Taisho Pharmaceutical Co., Japan) is a selective SGLT-2 inhibitor developed for the treatment of patients with type 2 diabetes. It has a 50% inhibitory concentration (IC_{50}) of 2.26 nm, which is 1765 times lower than its IC_{50} for SGLT-1.¹⁸ This selectivity allows lower doses of luseo to be used compared with other members of the class: the recommended doses for empagliflozin are 10–25 mg/day, ipragliflozin 25–50 mg/day, dapagliflozin 5–10 mg/day, and canagliflozin 100–300 mg/day, compared with 2.5–5.0 mg/day for luseo.¹⁹

The luseo phase III program was conducted predominantly in Japanese patients at doses of 2.5 and 5.0 mg and demonstrated significant reductions in HbA1c levels and body weight when administered as monotherapy^{20,21} or in combination with other oral glucose-lowering agents^{22–25} or insulin.²⁶ The safety and glucose-lowering efficacy of a 10 mg dosage have also been confirmed in a phase II clinical study conducted in a Japanese population.²⁷ While recent systematic reviews of SGLT-2 inhibitor studies conducted in Asian and non-Asian patients with type 2 diabetes indicate that the glucose-lowering efficacy and safety of these agents were mostly comparable in the two populations^{28,29} data on the efficacy and safety of luseo in a non-Asian population were lacking, mainly due to the fact that this SGLT-2 inhibitor was registered and therefore available only in Japan.

Given the potential racial/ethnic variations in drug disposition and pharmacodynamic response, different prevalence of obesity and adiposity or visceral fat and waist circumference, as well as the more pronounced defect in insulin secretion in Asian patients compared with non-Asians,^{28–33} it is conceivable that altered responses to glucose-lowering drugs may exist between different ethnic groups.^{28,34} For example, results from a pharmacokinetic/pharmacodynamic study conducted in a US non-Asian population suggested that exposure to luseo was lower in comparison with the Japanese population, implying that treatment doses might need to be higher to achieve hypoglycemic efficacy comparable with that shown in Asian populations.³⁵ Moreover, it was shown that the glucose-lowering efficacy of dapagliflozin was less pronounced in non-Asian patients with type 2 diabetes compared with Asians.³⁶ It was therefore of interest to conduct a randomized clinical study with the aim of evaluating the efficacy and safety of luseo at doses of 2.5, 5.0, and 10.0 mg once a day compared with placebo (PCB) as add-on therapy to metformin in a Caucasian population with inadequately controlled type 2 diabetes.

RESEARCH DESIGN AND METHODS

This was a multicenter, randomized, double-blind, PCB-controlled, parallel-group study conducted between February and August 2019 at 34 investigational sites across Russia (15 hospital clinics, 6 university clinics, 13 outpatient clinics and research medical centers). Caucasian outpatients aged 18–75 years with inadequately controlled type 2 diabetes ($HbA1c \geq 7\%$ to $\leq 10\%$ (≥ 53 to ≤ 86 mmol/mol)) despite undergoing a diet and exercise program and receiving a stable metformin regimen (≥ 1500 mg/day, unchanged for ≥ 3 months prior to randomization) were screened. The main exclusion criteria were a diabetes diagnosis of less than 3 months; body mass index (BMI) of ≥ 36 kg/m²; fasting plasma glucose (FPG) of >240 mg/dL (13.3 mmol/L) measured at the inclusion visit or by self-monitoring of blood glucose during the selection period; systolic blood pressure of >180 mm Hg and/or diastolic blood pressure of >100 mm Hg at the inclusion visit (mean of two measurements); estimated glomerular filtration rate of <45 mL/min/1.73 m² (assessed by the modification of diet in renal disease equation and measured during the selection period and at inclusion); any signs of a urinary tract infection or renal infection based on urine analysis during the selection period; a positive pregnancy test; and any severe, uncontrolled conditions incompatible with study treatment or likely to interfere with the conduct of the study.

The study consisted of three periods: a 2-week selection period, a 12-week (W12) double-blind treatment period, and a 2-week follow-up period. Eligible patients were randomized 1:1:1 to luseo 2.5, 5.0, and 10.0 mg or PCB for W12. Randomization was performed using a third-party interactive web response system using a block

randomization method with stratification based on baseline (W0) HbA1c level. Treatment was administered once a day before breakfast as add-on to metformin therapy (≥ 1500 mg/day). Study visits were scheduled at W0 and at weeks 4, 8 and 12; a follow-up visit occurred 2 weeks after the last administration of the study drug. During the double-blind treatment period, the doses of luseo and metformin, as well as the dosage frequency of metformin were not changed unless for safety reasons (eg, hypoglycemia); concomitant use of glucose-lowering medications other than metformin was not permitted during the study, except in case of rescue therapy.

In this study, all participants were instructed to follow a standard diet and physical exercise program during the W12 of follow-up which they adhered to until the end of the clinical phase of the study.

The primary endpoint was mean change in HbA1c from W0 to W12. Changes from W0 to W12 in FPG, postprandial plasma glucose 2 hours after a standardized meal (2 h PPG), body weight, and waist circumference were assessed as secondary endpoints. The proportion of patients achieving the target HbA1c levels of $<7\%$ and $<6.5\%$ at W12 of treatment was evaluated as exploratory endpoints.

Safety was assessed by the incidence of adverse events as well as changes in clinical laboratory parameters and vital signs. Adverse events were classified according to system organ class and preferred term and evaluated in terms of their causal relationship to the study drug and severity by the participating investigators. AESIs were hypoglycemia, polyuria, pollakiuria, events associated with a decrease in fluid volume (including dehydration and a decrease in blood pressure), ketoacidosis, urinary tract infections, and genital infections.

Statistical analyses

Main efficacy analyses for primary and secondary endpoints were performed on the randomized set, which included all patients to whom a therapeutic regimen was randomly assigned. Safety parameters were analyzed in the safety set (patients treated with one or more doses of study drug).

The study sample size was calculated based on the assumption of expected changes in HbA1c from W0 to W12 between at least one dose of luseo and PCB, based on a two-sided Student's t-test for independent samples and using the Bonferroni correction in order to maintain the experiment-wise type I error at 5% (bilateral situation). It was estimated that around 80 patients per treatment group (320 patients overall) would be required to conclude that at least one dose of luseo was superior to PCB with a power of 85%, if the true difference was 0.6% for an SD of 1.1%.

Analysis of covariance (ANCOVA) was used as the main method of assessment of the primary endpoint, with W0 HbA1c value as a covariate. Unrestricted least significant difference (LSD) method was applied to the ANCOVA results with the calculation of least-square (LS) means with 95% CIs for the difference between each dose level

and PCB. The 'imputation procedure' was used for the primary analysis of the primary endpoint. ANCOVA was used as the main method of assessment of the secondary endpoints, with W0 value as a covariate. The unrestricted LSD method was applied to the ANCOVA results with the calculation of LS means with 95% CIs for the difference between each dose level and PCB. Changes in quantitative data are presented as numbers of valid observations, mean, 95% CI for mean, and SD. All categorical and qualitative data are presented as absolute numbers and percentages. Assessment of normality for the quantitative data was performed using the Shapiro-Wilk test. Holm-Bonferroni correction was used in order to take into account a multiplicity of comparisons induced by the assessment of three luseo doses versus PCB.

RESULTS

A total of 447 patients were selected for the study, of whom 119 did not meet the inclusion criteria. As a result, 328 patients with stable uncontrolled type 2 diabetes despite metformin monotherapy were randomized: luseo 2.5 mg ($n=80$), luseo 5 mg ($n=86$), luseo 10 mg ($n=79$), and PCB ($n=83$). The efficacy and safety analysis sets included 328 patients each. A total of 318 (97%) patients completed the study with a similar frequency in each group. Of the 10 patients who withdrew from the study, 3 were discontinued due to the occurrence of an adverse event, 2 were withdrawn due to uncooperative behavior and inability to follow the protocol, and 4 patients withdrew from the study due to non-medical reasons. One patient was withdrawn from the PCB group at week 8 due to an FPG greater than 270 mg/dL.

Demographic and W0 characteristics were balanced across treatment groups with no statistically significant intergroup differences in demographic characteristics, W0 characteristics, or concomitant conditions (table 1). Mean age was 58.5 ± 8.8 years; 64.6% were women; BMI was 31.5 ± 3.4 kg/m²; HbA1c was 8.54 ± 0.70 ; FPG was 9.3 ± 2.2 mmol/L; 2 h PPG was 14.1 ± 3.8 mmol/L; and mean diabetes duration was 6.1 ± 5.1 years.

Efficacy of luseo on glycemic control

HbA1c reductions from W0 to W12 were statistically significant in all dose groups (figure 1). LS mean changes in HbA1c from W0 to W12 were -0.98% (95% CI -1.16 to -0.81) for luseo 2.5 mg, -1.09% (95% CI -1.26 to -0.93) for luseo 5.0 mg, and -1.18% (95% CI -1.36 to -1.01) for luseo 10.0 mg, compared with -0.73% (95% CI -0.91 to -0.56) in the PCB group.

The reductions in HbA1c were also statistically significant for all luseo dose groups compared with PCB: -0.25% ($p=0.045$) luseo 2.5 mg, -0.36% ($p=0.006$) luseo 5.0 mg, and -0.45% ($p=0.001$) luseo 10.0 mg (figure 2).

Secondary endpoints

Reductions in FPG and 2 h PPG at W12 compared with W0 were statistically significant in all groups (table 2). Comparisons between the luseo groups and PCB,

Table 1 W0 characteristics of the patients in the assigned treatment groups

Parameter	Luseo 2.5 mg (n=80)	Luseo 5 mg (n=86)	Luseo 10 mg (n=79)	Placebo (n=83)	Total (N=328)
Age (years)*	59.19±8.56	58.86±8.46	57.85±9.59	57.96±8.63	58.47±8.79
Female sex, n (%)	46 (57.5)	58 (67.4)	56 (70.9)	52 (62.7)	212 (64.6)
Race, n (%)	80 (100)	86 (100)	79 (100)	83 (100)	328 (100)
BMI (kg/m ²)*	32.13±2.87	30.66±3.87	31.54±3.20	31.70±3.40	31.49±3.39
BMI ≥30 kg/m ² , n (%)	62 (77.5)	53 (61.6)	54 (68.3)	62 (74.7)	231 (70.4)
Waist circumference (cm)*	105.51±10.76	102.33±12.39	102.70±10.60	103.30±11.90	103.44±11.48
HbA1c (%)*	8.52±0.66	8.54±0.71	8.56±0.73	8.54±0.71	8.54±0.70
HbA1c ≥8.5%, n (%)	27 (33.8)	33 (38.3)	29 (36.7)	39 (47.0)	128 (39.0)
FPG (mmol/L)*	9.15±2.17	9.07±2.29	9.28±2.01	9.54±2.16	9.26±2.16
eGFR >60 mL/min, n (%)	76 (95.0)	78 (90.7)	69 (87.3)	80 (96.4)	303 (92.4)
Diabetes duration (years)*	5.58±5.29	6.48±4.89	6.01±4.74	6.24±5.36	6.09±5.06
Concomitant comorbidities					
HTN, n (%)	54 (67.5)	55 (64.0)	52 (65.8)	56 (67.5)	217 (66.2)
Dyslipidemia, n (%)	33 (41.2)	34 (39.5)	32 (40.5)	31 (37.3)	130 (39.6)

W0 data are provided descriptively; no formal intergroup analysis was performed.

*Mean±SD percentages may not total 100 because of rounding.

BMI, body mass index; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin; HTN, arterial hypertension; luseo, luseogliflozin; W0, week 0.

expressed as LS means, revealed significant reductions in FPG of -0.63 and -0.66 mmol/L in the luseo 5 and 10 mg groups ($p=0.022$ for both groups); the -0.38 mmol/L reduction in the 2.5 mg group did not reach statistical significance ($p=0.131$). When compared with PCB, 2 h PPG was significantly decreased in the luseo 2.5 and 10.0 mg groups by -1.22 mmol/L ($p=0.019$) and -1.48 mmol/L ($p=0.005$), respectively, and the observed decrease of -0.73 mmol/L in the 5.0 mg group was nominal ($p=0.104$) (online supplemental table 1).

The combination of metformin and luseo was associated with statistically significant reductions in body weight from W0 of 2.32 kg (95% CI -2.89 to -1.75) for luseo 2.5 mg, 2.46 kg (95% CI -2.99 to -1.94) for luseo 5.0 mg, and 2.96 kg (95% CI -3.50 to -2.42) in those treated with luseo 10.0 mg

(table 2). When compared with PCB, body weight was significantly reduced from W0 by 0.87 ($p=0.029$), 1.02 ($p=0.015$), and 1.51 ($p<0.001$) kg in the luseo 2.5, 5.0, and 10.0 mg groups, respectively. Reductions in body weight were accompanied by decreases in waist circumference at W12, which were statistically significant in all groups compared with W0.

Exploratory endpoint

The proportions of patients achieving the predefined HbA1c target of less than 7% at W12 were around a third (31.3%; 95% CI 21.35% to 42.59%, $n=25$) in the PCB group, and 27.4% (95% CI 17.61% to 39.09%, $n=20$), 44.7% (95% CI 33.91% to 55.89%, $n=38$), and 41.6% (95% CI 30.43% to 53.36%, $n=32$) in the luseo 2.5, 5.0 and 10.0 mg groups, respectively. The proportions

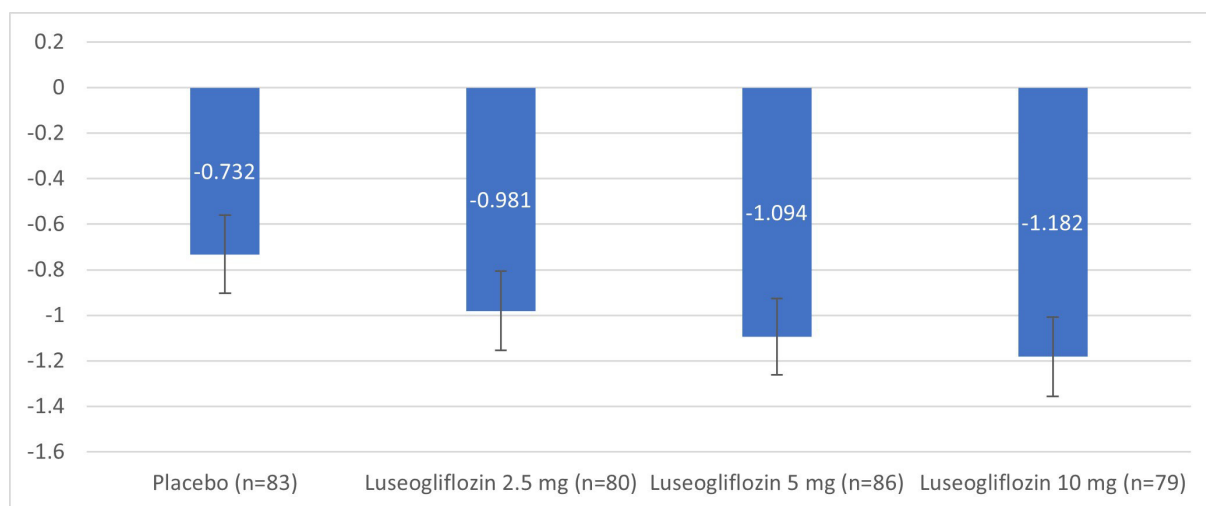


Figure 1 Mean change (±SD) in glycated hemoglobin level (%) from baseline to week 12.

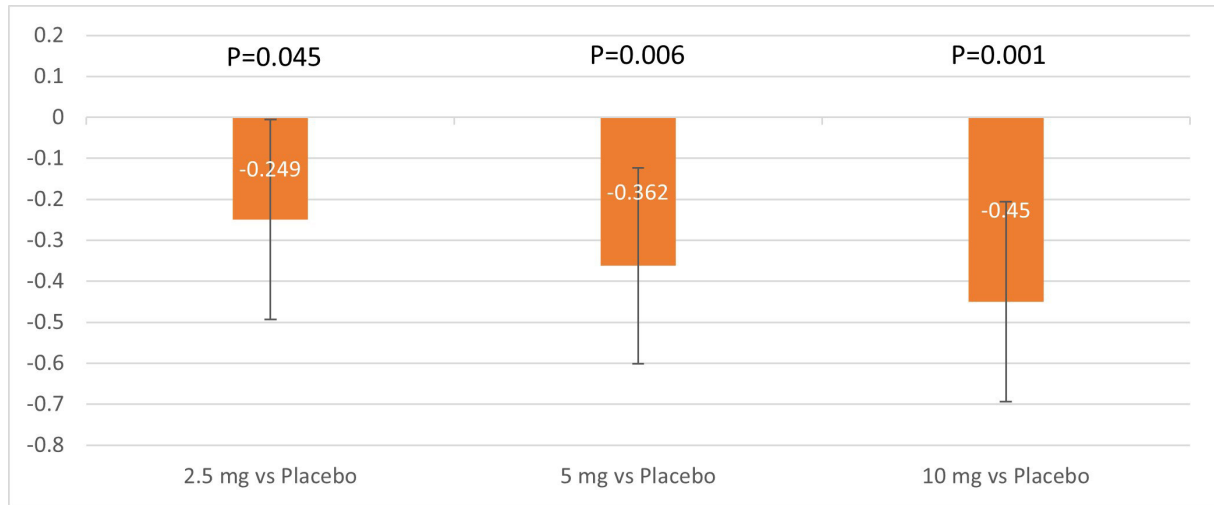


Figure 2 Mean difference (±SD) in glycated hemoglobin (%) in luseogliflozin groups versus placebo at week 12.

reaching a target HbA1c of <6.5% at W12 were 8.8% (95% CI 3.59% to 17.20%, n=7) in the PCB group, and 11.0% (95% CI 4.85% to 20.40%, n=8), 12.9% (95% CI 6.64% to 21.98%, n=11), and 13.0% (95% CI 6.41% to 22.59%, n=10), respectively, in the luseo 2.5, 5.0, and 10.0 mg groups (online supplemental figure 1).

Safety

Overall, 128 patients (39.0%) experienced at least one adverse event during the study (including treatment as well as follow-up period). The most frequent adverse event was hypoglycemia, which occurred in 31 patients (9.5%) (see table 3). Interestingly, there was a trend toward a decrease in the number of patients who experienced hypoglycemia with increased luseo dose (from 12% in the PCB group to 6.3% in the 10 mg group), although this trend was not tested statistically. Fifty-eight treatment-emergent hypoglycemic episodes occurred in 27 patients (8.2%). These episodes were all non-serious, evenly distributed between treatment arms: eight (9.6%) patients in the PCB arm and six (7.5%), eight (9.3%), and five (6.3%) patients, respectively, in the luseo 2.5, 5.0, and 10.0 mg arms. All hypoglycemia cases were mild, and the majority of cases were not causally related to the treatment. Approximately half of treatment-emergent

hypoglycemic episodes were associated with confounding factors (eg, skipped meal and increased physical activity). Among the 27 patients with treatment-emergent hypoglycemia, 11 had symptomatic hypoglycemic episodes, which corresponds to 3.4% of 328 patients. None of these episodes required medical assistance, and in half of the cases, symptoms resolved without any action.

A total of 41 (12.5%) patients experienced 78 adverse events of special interest (AESIs). The frequencies and distributions of AESI are provided in table 3. Apart from hypoglycemia, other AESIs included nine cases of genitourinary tract infections, whose rate was relatively low and occurred at similar frequency across treatment arms; two cases of pollakiuria; one case of polyuria; and two cases of hypotension in the luseo 10.0 mg group. The overall rates of ketonuria and increased blood ketone bodies were 1.5% and 0.3%, respectively, without clinically relevant difference between the luseo and PCB groups. Moreover, one case of nasopharyngitis and one case of pharyngitis were reported in the PCB group and classified as not related to the investigated medicinal product.

There were seven serious adverse events in six patients across all groups (less than 2% in each group): pneumonia and brain edema in the same patient in the luseo

Table 2 Changes from baseline to week 12 in secondary endpoints

Parameter	Luseo 2.5 mg (n=80)	Luseo 5 mg (n=86)	Luseo 10 mg (n=79)	Placebo (n=83)
FPG (mmol/L)	-0.82 (95% CI -1.17 to -0.47)	-1.07 (95% CI -1.40 to -0.74)	-1.11 (95% CI -1.45 to -0.77)	-0.44 (95% CI -0.78 to -0.10)
PPG (mmol/L)	-2.14 (95% CI -2.80 to -1.48)	-1.65 (95% CI -2.26 to -1.04)	-2.39 (95% CI -3.04 to -1.75)	-0.92 (95% CI -1.56 to -0.28)
Body weight (kg)	-2.32 (95% CI -2.89 to -1.75)	-2.46 (95% CI -2.99 to -1.94)	-2.96 (95% CI -3.50 to -2.42)	-1.45 (95% CI -1.98 to -0.91)
Waist circumference (cm)	-2.08 (95% CI -3.08 to -1.08)	-2.46 (95% CI -3.38 to -1.54)	-2.77 (95% CI -3.74 to -1.796)	-1.74 (95% CI -2.69 to -0.794)

FPG, fasting plasma glucose; luseo, luseogliflozin; PPG, postprandial plasma glucose.

Table 3 Safety profile according to randomized treatment arm

Adverse event type	Luseo 2.5 mg (n=80)	Luseo 5 mg (n=86)	Luseo 10 mg (n=79)	Placebo (n=83)	Total (n=328)
Adverse events	31 (38.75%)	28 (32.56%)	33 (41.77%)	36 (43.37%)	128 (39.02%)
Adverse events of special interest	8 (10.00%)	12 (13.95%)	8 (10.13%)	13 (15.66%)	41 (12.50%)
Urethritis	0 (0.0%)	1 (1.2%)	0 (0.0%)	0 (0.0%)	1 (0.3%)
Urinary tract infection	0 (0.0%)	1 (1.2%)	0 (0.0%)	2 (2.4%)	3 (0.9%)
Cystitis	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.2%)	1 (0.3%)
Orchitis	0 (0.0%)	1 (1.2%)	0 (0.0%)	0 (0.0%)	1 (0.3%)
Balanitis candida	0 (0.0%)	0 (0.0%)	1 (1.3%)	0 (0.0%)	1 (0.3%)
Hypoglycemia	8 (10.0%)	8 (9.3%)	5 (6.3%)	10 (12.0%)	31 (9.5%)
Polyuria	0 (0.0%)	0 (0.0%)	1 (1.3%)	0 (0.0%)	1 (0.3%)
Pollakiuria	0 (0.0%)	1 (1.2%)	1 (1.3%)	0 (0.0%)	2 (0.6%)
Hypotension	0 (0.0%)	0 (0.0%)	2 (2.5%)	0 (0.0%)	2 (0.6%)
Blood ketone bodies increased	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.2%)	1 (0.3%)
Ketonuria	0 (0.0%)	0 (0.0%)	4 (5.1%)	1 (1.2%)	5 (1.5%)
Serious adverse events	1 (1.25%)	1 (1.16%)	2 (2.53%)	2 (2.41%)	6 (1.83%)
Adverse events leading to study drug withdrawal	1 (1.2%)	0 (0.0%)	1 (1.3%)	1 (1.2%)	3 (0.9%)

luseo, luseogliflozin.

2.5 mg group, hospitalization due to unstable angina in the luseo 10.0 mg group, two cases of uncontrolled hypertension (hypertensive crisis in the luseo 10.0 mg group and decompensation of hypertension in the PCB group), one case of allergic urticaria in the luseo 5.0 mg group, and one case of drug-induced hepatitis in the PCB group. None of the serious adverse events were considered related to the study drug by the investigator. One patient died in the luseo 2.5 mg group with brain edema and pneumonia as the causes of death. This death was not considered by investigators to be related to the investigational drug. The rate of adverse events that led to study drug withdrawal was low (0.9%, n=3). In the luseo 2.5 mg group, one patient stopped taking the investigational drug due to the aforementioned occurrence of a serious adverse event not related to the study drug (brain edema), and one patient in the luseo 10.0 mg group withdrew from the assigned treatment due to palpitations. One patient in the PCB group discontinued due to cystitis.

DISCUSSION

In this study, all three dosages of luseo significantly decreased HbA1c levels after W12 of treatment in a Caucasian population with type 2 diabetes and inadequate glycemic control on diet/exercise and metformin monotherapy. The improvements in HbA1c occurred in conjunction with significant reductions in FPG and 2 h

PPG at W12 compared with W0. The obtained results for the primary endpoint were comparable with previously reported data on the efficacy of luseo in Asian patients with type 2 diabetes^{22–25} and showed that all therapeutic regimens of the drug (2.5, 5.0 and 10.0 mg once a day) as add-on to metformin were safe and effective in terms of glycemic control, primarily assessed as HbA1c reduction. However, it is important to highlight here that efficacy results from this study should not be directly compared with those obtained from Japanese studies as population characteristics and study designs may vary significantly.

In the current study, HbA1c reductions of 0.98% with luseo 2.5 mg, 1.09% (luseo 5.0 mg) and 1.18% (luseo 10.0 mg) were observed after W12 of treatment in patients inadequately controlled on metformin monotherapy. Increases in the proportion of patients achieving both HbA1c targets ($\leq 7\%$ and $\leq 6.5\%$) were also observed despite the short-term nature of the study. Reductions within a range of 1% are important, given that data from the Action in Diabetes and Vascular disease: Preterax and Diamicon Modified Release Controlled Evaluation trial indicated that every 1% HbA1c rise above 7% was associated with a 38% higher risk of a macrovascular event, and every 1% HbA1c rise above 6.5% was associated with a 40% higher risk of a microvascular event and a 38% higher risk of death (all $p < 0.0001$).³⁷ Similarly, data from United Kingdom Prospective Diabetes Study 35 showed that each 1% reduction in HbA1c in a newly diagnosed

population with type 2 diabetes was associated with a 21% lower odds of developing any complication related to diabetes, including 14% lower odds of having a myocardial infarction and 37% lower odds of developing microvascular complications.⁵

The results of a meta-analysis by Zhang *et al*, which included randomized controlled trials of adult patients with type 2 diabetes inadequately controlled on metformin monotherapy, showed that adding an SGLT-2 inhibitor to metformin resulted in additional significant reductions in HbA1c of 0.50% (95% CI -0.62% to -0.38%, $p < 0.0001$).³⁸ Our data showed that compared with PCB, patients receiving any dosages of luseo achieved a statistically significant HbA1c decrease at W12 of the study. Interestingly, the observed mean change of HbA1c in the PCB group versus W0 was unexpectedly high (0.73%). A potential explanation for this observation might be the presence of the so-called positive PCB effect in the current trial, which was slightly higher than that observed in previous trials conducted with luseo but similar to that observed with another SGLT-2 inhibitor versus PCB.³⁹ The presence of a significant PCB effect may reflect the better adherence of patients participating in clinical trials to the assigned treatment interventions including those aimed at lifestyle and diet modifications, the so-called Hawthorne effect.⁴⁰

There is considerable rationale for combining metformin with an SGLT-2 inhibitor. Both are administered orally, and the complementary mechanisms of action of the two agents offer the potential for improved glucose control compared with that achieved with the individual agents.^{41 42} Metformin is considered to be neutral in terms of weight gain, while SGLT-2 inhibitors are proven to be associated with weight loss in the range of 1.5–2.0 kg, a benefit that is independent of whether or not they are used as monotherapy or in combination with other glucose-lowering drugs.⁴³ This is an appealing clinical effect given that overweight and obesity are often comorbid conditions in patients with diabetes.⁴⁴ In two meta-analyses conducted by Cai *et al*²⁹ and Scheen,⁴⁵ it was shown that the SGLT-2 inhibitors have a positive effect on bodyweight reduction and that this effect was comparable in Asian and non-Asian patients with type 2 diabetes. Mechanisms of bodyweight reduction of SGLT-2 inhibitors are known to be related mainly to caloric loss due to glucose excretion in the urine as well as to reduction in body fat and lean body mass.^{29 45} Data from body composition analysis indicate that a reduction in fat mass is the main contributor to the reduction in body weight during luseo treatment and not lean body mass, including water and muscle.²⁴ In the meta-analysis of Cai *et al*,²⁹ treatment with luseo when compared with PCB was associated with a significant reduction of body weight (-1.68 kg, 95% CI -1.95 to -1.41 kg; $p < 0.01$). The decrease in body weight from W0 to W12 compared with PCB in the current study with a Caucasian population ranged from 0.87 kg with 2.5 mg to 1.02 and 1.51 kg with the 5.0 and 10.0 mg luseo doses, respectively. Interestingly, in the

aforementioned meta-analysis, the authors also conducted a metaregression analysis that did not show significant associations between bodyweight reductions observed in Asian as well as non-Asian patients and changes in HbA1c or W0 weight or BMI.²⁹ In the future, it might be reasonable to perform such an analysis to adjust the effect size of luseo on body weight.

Study treatment was well tolerated by the majority of patients in all study groups. Almost all treatment-related adverse events were of mild or moderate intensity (except one fatal case of pneumonia and brain edema in one patient, which was not considered related to the study drug). This study did not raise any new concerns, and the safety profile corresponded to the known safety data for luseo obtained mostly in an Asian population. The data obtained in our study indicate that treatment with luseo was well tolerated regardless of the luseo dose received.

The most common treatment-emergent adverse event was hypoglycemia, which occurred in 8.2% of patients with a similar frequency between the groups, including PCB. Neither metformin nor the SGLT-2 inhibitors act on the beta-cell to stimulate insulin release and the rate of symptomatic hypoglycemia was low, and not related to luseo dose. Further analysis revealed that approximately half of the episodes were associated with confounding factors such as skipped meals or increased physical activity. None of the symptomatic episodes required medical assistance.

It should be noted that the safety profile of the SGLT-2 inhibitors is generally comparable, and the drugs are well tolerated. However, there are some important concerns related to SGLT-2 inhibitor use such as risk of genital mycotic infections, diabetic ketoacidosis (DKA), bone fracture and lower limb amputation. Available data on luseo indicate that the rate of urinary tract and genital infections is lower than that observed in clinical studies with other SGLT-2 inhibitors.^{38 46 47} There was no significant difference in the rate of urinary tract and genital infections between the three luseo groups and PCB in the current study. In addition, the rates of other conditions relevant to urogenital infections such as dysuria, leukocyturia, genital itching and vulvovaginal itching were also similar.

There were no concerns that treatment with luseo could lead to an increase in DKA occurrence. An increase in ketone bodies in the blood as well as ketonuria was observed with both PCB and luseo 10.0 mg, but the rate was low and similar between these groups. There were no cases of bone fracture or limb amputation.

Study limitations

This study had some limitations. The endpoints selected did not include a comparative assessment of the effect of luseo on blood pressure and lipid profiles, which represent an interest to comprehensively evaluate additional effects of luseo.

This was a short-term study with only W12 of follow-up to evaluate the glucose-lowering efficacy of three dosages

of luseo in a Caucasian population of patients with type 2 diabetes. A W12 follow-up period was considered sufficient for evaluation of the dynamics of diabetes control when HbA1c is used as a primary parameter and for the development of any adverse events on therapy.⁴⁸ However, this short treatment duration precludes any conclusions being made on the long-term efficacy and safety of treatment with luseo including rare side effects.

CONCLUSIONS

This study evaluated the efficacy and safety of three doses of luseo versus PCB as add-on to metformin in Caucasian patients with inadequately controlled type 2 diabetes. The results confirmed that all therapeutic regimens of luseo (2.5, 5.0 and 10.0 mg once a day) as add-on to metformin safely and effectively improved glycemic control as well as other metabolic parameters. Study treatment was well tolerated by the majority of patients in all study groups. No new or specific safety concerns were detected with regard to any of the analyzed safety parameters. The findings of the study confirm glucose-lowering efficacy, beneficial effects on body weight, good safety profile and tolerability of luseo in a Caucasian population of patients with type 2 diabetes.

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Competing interests Luseogliflozin (luseo) was discovered and developed by Taisho Pharmaceutical Co. JSC Servier has signed a licensing and supply agreement with Taisho Pharmaceutical Co. Under this agreement, Taisho grants Servier the exclusive rights for manufacturing, development, distribution, commercialization and promotion of the finished pharmaceutical products containing luseo in Russia and the Eurasian Economic Union. MS is chief scientific secretary and member of the Presidium of the Board of the Russian Association of Endocrinologists. She has acted as a speaker for Servier and received support for congress participation. BK, EE, and EI are full-day contract employees of JSC Servier, Russia. AA is an ex-employee of JSC Servier, Russia.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by the Ministry of Health of the Russian Federation, the Ethics Council of the Ministry of

Health of the Russian Federation, and independent local ethics committees of the investigational sites. Approval by the Ministry of Health of the Russian Federation was obtained on September 4, 2018 (approval ID number 176). The study was performed in accordance with good clinical practice and the ethical principles derived from the revised Declaration of Helsinki. Signed informed consent was provided by all participants of this study, which was obtained before any research procedures were carried out.

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Supplementary data

Supplementary Table 1 Mean differences (\pm SD) between the luseogliflozin and placebo groups in secondary endpoints at week 12.

Comparison vs Placebo	Luseogliflozin 2.5 mg (n=80)	Luseogliflozin 5 mg (n=86)	Luseogliflozin 10 mg (n=79)
FPG (mmol/L)	-0.38 (95% CI: -0.86; 0.11) NS	-0.63 (95% CI: -1.09; -0.15) p=0.022	-0.66 (95% CI: -1.15; -0.18) p=0.022
PPG (mmol/L)	-1.22 (95% CI: -2.14; -0.3) p=0.019	-0.73 (95% CI: -1.62; 0.15) NS	-1.48 (95% CI: -2.38; -0.57) p=0.005
Body weight (kg)	-0.87 (95% CI: -1.64; -0.09) p=0.029	-1.02 (95% CI: -1.76; -0.27) p=0.015	-1.51 (95% CI: -2.28; -0.75) p<0.001
Waist circumference (cm)	-0.34 (95% CI: -1.72; 1.04) NS	-0.72 (95% CI: -2.04; 0.60) NS	-1.03 (95% CI: -2.38; 0.33) NS

FPG, fasting plasma glucose; PPG, postprandial plasma glucose; NS, non significant.

Supplementary Figure 1 Proportions of subjects reaching pre-defined HbA1c levels at W12 .

