Supplementary materials

Exclusion criteria

In addition to the criteria listed in the Methods, patients with any of the following were also excluded from the study: an endocrine disease likely to affect blood glucose levels; complication or history of malignancy (except patients treated ≥5 years ago and have not required treatment since then or experienced relapse); serious allergic disposition; use of an investigational drug ≤12 weeks before Week −6; received any luseogliflozin in the past; heavy alcohol consumption; mental disorder likely to affect ability to provide informed consent or may hinder participation; women with confirmed/suspected pregnancy or who are lactating); and patients deemed inappropriate for the study by the investigator.

Meal tolerance test

At Weeks 0 and 12 (or at discontinuation), the patients attended each institution in the morning after a 10-h fast. A fasting blood sample was obtained and the patient took the allocated study drug (only at Week 12) and consumed a fixed meal (516 kcal; 19.2% protein; 19.7% lipids, and 58.4% carbohydrates) provided by the sponsor. The fixed meal was consumed over 10 ± 5 min, and the allocated study drug was to be taken within 30 min before the meal. Postprandial blood samples were obtained at 0.5, 1, and 2 h. Urine samples were collected throughout the 2-h meal tolerance test. Variables assessed included plasma glucose, serum insulin, serum C-peptide immunoreactivity, and glucagon at each time-point, and the area under the glucose/insulin concentration curves for 0–2 h. Acetoacetic acid and β–hydroxybutanoic acid were also measured before and 2 h after the meal.

Sample size calculation

The null hypothesis was defined as θ_1 (placebo) = θ_2 (1 mg) = θ_3 (2.5 mg) = θ_4 (5 mg) = θ_5 (10 mg) for the change in HbA1c from baseline to end of treatment. The alternative hypothesis was (1) $\theta_1 \neq \theta_5$, (2) $\theta_1 \neq \theta_4$, (3) $\theta_1 \neq \theta_3$, and (4) $\theta_1 \neq \theta_2$, in this order. The sample size to address these hypotheses was calculated based on the values reported in the prior Phase II study[1], by assuming the difference versus placebo in changes in HbA1c from baseline to the end of treatment would be −0.68% in the 2.5 mg group, and −0.81% in the 5 and 10 mg groups. With a common standard deviation of 0.93%, the inclusion of 50 patients per group would provide 92.5% power for the 2.5 mg group, 96.8% for the 5 mg group, and 96.9% for the 10 mg group. The sample size was set at 55 patients per group to account for possible withdrawals.

Study populations

Efficacy analyses were conducted using the full analysis set, which consisted of all patients who received at least one dose of the study drug and who had efficacy data measured at least once after starting administration. AEs and other safety variables were assessed using the safety analysis set, which consisted of all patients who received at least one dose of the study drug and who had safety data measured at least once after starting administration. Two patients who were administered a study drug other than the allocated drug (1 subject in the placebo group, 1 subject in the 2.5 mg group) were included in the full analysis set according to their allocated group, and in the safety analysis set according to the actual drug administered.

References

1. Seino Y, Sasaki T, Fukatsu A, et al. Efficacy and safety of luseogliflozin monotherapy in Japanese patients with type 2 diabetes mellitus: a 12-week, randomized, placebo-controlled, Phase II study. Curr Med Res Opin: published online 19 March 2014. doi: 10.1185/03007995.2014.901943

Supplementary Table 1. HbA1c subgroup analyses (LOCF, full analysis set)

Variable	Placebo	Luseogliflozin			
		1 mg	2.5 mg	5 mg	10 mg
	n = 57	*n* = 55	*n* = 56	*n* = 54	*n* = 58
Baseline HbA1cby category*					
<7.0%, *n*	2	4	2	3	1
Baseline	6.85 (0.07)	6.85 (0.10)	6.90 (0.00)	6.83 (0.06)	6.90†
Change	0.30 (0.42)	−0.15 (0.21)	0.05 (0.49)	−0.03 (0.23)	0.00†
≥ 7.0 to<8.0%, *n*	34	36	28	34	29
Baseline	7.42 (0.25)	7.44 (0.29)	7.47 (0.26)	7.56 (0.27)	7.46 (0.26)
Change	0.20 (0.28)	−0.17 (0.28)	−0.20 (0.39)	−0.44 (0.38)	−0.24 (0.30)
≥ 8.0 to <9.0%, *n*	13	10	17	13	24
Baseline	8.34 (0.25)	8.41 (0.24)	8.55 (0.29)	8.33 (0.34)	8.33 (0.30)
Change	0.42 (0.56)	−0.44 (0.32)	−0.59 (0.76)	−0.38 (0.76)	−0.58 (0.60)
≥9.0%, *n*	8	5	9	4	4
Baseline	9.61 (0.42)	9.60 (0.66)	9.17 (0.25)	9.58 (0.59)	9.50 (0.29)
Change	−0.06 (0.75)	−0.60 (0.57)	−0.91 (0.24)	−1.10 (0.37)	−1.05 (0.58)

Values are *n* or means (SD).

LOCF, last observation carried forward; HbA1c, hemoglobin A1c

*The distribution of patients with HbA1c levels showed heterogeneity at $P<0.15$ within each category among the five groups (Kruskal–Wallis test)

†SD values could not be calculated because there was only one patient in this group.