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Original article

Efficacy and safety of luseogliflozin as monotherapy in Japanese patients with type 2 diabetes mellitus: a randomized, double-blind, placebo-controlled, phase 3 study

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Abstract

Objective:
Luseogliflozin – a novel, orally bioavailable, 1-thio-D-glucitol derivative and a selective sodium glucose cotransporter 2 inhibitor – has shown efficacy and tolerability in previous phase 2 studies. This phase 3, randomized, double-blind, placebo-controlled, comparative study aimed to confirm the superiority of 24 week luseogliflozin 2.5 mg monotherapy over placebo in reducing hemoglobin A1c (HbA1c) levels in Japanese patients with type 2 diabetes mellitus (T2DM).

Methods:
Patients with HbA1c levels of 6.9%–10.5% were randomized to receive luseogliflozin 2.5 mg or placebo once daily for 24 weeks ($n = 79$ in each group). The primary endpoint was change from baseline in HbA1c at end of treatment. Secondary endpoints included change from baseline in fasting plasma glucose (FPG) and postprandial plasma glucose (PPG) following a meal tolerance test, body weight, and abdominal circumference. Safety assessments included adverse events (AEs), clinical laboratory tests, and vital signs.

Results:
At the end of treatment, HbA1c was significantly decreased from baseline in the luseogliflozin 2.5 mg group (−0.63%) versus the placebo group (0.13%), with a between-group difference of −0.75% ($p < 0.001$). Additionally, significant reductions in FPG, PPG, body weight, and abdominal circumference were noted with luseogliflozin compared with placebo (all $p < 0.05$). Luseogliflozin was well tolerated; there was no significant difference between groups in the incidence of AEs (luseogliflozin, 59.5%; placebo, 57.0%). No AEs led to study drug discontinuation. Most AEs were mild in severity, with no severe AE reported. Limitations of this study include its short study duration and small sample size.

Conclusion:
Luseogliflozin monotherapy for 24 weeks was superior to placebo in reducing HbA1c levels. It also reduced FPG, PPG, body weight, and abdominal circumference and was well tolerated in Japanese patients with T2DM.

Clinical trial registration:
JapicCTI-111661.

Introduction

The International Diabetes Federation estimates that more than 382 million people worldwide have diabetes in 2013, and this number is expected to reach

592 million by 2035. The prevalence rate of diabetes in Japan is 7.56%, with 7.2 million diabetes cases[1]. Diabetes is associated with a greater incidence of both macrovascular (cardiovascular disease) and microvascular (nephropathy, retinopathy, and neuropathy) complications[2].

In addition to diet and exercise therapy, biguanides (e.g. metformin), sulfonylureas, α-glycosidase inhibitors, thiazolidine derivatives, dipeptidyl peptidase-4 inhibitors, glucagon-like peptide-1 receptor agonists, and insulin are used as antidiabetic therapy for type 2 diabetes mellitus[2–6]. However, currently available treatment options are inadequate to prevent disease progression, and many patients do not achieve hemoglobin A1c (HbA1c) levels <7.0%, recommended by the American Diabetes Association, to reduce diabetic complications[7]. Further, the existing antihyperglycemic therapy options are associated with adverse effects such as hypoglycemia, weight gain, gastrointestinal symptoms, and fluid retention[8]. Hence, an antidiabetic medication is expected to provide adequate glycemic control and be safe and well tolerated.

The sodium glucose cotransporter 2 (SGLT2) inhibitors are gaining attention as a new drug class for treatment of diabetes mellitus. Inhibition of SGLT2 promotes urinary glucose excretion by preventing the reuptake of filtered glucose in the proximal tubules of the kidney, consequently lowering plasma glucose levels[9,10]. Because SGLT2 inhibitors have an insulin-independent mechanism of action, these are expected to improve glycemic control with a low risk of major hypoglycemic events[11].

Luseogliflozin – a novel, orally bioavailable, 1-thio-D-glucitol derivative and a highly selective inhibitor of SGLT2[9,12] – lowered glucose levels by promoting urinary glucose excretion in animal models[12]. Results from the previous 12-week exploratory and dose-finding (phases 2a and 2b, respectively) clinical studies have shown that once daily administration of luseogliflozin leads to significant improvements in HbA1c as well as other glycemic parameters. In addition, the drug was found to be well tolerated, with a favorable safety profile[13,14]. Furthermore, the phase 2b study confirmed that luseogliflozin shows similar glycemic control at doses of 2.5 mg and higher[14].

In the previous phase 2a and 2b studies, luseogliflozin not only reduced plasma glucose levels but also reduced body weight continuously during the 12-week treatment period. Therefore, investigation of its effects on body weight, with related variables (e.g., abdominal circumference), in a longer study was considered important.

The present study was conducted to confirm the superiority of luseogliflozin over placebo in reducing HbA1c levels and to investigate the efficacy and safety of luseogliflozin 2.5 mg as a 24-week monotherapy in Japanese patients with type 2 diabetes mellitus.

Patients and methods

Study design

This was a randomized, double-blind, placebo-controlled, parallel-group, comparative, phase 3 study conducted at 23 institutions throughout Japan between October 2011 and August 2012. This study was registered with the Japan Pharmaceutical Information Center (identifier: JapicCTI-111661). The study was implemented in accordance with Good Clinical Practice guidelines and the ethical principles of the Declaration of Helsinki and approved by the Institutional Review Board of each participating institution.

Eligibility criteria

Japanese outpatients aged ≥20 years with type 2 diabetes mellitus, diagnosed according to the Japan Diabetes Society (JDS) guidelines[15], and HbA1c level ≥6.9% and ≤10.5% at Week -6 and Week -2, with its change being within the range of ±1.0% between the two visits; fasting plasma glucose (FPG) level ≥126 mg/dL confirmed at either Week -6 or Week -2; and stable diet therapy for ≥6 weeks before Week -6 were included in the study.

The important exclusion criteria were as follows: treatment with an insulin preparation or an antidiabetic drug within 6 weeks prior to Week -6; consecutively estimated values of glomerular filtration rate <45 mL/min/1.73 m^2 at Weeks -6 and -2; concurrent urinary tract or genital infection; clinically evident hepatic disorder; concurrent serious gastrointestinal or cardiac disorder; complications such as other cardiovascular disorders, cerebrovascular disorders, pancreatic disorders, and blood diseases; and concurrent severe diabetic microangiopathy.

A comprehensive list of exclusion criteria is included in the *Supplementary materials*. Written informed consent was obtained from all patients prior to participation.

Interventions

Patients were randomly assigned to receive luseogliflozin 2.5 mg or placebo (1:1 ratio). The study drug controller randomly allocated study drugs to the study groups and then prepared the randomization schedule. The Subject Registration Center allocated study drugs to each medical institution in a serial manner according to the study drug numbers for eligible subjects. Investigators prescribed the study drug to each patient according to the study drug number. The study drugs, both luseogliflozin and placebo, were provided in packs and tablets that were indistinguishable from each other.

Patients took the study drug (single tablet of luseogliflozin 2.5 mg or placebo once daily) for 24 weeks before breakfast. The study included an observation period

(Weeks -6 to 0), treatment period (Weeks 0–24), and post-treatment period (Weeks 24–26). Patients adhered to their pre-existent prescribed dietary therapy during the entire study period (Weeks -6 to 26), and the prescribed number of calories was not to be changed after Week -6. The use of antidiabetic drugs (e.g., oral drugs, glucagon-like peptide 1 agonists and insulin), corticosteroids (except for topical use), intravenous fluids containing sugars, and other investigational drugs was prohibited during the study period. However, concomitant drugs such as antidyslipidemic/antihypertensive/diuretics were allowed if they were started before Week -6, with their doses and types were unchanged throughout the study.

All clinical laboratory tests (efficacy and safety variables) were conducted at an independent laboratory by using routine methods (Mitsubishi Chemical Medience Corp., Tokyo, Japan). To maintain blinding, the quantitative urinary glucose values measured during the meal tolerance test were undisclosed to the sponsor or the participating institutions until database lock. Furthermore, no qualitative urinary glucose tests were performed during the study.

Assessments

Meal tolerance test (plasma glucose, insulin, glucagon, serum C-peptide immunoreactivity [CPR], and quantitative urinary glucose based on 2-hour pooled urine) was performed, and intact proinsulin was assessed at Weeks 0, 12, and 24. The procedure of the meal tolerance test is summarized in the *Supplementary materials*. HbA1c, FPG, glycosylated albumin, and body weight were assessed in addition to medical examination at all visits (Weeks -6 to 26). Abdominal circumference was measured, and electrocardiogram (ECG) was evaluated using the standard 12-lead digital Cardico 1211 (Suzuken Co. Ltd, Nagoya, Japan) provided by the sponsor at Weeks -6, 0, 12, and 24.

Outcomes

The primary efficacy endpoint was change in HbA1c from baseline to end of treatment. HbA1c was measured in JDS units, which were converted to National Glycohemoglobin Standardization Program (NGSP) units by using the certified equation: HbA1c (NGSP) (%) = 1.02 × HbA1c (JDS) (%) + 0.25%[16]. Secondary efficacy endpoints included plasma glucose, insulin, glucagon, serum CPR, intact proinsulin, glycosylated albumin, body weight, abdominal circumference, and urinary glucose (quantitative) as well as the homeostatic model assessment for insulin resistance (HOMA-R) and β-cell function (HOMA-β). Safety was assessed by the incidence of adverse events (AEs) as well as changes in clinical laboratory parameters and vital signs. AEs were classified according to the system organ class and preferred term defined by the Japanese version of the Medical Dictionary for Regulatory Activities (version 15.0). AEs were evaluated in terms of their causal relationship to the study drug (definitely related, probably related, possibly related, unrelated, or unknown) and severity (mild, moderate, or severe) by the participating investigators, who recorded this information on their patients' case-report forms.

Statistical analyses

Efficacy was evaluated for the full analysis set (FAS), comprising patients who were administered the study drug at least once and for whom efficacy variables were observed and measured at least once after study drug administration. Safety analyses were performed on the safety analysis set, comprising patients who received the study drug at least once and for whom safety variables were observed and measured at least once after study drug administration.

The heterogeneity of patient characteristics (with a significance level of 15%, two-sided) was examined by intergroup comparisons of baseline characteristics using the χ^2 test or two-sample *t*-test.

For primary and secondary efficacy endpoints, changes from baseline to each time point of evaluation as well as to end of treatment were calculated. Missing end-of-treatment data were imputed using last observation carried forward method. The unrestricted least significant difference method was applied to calculate the least squares (LS) mean and 95% confidence intervals for the changes in clinical parameters in each group as well as differences between the luseogliflozin and placebo groups. Between-group comparisons of the changes were analyzed by analysis of covariance – with the baseline value as a covariate for HbA1c, plasma glucose (FPG, postprandial plasma glucose [PPG], and area under the concentration-time curve for 0–2 hours during the meal tolerance test [AUC_{0-2h}] for PPG) and glycosylated albumin – and by a two-sample *t*-test for other efficacy variables. Between-group comparisons for incidence of AEs/adverse drug reactions (ADRs) were made using the χ^2 test or Fisher's exact test. Basic statistics as well as changes from baseline were calculated by group for laboratory values, vital signs, and 12-lead ECG findings at each evaluation time point and at the end of treatment period. In addition, between-group comparisons were made for changes in values at the end of treatment period using a two-sample *t*-test. A significance level of 5% (two-sided) was used. All statistical analyses were performed using SAS version 9.2 (SAS Inc., Cary, NC, USA).

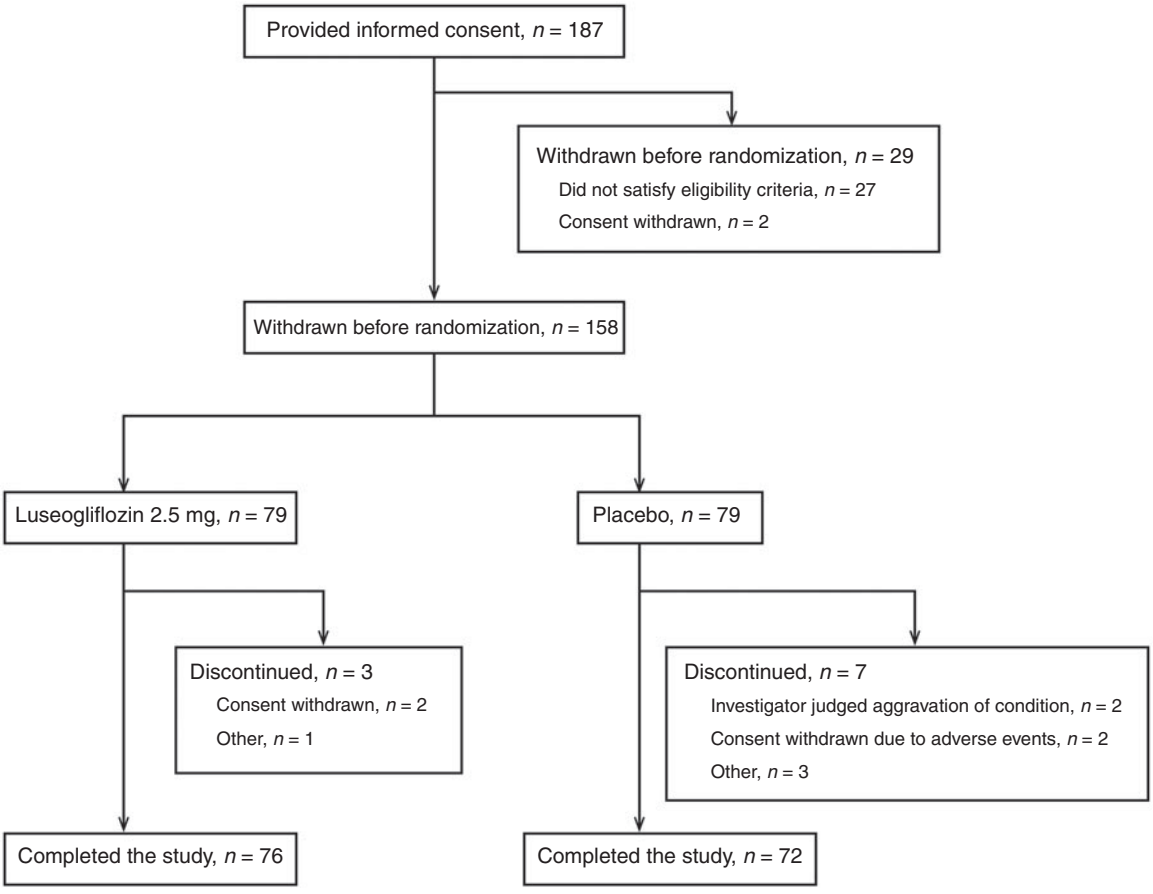

Figure 1. Patient disposition.

The sample size calculation is described in the *Supplementary materials*.

Results

Of the 187 patients who gave written informed consent, 158 were randomized (79 patients in each group), and 148 completed the entire 24 week treatment period (76 and 72 patients in the luseogliflozin and placebo groups, respectively). Ten patients (luseogliflozin, three [3.8%] and placebo, seven [8.9%]) discontinued the study (Figure 1 shows patient disposition). Both groups showed comparable demographic and baseline characteristics (Table 1), including HbA1c levels, although there were differences in body weight ($p = 0.079$), fasting intact proinsulin/insulin ratio ($p = 0.023$), and creatinine ($p = 0.128$). The mean age of patients in the luseogliflozin and placebo groups was 58.9 and 59.6 years, respectively, and their mean HbA1c was 8.14% and 8.17%, respectively. Treatment compliance of ≥80% throughout the study period was observed in the majority of patients (78 [98.7%] and 77 [97.5%] patients in the luseogliflozin and placebo groups, respectively).

Efficacy

HbA1c

The LS mean of the change in HbA1c from baseline to end of treatment was −0.63% and 0.13% in the luseogliflozin and placebo groups, respectively. The between-group difference of −0.75% demonstrated the superiority of luseogliflozin over placebo ($p < 0.001$; Table 2). Figure 2 shows the change from baseline in HbA1c at each time point. Statistically significant reductions in HbA1c levels in the luseogliflozin 2.5 mg versus the placebo group were observed as early as Week 2 (first observation after treatment initiation) and were sustained throughout the study period. Better glycemic control, with HbA1c <7.0% at the end of treatment period, was achieved by more patients in the luseogliflozin group (24.1%) than in the placebo group (3.8%).

The change in HbA1c from baseline to end of treatment was stratified by baseline HbA1c values (Table 3). Although there were only small numbers of patients in some categories, overall, the change was dependent on the baseline level; patients with a higher HbA1c level at baseline showed a greater decrease in HbA1c level with treatment.

Table 1. Patient demographics and baseline characteristics (full analysis set).

	Placebo ($n=79$)	Luseogliflozin 2.5 mg ($n=79$)	p Value
Gender, *n* (%)			
Male	56 (70.9)	60 (75.9)	0.471[a]
Female	23 (29.1)	19 (24.1)	
Age (years)	59.6 (9.3)	58.9 (10.1)	0.671[b]
Body weight (kg)	66.67 (11.23)	70.19 (13.65)	0.079[b]
BMI (kg/m^2)	25.34 (4.19)	25.98 (4.88)	0.378[b]
Abdominal circumference (cm)	88.68 (10.13)	90.47 (9.60)	0.256[b]
Duration of diabetes (years)	6.1 (5.4)	6.5 (5.9)	0.685[b]
Pretreatment for diabetes, *n* (%)[c]	18 (22.8)	16 (20.3)	0.699[a]
HbA1c (%)	8.17 (0.80)	8.14 (0.91)	0.860[b]
FPG (mg/dL)	161.9 (31.0)	160.8 (28.7)	0.815[b]
PPG (2 h) (mg/dL)	262.0 (59.7)	257.4 (50.9)	0.601[b]
Fasting insulin (μU/mL)	7.11 (4.90)	7.97 (6.41)	0.346[b]
SBP (mmHg)	128.9 (13.1)	129.1 (13.9)	–
DBP (mmHg)	76.6 (8.9)	76.9 (9.7)	–

Data are shown as mean (SD) unless otherwise indicated. Data are reported for the full analysis set for all variables, except SBP and DBP. Data from the safety analysis set have been reported for SBP and DBP.
BMI, body mass index; HbA1c, hemoglobin A1c; FPG, fasting plasma glucose; PPG, postprandial plasma glucose; SBP, systolic blood pressure; DBP, diastolic blood pressure; SD, standard deviation.
[a]Chi-square test.
[b]Two-sample *t*-test.
A significance level of $p<0.15$ (two-sided) was taken to indicate heterogeneity between the study groups.
[c]Subjects who received treatment for diabetes within 6 to 18 weeks before Week -6 (start of the observation period).

Other efficacy variables

Table 2 shows between-group comparisons of change from the baseline to end of treatment for efficacy variables. Compared with the placebo group, the luseogliflozin group showed a statistically significant decrease in FPG and body weight at end of treatment ($p<0.001$ for both variables). The decrease in FPG was apparent at Week 2, and the magnitude of decrease remained almost unchanged up to Week 24 (Figure 3). A reduction in body weight was observed as early as Week 2 and was sustained until Week 24 (Figure 4). Further, a decrease from baseline in body weight was observed in the post-treatment observation period (Week 26), with a slight increase from Weeks 24 to 26. The between-group comparison at Week 12 and at end of treatment showed a statistically significant decrease in abdominal circumference in the luseogliflozin group versus the placebo group ($p<0.001$ and $p=0.004$, respectively).

The effect of luseogliflozin 2.5 mg on PPG and insulin after the meal tolerance test is shown in Table 2 and Figure 5. Compared with the placebo group, reductions in PPG levels from baseline to Week 12 and end of treatment at each time point (0.5, 1, and 2 h after the meal) were significantly higher in the luseogliflozin group (all $p<0.001$). In addition, the AUC_{0-2h} of PPG during meal tolerance tests in the luseogliflozin 2.5 mg group significantly decreased relative to the placebo group at Week 12 and end of treatment (all $p<0.001$). Compared with the placebo group, reduction in AUC_{0-2h} of serum insulin from baseline to end of treatment was higher in the luseogliflozin group; however, the difference was not statistically significant. Compared with the placebo group, a significant increase in urinary glucose excretion up to 2 hours after the meal was noted at end of treatment in the luseogliflozin group ($p<0.001$) and was comparable at Week 12 and end of treatment (data not shown).

Safety

Table 4 shows the incidence rates of AEs; no significant difference between the luseogliflozin and placebo groups (59.5% versus 57.0%) was observed. Most of the AEs were of mild severity, with no severe AE or treatment discontinuation due to AE reported. No deaths occurred during the study. Gastroenteritis, the only serious adverse event (SAE) reported, was observed in the luseogliflozin group and was of moderate severity; it resolved and was considered 'unrelated to the study drug'.

The ADRs included pollakiuria (two patients [2.5%]); and increased free fatty acids, increased blood ketone bodies, hypoglycemia, polyuria, and pruritus genital (one patient each [1.3%]) in the luseogliflozin group. The ADRs included constipation, back pain, and somnolence (one patient each [1.3%]) in the placebo group. All ADRs were mild in severity.

The most common AEs (incidence in ≥2 patients in the luseogliflozin 2.5 mg group) were nasopharyngitis, increased C-reactive protein, upper respiratory tract infection, gastroenteritis, pharyngitis, increased white blood cell count, presence of albumin in urine, pollakiuria, eczema, contusion, and pruritus genital.

AEs of special interest included hypoglycemia; urinary tract infections; genital infections; and those related to renal function, pollakiuria, and volume depletion. These AEs had a low incidence, were mild in severity, and resolved (except for only one event of increased urine output in the placebo group, which was judged unnecessary for follow-up). Hypoglycemia observed in one patient in the luseogliflozin group was resolved by ingestion of some glucose and a meal. Genital infections were observed in one patient each in the luseogliflozin and placebo groups and included vulvovaginal candidiasis and genital herpes. AEs related to renal function were observed in six patients each in the luseogliflozin and placebo groups; these events were pollakiuria, polyuria, or laboratory test abnormalities, which were considered unrelated to the study drug. AEs related to pollakiuria were observed in three and two patients in the luseogliflozin and placebo groups,

Table 2. Change in efficacy variables from baseline to end of treatment (full analysis set).

	Placebo ($n = 79$)	Luseogliflozin 2.5 mg ($n = 79$)	Difference versus placebo
HbA1c (%)			
Baseline	8.17 (0.80)	8.14 (0.91)	
Change	0.13 (−0.04, 0.29)	−0.63 (−0.79, −0.46)	−0.75 (−0.99, −0.52)[a]
FPG (mg/dL)			
Baseline	161.9 (31.0)	160.8 (28.7)	
Change	−0.8 (−5.4, 3.7)	−28.3 (−32.9, −23.8)	−27.5 (−33.9, −21.1)[a]
PPG (2 h) (mg/dL)			
EOT, *n*	77	78	
Baseline	262.0 (59.7)	257.4 (50.9)	
Change	1.1 (−8.0, 10.1)	−55.8 (−64.7, −46.8)	−56.8 (−69.6, −44.1)[a]
PPG ($AUC_{0-2\ h}$) (mg·h/dL)			
EOT, *n*	77	78	
Baseline	504 (84.7)	502 (78.2)	
Change	−2.93 (−15.4, 9.51)	−88.3 (−101, −75.9)	−85.3 (−103, −67.8)[a]
Fasting insulin (μU/mL)			
EOT, *n*	77	78	
Baseline	7.11 (4.90)	7.97 (6.41)	
Change	−0.06 (−0.75, 0.63)	−1.88 (−2.57, −1.19)	−1.82 (−2.80, −0.84)[a]
Insulin (2 h) (μU/mL)			
EOT, *n*	77	78	
Baseline	37.75 (29.85)	37.87 (26.16)	
Change	−3.83 (−7.23, −0.42)	−6.01 (−9.39, −2.63)	−2.18 (−6.98, 2.62)
Insulin ($AUC_{0-2\ h}$) (μU·h/mL)			
EOT, *n*	77	78	
Baseline	56.0 (38.3)	59.2 (39.4)	
Change	−3.81 (−8.00, 0.383)	−5.45 (−9.61, −1.28)	−1.64 (−7.55, 4.27)
Glycosylated albumin (%)			
Baseline	21.35 (3.51)	20.95 (3.36)	
Change	0.84 (0.27, 1.41)	−2.49 (−3.06, −1.92)	−3.33 (−4.13, −2.52)[a]
Body weight (kg)			
Baseline	66.67 (11.23)	70.19 (13.65)	
Change	−0.93 (−1.30, −0.56)	−2.70 (−3.07, −2.32)	−1.77 (−2.30, −1.24)[a]
Abdominal circumference (cm)			
Baseline	88.68 (10.13)	90.47 (9.60)	
Change	−0.92 (−1.51, −0.33)	−2.17 (−2.77, −1.58)	−1.26 (−2.09, −0.42)[b]
Urinary glucose (0–2 h) (g/2 h)[c]			
EOT, *n*	77	78	
Baseline	3.35 (4.36)	3.24 (3.16)	
Change	−0.34 (−1.22, 0.54)	7.88 (7.00, 8.75)	8.22 (6.98, 9.46)[a]
HOMA-β (%)			
EOT, *n*	77	78	
Baseline	27.5 (18.4)	31.0 (23.7)	
Change	0.7 (−2.1, 3.5)	1.4 (−1.4, 4.1)	0.7 (−3.2, 4.6)
HOMA-R			
EOT, *n*	77	78	
Baseline	2.86 (2.12)	3.23 (3.02)	
Change	−0.03 (−0.37, 0.32)	−1.20 (−1.54, −0.86)	−1.17 (−1.65, −0.68)[a]
Intact proinsulin (pmol/L)			
EOT, *n*	79	78	
Baseline	9.61 (7.49)	8.95 (9.00)	
Change	−1.71 (−2.82, −0.61)	−2.70 (−3.81, −1.59)	−0.99 (−2.55, 0.58)
Intact proinsulin/insulin ratio			
EOT, *n*	77	78	
Baseline	0.22 (0.16)	0.18 (0.10)	
Change	−0.02 (−0.04, 0.00)	0.00 (−0.02, 0.02)	0.03 (0.00, 0.05)

Baseline values are means (standard deviation) and changes are least squares means (95% confidence interval).
HbA1c, hemoglobin A1c; FPG, fasting plasma glucose; PPG, postprandial plasma glucose; EOT, end of treatment; $AUC_{0-2\,h}$, area under the concentration–time curve for 0–2 h during the meal tolerance test; HOMA-β, homeostasis model assessment of β-cell function; HOMA-R, homeostasis model assessment of insulin resistance.
[a]$p < 0.001$ versus placebo.
[b]$p < 0.05$ versus placebo.
[c]Urine samples were collected for 0–2 h during the meal tolerance test.

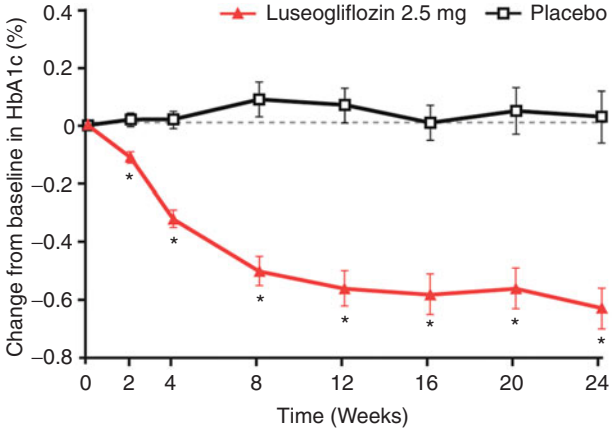

Figure 2. Changes in HbA1c from baseline to each visit. The values are shown as mean ± standard error. All data are shown for the full analysis set. Differences between the luseogliflozin and placebo groups were analyzed by analysis of covariance with the baseline value as a covariate. *$p < 0.001$ versus placebo. HbA1c, hemoglobin A1c.

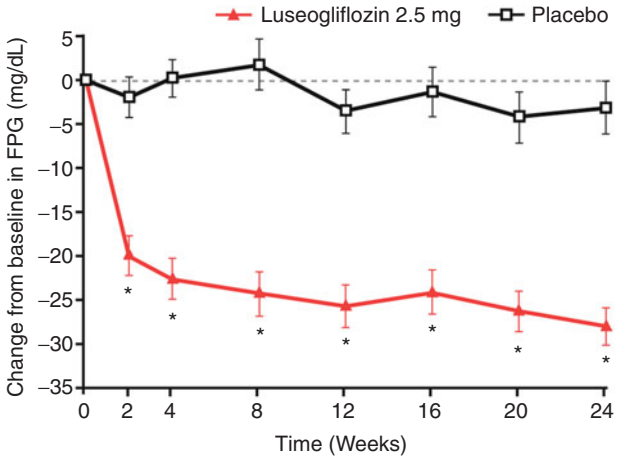

Figure 3. Changes in FPG from baseline to each visit. The values are shown as mean ± standard error. All data are shown for the full analysis set. Differences between the luseogliflozin and placebo groups were analyzed by analysis of covariance with the baseline value as a covariate. *$p < 0.001$ versus placebo. FPG, fasting plasma glucose.

Table 3. Change in HbA1c from baseline to end of treatment stratified by baseline HbA1c values.

Baseline HbA1c levels by category[a]	Placebo	Luseogliflozin 2.5 mg
<7%		
n	1	0
Baseline	6.90 (NC)	NC (NC)
Change	0.30 (NC)	NC (NC)
7% to <8%		
n	34	41
Baseline	7.53 (0.29)	7.50 (0.23)
Change	0.14 (0.98)	−0.45 (0.32)
8% to <9%		
n	30	27
Baseline	8.31 (0.28)	8.34 (0.25)
Change	0.30 (0.90)	−0.72 (0.46)
≥9%		
n	14	11
Baseline	9.49 (0.56)	10.03 (0.68)
Change	−0.31 (0.62)	−1.05 (1.17)

Values are means (standard deviation).
HbA1c, hemoglobin A1c; NC, not calculated.
[a]There was no evidence for a difference in the distribution of HbA1c levels in patients within each category between groups at $p < 0.15$ (Wilcoxon two-sample test).

respectively. All of these AEs occurred within 4 weeks of study drug administration. Neither urinary tract infections nor AEs related to volume depletion were observed in this study.

Table 5 shows the change from baseline to end of treatment in safety variables for the luseogliflozin and placebo groups. Compared with the placebo group, the luseogliflozin group showed a significant increase from baseline to end of treatment in red blood cell count, hemoglobin, hematocrit, total cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), blood urea nitrogen (BUN), and adiponectin. Compared with the placebo group, the luseogliflozin group showed a significant decrease from baseline to end of treatment in aspartate aminotransferase (AST), alanine aminotransferase (ALT), γ-glutamyl transpeptidase (γ-GTP), and serum uric acid. Although no significant changes were apparent for acetoacetic acid (fasting) and β-hydroxybutanoic acid (fasting) at end of treatment in the luseogliflozin group versus placebo group, increases in these parameters were significant in the luseogliflozin group versus placebo group during Weeks 2–20. Both parameters decreased after the meal and were close to baseline value in the post-treatment observation period (Week 26) (data not shown). Although differences in changes from baseline to end of treatment in serum phosphorus and magnesium were significant in the luseogliflozin group versus placebo group, these changes were not clinically meaningful (Table 5). There were no significant changes between the luseogliflozin 2.5 mg and placebo groups in other electrolytes (sodium, potassium, chlorine, calcium), bone-alkaline phosphatase, intact parathyroid hormone, and 1α, 25-dihydroxyvitamin D (data not shown).

Compared with the placebo group, the luseogliflozin group showed a significant decrease in systolic blood pressure (SBP) and diastolic blood pressure (DBP) at the end of treatment period ($p = 0.005$ and $p = 0.029$, respectively). No hypotension was reported, and no clinically meaningful changes were noted in the 12-lead ECG.

Discussion

Luseogliflozin 2.5 mg administered for 24 weeks improved glycemic control by reducing HbA1c, FPG, and PPG,

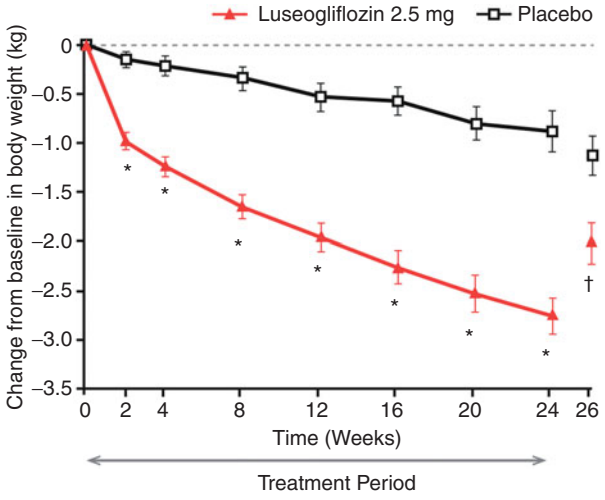

Figure 4. Changes in body weight from baseline to each visit. The values are shown as mean ± standard error. All data are shown for the full analysis set. Differences between the luseogliflozin and placebo groups were analyzed by a two-sample *t*-test. $^{*}p<0.001$ versus placebo; $^{\dagger}p<0.05$ versus placebo.

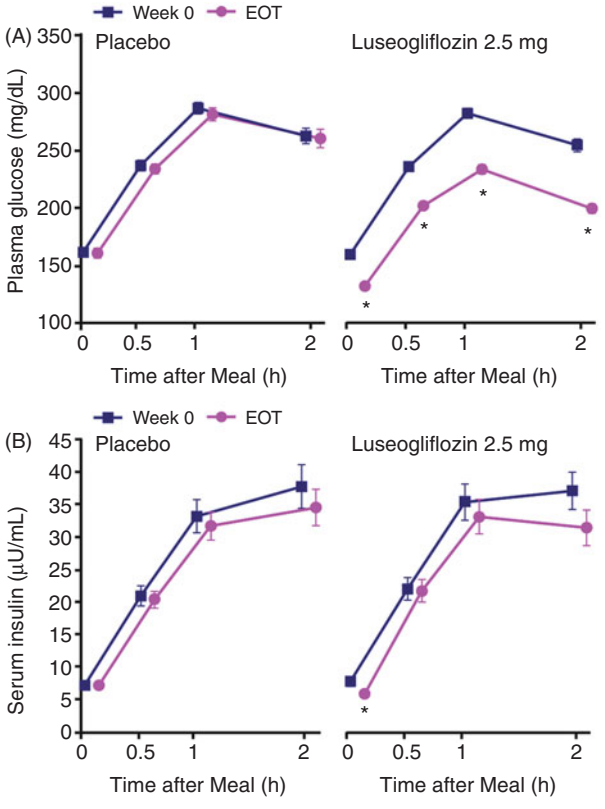

Figure 5. Changes in (A) plasma glucose and (B) serum insulin during meal tolerance test at Week 0 and EOT. The values are shown as mean ± standard error, and the values at the end of treatment are shown as values applied last observation carried forward method to missing data. All data are shown for the full analysis set. Differences in change from baseline to end of treatment between the luseogliflozin and placebo groups were analyzed by analysis of covariance with the baseline value as a covariate for plasma glucose and a two-sample *t*-test for insulin. $^{*}p<0.001$ versus placebo. EOT, end of treatment.

Table 4. List of adverse events (safety analysis set).

	Placebo ($n=79$)	Luseogliflozin 2.5 mg ($n=79$)
Any AE	45 (57.0)	47 (59.5)
Any ADR	2 (2.5)	6 (7.6)
Any SAE	0 (0)	1 (1.3)
AEs leading to discontinuation	0 (0)	0 (0)
Most common AEs (≥2 patients in luseogliflozin group)		
Nasopharyngitis	13 (16.5)	12 (15.2)
Increased C-reactive protein	8 (10.1)	4 (5.1)
Upper respiratory tract infection	5 (6.3)	4 (5.1)
Gastroenteritis	4 (5.1)	2 (2.5)
Pharyngitis	3 (3.8)	2 (2.5)
Increased white blood cell count	2 (2.5)	2 (2.5)
Presence of albumin in urine	1 (1.3)	2 (2.5)
Pollakiuria	1 (1.3)	2 (2.5)
Eczema	1 (1.3)	2 (2.5)
Contusion	0 (0)	2 (2.5)
Pruritus genital	0 (0)	2 (2.5)
AEs of special interest		
Hypoglycemia	0 (0)	1 (1.3)
Urinary tract infections	0 (0)	0 (0)
Genital infections[a]	1 (1.3)	1 (1.3)
AEs related to renal function[b]	6 (7.6)	6 (7.6)
AEs related to pollakiuria[c]	2 (2.5)	3 (3.8)
AEs related to volume depletion	0 (0)	0 (0)

Data are shown as number of patients and incidence (%).
AE, adverse event; ADR, adverse drug reaction; SAE, serious adverse event.
[a]Includes vulvovaginal candidiasis and genital herpes.
[b]Includes presence of albumin in urine, increased urinary β_2-microglobulin, increased β-N-acetyl-D-glucosaminidase, presence of blood in urine, presence of red blood cells in urine, and presence of white blood cells in urine, pollakiuria, and polyuria.
[c]Includes pollakiuria, polyuria, and increased urine output.

together with significant reductions in body weight and abdominal circumference and showed good tolerability in Japanese patients with type 2 diabetes mellitus. These findings suggest that luseogliflozin monotherapy is a potential treatment option for type 2 diabetes mellitus.

During the meal tolerance tests conducted at 12 and 24 weeks in this study, luseogliflozin was found to lower PPG while maintaining serum insulin at the pretreatment level, consistent with reductions in HbA1c and FPG. Because it has been demonstrated that luseogliflozin acts via an insulin-independent mechanism to reduce plasma glucose, it seems likely to show a sustained glucose-lowering effect with long-term treatment as well as a low risk of clinical hypoglycemia. Indeed, low incidence of hypoglycemia (only a single case of mild hypoglycemia in the present study) was observed, consistent with the previous phase 2 studies of luseogliflozin[13,14].

Weight management (together with glycemic control) is an important component of the treatment of many patients with type 2 diabetes. Because luseogliflozin significantly reduced body weight, which was apparent by 2 weeks of treatment, compared with placebo, it might provide support for weight management interventions in

Table 5. Change in safety variables from baseline to end of treatment for luseogliflozin 2.5 mg and placebo (safety analysis set).

	Placebo ($n=79$)	Luseogliflozin 2.5 mg ($n=79$)	Difference versus placebo
RBC ($10^4/\mu L$)			
EOT, *n*	79	78	
Baseline	451.9 (35.5)	456.1 (38.3)	
Change	0.9 (−3.5, 5.3)	21.0 (16.5, 25.4)	20.1 (13.8, 26.4)[a]
Hemoglobin concentration (g/dL)			
EOT, *n*	79	78	
Baseline	14.41 (1.12)	14.55 (1.14)	
Change	−0.20 (−0.33, −0.06)	0.36 (0.22, 0.50)	0.56 (0.36, 0.75)[a]
Hematocrit (%)			
EOT, *n*	79	78	
Baseline	42.13 (3.10)	42.64 (3.17)	
Change	0.09 (−0.32, 0.50)	1.86 (1.45, 2.27)	1.77 (1.19, 2.35)[a]
BUN (mg/dL)			
Baseline	14.7 (3.0)	14.8 (4.2)	
Change	−0.1 (−0.8, 0.6)	1.7 (1.0, 2.4)	1.8 (0.8, 2.8)[b]
LDL-C (mg/dL)			
Baseline	127.8 (33.3)	131.0 (27.6)	
Change	−5.2 (−10.0, −0.3)	3.2 (−1.6, 8.0)	8.4 (1.5, 15.2)[b]
HDL-C (mg/dL)			
Baseline	60.2 (16.1)	58.0 (16.7)	
Change	−1.1 (−2.6, 0.4)	2.8 (1.3, 4.3)	3.9 (1.7, 6.1)[b]
Total cholesterol (mg/dL)			
Baseline	207.8 (35.8)	209.8 (31.6)	
Change	−7.5 (−12.7, −2.3)	1.8 (−3.3, 7.0)	9.4 (2.0, 16.7)[b]
Triglycerides (mg/dL)			
Baseline	141.5 (87.3)	149.5 (91.9)	
Change	−5.9 (−22.2, 10.5)	−22.7 (−39.1, −6.3)	−16.8 (−40.0, 6.3)
Adiponectin (μg/mL)			
EOT, *n*	79	78	
Baseline	6.84 (4.09)	6.16 (2.69)	
Change	−0.17 (−0.41, 0.08)	0.63 (0.39, 0.88)	0.80 (0.45, 1.15)[a]
Acetoacetic acid (fasting) (μmol/L)			
Baseline	30.5 (25.0)	30.8 (20.8)	
Change	7.9 (−0.6, 16.4)	15.7 (7.3, 24.2)	7.9 (−4.1, 19.8)
Acetoacetic acid (2 h) (μmol/L)			
EOT, *n*	77	78	
Baseline	18.4 (6.0)	18.7 (6.7)	
Change	3.1 (1.2, 5.0)	6.4 (4.5, 8.3)	3.3 (0.6, 6.0)[b]
β-hydroxy butanoic acid (fasting) (μmol/L)			
Baseline	59.1 (52.6)	65.7 (48.8)	
Change	28.7 (1.6, 55.9)	40.4 (13.2, 67.5)	11.6 (−26.8, 50.0)
β-hydroxy butanoic acid (2 h) (μmol/L)			
EOT, *n*	77	78	
Baseline	21.0 (10.7)	21.6 (9.5)	
Change	0.8 (−1.5, 3.2)	3.1 (0.8, 5.4)	2.2 (−1.1, 5.5)
AST (IU/L)			
Baseline	27.7 (9.6)	28.7 (10.3)	
Change	−2.2 (−3.6, −0.8)	−5.6 (−7.0, −4.2)	−3.4 (−5.4, −1.5)[b]
ALT (IU/L)			
Baseline	30.4 (16.4)	32.9 (17.3)	
Change	−4.4 (−6.7, −2.1)	−10.4 (−12.8, −8.1)	−6.0 (−9.3, −2.7)[a]
γ-GTP (IU/L)			
Baseline	46.4 (36.2)	59.7 (67.8)	
Change	−2.2 (−8.7, 4.4)	−19.0 (−25.6, −12.5)	−16.8 (−26.1, −7.6)[a]
Serum uric acid (mg/dL)			
Baseline	4.96 (1.15)	5.18 (1.18)	
Change	0.14 (−0.02, 0.29)	−0.34 (−0.50, −0.19)	−0.48 (−0.70, −0.26)[a]
Serum creatinine (mg/dL)			
Baseline	0.672 (0.149)	0.711 (0.168)	
Change	0.015 (0.002, 0.029)	0.014 (0.000, 0.027)	−0.001 (−0.021, 0.018)
Serum phosphorus (mg/dL)			
Baseline	3.38 (0.48)	3.29 (0.44)	
Change	−0.09 (−0.16, −0.01)	0.03 (−0.05, 0.11)	0.12 (0.01, 0.23)[b]
Serum magnesium (mg/dL)			
Baseline	2.15 (0.16)	2.15 (0.15)	
Change	−0.04 (−0.07, −0.01)	0.08 (0.06, 0.11)	0.12 (0.08, 0.17)[a]

(continued)

Table 5. Continued.

	Placebo ($n=79$)	Luseogliflozin 2.5 mg ($n=79$)	Difference versus placebo
SBP (mmHg)			
Baseline	128.9 (13.1)	129.1 (13.9)	
Change	−3.6 (−6.4, −0.9)	−9.3 (−12.0, −6.5)	−5.6 (−9.5, −1.7)[b]
DBP (mmHg)			
Baseline	76.6 (8.9)	76.9 (9.7)	
Change	−1.1 (−2.7, 0.5)	−3.7 (−5.3, −2.1)	−2.5 (−4.8, −0.3)[b]
Urine volume (0–2 h) (mL)			
EOT, *n*	77	78	
Baseline	223.01 (150.49)	219.31 (159.51)	
Change	−8.72 (−43.40, 25.96)	40.83 (6.37, 75.29)	49.55 (0.65, 98.44)[b]

Baseline values are means (standard deviation) and changes are least squares means (95% confidence interval).
RBC, red blood cell; EOT, end of treatment; BUN, blood urea nitrogen; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; AST, aspartate aminotransferase; ALT, alanine aminotransferase; γ-GTP, γ-glutamyl transpeptidase; SBP, systolic blood pressure; DBP, diastolic blood pressure.
[a]$p<0.001$ versus placebo.
[b]$p<0.05$ versus placebo.

these patients. Further, luseogliflozin progressively reduced body weight throughout the treatment period. The reduction in body weight tended to return to baseline after treatment completion (Week 26) in the luseogliflozin group. Considering the reactionary reversal in body weight after treatment completion, the reduction in body weight at treatment initiation might be attributed to osmotic diuresis because of increased urinary glucose excretion. Osmotic diuresis might also have contributed to the reduction in blood pressure and the small increase in hematocrit in this study. Alternatively, progressive body weight reductions could be a consequence of energy loss. In the present study, a reduction in abdominal circumference consistent with the increase in plasma adiponectin was observed, as was the increase in ketone bodies. Also, a trend towards a reduction in triglyceride levels was noted. These results suggest that luseogliflozin might increase fat oxidation. Because the reduction in body weight did not reach a plateau and body composition was not measured in this study, a longer, more detailed investigation is necessary to clarify the effect of luseogliflozin on body weight.

Luseogliflozin improved some parameters related to metabolic syndrome or cardiovascular risk factors in this study. In addition to the changes in blood pressure, body weight, abdominal circumference, adiponectin and triglycerides described above, we found that liver function parameters (AST, ALT, and γ-GTP) decreased and HDL-C increased in the luseogliflozin 2.5 mg group. However, a slight increase in LDL-C, an important surrogate marker of cardiovascular risk, was also observed. Moreover, volume depletion could be occurred due to a mechanism of action of luseogliflozin, as demonstrated by the slight increase in hematocrit. No cardiovascular events occurred during this study, although the small sample size and short study duration may contribute to this finding. Therefore, further longer and larger studies are required to investigate the effects of luseogliflozin on metabolic syndrome or cardiovascular risk factors.

Compared with placebo, luseogliflozin 2.5 mg demonstrated a favorable safety profile and was well tolerated, with no significant difference in the incidence of AEs. Most AEs were mild in severity, and no deaths were reported; the only SAE observed was unrelated to study drug administration. The known side effects of SGLT2 inhibitors, such as urinary tract infections, or genital infections, or AEs related to volume depletion were reported in only few cases in this study. The safety profile of luseogliflozin was not altered despite the longer treatment period (24 weeks) in this study compared with the previous phase 2 studies[13,14].

Owing to their mechanism of action, SGLT2 inhibitors could potentially affect the renal tubular transportation of bone minerals. It was reported that dapagliflozin – another SGLT2 inhibitor – had no effect on markers of bone formation and resorption or bone mineral density after 50 weeks of treatment in both male and post-menopausal female patients whose type 2 diabetes mellitus was inadequately controlled with metformin[17]. In the present study, luseogliflozin indicated no clinically meaningful effect on electrolytes and markers of bone formation and resorption (e.g., crosslinked N-telopeptide of type I collagen) in patients with type 2 diabetes mellitus.

Limitations of this study were the short 24 week treatment period, small sample size, and study population that included only patients whose type 2 diabetes mellitus was inadequately controlled with diet and exercise therapy. Several 52-week studies using luseogliflozin as monotherapy and as an add-on to existing oral antidiabetic agents will provide further insights into the safety and efficacy profile of luseogliflozin.

Conclusion

In this study, luseogliflozin 2.5 mg monotherapy was well tolerated for 24 weeks and demonstrated superiority over placebo in effectively reducing HbA1c levels and decreasing FPG, PPG, and body weight in Japanese patients with type 2 diabetes mellitus.

Transparency

Declaration of funding

Luseogliflozin is being developed by Taisho Pharmaceutical Co. Ltd. This study was supported by Taisho Pharmaceutical Co. Ltd. The authors retained full control of the manuscript content.

Declaration of financial/other relationships

Y.S. has disclosed that he has received consultancy fees or lecture fees from Sanofi, Novo Nordisk, Eli Lilly and Company, GlaxoSmithKline, Astellas Pharma, Takeda Pharmaceuticals, Boehringer Ingelheim, Johnson & Johnson, Becton Dickinson and Company, AstraZeneca, and Taisho Pharmaceutical Co. Ltd. T.S. has disclosed that he has received joint research fund from Canon Inc. and consultancy fees from Taisho Pharmaceutical Co. Ltd. A.F. has disclosed that he has received consultancy fees from Taisho Pharmaceutical Co. Ltd. M.U., S.S. and Y.S. are employees of Taisho Pharmaceutical Co. Ltd, which is developing luseogliflozin.

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Previous presentation: Parts of this study were reported as an abstract and poster (abstract 956) at the 49th Annual Meeting of the European Association for the Study of Diabetes, 23–27 September 2013, Barcelona, Spain; and as an abstract and poster (abstract P-1472) at the International Diabetes Federation 2013 World Diabetes Congress, 2–6 December 2013, Melbourne, Australia.

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