Efficacy and safety of canagliflozin in combination with insulin: a double-blind, randomized, placebo-controlled study in Japanese patients with type 2 diabetes mellitus

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Abstract

Background: Combination therapy with canagliflozin and insulin was investigated in a prescribed substudy of the canagliflozin Cardiovascular Assessment Study (CANVAS); however, it was not evaluated in Japanese patients with type 2 diabetes mellitus (T2DM). Since the usage profile of insulin therapy and pathologic features of Japanese patients differ from those of Caucasian patients, we determined the clinical benefit of such a combination therapy in Japanese patients.

Methods: Patients who had inadequate glycemic control despite insulin, diet and exercise therapies were randomized into placebo (n = 70) and canagliflozin 100 mg (n = 76) groups that were administered once daily in addition to their prior insulin therapy in this double-blind, placebo-controlled study. The primary endpoint was the change in glycated hemoglobin (HbA1c) levels from the baseline to week 16.

Results: There was a statistically significant decrease in HbA1c levels from the baseline in the canagliflozin group (−0.97 ± 0.08 %) compared with the placebo group (0.13 ± 0.08 %) at week 16 [last observation carried forward (LOCF)]. The decrease in HbA1c levels in the canagliflozin group was independent of the insulin regimen (premixed, long-acting and long-acting plus rapid- or short-acting). Compared with the placebo group, canagliflozin significantly decreased fasting plasma glucose levels (−34.1 ± 4.8 vs −1.4 ± 5.0 mg/dL) and body weights (−2.13 ± 0.25 vs 0.24 ± 0.26 %), and significantly increased HDL cholesterol (3.3 ± 1.0 vs −0.5 ± 1.0 mg/dL) and HOMA2-%B (10.15 ± 1.37 vs 0.88 ± 1.42 %). The overall incidence of adverse events was similar between the two groups. The incidence and incidence per subject-year exposure of hypoglycemia (hypoglycemic symptoms and/or decreased blood glucose) were slightly higher in the canagliflozin group (40.0 % and 7.97) than in the placebo group (29.6 % and 4.51). However, hypoglycemic events in both groups were mild in severity and dose-reduction of insulin by <10 % from the baseline following hypoglycemic events decreased the incidence per subject-year exposure in the canagliflozin group. The incidence of hypoglycemia between the groups did not differ according to the insulin regimen.

Conclusion: Canagliflozin in combination with insulin was effective in improving glycemic control and reducing body weight and well tolerated by Japanese patients with T2DM.

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Background
Type 2 diabetes mellitus (T2DM) is a worldwide problem that is growing in prevalence. The International Diabetes Federation estimates that 382 million people had diabetes globally in 2013 and predicts that 592 million people will suffer from the disease in 2035 [1]. Chronic hyperglycemia caused by diabetes is associated with microvascular and macrovascular complications, which deteriorate the quality of life and increase cardiovascular events. Therefore, glycemic control is important to prevent diabetic complications and to maintain quality of life [2].

T2DM is conventionally treated with insulin secretagogues, insulin sensitizers, glucose absorption inhibitors, insulin, and glucagon-like peptide-1 receptor agonists [2, 3]. Intensive glycemic control with insulin therapy prevents diabetic complications [4–6]. However, insulin therapy is associated with the risk of hypoglycemia and weight gain [7–9]. Moreover, weight gain may exacerbate insulin resistance, resulting in the need for an increased dose of insulin, which may cause further weight gain. In addition, the effect of blood glucose, rate of hypoglycemia, and weight gain differ among insulin regimens [10]. Therefore, it is important to determine the insulin regimen according to the patient’s background [3].

Inhibitors of the sodium glucose co-transporter 2 (SGLT2) suppress glucose reabsorption in renal tubules and exert insulin-independent antihyperglycemic effects. In addition, this class of drugs decreases body weight [11, 12]. The SGLT2 inhibitor canagliflozin has been approved for the treatment of T2DM by the regulatory authorities of numerous countries across North America, Europe, Latin America, and Asia–Pacific [13]. The efficacy and safety of canagliflozin monotherapy and in combination with other oral antihyperglycemic agents were demonstrated by studies conducted in Japan [14, 15]. Combination therapy with canagliflozin and insulin was investigated in a prescribed sub study of the canagliflozin Cardiovascular Assessment Study (CANVAS) [16]. However, the effects of a combination of canagliflozin and insulin in Japanese patients with T2DM have not been investigated. The usage profile of insulin therapy and pathologic features of Japanese patients differ from those of Caucasian patients [17–19]. Therefore, it is important to determine the clinical benefit of such a combination therapy in Japanese patients. In the present study, we evaluated the efficacy and safety of canagliflozin in combination with insulin in Japanese patients with T2DM who had inadequate glycemic control despite insulin, diet, and exercise therapies. We further assessed the efficacy and safety of canagliflozin combined with different insulin regimens.

Methods
Study design
We conducted a randomized, parallel-group, double-blind study to evaluate the efficacy and safety of canagliflozin in Japanese patients with T2DM who had inadequate glycemic control despite insulin, diet and exercise therapies (Fig. 1). After a 4-week single-blind run-in period, eligible patients were randomized and administered placebo or 100 mg of canagliflozin once daily before breakfast for 16 weeks. Randomization was performed using a block allocation method (1:1, block sizes of 4 and 87 blocks).

The patients received one of the insulin regimens as follows: premixed, intermediate-acting, long-acting, premixed plus rapid- or short-acting, intermediate-acting plus rapid- or short-acting, long-acting plus rapid- or short-acting. The daily dose of insulin ranged from 8 to 60 units. In principle, the insulin dose was fixed during the study period; however, the change within ±10 % of the total daily dose of insulin from the baseline was allowed in order to avoid or treat hypoglycemia or other concomitant illnesses.

Compliance with the declaration of Helsinki and informed consent
This study was conducted in the spirit of the ethical principles grounded in the declaration of Helsinki and in compliance with Japanese laws related to ensuring drug/medical device quality, efficacy, and safety and Japanese ministerial orders and related regulations on good post-marketing surveillance practice and good clinical practice. The study was approved by the ethics committee/instructional review boards at all of the participating institutions (see List of participating investigators under "Acknowledgements" section). All patients provided written informed consent.

Inclusion and exclusion criteria
Criteria for including patients were as follows: fixed diet and exercise therapy, receiving a stable dose and regimen of insulin over the 12 weeks before the start of treatment (week 0), glycated hemoglobin (HbA1c) levels of ≥7.5 to <10.5 %, and not taking prohibited antidiabetic drugs during the 12 weeks before week 0. Criteria for excluding
patients were as follows: type 1 DM (T1DM), DM caused by a pancreatic disorder, or secondary DM (e.g. Cushing’s syndrome and acromegaly); severe diabetic complications (proliferative diabetic retinopathy, stage 4 nephropathy, or serious diabetic neuropathy); hereditary glucose–galactose malabsorption or primary renal glycosuria; systolic blood pressure of \( \geq 160 \text{ mmHg} \) or diastolic blood pressure of \( \geq 100 \text{ mmHg} \); serious renal or hepatic disease; estimated glomerular filtration rate of \(<45 \text{ mL/min/1.73 m}^2\); alcoholics; pregnant or possibly pregnant; breastfeeding a child; and refusal to use contraception.

Outcome measures

The primary endpoint was the change in HbA1c levels from the baseline to week 16 (last observation carried forward [LOCF]). The secondary endpoints were the changes from the baseline in HbA1c levels at each evaluation point, fasting plasma glucose (FPG), body weight, systolic and diastolic blood pressure, lipids [fasting triglycerides, high-density lipoprotein (HDL) cholesterol], fasting proinsulin/C-peptide ratio, and homeostasis model assessment 2 steady-state beta-cell function (HOMA2-%B). HOMA2- %B was calculated using FPG and fasting C-peptide values. An Excel version of the HOMA calculator of the Diabetes Trial Unit at the University of Oxford was used to calculate HOMA2- %B values.

Safety was assessed based on adverse events, hypoglycemic events, and laboratory test values. AEs were judged by the physicians, and the numbers of affected patients and incidence are listed using MedDRA (Ver. 18.0) system organ class and preferred term. Further, study patients performed self-monitoring of fasting blood glucose at least 3 days each week and when experiencing hypoglycemic symptoms. Low blood glucose without symptoms (\( \leq 70 \text{ mg/dL} \)) was classified as decreased blood glucose. Hypoglycemic episodes with a typical hypoglycemic symptom were classified as hypoglycemia, regardless of the blood glucose level.

Statistical analysis

For the primary and secondary endpoints, point estimates of intergroup difference (canagliflozin group – placebo group) in least squares (LS) means were calculated along with the corresponding standard error (SE), 95% confidence interval, and \( p \) value. Analysis of covariance (ANCOVA) was performed to determine absolute or percentage changes from the baseline to each evaluation point, with the baseline value as a covariate. Changes in HbA1c levels from the first day of treatment to each evaluation point were analyzed using mixed-model repeated-measures (MMRM) with restricted maximum likelihood. All statistical analyses were conducted using SAS 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

Patient disposition and demographic characteristics

Of the 201 patients who consented to participate, 186 entered in the run-in period, and 146 patients were randomized for treatment with placebo (\( n = 70 \)) or canagliflozin (\( n = 76 \)). One patient in the canagliflozin group...
was mistakenly administered placebo. This patient was included in the canagliflozin group in the full analysis set and in the placebo group in the safety analysis set (Additional file 1: Figure S1).

Table 1 shows patient characteristics of the full analysis set. In the placebo and canagliflozin groups, mean ages were 56.1 and 59.7 years, body weights were 69.68 and 69.95 kg, and durations of T2DM were 12.34 and 15.18 years, respectively. The mean HbA1c levels were 8.85 and 8.89 %, and FPG levels were 169.1 and 169.9 mg/dL in the placebo and canagliflozin groups, respectively (Table 1).

The mean daily dose of insulin was 28.1 units in the placebo group and 31.1 units in the canagliflozin group, and was not remarkably different between the regimens of the placebo and canagliflozin groups: premixed insulin, 29.0 and 33.1 units; long-acting insulin, 20.9 and 20.5 units; and long-acting and rapid- or short-acting insulin, 36.7 and 39.5 units, respectively. No patient used an intermediate-acting insulin product (Table 1).

Efficacy

The changes in HbA1c levels from the baseline at week 16 (LOCF, LS mean ± SE) were 0.13 ± 0.08 % in the placebo group and −0.97 ± 0.08 % in the canagliflozin group, corresponding to the placebo-adjusted changes of −1.10 % (95 % CI, −1.33 to −0.87; \( p < 0.001 \)), which were statistically significant. The MMRM were also statistically significant between the groups (\( p < 0.001 \)), indicating the robustness of the results (Table 2). The statistically significant decrease in HbA1c levels in the canagliflozin group compared with the placebo group were apparent at week 4 and reached a plateau at week 12, which were maintained until week 16 (all; \( p < 0.001 \)) (Fig. 2). The decrease in HbA1c levels in the canagliflozin group was observed independent of the type of insulin regimen (Table 2).
Table 2 Effect of canagliflozin on HbA1c levels

|                          | Placebo | Canagliflozin 100 mg |
|--------------------------|---------|----------------------|
| **Total**                |         |                      |
| N                        | 70      | 76                   |
| Mean (SD) baseline (%)   | 8.85 (0.84) | 8.89 (0.81)       |
| LS mean (SE) change (%)a | 0.13 (0.08) | –0.97 (0.08)        |
| Difference (95% CI) vs placebo (%) | –1.10 (–1.33, –0.87) | –1.13 (–1.36, –0.89) |
| p value                  | <0.001  | <0.001               |
| N                        | 66      | 73                   |
| LS mean (SE) change (%)b | 0.15 (0.08) | –0.98 (0.08)        |
| Difference (95% CI) vs placebo (%) | –0.88 (–1.24, –0.52) | –0.88 (–1.24, –0.52) |
| p value                  | <0.001  | <0.001               |
| **Each insulin regimen** |         |                      |
| **Premixed**             |         |                      |
| N                        | 26      | 28                   |
| Mean (SD) baseline (%)   | 8.70 (0.82) | 8.73 (0.73)       |
| LS mean (SE) change (%)  | –0.01 (0.13) | –0.89 (0.12)        |
| Difference (95% CI) vs placebo (%) | –0.88 (–1.24, –0.52) | –0.88 (–1.24, –0.52) |
| p value                  | <0.001  | <0.001               |
| **Long-acting**          |         |                      |
| N                        | 24      | 24                   |
| Mean (SD) baseline (%)   | 8.89 (0.85) | 9.02 (0.87)       |
| LS mean (SE) change (%)  | 0.26 (0.12) | –1.18 (0.12)        |
| Difference (95% CI) vs placebo (%) | –1.44 (–1.79, –1.09) | –1.44 (–1.79, –1.09) |
| p value                  | <0.001  | <0.001               |
| **Premixed + rapid- or short-acting** |         |                      |
| N                        | 1       | 0                    |
| Mean (SD) baseline (%)   | 7.50 (–) | –                    |
| LS mean (SE) change (%)  | 0.10 (0.00) | –                    |
| **Long-acting + rapid- or short-acting** |         |                      |
| N                        | 19      | 24                   |
| Mean (SD) baseline (%)   | 9.09 (0.80) | 8.96 (0.83)       |
| LS mean (SE) change (%)  | 0.17 (0.19) | –0.83 (0.17)        |
| Difference (95% CI) vs placebo (%) | –1.00 (–1.51, –0.49) | –1.00 (–1.51, –0.49) |
| p value                  | <0.001  | <0.001               |

N number of patients, LS mean least squares mean, 95% CI 95% confidence interval

a LS mean for change from the baseline to week 16, ANCOVA (Factor treatment, covariate HbA1C levels at baseline)

b LS mean for change from the baseline to week 16, MMRM

A significant decrease in FPG in the canagliflozin group compared with the placebo group was detected by week 4 and was maintained until week 16 (all; p < 0.001) (Fig. 3a). The difference between the canagliflozin and placebo groups regarding the change in FPG (LOCF, LS mean) was −32.6 mg/dL (95% CI, −46.3 to −18.9; p < 0.001) (Table 3).

The mean body weight of the canagliflozin group significantly decreased from weeks 4 to 12 and was maintained through week 16 (all; p < 0.001) (Fig. 3b). The difference between the canagliflozin and the placebo groups regarding the percentage change in body weight from the baseline to week 16 (LOCF, LS mean) was −2.37% (95% CI, −3.09 to −1.65; p < 0.001) (Table 3).

Other secondary endpoints, including the changes from the baseline to week 16 of systolic and diastolic blood pressures, triglycerides, HDL cholesterol, proinsulin/C-peptide ratio, and HOMA2-%B are summarized in Table 3. The systolic and diastolic blood pressure and triglycerides were decreased from baseline at week 16 in the canagliflozin group; however, there was no significant difference between the canagliflozin and placebo groups. HDL cholesterol was significantly increased in the canagliflozin group compared to the placebo group after 12 weeks of treatment, and the difference between two groups (LOCF, LS mean) was 3.7 mg/dL (95% CI, 1.0–6.5; p < 0.007). The difference between the canagliflozin and placebo groups regarding the change in the fasting proinsulin/C-peptide ratio and HOMA2-%B (LOCF, LS mean), as markers of beta cell function, was −0.0026 (95% CI, −0.0070 to 0.0017; p = 0.235) and 9.27% (95% CI, 5.35–13.19; p < 0.001), respectively (Table 3).

The insulin doses were increased in 10 patients (14.3%) and three patients (3.9%); increased and decreased in one patient (1.4%) and one patient (1.3%); and decreased in two patients (2.9%) and 13 patients (17.1%) in the placebo and canagliflozin groups, respectively.

**Safety**

The overall incidence of adverse events was similar between the two groups (64.8%, placebo group;
The adverse events that occurred more frequently in the canagliflozin group were decreased blood glucose, hypoglycemia, pollakiuria, and polyuria (Table 4). The incidence of hypoglycemia was slightly higher in the canagliflozin group (40.0 %) than in the placebo group (29.6 %). The difference in the incidence ratio between the placebo and canagliflozin groups was 10.4 %, which was not statistically significant (95 % CI, −6.0 to 26.3; \( p = 0.225 \)), and all hypoglycemic events were mild in severity.

The mean daily insulin dose during treatment was 29.7 units. Hypoglycemic events occurred similarly in patients receiving lower (<29.7 units), equal, or higher than (≥29.7 units) the average insulin dose. The incidence of hypoglycemia in patients receiving an insulin dose of <29.7 units or ≥29.7 units was 27.5 % (\( n = 11 \)) or 32.3 % (\( n = 10 \)), respectively, in the placebo group and 39.5 % (\( n = 15 \)) or 40.5 % (\( n = 15 \)), respectively, in the canagliflozin group.

The incidence of hypoglycemia and incidence per subject-year exposure did not differ substantially according to the type of insulin regimen received by either the placebo group or the canagliflozin group (Table 5).

Serious adverse events were as follows: cataracts (one patient on placebo and one patient on canagliflozin), retinal detachment (one patient on canagliflozin), vitreous hemorrhage (one patient on canagliflozin), and alcoholic liver disease (one patient on canagliflozin). However, a causality assessment of “not related” was assigned to each event. Alcoholic liver disease (in one patient on canagliflozin) resulted in withdrawal from the study.

Small increases in hemoglobin, hematocrit, and blood urea nitrogen levels were detected in the canagliflozin group. AST, ALT and γ-GTP levels were decreased from baseline in the canagliflozin group. The change of LDL-C was not different between placebo and canagliflozin groups. The mean value of the ketone bodies at baseline of both groups was higher than normal range, which was defined as 26.0–122 μmol/L in this study, and the slight increase of the ketone bodies was observed at 16 weeks in canagliflozin group (Additional file 3: Table S2).
In the present study, treatment with canagliflozin for 16 weeks improved glycemic control and other metabolic parameters, such as body weight and HDL cholesterol, in Japanese patients with T2DM who received insulin therapy. The decrease in HbA1c levels here was slightly greater than that observed in a previous study in non-Japanese patients, including Caucasians [difference between placebo and canagliflozin (100 mg each) at 18 weeks, −0.62 %] [16], suggesting that the effects of canagliflozin are independent of the pathologic features among races [20]. A significant decrease in HbA1c levels was observed regardless of the type of the insulin regimen.

Administration of insulin to patients with T2DM is often associated with weight gain, but the patients studied here experienced weight loss following combination therapy with canagliflozin and insulin. Similar results were reported by studies on the SGLT2 inhibitors dapagliflozin and empagliflozin used in combination with insulin, which were conducted outside Japan [21–24]. A study on a Japanese population administered a combination therapy of dapagliflozin and insulin demonstrated the improving glycemic control and reducing body weight. However, there are some differences in the present study: about 45 % of the participants were also treated with a dipeptidyl peptidase-4 inhibitor, and the data were not evaluated according to the type of insulin regimen [25]. The results of the present study demonstrated that the combination of canagliflozin and insulin, regardless of the insulin regimen, controlled plasma glucose levels without causing weight gain in Japanese patients with T2DM who were inadequately controlled by insulin.

Japanese patients with T2DM tend to have a long duration of disease and have high levels of HbA1c.

### Table 3 Effect of canagliflozin on secondary endpoints

| Parameters                  | Placebo | Canagliflozin 100 mg |
|-----------------------------|---------|----------------------|
| FPG (mg/dL)                 |         |                      |
| N                           | 70      | 75                   |
| Mean (SD) baseline          | 169.1 (52.6) | 170.6 (44.4) |
| LS mean (SE) change         | −1.4 (5.0) | −34.1 (4.8) |
| Difference (95 % CI) vs placebo | −32.6 (−46.3, −18.9) | −0.0026 (−0.0070, 0.0017) |
| p value                     | <0.001  |                      |
| Body weight (kg)            |         |                      |
| N                           | 70      | 75                   |
| Mean (SD) baseline          | 69.68 (13.13) | 70.19 (13.86) |
| LS mean (SE) change (%)     | 0.15 (0.18) | −1.49 (0.18) |
| LS mean (SE) percent change | 0.24 (0.26) | −2.13 (0.25) |
| Difference (95 % CI) vs placebo | −2.37 (−3.09, −1.65) | −2.37 (−3.09, −1.65) |
| p value                     | <0.001  |                      |
| SBP (mmHg)                  |         |                      |
| N                           | 70      | 75                   |
| Mean (SD) baseline          | 129.95 (16.32) | 136.85 (12.01) |
| LS mean (SE) change (%)     | −0.40 (1.19) | −3.58 (1.14) |
| Difference (95 % CI) vs placebo | −3.19 (−6.49, 0.11) | −3.19 (−6.49, 0.11) |
| p value                     | 0.058   |                      |
| DBP (mmHg)                  |         |                      |
| N                           | 70      | 75                   |
| Mean (SD) baseline          | 77.23 (10.87) | 78.34 (10.18) |
| LS mean (SE) change (%)     | −0.31 (0.74) | −1.55 (0.71) |
| Difference (95 % CI) vs placebo | −1.24 (−3.27, 0.80) | −1.24 (−3.27, 0.80) |
| p value                     | 0.232   |                      |
| Triglyceride (mg/dL)        |         |                      |
| N                           | 70      | 75                   |
| Mean (SD) baseline          | 144.0 (114.0) | 124.5 (112.3) |
| LS mean (SE) change (%)     | −4.0 (7.7) | −7.8 (7.4) |
| Difference (95 % CI) vs placebo | −3.8 (−25.0, 17.3) | −3.8 (−25.0, 17.3) |
| p value                     | 0.721   |                      |
| HDL-cholesterol (mg/dL)     |         |                      |
| N                           | 70      | 75                   |
| Mean (SD) baseline          | 57.6 (16.9) | 61.9 (16.1) |
| LS mean (SE) change (%)     | −0.5 (1.0) | 3.3 (1.0) |
| Difference (95 % CI) vs placebo | 3.7 (1.0, 6.5) | 3.7 (1.0, 6.5) |
| p value                     | 0.007   |                      |
| Proinsulin/C-peptide        |         |                      |
| N                           | 69      | 74                   |
| Mean (SD) baseline          | 0.0267 (0.0323) | 0.0235 (0.0380) |
| LS mean (SE) change (%)     | 0.0003 (0.0016) | −0.0024 (0.0015) |
| Difference (95 % CI) vs placebo | −0.0026 (−0.0070, 0.0017) | −0.0026 (−0.0070, 0.0017) |

### Table 3 continued

| Parameters                  | Placebo | Canagliflozin 100 mg |
|-----------------------------|---------|----------------------|
| HOMA2- %B (%)               |         |                      |
| N                           | 69      | 74                   |
| Mean (SD) baseline          | 24.26 (13.92) | 22.23 (11.12) |
| LS mean (SE) change (%)     | 0.88 (1.42) | 10.15 (1.37) |
| Difference (95 % CI) vs placebo | 9.27 (5.35, 13.19) | 9.27 (5.35, 13.19) |
| p value                     | <0.001  |                      |

N number of patients, FPG fasting plasma glucose, SBP systolic blood pressure, DBP diastolic blood pressure, HDL-cholesterol high-density lipoprotein cholesterol, HOMA2- %B homeostasis model assessment 2 steady state beta cell function, LS mean least squares mean, 95 % CI 95 % confidence interval.

a LS mean for change from the baseline to week 16, (factor treatment, covariate each parameter at baseline)

### Discussion

**Current findings and implications: efficacy**

In the present study, treatment with canagliflozin for 16 weeks improved glycemic control and other metabolic parameters, such as body weight and HDL cholesterol, in Japanese patients with T2DM who received insulin therapy. The decrease in HbA1c levels here was slightly greater than that observed in a previous study in non-Japanese patients, including Caucasians [difference between placebo and canagliflozin (100 mg each) at 18 weeks, −0.62 %] [16], suggesting that the effects of canagliflozin are independent of the pathologic features among races [20]. A significant decrease in HbA1c levels was observed regardless of the type of the insulin regimen.

Administration of insulin to patients with T2DM is often associated with weight gain, but the patients studied here experienced weight loss following combination therapy with canagliflozin and insulin. Similar results were reported by studies on the SGLT2 inhibitors dapagliflozin and empagliflozin used in combination with insulin, which were conducted outside Japan [21–24].

A study on a Japanese population administered a combination therapy of dapagliflozin and insulin demonstrated the improving glycemic control and reducing body weight. However, there are some differences in the present study: about 45 % of the participants were also treated with a dipeptidyl peptidase-4 inhibitor, and the data were not evaluated according to the type of insulin regimen [25]. The results of the present study demonstrated that the combination of canagliflozin and insulin, regardless of the insulin regimen, controlled plasma glucose levels without causing weight gain in Japanese patients with T2DM who were inadequately controlled by insulin.

Japanese patients with T2DM tend to have a long duration of disease and have high levels of HbA1c.
when insulin is initiated [17, 18]. Patients in the present study had a longer duration of DM (approximately 12–15 years) than that of previous studies (approximately 5–8 years in the Japanese phase 3 study) and a higher baseline level of HbA1c [14, 15]. Baseline values of HOMA2-%B and C-peptide were lower in the present study than in those previously reported, which suggests that the patients had a decreased capacity to secrete insulin. Nevertheless, canagliflozin treatment improved glycemic control. These findings are consistent with those of previous studies showing that canagliflozin decreases plasma glucose, regardless of insulin secretory capacity and duration of diabetes mellitus [26, 27]. Interestingly, canagliflozin combination with insulin slightly increased HOMA2-%B, suggesting improved beta-cell function. This is possibly resulting from a reduction of glucotoxicity [12, 28].

### Current findings and implications: Safety

Here the overall incidence of adverse events was similar between the placebo and canagliflozin groups. The incidence of hypoglycemia was slightly higher in the canagliflozin group than in the placebo group. All events were mild in severity, and severe hypoglycemia (i.e., requiring the assistance of another person) was not reported. Hypoglycemic events (hypoglycemic symptoms and/or decreased blood glucose) occurred most frequently at 6:00–11:59 h; therefore, caution may be exercised in the morning for patients who receive the combination of an SGLT2 inhibitor and insulin.

### Table 4 Summary of safety data (safety analysis set)

|                     | Placebo (N = 71) | n (%)     | 95 % CI       | Canagliflozin 100 mg (N = 75) | n (%)     | 95 % CI       |
|---------------------|------------------|-----------|---------------|------------------------------|-----------|---------------|
| Adverse events      | 46 (64.8)        | 51 (68.0) | 56.2–78.3     | Adverse drug reactions       | 16 (22.5) | 30 (40.0)     | 28.9–52.0     |
| Adverse drug reactions | 16 (22.5)     | 3 (4.0)   | 0.8–11.2      | Serious adverse events       | 0 (0.0)   | 0 (0.0)       | 0.0–4.8       |
| Serious adverse drug reactions | 0 (0.0)        | 0 (0.0)   | 0.0–4.8       | Adverse events leading to discontinuation | 0 (0.0)   | 1 (1.3)        | 0.0–7.2       |
| Adverse drug reactions leading to discontinuation | 0 (0.0)        | 0 (0.0)   | 0.0–4.8       | Deaths                       | 0 (0.0)   | 0 (0.0)       | 0.0–4.8       |
| AEs of special interest |                   |           |               | Documented hypoglycemiaa      | 11 (15.5) | 20 (26.7)     |               |
| Hypoglycemia        | 15 (21.1)        | 19 (25.3) |               | Blood glucose decreased      | 11 (15.5) | 20 (26.7)     |               |
| Urinary tract infection | 0 (0)          | 1 (1.3)   |               | Cystitis                     | 0 (0)     | 1 (1.3)       |               |
| Osmotic diuresis    | 2 (2.8)          | 4 (5.3)   |               | Polyuria                     | 0 (0)     | 3 (4.0)       |               |
| Pollakiuria         | 1 (1.4)          | 4 (5.3)   |               | Thirst                       | 1 (1.4)   | 1 (1.3)       |               |
| Polyuria            | 0 (0)            | 3 (4.0)   |               | Fracture                     | 1 (1.4)   | 0 (0)         |               |
| Thirst              | 1 (1.4)          | 1 (1.3)   |               | Foot Fracture                | 1 (1.4)   | 0 (0)         |               |
| Skin disorder       | 0 (0)            | 2 (2.7)   |               | Seborrheic dermatitis        | 0 (0)     | 1 (1.3)       |               |
| Urticaria           | 0 (0)            | 1 (1.3)   |               | Ketone bodies                | 2 (2.8)   | 3 (4.0)       |               |
| Ketone bodies       | 2 (2.8)          | 3 (4.0)   |               | Blood ketone bodies increased | 2 (2.8)   | 3 (4.0)       |               |
| (Number of female patients) | (N = 22)       | (N = 31)  |               | Vulvovaginitis               | 0 (0)     | 1 (3.2)       |               |
| Genital candidiasis | 0 (0)            | 1 (3.2)   |               |                              |           |               |               |

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* Number of patients, n number of patients with adverse event, % = n/N × 100

*a Hypoglycemia in the follow-up period was excluded
in patients administered 25 mg of empagliflozin than in those administered placebo or 10 mg of empagliflozin. However, after physicians were allowed to titrate the insulin dose, the incidence of hypoglycemia over the complete 78-week treatment was similar among the groups [24]. Similarly, in the present study, the incidence per subject-year exposure decreased in patients undergoing insulin dose reduction following a hypoglycemic event. These findings suggest that adjusting the insulin dose of the combined regimen prevents the occurrence of hypoglycemic events.

The slight increase of the ketone bodies (59.93 μmol/L) from baseline was observed at 16 weeks in canagliflozin group, although it was not notably higher than those reported by previous studies of canagliflozin [14, 15, 29] or other SGLT2 inhibitor [30]. Malaise and similar symptoms that may accompany the marked elevation of ketone bodies were not reported, and no patient was dismissed because of increased blood ketone bodies in this study. The elevation of ketone bodies was not accompanied by hyperglycemia and is therefore likely attributable to a compensatory increase in fatty acid metabolism in response to loss of calories because of canagliflozin-induced urinary glucose excretion.

**Future perspectives**

Several clinical studies have reported the safety and efficacy of SGLT2 inhibitors in combination with insulin in patients with T1DM, however diabetic ketoacidosis has been reported in some studies [28, 31–34]. In addition, diabetic ketoacidosis has been reported in patients with T1DM who were treated off-label with an SGLT2 inhibitor in daily clinical practice [35, 36]. Therefore application of SGLT2 inhibitors for T1DM still remains to be addressed.

On the other hand, some cases of diabetic ketoacidosis have also been reported in patients with T2DM who were treated with an SGLT2 inhibitor. Lowering the dose of insulin may increase the production of ketone bodies because of insufficient suppression of lipolysis and ketogenesis [35]. Therefore adjusting the insulin dose may be performed with care, particularly in T2DM patients with diminished capacity to secrete insulin.

There were no cardiovascular-related AEs both placebo and canagliflozin group in this study. Several studies of SGLT2 inhibitors for assessment of the cardiovascular outcome are conducting [37], and it was recently reported that the SGLT2 inhibitor empagliflozin reduces cardiovascular event in T2DM patient with high CVD risk, EMPA-REG OUTCOME trial, around 48 % of subjects were on insulin-combination therapy [38]. In the CANVAS trial, about half of the subjects were also treated with insulin [39]. These studies will provide the information on the effect of the combination of SGLT2 inhibitor and insulin on cardiovascular outcome.

**Limitations of the study**

The limitation of this study is the short course of treatment; hence, the present study has been extended for up to 52 weeks. In addition, patients who were treated with insulin in the form of an intermediate-acting or rapid-acting product were not involved, and there were a small number of patients in each type of insulin subgroup. Therefore, we did not discuss which insulin regime fit better with canagliflozin.
Conclusion
Canagliflozin added to insulin therapy was effective and well tolerated by Japanese patients with T2DM. This regimen provides a novel option in the treatment of patients with T2DM who require additional treatment.

Additional files

**Additional file 1: Figure S1.** Flow Diagram and number of subjects in each analysis set.

**Additional file 2: Table S1.** Time of onset of hypoglycemia (safety analysis set).

**Additional file 3: Table S2.** Laboratory variables at baseline and change from baseline on week 16 (safety analysis set).

Abbreviations
ANCOVA: analysis of covariance; Hba1c: glycated hemoglobin; FPG: fasting plasma glucose; HDL: high-density lipoprotein; LS: least squares; LOCF: last observation carried forward; HOMA2- %B: homeostasis model assessment 2 steady-state beta-cell function; MMRM: mixed-model repeated-measures; SGLT: sodium glucose co-transporter; SE: standard error; T2DM: type 2 diabetes mellitus.

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Competing interests

N Inagaki has received consulting fees and research support from Mitsubishi Tanabe Pharma Corp, and has served on speakers bureaus for Mitsubishi Tanabe Pharma Corp. He has also received consulting fees and/or research support from Astellas Pharma Inc, AstraZeneca KK, Daichi Sankyo Co, Ltd, Eli Lilly Japan K.K, GlaxoSmithKline K.K, Japan Diabetes Foundation, Japan Tobacco Inc, Kissei Pharmaceutical Co, Ltd, Kyowa Hakko Kirin Co, Ltd, MSD KK, Nippon Boehringer Ingelheim Co, Ltd, Novartis Pharma K.K, Novo Nordisk Pharma Ltd, Ono Pharmaceutical Co, Ltd, Pfizer Japan Inc, Roche Diagnostics K.K, Sanofi K.K, Sanwa Kagaku Kenkyusho Co, Ltd, Shiratori Pharmaceutical Co, Ltd, Sumitomo Dainippon Pharma Co, Ltd, Takeda Pharmaceutical Co, Ltd, and has served on speakers bureaus for Kyowa Hakko Kirin Co, Ltd, MSD KK, Nippon Boehringer Ingelheim Co, Ltd, Novartis Pharma K.K, Sanofi K.K, Sumitomo Dainippon Pharma Co, Ltd. S.Harashima has served on speakers bureaus for Mitsubishi Tanabe Pharma Corp. He has also received consulting fees and/or research support from Abbott Japan Co, Ltd, AstraZeneca KK, MSD K.K, Novo Nordisk Pharma Ltd, and Sanofi K.K, and has served on speakers bureaus for Astellas Pharma Inc, Eli Lilly Japan K.K, MSD K.K. All other authors are employees of Mitsubishi Tanabe Pharma Corp.

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