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Long-term efficacy and safety of canagliflozin in combination with insulin in Japanese patients with type 2 diabetes mellitus

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Aim: The aim of this study was to assess the long-term efficacy and safety of canagliflozin as add-on therapy in Japanese patients with type 2 diabetes mellitus who had inadequate glycaemic control with insulin.

Materials and methods: The study comprised a 16-week, double-blind period in which patients were randomized to either placebo (P; N = 70) or canagliflozin (100 mg, CAN; N = 76), followed by a 36-week open-label period in which all patients received canagliflozin. The efficacy endpoints included the change in HbA1c from baseline to end of treatment. The safety endpoints were adverse events, hypoglycaemic events, and laboratory test values.

Results: The changes from baseline (mean ± standard deviation, last observation carried forward) in the P/CAN and CAN/CAN groups, respectively, were −1.09% ± 0.85% and −0.88% ± 0.86% for HbA1c, −1.40% ± 2.54% and −2.14% ± 2.75% for body weight, and 7.84% ± 14.37% and 8.91% ± 10.80% for HOMA2-%B (all, $P < .001$). Adverse events occurred in 85.1% of the P/CAN group and 92.0% of the CAN/CAN group. Hypoglycaemic events occurred in 43.3% and 54.7%, respectively. All hypoglycaemic events were mild in severity and insulin dose reduction decreased the incidence rate of hypoglycaemic events. Post-hoc ordinal logistic modelling/logistic modelling showed that lower serum C-peptide at Week 0 was a risk factor for hypoglycaemia in both the P and CAN groups in the double-blind period as well as in the canagliflozin all-treatment period.

Conclusions: This study demonstrates the long-term efficacy and safety of canagliflozin combined with insulin in Japanese patients.

KEYWORDS

canagliflozin, hypoglycaemia, insulin, SGLT2 inhibitor, type 2 diabetes mellitus

1 | INTRODUCTION

The prevalence of type 2 diabetes mellitus (T2DM) is increasing worldwide. The International Diabetes Federation estimates that, globally, 415 million adults have diabetes and 318 million have impaired glucose tolerance. At the current rate of increase, 642 million people will have diabetes by the year 2040.[1] In Japan, an estimated

7.2 million individuals had T2DM and more than 60 000 died because of the disease in 2015.[1]

Intensive glycaemic control with insulin can prevent diabetic complications in T2DM.[2,3] However, intensive glycaemic control with insulin is associated with an increased risk of hypoglycaemia and weight gain.[4] If hypoglycaemic episodes recur often over time, the brain adapts to hypoglycaemia, with symptom responses at a lower than usual plasma

glucose concentration.[5] This reduces perception of hypoglycaemic symptoms, resulting in increased frequency, duration and severity of hypoglycaemia. Hypoglycaemia has been associated with increased cardiovascular risk, cognitive dysfunction, dementia and vision disorders.[6]

Sodium glucose co-transporter 2 (SGLT2) inhibitors suppress glucose reabsorption in the renal tubules and increase urinary glucose excretion, resulting in insulin-independent antihyperglycaemic effects.[7,8] While SGLT2 inhibitors, in combination with insulin, were evaluated in several studies, including a meta-analysis, and were found to significantly reduce glycated haemoglobin (HbA1c) in patients with T2DM, they did not increase the risk of hypoglycemia.[9,10] In contrast, in a post-marketing surveillance study, the SGLT2 inhibitor ipragliflozin, in combination with insulin, did increase the risk of hypoglycaemia in elderly Japanese patients.[11] In another report, SGLT2 inhibitors that caused severe hypoglycaemia in Japanese patients had usually been used in conjunction with insulin and/or sulphonylureas.[12] Therefore, the effect of the combination of an SGLT2 inhibitor and insulin on the risk of hypoglycaemia needs to be more fully addressed.

The pathophysiology of diabetes is different in East Asian vs Caucasian patients; East Asian patients, including Japanese patients, have reduced β-cell function and higher insulin sensitivity as compared to Caucasian patients.[13,14] In addition to lower insulin secretion after meals, the fasting insulin level is also low in Japanese patients.[15] Therefore, considering these pathological differences, it is important to evaluate this combination therapy in Japanese patients.

Clinical trials conducted in Japan showed that the SGLT2 inhibitor canagliflozin, when used either as monotherapy or in combination with oral antihyperglycaemic therapy, significantly improved glycaemic control, reduced body weight and was well tolerated.[16–19] The prespecified substudy of the Canagliflozin Cardiovascular Assessment Study (CANVAS) demonstrated the efficacy and safety of canagliflozin in combination with insulin therapy for 52 weeks.[20] However, the long-term safety and efficacy of this combination has not been evaluated in Japanese patients with T2DM.

We previously reported on the efficacy and safety of canagliflozin added to insulin therapy for 16 weeks in a double-blind, randomized, placebo-controlled study (NCT02220920).[21] The present study (NCT02622113) is a 36-week, open-label extension of the previous 16-week trial. The objective of this study was to assess the long-term efficacy and safety of continued treatment with canagliflozin, in combination with insulin, in Japanese patients who had inadequate glycaemic control with insulin alone. In addition, as hypoglycaemia is still an important issue of this combination therapy, we investigated factors that might cause hypoglycaemia in a *post-hoc* analysis.

2 | MATERIALS AND METHODS

2.1 | Study design

This was a multicentre, open-label extension study of eligible patients with T2DM who participated in the 16-week, double-blind, randomized phase IV study of canagliflozin as an add-on to insulin.[21] After the 16-week double-blind period, all eligible patients received once-daily oral canagliflozin (100 mg) before breakfast for a period of 36 weeks. Patients were visited every 4 weeks, and were followed for 2 weeks after the end of treatment (Figure S1).

The patients received insulin regimens that were consistent with those in the double-blind period: premixed, intermediate-acting, long-acting, premixed plus rapid- or short-acting, intermediate-acting plus rapid- or short-acting, or long-acting plus rapid- or short-acting. The daily insulin dose ranged from 8 to 60 units. The insulin type(s) used remained the same from the first day of treatment to the end of the 52-week total treatment period. The insulin dose was fixed during the study period, except for a temporary increase or decrease if considered to be necessary by the investigator.

2.2 | Compliance with 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: (1) Japanese laws related to ensuring drug/medical device quality, efficacy and safety and (2) Japanese ministerial orders and related regulations on good post-marketing surveillance practice and good clinical practice. The study was approved by the ethics committee/institutional review boards at all of the participating institutions (see Acknowledgements section). All patients provided written informed consent for participation in the extension study.

2.3 | Efficacy and safety outcome measures

The efficacy evaluation included the following assessments: change from baseline in HbA1c, body weight, blood pressure and fasting plasma glucose (FPG), proinsulin/C-peptide ratio, homeostasis model assessment 2 steady-state β-cell function (HOMA2-%B), high-density lipoprotein cholesterol (HDL-C) and triglycerides.

The safety assessment was based on adverse events (AEs), hypoglycaemic events, laboratory test values and vital signs. The numbers of affected patients and incidences of AEs were described using the Medical Dictionary for Regulatory Activities (MedDRA)/Japanese, version 18.1. AEs were classified as mild, moderate or severe. Severe AEs were defined as those that interfered with daily-life activities. Low blood glucose (≤70 mg/dL) without symptoms was classified as "blood glucose decreased." Hypoglycaemic episodes with typical hypoglycaemic symptoms were classified as hypoglycaemia, regardless of the blood glucose level. Severe hypoglycaemia was defined as events requiring assistance by another person to actively administer carbohydrate or glucagon, or perform other resuscitation actions. Hypoglycaemia accompanied by symptoms of seizures was considered to be a hypoglycaemic seizure, which is classified as hypoglycaemia. In addition to the classification of hypoglycaemia by MedDRA, the classification by a workgroup of the American Diabetes Association and The Endocrine Society was also performed.[22] The "hypoglycaemia" defined by MedDRA is classified into "severe hypoglycaemia," "documented symptomatic hypoglycaemia," "probable symptomatic hypoglycaemia" and "pseudo-hypoglycaemia." In accordance with hypoglycaemic symptom(s) and plasma glucose level, "blood glucose decreased" is classified into "asymptomatic hypoglycaemia."

2.4 | Statistical methods

Efficacy analyses were performed on the full analysis set (FAS) which comprised all patients, excluding those who did not receive a dose of canagliflozin or for whom there was no efficacy data after initiating treatment with canagliflozin. Safety analyses were performed in the safety analysis set (SAS), which comprised all patients, excluding those who did not receive a dose of canagliflozin or for whom there was no safety data after initiating treatment with canagliflozin. Data obtained at the start of the double-blind study (Week 0) was used to analyse patient demographics; no demographic characteristics were investigated at the start of the extension study.

The Baseline for the analyses was the initiating of canagliflozin administration, defined as Week 16 for patients who received placebo in the double-blind period (P/CAN group) and Week 0 for patients who received canagliflozin in the double-blind period (CAN/CAN group). Statistics for efficacy endpoints were summarized as change from baseline to the end of the treatment period (last observation carried forward [LOCF]). Descriptive statistics of actual value and change from baseline at each time point were calculated. The paired-t test was used to assess efficacy endpoints between baseline and end of treatment.

In order to investigate risk factors for hypoglycaemia in the *post-hoc* analysis, an ordinal logistic regression analysis with a cumulative logistic model was applied to hypoglycaemia, and was categorized according to whether the patients had 0, 1 to 2, 3 to 7 or ≥8 hypoglycaemic events during the entire period of canagliflozin treatment (36 weeks in the P/CAN group; 52 weeks in the CAN/CAN group). Variables were selected using the stepwise method, as potential risk factors for hypoglycaemia included certain patient characteristics (Table S1) during the entire CAN treatment period (both entry and retention criteria were set at $P = .05$). To evaluate whether factors found here were derived from canagliflozin or insulin, the variables found here were characterized by logistic regression analysis in the double-blind period. As the total exposure period was short in the double-blind period (placebo, 21.30; CAN, 22.57 vs all CAN treatment, 113.56 person years), we could not divide the groups into 4 for the double-blind period. Therefore, the placebo and canagliflozin groups were divided into 2 groups according to the number of hypoglycaemic events (0 and ≥1) and a logistic regression model was applied.

All statistical tests were 2-sided, with a level of significance of 5%. A 2-sided confidence interval with a confidence coefficient of 95% was used. All statistical analyses were conducted using SAS version 9.4 (SAS Institute Inc., Cary, North Carolina).

3 | RESULTS

3.1 | Patients

Among the 146 patients enrolled in the double-blind period (P, 70; CAN, 76), 140 patients (P, 67; CAN, 73) had given consent to enter the extension study. However, 1 patient did not enter the extension study; therefore, 139 patients (P, 67; CAN, 72) continued treatment in the extension study. Three patients in the canagliflozin group who

did not consent to enter the open-label period, and 1 patient described above were included in the analysis set. Hence, 143 patients (P, 67; CAN, 76) were included in the analysis set of the open-label period. One patient in the canagliflozin group, who mistakenly received placebo during the double-blind period, did not enter the extension study; this patient was included in the FAS and was not included in the SAS. Therefore, 143 patients (P, 67; CAN, 76) were included in the FAS and 142 patients (P, 67; CAN, 75) were included in the SAS (Figure S2).

Patient demographics and characteristics at Week 0 for the P/CAN group and the CAN/CAN group are shown in Table S1. Patient characteristics were similar in both groups; the mean HbA1c ± SD was 8.80% ± 0.81% in the P/CAN group and 8.89% ± 0.81% in the CAN/CAN group, and the mean body weights ± SD were 69.54 ± 13.40 kg and 69.95 ± 13.93 kg, respectively. The daily insulin dose was 27.9 ± 14.0 U in the P/CAN group and 31.1 ± 15.1 U in the CAN/CAN group.

3.2 | Efficacy

HbA1c decreased progressively during the first 4 weeks of treatment and remained stable thereafter in the CAN/CAN group (Figure 1). In comparison, in the P/CAN group, HbA1c was stable up to Week 16 and then declined from Week 16 (corresponding to initiation of canagliflozin treatment) through Week 24, after which it remained stable.

Figure S3 shows the changes from baseline in HbA1c, FPG and body weight. The change in HbA1c from baseline to the end of treatment (LOCF, mean ± SD) was −1.09% ± 0.85% in the P/CAN group and −0.88% ± 0.86% in the CAN/CAN group (Table 1). The decrease in HbA1c was observed independent of the type of insulin regimen (Table S2). The change in FPG (LOCF, mean ± SD) decreased significantly from baseline to the end of the treatment period in the P/CAN group (−33.1 ± 44.1 mg/dL) and in the CAN/CAN group (−32.8 ± 45.7 mg/dL). A statistically significant reduction in percentage body weight (LOCF, mean ± SD) was also observed in the

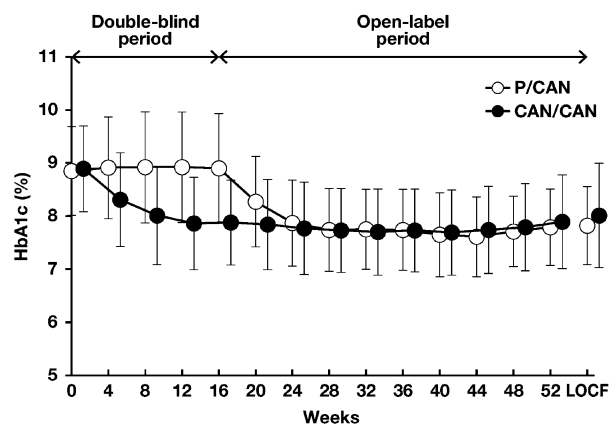| No. of patients														
P/CAN	70	70	69	69	67	65	65	64	62	62	62	62	62	67
CAN/CAN	76	76	75	74	73	72	70	70	70	69	69	68	66	65	76

FIGURE 1 Glycated haemoglobin (HbA1c) measured from baseline to the end of treatment (LOCF). Each *point* and *bar* represents mean ± SD. Abbreviations: CAN/CAN, canagliflozin/canagliflozin group; LOCF, last observation carried forward, P/CAN, placebo/canagliflozin group

TABLE 1 Change in efficacy endpoints from baseline to the end of canagliflozin treatment (LOCF, full analysis set, N = 143)

	P/CAN (Open-label period, N = 67)	CAN/CAN[a] (Double-blind and open-label period, N = 76)
HbA1c (%)		
n	67	76
Baseline, mean (SD)	8.90 (1.03)	8.89 (0.81)
Change from baseline, mean (SD)	−1.09 (0.85)	−0.88 (0.86)
P value[b]	<.001	<.001
FPG (mg/dL)		
n	65	75
Baseline, mean (SD)	168.9(55.8)	170.6(44.4)
Change from baseline, mean (SD)	−33.1 (44.1)	−32.8 (45.7)
P value[b]	<.001	<.001
Body weight (kg)		
n	65	75
Baseline, mean (SD)	69.88 (13.60)	70.19 (13.86)
Change from baseline, mean (SD)	−0.99(1.76)	−1.52(1.96)
P value[b]	<0.001	<0.001
(%)		
Change from baseline, mean (SD)	−1.40 (2.54)	−2.14 (2.75)
P value[b]	<.001	<.001
SBP (mm Hg)		
n	67	76
Baseline, mean (SD)	130.54 (17.23)	136.85 (12.01)
Change from baseline, mean (SD)	−2.51 (12.94)	−4.71 (11.71)
P value[b]	.117	<.001
DBP (mm Hg)		
n	67	76
Baseline, mean (SD)	77.41 (10.25)	78.34 (10.18)
Change from baseline, mean (SD)	−1.83 (8.48)	−2.25 (7.46)
P value[b]	.082	.010
Triglyceride (mg/dL)		
n	65	75
Baseline, mean (SD)	140.6 (111.4)	124.5 (112.3)
Change from baseline, mean (SD)	−3.0 (72.1)	−6.3 (83.9)
P value[b]	.736	.515

(Continues)

TABLE 1 (Continued)

	P/CAN (Open-label period, N = 67)	CAN/CAN[a] (Double-blind and open-label period, N = 76)
HDL-cholesterol (mg/dL)		
n	65	75
Baseline, mean (SD)	57.5 (16.2)	61.9 (16.1)
Change from baseline, mean (SD)	2.3(9.0)	1.8(8.2)
P value[b]	0.043	0.059
(%)		
Change from baseline, mean (SD)	4.98 (15.59)	3.92 (13.79)
P value[b]	.012	.016
Proinsulin/C-peptide		
n	64	74
Baseline, mean (SD)	0.0259 (0.0225)	0.0235 (0.0380)
Change from baseline, mean (SD)	−0.0015 (0.0150)	−0.0007 (0.0080)
P value[b]	.443	.452
HOMA2-%B (%)		
n	64	74
Baseline, mean (SD)	24.84 (15.44)	22.23 (11.12)
Change from baseline, mean (SD)	7.84 (14.37)	8.91 (10.80)
P value[b]	<.001	<.001

Abbreviations: CAN/CAN, canagliflozin/canagliflozin group; DBP, diastolic blood pressure; FPG, fasting plasma glucose; HDL, high-density lipoprotein; HOMA2-%B, homeostasis model assessment 2 steady-state β-cell function; LOCF, last observation carried forward; N, number of patients in each group; n, number of patients who had LOCF data; P/CAN, placebo/canagliflozin group; SBP, systolic blood pressure; SD, standard deviation.

[a] P/CAN week 36, CAN/CAN week 52.

[b] Paired-t, vs baseline.

P/CAN group (−1.40% ± 2.54%) and the CAN/CAN group (−2.14% ± 2.75%) (Table 1). The reductions in HbA1c, FPG and body weight from baseline were statistically significant at all evaluation points and were maintained until the end of treatment in both groups (P < .001).

Table 1 also shows the changes (LOCF, mean ± SD) in other efficacy endpoints from baseline. SBP/DBP significantly decreased in the CAN/CAN group, but not in the P/CAN group. The value of HDL-cholesterol significantly increased in the the P/CAN group, but not in the CAN/CAN group. The percent change in HDL-cholesterol significantly increased in both group. Fasting triglycerides and the fasting proinsulin/C-peptide ratio decreased in both groups, but the decreases were not statistically significant.

HOMA2-%B increased significantly from baseline in both the P/CAN (7.84% ± 14.37%) and CAN/CAN (8.91% ± 10.80%) groups (P < .001 for both groups).

TABLE 2 Adverse events (safety analysis set, N = 142)

	n (%)	
	P/CAN (Open-label period, N = 67)	CAN/CAN[a] (Double-blind and open-label period, N = 75)
Adverse events	57 (85.1)	69 (92.0)
Serious	7 (10.4)	7 (9.3)
Leading to discontinuation	4 (6.0)	4 (5.3)
Adverse drug reactions	33 (49.3)	41 (54.7)
Serious	0 (0.0)	0 (0.0)
Leading to discontinuation	2 (3.0)	1 (1.3)
Deaths	0 (0.0)	0 (0.0)
Adverse events of special interest		
All hypoglycaemic events	29 (43.3)	41 (54.7)
Hypoglycaemia	20 (29.9)	28 (37.3)
Hypoglycaemic seizure	1 (1.5)	0 (0.0)
Blood glucose decreased	16 (23.9)	29 (38.7)
Urinary tract infection	1 (1.5)	1 (1.3)
Male genital infection	0/46 (0.0)	1/44 (2.3)
Female genital infection	3/21 (14.3)	2/31 (6.5)
Osmotic diuresis	6 (9.0)	5 (6.7)
Volume depletion	0 (0.0)	1 (1.3)
Fracture	2 (3.0)	1 (1.3)
Skin and subcutaneous tissue disorder	4 (6.0)	7 (9.3)
Malignant neoplasm	1 (1.5)	1 (1.3)
Cardiovascular-related events	1 (1.5)	0 (0.0)
Hepatic function impairment	0 (0.0)	2 (2.7)
Blood ketone bodies increased	1 (1.5)	3 (4.0)
Renal impairment	0 (0.0)	0 (0.0)

Abbreviations: CAN/CAN, canagliflozin/canagliflozin group; N, number of patients in each group; n, number of patients who experienced adverse events; P/CAN, placebo/canagliflozin group.
[a] P/CAN for 36 weeks, CAN/CAN for 52 weeks.

The change in daily dose of insulin (mean ± SD) from baseline to the end of treatment was −0.67 ± 2.31 U in the P/CAN group (baseline, 28.59 ± 14.39 U) and −0.37 ± 2.01 U in the CAN/CAN group (baseline, 30.07 ± 15.45 U).

3.3 | Safety

AEs were defined as all medically undesirable events occurring in treated patients, regardless of causal relationship. The safety analysis was conducted in 67 patients in the P/CAN group and in 75 patients in the CAN/CAN group.

AEs were reported in 85.1% of patients in the P/CAN group and in 92.0% of patients in the CAN/CAN group (Table 2). Serious AEs occurred in 7 of 67 patients (10.4%) in the P/CAN group and in 7 of 75 patients (9.3%) in the CAN/CAN group. AEs leading to treatment discontinuation occurred in 6.0% of patients in the P/CAN group (4 events: vulvovaginal candidiasis, colon cancer, lacunar infarction and drug eruption) and in 5.3% of patients in the CAN/CAN group (4 events: atrial fibrillation, alcoholic liver disease, vulvovaginal pruritus and lower limb fracture). There were no deaths in either group.

All AEs judged to have a reasonably possible causal relationship with the study drug were considered adverse drug reactions (ADRs). ADRs occurred in 49.3% of patients in the P/CAN group and in 54.7% of patients in the CAN/CAN group. No serious ADRs were reported in either group.

The most common AE of special interest was hypoglycaemic events (hypoglycaemia, hypoglycaemic seizure and blood glucose decreased), which were reported in 29 of 67 patients (43.3%) in the P/CAN group and in 41 of 75 patients (54.7%) in the CAN/CAN group (Table 2). All hypoglycaemic events were mild in severity. Hypoglycaemic classification was undertaken by a workgroup of the American Diabetes Association and The Endocrine Society (Table S3). No severe hypoglycaemic events occurred in any group. Other common AEs of special interest were vulvovaginitis, osmotic diuresis and skin and subcutaneous disorders.

A total of 551 hypoglycaemic events of any type occurred during the entire treatment period with canagliflozin (36 weeks of treatment in the P/CAN group; 52 weeks in the CAN/CAN group). The incidence of hypoglycaemic events for all patients was 4.85 per subject-year exposure, with the highest incidence in patients who received long-acting insulin plus either rapid- or short-acting formulations (Table S4). The incidence of hypoglycaemic events did not increase with long-term administration of canagliflozin. The incidence rates of hypoglycaemia per subject-year exposure were 4.51 and 7.97 in the P and CAN groups, respectively, during the double-blind period, and 4.85 during the entire canagliflozin treatment period. The insulin dose reduction (approximately 10% reduction) decreased the incidence rate of hypoglycaemic events per subject-year of exposure (14.76 before dose reduction, 9.30 after dose reduction; N = 38) (Table 3). Hypoglycaemic events occurred most frequently between 06:00 and 11:59 AM (Table S5).

To evaluate hypoglycaemic events in detail, the patients were divided into 4 groups according to the number of hypoglycaemic events experienced: 0, 1 to 2, 3 to 7 and ≥8. The demographics of each patient group are shown in Table S6. Patients who experienced more frequent hypoglycaemic events tended to be older and had a longer duration of diabetes, lower BMI, higher prevalence of diabetic neuropathy, lower prevalence of diabetic nephropathy, lower levels of FPG, serum C-peptide and HOMA2-%B, and higher does of insulin.

To investigate the risk factors for hypoglycaemic events, the ordinal logistic model was applied to the entire period of treatment with canagliflozin, categorized according to whether patients experienced 0, 1 to 2, 3 to 7 or ≥8 hypoglycaemic events. Serum C-peptide, diabetic neuropathy and insulin regimen at Week 0 were found to be risk factors. To determine which insulin regimen is related to

TABLE 3 Incidence rates of hypoglycaemic events before and after insulin dose reduction

	Entire CAN treatment period[a] (N = 38)				
	All (N = 38)	Premixed (N = 12)	Long-acting (N = 10)	Premixed + rapid- or short-acting (N = 1)	Long-acting + rapid- or short-acting (N = 15)
Before first dose reduction					
Total exposure period (subject-years)	8.94	2.87	2.07	0.07	3.94
No. of hypoglycaemic events	132	29	37	1	65
Incidence per subject-year exposure	14.76	10.12	17.85	14.61	16.51
After first dose reduction					
Total exposure period (subject-years)	21.84	6.14	6.67	0.64	8.38
No. of hypoglycaemic events	203	27	72	2	102
Incidence per subject-year exposure	9.30	4.39	10.79	3.14	12.17

Incidence rate per subject-year: number of events/total exposure period (subject-years). Abbreviations: CAN/CAN, canagliflozin/canagliflozin group; N, number of patients. P/CAN, placebo/canagliflozin group.

[a] P/CAN for 36 weeks, CAN/CAN for 52 weeks.

hypoglycaemia, we performed a relative risk analysis of each insulin regimen compared to long-acting only and found that a long-acting plus rapid- or short-acting insulin regimen was a risk factor for hypoglycaemia. Collectively, the presence of diabetic neuropathy and the use of long-acting plus rapid- or short-acting insulin regimens increased the risk of hypoglycaemia. Conversely, high serum C-peptide levels decreased the risk of hypoglycaemia, that is, low serum C-peptide was a risk factor for hypoglycaemia.

To evaluate whether these factors (serum C-peptide, diabetic neuropathy and insulin regimen) were derived from canagliflozin or insulin, binominal analysis was performed during the double-blind period. Low serum C-peptide was identified as a risk factor in both the placebo and canagliflozin groups in the double-blind period (Table 4). With the exception of an insulin regimen in the placebo group, no other factors were identified.

The changes in laboratory values from baseline to the end of treatment are shown in Table S7. The changes of low-density lipoprotein-cholesterol from baseline were 6.1 ± 22.5 mg/dL in the P/CAN group and 1.8 ± 19.7 mg/dL in the CAN/CAN group. The changes in total ketone bodies from baseline were 141.05 ± 372.80 μmol/L and 112.93 ± 244.19 μmol/L in the P/CAN and CAN/CAN groups, respectively. However, no AEs associated with increased ketone bodies, such as ketoacidosis, were observed.

4 | DISCUSSION

In this extension study, treatment with canagliflozin plus insulin improved glycaemic control in Japanese patients with T2DM who had inadequate glycaemic control with insulin monotherapy, as evidenced by significant reductions in HbA1c, FPG and body weight over the course of treatment. These beneficial effects were maintained for the entire 36 weeks in the P/CAN group and the entire 52 weeks in the CAN/CAN group.

T2DM is a progressive disease characterized by increasing deterioration of pancreatic β-cell function.[23] As a result, the proportion of patients receiving insulin therapy increases as the duration of diabetes increases.[24,25] Compared with previous studies, the patients in our study had longer disease duration, higher HbA1c and lower HOMA2-%B, which suggests greater deterioration of β-cell function

TABLE 4 Ordinal logistic regression analysis with cumulative logistic model and logistic regression analysis[a] of risk factors for hypoglycaemic events

	Odds ratio (95% CI)		
	Entire CAN treatment period	Double-blind period	
Factors	Multi-nominal (ordinal logistic model)	Bi-nominal (logistic model)	
	CAN group	Placebo group	CAN group
Fasting serum C-peptide	0.351 (0.195, 0.632)	0.054 (0.007, 0.387)	0.376 (0.153, 0.925)
Diabetic neuropathy	3.382 (1.488, 7.685)	2.344 (0.479, 11.481)	1.071 (0.308, 3.724)
Insulin regimen			
Long-acting + rapid or short-acting vs long-acting	4.127 (1.801, 9.457)	6.972 (1.136, 42.784)	1.382 (0.404, 4.731)
Premixed vs long-acting	1.281 (0.559, 2.936)	3.102 (0.502, 19.166)	2.050 (0.612, 6.864)
Premixed + rapid or short-acting vs long-acting[b]	ND	ND	–

Abbreviations: CAN, canagliflozin; CI, confidence interval.

[a] The ordinal logistic regression analysis with cumulative logistic model was applied to hypoglycaemia, categorized according to whether the patients experienced 0, 1-2, 3-7 or ≥8 hypoglycaemic events during the entire period of canagliflozin treatment or logistic regression analysis categorized as 0 or ≥1 hypoglycaemic events during the double-blind period. Variables were selected using the stepwise method, as potential risk factors for hypoglycaemia included certain patient characteristics (Table S1) (both entry and retention criteria were set at $P = .05$) during the entire CAN treatment period. The variables found here were characterized by logistic regression analysis during the double-blind period.

[b] Entire CAN treatment period (N = 1); Double-blind period (Placebo: N = 1, CAN: N = 0).

at study enrollment.[17-19] Despite the advanced disease profile of the patients, canagliflozin treatment improved glycaemic control for 52 weeks. In addition, HOMA2-%B, a marker of pancreatic β-cell function, was significantly increased from baseline in both treatment groups and was maintained until the end of treatment, suggesting that canagliflozin improved β-cell function. Reduced glucose toxicity with canagliflozin treatment may be a possible mechanism for this improvement.

Most patients with diabetes have concomitant conditions including obesity, hypertension and lipid metabolism disorders, which can lead to micro- and macrovascular complications. Prevention of micro- and macrovascular complications requires effective glycaemic control and management of body weight, blood pressure and plasma lipids.[26,27] In this extension study, body weight, BMI and waist circumference were significantly decreased in both groups, and the reductions were maintained until the end of treatment. Studies have shown that weight gain is an issue with insulin treatment, at times requiring higher insulin doses.[28-30] In contrast, patients in our study lost weight despite receiving insulin therapy.

Prior evidence has demonstrated that insulin doses typically need to be increased to maintain glycaemic control as the duration of treatment increases.[31,32] In this study, the combination of canagliflozin and insulin allowed for long-term glycaemic control without increases in insulin doses. A meta-analysis reported that treatment with SGLT2 inhibitors, in combination with insulin, led to insulin dose reductions; the studies in this meta-analysis permitted an increase or decrease in insulin dose according to the respective titration criteria.[9] In the present study, the mean change in daily dose of insulin from baseline was very small, and the number of patients with insulin dose reductions was 38. This may be explained by the protocol requirements of the study; the insulin dose was fixed during the study period, with the exception of a temporary increase or decrease if considered necessary by the investigator. Another explanation may be the lower mean baseline insulin dose in this Japanese patient population compared with Western populations (approximately 30 U in this study vs 47.1 to 91.5 U in the Western populations included in the meta-analysis).[9]

The most common AE was hypoglycaemic events (hypoglycaemia, blood glucose decreased). However, all hypoglycaemic events were mild in severity, and insulin dose reductions resulted in a decreased incidence rate of hypoglycaemic events per subject-year of exposure, which is consistent with the double-blind period.[21]

Based on analysis using the cumulative logistic model, high serum C-peptide levels decreased the risk of hypoglycaemia; that is, lower fasting serum C-peptide at Week 0 was identified as a risk factor for hypoglycaemia. This was true in the open-label period, in which all patients were treated with canagliflozin, as well as in both the placebo and canagliflozin groups in the double-blind period, suggesting that the increased risk of hypoglycaemia was not due to canagliflozin treatment. Importantly, no risk factors specific to the canagliflozin group were identified. These results, alongside the fact that all patients received insulin, suggest that lower serum C-peptide at Week 0 may be a risk factor for hypoglycaemia when patients are treated with insulin. Similarly, in the *post-hoc* analysis of the ACCORD trial, a fasting C-peptide level of ≤0.15 nmol/L (0.45 ng/mL) was identified as a risk factor for severe hypoglycemia.[33]

In patients with type 1 diabetes or advanced T2DM, absolute β-cell failure results in no decrease in β-cell insulin secretion and, thus, no increase in α-cell glucagon secretion during hypoglycaemia.[34,35] Hypoglycaemia may be caused by this lack of response to glucagon among patients who have low fasting C-peptide (ie, low insulin production). Therefore, caution may be exercised with insulin treatment among patients with low insulin production. However, all cases of hypoglycaemia in this study were mild, and no cases of severe hypoglycaemia were reported. In patients at a higher risk for hypoglycaemia, the risk may be decreased by reducing the insulin dosage. Because insulin suppresses lipolysis, lowering the dose of insulin when used in combination with an SGLT2 inhibitor may increase the production of ketone bodies.[36] The increased ketone bodies can cause diabetic ketoacidosis; therefore, large reductions in insulin dose may not be appropriate. In the present study, no AEs associated with increased ketone bodies, such as ketoacidosis, were observed in either treatment group.

Our study has some limitations that must be acknowledged. Although the sample size of this study was calculated to detect a difference between the placebo and canagliflozin groups during the double-blind period, it might be considered relatively small for long-term evaluation. In addition, the study lacks a control group. However, long-term data on the use of this combination in Japanese patients are important, particularly considering the differences in pathophysiology between Japanese and non-Japanese patients.

In conclusion, this study demonstrated the long-term efficacy and safety of canagliflozin in combination with insulin in Japanese patients.

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Conflict of interest

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Author contributions

N. I. supervised the study and contributed to the design and protocol of the study. S. H., K. Ka and K. Ko. contributed to the design and protocol of the study. N. M. and M. O. contributed to development of the protocol and the design, and prepared the data. Y. K. contributed to data processing and statistical analyses. H. I. contributed to preparation of the manuscript. All authors contributed to manuscript preparation, the interpretation and discussion of the data, and have approved the final draft.

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REFERENCES

1. International Diabetes Federation. Diabetes Atlas. 7th ed. http://www.diabetesatlas.org/resources/2015-atlas.html. 2015. Accessed May 1, 2017.
2. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-year follow-up of intensive glucose control in type 2 diabetes. *N Engl J Med*. 2008;359:1577–1589.
3. Shichiri M, Kishikawa H, Ohkubo Y, Wake N. Long-term results of the Kumamoto study on optimal diabetes control in type 2 diabetic patients. *Diabetes Care*. 2000;23(suppl 2):B21–B29.
4. Home P, Riddle M, Cefalu WT, et al. Insulin therapy in people with type 2 diabetes: opportunities and challenges? *Diabetes Care*. 2014;37:1499–1508.
5. Desouza CV, Bolli GB, Fonseca V. Hypoglycemia, diabetes, and cardiovascular events. *Diabetes Care*. 2010;33:1389–1394.
6. Kalra S, Mukherjee JJ, Venkataraman S, et al. Hypoglycemia: the neglected complication. *Indian J Endocrinol Metab*. 2013;17:819–834.
7. Fujita Y, Inagaki N. Renal sodium glucose cotransporter 2 inhibitors as a novel therapeutic approach to treatment of type 2 diabetes: clinical data and mechanism of action. *J Diabetes Investig*. 2014;5:265–275.
8. Mudaliar S, Polidori D, Zambrowicz B, Henry RR. Sodium-glucose cotransporter inhibitors: effects on renal and intestinal glucose transport: from bench to bedside. *Diabetes Care*. 2015;38:2344–2353.
9. Tang H, Cui W, Li D, et al. Sodium-glucose co-transporter 2 inhibitors in addition to insulin therapy for management of type 2 diabetes mellitus: a meta-analysis of randomized controlled trials. *Diabetes Obes Metab*. 2017;19:142–147.
10. John M, Gopinath D, Jagesh R. Sodium-glucose cotransporter 2 inhibitors with insulin in type 2 diabetes: clinical perspectives. *Indian J Endocrinol Metab*. 2016;20:22–31.
11. Yokote K, Terauchi Y, Nakamura I, Sugamori H. Real-world evidence for the safety of ipragliflozin in elderly Japanese patients with type 2 diabetes mellitus (STELLA-ELDER): final results of a post-marketing surveillance study. *Expert Opin Pharmacother*. 2016;17:1995–2003.
12. Yabe D, Nishikino R, Kaneko M, Iwasaki M, Seino Y. Short-term impacts of sodium/glucose co-transporter 2 inhibitors in Japanese clinical practice: considerations for their appropriate use to avoid serious adverse events. *Expert Opin Drug Saf*. 2015;14:795–800.
13. Ma RC, Chan JC. Type 2 diabetes in East Asians: similarities and differences with populations in Europe and the United States. *Ann N Y Acad Sci*. 2013;1281:64–91.
14. Moller JB, Pedersen M, Tanaka H, et al. Body composition is the main determinant for the difference in type 2 diabetes pathophysiology between Japanese and Caucasians. *Diabetes Care*. 2014;37:796–804.
15. Ikezaki H, Ai M, Schaefer EJ, et al. Ethnic differences in glucose homeostasis markers between the Kyushu-Okinawa Population Study and the Framingham Offspring Study. *Sci Rep*. 2016;6:36725.
16. Inagaki N, Kondo K, Yoshinari T, Maruyama N, Susuta Y, Kuki H. Efficacy and safety of canagliflozin in Japanese patients with type 2 diabetes: a randomized, double-blind, placebo-controlled, 12-week study. *Diabetes Obes Metab*. 2013;15:1136–1145.
17. Inagaki N, Kondo K, Yoshinari T, Takahashi N, Susuta Y, Kuki H. Efficacy and safety of canagliflozin monotherapy in Japanese patients with type 2 diabetes inadequately controlled with diet and exercise: a 24-week, randomized, double-blind, placebo-controlled, Phase III study. *Expert Opin Pharmacother*. 2014;15:1501–1515.
18. Inagaki N, Kondo K, Yoshinari T, Kuki H. Efficacy and safety of canagliflozin alone or as add-on to other oral antihyperglycemic drugs in Japanese patients with type 2 diabetes: a 52-week open-label study. *J Diabetes Investig*. 2015;6:210–218.
19. Kadowaki T, Inagaki N, Kondo K, et al. Efficacy and safety of canagliflozin as add-on therapy to teneligliptin in Japanese patients with type 2 diabetes mellitus: results of a 24-week, randomized, double-blind, placebo-controlled trial. *Diabetes Obes Metab*. 2017;19:874–882.
20. Neal B, Perkovic V, de Zeeuw D, et al. Efficacy and safety of canagliflozin, an inhibitor of sodium-glucose cotransporter 2, when used in conjunction with insulin therapy in patients with type 2 diabetes. *Diabetes Care*. 2015;38:403–411.

21. Inagaki N, Harashima S, Maruyama N, Kawaguchi Y, Goda M, Iijima H. Efficacy and safety of canagliflozin in combination with insulin: a double-blind, randomized, placebo-controlled study in Japanese patients with type 2 diabetes mellitus. *Cardiovasc Diabetol*. 2016;15:89.

22. Seaquist ER, Anderson J, Childs B, et al. Hypoglycemia and diabetes: a report of a workgroup of the American Diabetes Association and the Endocrine Society. *Diabetes Care*. 2013;36:1384–1395.

23. Kahn SE, Cooper ME, Del PS. Pathophysiology and treatment of type 2 diabetes: perspectives on the past, present, and future. *Lancet*. 2014;383:1068–1083.

24. Hayashino Y, Izumi K, Okamura S, Nishimura R, Origasa H, Tajima N. Duration of diabetes and types of diabetes therapy in Japanese patients with type 2 diabetes: The Japan Diabetes Complication and its Prevention prospective study 3 (JDCP study 3). *J Diabetes Investig*. 2017;8:243–249.

25. Kanatsuka A, Sato Y, Kawai K, Hirao K, Kobayashi M, Kashiwagi A. Evaluation of insulin regimens as an effective option for glycemic control in patients with type 2 diabetes: a propensity score-matched cohort study across Japan (JDDM31). *J Diabetes Investig*. 2014;5:539–547.

26. Lorber D. Importance of cardiovascular disease risk management in patients with type 2 diabetes mellitus. *Diabetes Metab Syndr Obes*. 2014;7:169–183.

27. Tajima N, Noda M, Origasa H, et al. Evidence-based practice guideline for the treatment for diabetes in Japan 2013. *Diabetol Int*. 2015;6:151–187.

28. Carver C. Insulin treatment and the problem of weight gain in type 2 diabetes. *Diabetes Educ*. 2006;32:910–917.

29. Balkau B, Home PD, Vincent M, Marre M, Freemantle N. Factors associated with weight gain in people with type 2 diabetes starting on insulin. *Diabetes Care*. 2014;37:2108–2113.

30. Yki-Jarvinen H. Combination therapies with insulin in type 2 diabetes. *Diabetes Care*. 2001;24:758–767.

31. Home PD, Dain MP, Freemantle N, et al. Four-year evolution of insulin regimens, glycaemic control, hypoglycaemia and body weight after starting insulin therapy in type 2 diabetes across three continents. *Diabetes Res Clin Pract*. 2015;108:350–359.

32. Holman RR, Farmer AJ, Davies MJ, et al. Three-year efficacy of complex insulin regimens in type 2 diabetes. *N Engl J Med*. 2009;361:1736–1747.

33. Chow LS, Chen H, Miller ME, Marcovina SM, Seaquist ER. Biomarkers associated with severe hypoglycaemia and death in ACCORD. *Diabet Med*. 2016;33:1076–1083.

34. Cryer PE. Mechanisms of hypoglycemia-associated autonomic failure in diabetes. *N Engl J Med*. 2013;369:362–372.

35. Cryer PE. Minireview: glucagon in the pathogenesis of hypoglycemia and hyperglycemia in diabetes. *Endocrinology*. 2012;153:1039–1048.

36. Taylor SI, Blau JE, Rother KI. SGLT2 inhibitors may predispose to ketoacidosis. *J Clin Endocrinol Metab*. 2015;100:2849–2852.

SUPPORTING INFORMATION

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