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CLINICAL TRIAL

Efficacy and safety of dapagliflozin in addition to insulin therapy in Japanese patients with type 2 diabetes: Results of the interim analysis of 16-week double-blind treatment period

Eiichi Araki[1]*, Yukiko Onishi[2], Michiko Asano[3], Hyosung Kim[3], Ella Ekholm[4], Eva Johnsson[4], Toshitaka Yajima[3]

[1]Department of Metabolic Medicine, Faculty of Life Sciences, Kumamoto University, Kumamoto, [2]The institute for adult diseases, Asahi Life Foundation, Tokyo, [3]AstraZeneca K.K., Osaka, Japan, [4]AstraZeneca R&D, Mölndal, Sweden

ABSTRACT

Introduction: Dapagliflozin treatment when added to insulin therapy in Japanese patients with type 2 diabetes remains to be evaluated.

Materials and Methods: This was a multicenter, randomized, double-blind, parallel-group, placebo-controlled study to evaluate efficacy (at 16 weeks) and long-term safety (at 52 weeks) of dapagliflozin in addition to insulin therapy. The interim analysis was carried out at week 16 to assess the efficacy and safety profiles. The patients receiving insulin (*n* = 182) were randomized to either dapagliflozin 5 mg or a placebo at a 2:1 ratio. The primary efficacy end-point was the change in hemoglobin A1c (HbA1c) from baseline at week 16.

Results: Patients in the dapagliflozin group showed an adjusted decrease in HbA1c of −0.55% from baseline, whereas the placebo showed a marginal increase of 0.05%. The placebo-corrected mean change of HbA1c from baseline to week 16 in dapagliflozin was −0.60% (*P* < 0.0001). In addition, the placebo-corrected mean change of fasting plasma glucose and bodyweight from baseline to week 16 in the dapagliflozin group was −22.7 mg/dL (*P* < 0.0001) and −1.21 kg (*P* < 0.0001), respectively. The placebo-corrected mean daily insulin dose in the dapagliflozin group was numerically decreased (treatment difference: −0.72 IU/day; *P* = 0.0743). No major episodes or discontinuations as a result of hypoglycemia were reported during the study period.

Conclusions: Dapagliflozin used as add-on treatment to insulin therapy showed significantly greater reduction of HbA1c, fasting plasma glucose and bodyweight without severe hypoglycemia compared with the placebo at week 16. These results show the clinical benefit of prescribing dapagliflozin for Japanese patients with insufficient glycemic control even with insulin therapy.

INTRODUCTION

Type 2 diabetes mellitus is characterized by β-cell dysfunction and peripheral insulin resistance leading to hyperglycemia[1,2]. Chronic hyperglycemia has been associated with the development of both macrovascular and microvascular complications[3–5]. The majority of patients with type 2 diabetes mellitus eventually require more than one oral antihyperglycemic agents to achieve glycemic targets over time; however, less than 50% of patients can reach their goals for glycemic control[4,6,7]. Of those, most of the patients require insulin therapy; however, insulin therapy harbors additional side-effects, and does not always lead to optimum glycemic control. Therefore, it is evident that there still remain medical requirements for the treatment of type 2 diabetes mellitus even with insulin therapy, and additional oral antidiabetic drugs (OADs) that can reduce blood glucose independent of insulin has been awaited.

Dapagliflozin is a potent, highly selective and orally active inhibitor of renal sodium-glucose co-transporter 2 (SGLT2), a major transporter responsible for renal glucose reabsorption. Dapagliflozin increases urinary excretion of glucose by inhibiting renal glucose reabsorption and thereby lowering plasma glucose. Results from non-clinical and clinical studies show that dapagliflozin can be used as a safe and effective agent for diabetic patients. The novel insulin-independent mechanism of action, inhibition of SGLT2, can result in lowering plasma glucose regardless of the patient's insulin sensitivity and β-cell function. In addition, the unique mechanism might provide an opportunity to lower risks of hypoglycemia and weight gain, potential exacerbating factors for the management of patients with type 2 diabetes mellitus.

Insulin is frequently chosen as an additional antidiabetic agent for type 2 diabetes mellitus patients with insufficient glycemic control under OAD therapy[8,9]. It has been reported that in a multicenter, controlled trial observing more than 4,000 patients with type 2 diabetes mellitus for more than 9 years[10], insulin therapy was not necessarily sufficient to achieve the therapeutic goals, particularly for patients with severe hyperglycemia. Furthermore, weight gain, fluid retention and the risk of hypoglycemia were identified as common problems of insulin therapy. Therefore, it might be beneficial for insulin users with inadequate glycemic control to be treated with an OAD, such as dapagliflozin, that can reduce blood glucose in an insulin-independent mechanism. In addition, the use of dapagliflozin in addition to insulin could potentially reduce the total insulin dose, which could decrease the side-effects, such as hypoglycemia and excessive weight gain, during the patient's management.

The purpose of the present study was to investigate the efficacy and safety profiles of dapagliflozin in addition to insulin in the first 16-week treatment period of the Study D1692C00013 in Japanese.

MATERIALS AND METHODS

Study Design
The original study (D1692C00013) was designed as 52-week period study that included a 16-week, multicenter, randomized, double-blind, parallel-group, placebo-controlled study followed by a 36-week open extension period to evaluate efficacy (at 16 weeks) and long-term safety (at 52 weeks) of dapagliflozin 5 mg in addition to insulin therapy in Japanese patients with type 2 diabetes mellitus. The data presented in the current manuscript are from the interim analysis carried out at 16 weeks to assess the efficacy and safety profiles of dapagliflozin when added to insulin therapy. The study consisted of a 2-week screening period; an 8-week washout period if required; a 2-week single-blind placebo lead in period; a 16-week double-blind, placebo-controlled treatment period; a 36-week open extension treatment period with a titration of dapagliflozin 5 and 10 mg; and a 3-week follow-up period (Figure S1).

The present study was carried out in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with International Conference on Harmonization/Good Clinical Practice and registered at https://clinicaltrials.gov/ (ClinicalTrials.gov identifier: NCT021 57298). The protocol, amendments and informed consent forms for the present study were approved by an independent ethics committee before the study began. All participants provided written informed consent.

Patients
Eligible study participants were men and women aged 20 years and older with type 2 diabetes receiving insulin (≥0.2 IU/kg/day and ≥15 IU/body/day) for the past 8 weeks before enrolment, and with hemoglobin A1c (HbA1c) level of 7.2–11%. Additional treatment with a concomitant dipeptidyl peptidase-4 (DPP-4) inhibitor was allowed, and patients with estimated glomerular filtration rate (eGFR) of 45 mL/min/1.73 m^2 and higher were enrolled. Patients having a history of cardiovascular events (acute coronary syndrome, unstable angina or acute myocardial infarction with hospitalization, acute stroke or transit ischemic attacks) within 2 months before enrolment and treatment with thiazolidinediones within 6 months before enrolment were excluded from the study.

Criteria of Insulin Up/Downtitration
During the 16-week double-blind phase, a fixed insulin dose regimen was applied in order to evaluate the efficacy of dapagliflozin on HbA1c accurately unless there was an obvious clinical indication for the titration as follows: (i) hypoglycemic symptom with self-monitoring of blood glucose (SMBG) <70 mg/dL without drastic changes in daily life/activities or hypoglycemia judged by the investigator; or (ii) two consecutive occasions of SMBG <80 mg/dL and when the investigators judge patients at a high risk of hypoglycemia. Criteria of insulin uptitration were: (i) two consecutive occasions of fasting plasma glucose (FPG) >240 mg/dL with SMBG; or (ii) one FPG >240 mg/dL at the center. In each case of insulin titration, the range of insulin dose was decided by investigators.

Outcome Measures
The primary outcome measure was the change in HbA1c from baseline to week 16. Secondary outcome measures included changes in FPG, bodyweight and calculated mean daily insulin dose from baseline to week 16. In addition, the proportion of patients whose mean daily insulin dose was reduced by 10% or more from baseline to week 16 was also examined. Exploratory outcome measures included, but were not limited to, changes in waist circumference, 2-h post prandial glucose (2 h-PPG; SMBG), glycoalbumin, uric acid, and seated systolic and diastolic blood pressure from baseline to week 16.

For the safety evaluation, adverse events (AEs), the changes in laboratory values, electrocardiogram, vital signs, incidence of hypoglycemic events, eGFR, total albumin/creatinine ratio (mg/g) and physical examination findings were assessed at each visit.

Statistical Analysis

Analysis Sets

All efficacy analyses were carried out with a full analysis set, which included all randomized patients who received at least one dose of randomized study medication, and who had a non-missing baseline and at least one post-baseline for at least one efficacy variable.

All safety analyses were carried out with a safety analysis set, which included all patients who received at least one dose of double-blind study medication and provided any safety records.

Confirmatory Hypotheses and Multiplicity

The primary hypothesis was superiority of dapagliflozin to placebo in the change from baseline in HbA1c at week 16. Four secondary hypotheses of superiority of dapagliflozin to placebo in: (i) change from baseline in FPG at week 16; (ii) change from baseline in bodyweight at week 16; (iii) change from baseline in mean daily insulin dose at week 16; and (iv) proportion of patients with insulin downtitration by at least 10% at week 16 were also included in the confirmatory testing procedure. Statistical testing of primary and four secondary variables were proceeded in a sequential manner following the aforementioned prespecified order to maintain the familywise error rate at 0.05 (two-sided).

Analysis Methods

The change from baseline in HbA1c was analyzed by a mixed model with repeated measures including treatment, week, treatment-by-week interaction, DPP-4 inhibitor usage and baseline eGFR category as fixed categorical effects, as well as the fixed covariate of baseline HbA1c. An unstructured variance matrix for the within-patient error was used.

The change from baseline in FPG, bodyweight and mean daily insulin dose were analyzed by a similar mixed model with repeated measures. The proportion of patients with insulin downtitration was analyzed by logistic regression analysis adjusted for baseline value and DPP-4 inhibitor usage using the methodology of Zhang et al.[11]

Efficacy data obtained after insulin uptitration of 10% or more was excluded from analysis, except for the analyses of mean total daily insulin dose and of patients with insulin downtitration.

Sample Size Determination

Sample size was determined on the basis of anticipated differences for the primary end-point. To detect a difference of 0.5% between dapagliflozin and the placebo for changes from baseline to week 16 in HbA1c based on two-sample t-test, assuming a standard deviation (SD) of 0.9%, and at a two-sided significance level of 0.05, a total of 156 evaluable patients are required to provide 90% power where randomization was carried out in a 2:1 ratio. Assuming 10% were not evaluable patients, a total of 180 patients were planned for randomization.

RESULTS

Patient Characteristics

The disposition of the enrolled patients is represented in Figure 1. A total of 182 patients out of 266 patients were randomized to either the dapagliflozin 5 mg or the placebo group
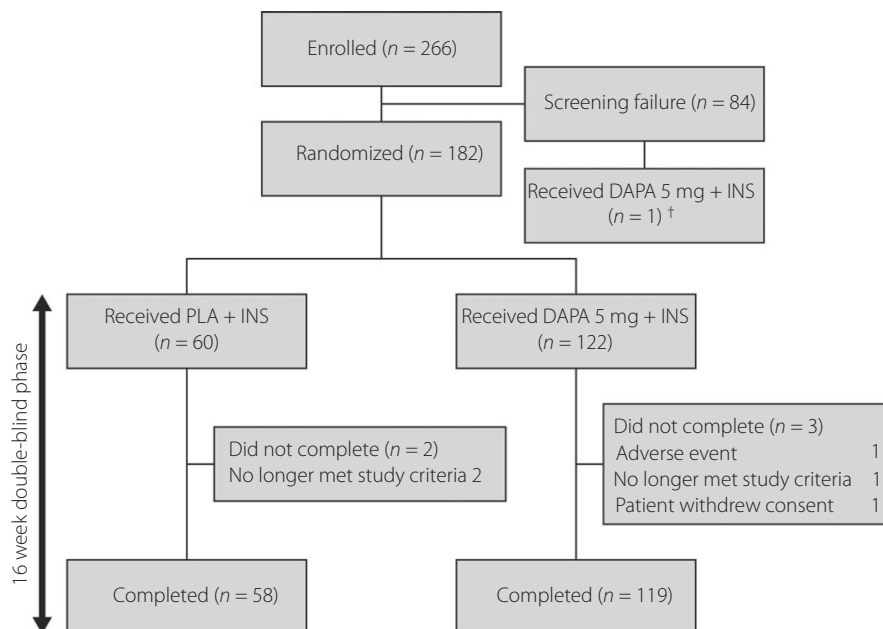

Figure 1 | Patient disposition. †One patient was not randomized, but received double-blind study medication because of a dispensing error. This patient was not included in the full analysis set ($n = 182$), but was included in the safety analysis set ($n = 183$). DAPA, dapagliflozin; INS, insulin; PLA, placebo.

at a 2:1 ratio. Demographic and baseline characteristics were similar across both groups (Table 1). There were approximately 71% males and 29% females, and on average, the patients were aged 58 years with approximately 30% of the patients aged above 65 years. All patients were Japanese. Approximately 63% of the patients were overweight (body mass index [BMI] ≥ 25 kg/m^2). At baseline, mean HbA1c was 8.34%, and there was no big difference between the dapagliflozin group (8.26%) and the placebo group (8.52%). Baseline eGFR did not show a meaningful difference in renal function between the treatment groups. The median duration of insulin treatment was slightly shorter in the dapagliflozin group (5.15 years) compared with the placebo group (6.40 years). At baseline, the mean daily doses of insulin were 37.87 and 40.58 IU in the dapagliflozin group and the placebo group, respectively. There was no difference in insulin regimen between both groups, approximately 28% for basal insulin, 29% for short acting insulin and 43% for combination of short acting and basal. A total of 44.5% of patients used DPP-4 inhibitors.

Changes in Glycemic Control

Patients in the dapagliflozin group showed a steep, continuous decrease in mean HbA1c from 8.26% at baseline to 7.54% at week 8, which was followed by a plateau until week 16, whereas there were no obvious changes in HbA1c in the placebo group during the study period. The significant difference of the dapagliflozin group compared with the placebo group could be found from week 4 (nominal *P*-value <0.05). At week 16, baseline adjusted HbA1c was decreased by −0.55% in the dapagliflozin group. In addition, the placebo-adjusted mean HbA1c of the dapagliflozin group was decreased by −0.60% (95% confidence interval [CI] −0.81 to −0.39; *P* < 0.0001; Figure 2).

Subgroup analyses for change in HbA1c from baseline to week 16 were carried out for sex, age (<65 years, ≥65 years), baseline BMI (<25 kg/m^2, ≥25 kg/m^2), baseline HbA1c (<7.5, ≥7.5 to < 8.5 and ≥8.5%) and baseline eGFR (<60 mL/min/1.73 m^2, ≥60 mL/min/1.73 m^2). However, a statistically significant treatment-by-subgroup interaction was not observed for any subgroup categories described.

In the dapagliflozin group, the mean adjusted FPG was decreased by −21.7 mg/dL (95% CI −28.3 to −15.1) from baseline to week 16, whereas a marginal mean increase in FPG of 1.0 mg/dL (95% CI −8.4 to 10.3) was observed in the placebo group. The placebo-corrected mean change of FPG from baseline to week 16 was −22.7% (95% CI −33.2 to −12.2; *P* < 0.0001) in the dapagliflozin group (Figure 3).

Change in Bodyweight

Patients in the dapagliflozin group showed a decrease in total bodyweight of −0.55 kg (95% CI −0.86 to −0.24) from baseline to week 16. In the placebo group, a slight increase in bodyweight of 0.66 kg (95% CI 0.23 to 1.10) was observed. The decrease in bodyweight from baseline to week 16 was significantly larger in the dapagliflozin group compared with the pla-

cebo group (*P* < 0.0001). The placebo-adjusted mean bodyweight change in the dapagliflozin group was −1.21 kg (95% CI −1.72 to −0.71; Figure 4).

Changes in Insulin Dose

The dapagliflozin group showed a decrease in mean daily insulin dose of −0.74 IU/day (95% CI −1.21 to −0.27) from baseline to week 16. In the placebo group, a marginal mean decrease in mean daily insulin dose of −0.02 IU/day (95% CI −0.68 to 0.64) was observed. The placebo-corrected mean daily insulin dose in the dapagliflozin group was numerically decreased, but was not statistically significant (treatment difference −0.72 IU [95% CI −1.51 to 0.07]; *P* = 0.0743). Dapagliflozin compared with the placebo led to a numerically higher proportion of patients whose insulin dose was reduced by 10% or more at week 16 (8.2% *vs* 4.9%, respectively).

Exploratory Measures

In the dapagliflozin group, the mean adjusted 2 h-PPG was decreased by −37.63 mg/dL (95% CI −49.10 to −26.17) from baseline to week 16. In the placebo group, a small increase in mean adjusted 2 h-PPG of 8.74 mg/dL (95% CI −7.47 to 24.95) was observed. A placebo-corrected mean 2 h-PPG of the dapagliflozin group was −46.37 mg/dL (95% CI −63.67 to −29.07; *P* < 0.0001). Patients in the dapagliflozin group showed a placebo-corrected relative decrease in glycoalbumin of −12.88% (% change from baseline; *P* < 0.0001), whereas there was essentially no meaningful change in the placebo group (0.60%). Patients in the dapagliflozin group and the placebo group showed numerical changes in high-density lipoprotein cholesterol from baseline to week 16 by 6.17 and −0.72%, respectively. The dapagliflozin group showed no significant changes in a placebo-corrected relative change in systolic blood pressure (−1.1 mmHg [95% CI −4.6 to 2.4], *P* = 0.5324), diastolic blood pressure (−1.0 mmHg [95% CI −3.4 to 1.3], *P* = 0.3797) and serum uric acid (−0.14 mg/dL [95% CI −0.36 to 0.07], *P* = 0.1785). Patients in the dapagliflozin group showed a significant placebo-corrected mean reduction in waist circumference from baseline to week 16 (−1.0 cm [95% CI −2.0 to −0.1], *P* = 0.0378).

Safety

The proportion of patients with overall AEs was slightly higher in the dapagliflozin group (48.8%) than the placebo group (36.7%; Table S1). There was one AE leading to discontinuation in each treatment group. Three serious AEs (cholelithiasis, hand fracture, osteochondrosis) were reported in the dapagliflozin group and none in the placebo group. However, none of the serious AEs was related to the study drug administration by the investigators' evaluation, and there were no discontinuations of the study medication. There was no death during the 16-week double-blind treatment period. Slightly fewer patients in the dapagliflozin group (19.5%) than in the placebo group (23.3%) experienced an event of hypoglycemia. No major episodes and no discontinuations as a result of hypoglycemic

Table 1 | Demographic characteristics and baseline measurements

Full analysis set	Total $n = 182$	PLA + INS $n = 60$	DAPA 5 mg + INS $n = 122$
Age			
Mean	58.0	57.6	58.3
Standard deviation	9.82	9.86	9.83
Sex†			
Male	129 (70.9)	40 (66.7)	89 (73.0)
Female	53 (29.1)	20 (33.3)	33 (27.0)
Body mass index categorization (kg/m^2)†			
<25	68 (37.4)	24 (40.0)	44 (36.1)
≥25	114 (62.6)	36 (60.0)	78 (63.9)
≥27	77 (42.3)	22 (36.7)	55 (45.1)
≥30	31 (17.0)	8 (13.3)	23 (18.9)
Duration of insulin treatment (years)			
Mean	6.77	8.33	6.01
Standard deviation	5.872	7.532	4.703
Calculated mean daily insulin dose (IU)			
Mean	38.76	40.58	37.87
Standard deviation	17.625	16.764	18.033
DPP-4 inhibitor usage†			
Yes	81 (44.5)	27 (45.0)	54 (44.3)
No	101 (55.5)	33 (55.0)	68 (55.7)
Weight (kg)			
Mean	73.24	71.89	73.9
Standard deviation	14.956	13.430	15.663
Body mass index (kg/m^2)			
Mean	26.64	26.12	26.89
Standard deviation	4.510	3.485	4.930
Waist circumference (cm)			
Mean	92.9	92.3	93.2
Standard deviation	10.96	9.00	11.83
Duration of type 2 diabetes (years)			
Mean	14.97	14.24	15.32
Standard deviation	8.952	8.919	8.983
HbA1c			
Mean	8.34	8.52	8.26
Standard deviation	0.849	0.937	0.792
Fasting plasma glucose (mg/dL)			
Mean	160.36	159.68	160.70
Standard deviation	42.679	38.001	44.948
eGFR (mL/min/1.73 m^2)†			
<60	33 (18.1)	9 (15.0)	24 (19.7)
≥60–<90	98 (53.8)	32 (53.3)	66 (54.1)
≥90	51 (28.0)	19 (31.7)	32 (26.2)
Safety analysis set†	$n = 183$	$n = 60$	$n = 123$
Total patients using concomitant medication	170 (92.9)	51 (85.0)	119 (96.7)
Diuretics medication‡	21 (11.5)	6 (10.0)	15 (12.2)
Thiazide diuretic medication‡	15 (8.2)	3 (5.0)	12 (9.8)
Loop diuretics medication‡	2 (1.1)	1 (1.7)	1 (0.8)
Antihypertensive medication‡	95 (51.9)	34 (56.7)	61 (49.6)
ARB and/or ACEI medication‡	75 (41.0)	25 (41.7)	50 (40.7)
Lipid lowering medication‡	98 (53.6)	25 (41.7)	73 (59.3)

†Data represent number (%). ‡Based on predefined lists of diuretic, angiotensin receptor blocker (ARB) and/or angiotensin-converting-enzyme inhibitor (ACEI), antihypertensive, thiazide diuretic, loop diuretic and lipid-lowering medications. DAPA, dapagliflozin; DPP-4, dipeptidyl peptidase-4; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; INS, insulin; PLA, placebo.
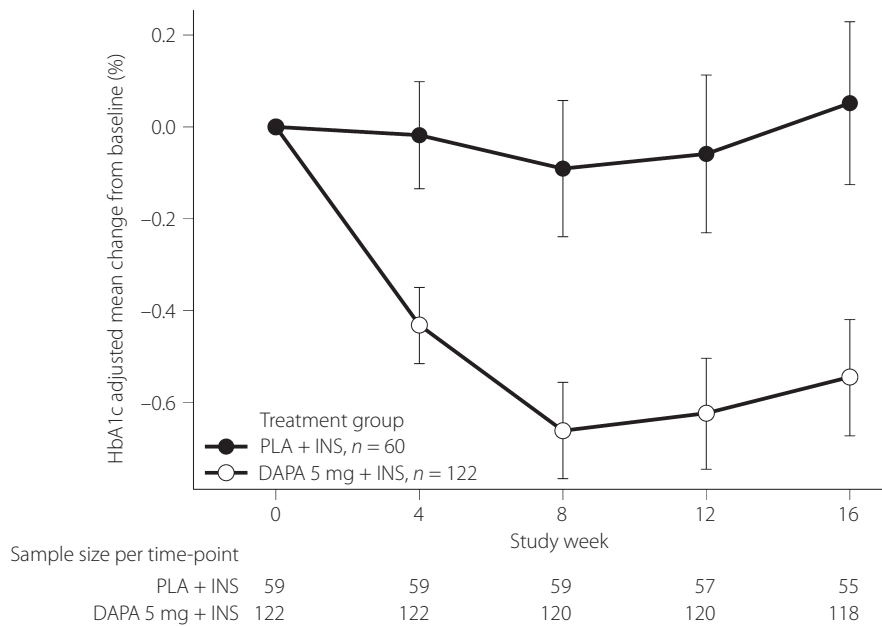
Figure 2 | Hemoglobin A1c (HbA1c; %) adjusted mean change from baseline over time for the 16-week short-term double-blind treatment period, excluding data after uptitration (full analysis set). Data represent adjusted mean with 95% confidence interval. DAPA, dapagliflozin; INS, insulin; PLA, placebo.
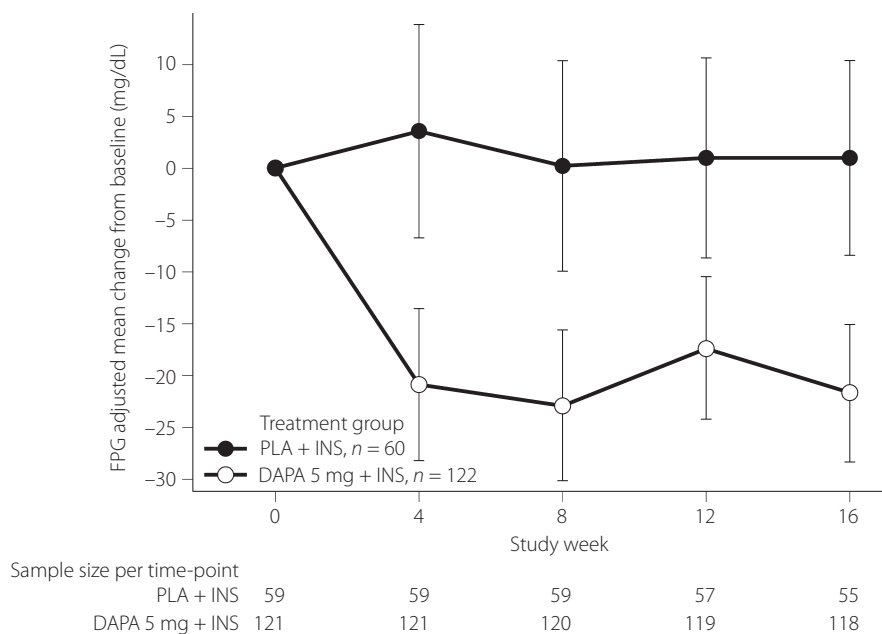

Figure 3 | Fasting plasma glucose (FPG; mg/dL) adjusted mean change from baseline over time for the 16-week double-blind treatment period, excluding data after insulin uptitration (full analysis set). Data represent adjusted mean with 95% confidence interval. DAPA, dapagliflozin; INS, insulin; PLA, placebo.

events were reported in both groups. An AE of genital infection that was assessed as being related to study medication was observed in one patient in the dapagliflozin group. Urinary tract infection was reported in two female patients in the dapagliflozin group. One genital infection in a woman was seen in the dapagliflozin group.
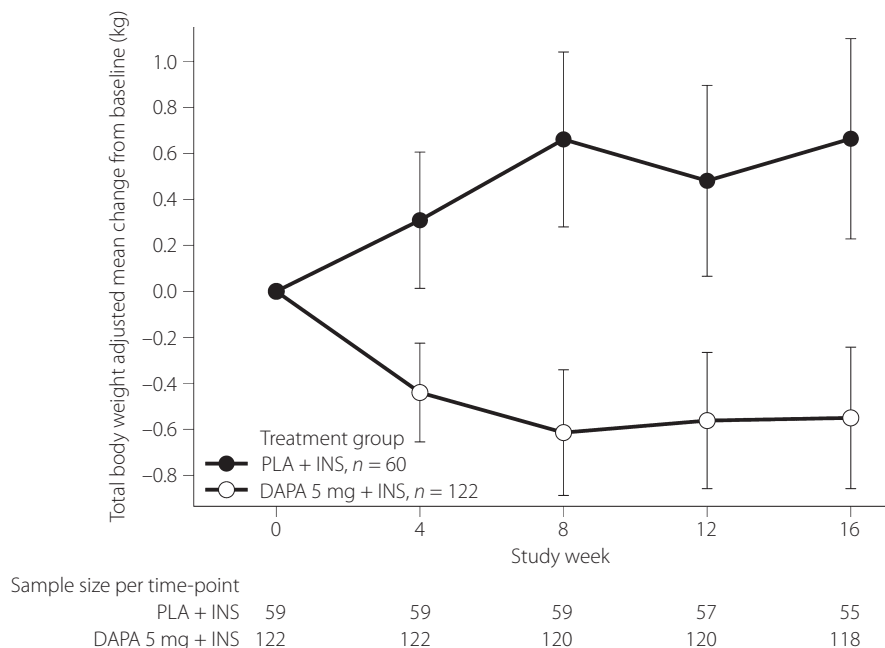
Figure 4 | Total bodyweight (kg) adjusted mean change from baseline over time for the 16-week double-blind treatment period, excluding data after uptitration (full analysis set). Data represent adjusted mean with 95% confidence interval. DAPA, dapagliflozin; INS, insulin; PLA, placebo.

Adverse events of renal impairment/failure that were assessed as being related to study medication were reported in one patient in the placebo group. Hematocrit (%; dapagliflozin: 3.08 [0.2019] for mean [standard error], placebo: 0.96 [0.2479]) and hemoglobin (mg/dL; dapagliflozin: 0.86 [0.0659], placebo: 0.26 [0.0835]) showed a mean increase in the dapagliflozin group compared with the placebo group.

DISCUSSION

Type 2 diabetes patients who have inadequate glycemic control with OADs eventually require insulin therapy in order to maintain better glycemic control over a long period of time. In contrast, insulin therapy itself can increase risks of hypoglycemia and weight gain. The present study shows the beneficial effect of dapagliflozin as an additional OAD on insulin therapy for Japanese patients with type 2 diabetes who had inadequate glycemic control. We found superiority of dapagliflozin to the placebo in improving glycemic control based on the reduction in HbA1c and FPG from baseline to week 16. It has been reported that the effect of dapagliflozin is dependent on eGFR and baseline HbA1c level[12]. However, we observed no clear interaction between the effect of dapagliflozin and eGFR or baseline HbA1c level in the current study, probably because of the limited sample size and small proportion (18.1%) of patients with renal impairment (eGFR <60 mL/min/1.73 m^2). The HbA1c level of the dapagliflozin group decreased steeply from the first week to week 4, and reached to the lowest level at week 8, whereas the FPG level decreased at week 4 followed by a plateau through week 16 (Figures 3 and 4). The rapid glu-

cose lowering effects by dapagliflozin were consistent with previous clinical trials, which include: monotherapy[13,14], additional therapy on metformin[15,16], on glimepirid[17], on pioglitazon[18] and on insulin[19]. These results show the effectiveness of dapagliflozin in combination with other OADs and insulin as a result of its insulin-independent glucose-lowering mechanism. In a previous global study that examined the long-term efficacy of dapagliflozin in addition to insulin[19], approximately 95% patients enrolled were Caucasian with much higher BMI (approximately 33 kg/m^2) than East Asian patients. In addition, the insulin dose used was much higher compared with that used for East Asian patients (total average >70 U/day). In the present study, we showed a significant effect of dapagliflozin on glycemic improvement, even in East Asian patients who had already been treated with insulin, especially in the Japanese population with smaller BMI (approximately 26 kg/m^2) and a lower dose of insulin (total average <41 U/day) than in Caucasian patients. Furthermore, the present study was carried out under a fixed insulin dose regimen to evaluate the efficacy of dapagliflozin accurately by minimizing the insulin dose bias on changes in HbA1c and FPG compared with previous reports[19,20].

Continuous reductions in total bodyweight from baseline to week 16 were observed in the dapagliflozin group, whereas slight increases were seen in the placebo group (Figure 4). The reduction of bodyweight at week 16 in the present study (−0.55 kg) was smaller than that reported in previous Japanese trials (approximately −2 kg)[14,21,22] when comparing the data at week 16. However, as the placebo group showed a slight

increase in bodyweight (0.66 kg), the placebo-corrected increase in bodyweight in the dapagliflozin group was −1.2 kg at week 16 ($P < 0.0001$). Dapagliflozin reduces bodyweight by caloric loss in the form of urinary glucose and fluid loss. In a composition study, most of the weight loss (approximately two-thirds) associated with dapagliflozin was explained by the reduction of fat mass[23]. In the present study, we also observed a placebo corrected waist circumference reduction by −1 cm. Given the association between visceral fat mass and waist circumference[24], it is possible that the weight loss observed in the dapagliflozin group was partly as a result of fat loss. Consistently reported for SGLT2 inhibitors[25], a slight increase in hematocrit was seen in the present study, which might also indicate a modest fluid loss by dapagliflozin-mediated osmotic diuresis.

It is expected that the use of dapagliflozin in addition to insulin could potentially reduce the total insulin dose. In the previous dapagliflozin pilot study, basal insulin dose was reduced by 50% before adding dapagliflozin. Even under the condition, 10 mg or 20 mg of dapagliflozin showed significant improvement in HbA1c compared with the placebo without increasing hypoglycemic events[26]. In the present study, the baseline insulin dose was fixed, unless there were safety concerns, to show whether dapagliflozin improved glycemic control when added on to unchanged background insulin therapy. The significant hypoglycemic effect of dapagliflozin in addition to fixed insulin dose indicates a possibility of reduction of insulin dose after adding dapagliflozin if flexible insulin titration is allowed, as is common in clinical settings. In fact, even in the current study without allowing insulin titration except under specific and limited conditions, mean insulin dose in the dapagliflozin group was slightly decreased, whereas that in the placebo group showed a numerical increase at 16 weeks. In a different study mainly using Caucasian type 2 diabetes mellitus patients aged 18–80 years with inadequate glycemic control (HbA1c 7.5–10.5%) on a stable dose of insulin for at least 8 weeks with or without up to two OADs, it has also been reported that the differences from the placebo in adjusted mean change in daily insulin dose from baseline at 104 weeks were −16.8 IU (95% CI −20.5 to −8.0; $P < 0.0001$) and −19.2 IU (95% CI −25.5 to −12.9; $P < 0.0001$) in the dapagliflozin 5/10-mg and 10-mg groups, respectively, whereas there were substantial differences in the mean daily insulin dose at baseline between that study (approximately 37–41 IU) and the current study (approximately 74–80 U)[20].

The most common AE occurring in the dapagliflozin group was nasopharyngitis, as noted in previous trials[14,21,22]. Urinary tract infections and genital infections can be frequently observed in the general diabetic population[27], and occur more often with SGLT2 inhibitors as a consequence of glucosuria (5.7%)[28]. In the present study, we found there were few patients who had urinary tract infections and genital infections in the dapagliflozin group (2.4%), whereas none were reported in the placebo group. With regard to hypoglycemic events, we found no severe events in the current study; however, the incidence of mild events were 19.5 and 23.3% in the dapagliflozin and pla-

cebo groups, respectively, which were much higher incidence rates compared with that reported in a previous dapagliflozin monotherapy trial (1.9%)[21]. A dapagliflozin add on to higher dose insulin study carried out in the USA reported two and one severe hypoglycemic event for dapagliflozin and a placebo, respectively. In addition, the incidence of mild hypoglycemic events was 56.6 and 51.8% in dapagliflozin vs placebo, respectively[19]. These results show that, under proper management, dapagliflozin can be added to insulin therapy without a significant increase in hypoglycemia.

In conclusion, dapagliflozin used as add-on to insulin therapy showed significantly higher reductions in HbA1c, FPG and bodyweight during 16 weeks of treatment, with a numerical decrease in insulin dose in the East Asian population. Furthermore, dapagliflozin was well tolerated and showed no major hypoglycemic events in combination with insulin therapy. These results demonstrate a positive clinical benefit/risk balance of dapagliflozin in addition to insulin therapy in Japanese patients requiring additional glycemic control.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Figure S1 | Flow chart of study design. †The washout period was applicable only for patients with ongoing treatment with antidiabetic agents other than dipeptidyl peptidase-4 (DPP-4) inhibitor. The patients on insulin monotherapy or combination therapy of insulin and a DPP-4 inhibitor could skip the washout period and directly proceed to the placebo lead-in period. ‡Visits 9, 13, 15 and 17 were carried out by telephone contact. E, enrolment; R, randomization.

Table S1 | Overall adverse events summary (safety analysis set).