Received: 1 August 2019 | Revised: 10 November 2019 | Accepted: 14 November 2019

DOI: 10.1111/dom.13922

ORIGINAL ARTICLE

WILEY

Efficacy and safety of dapagliflozin in Japanese patients with inadequately controlled type 1 diabetes (DEPICT-5): 52-week results from a randomized, open-label, phase III clinical trial

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Funding information
AstraZeneca K.K.; AstraZeneca

Peer Review
The peer review history for this article is available at https://publons.com/publon/10.1111/dom.13922.

Abstract

Aims: To investigate the safety and tolerability of 5 and 10 mg dapagliflozin added to insulin therapy over 52 weeks in Japanese patients with inadequately controlled type 1 diabetes mellitus (T1DM).

Materials and methods: This randomized, open-label, parallel-group, multicentre phase III clinical trial was conducted from October 26, 2015 to June 15, 2017. The primary endpoint was the occurrence of adverse events such as hypoglycaemia and diabetic ketoacidosis. Secondary endpoints included changes in glycaemic parameters, total daily insulin dosage and body weight over time. The efficacy of dapagliflozin in patients stratified by body mass index (BMI) <25.0 and ≥25.0 kg/m^2 was evaluated in a subgroup analysis.

Results: In total, 151 patients received 5 mg (n = 76) or 10 mg (n = 75) dapagliflozin once daily for 52 weeks. Adverse events were observed in 88.2% and 73.3% of patients in the 5 and 10 mg dapagliflozin groups, respectively. Severe hypoglycaemia was reported in 2.6% (n = 2) and 6.7% (n = 5) of patients, and diabetic ketoacidosis in 2.6% (n = 2) and 1.3% (n = 1) of patients in the 5 and 10 mg dapagliflozin groups, respectively. The adjusted mean (95% confidence interval) changes in glycated haemoglobin at week 52 were −0.33% (−0.50, −0.15) and −0.36% (−0.53, −0.18) in the 5 and 10 mg dapagliflozin groups, respectively. There were no differences in efficacy parameters when stratified by BMI.

Conclusions: This study demonstrated the long-term safety and tolerability of dapagliflozin added to insulin therapy in Japanese patients with inadequately controlled T1DM.

1 | INTRODUCTION

Type 1 diabetes mellitus (T1DM) is a chronic disorder characterized by the destruction of pancreatic β-cells, and patients require lifelong insulin therapy because of their inability to produce endogenous insulin.[1] Insulin therapy is the only established therapeutic option for T1DM that provides immediate glucose control; however, these patients have a higher risk of weight gain and increases in waist circumference compared with the general population.[2,3] As such, individuals with T1DM have a two- to threefold risk of developing cardiovascular disease with glycaemic variability, as well as increased overall mortality compared with the general population.[4-6] Furthermore, insulin-related hypoglycaemia is a common event, with 11.8% of patients with T1DM experiencing at least one episode of severe hypoglycaemia every year.[7]

Reduced insulin sensitivity together with poor glycaemic control and insulin-related weight gain probably contributes to insulin therapy resistance in patients with T1DM.[8] Insulin resistance caused by insulin-related weight gain can affect cardiovascular risk factors in these patients, and cardiovascular dysfunction has been associated with significantly increased mortality rates.[9-12] Add-on therapies to insulin, which can influence insulin sensitivity, are therefore required to improve glucose control and reduce weight gain. At present, novel hypoglycaemic therapies are being developed as an adjunct to insulin to improve glycaemic control and reduce the risk of recurrent hypoglycaemia and weight gain.[13]

Sodium-glucose co-transporter 2 (SGLT2) is a glucose transporter expressed in the proximal renal tubules and is mainly responsible for glucose reabsorption from urine. Its mechanism of action is independent of insulin; therefore, inhibition of SGLT2 can improve glycaemic control in patients with type 2 diabetes mellitus (T2DM).[14] Accordingly, inhibitors of SGLT2 have been developed to enhance urinary glucose excretion.[14,15] Dapagliflozin is an orally administered, potent and selective inhibitor of SGLT2 that significantly reduces blood glucose levels and improves glycaemic variability.[16] Dapagliflozin is approved for the treatment of T2DM and has been shown to improve glycaemic control, stabilize insulin dosages and reduce body weight with low rates of hypoglycaemia.[17-22] When assessing dapagliflozin in patients with T1DM, the pharmacokinetic profile is dose-dependent and similar across Japanese[23] and Caucasian[24] patients. A previous phase II study showed that dapagliflozin as an adjunct to insulin therapy significantly reduced fasting and postprandial glucose in patients with T1DM (NCT01498185). Furthermore, a number of other SGLT inhibitors (empagliflozin, canagliflozin, sotagliflozin and ipragliflozin) have been or are being studied in patients with T1DM.[25-27]

The current phase III study evaluated the safety and tolerability of 5 and 10 mg dapagliflozin over 52 weeks in Japanese patients with T1DM and inadequate glycaemic control with insulin therapy. This open-label study was conducted in parallel with two global, randomized, double-blind, placebo-controlled phase III studies that showed that dapagliflozin was well tolerated and improved glycaemic control in patients with inadequately controlled T1DM.[28-30] The current study aimed to confirm whether dapagliflozin is a safe and tolerable option for adjunct therapy in Japanese patients with T1DM who require tight glycaemic control and a sustained improvement across key glycaemic-related parameters and to satisfy regulatory requirements.

2 | MATERIALS AND METHODS

2.1 | Patients

Patients were included if they met the following criteria: aged 18–75 years, body mass index (BMI) of ≥20.0 kg/m^2, glycated haemoglobin (HbA1c) ≥7.5% and ≤10.5%, insulin therapy for ≥1 year before enrolment and C-peptide level of <0.7 ng/mL. The method of insulin administration [multiple daily injections (MDI) or continuous subcutaneous insulin infusion] had to be unchanged, and the total daily insulin dosage was required to be ≥0.3 U/kg/day for at least 3 months before enrolment. Moreover, patients using MDI had to be on ≥3 injections per day.

The main exclusion criteria were: a history of T2DM; maturity-onset diabetes of the young; previous pancreatic surgery; use of antihyperglycaemic drugs except α-glucosidase inhibitors or insulin within 1 month before enrolment (the use of α-glucosidase inhibitors within 1 month was permitted if the patient was able to undergo a drug washout); history of diabetic ketoacidosis requiring medical intervention (e.g. emergency care and/or hospitalisation) within 1 month before enrolment; hospital admission for hyperglycaemia or hypoglycaemia within 1 month before enrolment; or frequent episodes (>1) of severe hypoglycaemia requiring medical assistance, emergency care or glucagon therapy administered by a third party within 1 month before enrolment.

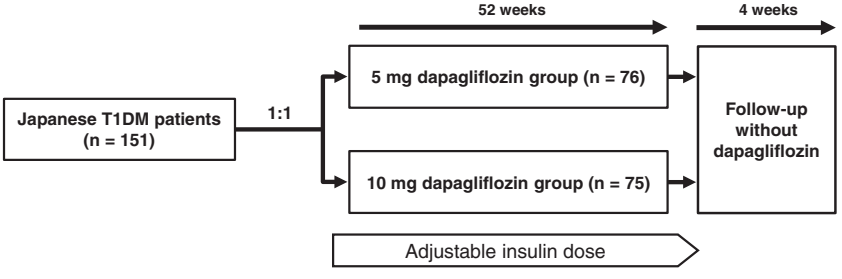

FIGURE 1 Study design. Abbreviation: T1DM, type 1 diabetes mellitus

2.2 | Study design and treatment

This study was a randomized, open-label, parallel-group, multicentre phase III clinical trial across 29 centres in Japan conducted between October 26, 2015 and June 15, 2017. Dapagliflozin tablets (5 or 10 mg) were administered once daily for 52 weeks at approximately the same time of day (Figure 1). Randomisation was stratified by HbA1c <9% and ≥9% at time of screening. If necessary, insulin therapy could be reduced by <20% on day 1 before starting dapagliflozin treatment to prevent hypoglycaemia at treatment initiation; however, the insulin dosage could then be adjusted throughout the study to be consistent with self-monitored blood glucose (SMBG) readings. Reducing the total daily dose by >20% from baseline during the study was not recommended unless medically indicated. Patients were trained to test their blood ketone levels and requested to do so before breakfast, on any 3 days within the week before each visit. Patients were also instructed to recognize the symptoms and signs of diabetic ketoacidosis and to perform blood ketone testing if any symptoms or signs that could be indicative of diabetic ketoacidosis were present. If the self-monitored blood ketone assessment showed β-hydroxybutyrate levels >0.6 mmol/L, then patients were to contact the investigators.

Ethical approval was obtained from the institutional review boards and this study was performed in accordance with the Declaration of Helsinki, the International Council on Harmonization and Good Clinical Practice guidelines. This trial was registered on ClinicalTrials.gov (NCT02582814). All patients provided written informed consent.

2.3 | Safety assessments

The primary endpoints were the safety and tolerability of long-term dapagliflozin treatment. This involved assessment of adverse events (including hypoglycaemic episodes and diabetic ketoacidosis), vital signs (blood pressure and heart rate), 12-lead electrocardiography and general laboratory tests.

Following the recommendations of the American Diabetes Association (ADA),[31] hypoglycaemia was categorized as severe, documented symptomatic, asymptomatic, probable symptomatic or relative hypoglycaemia (see Table S1; see Supporting Information).

All patient-reported symptoms, self-measured ketone and SMBG values that were assessed by an investigator as being potential diabetic ketoacidosis events, and investigator-diagnosed adverse events of potential diabetic ketoacidosis were assessed by an independent and blinded diabetic ketoacidosis adjudication committee. This committee was responsible for determining whether the reported diabetic ketoacidosis events were consistent with the criteria outlined in the ADA consensus.[32] Events consistent with the ADA consensus were classified as "definite", whereas "possible" and "unlikely" were not defined but were at the discretion of the adjudicators.

2.4 | Efficacy assessments

The secondary endpoint was the efficacy of long-term dapagliflozin treatment. Efficacy outcomes included changes in HbA1c, glycoalbumin, average daily glucose as measured by six-point SMBG, postprandial glucose as measured by six-point SMBG, and percentage changes in total daily insulin dosage and body weight. These outcomes were assessed at baseline and throughout the study.

2.5 | Subgroup analysis

A subgroup analysis was performed to investigate the efficacy of dapagliflozin in patients with BMIs <25.0 and ≥25.0 kg/m^2.

2.6 | Statistical methods

This study was intended to complement the safety database on Japanese patients and therefore 100 patients were required to be exposed to dapagliflozin for 1 year according to the International Council for Harmonisation E1 Clinical Safety for Drugs used in Long-Term Treatment guidelines (1994). Assuming a 15% dropout rate, 140 patients were planned for randomisation so that approximately 59 patients would be expected to complete the study in each treatment group.

The safety analysis set included all randomized patients who received at least one dose of dapagliflozin and provided any safety data. The full analysis set included all randomized patients who received at least one dose of dapagliflozin, had no missing baseline values and had at least one efficacy measurement recorded.

For all safety analyses, the number and proportion of adverse events and serious adverse events were reported for each treatment group. Statistical analyses on the change from baseline in efficacy parameters were performed using a mixed model with repeated measures (MMRM), and point estimates with 95% confidence intervals (CI) for each treatment time point. For within-subject correlations, an unstructured covariance matrix was assumed. Analyses on the percentage change from baseline in efficacy parameters were performed with log-transformed values using a similar MMRM model. Point estimates and 95% CIs for the percentage change from baseline were derived from exponentiated estimates, which were obtained from this model.

Data analysis was performed using SAS version 9.4 (SAS Institute Inc., Cary, North Carolina).

3 | RESULTS

3.1 | Patients

In total, 173 patients were enrolled, 151 were randomized and 135 completed the study (Figure S1; see Supporting Information). The most common reasons for withdrawal included adverse events (5.3%) and patients who met the study-specific withdrawal criteria.

TABLE 1 Baseline characteristics

	5 mg dapagliflozin	10 mg dapagliflozin
n	76	75
Male (%)	56.6	44.0
Age (years)	47.7 ± 12.9	48.9 ± 12.9
Body weight (kg)	68.9 ± 12.2	65.6 ± 10.3
Body mass index (kg/m^2)	25.3 ± 3.6	24.7 ± 2.8
Duration of T1DM (years)	14.6 ± 8.4	15.9 ± 10.3
HbA1c (%)	8.4 ± 0.7	8.4 ± 0.7
C-peptide (%)		
<0.1 ng/mL	82.9	86.7
≥0.1 to <0.7 ng/mL	17.1	13.3
eGFR (%)		
45 to <60 mL/min per 1.73 m^2	2.6	1.3
60 to <90 mL/min per 1.73 m^2	48.7	50.7
≥90 mL/min per 1.73 m^2	48.7	48.0
Multiple daily injection (%)	94.7	93.3
Total daily insulin dose (IU/day)	53.5 ± 19.8	44.7 ± 16.1
Daily basal insulin dose (IU/day)	20.7 ± 8.7	17.7 ± 7.3
Daily bolus insulin dose (IU/day)	31.1 ± 16.0	26.9 ± 11.8
Diabetes-related diseases (%)		
Retinopathy	35.5	30.7
Neuropathy, autonomic	5.3	5.3
Neuropathy, peripheral	27.6	16.0
Nephropathy	15.8	13.3
Angiopathy	3.9	4.0

Abbreviations: eGFR, estimated glomerular filtration rate; HbA1c, glycated haemoglobin; T1DM, type 1 diabetes mellitus; IU, international units.
Note: Data are means ± standard deviations unless otherwise indicated.

Patients were randomized 1:1 to receive 5 or 10 mg dapagliflozin for 52 weeks (76 and 75 patients, respectively). All 151 patients were included in the preplanned full analysis set and safety analysis set.

In general, both treatment groups had comparable demographics, disease-specific history and baseline characteristics (Table 1). More than 90% of patients were treated with MDI and almost all patients showed abolished β-cell function as evidenced by C-peptide levels of <0.1 ng/mL (Table 1). Approximately 50% of patients had normal renal function with very few patients having an estimated glomerular filtration rate level of 45 to <60 mL/min/1.73 m^2. Patients in the 5 and 10 mg dapagliflozin groups had similar mean ± standard deviation (SD) BMIs of 25.3 ± 3.6 and 24.7 ± 2.8 kg/m^2, respectively (Table 1). All patients had >80% treatment compliance throughout this study.

TABLE 2 Summary of adverse events

	5 mg dapagliflozin (n = 76)	10 mg dapagliflozin (n = 75)
Adverse events	67 (88.2)	55 (73.3)
Related to drug	23 (30.3)	22 (29.3)
Leading to discontinuation	4 (5.3)	4 (5.3)
Serious adverse events	7 (9.2)	3 (4.0)
Diabetic ketoacidosis	2 (2.6)	1 (1.3)
Hypoglycaemic coma	0	1 (1.3)
Vitreous haemorrhage	0	1 (1.3)
Atrial fibrillation	1 (1.3)	0
Hepatic function abnormal	1 (1.3)	0
Gastroenteritis	1 (1.3)	0
Colitis	0	1 (1.3)
Osteoarthritis	1 (1.3)	0
Abortion spontaneous	1 (1.3)	0
Serious adverse events leading to discontinuation	1 (1.3)	2 (2.7)

Note: Data are n (%).

3.2 | Safety

In this study, 67 (88.2%) and 55 (73.3%) patients in the 5 and 10 mg dapagliflozin groups, respectively, experienced at least one adverse event (Table 2). The most common adverse events in the 5 mg dapagliflozin group were nasopharyngitis (32.9%), gastroenteritis (9.2%), pollakiuria (9.2%), back pain (7.9%) and pharyngitis (6.6%); and in the 10 mg group, nasopharyngitis (42.7%), pharyngitis (12.0%), gastroenteritis (10.7%), ketosis (9.3%), pollakiuria (8.0%) and headache (8.0%). The most common adverse events that were assessed by the investigators to be related to treatment were pollakiuria (9.2% and 6.7%), ketosis (3.9% and 6.7%) and thirst (5.3% and 4.0%) in the 5 and 10 mg dapagliflozin treatment groups, respectively. Urinary tract and genital infections were observed in 0.0% (n = 0) and 2.6% (n = 2) of patients in the 5 mg dapagliflozin group and 4.0% (n = 3) and 2.7% (n = 2) of patients in the 10 mg dapagliflozin group, respectively.

Seven (9.2%) and three (4.0%) patients in the 5 and 10 mg dapagliflozin groups, respectively, experienced at least one serious adverse event (Table 2). Serious adverse events included diabetic ketoacidosis, which was reported in two patients in the 5 mg dapagliflozin group and one patient in the 10 mg group. Additionally, one patient in the 10 mg group experienced a hypoglycaemic event that was classified as a serious adverse event. Four patients withdrew

TABLE 3 Summary of adverse events related to hypoglycaemia and diabetic ketoacidosis

	5 mg dapagliflozin (n = 76)	10 mg dapagliflozin (n = 75)
Hypoglycaemia	75 (98.7)	75 (100.0)
Leading to discontinuation	1 (1.3)	1 (1.3)
Diabetic ketoacidosis	3 (3.9)	1 (1.3)
Leading to discontinuation	1 (1.3)	1 (1.3)

Note: Data are n (%).

from each group because of adverse events. No patient died during the study and most adverse events were mild in severity.

The incidences of any hypoglycaemic episodes were 98.7% (n = 75) in the 5 mg dapagliflozin group and 100.0% (n = 75) in the 10 mg group (Table 3). At least one documented symptomatic hypoglycaemic event was reported by 88.2% (n = 67) and 97.3% (n = 73) of patients in the 5 and 10 mg dapagliflozin groups, respectively, while asymptomatic hypoglycaemia was reported by 78.9% (n = 60) and 85.3% (n = 64) of patients in the 5 and 10 mg dapagliflozin groups, respectively.

Severe hypoglycaemia was reported in 2.6% (n = 2) and 6.7% (n = 5) of patients in the 5 and 10 mg dapagliflozin groups, respectively, and all events were singular cases. One of these events (temporary loss of consciousness) was reported as an adverse event and another (hypoglycaemic coma) was reported as a serious adverse event, and both patients discontinued the study because of these hypoglycaemia-related adverse events. There were no major differences in the incidence of hypoglycaemic symptoms (severe, documented symptomatic, asymptomatic, probable symptomatic or relative hypoglycaemia) between dapagliflozin treatment groups (Table S1; see Supporting Information).

Four serious adverse events of "diabetic ketoacidosis" were reported by the investigators (Table 3). Of these, two patients (2.6%) in the 5 mg dapagliflozin group and one patient (1.3%) in the 10 mg group were adjudicated as experiencing definite diabetic ketoacidosis (Table S2; see Supporting Information). The fourth serious adverse event was in the 5 mg dapagliflozin group and was adjudicated as possible diabetic ketoacidosis. The three patients who developed diabetic ketoacidosis were female, had their insulin doses reduced because of appetite loss on a sick day before diabetic ketoacidosis, had glycaemic levels <250 mg/dL, and recovered in the hospital after standard treatment with a saline and insulin infusion. Two of these patients discontinued dapagliflozin, while the remaining patient restarted therapy after recovery. In the overall population, mean self-monitored blood ketone levels (measured before breakfast and regularly regardless of any symptoms) were slightly increased from baseline in both the 5 and 10 mg dapagliflozin groups (Table S3; see Supporting Information).

3.3 | Efficacy

Reductions in HbA1c levels were apparent as early as week 4. The adjusted mean (95% CI) changes in HbA1c at week 24 were −0.52% (−0.66, −0.38) in the 5 mg dapagliflozin group and −0.66% (−0.80, −0.53) in the 10 mg group (Figure 2A). The adjusted mean (95% CI) changes in HbA1c from baseline at week 52 were −0.33% (−0.50, −0.15) in the 5 mg dapagliflozin group and −0.36% (−0.53, −0.18) in the 10 mg group.

Reductions in glycoalbumin levels were also observed from week 4 in both groups. The mean (95% CI) changes in glycoalbumin from baseline at week 52 were −1.48% (−2.18, −0.77) in the 5 mg dapagliflozin group and −1.68% (−2.41, −0.96) in the 10 mg group. Mean daily glucose levels measured by six-point SMBG also declined. The mean (95% CI) changes at week 52 were −11.62 mg/dL (−18.62, −4.62) in the 5 mg dapagliflozin group and −12.93 mg/dL (−19.99, −5.88) in the 10 mg group.

The proportions of patients with ≥0.5% reduction of HbA1c without severe hypoglycaemia at week 24 were 60.8% and 61.3%, and then 51.4% and 41.3% at week 52 in the 5 and 10 mg dapagliflozin groups, respectively (Figure S2; see Supporting Information).

The percentage change from baseline in total daily insulin dosage is shown in Figure 2(B). At week 52, the mean (95% CI) changes in total daily insulin dosage were −12.27% (−15.92, −8.46) in the 5 mg dapagliflozin group and −13.13% (−16.77, −9.33) in the 10 mg group.

The percentage change in body weight over time is shown in Figure 2(C). The mean ± SD body weight of patients at baseline were 68.9 ± 12.2 kg and 65.6 ± 10.3 kg in the 5 and 10 mg dapagliflozin groups, respectively. The mean (95% CI) changes in body weight from baseline were −3.88% (−4.74, −3.02) in the 5 mg dapagliflozin group and −5.26% (−6.11, −4.41) in the 10 mg group at week 24. Thereafter, a more gradual reduction continued, and the mean (95% CI) changes in body weight at week 52 were −4.25% (−5.29, −3.21) in the 5 mg dapagliflozin group and −5.96% (−6.98, −4.93) in the 10 mg group.

3.4 | Subgroup analysis

In the subgroup analysis, there appeared to be no substantial differences in efficacy parameter trends when stratified by BMI <25.0 kg/m^2 and ≥25.0 kg/m^2 in either dapagliflozin treatment group (Table S4; see Supporting Information). Although it was difficult to compare groups in the subgroup analysis because of the small number of patients, there did not appear to be any marked differences in the safety profiles between patients with BMI ≤25.0 and >25.0 kg/m^2 (Table S5; see Supporting Information).

4 | DISCUSSION

To the best of our knowledge, this is the first Asian study to report the long-term safety of an SGLT2 inhibitor as an adjunct therapy to

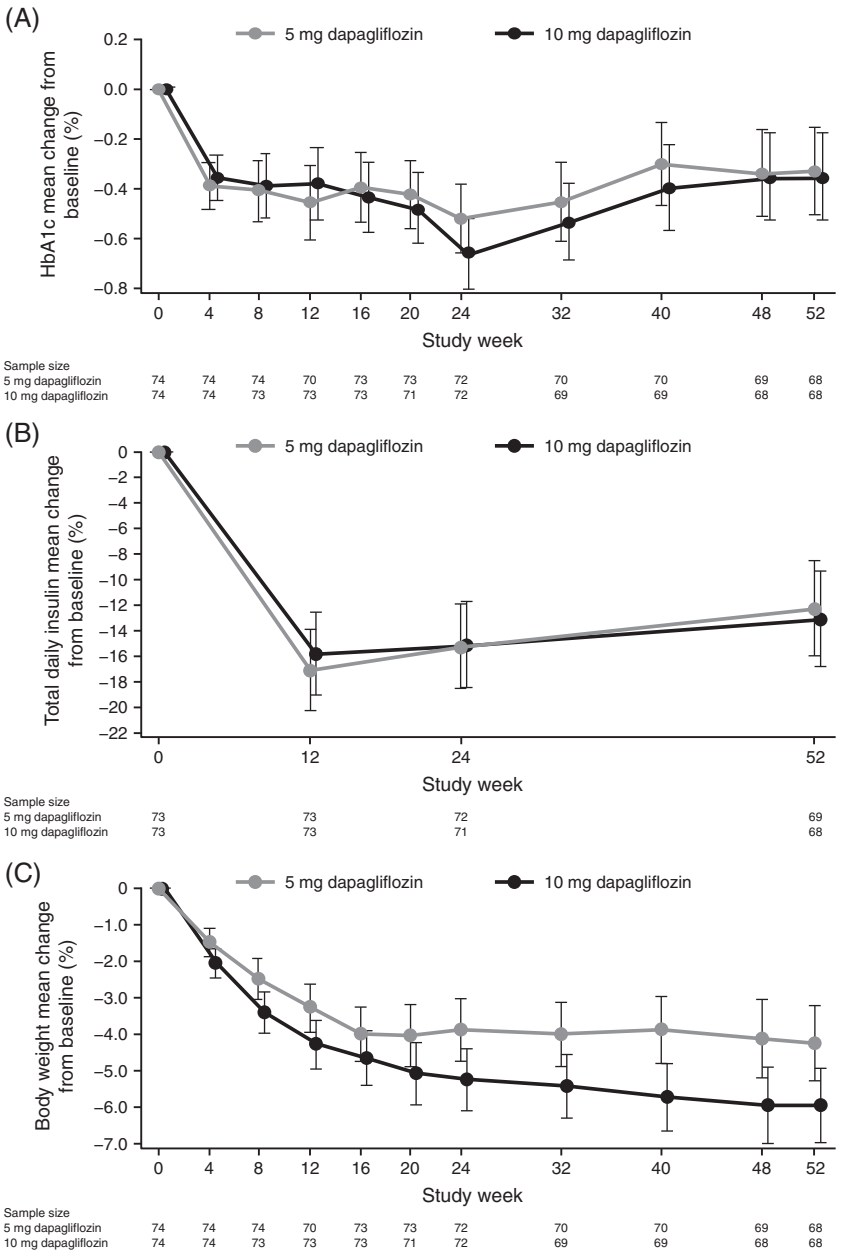

FIGURE 2 Mean change from baseline in the following. A, HbA1c. B, Total daily insulin dose. C, Body weight. Error bars represent 95% confidence intervals for the adjusted mean change from baseline. Abbreviation: HbA1c, glycated haemoglobin

insulin for patients with T1DM. This study was designed to fulfil Japanese regulatory requirements and therefore is similar in design, albeit without a placebo treatment group, to both the DEPICT-1 and DEPICT-2 studies.[28-30] Current findings are consistent with those reported in the 24-week DEPICT-1 and DEPICT-2 studies, and the 52-week DEPICT-1 extension study.

This study showed that add-on therapy with dapagliflozin for 52 weeks was generally well tolerated with most adverse events mild in severity. When used to treat T2DM, dapagliflozin has been reported to be associated with pollakiuria,[33] volume depletion[34] and more frequent urinary[35] and genital tract infections,[36] although there have been fewer reported events of urinary and genital tract infections in Japanese patients compared with other populations.[22] The DECLARE-TIMI 58 study reported that the incidence of hypoglycaemic events did not increase in patients with T2DM when treated with dapagliflozin; however, a slightly higher incidence of diabetic ketoacidosis events was reported in these patients (0.3%) compared with placebo (0.1%).[37] When comparing the overall safety profile of dapagliflozin in patients with T2DM with the overall safety profile of dapagliflozin in the present study, the adverse events reported are broadly similar with no new safety concerns observed over 52 weeks. As expected, the overall incidences of hypoglycaemia and diabetic ketoacidosis were higher in these patients with T1DM compared with the T2DM population. Therefore, the occurrence of hypoglycaemia and diabetic ketoacidosis in those receiving dapagliflozin was carefully investigated in this study.

Hypoglycaemia is a frequent adverse event with insulin therapy, and severe hypoglycaemia can result in loss of consciousness and even death. Symptomatic hypoglycaemia affects a patient's health-related quality of life; therefore, new hypoglycaemic therapies that do not increase hypoglycaemic risk are desirable. Dapagliflozin added to insulin therapy showed clinically significant improvements in

glycaemic control without increasing hypoglycaemia risk in the 52-week DEPICT-1 study and the 24-week DEPICT-2 study compared with placebo.[29,30] In the DEPICT-1 52-week study, severe hypoglycaemia was observed in 10.5%, 8.4% and 11.5% of patients in the 5 and 10 mg dapagliflozin and placebo groups, respectively, whereas in the 24-week DEPICT-2 study, severe hypoglycaemia was observed in 6.3%, 8.5% and 7.7% of patients in the 5 and 10 mg dapagliflozin and placebo groups, respectively.[29,30] In this study, severe hypoglycaemia was observed in 2.6% (n = 2) and 6.7% (n = 5) of patients in the 5 and 10 mg dapagliflozin groups, respectively. Most hypoglycaemic events were not serious and only two patients discontinued the study because of severe hypoglycaemia. When dapagliflozin is added to insulin treatment, it is recommended that the insulin dose is reduced if there is a risk of hypoglycaemia; however, the reduction rate should not be >20% because of the potential increase in diabetic ketoacidosis risk.

Diabetic ketoacidosis is a serious and potentially life-threatening event that occurs when there is insufficient insulin. When compared with patients with T2DM, diabetic ketoacidosis is relatively frequent in patients with T1DM who are unable to produce sufficient insulin.[7,38] Diabetic ketoacidosis occurs under specific conditions and probably occurs on sick days. In the 24-week DEPICT-2 study, 2.6%, 2.2% and 0.0% of patients had definite diabetic ketoacidosis in the 5 mg dapagliflozin, 10 mg dapagliflozin and placebo groups, respectively; while in the 52-week DEPICT-1 study, 4.0%, 3.4% and 1.9% of patients in the respective groups had definite diabetic ketoacidosis.[29,30] In both DEPICT-1 and -2, there were more events of diabetic ketoacidosis in those treated with dapagliflozin than in those treated with placebo. The most common causes in DEPICT-1 and -2 were missed insulin doses, insufficient insulin dosage and insulin pump failure.[29,30] In the present study, two (2.6%) patients in the 5 mg dapagliflozin group and one (1.3%) patient in the 10 mg group developed definite diabetic ketoacidosis. In addition to the use of dapagliflozin, the insulin dose was reduced before these three patients developed diabetic ketoacidosis on sick days. It has been shown that an insulin dose reduction of >20% increases β-hydroxybutyrate levels, which subsequently may increase the risk of diabetic ketoacidosis when dapagliflozin is added to insulin therapy in patients with T1DM.[39]

It was recently reported that euglycaemic diabetic ketoacidosis occurs in both patients with T1DM and patients with T2DM being treated with SGLT2 inhibitors.[40] In this study, the three patients who developed diabetic ketoacidosis experienced euglycaemic diabetic ketoacidosis. Therefore, patients, physicians and medical staff should be educated to always suspect diabetic ketoacidosis when patients present with diabetic ketoacidosis-associated symptoms, such as malaise, nausea, and vomiting even if the patient's glucose level is <250 mg/dL. When emerging diabetic ketoacidosis is suspected, ketone monitoring is a valuable tool to prevent its progression to diabetic ketoacidosis.[41]

It has been reported that dapagliflozin add-on therapy in patients with T1DM results in clinically meaningful improvements in glycaemic control from baseline across various glycaemic parameters, including HbA1c, glycoalbumin and average SMBG levels in both the 5 and 10 mg dapagliflozin groups. In DEPICT-1, there were significant reductions in HbA1c compared with placebo [−0.42% (95% CI: −0.56, −0.28; P <0.0001) for 5 mg dapagliflozin and −0.45% (95% CI: −0.58, −0.31; P <0.0001) for 10 mg dapagliflozin] over 24 weeks.[28] DEPICT-2 was consistent with DEPICT-1 and similarly, the present study also reported significant HbA1c reductions [−0.33% (95% CI: −0.50, −0.15) and −0.36% (95% CI: −0.53, −0.18)] from baseline for both 5 and 10 mg dapagliflozin add-on therapy, respectively. Additionally, our results were consistent with the mean reductions in HbA1c that were reported in the 52-week DEPICT-1 study (−0.27% for 5 mg dapagliflozin and −0.31% for 10 mg dapagliflozin).[30] The proportions of patients with HbA1c reductions of ≥0.5% without severe hypoglycaemia were 51.4% (95% CI: 39.4, 63.1) in the 5 mg dapagliflozin group and 41.3% (95% CI: 30.1, 53.3) in the 10 mg group, which is similar to the 52-week data in DEPICT-1 (40.2% and 42.1%, respectively). There were also clinically meaningful reductions from baseline in both total daily insulin dosage and body weight, and these effects were maintained over 52 weeks. These improvements were also observed in the subgroup analysis when the changes from baseline in efficacy parameters were stratified by a BMI of 25 kg/m^2. The average BMI (24–25 kg/m^2) at baseline in this study was slightly lower than that of 27–28 kg/m^2 in the DEPICT-1 and -2 studies, but was slightly higher than the average BMI of 23 kg/m^2 in the general Japanese population with T1DM, as patients with lower BMI (<20 kg/m^2) were excluded from this study. The efficacy and safety profile of dapagliflozin was consistent in both BMI strata in Japanese patients with T1DM in this study, excluding patients with lower BMI (<20 kg/m^2).

Limitations need to be acknowledged in that, as this was an open-label, uncontrolled study, a causal relationship between dapagliflozin and efficacy/safety cannot be concluded.

In conclusion, this phase III study reveals favourable safety and tolerability profiles for dapagliflozin add-on therapy with insulin in the treatment of Japanese patients with inadequately controlled T1DM over 52 weeks.

ACKNOWLEDGMENTS

This study was funded by AstraZeneca K.K. We thank James Graham, PhD, of Edanz Medical Writing for providing medical writing support, which was funded by AstraZeneca K.K. through EMC K.K. in accordance with Good Publication Practice (GPP3) guidelines (http://www.ismpp.org/gpp3).

CONFLICT OF INTEREST

E.A. has participated on advisory panels for Alcon, Astellas Pharma, AstraZeneca, Eli Lilly, Kowa Pharmaceutical, Nippon Boehringer Ingelheim, Novo Nordisk Pharma, Sanofi, and Terumo Corporation; has received honoraria for lectures from Astellas Pharma, MSD, Ono Pharmaceutical, Novo Nordisk Pharma, and Sanofi; and has received scholarship grants from Astellas Pharma, Daiichi Sankyo, Mitsubishi Tanabe Pharma, Nippon Boehringer Ingelheim, Novo Nordisk Pharma, Ono Pharmaceutical, Sanofi, Shionogi, Sumitomo Dainippon Pharma,

and Takeda Pharmaceutical. H.W. reports acting as an advisory board member for Novo Nordisk and as a speaker for Astellas Pharma, Sanofi, Mitsubishi Tanabe Pharma, Novo Nordisk, Kowa Pharmaceutical, AstraZeneca, Takeda Pharmaceutical, Novartis, Nippon Boehringer Ingelheim, Merck Sharp & Dohme, Sumitomo Dainippon Pharma, Eli Lilly Japan, Sanwa Kagaku Kenkyusho, Ono Pharmaceutical, Kissei Pharmaceutical, and FUJIFILM Pharma; and receiving grants from Astellas Pharma, Sanofi, Mitsubishi Tanabe Pharma, Novo Nordisk Pharma, AstraZeneca, Takeda Pharmaceutical, Novartis Pharma, Nippon Boehringer Ingelheim, Merck Sharp & Dohme, Sumitomo Dainippon Pharma, Eli Lilly Japan, Ono Pharmaceutical, Kyowa Kirin, Daiichi Sankyo, Terumo, Pfizer Japan, Mochida Pharmaceutical, Taisho Toyama Pharmaceutical, Johnson & Johnson, and Kowa. Y.U. has received grants and honoraria from AstraZeneca K.K. and holds a position as a board member for AstraZeneca K.K. O.T., H.F., H.O. and T.O. have no conflict of interest to disclose. F.T. and A.M.L. are employees of AstraZeneca. M.A., H.K. and T.Y. are employees of AstraZeneca K.K.

AUTHOR CONTRIBUTIONS

E.A. contributed to the acquisition, analysis and interpretation of data; drafted and revised the manuscript; was responsible for the integrity of the data and the accuracy of the data analysis as a signatory investigator. H.W. contributed to the analysis and interpretation of data; and reviewed the manuscript. Y.U. conducted the study; contributed to the acquisition, analysis and interpretation of data; and reviewed the manuscript. O.T. conducted the study; contributed to the data acquisition; and reviewed the manuscript. H.F. conducted the study and contributed to the data acquisition; and reviewed the manuscript. H.O. conducted the study and contributed to the data acquisition; and reviewed the manuscript. T.O. conducted the study and contributed to the data acquisition; and reviewed the manuscript. M.A. conducted the study; contributed to the study design, data analysis and interpretation; and reviewed the manuscript. F.T. conducted the study; contributed to the study design, data analysis and interpretation; and reviewed the manuscript. H.K. contributed to the study design, data analysis, and interpretation; and reviewed the manuscript. T.Y. contributed to the study design; and reviewed the manuscript. A.M.L. contributed to the study design and interpretation; and reviewed the manuscript. All authors have read and approved the final version of manuscript for publication.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

How to cite this article: Araki E, Watada H, Uchigata Y, et al. Efficacy and safety of dapagliflozin in Japanese patients with inadequately controlled type 1 diabetes (DEPICT-5): 52-week results from a randomized, open-label, phase III clinical trial. *Diabetes Obes Metab*. 2020;22:540–548. https://doi.org/10.1111/dom.13922