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ORIGINAL ARTICLE

Pharmacokinetics and pharmacodynamics of dapagliflozin in combination with insulin in Japanese patients with type 1 diabetes

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Aims: To assess the pharmacokinetics/pharmacodynamics (PK/PD) of dapagliflozin, a sodium-glucose co-transporter 2 inhibitor that increases urinary glucose excretion (UGE) and its major metabolite, dapagliflozin-3-O-glucuronide (D3OG), in Japanese patients with type 1 diabetes (T1D) and inadequate glycaemic control (HbA1c 7%-10%).

Materials and methods: Japanese patients (18-65 years) with inadequately controlled T1D were randomized 1:1:1 to dapagliflozin 5 mg, 10 mg or placebo (n = 14 each) once daily for 7 days, with adjustable insulin. The PK/PD characteristics of dapagliflozin and D3OG were assessed on Day 7. Patients underwent follow-up evaluation on Days 8 and 14. Adverse events (AEs), hypoglycaemic episodes and events of diabetic ketoacidosis (DKA) were recorded over the treatment and follow-up periods.

Results: A total of 42 randomized patients received dapagliflozin or placebo. PK variables increased in a dose-dependent manner. D3OG was generated rapidly, with a median time to maximum plasma concentration of 2.0 hours (1.0-3.0). The dapagliflozin dose-UGE relationship was attenuated, with larger insulin dose reductions than anticipated. Mean percent (standard error) changes in total daily insulin dose from baseline to Day 7 were − 36.86% (3.32), −39.13% (2.68) and − 4.97% (5.28) for dapagliflozin 5 mg and 10 mg and for placebo, respectively. No DKA was reported. AEs were consistent with the established dapagliflozin safety profile. There was no increase in hypoglycaemia.

Conclusions: The PK and safety profiles of dapagliflozin in Japanese patients with T1D were consistent with previous studies, but with an unanticipated attenuation of the PD dose-response measured as UGE.

KEYWORDS

dapagliflozin, Japan, pharmacodynamics, pharmacokinetics, type 1 diabetes

1 | INTRODUCTION

The Japan Diabetes Society recommends a glycaemic goal of HbA1c less than 7.0% for Japanese patients with any type of diabetes to prevent complications.[1] Intensive insulin treatment is required in patients with type 1 diabetes (T1D); however, this is often associated with sustained increases in body weight, dyslipidaemia, hypoglycaemia and insulin resistance.[2–4] Despite advances in insulin therapy, some patients with T1D cannot achieve recommended goals.[5] For optimal glycaemic control, it has been of importance to assess the potential use of treatments as adjunct to insulin in patients with T1D.

Dapagliflozin is a potent sodium-glucose co-transporter-2 (SGLT-2) inhibitor that reduces blood glucose through an insulin-independent mechanism, with a reduction in renal glucose reabsorption accompanied by an increase in urinary glucose excretion (UGE).[6] It was approved as a once-daily oral treatment for patients with type 2 diabetes (T2D) in Japan in 2014.[7] In patients with T1D, dapagliflozin treatment has been shown to involve a dose-dependent increase in UGE, resulting in dose-dependent reductions in mean blood glucose over 24 hours,[8] but it is not currently approved for use in T1D.

In a Phase III study of predominantly Caucasian patients with inadequately controlled T1D, the DEPICT-1 study (NCT02268214), dapagliflozin as adjunct to adjustable insulin therapy improved glycaemic control without increasing the risk of hypoglycaemia.[9] Data from the DEPICT-1 and DEPICT-2 studies at 24 weeks showed that dapagliflozin was associated with a significant reduction in HbA1c, total daily insulin dose and body weight, as well as with improvements in several continuous glucose-monitoring parameters in patients with T1D.[9,10] Participants in the DEPICT-1 study also showed improvement in glycaemic control up to 52 weeks following dapagliflozin administration.[11]

Although no notable difference in the pharmacokinetics (PK) or pharmacodynamics (PD) of dapagliflozin, (assessed by UGE), has been observed in Caucasian vs Japanese patients with T2D, differences in response to treatment between these ethnic groups with T1D remains to be explored.[12] The aim of this study was to assess the PK and PD of dapagliflozin and its major metabolite, dapagliflozin-3-O-glucuronide (D3OG), in Japanese patients with T1D and inadequate glycaemic control (HbA1c > 7%).

2 | MATERIALS AND METHODS

2.1 | Study design

This was a Phase Ib randomized, single-blind, three-arm, placebo-controlled study (ClinicalTrials.gov NCT02582840) to characterize the PK and PD of dapagliflozin and D3OG in Japanese patients with T1D and inadequate glycaemic control. The study was conducted at a single centre, SOUSEIKAI Hakata Clinic in Fukuoka, Japan, in accordance with the Declaration of Helsinki and consistent with the International Conference on Harmonization (ICH)/Good Clinical Practice (GCP). The study was approved by an Institutional Review Board and independent ethics committees. All participants provided written informed consent. Parents or legal guardians of patients between 18 to less than 20 years of age were requested to sign and date assent forms.

2.2 | Study participants

Japanese men and women (18-65 years) with inadequately controlled T1D (HbA1C, 7%-10% at screening) who had undergone adjustable insulin treatment (total insulin dose ≥0.3 IU/kg/d for ≥3 months prior to screening) for at least 12 months prior to enrolment were included. The method of insulin administration must have been unchanged for at least 3 months prior to enrolment, and participants must have had fasting C-peptide less than 0.7 ng/mL and a body mass index between at least 20–35 kg/m^2. If patients were undergoing multiple daily insulin injection therapy, they must have been using at least three injections/day.

Patients were excluded if the investigators considered them unlikely to comply with the protocol or if they were unable to correctly administer subcutaneous insulin injections and/or manage the insulin pump. If patients had a history of T2D or maturity-onset diabetes of the young, if they had undergone pancreatic surgery, or if they had chronic pancreatitis or other pancreatic disorders that resulted in decreased β-cell capacity, they were also excluded. In addition, patients were excluded for the following reasons: use of thiazolidinediones within 6 months prior to screening; previous use of an SGLT-2 inhibitor; use of any other non-insulin anti-hyperglycaemic agent within 1 month prior to screening; and allergies to or contraindication for the contents of dapagliflozin tablets or insulin. Patients with an estimated glomerular filtration rate (eGFR) of 60 mL/min/1.73m^2 or less within 6 months prior to enrolment were excluded. For women of childbearing potential to be included, they must have had a negative serum or urine pregnancy test and must have agreed to follow instructions for method of contraception for the duration of treatment. Women were excluded if they were pregnant or breastfeeding at enrolment. Participation in another clinical study within 30 days of enrolment was not permitted. Other exclusion criteria are given online in Supporting Information.

2.3 | Study medications and procedures

Eligible patients were randomized (1:1:1) to receive dapagliflozin 5, 10 mg or matched placebo, all of which were administered orally once daily in the morning and as as adjunct to adjustable insulin, for 7 days. Participants were advised to adjust insulin dose as required following self-monitoring of blood glucose (SMBG) between screening and end of the follow-up period, but they were not allowed to change the method of insulin administration during the study. It was recommended that participants self-monitor their blood glucose at least 7 times/day during the treatment period, generally before and after breakfast, lunch and dinner and at bedtime. In the event of suspected hypoglycaemia, patients were to report blood glucose values and/or signs and symptoms to the investigators.

Visits were planned at Days −14, −2, −1 and 1 (randomization) during the screening period. Telephone, fax or email contact was planned at least once daily between Days 2 and 6. Patients underwent a follow-up evaluation on Days 7, 8 and 14.

2.4 | Analysis of blood and urine samples

Blood samples were taken on Days 1, 7 and 8 for PK analysis. On Day 1, blood samples were collected prior to dapagliflozin administration. On Day 7, blood samples were collected over 24 hours at 60 minutes prior to administration and at 0.5, 1, 2, 3, 4, 6, 8, 12 and 24 hours after administration. Blood samples were analysed to determine the PK of dapagliflozin and D3OG.

Blood samples were taken to analyse the change from baseline in concentration of glucose, sodium, uric acid and creatinine on Days −14, 1, 8 and 14. Urine samples were also collected for analysis.

Collection of 24-hour urine was carried out on Days −1, 1, 7 and 8. Urine was also collected via dipstick on Days −14, 1, 8 and 14. Urine samples were analysed to determine changes in concentration of glucose, sodium, uric acid and creatinine on Days −14, −1, 8 and 14. Laboratory analyses of serum β-hydroxybutyrate, acetoacetic acid and serum ketones were also carried out. Additional laboratory analyses of serum samples were carried out to determine eGFR and creatinine clearance.

2.5 | Outcomes: Primary, secondary and exploratory endpoints

The primary endpoint was the PK of dapagliflozin and its metabolite D3OG. PK variables were: maximum plasma concentration (C_{max}), minimum plasma concentration (C_{min}), time to maximum plasma concentration (T_{max}) and area under the plasma concentration curve over a dose interval (AUCτ). The mean ratio of D3OG AUCτ to dapagliflozin AUCτ on Day 7 was determined. Co-primary endpoints were change from baseline in 24-hour UGE on Day 7 (PD variable).

Secondary endpoints were change from baseline to Day 7 in fasting plasma glucose (FPG), daily insulin dose and seated systolic blood pressure (SBP). A *post-hoc* exploratory PD endpoint was the relationship between changes in 7-point SMBG measurements and 24-hour UGE and total daily insulin dose, defined as the sum of all insulin doses (basal plus bolus plus premixed) for each day, where participants were stratified according to their average 7-point SMBG on Day 7 (<180 mg/dL or ≥ 180 mg/dL).

2.6 | Safety assessments

Any adverse events (AEs) or hypoglycaemic episodes, and events of diabetic ketoacidosis (DKA) were recorded over the treatment and follow-up periods. Information concerning intensity of AEs was recorded. A DKA adjudication committee, blinded to treatment, independently adjudicated all DKA events reported by the investigator throughout the study period. The frequency of AEs was summarized by system organ class, Medical Dictionary for Regulatory Activities preferred terms and treatment group. SAEs were summarized separately. Any marked laboratory abnormalities from baseline were noted, and electrocardiograms and vital signs recorded.

Insulin adjustment was performed to ensure patient safety in the event of a significant change in insulin requirements. Blood glucose readings between 70 and 220 mg/dL were considered adequate glycaemic control throughout the study. An additional goal was to maintain FPG between 70 and 140 mg/dL and post-prandial blood glucose below 220 mg/dL, individualized according to a specific patient's personal targets and stability of glycaemic control at baseline. Insulin dosing was adjusted if patients presented with unexpected events of hypoglycaemia or hyperglycaemia. If insulin dose adjustments were deemed necessary, investigators guided these with reviews of insulin and glucose logs and according to potential circumstances that contributed to erratic glucose control, such as insulin dosing errors, missed meals or physical activity. Consultation with the patient's diabetes management team was strongly recommended.

2.7 | Sample size

Sample size was not based on a statistical power calculation. A precision-based approach was used to calculate sample size. With 10 to 14 evaluable patients per arm, the half-width of the 95% CI for UGE change from baseline was estimated to be approximately 42–50 g/24 h, assuming the common standard deviation of 56 g/24 h.

2.8 | Statistical analysis

Demographic and other baseline characteristics were analysed descriptively by treatment group and overall. PK analyses were carried out on all randomized patients who received at least one dose of study mediation and for whom evaluable data concerning dapagliflozin and/or D3OG plasma concentration were available. PD analyses were carried out for all randomized participants who received at least one dose of study medication, who had a non-missing baseline value, and who had at least one post-baseline value for at least one PD variable. Treatment outcomes were summarized by treatment group. All analyses were performed using ICON CR with Statistical Analysis System (SAS).

3 | RESULTS

3.1 | Patient disposition

Of a total of 62 patients enrolled, 17 patients did not meet inclusion criteria and three patients withdrew. Of these 42 randomized patients, 14 were included in each treatment group. All 42 patients were included in the PD analysis set. In the PK analysis set, four patients in the 5 mg group and four in the 10 mg group were not considered evaluable for PK analysis following an incident related to the anticoagulant coating of the laboratory sampling tubes which were then recalled. Ten patients each from the dapagliflozin 5 and 10 mg groups were included in the PK analysis set. Of the 42 randomized patients, 100% completed the seven-day treatment period.

Baseline characteristics and demographics were generally balanced among the three treatment groups. There were more women than men in the dapagliflozin 5 mg and placebo groups, and equal numbers in the dapagliflozin 10 mg group. At baseline, the majority (62%) of participants had an eGFR corresponding to normal renal function (≥90 mL/min/1.73m^2), while the remaining 38% of participants had an eGFR corresponding to mild renal impairment (≥60 and <90 mL/min/1.73m^2). Baseline eGFR is shown in Table 1. A higher mean FPG was observed in the dapagliflozin 5 mg group compared with the other arms (Table 1). All participants were Japanese.

3.2 | Primary endpoints

Dapagliflozin and D3OG exposure increased in a dose-dependent manner (Figure 1A,B). There was a dose-dependent increase in C_{max}, C_{min} and AUCτ following dapagliflozin administration (Table 2). Dapagliflozin was absorbed rapidly (t_{max} 2.0 hours [1.0-3.0]) and D3OG was generated rapidly. The mean ratio of the AUCτ of D3OG to the

TABLE 1 Demographics and baseline characteristics

	Placebo (N = 14)	Dapagliflozin 5 mg (N = 14)	Dapagliflozin 10 mg (N = 14)	Total (N = 42)
Men, n (%)	3 (21.4)	8 (57.1)	7 (50.0)	18 (42.9)
Age, years, mean (SD)	42.6 (10.6)	37.0 (10.1)	37.1 (10.2)	38.9 (10.4)
Body weight, kg, mean (SD)	57.2 (10.7)	61.6 (7.6)	59.8 (8.6)	59.6 (9.0)
BMI, kg/m^2, mean (SD)	22.9 (3.4)	23.0 (2.3)	22.2 (2.1)	22.7 (2.6)
Duration of T1D, ys, mean (SD)	16.9 (10.5)	15.9 (9.2)	14.7 (12.4)	15.8 (10.6)
HbA1c, %, mean (SD)	8.1 (0.8)	7.9 (0.6)	7.9 (0.6)	8.0 (0.7)
FPG, mg/dL, mean (SD)	134.0 (63.9)	142.9 (49.9)	133.4 (42.2)	136.8 (51.7)
Average of 7-point SMBG, mg/dL, mean (SD)[a]	178.70 (52.95)	184.32 (34.85)	177.01 (34.25)	-
eGFR, mL/min/1.73m^2, mean (SD)	95.4 (17.9)	91.6 (13.1)	94.6 (15.6)	93.9 (15.4)
Seated SBP, mmHg, mean (SD)[a]	111.5 (15.0)	112.8 (11.8)	109.9 (8.3)	-

Abbreviations: BMI, body mass index; eGFR, estimated glomerular filtration rate based on Japanese Society of Nephrology formula (≤60 mL/min/1.73 m^2)[13]; HbA1c, glycated hemoglobin; SBP, systolic blood pressure; SD, standard deviation; SMBG, self-monitored blood glucose.
[a] Participants in the PD analysis set with non-missing baseline value and at least one post-baseline value.

AUCτ of dapagliflozin was 0.8 and 0.7 in the dapagliflozin 5 mg and 10 mg groups, respectively (Table 2).

Mean 24-hour UGE increased from baseline following dapagliflozin administration, with a numerically greater increase in the dapagliflozin 10 mg group. No notable change was observed in the placebo group (Table 3).

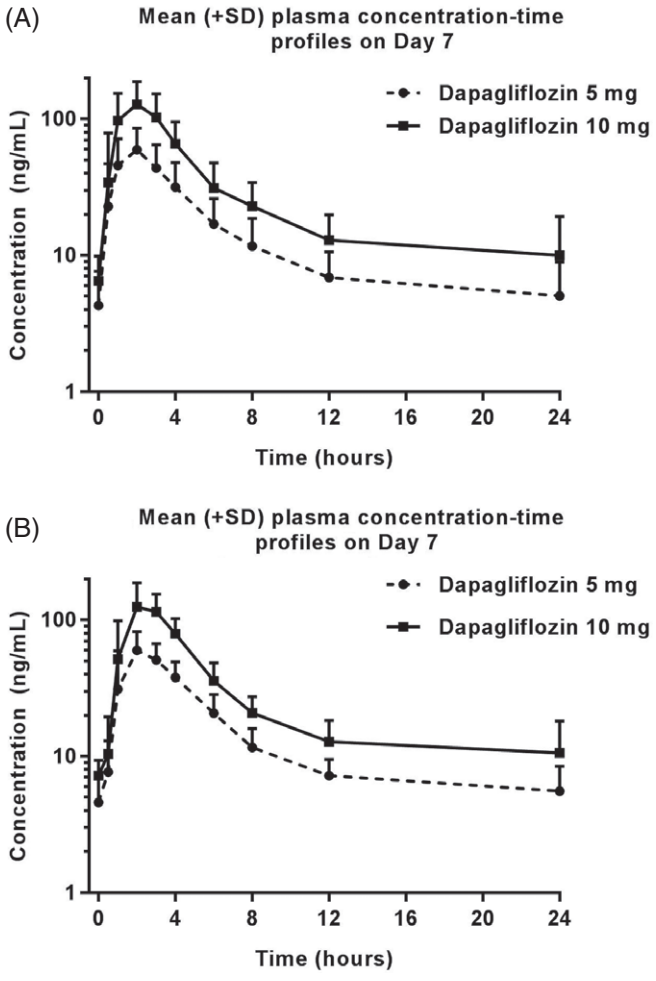

FIGURE 1 Mean (+SD) plasma concentration-time profiles for A, dapagliflozin and B, dapagliflozin 3-O-glucuronide (AUCτ; C_{min}, C_{max}, and T_{max}). Abbreviations: DAPA, dapagliflozin; SD, standard deviation

3.3 | Secondary endpoints

Mean percent (SE) changes in total daily insulin dose from baseline to Day 7 in the dapagliflozin arms were larger than expected: −36.86% (3.32), −39.13% (2.68) and −4.97% (5.28) for dapagliflozin 5 mg and

TABLE 2 Summary statistics for dapagliflozin and D3OG PK parameters at Day 7

	Dapagliflozin 5 mg (N = 10)	Dapagliflozin 10 mg (N = 10)
Dapagliflozin		
C_{max}, ng/mL, mean (SD)	71.9 (19.0)	167.5 (43.6)
AUCτ, h*ng/mL, mean (SD)	346.1 (154.7)	702.9 (259.5)
t_{max}, h, median (range)	2.0 (1.0-3.0)	2.0 (1.0-3.0)
D3OG		
C_{max}, ng/mL, mean (SD)	64.5 (20.6)	142.9 (45.7)
AUCτ, h*ng/mL, mean (SD)	358.8 (105.2)	692.4 (163.9)
t_{max}, h, median (range)	2.0 (1.0-4.0)	2.0 (1.0-3.0)
Ratio of metabolite: parent AUCτ, mean (SD)	0.8 (0.4)	0.7 (0.2)

Abbreviations: AUCτ, area under plasma concentration-time curve to the end of dosing interval; C_{max}, maximum observed plasma concentration; D3OG, dapagliflozin-3-O-glucuronide; t_{max}, time to C_{max}.

TABLE 3 Mean change in 24-hour urinary glucose (g/24 h) (PD analysis set)

	Value at visit	Change from baseline			
	Mean (SD)	Mean	SD	Median	95% CI
Placebo (N = 14)					
Baseline	20.6 (29.1)				
Day 7	14.4 (10.3)	−6.2	30.3	−1.0	−23.7, 11.4
Dapagliflozin 5 mg (N = 14)					
Baseline	18.6 (15.2)				
Day 7	115.1 (25.0)	96.6	30.1	96.0	79.2, 113.9
Dapagliflozin 10 mg (N = 14)					
Baseline	14.3 (13.1)				
Day 7	115.6 (17.2)	101.3	20.1	101.1	89.7, 112.9

Abbreviations: CI, confidence interval; PD, pharmacodynamics; SD, standard deviation; SE, standard error.

10 mg and for placebo, respectively. At Day 13, the total daily insulin dose approached baseline values (Table 4).

There were mean decreases (SD) in FPG from baseline to Day 7 of −10.4 (62.1) and −13.1 (44.7) mg/dL in the dapagliflozin 5 mg and 10 mg groups, respectively, compared with a mean increase of 11.0 (41.3) mg/dL in the placebo group (Table S1). There were minor differences in mean change of seated SBP over the seven-day period between the treatment and placebo groups (data not shown).

3.4 | Exploratory endpoint

Baseline SMBG readings are given in Table 1. Mean (SD) SMBG readings at Day 7 were 182.33 (23.37), 171.33 (18.57) and 185.24 (29.71) mg/dL for dapagliflozin 5 mg and 10 mg and for placebo, respectively. Mean (SD) changes in 7-point SMBG from baseline to Day 7 were −1.99 (23.58) for dapagliflozin 5 mg, −5.68 (40.36) for dapagliflozin 10 mg and + 6.54 (52.69) for placebo. When change in UGE from baseline to Day 7 was stratified by average 7-point SMBG on Day 7 (mean < 180 or ≥ 180 mg/dL), a clearer dapagliflozin dose-dependent response with respect to UGE was seen (Table S3).

There was a slightly greater decrease in total daily insulin dose in the dapagliflozin 10 mg group in the stratum with a 7-point SMBG ≥180 mg/dL than <180 mg/dL on Day 7 (Table S3). The study was not large enough to ensure balance of baseline characteristics and average 7-point SMBG on Day 7.

3.5 | Safety assessments

Two (14.3%) patients experienced at least one AE in the dapagliflozin 5 mg group, five (35.7%) in the 10 mg group and one (7.1%) in the placebo group, but all AEs were mild or moderate in intensity (Table S2).

TABLE 4 Percent change in total daily insulin dose (IU) in the PD analysis set

	Value at visit	Percent change from baseline			
	Mean (SD)	Mean	SE	Median	95% CI
Placebo (N = 14)					
Baseline	36.9 (14.8)				
Day 1	34.1 (11.7)	−6.3	3.5	−9.0	−13.4, 1.5
Day 7	35.1 (14.0)	−5.0	5.3	−8.2	−15.7, 7.2
Day 13	38.7 (16.6)	3.2	5.6	3.8	−8.2, 16.1
Dapagliflozin 5 mg (N = 14)					
Baseline	37.5 (9.6)				
Day 1	28.1 (7.0)	−25.0	2.0	−24.6	−29.2, −20.6
Day 7	24.4 (8.2)	−36.9	3.3	−37.8	−43.7, −29.3
Day 13	42.1 (12.3)	11.3	4.1	12.9	2.8, 20.4
Dapagliflozin 10 mg (N = 14)					
Baseline	38.1 (14.7)				
Day 1	26.4 (10.7)	−30.9	2.2	−28.9	−35.4, −26.0
Day 7	23.6 (11.9)	−39.1	2.7	−41.7	−44.6, −33.1
Day 13	38.2 (17.2)	−2.03	5.8	−5.76	−13.8, 11.4

Abbreviations: CI, confidence interval; PD, pharmacodynamics; SD, standard deviation; SE, standard error.
Mean percent change from baseline was derived following exponentiation of the least square mean estimates of the expected difference on the natural logarithmic scale.

AEs considered to be related to study medication were reported in two (14.3%) and three (21.4%) patients in the dapagliflozin 5 mg and 10 mg groups, respectively. Thirst was the most common related AE; this was higher in the 10 mg group than in the 5 mg group (four patients [21.4%] and one patient [7.1%], respectively). Pollakiuria was observed in both dapagliflozin arms (14.3% [n = 2] in each). No AE was considered serious. Hypoglycaemia, including severe, documented, asymptomatic, probable asymptomatic and relative, was reported by 14 (100%) patients in both the dapagliflozin 10 mg and the placebo groups. In the dapagliflozin 5 mg group, episodes of hypoglycaemia were reported by 12 (85.7%) patients. There were no episodes of severe hypoglycaemia in any treatment group (Table S2). No AE, no episode of hypoglycemia, or any event adjudicated as DKA led to discontinuation of the study or to medication. There were no deaths during the study.

3.6 | Laboratory assessments

Mean changes in potassium, calcium and chloride from baseline to Day 8 were minor, with no notable differences within groups. There was no change in hepatic function, total protein, albumin, sodium, creatinine clearance or uric acid from baseline to Day 8. As expected, a small transient decrease in eGFR was observed in the dapagliflozin treatment groups at Day 8, and readings were similar to baseline values at Day 14.

A small decrease in bicarbonate was observed from baseline to Day 8 in the dapagliflozin 5 mg and 10 mg groups (−1.79 and −2.52 mEq/L, respectively) vs a mean increase of 0.15 mEq/L in the placebo group. Dapagliflozin 5 mg and 10 mg vs placebo were associated with small increases in β-hydroxybutyrate (0.50 and 0.62 vs 0.02 mmol/L, respectively), acetoacetatic acid (0.11 and 0.16 vs 0.01 mmol/L, respectively), and total ketone (0.62 and 0.78 vs 0.03 mmol/L, respectively) from baseline to Day 8, and trended to baseline values at Day 14. No changes over time were found in haematology assessments.

4 | DISCUSSION

This study characterized the PK/PD profile of dapagliflozin in Japanese patients with T1D. The PK profile of dapagliflozin in this population was consistent with that seen in Caucasian patients with T1D.[8] Dose-dependent increases in C_{max} and AUCτ were observed for both dapagliflozin and D3OG. The ratio of the metabolite/parent compound was within the expected range in patients with T1D.[8]

In Japanese patients with T1D in this study, the dapagliflozin dose-UGE relationship was attenuated, which was unanticipated based on previous studies in T1D and T2D. The inhibition of urinary glucose reabsorption associated with dapagliflozin administration in Japanese patients with T1D was expected to produce dose-dependent glucose lowering similar to that previously observed in both healthy Japanese participants and those with T2D.[14]

Insulin dose reductions of more than 30% were seen in the Japanese patients with T1D in both dapagliflozin treatment groups in the present study. The reduction in insulin dose may have confounded

differences between the dapagliflozin treatment arms and from baseline. Treatment with dapagliflozin 5 mg and 10 mg as adjunct to adjustable insulin may improve glycaemic control in patients with T1D, while reducing insulin dose, as shown in a two-week proof-of-concept study outside Japan, in which reductions in insulin dose of −19.3% (95% CI, −30.1 to −6.8) and − 16.2% (95% CI, −29.4 to −0.5) were observed following administration of dapagliflozin 5 mg and 10 mg, respectively.[8] As reported by Henry et al., standardized diets and guidance on insulin dose adjustment took place during the inpatient treatment period and both patients and investigators were advised to adjust total daily insulin dose.[8] Dandona et al. monitored carbohydrate intake, together with insulin adjustments, to monitor insulin reduction so that it would not fall below 20%, as this restriction has been recommended before titrating back to baseline levels.[9] This limit on dose reduction was suggested to minimize the risk of hypoglycaemia, and to avoid inappropriate ketogenic reductions in the global pivotal studies. In the present study, the risk of DKA was monitored when insulin dose was reduced more than anticipated. As may be expected from these reductions in insulin dose, there were small elevations in ketones and reductions in bicarbonate, but without clinical manifestations, and no DKA events were observed.

The endpoints, treatment period and the major inclusion and exclusion criteria of this study were designed to allow for an indirect comparison with other studies involving non-Japanese participants and participants with T2D. An exposure-response non-linear mixed-effect modelling approach was used to characterize the relationship between dapagliflozin and 24-hour UGE in this study and in an international study of patients with T1D. The methodology and results are presented by Sokolov et al.[8,15] The model suggested that attenuation of the dose-response for UGE may be explained by the greater than expected reductions in insulin dose.[15] In addition, Sokolov et al. found that Japanese and Caucasian patients with T1D had similar dapagliflozin exposure-response relationships.

Dapagliflozin was well-tolerated in Japanese patients with T1D, with all AEs being mild or moderate in intensity. No relevant changes in vital signs were observed throughout the course of the study. Long-term safety studies are required to further assess this tolerability profile. A 52-week study has been conducted to evaluate the safety of dapagliflozin in Japanese patients with T1D.[16]

This study had some limitations. The study design was single-blinded, with the investigator unblinded and assisting with insulin dose adjustments. In addition, the trial did not include an insulin optimization period. Non-hospitalized patients may not have adequately controlled their glucose levels. The exploratory analyses necessary to interpret data in context were conducted *post-hoc*, to which the usual cautions apply.[17] The greater reductions in insulin dose in this study, and the resulting difference in SMBG at Day 7, should be considered in interpreting PD results.

In conclusion, the PK profile of dapagliflozin in Japanese patients with T1D was consistent with that observed in Caucasian patients with T1D. PK variables increased in a dose-dependent manner. However, there was attenuation of the PD dose-response measured as UGE. Studies on the efficacy of dapagliflozin in Japanese patients with T1D are required to support the favoured dose as adjunct to insulin therapy in this population. The safety profile of dapagliflozin in this study was consistent with previous studies.

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5 | CONFLICT OF INTEREST

W. T., M. A., S. U., H. K., D. W. B., T. Y. and F. T. are employees of AstraZeneca.

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Author contributions

Conception/design of the work: D. W. B., E. A., F. T., M. A., S. U., T. Y., W. T.; conduct and/or data collection: M.A., M. S., T. Y.; analysis/interpretation of the data: E. A., H. K., M. A., S. U., W. T., H. W.; writing first draft of manuscript: D. W. B., W. T.; critically revising manuscript for important intellectual content and providing approval of the final manuscript: D. W. B., E. A., F. T., H. K., H. W., M. A., M. S., S. U., T. Y., W. T.; agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved: D. W. B., E. A., F. T., H. K., H. W., M. A., M. S., S. U., T. Y., W. T.

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SUPPORTING INFORMATION

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

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