Efficacy and Safety of Dapagliflozin in Patients With Inadequately Controlled Type 1 Diabetes (the DEPICT-2 Study): 24-Week Results From a Randomized Controlled Trial

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https://doi.org/10.2337/dc18-0623

OBJECTIVE

This 24-week, double-blinded, phase 3 clinical trial (DEPICT-2; ClinicalTrials.gov, NCT02460978) evaluated efficacy and safety of dapagliflozin as adjunct therapy to adjustable insulin in patients with inadequately controlled type 1 diabetes (HbA_{1c} 7.5–10.5%).

RESEARCH DESIGN AND METHODS

Patients were randomized 1:1:1 to dapagliflozin 5 mg (*n* = 271), dapagliflozin 10 mg (*n* = 270), or placebo (*n* = 272) plus insulin. Insulin dose was adjusted by investigators according to self-monitored glucose readings, local guidance, and individual circumstances.

RESULTS

Baseline characteristics were balanced between treatment groups. At week 24, dapagliflozin significantly decreased HbA_{1c} (primary outcome; difference vs. placebo: dapagliflozin 5 mg −0.37% [95% CI −0.49, −0.26], dapagliflozin 10 mg –0.42% [−0.53, −0.30]), total daily insulin dose (−10.78% [−13.73, −7.72] and −11.08% [−14.04, −8.02], respectively), and body weight (−3.21% [−3.96, −2.45] and −3.74% [−4.49, −2.99], respectively) ($P < 0.0001$ for all). Mean interstitial glucose, amplitude of glucose excursion, and percent of readings within target glycemic range (>70 to ≤180 mg/dL) versus placebo were significantly improved. More patients receiving dapagliflozin achieved a reduction in HbA_{1c} ≥0.5% without severe hypoglycemia compared with placebo. Adverse events were reported for 72.7%, 67.0%, and 63.2% of patients receiving dapagliflozin 5 mg, dapagliflozin 10 mg, and placebo, respectively. Hypoglycemia, including severe hypoglycemia, was balanced between groups. There were more adjudicated definite diabetic ketoacidosis (DKA) events with dapagliflozin: 2.6%, 2.2%, and 0% for dapagliflozin 5 mg, dapagliflozin 10 mg, and placebo, respectively.

CONCLUSIONS

Dapagliflozin as adjunct therapy to adjustable insulin in patients with type 1 diabetes was well tolerated and improved glycemic control with no increase in hypoglycemia versus placebo but with more DKA events.

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Received 21 March 2018 and accepted 18 June 2018.

Clinical trial reg. no. NCT02460978, clinicaltrials.gov.

This article contains Supplementary Data online at http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc18-0623/-/DC1.

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**A complete list of the DEPICT-2 Investigators can be found in the Supplementary Data online.*

See accompanying articles, pp. 1970 and 1981.

Less than one-third of patients with type 1 diabetes achieve optimal glycemic control (HbA_{1c} <7% [<53 mmol/mol]) (1,2). Even when target HbA_{1c} levels are achieved, there is still evidence for excess mortality in patients with type 1 diabetes (3). Insulin therapy is the mainstay of treatment (4); however, it is associated with hypoglycemia (5–7) and weight gain (8), both of which are important cardiovascular risk factors (9,10). Occurrence of hypoglycemia hinders the achievement of glycemic targets and affects the quality of life of patients (11–13), and severe hypoglycemia is a potentially serious event. Other challenges for patients with type 1 diabetes include excessive glycemic variability and hypoglycemia unawareness (11). Thus, strategies to improve glycemic control, without increasing hypoglycemia or weight gain, would fulfill an unmet need.

Sodium–glucose cotransporter 2 (SGLT2) inhibitors are insulin-independent, glucose-dependent antihyperglycemic agents that have demonstrated potential for use as adjunct therapy to insulin in the treatment of type 1 diabetes, providing additional treatment benefits such as weight loss and decreased glycemic variability. Dapagliflozin, an SGLT2 inhibitor approved for the treatment of type 2 diabetes, and sotagliflozin, a nonselective SGLT2/SGLT1 inhibitor, have shown promise as adjunct treatments for type 1 diabetes in previous studies (14–17). The recent randomized, placebo-controlled, phase 3, 24-week DEPICT-1 (Efficacy and safety of dapagliflozin in patients with inadequately controlled type 1 diabetes [16]) study demonstrated that when used as adjunct therapy to adjustable insulin in patients with inadequately controlled type 1 diabetes, dapagliflozin significantly decreased HbA_{1c}, body weight, total insulin dose, and glycemic variability. Treatment was generally well tolerated, with similar levels of hypoglycemia compared with placebo (16). The overall adverse event (AE) profile was consistent with that observed in patients with type 2 diabetes. There were few events of diabetic ketoacidosis (DKA), and these were manageable with standard care.

Similar to the DEPICT-1 study, the current 24-week DEPICT-2 study investigated the efficacy and safety of dapagliflozin as adjunct therapy to adjustable insulin, providing further supportive evidence for its use in the treatment of type 1 diabetes.

RESEARCH DESIGN AND METHODS

Study Design

DEPICT-2 was the second of two randomized, double-blind, parallel-controlled, three-arm, multicenter, phase 3 studies evaluating the efficacy and safety of dapagliflozin 5 mg and 10 mg as adjunct therapy to adjustable insulin in adult patients with type 1 diabetes and inadequate glycemic control. The methodology has been published previously (16). The study was conducted at 148 sites in the following countries: Argentina, Belgium, Canada, Chile, Germany, Japan, the Netherlands, Poland, the Russian Federation, Sweden, Switzerland, the U.K., and the U.S., in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines as defined by the International Council for Harmonisation. It was approved by the institutional review boards and independent ethics committees for all participating centers. All participants provided written informed consent. For Japanese patients ≥18 to <20 years old, informed consent was obtained from their parents/guardians. The DEPICT-2 study is registered on ClinicalTrials.gov (NCT02460978).

Study Participants

This study included adult patients with inadequately controlled type 1 diabetes (HbA_{1c} 7.7–11.0% [61–97 mmol/mol] at screening/enrollment; 7.5–10.5% [58–91 mmol/mol] at randomization) receiving adjustable insulin via multiple daily injections (MDI) or continuous subcutaneous insulin infusion (CSII) for ≥12 months prior to screening (total insulin dose ≥0.3 IU/kg/day for ≥3 months prior to screening), and with C-peptide <0.7 ng/mL and BMI ≥18.5 kg/m^2. Patients were excluded if they had type 2 diabetes, a history of pancreatic surgery, chronic pancreatitis, or other pancreatic disorders resulting in decreased β-cell capacity, signs of poorly controlled diabetes (including DKA requiring medical intervention or hospitalization for hyperglycemia or hypoglycemia within 1 month prior to screening), cardiovascular disease (within 6 months prior to screening), unstable/rapidly progressing renal disease, significant hepatic disease, or malignancy (within 5 years) or had previously used any SGLT2 inhibitor. A comprehensive list of inclusion and exclusion criteria is provided in Supplementary Table 1.

Study Medications and Procedures

Eligible patients entered an 8-week lead-in period to optimize diabetes management. On completing the lead-in period, patients with an HbA_{1c} of 7.5–10.5% (58–91 mmol/mol) were randomized 1:1:1 using an interactive voice/web response system to oral dapagliflozin 5 mg, dapagliflozin 10 mg, or placebo once daily. Patients were stratified by use of continuous glucose monitoring (CGM) at baseline (in which case they would continue to use their own device during the study in addition to the masked study CGM), use of CSII or MDI for insulin administration at baseline, and baseline HbA_{1c} (7.5 to <9.0% [58 to <75 mmol/mol] or 9.0–10.5% [75–91 mmol/mol]). The lead-in period was followed by a 24-week, short-term, double-blind treatment period and a 28-week, long-term subject- and site-blinded extension phase assessing safety, followed by a 4-week follow-up period. The 24-week results are reported here.

Glycemic control (including self-monitoring of blood glucose [SMBG]) and home ketone (β-hydroxybutyrate [BOHB]) measurements were assessed at each study visit. Insulin doses were adjusted as deemed appropriate by the investigator, based on SMBG readings (recommended four times per day at a minimum and six times per day during protocol-specified periods of intense glucose monitoring), local guidance, and individual circumstances. The protocol did not specify uniform insulin titration algorithms. After the first dose of the study drug, the daily insulin dose was recommended to be reduced by up to 20% to balance the risk of hypoglycemia and DKA due to excessive insulin dose reduction (14,18,19), before subsequently attempting to titrate it back as far as possible to baseline levels. Events of potential DKA were monitored throughout the study. Patients were educated on identifying potential signs/symptoms of DKA and its management at each visit and were provided with combined glucose and ketone meters and instructions for use. Patients were required to record blood ketone

test results and relevant risk factors and contact the study site if their self-measured blood ketone reading was ≥0.6 mmol/L, irrespective of glucose values to avoid missing any events of euglycemic DKA. CGM was done using the electronic CGM sensor, Dexcom G4 platinum, over 2-week periods. Patients were trained to wear and operate the sensor as required for the study according to the manufacturer's instructions. Supplementary Table 2 provides additional details about the study methodology.

Outcomes

The primary efficacy outcome was the change in HbA_{1c} from baseline after 24 weeks of double-blinded treatment with dapagliflozin 5 mg or dapagliflozin 10 mg plus adjustable insulin versus placebo plus adjustable insulin. A sensitivity analysis for the primary efficacy end point was performed for patients who discontinued treatment early and did not have HbA_{1c} measurements at week 24. Secondary efficacy outcomes included evaluation of the following changes from baseline after 24 weeks of study treatment: percent change in total daily insulin dose (TDD); percent change in body weight; masked CGM end points, including change in mean value of 24-h glucose readings, change in mean amplitude of glucose excursion (MAGE; the arithmetic mean of the blood glucose increases or decreases when both ascending and descending segments exceeded the value of 1 SD of the blood glucose for the same 24-h period [20]), and change in the percent of 24-h glucose readings within the target range of >70 to ≤180 mg/dL (>3.9 to ≤10.0 mmol/L); and finally, the proportion of patients achieving an HbA_{1c} decrease of ≥0.5% without severe hypoglycemia. The proportion of patients achieving HbA_{1c} reduction of ≥0.5% and those achieving HbA_{1c} <7% after 24 weeks of treatment were investigated as exploratory outcomes.

Safety and tolerability were evaluated throughout the study by assessing AEs and serious AEs (SAEs), vital signs, physical examination findings, electrocardiogram and laboratory values, and home BOHB readings. AEs of special interest included hypoglycemia, DKA, hepatobiliary AEs, genital infections, urinary tract infections, volume depletion, fractures, worsening renal function, hypersensitivity, and cardiovascular AEs. Hypoglycemia was classified according to the American Diabetes Association (ADA) classification criteria (21) into severe hypoglycemia (requiring assistance of another person to raise glucose levels and promote neurological recovery), documented symptomatic hypoglycemia (featuring typical hypoglycemia symptoms and a plasma glucose concentration ≤70 mg/dL [≤3.9 mmol/L]), asymptomatic hypoglycemia (unaccompanied by typical hypoglycemia symptoms, but with plasma glucose ≤70 mg/dL [≤3.9 mmol/L]), probable symptomatic hypoglycemia (typical hypoglycemia symptoms but without a plasma glucose determination), and pseudo/relative hypoglycemia (patient-reported hypoglycemia symptoms with plasma glucose >70 mg/dL [>3.9 mmol/L] but approaching that level). Glucose levels used in the analysis of hypoglycemia were based on capillary, patient-measured, SMBG values.

Events of potential DKA were identified based on symptoms, diagnoses, or home ketone values. Additionally, investigators were asked whether AEs satisfying a wide list of preferred terms (from MedDRA queries) could be potential DKA events. All such events were then adjudicated by an independent blinded DKA Adjudication Committee and classified as definite, possible, or unlikely DKA. Definite DKA cases were confirmed by the presence of acidosis, diagnosis of low blood pH of <7.3, decreased serum bicarbonate levels (≤18 mEq/L), and symptoms/signs, as listed by the ADA consensus statement on diagnosis of DKA (22). The other two adjudication categories, "possible" and "unlikely," were not explicitly defined. Hyperglycemia was not included in the criteria in order to not miss any events of euglycemic DKA.

Sample Size and Power

To detect a difference in mean HbA_{1c} of 0.35% between each dapagliflozin treatment group and placebo at the two-sided 0.0262 significance level (based on Dunnett and Tamhane step-up procedure) (23), with an SD of 1.1%, 243 patients were required in each treatment group to provide ~90% power. Assuming that 5% of patients would not have a postbaseline assessment, 768 patients (256 patients per treatment arm) were planned to be randomized to one of the three treatment groups in a 1:1:1 ratio. Among these 768 subjects, ~160 were planned to be enrolled in Japan.

Statistical Analysis

Efficacy analyses were performed on the full analysis set, comprising all randomized patients receiving one or more doses of study medication during the short-term double-blind period, who had a baseline and any postbaseline assessment. Safety analyses were performed on the safety analysis set, comprising all randomized patients receiving one or more doses of study medication. Treatment effects were determined through pairwise comparisons between each dapagliflozin group and placebo.

For an overall type I error rate of 5% for the primary end point, a Dunnett and Tamhane step-up procedure (23) was used. This allowed for the correlation of 0.5 between the standard normal deviate for each comparison. Statistical significance would be declared for both doses at the two-sided 5% level if the two-sided *P* values from both pairwise comparisons were smaller than 5%. If the larger *P* value among the two pairwise comparisons was greater than 5% and the smaller *P* value was below 2.62%, then statistical significance would be declared for the latter comparison. Statistical analyses for secondary efficacy end points were only conducted if there was a statistically significant difference in the primary end point for both pairwise comparisons (i.e., dapagliflozin 5 mg vs. placebo and dapagliflozin 10 mg vs. placebo) using the Dunnett and Tamhane step-up procedure (23). The primary estimand for the primary end point was treatment difference at week 24 if subjects did not discontinue randomized treatment. The primary analysis of the change in HbA_{1c} from baseline to week 24 was based on a longitudinal repeated-measures analysis using direct likelihood. The model included the fixed categorical effects of treatment, week, randomization stratification factor (one term for each combination of all stratification factors), and treatment-by-week interaction as well as the continuous fixed covariates of baseline measurement and baseline measurement-by-week interaction.

For secondary end points, point estimates and two-sided 95% CI for the mean change within each treatment group and the difference in mean change between

each dapagliflozin treatment group and placebo were calculated. The *T* statistics corresponding to the type III sums of squares for the differences in the least squares means between each dapagliflozin group and placebo at week 24 were calculated. For efficacy parameters measured during every visit (e.g., parameters from CGM or from six-point SMBG), longitudinal repeated-measures analyses using direct likelihood and the SAS procedure PROC MIXED were used. Relevant protocol deviations (those having the potential to impact the results of the primary analysis) were reviewed prior to the unblinding of the study.

The proportion of subjects achieving an HbA_{1c} reduction of ≥0.5% at week 24 and the proportion of patients achieving an HbA_{1c} <7% at week 24 were analyzed using logistic regression with adjustment for baseline HbA_{1c} and stratum and using last observation carried forward. Odds ratios (ORs) and corresponding 95% CIs for each treatment group versus placebo were presented for each of these end points.

RESULTS

Patient Disposition

Between 8 July 2015 and 2 September 2017, 1,465 patients were enrolled in the study, of which 815 were randomly assigned to either dapagliflozin 5 mg (*n* = 271), dapagliflozin 10 mg (*n* = 270), or placebo (*n* = 272); two patients were randomized but not dosed (Fig. 1). Overall, 728 patients (89.5%) completed the double-blind treatment period. The main reasons for study discontinuation were occurrence of AEs (4.8%), withdrawal of consent by the patient (1.7%), and patient request for treatment discontinuation (1.2%).

Patients

Baseline characteristics and demographics were balanced across treatment groups (Table 1). The mean age of the study population was 42.7 years, with a mean time since diagnosis of type 1 diabetes of 19.3 years. The majority of the patients were white (78.4%), and overall, 34.6%, 33.5%, and 18.9% of the patients were from North America, Europe, and Japan, respectively. The mean baseline HbA_{1c} was 8.43%, mean baseline body weight was 79.2 kg, and mean baseline BMI was 27.6 kg/m^2. The mean TDD at baseline was 57.81 IU (0.72 IU/kg), with 537 patients (66.1%) using MDI and 276 (33.9%) using CSII; 258 patients (31.7%) were using CGM at baseline.

Efficacy

At week 24, there were significant reductions in HbA_{1c} with both dapagliflozin doses versus placebo. Mean changes (95% CI) in HbA_{1c} from baseline to week 24 versus placebo were −0.37% (−0.49, −0.26; $P < 0.0001$) and −0.42% (−0.53, −0.30; $P < 0.0001$) (Fig. 2*A*) for dapagliflozin 5 mg and 10 mg, respectively. The initial reduction in HbA_{1c} was observed in the first 4 weeks and the effect was maintained throughout the study. A sensitivity analysis showed that these results were not affected by missing data (Supplementary Table 3). Other changes in HbA_{1c} based on subgroup analyses (use of CGM and method of insulin administration) have been detailed in Supplementary Tables 4 and 5.

At week 24, dapagliflozin had significant effects on all secondary end points. Mean percent change (95% CI) in TDD from baseline to week 24 for dapagliflozin 5 mg and 10 mg versus placebo was −10.78% (−13.73, −7.72; $P < 0.0001$) and −11.08% (−14.04, −8.02; $P < 0.0001$) (Fig. 2*B*), respectively. Reductions in TDD occurred in the first 2 weeks of treatment and were maintained thereafter throughout the study. At week 24, adjusted mean changes (SE) for basal insulin for dapagliflozin 5 mg, dapagliflozin 10 mg, and placebo were −11.19% (1.5), −16.71% (1.4), and 1.46% (1.7), respectively; for bolus insulin, these were −11.60% (2.0), −8.30%

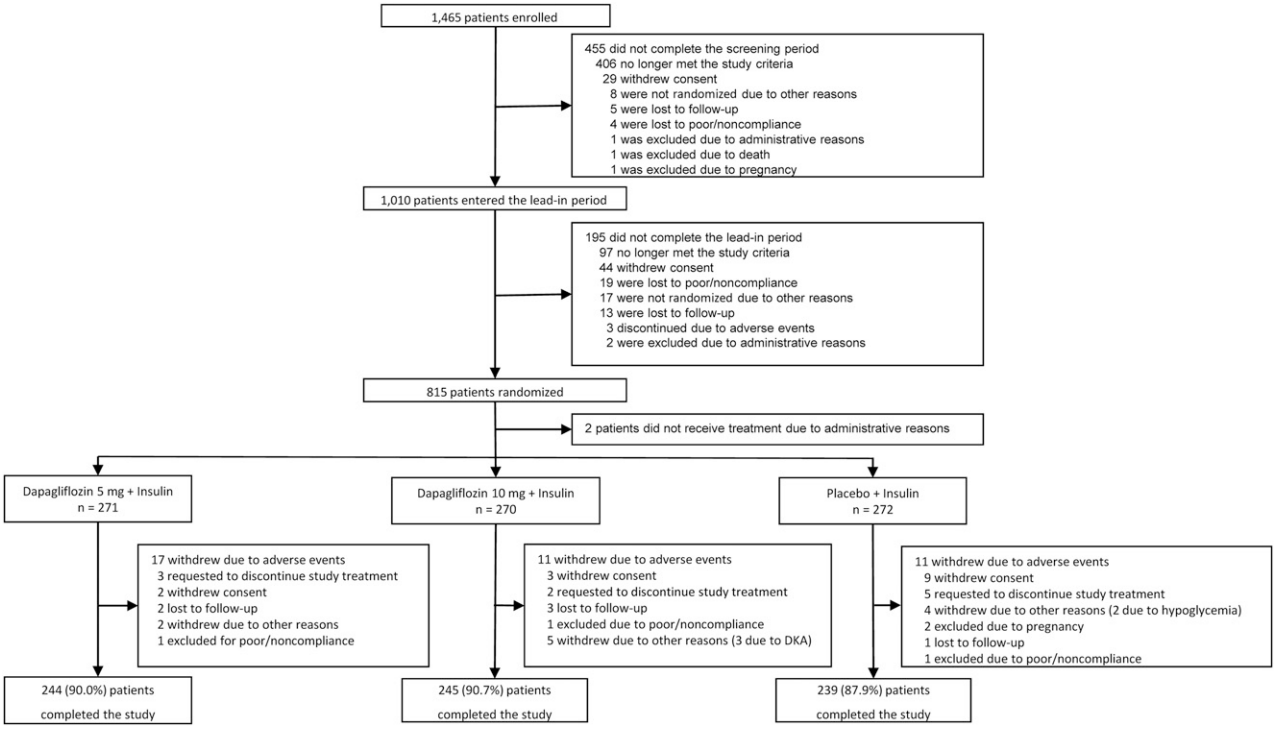

Figure 1—Patient disposition.

Table 1—Demographic and baseline characteristics

Characteristic	Dapagliflozin 5 mg + insulin (*n* = 271)	Dapagliflozin 10 mg + insulin (*n* = 270)	Placebo + insulin (*n* = 272)
Sex			
Male	118 (43.5%)	121 (44.8%)	119 (43.8%)
Female	153 (56.5%)	149 (55.2%)	153 (56.3%)
Age (years)	42.7 (13.35)	42.4 (12.80)	43.0 (13.73)
Body weight (kg)	78.74 (17.38)	80.06 (18.30)	78.88 (18.87)
BMI (kg/m^2)	27.27 (5.13)	27.80 (5.53)	27.62 (5.41)
Race			
White	210 (77.5%)	219 (81.1%)	208 (76.5%)
Black or African American	4 (1.5%)	7 (2.6%)	1 (0.4%)
Asian	57 (21.0%)	44 (16.3%)	59 (21.7%)
Other	0	0	4 (1.5)
Geographic region			
North America	96 (35.4%)	96 (35.6%)	89 (32.7%)
Latin America	41 (15.1%)	32 (11.9%)	33 (12.1%)
Europe	79 (29.2%)	101 (37.4%)	92 (33.8%)
Asia-Pacific	55 (20.3%)	41 (15.2%)	58 (21.3%)
Duration of T1D (years)	19.35 (11.79)	19.45 (11.90)	18.98 (11.65)
Total baseline insulin dose			
Dose (IU)	58.19 (27.93)	58.68 (28.26)	56.57 (25.23)
Dose/weight (IU/kg)	0.73 (0.26)	0.73 (0.27)	0.71 (0.24)
Method of insulin administration			
MDI	179 (66.1%)	178 (65.9%)	180 (66.2%)
CSII	92 (33.9%)	92 (34.1%)	92 (33.8%)
Use of CGM (Yes)	88 (32.5%)	85 (31.5%)	85 (31.3%)
HbA_{1c} (%)	8.45 (0.69)	8.43 (0.69)	8.43 (0.65)
HbA_{1c} (mmol/mol)	69 (7.5)	69 (7.5)	69 (7.1)
HbA_{1c} at randomization			
≥7.5% and <9.0%	211 (77.9%)	210 (77.8%)	211 (77.6%)
≥9.0% and ≤10.5%	60 (22.1%)	60 (22.2%)	61 (22.4%)

Data are *n* (%) or mean (SD). T1D, type 1 diabetes.

(2.1), and −2.59% (2.2), respectively. Compared with placebo, mean change (95% CI) in body weight from baseline to week 24 was −3.21% (−3.96, −2.45; $P < 0.0001$) for dapagliflozin 5 mg and −3.74% (−4.49, −2.99; $P < 0.0001$) for 10 mg (Fig. 2*C*). Reduction in body weight was consistent through the study, without plateauing at week 24.

At week 24, a greater proportion of patients on dapagliflozin showed an HbA_{1c} reduction of ≥0.5% without severe hypoglycemia (dapagliflozin 5 mg: 105 of 266, 39.5%; 10 mg: 111 of 267, 41.6%; placebo: 54 of 269, 20.1%). The OR (95% CI) versus placebo for achieving an HbA_{1c} reduction of ≥0.5% without experiencing severe hypoglycemia was statistically significant for both dapagliflozin doses: 2.71 (1.81, 4.06) for dapagliflozin 5 mg versus placebo and 3.07 (2.05, 4.60) for dapagliflozin 10 mg versus placebo ($P < 0.0001$ for both) (Fig. 2*D*). After 24 weeks of treatment, the proportion of patients achieving an HbA_{1c} reduction of ≥0.5% after 24 weeks of treatment was 42.9%, 44.6%, and 21.2% for dapagliflozin 5 mg, dapagliflozin 10 mg, and placebo, respectively (OR for dapagliflozin 5 mg vs. placebo, 2.97 [95% CI 1.99, 4.42]; OR for dapagliflozin 10 mg vs. placebo, 3.30 [2.22, 4.92]). Given that the lower bound of HbA_{1c} at inclusion was 7.5% at baseline, a relatively small proportion of patients achieved an HbA_{1c} of <7% after 24 weeks of treatment. The percentages were 4.9%, 3.7%, and 1.5% for dapagliflozin 5 mg, dapagliflozin 10 mg, and placebo, respectively (OR for dapagliflozin 5 mg vs. placebo, 3.55 [95% CI 1.12, 11.18]; OR for dapagliflozin 10 mg vs. placebo, 2.45 [0.75, 8.03]).

Based on the CGM data, the change in mean interstitial glucose, MAGE, and time in the target glycemic range from baseline to week 24 showed significant improvements for both dapagliflozin doses versus placebo (Supplementary Table 6). Mean change from baseline (95% CI) in 24-h CGM values at week 24 versus placebo was –15.66 mg/dL (–20.26, –11.05; $P < 0.0001$) and –19.74 mg/dL (–24.34, –15.14; $P < 0.0001$) for dapagliflozin 5 mg and 10 mg, respectively. Mean change (95% CI) in MAGE at week 24 from baseline versus placebo was –9.85 mg/dL (–14.66, –5.03; $P < 0.0001$) for dapagliflozin 5 mg and –9.36 mg/dL (–14.16, –4.55; $P = 0.0001$) for dapagliflozin 10 mg. Mean change from baseline (95% CI) versus placebo in the 24-h CGM values within the target glucose range (>70 to ≤180 mg/dL [>3.9 to ≤10.0 mmol/L]) at week 24 was 9.02% (6.97, 11.06; $P < 0.0001$) and 10.70% (8.66, 12.74; $P < 0.0001$) for dapagliflozin 5 mg and 10 mg, respectively. More than 50% of the CGM readings were in the target range at week 24 for the dapagliflozin groups.

Safety

AEs were reported for 72.7%, 67.0%, and 63.2% of the patients receiving dapagliflozin 5 mg, dapagliflozin 10 mg, and placebo, respectively, and SAEs were reported for 6.6%, 2.6%, and 1.8% of the patients (Table 2). The majority of AEs were of mild or moderate intensity.

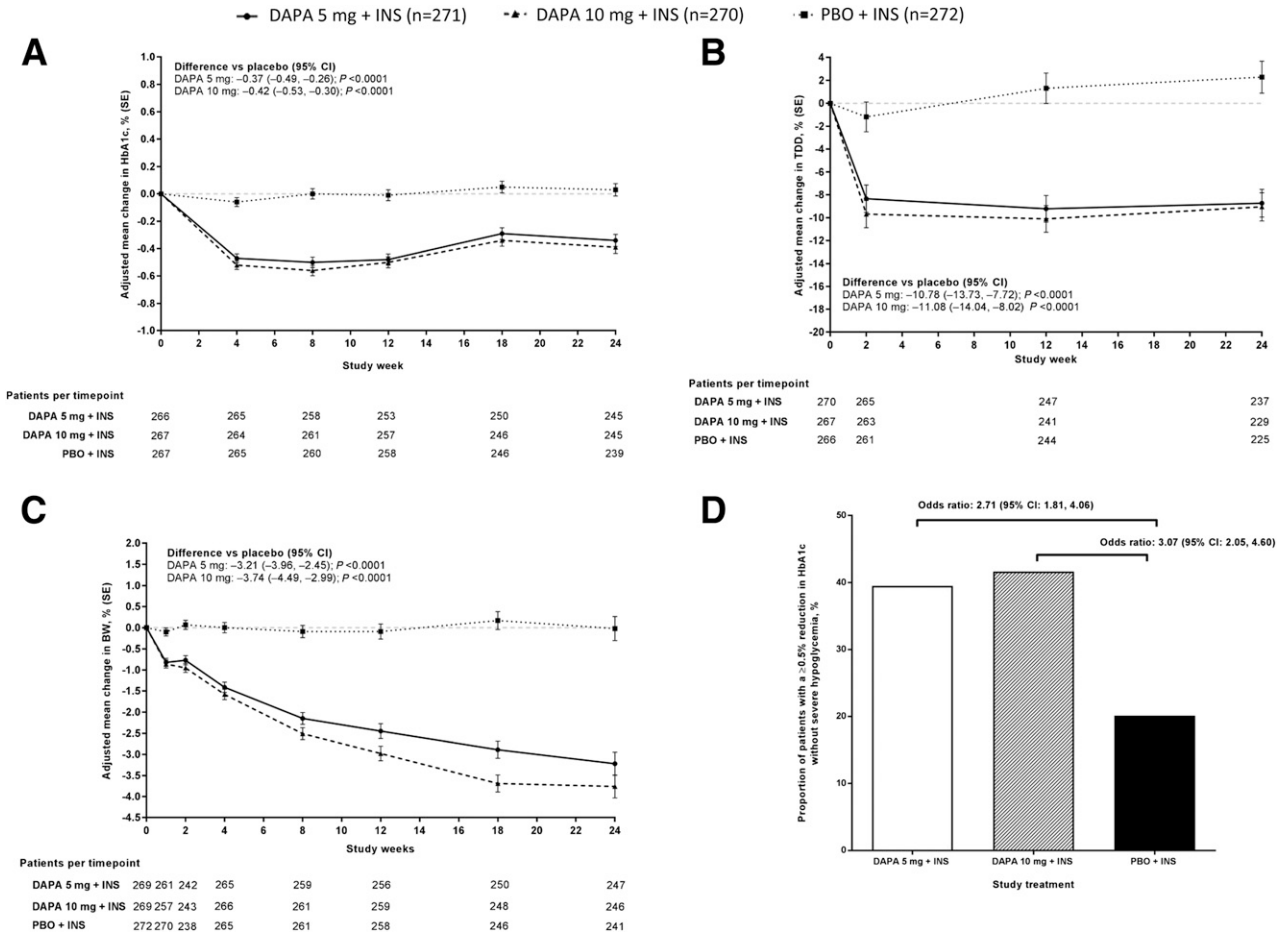

Figure 2—Change in HbA_{1c} (%) (*A*), TDD (%) (*B*), and total body weight (kg) over 24 weeks (*C*), and proportion of patients achieving an HbA_{1c} reduction of ≥0.5% without severe hypoglycemia (%) at week 24 (*D*). Patients per timepoint indicate the number of patients with data at that timepoint as defined by the visit windows in the protocol regardless of whether that patient was still receiving randomized treatment. BL, baseline; BW, body weight; DAPA, dapagliflozin; INS, insulin; PBO, placebo; TDD, total daily dose of insulin.

Discontinuations due to AEs occurred in 6.3%, 4.4%, and 4.0% of subjects in the dapagliflozin 5 mg, dapagliflozin 10 mg, and placebo groups, respectively. There was one death during the screening period and none during the double-blind period.

The most common AEs were viral upper respiratory tract infection (occurring in 39 [14.4%], 44 [16.3%], and 42 [15.4%] patients in the dapagliflozin 5 mg, dapagliflozin 10 mg, and placebo groups, respectively), upper respiratory tract infection (in 16 [5.9%], 12 [4.4%], and 12 [4.4%] patients), headache (in 10 [3.7%], 15 [5.6%], and 10 [3.7%] patients), and pollakiuria (in 22 [8.1%], 14 [5.2%], and 6 [2.2%] patients). There were few cardiovascular (one, three, and two in the dapagliflozin 5 mg, dapagliflozin 10 mg, and placebo groups, respectively) or hepatic events (five, five, and six). Genital infections were more common in the dapagliflozin groups versus placebo, with a similar frequency in both dapagliflozin groups, and these occurred more commonly in females than in males (dapagliflozin 5 mg: 15.7% vs. 2.5%; dapagliflozin 10 mg: 12.8% vs. 1.7%; placebo: 3.3% vs. 0%). SAEs of genital infection were not reported in any treatment group. Occurrence of urinary tract infection was balanced across treatment groups but was more common in females than in males (dapagliflozin 5 mg: 11.8% vs. 0%; dapagliflozin 10 mg: 6.0% vs. 0.8%; placebo: 7.2% vs. 0.8%).

Overall, a similar proportion of subjects in each treatment group experienced hypoglycemia and severe hypoglycemia (hypoglycemia: 82.3%, 85.6%, and 86.0% of patients receiving dapagliflozin 5 mg, dapagliflozin 10 mg, and placebo, respectively; severe hypoglycemia: 6.3%, 8.5%, and 7.7%). Occurrence of different types of hypoglycemia based on ADA classification is shown in Supplementary Table 7. Two (0.7%) patients receiving dapagliflozin 5 mg discontinued medication due to an SAE of hypoglycemia.

DKA events adjudicated as definite, possible, or unlikely are shown in Table 2; only definite events had findings consistent with the ADA definition (22), but without the requirement for hyperglycemia, as outlined in the adjudication charter. Thirteen definite DKA events were observed (7 [2.6%], 6 [2.2%], and 0 patients receiving dapagliflozin 5 mg, dapagliflozin 10 mg, and placebo, respectively). Of these, 10 were SAEs, with 6 and 4 events in the dapagliflozin 5 and 10 mg groups, respectively. All but three events in three patients were documented as receiving conventional DKA treatment, including administration of i.v. fluids and insulin. Of the three aforementioned patients, two received only i.v. fluids as treatment for DKA and one patient did not have treatment recorded.

Table 2—Safety summary

Characteristic	Dapagliflozin 5 mg + insulin (*n* = 271)	Dapagliflozin 10 mg + insulin (*n* = 270)	Placebo + insulin (*n* = 272)
AEs			
≥1 AEs	197 (72.7%)	181 (67.0%)	172 (63.2%)
≥1 AEs related to the study drug	78 (28.8%)	71 (26.3%)	32 (11.8%)
AE leading to study discontinuation	17 (6.3%)	12 (4.4%)	11 (4.0%)
AEs of special interest			
Genital infection	27 (10.0%)	21 (7.8%)	5 (1.8%)
Urinary tract infection	18 (6.6%)	10 (3.7%)	12 (4.4%)
Renal impairment/failure	2 (0.7%)	0	0
Fractures	4 (1.5%)	3 (1.1%)	2 (0.7%)
Hypotension/dehydration/hypovolemia	8 (3.0%)	2 (0.7%)	2 (0.7%)
Hypersensitivity	18 (6.6%)	10 (3.7%)	17 (6.3)
Cardiovascular events	1 (0.4%)	3 (1.1%)	2 (0.7%)
SAEs			
≥1 SAEs	18 (6.6%)	7 (2.6%)	5 (1.8%)
≥1 SAEs related to the study drug	13 (4.8%)	3 (1.1%)	2 (0.7%)
SAEs leading to study discontinuation	12 (4.4%)	3 (1.1%)	3 (1.1%)
Death	0	0	0
Hypoglycemia			
≥1 SAE of hypoglycemia	5 (1.8%)	0	1 (0.4%)
Hypoglycemia leading to study discontinuation	2 (0.7%)	0	0
Ketone-related events			
≥1 ketone-related SAEs	9 (3.3%)	3 (1.1%)	0
Ketone-related SAE leading to study discontinuation	8 (3.0%)	2 (0.7%)	0
Adjudicated definite DKA			
Number of patients with definite DKA	7 (2.6%)	6 (2.2%)	0
Number of events adjudicated as definite DKA	7 (25.0%)	6 (33.3%)	0
Incidence rate per 100 patient-years	5.83	4.99	0
Number of CSII users experiencing definite DKA	6 (6.5%)	3 (3.3%)	0
Male-to-female ratio in patients experiencing definite DKA	2:5	1:5	0
Severity of adjudicated DKA events			
Mild	3 (42.9%)	3 (50.0%)	NA
Moderate	3 (42.9%)	1 (16.7%)	NA
Severe	1 (14.3%)	2 (33.3%)	NA
Primary cause for adjudicated definite DKA events			
Insulin pump failure	1 (14.3%)	2 (33.3%)	0
Missed insulin dose	2 (28.6%)	1 (16.7%)	0
Not identified	4 (57.1%)	0	0
Other	0	3 (50.0%)*	0
Mean percent TDD (IU) reduction compared with baseline for week before DKA event†	−16.83	−21.97	NA
Mean percent TDD (IU) reduction compared with baseline at the end of 24-week treatment period†	−15.68	−22.93	NA
Events adjudicated as not DKA			
Number of patients with event(s) adjudicated as possible DKA	6 (2.2%)	4 (1.5%)	2 (0.7%)
Number of events adjudicated as possible DKA	7 (25.0%)	4 (22.2%)	2 (13.3%)
Number of patients with event(s) adjudicated as unlikely DKA	8 (3.0%)	4 (1.5%)	7 (2.6%)
Number of events adjudicated as unlikely DKA	14 (50.0%)	8 (44.4%)	13 (86.7%)

All data are *n* (%) unless otherwise indicated. The table includes non-SAEs with onset on or after the first date/time of double-blind treatment and on or prior to the last day of short-term double-blind treatment plus 4 days or up to the start date of the long-term period if earlier. The table includes SAEs with onset on or after the first date/time of double-blind treatment and on or prior to the last day of short-term double-blind treatment plus 30 days or up to the start date of the long-term period if earlier. Only hypoglycemia and DKA reported by the investigator as SAE are included in the AE, related AE, SAE, related SAE, and AE leading to discontinuation summary lines. All reported hypoglycemia events and events sent for DKA adjudication with onset within 4 days of last day of treatment are included in the hypoglycemia and events sent for DKA adjudication lines, respectively. NA, not applicable. *Cause for DKA included alcohol intake, stress, and stroke. †Means apply for patients with definite DKA.

Insulin pump failure and missed insulin dose were the most common primary causes of definite DKA. Events identified as possible or unlikely did not fulfill the ADA criteria. Conventional DKA treatment with i.v. fluids and insulin was only documented for two of the possible events. Two of the possible DKA events (both in the dapagliflozin 5 mg group) and none of the unlikely events were reported as SAEs. Euglycemic DKA, defined as plasma glucose <250 mg/dL on

the home meter when highest BOHB levels are observed, occurred in two events of definite DKA in those receiving dapagliflozin 5 mg and in one event in a subject receiving dapagliflozin 10 mg. Data on concurrent glucose and BOHB were not available for six events. Details about self-monitored blood ketone measurements and a listing of maximum ketone values for patients with definite DKA events are provided in Supplementary Tables 8 and 9.

CONCLUSIONS

DEPICT-2 is the second of two randomized, double-blind, phase 3 studies evaluating the efficacy and safety of dapagliflozin as adjunct therapy to adjustable insulin in adult patients with inadequately controlled type 1 diabetes. The study design is the same as that of the 24-week DEPICT-1 study. However, there are some differences between the studies, such as fewer site visits in the DEPICT-2 study and the geographical footprint of DEPICT-2, which included patients from North America, Latin America, Europe, and Japan (with 19.7% Asian and 18.9% Japanese patients). In contrast, the DEPICT-1 study predominantly had European (59.3%) and North American (27.0%) populations, with only 3.6% of patients from the Asia-Pacific region (Australia).

Consistent with the DEPICT-1 results, in the current study, dapagliflozin significantly improved glycemic control, mean glucose levels, glycemic variability, and time in glycemic target range and decreased body weight and TDD. Treatment was well tolerated, with no increase in hypoglycemia compared with placebo. This strengthens the weight of evidence that dapagliflozin could play an important role in the management of type 1 diabetes, helping to address several important unmet treatment needs, including improved glycemic control with decreased glycemic variability, weight loss, and decrease in insulin dose.

The results seen with dapagliflozin in the DEPICT studies are broadly aligned with those seen in the phase 3 InTandem3 study, which examined the effects of sotagliflozin, a nonselective SGLT2/SGLT1 inhibitor, added to insulin treatment in patients with type 1 diabetes (17). Direct comparisons between the DEPICT studies and InTandem3 are difficult as definitions around safety events could potentially differ. Further, InTandem3 had particular instructions for insulin adjustment, whereas in the DEPICT studies, insulin dose was adjusted as deemed appropriate by the investigator, local guidance, and individual circumstances. No results are yet reported from ongoing phase 3 studies of other selective SGLT2 inhibitors in type 1 diabetes, such as the empagliflozin EASE studies (24,25).

Benefits of using SGLT2 inhibitors in the treatment of type 1 diabetes should be balanced against the increased risk of DKA. The incidence of definite DKA events in DEPICT-2 was higher compared with DEPICT-1 (dapagliflozin 5 mg vs. dapagliflozin 10 mg vs. placebo: 5.83, 4.99, and 0 per 100 patient-years in DEPICT-2, respectively; 3.29, 3.78, and 2.64 per 100 patient-years in DEPICT-1). This difference between the studies does not appear to be related to the study conduct or geography, since the studies were very similar and the events tended to occur in the same regions in both studies. We postulate that chance variability due to the small number of events is a more likely explanation for the interstudy differences. Further, the risk factors for developing DKA in DEPICT-2 were generally consistent with those seen in other studies of SGLT2 inhibitors in the treatment of type 1 diabetes (17,19,26), with events often associated with missed insulin doses or insulin pump failure. The imbalance in DKA events seen in the dapagliflozin versus placebo groups in DEPICT-2, despite receiving the same education and monitoring instructions as in DEPICT-1, suggests that if approved for the indication, the DKA risk should be carefully considered if using dapagliflozin for the treatment of type 1 diabetes in the real world. It must be noted that when they did occur, events of DKA were resolved using conventional treatment. The increased risk of DKA when using dapagliflozin in type 1 treatment may be partly mitigated by educating patients about the risk factors for DKA and by ensuring that they are able to monitor blood glucose regularly as well as ketones. Avoiding excessive insulin dose reductions (>20% reduction) on initiation of adjunct dapagliflozin therapy (14,16,18,19) and subsequent caution in insulin dose reduction during treatment may be important to mitigate the risk of DKA. Any insulin dose reduction should be based on the physician's judgment and individual patient requirements. Since the risk of DKA seems to be elevated in those with type 1 diabetes on SGLT (2 or 1/2) inhibitors, extra caution should be exercised when factors that predispose to DKA occur, such as infections or sick days that may also require interruption of dosing of the SGLT inhibitors.

There are some limitations to this study. First, the current 24-week results only provide evidence of relatively short-term data regarding therapeutic benefit and risks; this will be addressed in the ongoing 28-week extension phase for this study and the preceding DEPICT-1 study. Second, exclusion of DKA- and hypoglycemia-prone patients and strict monitoring of DKA and hypoglycemia in this trial setting differ from the real-world situation. Finally, the decision not to include a protocol-mandated insulin titration algorithm, chosen to more closely reflect clinical practice and the real-world setting, could potentially mask the full glycemic potential of dapagliflozin.

In summary, these results demonstrate that in patients with type 1 diabetes inadequately controlled on insulin, adjunct dapagliflozin (5 and 10 mg) therapy significantly improves HbA_{1c}, mean glucose levels, glycemic variability, and time in glycemic target range and reduces body weight and TDD. Overall, the treatment was well tolerated, with no increase in hypoglycemia versus placebo, although there were more events of DKA in patients receiving dapagliflozin in this study. Taken together, the DEPICT studies provide robust short-term evidence for dapagliflozin as a suitable candidate for use as adjunct therapy to adjustable insulin to improve glycemic control in patients with type 1 diabetes.

Acknowledgments. The authors thank the patients for their participation in this study and the study investigators and contributors from each study site. Writing support was provided by Parita Sheth and Mark Davies (inScience Communications, Springer Healthcare) and was funded by AstraZeneca.

Funding and Duality of Interest. This study was funded by AstraZeneca and Bristol-Myers Squibb. C.M. serves or has served on advisory boards for Novo Nordisk, Sanofi, Merck Sharp and Dohme, Eli Lilly, Novartis, Bristol-Myers Squibb, AstraZeneca, Pfizer, Janssen Pharmaceuticals, Boehringer Ingelheim, Hanmi

Pharmaceuticals, Roche Diagnostics, Medtronic, MannKind, Intrexon, and UCB and serves or has served on speakers' bureaus for Novo Nordisk, Sanofi, Merck Sharp and Dohme, Eli Lilly, Boehringer Ingelheim, AstraZeneca, and Novartis. C.M.'s institute has received research support for C.M. from Novo Nordisk, Sanofi, Merck Sharp and Dohme, Eli Lilly, Roche Diagnostics, Abbott, Intrexon, and Novartis. P.D. serves on the advisory boards of AstraZeneca, Novo Nordisk, Sanofi, Boehringer Ingelheim, Merck Intarcia, and AbbVie and has received research grants from all of these companies, apart from Intarcia. P.G. serves or has served on advisory boards for Novo Nordisk, Sanofi, Eli Lilly, Boehringer Ingelheim, Janssen Pharmaceuticals, LifeScan, Roche Diagnostics, Medtronic, Abbott, Dexcom, and Ypsomed and serves or has served on speakers' bureaus for Boehringer Ingelheim, Bayer, Medtronic, Roche Diagnostics, and Abbott. P.G.'s institute has received research support for P.G. from Medtronic, Abbott, Roche Diagnostics, Merck Sharp and Dohme, and Menarini. P.S. has received consulting fees from Abbott, AstraZeneca, Boehringer Ingelheim, Eli Lilly, Janssen, Novo Nordisk, and Sanofi, honoraria for delivering accredited CME from Abbott, AstraZeneca, Boehringer Ingelheim, Eli Lilly, Janssen, Merck Sharp and Dohme, Novo Nordisk, and Sanofi, and his institution has received research support from Allergan, AstraZeneca, Genzyme, Novo Nordisk, Prometic, Sanofi, and Viacyte. E.A. has received grants from Astellas Pharma, AstraZeneca, Daiichi Sankyo, Mitsubishi Tanabe Pharma, Nippon Boehringer Ingelheim, Kowa Pharmaceutical, Nordisk Pharma, Novartis Pharma, Novo, Ono Pharmaceutical, Sanofi, Taisho Toyama Pharmaceutical, Takeda Pharmaceutical, and Pfizer Japan and has received personal fees from Astellas Pharma, AstraZeneca, Daiichi Sankyo, Eli Lilly, Kowa Pharmaceutical, Mitsubishi Tanabe Pharma, Merck Sharp and Dohme, Nippon Boehringer Ingelheim, Novo Nordisk Pharma, Novartis Pharma, Ono Pharmaceutical, Sanofi, Taisho Toyama Pharmaceutical, and Takeda Pharmaceutical. M.L. has received research grants from AstraZeneca, DexCom, Novo Nordisk, and Pfizer, has been a consultant for or received honoraria from AstraZeneca, Eli Lilly, Medtronic, Novo Nordisk, and Rubin Medical, and participated in advisory boards for Merck Sharp and Dohme and Novo Nordisk. S.C.B. has received research grants from Healthcare and Research Wales (Welsh Government) and Novo Nordisk, other research support from Healthcare and Research Wales (Welsh Government) infrastructure support, and honoraria from Novo Nordisk, Sanofi, Lilly, Boehringer Ingelheim, and Merck Sharp and Dohme and has ownership interest in Glycosmedia (diabetes online news service). S.J. is a consultant for AstraZeneca, Janssen, and Eli Lilly. N.A. and F.T. are employees of AstraZeneca. L.H. was an employee of Bristol-Myers Squibb during the conduct of this study, is currently an employee of MedImmune, and is a shareholder of Bristol-Myers Squibb and Novo Nordisk A/S. A.M.L. is an employee and shareholder of AstraZeneca. No other conflicts of interest relevant to this article were reported.

Author Contributions. C.M., P.D., P.G., P.S., C.H., E.A., M.L., S.C.B., S.J., N.A., L.H., F.T., and A.M.L. contributed to the study concept and design, analysis, interpretation of the study data, and drafting of the manuscript and critical revision for intellectual content. C.M. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Prior Presentation. This study was presented as an oral presentation at the 78th Scientific Sessions of the American Diabetes Association, Orlando, FL, 22–26 June 2018.

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