Efficacy and Safety of Dapagliflozin in Patients With Inadequately Controlled Type 1 Diabetes: The DEPICT-1 52-Week Study

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OBJECTIVE

This study evaluated the long-term safety and efficacy of dapagliflozin as an adjunct to adjustable insulin in patients with type 1 diabetes and inadequate glycemic control.

RESEARCH DESIGN AND METHODS

DEPICT-1 (Dapagliflozin Evaluation in Patients With Inadequately Controlled Type 1 Diabetes) was a randomized (1:1:1), double-blind, placebo-controlled phase 3 study of dapagliflozin 5 mg and 10 mg in patients with type 1 diabetes (HbA_{1c} 7.5–10.5% [58–91 mmol/mol]) (NCT02268214). The results of the 52-week study, consisting of the 24-week short-term and 28-week extension period, are reported here.

RESULTS

Of the 833 patients randomized into the study, 708 (85%) completed the 52-week study. Over 52 weeks, dapagliflozin 5 mg and 10 mg led to clinically significant reductions in HbA_{1c} (difference vs. placebo [95% CI] −0.33% [−0.49, −0.17] [−3.6 mmol/mol (−5.4, −1.9)] and −0.36% [−0.53, −0.20] [−3.9 mmol/mol (−5.8, −2.2)], respectively) and body weight (difference vs. placebo [95% CI] −2.95% [−3.83, −2.06] and −4.54% [−5.40, −3.66], respectively). Serious adverse events were reported in 13.4%, 13.5%, and 11.5% of patients in the dapagliflozin 5 mg, 10 mg, and placebo groups, respectively. Although hypoglycemia events were comparable across treatment groups, more patients in the dapagliflozin groups had events adjudicated as definite diabetic ketoacidosis (DKA; 4.0%, 3.4%, and 1.9% in dapagliflozin 5 mg, 10 mg, and placebo groups, respectively).

CONCLUSIONS

Over 52 weeks, dapagliflozin led to improvements in glycemic control and weight loss in patients with type 1 diabetes, while increasing the risk of DKA.

Many patients with type 1 diabetes are still not achieving glycemic targets (1), despite improvements in insulin analogs and methods of insulin delivery and glucose monitoring technology over recent years (2,3). Consequently, there is an unmet need for additional therapies that can be used alongside insulin in patients with type 1

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diabetes, without adding to the risk of hypoglycemia and weight gain. Currently, no oral antihyperglycemic agent has been approved for use in type 1 diabetes alongside insulin. Dapagliflozin, a sodium–glucose cotransporter 2 (SGLT2) inhibitor, acts through an insulin-independent mechanism, reducing renal glucose reabsorption and consequently promoting urinary glucose excretion (4). Dapagliflozin has been used extensively in patients with type 2 diabetes, improving glycemic control with minimal hypoglycemia, and is also associated with weight loss and systolic blood pressure (SBP) reduction (5–8).

DEPICT-1 (Dapagliflozin Evaluation in Patients With Inadequately Controlled Type 1 Diabetes) is a phase 3 study of dapagliflozin as an adjunct to adjustable insulin in patients with type 1 diabetes and inadequate glycemic control. The 24-week results showed a clinically and statistically significant reduction in HbA_{1c}, body weight, and total insulin dose and improvements in glycemic variability, with no increase in the risk of hypoglycemia or diabetic ketoacidosis (DKA) (9). There are currently no longer-term studies of selective SGLT2 inhibitors in patients with type 1 diabetes. Here we present the 52-week results of the DEPICT-1 study, which aimed to evaluate the long-term safety and efficacy of dapagliflozin in patients with type 1 diabetes and inadequate glycemic control.

RESEARCH DESIGN AND METHODS

Study Design

This was a randomized, three-arm, parallel-group, multicenter phase 3 study to evaluate the efficacy and safety of dapagliflozin 5 mg and 10 mg as an add-on to adjustable insulin in patients with type 1 diabetes. The results from the full 52 weeks of the study are reported here, consisting of the 24-week double-blind short-term period, the results from which have been published (9), followed by a 28-week long-term subject- and study sites–blinded extension period.

The study complied with the Declaration of Helsinki and the International Conference on Harmonization/Good Clinical Practice Guidelines and was approved by institutional review boards and independent ethics committees for the participating centers. All participants provided informed consent before entering the study. The study is registered with ClinicalTrials.gov (NCT02268214).

Study Participants

Adult patients with inadequately controlled type 1 diabetes (HbA_{1c} 7.7–11.0% [61–97 mmol/mol] at screening; 7.5–10.5% [58–91 mmol/mol] at randomization) were eligible for inclusion. Patients had to have been prescribed insulin for ≥12 months, with a total insulin dose ≥0.3 IU/kg/day for ≥3 months before screening. In addition, C-peptide had to be <0.7 ng/mL and BMI ≥18.5 kg/m^2. Patients were excluded if they had a history of type 2 diabetes, pancreatic surgery, or chronic pancreatitis or other pancreatic disorders resulting in decreased β-cell capacity, DKA requiring medical intervention, or hospitalization for hyperglycemia or hypoglycemia within 1 month before screening, or if they had frequent episodes of severe hypoglycemia, showed symptoms of poorly controlled diabetes, or had previously used any SGLT2 inhibitor. Detailed inclusion and exclusion criteria have been described previously (9).

Treatments and Interventions

Patients continued to receive their randomly assigned medication from the short-term period of the study, either dapagliflozin 5 mg, 10 mg, or placebo (randomized 1:1:1) (9). During the 28-week extension, patients and study sites remained blinded to the study medication, and study visits occurred at weeks 32, 40, 48, and 52. There was an additional 30-day posttreatment follow-up at week 56.

End Points and Safety Assessments

Efficacy variables assessed included changes from baseline in HbA_{1c} (primary end point at week 24) and the percentage change from baseline in the total daily insulin dose (collected by collecting the daily record or collecting weekly minimum and maximum) and body weight after 52 weeks. Other efficacy outcomes included the proportion of patients achieving an HbA_{1c} reduction ≥0.5% (5.5 mmol/mol) from baseline to week 52 (last observation carried forward [LOCF] for those without week 52 values), those achieving an HbA_{1c} reduction ≥0.5% (5.5 mmol/mol) without a severe hypoglycemia event at week 52 (LOCF for those without week 52 values), the proportion of patients with HbA_{1c} of <7.0% (53 mmol/mol) at week 52 (LOCF for those without week 52 values), change in fasting plasma glucose from baseline to week 52, and change in seated SBP among patients with hypertension at baseline (seated SBP ≥140 mmHg and/or seated diastolic blood pressure ≥90 mmHg) from baseline to week 52.

Additional post hoc analyses examined changes from baseline in HbA_{1c} stratified by baseline HbA_{1c}, continuous glucose monitoring (CGM) use, or method of insulin administration (continuous subcutaneous insulin infusion or multiple daily injections), as well as changes from baseline in body weight stratified by baseline HbA_{1c} and BMI.

Safety assessment included adverse events (AEs), serious AEs (SAEs), physical examination findings, vital signs, electrocardiograms, and laboratory values. AEs of special interest were hypoglycemia, DKA, hepatobiliary AEs, genital infections, urinary tract infections, volume depletion, fractures, worsening renal function, hypersensitivity, and cardiovascular AEs, based on a list of prespecified preferred terms.

Hypoglycemia was assessed as the proportion of patients with an event and the frequency and severity of the events. Hypoglycemic events were defined in accordance with the American Diabetes Association (ADA) classification criteria (10):

- severe hypoglycemia was defined as that requiring assistance of another person to raise glucose levels and promote neurological recovery;
- documented symptomatic hypoglycemia featured typical hypoglycemia symptoms and a plasma glucose concentration ≤70 mg/dL (3.9 mmol/L);
- asymptomatic hypoglycemia was unaccompanied by typical hypoglycemia symptoms, but plasma glucose was ≤70 mg/dL (3.9 mmol/L);
- probable symptomatic hypoglycemia had typical hypoglycemia symptoms but without a plasma glucose determination; and
- pseudohypoglycemia (or relative hypoglycemia) was defined as patient-reported hypoglycemia symptoms with plasma glucose >70 mg/dL (3.9 mmol/L) but approaching that level.

Events of suspected DKA were identified based on symptoms, diagnoses, and/or home ketone values (β-hydroxybutyrate [BOHB]), and investigators were asked whether a broad list of AEs satisfying a list of preferred terms (customized standard Medical Dictionary for Regulatory Activities queries) could be potential DKA events. All potential events of DKA were adjudicated by an independent blinded DKA Adjudication Committee and classified as definite, possible, or unlikely DKA. Definite DKA criteria included acidosis, diagnosed with low blood pH of <7.3 and/or decreased serum bicarbonate levels (≤18 mEq/L), and symptoms/signs as listed by the ADA consensus statement on the diagnosis of DKA (11). BOHB measurements were not part of the criteria because the ADA consensus statement does not include quantified BOHB in the diagnosis of DKA (11), and in addition, the weight loss induced by SGLT2 inhibitors is expected to cause some baseline elevations through lipolysis (12,13). Raised glucose was not a requirement for sending an event to adjudication nor was it a criterion in the adjudication charter in order to avoid missing episodes of euglycemic DKA. There were no adjudication criteria for possible and unlikely DKA.

Statistical Analysis

Efficacy was assessed using the full analysis set, which comprised all patients who had received at least one dose of study medication during the 24-week short-term period. As described previously (9), the first 55 randomized patients were excluded from the full analysis set due to the presence of an interactive voice-response system randomization error which allocated them to only one of the dapagliflozin treatment arms. Insulin dose data were summarized using patient-recorded basal and bolus insulin dose ranges for each week between the visits on week 2 and week 10, week 12 and week 22, and week 24 to week 56; where daily dose data were available, it was converted into weekly ranges and then combined for analysis. Because the 52-week efficacy analyses were exploratory, no *P* values were calculated for treatment group comparisons. A longitudinal repeated-measures analysis, with a model including fixed categorical effects of treatment, week, randomization stratification factors (one term for each combination of all stratification factors), and treatment-by-week interaction, and also the continuous fixed covariates of baseline measurement and baseline measurement-by-week interaction, was performed for analyses of variables in terms of change or percentage change (using log transformation for the end point) from baseline. This approach has the effect of estimating treatment effects as if treatments for all patients had been continued until week 52. Mean change or percentage changes from baseline and 95% CI were calculated for all postbaseline visits, except the follow-up visit. In cases where the proportion of patients reaching a target at week 52 were examined, analyses used logistic regression models with adjustment for randomization stratification factor and baseline values.

Safety outcomes were assessed in the safety analysis set, which comprised all patients who received at least one dose of study drug, including those randomized in error. Safety variables were summarized descriptively, and no statistical tests were performed to compare rates between treatment groups.

RESULTS

Of the 833 patients randomized into the 24-week short-term study, 747 patients (90%) entered the 28-week long-term treatment period. In the full analysis set, 85%, 86%, and 84% of randomized patients in the dapagliflozin 5 mg, 10 mg, and placebo groups, respectively, completed the entire 52-week study (Supplementary Fig. 1). The main reasons for discontinuation were AEs and patient withdrawal of consent. The demographics and characteristics of patients included in this study were previously presented in full (9), and the treatment groups were well balanced (Supplementary Table 1).

Efficacy Outcomes

The improvements in HbA_{1c} shown in the 24-week short-term study with dapagliflozin 5 mg and 10 mg were also observed over the 28-week extension period (Fig. 1*A*). Adjusted mean change in HbA_{1c} (SE) from baseline to week 52 for dapagliflozin 5 mg was −0.27% (0.06) (−3.0 mmol/mol [0.7]), for dapagliflozin 10 mg it was −0.31% (0.06) (−3.4 mmol/mol [0.7]), and for placebo it was 0.06% (0.06) (−0.7 mmol/mol [0.7]), with a difference [95% CI] versus placebo for dapagliflozin 5 mg of −0.33% (−0.49, −0.17) (−3.6 mmol/mol [−5.4, −1.9]) and for dapagliflozin 10 mg of −0.36% (−0.53, −0.20) (−3.9 mmol/mol [−5.8, −2.2]). HbA_{1c} values at week 52 were 8.2% (66 mmol/mol), 8.2% (66 mmol/mol), and 8.5% (69 mmol/mol) for dapagliflozin 5 mg, 10 mg, and placebo, respectively. Four weeks after discontinuation of the study drug, HbA_{1c} levels returned to baseline levels (Fig. 1*A*).

Total insulin daily dose in the dapagliflozin 5 mg and 10 mg groups was reduced at week 2 and remained lower over the 52 weeks of treatment compared with placebo (Fig. 1*B*).

The reductions in body weight observed with dapagliflozin 5 mg versus placebo at week 24 were maintained over the additional 28 weeks of treatment, with additional decreases in weight seen with dapagliflozin 10 mg (Fig. 1*C*). The adjusted mean percentage change in body weight (SE) from baseline to week 52 was −2.80% (0.33) for dapagliflozin 5 mg, −4.39% (0.31) for dapagliflozin 10 mg, and 0.15% (0.32) for placebo (difference [95% CI] vs. placebo, dapagliflozin 5 mg: −2.95% [−3.83, −2.06] and dapagliflozin 10 mg: −4.54% [−5.40, −3.66]), whereas the adjusted mean (SE) changes from baseline to week 52 were −2.31 kg (0.27), −3.65 kg (0.27), and 0.25 kg (0.27) for dapagliflozin 5 mg, 10 mg, and placebo, respectively, with week 52 body weight values of 79.7 kg, 78.8 kg, and 84.3 kg, respectively. Body weight in the dapagliflozin groups increased, trending toward baseline levels on cessation of the study treatment at week 56 (mean [SD] reduction from baseline of −1.86% [4.96] for dapagliflozin 5 mg, −2.96% [5.75] for dapagliflozin 10 mg, and 0.15% [4.29] for placebo).

More patients in the dapagliflozin 5 mg and 10 mg groups compared with placebo achieved an HbA_{1c} reduction ≥0.5% (5.5 mmol/mol) (43.0%, 45.7%, and 25.3%, respectively) and the composite of an HbA_{1c} reduction ≥0.5% (5.5 mmol/mol) without an episode of severe hypoglycemia (40.2%, 42.1%, and 23.7%, respectively) (Supplementary Table 2). At week 52, there were reductions in fasting plasma glucose in the dapagliflozin 5 mg and 10 mg groups compared with placebo, and a greater proportion of patients achieved an HbA_{1c} <7.0% (53 mmol/mol)

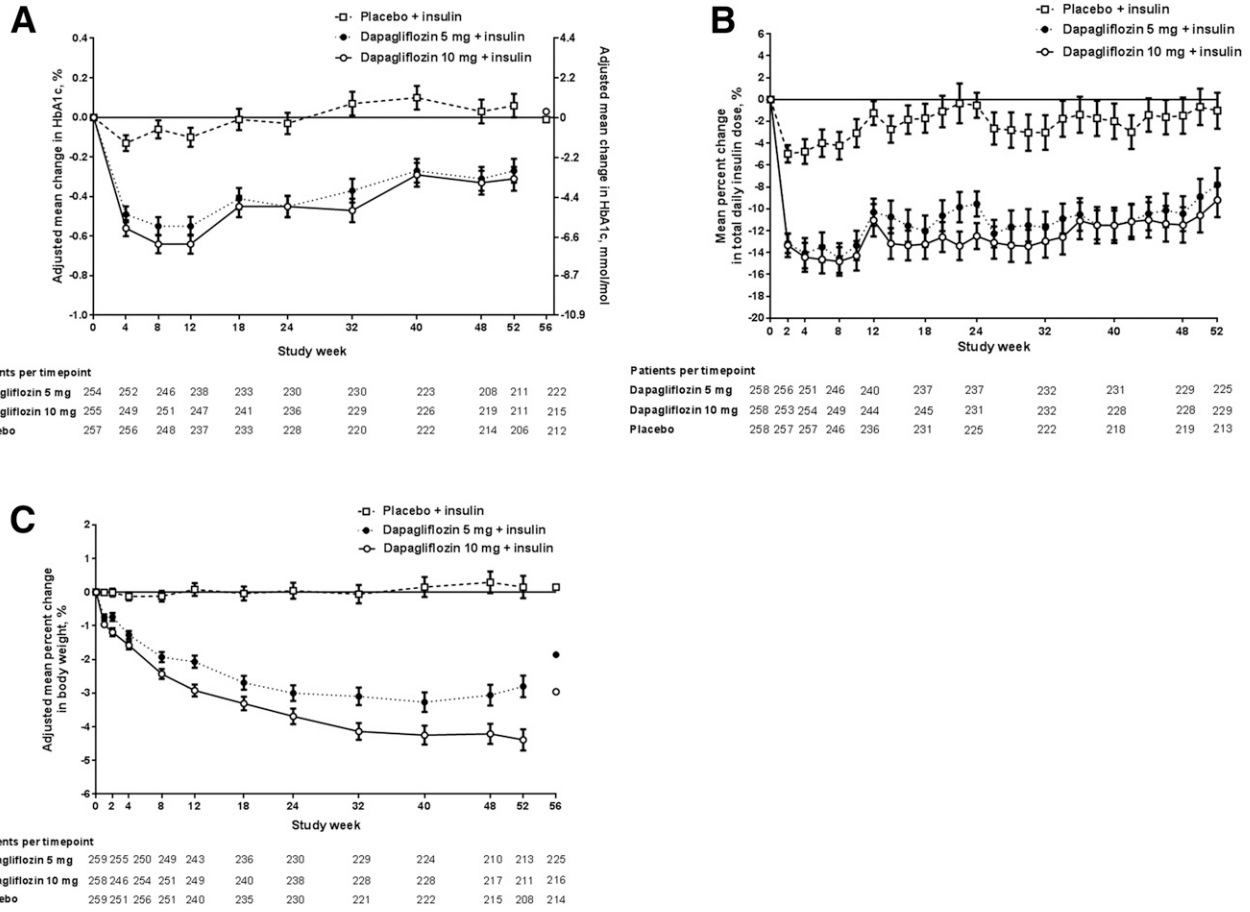

Figure 1—Adjusted* mean (SE) change from baseline to week 52 in HbA_{1c} (*A*), mean (SE) percent change from baseline to week 52 in total daily insulin dose (*B*), and adjusted* mean (SE) percent change from baseline to week 52 in body weight (*C*) (full analysis set). *Adjusted mean (SE) change/percent change is shown for values from baseline to week 52 for HbA_{1c} and body weight (insulin data is descriptive only); values at week 56 are mean (SD).

at week 52 with dapagliflozin (Supplementary Table 2).

In patients with hypertension at baseline, seated SBP reduced across all of the treatment groups at week 52, with the dapagliflozin groups trending toward a greater reduction than the placebo group (Supplementary Table 2).

Post Hoc Analyses

Greater reductions in HbA_{1c} were observed in the dapagliflozin 5 mg and 10 mg groups compared with placebo across baseline characteristics, HbA_{1c}, CGM use, and insulin administration method in both groups (Supplementary Fig. 2). Improvements in body weight with dapagliflozin 5 mg and 10 mg compared with placebo were also generally seen across subgroups, with no clear trend with respect to baseline HbA_{1c} or BMI (Supplementary Fig. 3).

Safety Outcomes

The safety results are presented for the cumulative study period, including the short-term, long-term, and follow-up periods (56 weeks in total). The proportion of patients with any AE over 56 weeks was higher in the dapagliflozin treatment groups than in the placebo group (Table 1). The higher proportion of AEs in the dapagliflozin treatment groups can primarily be attributed to differences in the system organ class of "infections and infestations"; events occurred in 55.6%, 53.7%, and 48.1% of the dapagliflozin 5 mg, 10 mg, and placebo groups, respectively. The most common AEs by preferred term in the dapagliflozin 5 mg, 10 mg, and placebo groups were viral upper respiratory tract infection (18.4%, 15.5%, and 18.5%, respectively), upper respiratory tract infection (6.9%, 9.5%, and 6.2%, respectively), urinary tract infection (10.1%, 3.7%, and 7.3%, respectively), and headache (5.1%, 6.8%, and 5.0%, respectively). Discontinuations due to AEs occurred in 4.0%, 4.4%, and 3.5% of patients in the dapagliflozin 5 mg, 10 mg, and placebo groups, respectively. SAEs were reported in 13.4%, 13.5%, and 11.5% of patients in the dapagliflozin 5 mg, dapagliflozin 10 mg, and placebo groups, respectively (Table 1 and Supplementary Table 3). In addition, SAEs related to the study drug were reported in 2.9%, 4.4%, and 0.8% of patients in the dapagliflozin 5 mg, dapagliflozin 10 mg, and placebo groups, respectively (Table 1).

For the AEs of special interest, there were more genital infection AEs in the dapagliflozin treatment groups than in the placebo group (Table 1); genital infection AEs were more common in women than men, 21.5% vs. 7.6% in the dapagliflozin 5 mg group, 18.8% vs. 8.6% in the dapagliflozin 10 mg group, and 6.3% vs. 0% in the placebo group. Potential hypersensitivity AEs occurred in 5.4%, 5.1%, and 2.3% of patients in the dapagliflozin 5 mg, 10 mg, and placebo groups, respectively; most were mild, skin-related events such as rash, dermatitis, and eczema. Other AEs of special

Table 1—Safety summary (safety analysis set)*

	Dapagliflozin 5 mg (*n* = 277)	Dapagliflozin 10 mg (*n* = 296)	Placebo (*n* = 260)
AEs			
≥1 AE	215 (77.6)	236 (79.7)	189 (72.7)
≥1 AE related to study drug	93 (33.6)	97 (32.8)	39 (15.0)
AE leading to study discontinuation	11 (4.0)	13 (4.4)	9 (3.5)
AE of special interest			
Genital infection	43 (15.5)	40 (13.5)	8 (3.1)
Urinary tract infection†	32 (11.6)	16 (5.4)	21 (8.1)
Renal impairment/failure	4 (1.4)	2 (0.7)	3 (1.2)
Fractures	4 (1.4)	6 (2.0)	8 (3.1)
Hypotension/dehydration or hypovolemia	0	3 (1.0)	5 (1.9)
Hypersensitivity	15 (5.4)	15 (5.1)	6 (2.3)
Cardiovascular events	1 (0.4)	2 (0.7)	1 (0.4)
SAEs			
≥1 SAE	37 (13.4)	40 (13.5)	30 (11.5)
≥1 SAE related to study drug	8 (2.9)	13 (4.4)	2 (0.8)
SAE leading to study discontinuation	5 (1.8)	8 (2.7)	3 (1.2)
Hypoglycemia			
≥1 SAE of hypoglycemia	3 (1.1)	4 (1.4)	3 (1.2)
Hypoglycemia leading to study discontinuation	1 (0.4)	0	1 (0.4)
Ketone-related events			
≥1 ketone-related SAE	13 (4.7)	13 (4.4)	3 (1.2)
Ketone-related SAE leading to study discontinuation	2 (0.7)	7 (2.4)	0
Death	0	0	1 (0.4)

Data are presented as *n* (%). *Includes AE and SAE with onset on or after day 1 of the treatment period up to and 30 days after the last dose date in the treatment period. †Includes urinary tract infections, cystitis, genitourinary tract infections, urogenital fungal infections, and pyelonephritis.

interest were balanced between the treatment groups, with few reports of fractures in any of the groups (Table 1).

A comparable proportion of patients in each of the treatment groups experienced at least one hypoglycemic event (Table 2). The proportion of patients experiencing severe hypoglycemia was also balanced across the treatment groups, 10.5%, 8.4%, and 11.5%, in the dapagliflozin 5 mg, 10 mg, and placebo groups, respectively. Only two patients, one in the dapagliflozin 5 mg group and one in the placebo group, discontinued due to an SAE of hypoglycemia.

Potential events of DKA were evaluated by an independent adjudication committee blinded to treatment allocation. In contrast to the short-term period alone where the occurrence of events was balanced, over the randomized study period and including follow-up, more patients in the dapagliflozin groups had events adjudicated as definite DKA, at 4.0%, 3.4%, and 1.9% in the dapagliflozin 5 mg, 10 mg, and placebo groups, respectively (Table 3), with 24 of the definite DKA events reported as SAEs. Of the definite DKA events, 37.0% (10 of 27) were adjudicated as mild, 37.0% (10 of 27) as moderate, and 25.9% (7 of 27) as severe. Most events (70% [19 of 27]) were treated with standard therapy, intravenous fluids, and additional insulin. The most common primary causes of definite DKA were missed insulin dose and insulin pump failure (Table 3). Of the 27 events of definite DKA, 1 event was reported during the 30-day follow-up period (when the subject was no longer receiving study medication) in a subject who had been randomized to dapagliflozin 5 mg. A Kaplan-Meier plot of the time to the first definite DKA event is shown in Supplementary Fig. 4.

There were no clinically significant changes in week 52 vital signs and electrocardiogram data in the treatment groups (Supplementary Table 4).

CONCLUSIONS

This is the first report of the long-term use of a selective SGLT2 inhibitor as an adjunct to insulin for the treatment of type 1 diabetes, with other similar studies only reporting the short-term effects (up to 24 weeks) (9,14–18).

Consistent with the 24-week DEPICT-1 and -2 studies (9,18), the current study demonstrates that dapagliflozin as an adjunct to adjustable insulin leads to a clinically relevant decrease in HbA_{1c} over 52 weeks. Importantly, these improvements in HbA_{1c} were seen in the presence of total daily insulin dose reductions and across patient groups stratified by baseline characteristics (HbA_{1c}, CGM use, and insulin administration method). Achieving and maintaining glycemic control in patients with type 1 diabetes is important, providing clear benefits in terms of preventing micro- (19) and macrovascular disease (20,21), but many patients are still failing to achieve and maintain their targets (1). Thus, dapagliflozin as an adjunct to insulin in patients with type 1 diabetes may help overcome an unmet medical need.

Overweight and obesity are important cardiovascular risk factors (22,23) that are becoming increasingly prevalent in patients with type 1 diabetes (24–26). Intensive insulin treatment leads to weight gain and increases in cardiovascular risk factors (27,28), which may reduce the benefits from improved glycemic control. In this study, the improved glycemic control with dapagliflozin was accompanied by a meaningful and sustained decrease in body weight. The reductions continued over the entire 52 weeks of the study, resulting in a 4.5% reduction with dapagliflozin 10 mg, with the greater decreases in body weight in the dapagliflozin groups still seen when patients were stratified by

Table 2—Summary of hypoglycemia events (safety analysis set)*

	Dapagliflozin 5 mg (*n* = 277)	Dapagliflozin 10 mg (*n* = 296)	Placebo (*n* = 260)
Hypoglycemia events, *n*	7,146	8,451	7,670
Patients with ≥1 events, *n* (%)	227 (81.9)	241 (81.4)	212 (81.5)
Exposure-adjusted incidence rate, per 100 patient-years	2,834.67	3,099.87	3,300.58
Severe hypoglycemia			
Events, *n*	46	58	85
Patients with ≥1 events, *n* (%)	29 (10.5)	25 (8.4)	30 (11.5)
Exposure-adjusted incidence rate, per 100 patient-years	18.25	21.27	36.58
Documented symptomatic hypoglycemia			
Events, *n*	5,775	6,744	6,010
Patients with ≥1 events, *n* (%)	215 (77.6)	227 (76.7)	198 (76.2)
Exposure-adjusted incidence rate, per 100 patient-years	2,290.82	2,473.73	2,586.24
Asymptomatic hypoglycemia			
Events, *n*	1,035	1,293	1,279
Patients with ≥1 events, *n* (%)	110 (39.7)	135 (45.6)	104 (40.0)
Exposure-adjusted incidence rate, per 100 patient-years	410.56	474.28	550.38
Probable symptomatic hypoglycemia			
Events, *n*	131	149	182
Patients with ≥1 events, *n* (%)	48 (17.3)	47 (15.9)	49 (18.8)
Exposure-adjusted incidence rate, per 100 patient-years	51.96	54.65	78.32
Relative hypoglycemia			
Events, *n*	133	177	96
Patients with ≥1 events, *n* (%)	43 (15.5)	40 (13.5)	31 (11.9)
Exposure-adjusted incidence rate, per 100 patient-years	52.76	64.92	41.31
Other hypoglycemia			
Events, *n*	26	30	18
Patients with ≥1 events, *n* (%)	12 (4.3)	14 (4.7)	13 (5.0)
Exposure-adjusted incidence rate, per 100 patient-years	10.31	11.00	7.75

*Includes events on or after day 1 of the treatment period up to and 30 days after the last dose date in the treatment period.

baseline HbA_{1c} and BMI levels. Previous evidence indicates that the weight loss with dapagliflozin is related to caloric loss from glucosuria (29). Modest reductions in weight have also been shown to have beneficial effects on cardiovascular risk factors (30,31), suggesting that the beneficial effect of dapagliflozin on weight may help to redress the negative effect on cardiovascular risk factors. Weight loss may also help to keep patients psychologically empowered with their treatment schedule.

The risk of hypoglycemia is an important barrier to treatment intensification in type 1 diabetes. Hypoglycemia can lead to confusion, loss of consciousness, seizures, and even death, and frequent episodes of hypoglycemia can lead to physiological changes that reduce awareness for future events (10,32). The fear of hypoglycemia in patients with diabetes can also lead to alteration in their behavior and affect their adherence to treatment (33); consequently, it is essential that new therapies that target hyperglycemia should also minimize the risk for hypoglycemia. In this study, despite the observed decrease in HbA_{1c}, there was no increase in severe hypoglycemia or in the overall incidence of hypoglycemia.

DKA, another risk seen in patients with type 1 diabetes, occurs in ~5% of patients per year (34). This is a serious and potentially fatal complication of diabetes, although the in-hospital mortality rate appears to have decreased in recent years to ~0.4% (35). Over the entire 52-week and 4-week follow-up periods, more confirmed events of DKA were seen with dapagliflozin treatment than with placebo (4.0%, 3.4%, and 1.9% for dapagliflozin 5 mg, 10 mg, and placebo, respectively), which is not accounted for by the extra 55 patients on dapagliflozin in this study. All episodes of definite DKA in this study were successfully managed with standard care for DKA. In other studies of SGLT (SGLT2 or SGLT1/2) inhibitors in patients with type 1 diabetes (15–18), DKA events were more common in the active treatment groups compared with placebo, which is consistent with the overall pattern now seen in DEPICT-1. This suggests that the previous balance seen in the short-term part of the study (9) may be driven by randomness due to a small number of events, because the overall rate of occurrence of DKAs in this study was consistent between the 24-week short-term and 28-week long-term periods (12 events vs. 14 events plus 1 in the follow-up period) with no clustering at specific time points. A possible explanation for the increased occurrence of DKA in those receiving SGLT2 inhibitors may be that during an incipient DKA event, lower glucose values than expected may delay detection (36). These findings highlight the need for awareness of the potential for DKA and that the risk persists over time, including the repeated education of patients, caregivers, and physicians on the signs and symptoms of DKA, management of a DKA event, and knowledge of the risk factors for a DKA event for as long as adjunctive therapies are used. Despite the imbalance seen in the occurrence of DKA events in this study between treatment groups, it is possible that the recommendation to limit the reduction of total insulin dose to less than 20% may have mitigated the risk. However, given the overall small number of events in the different studies, this remains speculation.

Table 3—Summary of DKA events*

	Dapagliflozin 5 mg (*n* = 277)	Dapagliflozin 10 mg (*n* = 296)	Placebo (*n* = 260)
Patients with events sent for adjudication, *n* (%)	24 (8.7)	28 (9.5)	9 (3.5)
Patients with definite DKA, *n* (%)	11 (4.0)	10 (3.4)	5 (1.9)
Definite DKA events, *n*	12	10	5
Incidence rate, per 100 patient-years	4.76	3.67	2.15
Severity of event as adjudicated, *n*			
Mild	5	2	3
Moderate	3	6	1
Severe	4	2	1
Euglycemic DKA events, *n*†	3	5	1
Primary cause for definite DKA events, *n*			
Insulin pump failure	3	2	2
Missed insulin dose	4	4	1
Severe illness	0	0	0
Not identified	3	2	0
Other	2	2	2
Mean percent total insulin dose reduction compared with baseline			
For the week before definite DKA events, %	10.21‡	−23.05	−11.63
At end of week 52 in patients with definite DKA events, %	−11.89	−17.57	5.05
Events adjudicated as not DKA			
Patients with possible DKA, *n* (%)	8 (2.9)	9 (3.0)	2 (0.8)
Possible DKA events, *n*	13	10	4
Patients with unlikely DKA, *n* (%)	9 (3.2)	11 (3.7)	3 (1.2)
Unlikely DKA events, *n*	16	15	7

*Includes events with onset on or after day 1 of the treatment period up to and 30 days after the last dose date in the treatment period. †Self-monitored blood glucose <250 mg/dL (13.9 mmol/L). ‡The increase seen is due to an outlier: one patient had a very large increase in insulin dose, 188.9%, 1 week before the DKA event.

This is first report of the long-term use of a selective SGLT2 inhibitor for the treatment of type 1 diabetes. There was a high completion rate, with ~85% (708 of 833) completing the 52-week study.

This study has some limitations. Firstly, insulin was not titrated using a protocol-mandated algorithm, which could prevent the full glycemic potential of dapagliflozin, although it may more accurately reflect real-world practice. Secondly, two methods were used for reporting insulin dose: for the 52-week study, patients recorded the midpoint for basal and bolus insulin dose for each week, whereas for the 24-week short-term study, each insulin dose taken was recorded daily at set times to generate the total daily insulin dose. As such, the insulin dose reductions reported here cannot be directly compared with the 24-week report (9). Finally, the population of this study was predominantly Caucasian and so may not be as reflective of other ethnicities; importantly, the DEPICT-2 study with dapagliflozin in patients with type 1 diabetes included a large number of Asian patients from Japan in addition to countries with predominantly Caucasian patients (18).

In conclusion, this study evaluated the potential for dapagliflozin to be used as an adjunct to insulin in patients with type 1 diabetes and inadequate glycemic control. It was well tolerated and led to a clinically relevant improvement in glycemic control and weight loss, without additional risk for hypoglycemia and with a reduction in daily insulin dose which helps to resolve major problems around metabolic control in type 1 diabetes. Furthermore, all DKA events were successfully managed and did not cause any further complications. However, because more patients experienced DKA with dapagliflozin treatment, patients and health care professionals should be made aware of this risk and provided with guidance on management and reporting of DKA episodes.

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