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

Short running title (>47 characters and spaces combined): DEPICT-2: Dapagliflozin in type 1 diabetes

Chantal Mathieu[1], MD; Paresh Dandona[2], MD; Pieter Gillard[1], MD; Peter Senior[3], MBBS, PhD; Christoph Hasslacher[4], MD; Eiichi Araki[5], MD, PhD; Marcus Lind[6,7], MD, PhD; Stephen C Bain[8], FRCP; Serge Jabbour[9], MD; Niki Arya[10], MS; Lars Hansen[11*], MD, PhD; Fredrik Thorén[12],MD; Anna Maria Langkilde[12], MD; on behalf of the DEPICT-2 Investigators*

[1]Clinical and Experimental Endocrinology, University of Leuven, Leuven, Belgium; [2]Department of Medicine, State University of New York at Buffalo, Buffalo, NY, USA; [3]Division of Endocrinology, University of Alberta, Edmonton, Canada; [4]Diabetesinstitut Heidelberg, Heidelberg, Germany; [5]Department of Metabolic Medicine, Faculty of Life Sciences, Kumamoto University, Kumamoto, Japan; [6]Institute of Medicine, University of Gothenburg, Gothenburg, Sweden; [7]Department of Medicine, NU-Hospital Group, Uddevalla, Sweden; [8]Diabetes Research Unit, Swansea University, Wales, United Kingdom; [9]Department of Endocrinology, Diabetes and Metabolic Disease, Sidney Kimmel Medical College at Thomas Jefferson University, Philadelphia, Pennsylvania, USA; [10]AstraZeneca, Gaithersburg, MD, USA; [11]MedImmune, Gaithersburg, MD, USA; [12]AstraZeneca, Gothenburg, Sweden.

*At the time of the study, LH worked at Bristol-Myers Squibb, Princeton, NJ, USA

Corresponding author: Chantal Mathieu

Address: Clinical and Experimental Endocrinology, University of Leuven, Leuven, Belgium

Email: chantal.mathieu@uzleuven.be

Telephone number: 003216346994

Fax number: 003216346989

Word count: 4342

Number of Tables: 2

Number of Figures: 2

Abstract

Objective: This 24-week, double-blinded, phase 3 clinical trial (DEPICT-2; NCT02460978) evaluated efficacy and safety of dapagliflozin as adjunct therapy to adjustable insulin in patients with inadequately controlled type 1 diabetes (HbA1c 7.5–10.5%).

Methods: Patients were randomized 1:1:1 to dapagliflozin 5 mg (n=271), 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 HbA1c (primary outcome; difference versus placebo [95% CI]: dapagliflozin 5 mg, −0.37% [−0.49, −0.26]; dapagliflozin 10 mg, –0.42% [−0.53, −0.30]), total daily insulin dose (−10.78% [−13.73, −7.72], −11.08% [−14.04, −8.02], respectively), and body weight (−3.21% [−3.96, −2.45], −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–≤180 mg/dL) versus placebo were significantly improved. More patients receiving dapagliflozin achieved a reduction in HbA1c ≥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, 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, 10 mg and placebo, respectively.

Conclusion: 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.

Current word count: 249 (**maximum 250 words**)

Funding by AstraZeneca and Bristol-Myers Squibb

Introduction

Less than one third of patients with type 1 diabetes achieve optimal glycemic control (HbA1c <7% [<53 mmol/mol]) (1, 2). Even when target HbA1c 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 study demonstrated that when used as adjunct therapy to adjustable insulin in patients with inadequately controlled type 1 diabetes, dapagliflozin significantly decreased HbA1c, 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.

Materials 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 136 sites in the following countries: Argentina, Belgium, Canada, Chile, Germany, Japan, the Netherlands, Poland, the Russian Federation, Sweden, Switzerland, the United Kingdom, and the United States, in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines as defined by the International Conference on Harmonization. It was approved by the institutional review boards and independent ethics committees for all participating centers. All participants provided written informed consent. For ≥18–<20-year-old patients from Japan, 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 (HbA1c, 7.7–11.0% [61–97 mmol/mol] at screening/enrolment; 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, or 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, 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 HbA1c 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, 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 HbA1c (7.5–<9.0% [58–<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; 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 (Beta-hydroxybutyrate [BOHB]) measurements were assessed at each study visit. Insulin doses were adjusted as deemed appropriate by the investigator, based on SMBG readings (recommended 4 times/day at a minimum and 6 times/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 from baseline in HbA1c after 24 weeks of double-blinded treatment with dapagliflozin 5 mg or 10 mg plus adjustable insulin versus placebo plus adjustable insulin. A sensitivity analysis for the primary efficacy endpoint was done for patients discontinuing treatment early. 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 endpoints including change in mean value of 24-hour 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-hour glucose readings within the target range of >70 mg/dL–≤180 mg/dL (>3.9–≤10.0 mmol/L) and finally, the proportion of patients achieving an HbA1c decrease of ≥0.5% without severe hypoglycemia. The proportion of patients achieving HbA1c reduction of ≥0.5% and those achieving HbA1c <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 of ≤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). Analysis of hypoglycemia was 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 HbA1c 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 a standard deviation (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 post-baseline assessment, 768 patients (256 patients per treatment arm) were planned to be randomized to one of the three treatment groups in 1:1:1 ratio. Among these 768 subjects, approximately 160 were planned to be enrolled in Japan.

Statistical analysis

Efficacy analyses were performed on the full analysis set, comprising all randomized patients receiving ≥1 dose of study medication during the short-term double-blind period, who had a baseline and any post-baseline assessment. Safety analyses were performed on the safety analysis set, comprising all randomized patients receiving ≥1 dose of study medication. Treatment effects were determined through pair-wise comparisons between each dapagliflozin group and placebo.

For an overall Type I error rate of 5% for the primary endpoint, 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 endpoints were only conducted if there was a statistically significant difference in the primary endpoint for both pairwise comparisons (i.e., dapagliflozin 5 mg versus placebo and dapagliflozin 10 mg versus placebo) using the Dunnett and Tamhane step-up procedure (23). The primary estimand for the primary endpoint was treatment difference at Week 24 if subjects did not discontinue randomized treatment. The primary analysis of the change in HbA1c 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 endpoints, point estimates and 2-sided 95% confidence intervals (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 6-point SMBG), longitudinal repeated measures analyses using direct likelihood and the SAS procedure PROC MIXED was 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 HbA1c reduction of ≥0.5% at Week 24 and the proportion of patients achieving HbA1c of <7% at Week 24 was analyzed using logistic regression with adjustment for baseline HbA1c and stratum and using last observation carried forward. Odds ratios (ORs) and corresponding 95% CIs for each treatment group vs. placebo were presented for each of these endpoints.

Results

Patient disposition

Between July 08, 2015 and September 02, 2017, 1465 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 (**Figure 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 HbA1c was 8.44%, 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 HbA1c with both dapagliflozin doses versus placebo. Mean changes (95% CI) in HbA1c 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; **Figure 2a**) for dapagliflozin 5 mg and 10 mg, respectively. Initial reduction in HbA1c 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 HbA1c 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 endpoints. 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; **Figure 2b**), 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 (standard error [SE]) for basal insulin for dapagliflozin 5 mg, 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% (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 (**Figure 2c**). 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 HbA1c reduction of ≥0.5% without severe hypoglycemia (dapagliflozin 5 mg: 105/266, 39.5%; 10 mg: 111/267, 41.6%; placebo: 54/269, 20.1%). The OR (95% CI) versus placebo for achieving an HbA1c reduction of ≥0.5% without experiencing severe hypoglycemia were statistically significant for both dapagliflozin doses: 2.71 (1.81, 4.06) for dapagliflozin 5 mg versus placebo; 3.07 (2.05, 4.60) for dapagliflozin 10 mg versus placebo; p<0.0001 for both (**Figure 2D**). After 24 weeks of treatment, the proportion of patients achieving HbA1c reduction of ≥0.5% after 24 weeks of treatment was 42.9%, 44.6%, 21.2% for dapagliflozin 5 mg, 10 mg and placebo, respectively (OR [95% CI] for dapagliflozin 5 mg versus placebo, 2.97 [1.99, 4.42]; OR [95% CI] for dapagliflozin 10 mg versus placebo, 3.30 [2.22, 4.92]). Given that the lower bound of HbA1c at inclusion was 7.5% at baseline, a relatively small, the proportion of patients achieved an HbA1c of <7% after 24 weeks of treatment. The percentages were 4.9%, 3.7%, 1.5% for dapagliflozin 5 mg, 10 mg and placebo, respectively (OR [95% CI] for dapagliflozin 5 mg versus placebo, 3.55 [1.12, 11.18]; OR [95% CI] for dapagliflozin 10 mg versus 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–≤180 mg/dL [>3.9–≤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, 10 mg and placebo, respectively, while 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. Discontinuations due to AEs occurred in 6.3%, 4.4%, and 4.0% of subjects in the dapagliflozin 5 mg, 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, 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%], 10 [3.7%] patients), and

pollakiuria (in 22 [8.1], 14 [5.2], and 6 [2.2%] patients). There were few cardiovascular (1, 3, and 2 in the dapagliflozin 5 mg, 10 mg, and placebo groups, respectively) or hepatic events (5, 5, and 6). 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% versus 2.5%; dapagliflozin 10 mg: 12.8% versus 1.7%; placebo: 3.3% versus 0%). SAEs of genital infection were not reported in any treatment group. Occurrence of UTI was balanced across treatment groups, but was more common in females than in males (dapagliflozin 5 mg: 11.8% versus 0%; dapagliflozin 10 mg: 6.0% versus 0.8%; placebo: 7.2% versus 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, 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 4**; 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, 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

intravenous (IV) fluids and insulin. Of the three aforementioned patients, two received only IV fluids as treatment for DKA while one patient did not have treatment recorded. 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 IV 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 BOBH 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 beta-hydroxybutyrate 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% 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 to those seen in the phase 3 inTandem3 study, which examined the effects of sotagliflozin, a non-selective SGLT2/SGLT1 inhibitor, added to insulin treatment in patients with type 1 diabetes (17). Direct comparisons between the DEPICT studies and InTandem 3 are difficult as definitions around safety events could potentially differ. Further, InTandem 3 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 versus dapagliflozin 10 mg versus 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 inter-study differences. Further, the risk factors for developing DKA in DEPICT-2 was generally consistent with that 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 against the increased DKA risk. 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 T1DM 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. Firstly, 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. Secondly, 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 HbA1c, mean glucose levels, glycemic variability, 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.

Acknowledgements

Funding: This study was funded by AstraZeneca and Bristol-Myers Squibb.

The authors would like to 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 funded by AstraZeneca.

CM is the guarantor for 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.

All authors have contributed to the study concept and design, analysis, and interpretation of the study data. All authors have also contributed to the drafting of the manuscript and revising it critically for intellectual content.

Disclosures

CM 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 bureaux for Novo Nordisk, Sanofi, Merck Sharp and Dohme, Eli Lilly, Boehringer Ingelheim, AstraZeneca, and Novartis. CM's institute has received research support for CM from Novo Nordisk, Sanofi, Merck Sharp and Dohme, Eli Lilly, Roche Diagnostics, Abbott, Intrexon, and Novartis. PD 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. PG serves or has

served on advisory boards for Novo Nordisk, Sanofi, Eli Lilly, Boehringer Ingelheim, Janssen Pharmaceuticals, Lifescan, Roche Diagnostics, Medtronic, Abbott, Dexcom, Ypsomed and serves or has served on speakers' bureaus for Boehringer Ingelheim, Bayer, Medtronic, Roche Diagnostics, and Abbott. PG's institute has received research support for him from Medtronic, Abbott, Roche Diagnostics, Merck Sharp and Dome and Menarini. PS has received consulting fees from Abbott, Astra-Zeneca, Boehringer Ingelheim, Eli Lilly, Janssen, Novo Nordisk, and Sanofi ; honoraria for delivering accredited CME from Abbott, Astra-Zeneca, Boehringer Ingelheim, Eli Lilly, Janssen, Merck, Novo Nordisk, and Sanofi; and his institution has received research support from Allergan, Astra-Zeneca, Genzyme, Novo Nordisk, Prometic, Sanofi, and Viacyte. CH has no conflicts of interests. EA 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, MSD, Nippon Boehringer Ingelheim, Novo Nordisk Pharma, Novartis Pharma, Ono Pharmaceutical, Sanofi, Taisho Toyama Pharmaceutical, and Takeda Pharmaceutical. ML has received research grants from Astra Zeneca, DexCom, Novo Nordisk, and Pfizer, been consultant for or received honoraria from Astra Zeneca, Eli Lilly, Medtronic, Novo Nordisk, and Rubin Medical, and participated in advisory boards for MSD and Novo Nordisk. SCB 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; honoraria from Novo Nordisk, Sanofi, Lilly, Boehringer Ingelheim, and Merck; and has ownership interest in Glycosmedia (diabetes on-line news service). SJ is a consultant for AstraZeneca, Janssen, and Eli Lilly. LH was an employee of Bristol-Myers Squibb during the conduct of this study and is currently an employee of Medimmune, and is a shareholder of Bristol-Myers Squibb and Novo Nordisk A/S. NA and FT are employees of AstraZeneca. AML is an employee and shareholder of AstraZeneca.

References

1. McKnight JA, Wild SH, Lamb MJ, Cooper MN, Jones TW, Davis EA, Hofer S, Fritsch M, Schober E, Svensson J, Almdal T, Young R, Warner JT, Delemer B, Souchon PF, Holl RW, Karges W, Kieninger DM, Tigas S, Bargiota A, Sampanis C, Cherubini V, Gesuita R, Strele I, Pildava S, Coppell KJ, Magee G, Cooper JG, Dinneen SF, Eeg-Olofsson K, Svensson AM, Gudbjornsdottir S, Veeze H, Aanstoot HJ, Khalangot M, Tamborlane WV, Miller KM. Glycaemic control of Type 1 diabetes in clinical practice early in the 21st century: an international comparison. *Diabet Med* 2015;**32**:1036-1050

2. Miller KM, Foster NC, Beck RW, Bergenstal RM, DuBose SN, DiMeglio LA, Maahs DM, Tamborlane WV. Current state of type 1 diabetes treatment in the U.S.: updated data from the T1D Exchange clinic registry. *Diabetes Care* 2015;**38**:971-978

3. Lind M, Svensson AM, Kosiborod M, Gudbjornsdottir S, Pivodic A, Wedel H, Dahlqvist S, Clements M, Rosengren A. Glycemic control and excess mortality in type 1 diabetes. *N Engl J Med* 2014;**371**:1972-1982

4. Type 1 diabetes in adults: diagnosis and management [article online], 2015 Available from https://www.nice.org.uk/guidance/ng17. Accessed January 2018 2018

5. Donnelly LA, Morris AD, Frier BM, Ellis JD, Donnan PT, Durrant R, Band MM, Reekie G, Leese GP. Frequency and predictors of hypoglycaemia in Type 1 and insulin-treated Type 2 diabetes: a population-based study. *Diabet Med* 2005;**22**:749-755

6. Nathan DM. The diabetes control and complications trial/epidemiology of diabetes interventions and complications study at 30 years: overview. *Diabetes Care* 2014;**37**:9-16

7. UK Hypoglycaemia Study Group. Risk of hypoglycaemia in types 1 and 2 diabetes: effects of treatment modalities and their duration. *Diabetologia* 2007;**50**:1140-1147

8. Russell-Jones D, Khan R. Insulin-associated weight gain in diabetes--causes, effects and coping strategies. *Diabetes Obes Metab* 2007;**9**:799-812

9. Frier BM, Schernthaner G, Heller SR. Hypoglycemia and cardiovascular risks. *Diabetes Care* 2011;**34 Suppl 2**:S132-137

10. Lavie CJ, Milani RV, Ventura HO. Obesity and cardiovascular disease: risk factor, paradox, and impact of weight loss. *J Am Coll Cardiol* 2009;**53**:1925-1932

11. Kalra S, Mukherjee JJ, Venkataraman S, Bantwal G, Shaikh S, Saboo B, Das AK, Ramachandran A. Hypoglycemia: The neglected complication. *Indian J Endocrinol Metab* 2013;**17**:819-834

12. Harris S, Mamdani M, Galbo-Jorgensen CB, Bogelund M, Gundgaard J, Groleau D. The effect of hypoglycemia on health-related quality of life: Canadian results from a multinational time trade-off survey. *Can J Diabetes* 2014;**38**:45-52

13. Davis RE, Morrissey M, Peters JR, Wittrup-Jensen K, Kennedy-Martin T, Currie CJ. Impact of hypoglycaemia on quality of life and productivity in type 1 and type 2 diabetes. *Curr Med Res Opin* 2005;**21**:1477-1483

14. Henry RR, Rosenstock J, Edelman S, Mudaliar S, Chalamandaris AG, Kasichayanula S, Bogle A, Iqbal N, List J, Griffen SC. Exploring the potential of the SGLT2 inhibitor dapagliflozin in type 1 diabetes: a randomized, double-blind, placebo-controlled pilot study. *Diabetes Care* 2015;**38**:412-419

15. Chen J, Fan F, Wang JY, Long Y, Gao CL, Stanton RC, Xu Y. The efficacy and safety of SGLT2 inhibitors for adjunctive treatment of type 1 diabetes: a systematic review and meta-analysis. *Sci Rep* 2017;**7**:44128

16. Dandona P, Mathieu C, Phillip M, Hansen L, Griffen SC, Tschope D, Thoren F, Xu J, Langkilde AM. Efficacy and safety of dapagliflozin in patients with inadequately controlled type 1 diabetes (DEPICT-1): 24 week results from a multicentre, double-blind, phase 3, randomised controlled trial. *Lancet Diabetes Endocrinol* 2017;**5**:864-876

17. Garg SK, Henry RR, Banks P, Buse JB, Davies MJ, Fulcher GR, Pozzilli P, Gesty-Palmer D, Lapuerta P, Simo R, Danne T, McGuire DK, Kushner JA, Peters A, Strumph P. Effects of Sotagliflozin Added to Insulin in Patients with Type 1 Diabetes. *N Engl J Med* 2017;**377**:2337-2348

18. Henry RR, Dandona P, Pettus J, Mudaliar S, Xu J, Hansen L. Dapagliflozin in patients with type 1 diabetes: A post hoc analysis of the effect of insulin dose adjustments on 24-hour continuously monitored mean glucose and fasting beta-hydroxybutyrate levels in a phase IIa pilot study. *Diabetes Obes Metab* 2017;**19**:814-821

19. Kuhadiya ND, Ghanim H, Mehta A, Garg M, Khan S, Hejna J, Torre B, Makdissi A, Chaudhuri A, Batra M, Dandona P. Dapagliflozin as Additional Treatment to Liraglutide and Insulin in Patients With Type 1 Diabetes. *J Clin Endocrinol Metab* 2016;**101**:3506-3515

20. Service FJ, Molnar GD, Rosevear JW, Ackerman E, Gatewood LC, Taylor WF. Mean amplitude of glycemic excursions, a measure of diabetic instability. *Diabetes* 1970;**19**:644-655

21. Seaquist ER, Anderson J, Childs B, Cryer P, Dagogo-Jack S, Fish L, Heller SR, Rodriguez H, Rosenzweig J, Vigersky R. Hypoglycemia and diabetes: a report of a workgroup of the American Diabetes Association and the Endocrine Society. *Diabetes Care* 2013;**36**:1384-1395

22. Kitabchi AE, Umpierrez GE, Miles JM, Fisher JN. Hyperglycemic crises in adult patients with diabetes. *Diabetes care* 2009;**32**:1335-1343

23. Dunnett CW, Tamhane AC. A Step-Up Multiple Test Procedure. *Journal of the American Statistical Association* 1992;**87**:162-170

24. Empagliflozin as Adjunctive to InSulin thErapy Over 52 Weeks in Patients With Type 1 Diabetes Mellitus (EASE-2) [article online], 2018. Available from https://clinicaltrials.gov/ct2/show/NCT02414958.

25. Empagliflozin as Adjunctive to Insulin Therapy Over 26 Weeks in Patients With T1DM (EASE-3) [article online], 2018. Available from https://clinicaltrials.gov/ct2/show/NCT02580591.

26. Henry RR, Thakkar P, Tong C, Polidori D, Alba M. Efficacy and Safety of Canagliflozin, a Sodium-Glucose Cotransporter 2 Inhibitor, as Add-on to Insulin in Patients With Type 1 Diabetes. *Diabetes Care* 2015;**38**:2258-2265

Table 1: Demographic and baseline characteristics

Characteristic	Dapagliflozin 5 mg + Insulin (n=271)	Dapagliflozin 10 mg + Insulin (n=270)	Placebo + Insulin (n=272)
Gender			
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)	0.72 (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%)
HbA1c (%)	8.45 (0.69)	8.43 (0.69)	8.43 (0.65)
HbA1c (mmol/mol)	69 (7.5)	69 (7.5)	69 (7.1)
HbA1c 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).

BMI, body mass index; CGM, continuous glucose monitoring; CSII, continuous subcutaneous insulin infusion; HbA1c, glycated hemoglobin; MDI, multiple daily injections; T1D, type 1 diabetes; SD, standard deviation.

Table 2: Safety summary

Characteristic	Dapagliflozin 5 mg + Insulin (n=271)	Dapagliflozin 10 mg + Insulin (n=270)	Placebo + Insulin (n=272)
Adverse events			
≥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%)
Serious adverse events			
≥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: female ratio in patients experiencing definite DKA			
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 insulin total daily dose (IU) reduction compared with baseline for week before DKA event†	–16.83	–21.97	NA
Mean percent insulin total daily dose (IU)	–15.68	–22.93	NA

reduction compared with baseline at the end of 24 week treatment period†			
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 (%). 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. 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.

*Cause for DKA included alcohol intake, stress and stroke.

†Means apply for patients with definite DKA.

AE, adverse event; CSII, continuous subcutaneous insulin infusion; DKA, diabetic ketoacidosis; NA, not applicable; SAE, serious adverse event.

Figure legends

Figure 1: Patient disposition.

Figure 2: Change in (A) HbA1c (%), (B) total daily dose of insulin (%), and (C) total body weight (kg) over 24 weeks and (D) proportion of patients achieving an HbA1c reduction of ≥0.5% without severe hypoglycemia (%) at Week 24*

*Patients per time point indicate the number of patients with data at that time point as defined by the visit windows in the protocol regardless of whether that patient was still receiving randomized treatment.

BL, baseline; CI, confidence interval; DAPA, dapagliflozin; HbA1c, glycated hemoglobin; PBO, placebo; INS, insulin; SD, standard deviation; SE, standard error