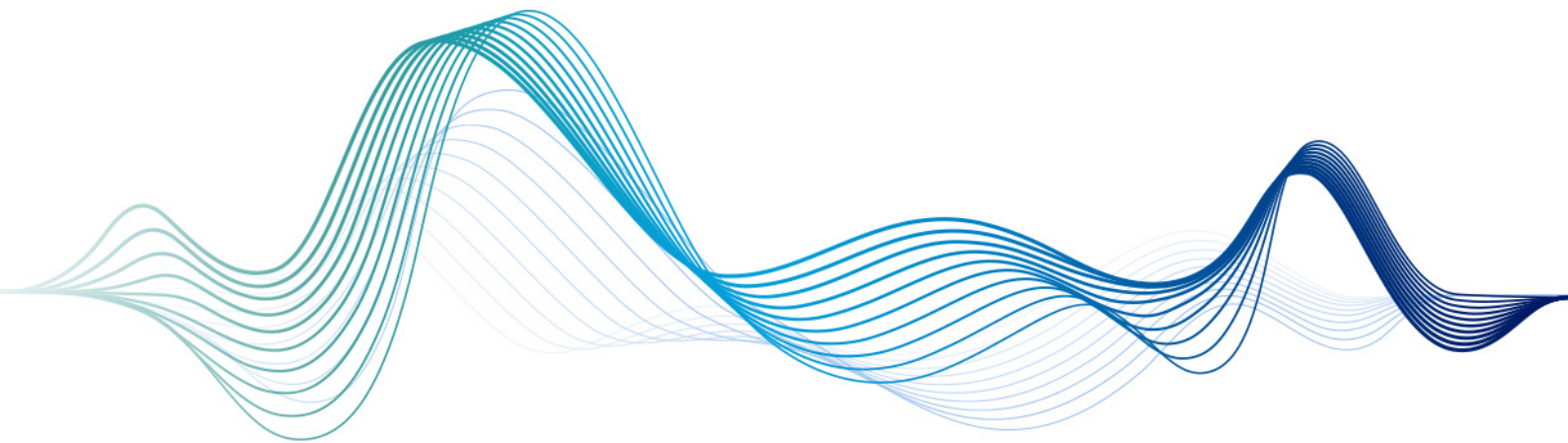


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**ORIGINAL ARTICLE**

Benefit/risk profile of dapagliflozin 5 mg in the DEPICT-1 and -2 trials in individuals with type 1 diabetes and body mass index ≥ 27 kg/m²

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Abstract

Aim: The DEPICT-1 and -2 studies (NCT02268214, NCT02460978) evaluated the efficacy and safety of dapagliflozin in individuals with type 1 diabetes who were receiving intensive insulin therapy. The DEPICT-1 and -2 studies (NCT02268214, NCT02460978) evaluated the efficacy and safety of dapagliflozin in individuals with type 1 diabetes. This *post-hoc* study investigated the safety and efficacy of dapagliflozin in individuals with BMI ≥ 27 kg/m² to assess if the benefit/risk ratio associated with dapagliflozin treatment can be further improved than that observed in the overall DEPICT population.

Methods: Changes in glycated haemoglobin (HbA1c) and body weight, percentage change in daily insulin dose and proportion of participants achieving HbA1c reduction $\geq 0.5\%$ without severe hypoglycaemia were evaluated at weeks 24 and 52. Changes in mean interstitial glucose, mean amplitude of glycaemic excursions and time in target glycaemic range were evaluated at week 24. Safety was assessed until week 56.

Abbreviations: AE, adverse event; DKA, diabetic ketoacidosis; HbA1c, glycated haemoglobin; SAE, serious adverse event; SGLT2, sodium-glucose cotransporter-2.

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Results: Week-52 adjusted mean (SE) change from baseline for HbA1c was -0.26% (0.05) with dapagliflozin versus $+0.08\%$ (0.05) with placebo and for body weight was -2.74 kg (0.25) with dapagliflozin versus $+0.81$ kg (0.26) with placebo. Mean (SE) percentage change in daily insulin dose was -10.5% (1.23) with dapagliflozin versus -1.4% (1.36) with placebo. Time spent in target glycaemic range increased by 2.2 h/day versus placebo. Dapagliflozin was well tolerated, with fewer participants experiencing diabetic ketoacidosis (dapagliflozin, 1.7%; placebo, 1.0%) than dapagliflozin 5 mg receiving participants in the pooled DEPICT populations.

Conclusions: Compared with the pooled DEPICT population, the benefit/risk profile of adjunct dapagliflozin therapy was more favourable in individuals with type 1 diabetes with body mass index ≥ 27 kg/m² because of the reduced risk of diabetic ketoacidosis in this population.

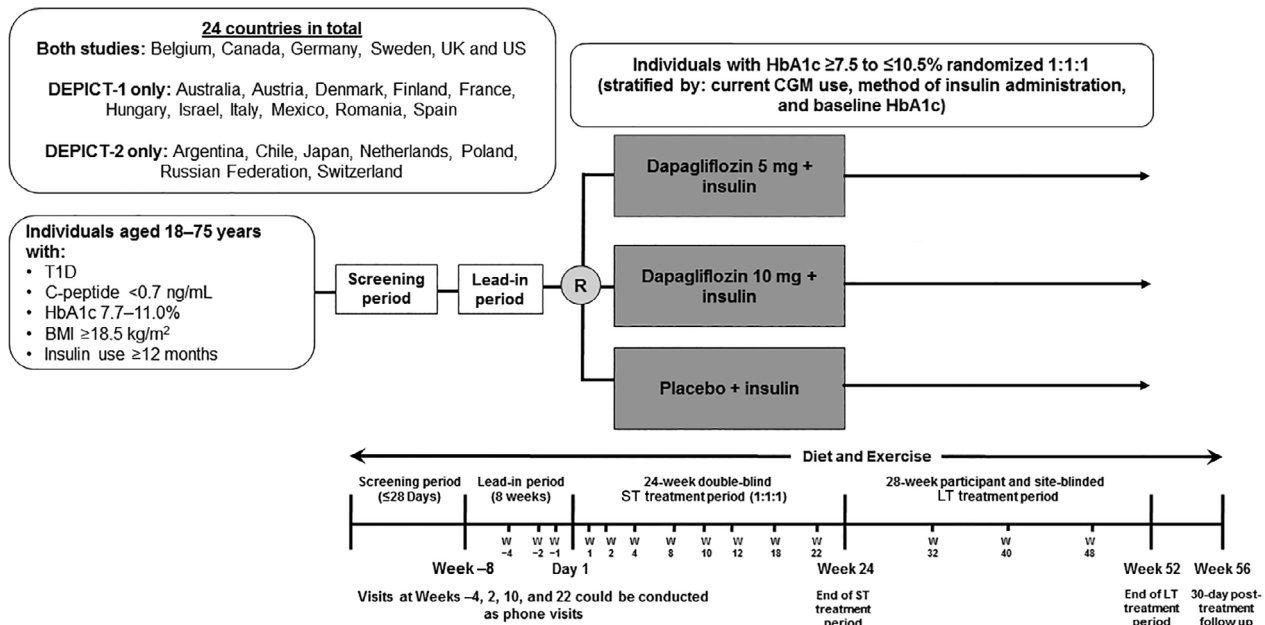
KEYWORDS

benefit/risk, BMI, body weight, dapagliflozin, DEPICT, DKA, HbA1c, T1D, type 1 diabetes

1 | INTRODUCTION

The DEPICT (Dapagliflozin Evaluation in Patients with Inadequately Controlled Type 1 Diabetes) -1 and -2 trials evaluated the use of dapagliflozin as an adjunct to insulin in individuals with type 1 diabetes (T1D) over 24 weeks, with a 28-week long-term extension (52 weeks in total) and a 4-week post-treatment follow-up.¹⁻⁴ Results from these trials showed reductions in glycated haemoglobin (HbA1c),

body weight and glycaemic variability, with improved time in target blood glucose range and no increased risk of hypoglycaemia in participants receiving dapagliflozin (5 and 10 mg) compared with those receiving placebo; these effects were maintained until week 52.¹⁻⁴ Although generally well tolerated, over 52 weeks, participants treated with dapagliflozin in the DEPICT trials showed an increased incidence of diabetic ketoacidosis (DKA) compared with those receiving placebo.¹⁻⁴ In the pooled DEPICT-1 and -2 populations, over



Total daily insulin dose recommended to be reduced by up to 20% on Day 1, before attempting to titrate back to baseline levels taking into account self-monitored blood glucose, local guidance and individual circumstances. BMI, body mass index; CGM, continuous glucose monitoring; LT, long term; ST, short term; T1D, type 1 diabetes

FIGURE 1 Study design for the DEPICT-1 and -2 studies. Total daily insulin dose recommended to be reduced by up to 20% on Day 1, before attempting to titrate back to baseline levels taking into account self-monitored blood glucose, local guidance and individual circumstances. BMI, body mass index; CGM, continuous glucose monitoring; HbA1c, glycated haemoglobin; LT, long term; R, randomization; ST, short term; T1D, type 1 diabetes; W, week

52 weeks, 4.0%, 3.5% and 1.1% of participants receiving dapagliflozin 5 mg, 10 mg and placebo, respectively, had events adjudicated as definite DKA (incidence rates: 4.6, 3.9 and 1.3 per 100 patient-years, respectively).⁵ The benefit/risk profile of drugs may vary across patient populations/subgroups. Post-hoc analysis of five different body mass index (BMI) subgroups in the pooled DEPICT-1 and -2 populations suggested that the risk of DKA was lower in participants with higher BMI.⁶ Thus, in this study, we evaluated the efficacy and safety of dapagliflozin 5 mg compared with placebo, both used as an adjunct to insulin, in participants with BMI ≥ 27 kg/m² in the pooled DEPICT population.

2 | METHODS

2.1 | Study design and participants

This post-hoc analysis used pooled data from the DEPICT-1 and -2 trials (NCT02268214 and NCT02460978, respectively), which were Phase III, randomized, double-blind, three-arm, parallel-group, placebo-controlled, multicentre studies of near-identical design conducted in the following 24 countries: Australia, Austria, Argentina, Belgium, Canada, Chile, Denmark, Finland, France, Germany, Hungary, Israel, Italy, Japan, Mexico, the Netherlands, Poland, Romania, the Russian Federation, Spain, Sweden, Switzerland, the United Kingdom and the United States of America. Both DEPICT trials were conducted in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines as defined by the International Conference on Harmonization, and approved by the Institutional Review Boards and Independent Ethics Committees for all participating centres. Written informed consent was obtained for all participants. The study design for the DEPICT-1 and -2 trials have been published previously (Figure 1).^{1-3,7} This post-hoc analysis included participants from the pooled DEPICT population with BMI ≥ 27 kg/m² at baseline.

2.2 | Procedures

Detailed procedures for the DEPICT trials have been reported previously.^{1-3,7} Eligible participants with T1D entered an 8-week, lead-in period for the optimization of diabetes management. Participants completing this period were randomized (1:1:1) to receive dapagliflozin (5 or 10 mg) or matched placebo, orally once daily during the treatment period. Participants completing 24 weeks of randomized treatment (short-term study) who were eligible for the 28-week extension (long-term study) continued their allocated randomized therapy until week 52. The last follow-up was at week 56. In the DEPICT-1 study, 55 participants (with any BMI) were randomized incorrectly; these participants, where applicable, were excluded from efficacy analyses but included in safety analyses.

Glucose control (including self-monitoring of blood glucose) and home blood ketone (beta-hydroxybutyrate) measurements were reviewed at each study visit. Self-monitoring blood-glucose readings, local

guidance and individual circumstances were used to adjust insulin dose as needed. Mode of insulin administration could not be changed during the trial, unless an insulin pump needed replacement, in which case the participant could temporarily use multiple daily injections, restarting continuous subcutaneous insulin infusion at the earliest possible time.

Safety and tolerability were assessed throughout the study and during the last follow-up visit. Adverse events (AEs), serious AEs (SAEs), vital signs, physical examination findings, electrocardiogram and laboratory values were monitored.

2.3 | Endpoints

The following efficacy outcomes were analysed at weeks 24 and 52: changes from baseline in HbA1c and body weight, percentage change from baseline in daily insulin dose and proportion of participants achieving HbA1c reduction $\geq 0.5\%$ with no severe hypoglycaemia. Changes from baseline in mean interstitial glucose measured using

TABLE 1 Demographics and baseline characteristics for participants with BMI ≥ 27 kg/m²

	Dapagliflozin 5 mg + insulin (N = 286)	Placebo + insulin (N = 289)
Age, years	44.5 \pm 13.13	45.0 \pm 13.40
Male, n (%)	120 (42.0)	144 (49.8)
Geographic region, n (%)		
North America	113 (39.5)	109 (37.7)
Latin America	23 (8.0)	19 (6.6)
Europe	123 (43.0)	143 (49.5)
Asia/Pacific	27 (9.4)	18 (6.2)
Body weight, kg	91.12 \pm 15.68	92.89 \pm 16.51
BMI, kg/m ²	31.72 \pm 4.62	31.85 \pm 4.24
Duration of T1D, years	21.26 \pm 11.54	22.25 \pm 12.10
Total baseline insulin, IU	71.94 \pm 44.19	70.75 \pm 30.08
Total baseline insulin, IU/kg	0.78 \pm 0.50	0.76 \pm 0.27
HbA1c, %	8.43 \pm 0.63	8.40 \pm 0.61
Fasting plasma glucose, mg/dL	185.2 \pm 76.00	192.6 \pm 80.51
Fasting C-peptide, ng/mL	0.085 \pm 0.111	0.082 \pm 0.105
Mode of insulin administration, n (%)		
MDI	160 (55.9)	168 (58.1)
CSII	126 (44.1)	121 (41.9)
Use of CGM, n (%)	90 (31.5)	81 (28.0)
eGFR, n (%)		
<60 mL/min/1.73 m ²	17 (5.9)	18 (6.2)
≥ 60 –<90 mL/min/1.73 m ²	148 (51.7)	146 (50.5)
≥ 90 mL/min/1.73 m ²	121 (42.3)	125 (43.3)

Note: Data are mean \pm SD, unless otherwise stated. Abbreviations: BMI, body mass index; CGM, continuous glucose monitoring; CSII, continuous subcutaneous insulin infusion. eGFR, estimated glomerular filtration rate; HbA1c, glycated haemoglobin; MDI, multiple daily injections; T1D, type 1 diabetes.

continuous glucose monitoring, mean amplitude of glycaemic excursions and time in target glycaemic range [>70 and ≤ 180 mg/dL (>3.9 and ≤ 10.0 mmol/L)] at week 24 were also assessed. Safety analyses included assessment of AEs, SAEs and AEs of special interest, including hypoglycaemia (classified according to the American Diabetes Association classification criteria)⁸ and events of DKA (subject to adjudication). Safety analyses were assessed up to week 56.

2.4 | Statistics

Efficacy analyses were performed using the full analysis set for all participants correctly randomized to dapagliflozin 5 mg or placebo, with

BMI ≥ 27 kg/m² at baseline and having both baseline and any post-baseline assessments. Treatment effects were measured by pairwise comparisons between dapagliflozin and placebo groups. In general, *P*-values were not calculated for treatment group comparisons, as these subgroup analyses were exploratory in nature. Longitudinal repeated-measures analyses of variables with fixed categorical effects for study, treatment, week, randomization-stratification factors (one term for each combination of all stratification factors), treatment-by-week interaction, subgroup, treatment-by-subgroup interaction, week-by-subgroup interaction, treatment-by-week-by-subgroup interaction and continuous fixed covariates (baseline measurement and baseline measurement-by-week interaction) were performed to measure change or percentage change (log-transformed endpoint) from baseline. Mean or percentage

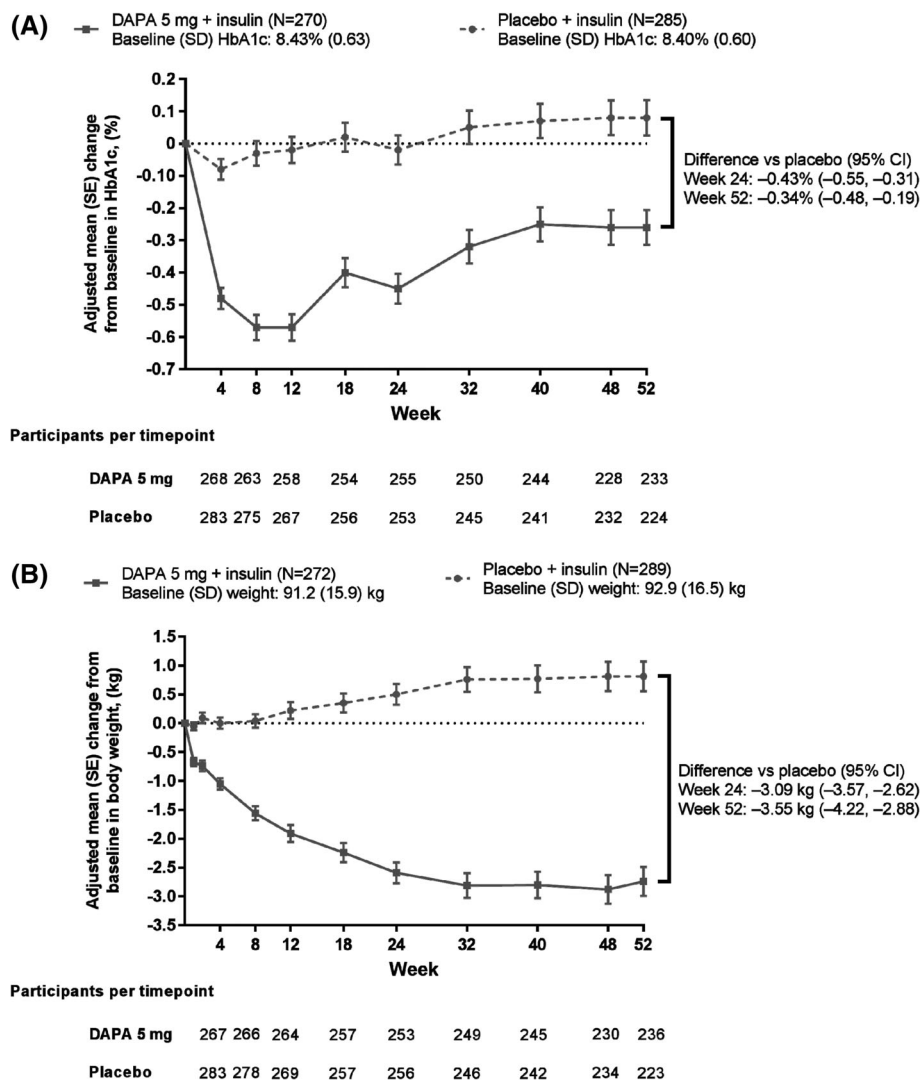


FIGURE 2 Efficacy endpoints in patients with BMI ≥ 27 kg/m². A, Change from baseline to week 52 in HbA1c, B, change from baseline to week 52 in body weight, C, time in target glycaemic range at week 24, and D, proportion of participants achieving a reduction in HbA1c $\geq 0.5\%$ without experiencing severe hypoglycaemia at week 24 and week 52. Mixed model included terms for baseline, treatment, study, week, stratum, week*treatment, week*baseline, subgroup, treatment*subgroup, week*subgroup and treatment*week*subgroup. Stratum includes one term for each combination of the three stratification factors on baseline HbA1c, use of personal continuous glucose monitoring system and methods of insulin administration. Bars show SE in Figure 1A,B). ^aUnadjusted *P*-value indicated in Figure 1D and logistic regression adjusted for baseline HbA1c, study and randomization strata. DAPA, dapagliflozin; HbA1c, glycated haemoglobin; T1D, type 1 diabetes

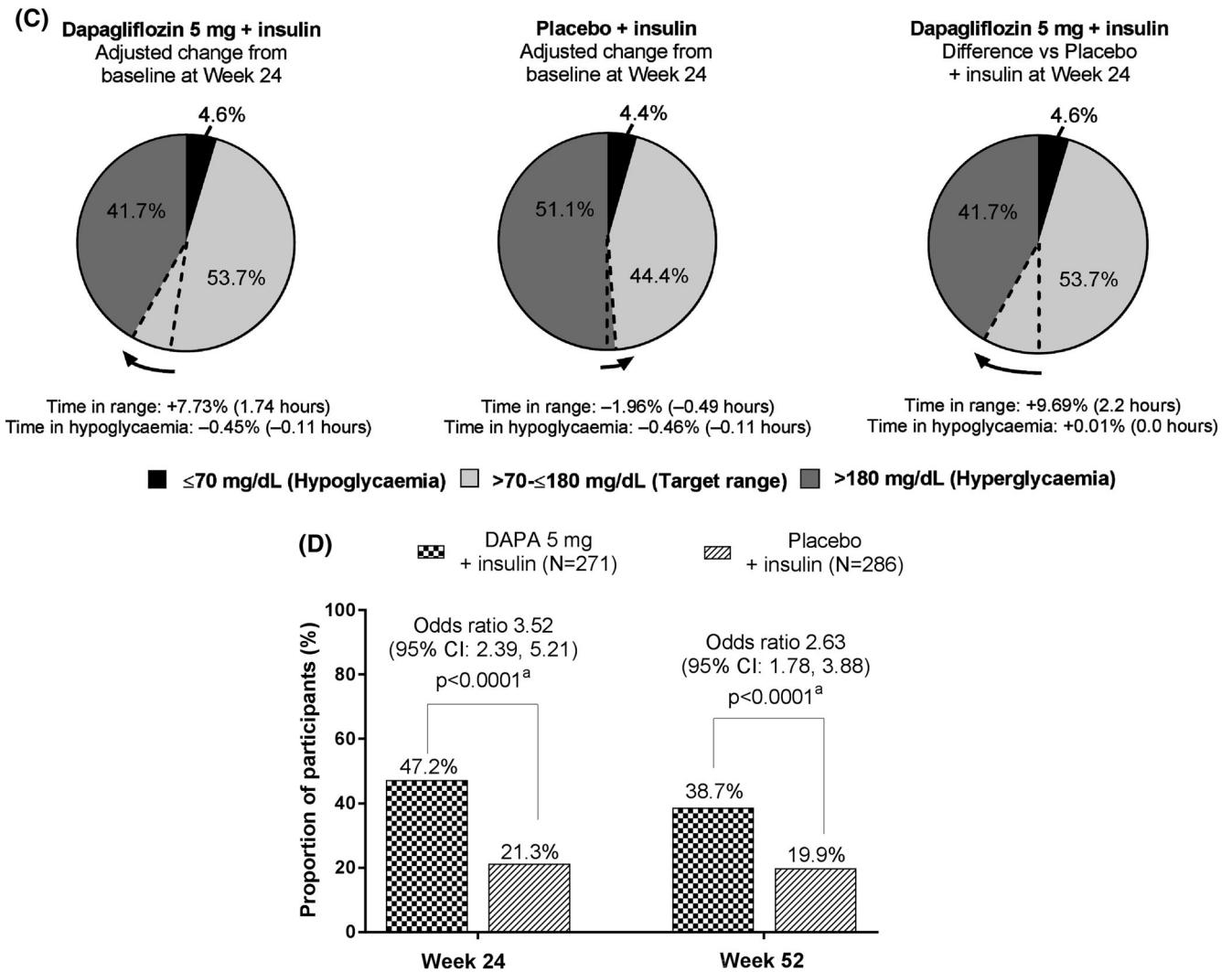


FIGURE 2 (Continued)

change from baseline and 95% confidence intervals (CI) were calculated for all post-baseline visits, except for a follow-up visit at week 56. Logistic regression adjusted for baseline HbA1c, study and combination of randomization stratification factors was used to calculate the proportion of participants reaching a target at week 52. Up to week 24, insulin dose was recorded daily at set times, but between weeks 24 and 52, participants recorded the midpoint for basal and bolus insulin dose each week. Therefore, the mean percentage change over time (descriptive only) was reported for this variable.

Safety analyses were performed using the safety analysis set comprising all participants randomized to dapagliflozin 5 mg or placebo with BMI ≥ 27 kg/m². Safety variables were summarized descriptively. No statistical tests were performed to compare rates between treatment groups. To compare the incidence of DKA in this population with that in the pooled DEPICT populations, a summary of events adjudicated as definite DKA in the overall pooled DEPICT populations for participants randomized to dapagliflozin 5 mg or equivalent placebo, is also included in this study.

SAS version 9.4 or higher was used for all analyses.

3 | RESULTS

3.1 | Participants

This analysis included 575 participants with T1D and BMI ≥ 27 kg/m²; 286 in the dapagliflozin 5 mg group and 289 in the placebo group. In total, 52.2% of the participants receiving dapagliflozin 5 mg and 54.3% of the participants receiving placebo from the pooled DEPICT population had a BMI of ≥ 27 kg/m² and were included in these post-hoc analyses. Baseline characteristics were balanced between the treatment groups (Table 1).

3.2 | Efficacy

Dapagliflozin 5 mg used as an adjunct to insulin reduced HbA1c levels from baseline to weeks 24 and 52 compared with placebo (Figure 2A). At week 52, the adjusted mean (SE) change in HbA1c from baseline was -0.26% (0.05) for dapagliflozin and +0.08% (0.05) for placebo

TABLE 2 Efficacy endpoints at week 24 and week 52 in participants with BMI ≥ 27 kg/m² from the DEPICT studies

		Dapagliflozin 5 mg + insulin	Placebo + insulin
HbA1c, %		n = 270	n = 285
Week 24	Adjusted mean change (SE)	-0.45 (0.05)	-0.02 (0.05)
	Difference versus placebo (95% CI)	-0.43 (-0.55, 0.31)	-
Week 52	Adjusted mean change (SE)	-0.26 (0.05)	0.08 (0.05)
	Difference versus placebo (95% CI)	-0.34 (-0.48, -0.19)	-
Body weight, kg		n = 272	n = 289
Week 24	Adjusted mean percentage change (SE)	-2.59 (0.18)	0.50 (0.18)
	Difference versus placebo (95% CI)	-3.09 (-3.57, -2.62)	-
Week 52	Adjusted mean percentage change (SE)	-2.74 (0.25)	0.81 (0.26)
	Difference versus placebo (95% CI)	-3.55 (-4.22, -2.88)	-
Body weight, %		n = 272	n = 289
Week 24	Adjusted mean percentage change (SE)	-3.15 (0.23)	0.22 (0.23)
	Difference versus placebo (95% CI)	-3.36 (-3.94, -2.77)	-
Week 52	Adjusted mean percentage change (SE)	-3.31 (0.31)	0.49 (0.32)
	Difference versus placebo (95% CI)	-3.78 (-4.58, -2.98)	-
Total daily insulin dose, % ^a		n = 272	n = 287
Week 24	Mean percentage change (SE)	-10.80 (0.98)	-0.57 (1.13)
Week 52	Mean percentage change (SE)	-10.52 (1.23)	-0.37 (1.36)

^aUp to week 24 insulin dose was recorded daily at set times, but between week 24 and week 52 participants recorded the midpoint for basal and bolus insulin dose each week. Therefore, mean percentage change over time (descriptive only) are reported here.

Abbreviations: CI, confidence interval; HbA1c, glycated haemoglobin; SE, standard error.

[difference vs. placebo (CI): -0.34% (-0.48, -0.19)]. Compared with placebo, adjunct dapagliflozin treatment reduced body weight and daily insulin dose from baseline to weeks 24 and 52 (Figure 2B; Figure S1). At week 52, adjusted mean (SE) change in body weight from baseline was -2.74 kg (0.25) with dapagliflozin and +0.81 kg (0.26) with placebo [difference vs. placebo (95% CI): -3.55 kg (-4.22, -2.88)]. Adjusted mean (SE) percentage change in body weight from baseline was -3.31% (0.31) with dapagliflozin and +0.49% (0.32) with placebo [difference vs. placebo (95% CI): -3.78% (-4.58, -2.98)]. Mean (SE) percentage change in daily insulin dose was -10.52% (1.23) and -1.37% (1.36) with dapagliflozin and placebo, respectively, at week 52. Compared with placebo, treatment with dapagliflozin increased the mean time in target glycaemic range (glucose >70 to ≤ 180 mg/dL) from baseline to week 24 [Figure 2C; difference vs. placebo (95% CI): 9.69% (7.61, 11.77)], amounting to an additional 2.2 h/day. No increase was observed in time in hypoglycaemic state (glucose ≤ 70 mg/dL). Table 2 shows changes in HbA1c, body weight and daily insulin dose at weeks 24 and 52. Mean interstitial glucose decreased from 192.52 mg/dL at baseline to 176.19 mg/dL at week 24 with dapagliflozin, and increased from 191.25 to 192.38 mg/dL with placebo. The difference versus placebo (95% CI) at week 24 for dapagliflozin was -16.81 mg/dL (-21.37, -12.25). Glucose variability decreased from 169.10 mg/dL at baseline to 148.78 mg/dL at week 24 with dapagliflozin, and from 164.94 mg/dL to 163.71 mg/dL with placebo. The difference versus placebo (95% CI) for dapagliflozin was -17.48 mg/dL (-22.28, -12.67) at week 24. A higher proportion of participants receiving dapagliflozin treatment

achieved $\geq 0.5\%$ reduction in HbA1c without severe hypoglycaemia at week 52 compared with participants receiving placebo [odds ratio (95% CI): 2.63 (1.78, 3.88)] (Figure 2D).

3.3 | Safety

AEs were reported for 79.4% of participants receiving dapagliflozin and 75.1% receiving placebo; SAEs were reported for 11.2% and 8.7% of participants, respectively (Table 3). Discontinuations because of AEs were slightly more frequent in participants receiving dapagliflozin than those receiving placebo. There were no deaths in either treatment group. There were more AEs of genital infection and urinary tract infection in the dapagliflozin group than in the placebo group, with events more frequent in females than males. There was no increase in the proportion of participants experiencing hypoglycaemia or severe hypoglycaemia with dapagliflozin compared with placebo.

Definite DKA was observed in five (1.7%) and three (1.0%) participants receiving dapagliflozin and placebo, respectively, with incidence rates of 1.9 and 1.2 per 100 patient-years. Table 4 lists the incidence of events adjudicated as definite DKA in participants from the overall pooled DEPICT population and in patients with BMI ≥ 27 kg/m². Compared with the overall pooled DEPICT population and therefore, in particular, to the patients with BMI <27 kg/m², fewer events of definite DKA were observed in the BMI ≥ 27 kg/m² group.

TABLE 3 Safety summary

n (%)	Dapagliflozin 5 mg + insulin (N = 286) 269.1 pt-yrs	Placebo + insulin (N = 289) 256.0 pt-yrs
AEs		
≥1 AE	227 (79.4)	217 (75.1)
AE leading to discontinuation	17 (5.9)	13 (4.5)
SAEs		
≥1 SAE	32 (11.2)	25 (8.7)
SAE leading to discontinuation	9 (3.1)	3 (1.0)
Most frequently reported AEs		
Nasopharyngitis	63 (22.0)	63 (21.8)
Upper respiratory tract infection	32 (11.2)	23 (8.0)
Urinary tract infection	23 (8.0)	19 (6.6)
Headache	19 (6.6)	17 (5.9)
Pollakiuria	19 (6.6)	11 (3.8)
Gastroenteritis	16 (5.6)	9 (3.1)
Events of genital infection^a		
Total	43 (15.0)	12 (4.2)
Male	9 (7.5)	0
Female	34 (20.5)	12 (8.3)
Events of urinary tract infection^a		
Total	32 (11.2)	20 (6.9)
Male	3 (2.5)	2 (1.4)
Female	29 (17.5)	18 (12.4)
Hypoglycaemia^b		
Events, n	7906	7888
Participants with ≥1 event, n (%)	245 (85.7)	236 (81.7)
Exposure-adjusted IR/100 pt-yrs	2937.93	3081.12
Severe hypoglycaemia^c		
Events, n (%)	43 (0.5) ^a	62 (0.8) ^a
Participants with ≥1 event, n (%)	33 (11.5)	26 (9.0)
Exposure-adjusted IR/100 pt-yrs	15.98	24.22
Documented symptomatic hypoglycaemia^d		
Events, n (%)	6498 (82.2) ^b	6420 (81.4) ^b
Participants with ≥1 event, n (%)	236 (82.5)	222 (76.8)
Exposure-adjusted IR/100 pt-yrs	2414.71	2507.71

^aBased on a predefined limited list of events of genital infection and urinary tract infection. Percentages experiencing these events by gender are calculated using the number of male (n = 120 for dapagliflozin 5 mg and n = 144 for placebo) and female (n = 166 for dapagliflozin 5 mg and n = 145 for placebo) participants in each group.

^bHypoglycaemia was classified in accordance with the American Diabetes Association classification criteria, and percentages are based on total number of events of hypoglycaemia.

^cSevere hypoglycaemia is defined as an event requiring assistance of another person to administer actively the carbohydrates, glucagon, or take other corrective actions; plasma glucose concentrations may not be available during an event, but neurological recovery following the return of plasma glucose to normal is considered sufficient evidence that the event was induced by a low plasma glucose concentration.

^dDocumented symptomatic hypoglycaemia is defined as an event during which typical symptoms of hypoglycaemia are accompanied by a measured plasma glucose concentration of ≤70 mg/dL (≤3.9 mmol/L).

Abbreviations: AE, adverse event; DKA, diabetic ketoacidosis; IR, incidence rate; pt-yrs, patient-years; SAE, serious adverse event.

4 | DISCUSSION

Since the first studies assessing the efficacy and safety of SGLT inhibitors as adjunct to insulin in individuals with type 1 diabetes were

published, it has been questioned whether the benefit/risk ratio of these agents in this indication could be optimised. Therefore this study evaluated the benefit/risk of the SGLT2 inhibitor, dapagliflozin, in a specific sub-population of the overall DEPICT population – i.e, in those with BMI

TABLE 4 Summary of events adjudicated as definite DKA in the BMI ≥ 27 kg/m² and overall pooled DEPICT populations

	Dapagliflozin 5 mg + insulin	Placebo + insulin
Pooled DEPICT-1 and -2 population ^a	548	532
Events of definite DKA, n	23	6
Participants with ≥ 1 event adjudicated as definite DKA, n (%)	22 (4.0)	6 (1.1)
Incidence rate/100 pt-yrs	4.62	1.27
BMI ≥ 27 kg/m²		
N	286	289
Events of definite DKA, n	5	3
Participants with ≥ 1 event adjudicated as definite DKA, n (%)	5 (1.7)	3 (1.0)
Incidence rate/100 pt-yrs	1.86	1.17

^aData for the overall pooled DEPICT population are being included here for comparison and completeness with respect to the DKA safety profile of dapagliflozin.⁷

Abbreviations: BMI, body mass index; DKA, diabetic ketoacidosis, pt-yrs, patient-years.

≥ 27 kg/m². Here, we present evidence for the further improved benefit/risk ratio when using the SGLT2 inhibitor – dapagliflozin – in individuals with type 1 diabetes with BMI ≥ 27 kg/m² and receiving intensive insulin therapy, based on data available from the DEPICT trials.

Individuals with BMI ≥ 27 kg/m² comprised over half of the participants in the overall DEPICT study population. This pooled analysis showed similar efficacy of dapagliflozin 5 mg in individuals with BMI ≥ 27 kg/m² to that seen in the overall DEPICT population.⁵ Benefit was reflected in improved glycaemic control, with reduction in HbA1c, increase in time in range (>70 to ≤ 180 mg/dL) and decrease in glucose variability.

Another important benefit observed was weight loss. As reported previously, individuals with T1D struggle with undesirable weight gain.^{9,10} Achieving weight loss when receiving intensive insulin therapy and maintaining good glycaemic control is very difficult, particularly in this group with pre-obesity (overweight) or obesity (BMI ≥ 27 kg/m²).¹¹ The ability of dapagliflozin to reduce body weight, in addition to its other benefits, including improved glycaemic control and reduced glycaemic variability, may make it particularly beneficial for individuals with T1D and BMI ≥ 27 kg/m², facilitating reduced risk for diabetic complications in this subgroup. Notably, absolute weight loss seen in the current analysis population was greater than that observed in the overall DEPICT study population. Weight loss in the current analysis population may also support a decrease in the insulin dose required to maintain optimal glycaemia; indeed, a greater reduction in daily insulin dose was observed at week 24 in this population compared with the overall DEPICT population. A further consideration of the weight loss observed in this study is that patients' weight may decrease below the BMI >27 kg/m² cut-off for which dapagliflozin is licensed to be

initiated in T1D. The benefit/risk of continued treatment should be monitored by the patients' physicians.

Although many clinicians are convinced of the potential benefits of SGLT2 inhibitors as adjunct therapies in individuals with T1D, there are concerns, particularly regarding the risk of DKA, which appear to be inherent to using SGLT inhibitors as adjunct treatment for individuals with T1D.^{12,13} The mechanism behind the increased DKA risk when introducing SGLT2 inhibitors in individuals with T1D remains unclear, but factors such as a small increase in glucagon, and in particular, the need for insulin dose reduction to avoid hypoglycaemia because of the glucose-lowering effects of SGLT2 inhibitors via urinary glucose loss, are postulated factors. Indeed, a decrease in the insulin dose will also reduce the effect of insulin on lipolysis and promote the generation of ketone bodies.¹⁴ Therefore, in the DEPICT programme, it was recommended that participants did not reduce their insulin dose by more than 20% during the study. Results of this analysis show that, in individuals with T1D and BMI ≥ 27 kg/m², treatment with dapagliflozin 5 mg resulted in a relative balance of DKA risk (BMI ≥ 27 kg/m² subpopulation: dapagliflozin-treated vs. placebo treated, 1.7% vs. 1.0%; overall DEPICT population: 4.0% vs. 1.1%). This more favourable benefit/risk profile observed in the BMI ≥ 27 kg/m² population, in part, may be related to individuals with higher BMI receiving larger total insulin doses – even at the same insulin dose per kilogram and additionally, the higher BMI may contribute to more insulin resistance, yielding slightly higher doses per kilogram. Indeed, at baseline, participants in the pooled DEPICT population receiving 5 mg dapagliflozin and placebo were administered insulin at a mean of 60.3 and 59.8 IU (0.74 and 0.73 IU/kg),⁵ respectively, compared with those in the BMI ≥ 27 kg/m² subgroup, where participants receiving dapagliflozin and placebo received insulin at a mean of 71.94 and 70.75 IU (0.78 and 0.76 IU/kg). The recommendation is that dapagliflozin should not be initiated in patients with low insulin needs.¹⁵ In the UK, NICE has specified that in addition to the requirement of BMI ≥ 27 kg/m², patients must be receiving ≥ 0.5 U/kg/day of insulin to mitigate the risk of DKA.¹⁶

In line with the recently updated guidelines, DKA risk should be mitigated through patient, health care practitioner and caregiver vigilance and education about its occurrence, detection, prevention and management.¹⁶ When using an SGLT inhibitor as an adjunct to insulin in individuals with T1D, it is important that individuals are educated to respond to an emerging DKA event, even when their glucose levels are lower than might normally be expected in cases of DKA.¹⁷ This is because DKA can more readily occur in the absence of hyperglycaemia when an SGLT inhibitor is being used.¹⁶

The increase in the number of genital tract infections and urinary tract infections that are commonly seen with SGLT2 inhibitors were also seen with dapagliflozin 5 mg in studies in T1D. The proportion of patients reporting these infections were similar in this subgroup to those reported in the total populations of DEPICT-1 and -2 studies.¹⁻⁴

A key limitation of the analyses reported here was that, as they were post hoc in a pooled population, there was no control for type 1 error. It must also be noted that strict monitoring of hypoglycaemia and DKA in a trial setting may differ from the real-world situation.

5 | CONCLUSIONS

Participants with BMI ≥ 27 kg/m² treated with dapagliflozin 5 mg in the DEPICT trials experienced reductions in HbA1c and body weight over 52 weeks; however, compared with the pooled DEPICT populations, a lower incidence of DKA was observed in this subgroup. While treatment with dapagliflozin showed several benefits compared with placebo in the pooled DEPICT populations,^{1–4} this post-hoc analysis suggests that the benefit/risk profile of dapagliflozin is more favourable in individuals with T1D and BMI ≥ 27 kg/m² because of the lower risk of DKA in this population. We believe this observation is of great importance in orienting clinical guidance regarding an optimal population with T1D that may experience the greatest benefit and the lowest risks, with adjunct therapy with SGLT2 inhibitors.

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DATA AVAILABILITY

Data underlying the findings described in this manuscript may be obtained in accordance with AstraZeneca's data sharing policy described at <https://astrazenecagrouptrials.pharmacm.com/ST/Submission/Disclosure>

CONFLICTS OF INTERESTS

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. ALB has served on advisory boards for Novo Nordisk, Sanofi, Merck Sharp and Dohme, AstraZeneca and Boehringer Ingelheim; and has served on speakers bureaux for Novo Nordisk, Sanofi, Eli Lilly, Boehringer Ingelheim and AstraZeneca. TKH has served on advisory boards for Novo Nordisk, Sanofi, Merck Sharp and Dohme, AstraZeneca, Abbott, and Boehringer Ingelheim. NI is an employee of AstraZeneca. JX is an employee and shareholder of AstraZeneca. ER is an employee of AstraZeneca. MFS was an employee of AstraZeneca during the preparation of this manuscript and is currently employed at Bayer pharmaceuticals. FT is an employee of AstraZeneca. MP's institute has received grants or research support from Medtronic, Novo Nordisk, Roche, Eli Lilly, Merck, Sanofi, Bristol-Myers Squibb, Kamada, AstraZeneca, and Lexicon. MP has received honoraria or consultation

fees from Sanofi, Medtronic, Novo Nordisk, and Eli Lilly; has participated in advisory boards for Sanofi, Medtronic, AstraZeneca, and Eli Lilly; and is a stock shareholder in DreaMed Diabetes.

AUTHOR CONTRIBUTIONS

CM, PD, NI, JX, MFS, FT and MP contributed to the study concept and design, analysis and interpretation of the study data. CM, PD, ALB, TKH, NI, JX, ER, MFS, FT and MP contributed to the drafting of the manuscript and critical revision for intellectual content. CM is the guarantor of this work and, as such, had full access to all the data in the study and takes full responsibility for the integrity of the data and the accuracy of the data analysis.

PEER REVIEW

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SUPPORTING INFORMATION

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

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