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

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Lancet Diabetes Endocrinol 2017; 5: 864–76

Published Online
September 14, 2017
http://dx.doi.org/10.1016/S2213-8587(17)30308-X

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*Listed in the appendix

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Summary

Background Dapagliflozin is a sodium-glucose cotransporter-2 inhibitor approved for the treatment of type 2 diabetes. We aimed to assess the efficacy and safety of dapagliflozin as an add-on to adjustable insulin in patients with inadequately controlled type 1 diabetes.

Methods DEPICT-1 was a double-blind, randomised, parallel-controlled, three-arm, phase 3, multicentre study done at 143 sites in 17 countries. Eligible patients were aged 18–75 years and had inadequately controlled type 1 diabetes (HbA_{1c} between ≥7·7% and ≤11·0% [≥61·0 mmol/mol and ≤97·0 mmol/mol]) and had been prescribed insulin for at least 12 months before enrolment. After an 8 week lead-in period to optimise diabetes management, patients were randomly assigned (1:1:1) using an interactive voice response system to dapagliflozin 5 mg or 10 mg once daily, given orally, or matched placebo. Randomisation was stratified by current use of continuous glucose monitoring, method of insulin administration, and baseline HbA_{1c}. The primary efficacy outcome was the change from baseline in HbA_{1c} after 24 weeks of treatment in the full analysis set, which consisted of all randomly assigned patients who received at least one dose of study drug. An additional 55 patients who were incorrectly and non-randomly allocated to only dapagliflozin treatment groups were included in the safety analysis set. This study was registered with ClinicalTrials.gov, number NCT02268214; data collection for the present analysis was completed on Jan 4, 2017, and a 28 week extension phase is ongoing.

Findings Between Nov 11, 2014, and April 16, 2016, 833 patients were assigned to treatment groups and included in safety analyses (dapagliflozin 5 mg [n=277] *vs* dapagliflozin 10 mg [n=296] *vs* placebo [n=260]; 778 of these patients were randomly assigned and included in the full analysis set for efficacy analyses (259 *vs* 259 *vs* 260; difference due to randomisation error affecting 55 patients). Mean baseline HbA_{1c} was 8·53% (70 mmol/mol; SD 0·67% [7·3 mmol/mol]). At week 24, both doses of dapagliflozin significantly reduced HbA_{1c} compared with placebo (mean difference from baseline to week 24 for dapagliflozin 5 mg *vs* placebo was –0·42% [95% CI –0·56 to –0·28; p<0·0001] and for dapagliflozin 10 mg *vs* placebo was –0·45% [–0·58 to –0·31; p<0·0001]). Among patients in the dapagliflozin 5 mg (n=277), dapagliflozin 10 mg (n=296), and placebo (n=260) groups, the most common adverse events were nasopharyngitis (38 [14%] *vs* 36 [12%] *vs* 39 [15%]), urinary tract infection (19 [7%] *vs* 11 [4%] *vs* 13 [5%]), upper respiratory tract infection (15 [5%] *vs* 15 [5%] *vs* 11 [4%]), and headache (12 [4%] *vs* 17 [6%] *vs* 11 [4%]). Hypoglycaemia occurred in 220 (79%), 235 (79%), and 207 (80%) patients in the dapagliflozin 5 mg, dapagliflozin 10 mg, and placebo groups, respectively; severe hypoglycaemia occurred in 21 (8%), 19 (6%), and 19 (7%) patients, respectively. Adjudicated definite diabetic ketoacidosis occurred in four (1%) patients in the dapagliflozin 5 mg group, five (2%) in the dapagliflozin 10 mg group, and three (1%) in the placebo group.

Interpretation Our results suggest that dapagliflozin is a promising adjunct treatment to insulin to improve glycaemic control in patients with inadequately controlled type 1 diabetes.

Funding AstraZeneca and Bristol-Myers Squibb.

Introduction

People with type 1 diabetes require treatment with insulin for survival. The Diabetes Control and Complications Trial (DCCT) and the Epidemiology of Diabetes Interventions and Complications (EDIC) follow-up study showed that most people with type 1 diabetes should be treated intensively to achieve target glycaemic levels as close to normal range and as early in the disease as possible to prevent and delay late microvascular and macrovascular complications.[1,2] Delay in achieving glycaemic control is probably a contributing factor to the increased risk of death in people with type 1 diabetes, even when patients later become well controlled (HbA_{1c} ≤6·9% [≤52 mmol/mol]).[3–5]

Newer insulin analogues with improved pharmacokinetic characteristics, and improved insulin-delivery systems and glucose-monitoring systems, have enabled

Research in context

Evidence before this study

In 2017, Chen and colleagues published a systematic review and meta-analysis of the efficacy and safety of sodium-glucose cotransporter-2 (SGLT2) inhibitors for adjunctive treatment of type 1 diabetes. They searched PubMed, Embase, the Cochrane Library, and CENTRRAI from inception to April 5, 2016, for human clinical trials of all types using the search terms "type 1 diabetes", "SGLT2 inhibitor", "Sodium glucose cotransporter 2 inhibitor", "dapagliflozin", "BMS-512148", "canagliflozin", "JNJ-28431754", "empagliflozin", "BI-10773", "ASP-1941", "ipragliflozin", "tofogliflozin", "remogliflozin", "GSK 189075", "LX4211", and "sergliflozin". They identified seven clinical trials, including four randomised, placebo-controlled trials of dapagliflozin, sotagliflozin, canagliflozin, and empagliflozin. The randomised controlled trials were of limited duration (2–18 weeks) and size (33–351 patients). On June 29, 2017, we did our own search of PubMed using the same search terms as Chen and colleagues and did not identify any additional clinical trials. Overall, results of the studies reported so far suggested potential benefits of SGLT2 inhibitors in patients with type 1 diabetes for glycaemic control, bodyweight, and reduced insulin requirements, as well as metabolic parameters such as blood pressure and plasma lipids. SGLT2 inhibitors were well tolerated, with frequencies of total adverse events, hypoglycaemia, and genital and urinary infections similar to placebo comparators. Diabetic ketoacidosis was more common in the SGLT2 inhibitor groups (16 [4%] of 442 patients receiving SGLT2 inhibitors *vs* 0 of 166 patients receiving placebo); these events most often occurred in patients with mild hyperglycaemia or euglycaemia.

Added value of this study

The evidence before this study suggested potential benefits of SGLT2 inhibitors, but also raised some safety concerns, particularly around diabetic ketoacidosis. DEPICT-1 is the first phase 3, randomised, blinded, clinical trial of a selective SGLT2 inhibitor in type 1 diabetes, and provides strong evidence on the safety and efficacy of the SGLT2 inhibitor dapagliflozin as an adjunct to insulin therapy in patients with type 1 diabetes. After 24 weeks of treatment, dapagliflozin provided significant and clinically important reductions in HbA_{1c}, total daily insulin dose, and bodyweight. Furthermore, dapagliflozin was well tolerated, with no new safety signals emerging. A small increase in ketone-related events seen with dapagliflozin was manageable with standard care.

Implications of all the available evidence

Dapagliflozin should be regarded as a good candidate for adjunct therapy to improve glycaemic control in patients with inadequately controlled type 1 diabetes.

caregivers and patients to achieve glycaemic targets more easily and safely.[6] However, data from large type 1 diabetes clinical registries suggest that glycaemic control frequently remains suboptimum.[7,8] Such data emphasise the need for adjunctive non-insulin glucose-lowering therapy to be used alongside insulin in patients with type 1 diabetes.[9] Ideally, an adjunctive therapy should have an insulin-independent mechanism of action, be safe, and preferably provide additional non-glycaemic benefits, such as improvements in blood pressure and bodyweight, in view of the suboptimum blood pressure control in many people with type 1 diabetes and the increasing prevalence of overweight and obesity in this population.[10–12]

Sodium-glucose cotransporter-2 (SGLT2) inhibitors are the most recent class of antihyperglycaemic drugs approved for the treatment of type 2 diabetes. SGLT2 inhibitors improve glycaemic control independently from insulin by blocking reabsorption of glucose in the renal proximal tubules, leading to increased glucose excretion in the urine, loss of calories, and reduction in bodyweight.[13] The accompanying blood pressure reduction and cardiovascular and renal benefits are probably linked to the natriuretic effect of these drugs.[14]

Dapagliflozin is an SGLT2 inhibitor approved for treatment of type 2 diabetes. In a 2 week pilot study[15] in patients with type 1 diabetes, dapagliflozin, given as an add-on to insulin, showed acceptable tolerability and safety, and induced a dose-related increase in urinary glucose excretion, reductions in 24 h mean glucose, and reductions in glucose variability. Furthermore, results from a 2017 meta-analysis[16] of clinical trials suggested potential benefits of SGLT2 inhibitors as adjunctive treatment of type 1 diabetes.

The aim of the present study was to assess if dapagliflozin (5 mg or 10 mg once daily) added to adjustable insulin can safely improve glycaemic control in people with type 1 diabetes over 24 weeks.

Methods

Study design and participants

DEPICT-1 was a double-blind, randomised, parallel-controlled, three-arm, phase 3, multicentre study done at 143 sites in 17 countries: Australia, Austria, Belgium, Canada, Germany, Denmark, Finland, France, Hungary, Israel, Italy, Mexico, Romania, Spain, Sweden, the UK, and the USA. It was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines as defined by the International Conference on Harmonisation. The study was approved by the institutional review boards and independent ethics committees for all participating centres. The study protocol is available online.

For the **protocol** see https://astrazenecagrouptrials.pharmacm.com/ST/Submission/View?id=12385

This study included adult patients (aged 18–75 years) with inadequately controlled type 1 diabetes (HbA_{1c} at screening: 7·7–11·0% [60·7–96·7 mmol/mol]; HbA_{1c} at randomisation: 7·5–10·5% [58·5–91·3 mmol/mol]) prescribed insulin for 12 months or longer before

enrolment (total insulin dose ≥0·3 IU/kg per day for ≥3 months before screening), and with C-peptide of less than 0·7 ng/mL and a BMI of 18·5 kg/m² or higher. Patients were excluded if they had a history of type 2 diabetes; maturity onset diabetes of the young; had received pancreatic surgery previously; chronic pancreatitis or other pancreatic disorders resulting in decreased β-cell capacity; diabetes insipidus; diabetic ketoacidosis requiring medical intervention within 1 month before screening; been admitted to a hospital for hyperglycaemia or hypoglycaemia within 1 month before screening; cardiovascular disease (within 6 months before screening); unstable or rapidly progressing renal disease; significant hepatic disease; or malignancy (within 5 years). Patients were also excluded if they had frequent episodes of severe hypoglycaemia (more than one episode requiring medical assistance, emergency care, or glucagon therapy administered by a third party within 1 month before screening); showed symptoms of poorly controlled diabetes (including marked polyuria and polydipsia with >10% weight loss during the 3 months before enrolment or other signs and symptoms of poor glycaemic control in the opinion of the investigator); had previously used any SGLT2 inhibitor; or had a calculated creatinine clearance of less than 60 mL/min. A complete list of inclusion and exclusion criteria are reported in the appendix. Patients were recruited at sites, locally, by referral and via advertisement in local media (advertisement material following approval by ethics committees and institutional review boards). All participants provided written informed consent.

See Online for appendix

Randomisation and masking

Patients were randomly assigned (1:1:1) using an interactive voice response system to either dapagliflozin 5 mg, dapagliflozin 10 mg, or matched placebo. Randomisation was stratified by current use of continuous glucose monitoring, method of insulin administration (multiple daily injections *vs* continuous subcutaneous insulin infusion), and baseline HbA_{1c} (≥7·5 to <9·0% *vs* ≥9·0% to ≤10·5% [≥58·5 to <74·9 mmol/mol *vs* ≥74·9 to ≤91·3 mmol/mol]). Method of allocation concealment is described in the appendix. The investigator and other site personnel, sponsor company personnel, and patients remained masked to treatment allocation throughout the 24 week, double-blind treatment period.

Procedures

Eligible patients entered an 8 week lead-in period to optimise diabetes management on the basis of individual glycaemic control, and to assess variability in blood glucose profiles and frequency of hypoglycaemic episodes at baseline. Patients were provided counselling for diet and exercise throughout the lead-in and treatment periods. On completing the lead-in period, patients were randomly assigned to either dapagliflozin 5 mg, dapagliflozin 10 mg, or placebo, all of which were given orally once per day. Results from the 24 week primary treatment period are reported here; after this period, patients entered a 28 week patient-blinded and site-blinded extension phase to assess longer-term safety (ongoing), which will be followed by a 4 week follow-up period.

In addition to visits at weeks –8, –4, –2, and –1 during the lead-in period, study visits occurred on day 1 (randomisation), and at weeks 1, 2, 4, 8, 10, 12, 18, 22, and 24. Telephone visits occurred on days 2, 4, and 10. HbA_{1c} was recorded at weeks 4, 8, 12, 18, and 24; daily insulin dose at weeks 2, 12, and 24; and bodyweight at weeks 1, 2, 4, 8, 12, 18, and 24.

Glycaemic control, which included self-monitored blood glucose values, ketone readings, and continuous glucose monitoring if the patient was on unmasked continuous glucose monitoring before the study, was assessed at each study visit, and insulin doses were adjusted as deemed appropriate on the basis of self-monitored blood glucose readings (recommended four times per day at a minimum and six times per day in protocol-specified periods of intense glucose monitoring [on any 3 days within a week before the week –4 visit, day 1 visit, week 12 visit, and week 24 visit]), local guidance, and individual circumstances; the protocol did not specify uniform insulin titration algorithms. After the first dose of study drug, the total daily insulin dose was recommended to be reduced symmetrically in basal and bolus insulin by up to 20% to minimise the risk of hypoglycaemia and not to exceed 20% to avoid inappropriate (ketogenic) reductions,[15,17] before subsequently titrating back as far as possible to baseline levels. Patients were not allowed to change their insulin administration method (multiple daily injections or continuous subcutaneous insulin infusion) during the study, apart from a temporary switch (<2 weeks) from continuous subcutaneous insulin infusion to multiple daily injections, in cases where a patient using an insulin pump needed pump replacement, reverting as soon as possible. Continuous glucose monitoring was used to measure interstitial glucose levels over 2 week periods. A continuous glucose monitoring sensor was inserted subcutaneously during clinic visits, with measurements taken from the week –2 visit to the day 1 visit (providing baseline values), from the week 10 visit to the week 12 visit, and from the week 22 visit to the week 24 visit (providing week 24 values). The sensor was replaced at weeks –1, 11, and 23 in accordance with manufacturer instructions. The data remained blinded to the patient, the investigator, and the sponsor during recording and was downloaded into a data file.

Several measures were used to detect any events that could be consistent with diabetic ketoacidosis. Patients were advised about how to identify potential symptoms of diabetic ketoacidosis and were provided with blood ketone meters and instructions for use. Patients were required to measure their ketones if any symptom

occurred (even if suspected only) that could be related to diabetic ketoacidosis or illness, to record these blood ketone test results and relevant risk factors, and to contact the study site if their self-measured blood ketone reading was 0·6 mmol/L or higher, irrespective of the measured glucose value. Likewise, investigators were continuously educated in management of ketonaemia to help prevent progression to diabetic ketoacidosis, with emphasis on concomitant carbohydrate intake (in case of euglycaemia) together with insulin adjustments.

Outcomes

The primary efficacy outcome was the change from baseline in HbA_{1c} after 24 weeks of treatment with dapagliflozin 5 mg or 10 mg plus adjustable insulin versus placebo plus adjustable insulin. Secondary efficacy outcomes (all assessed at 24 weeks) were: percentage change in total daily insulin dose; percentage change in bodyweight; change in mean value of 24 h glucose readings obtained from continuous glucose monitoring; change in mean amplitude of glucose excursion of 24 h

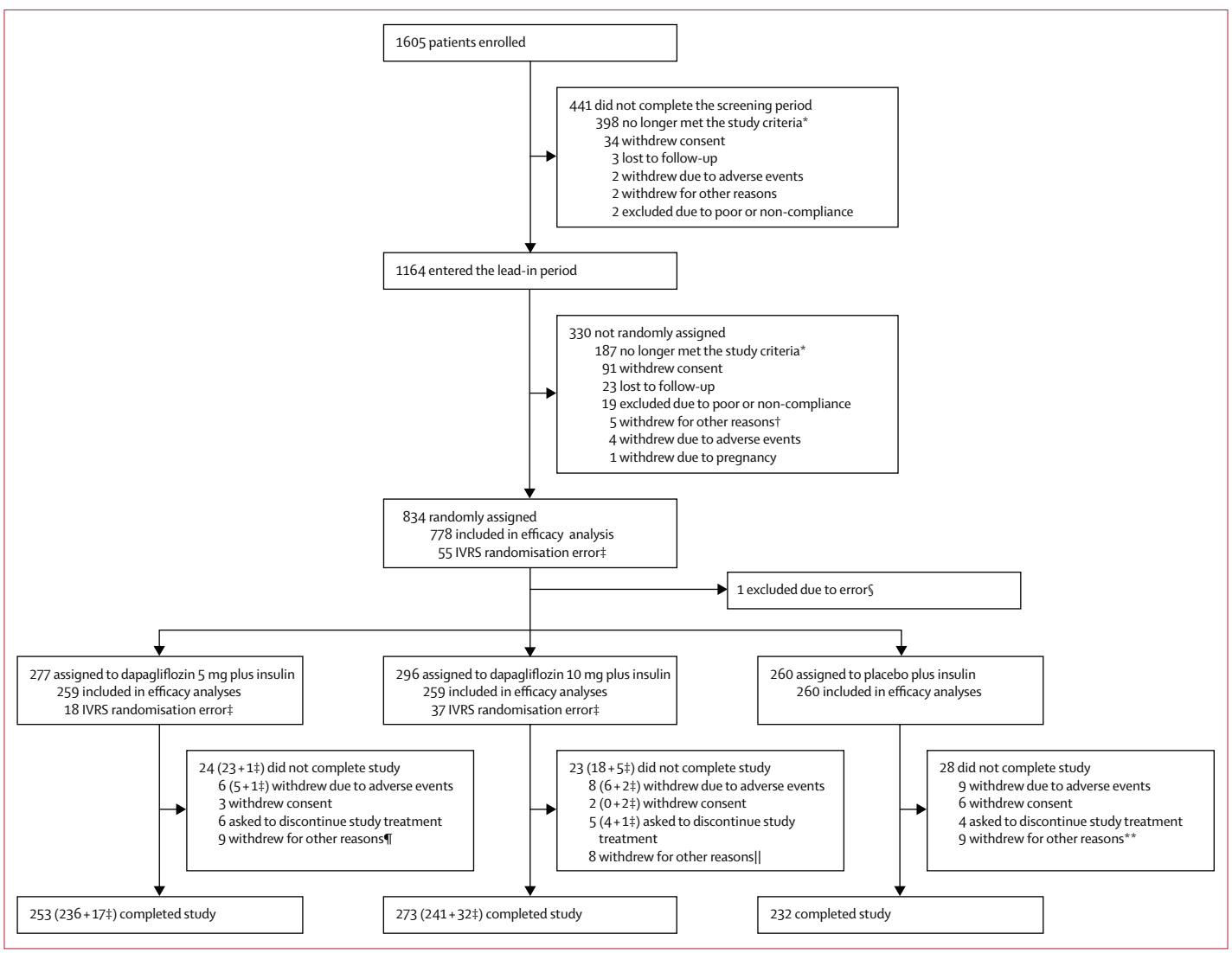

Figure 1: **Trial profile**

All efficacy analyses were done on the full analysis set (n=778) and safety analyses were done on the safety analysis set (n=833). *Most patients no longer met study criteria because of a decrease in their HbA_{1c} values by more than 0·5%. †Reasons for withdrawal: site no longer participating (n=1), site closure (n=1), patient had a severe reduction in blood glucose during the lead-in period (n=1), HbA_{1c} was below the allowed range (n=1), and patient relocated (n=1). ‡55 patients were randomly assigned before discovery of an error with the interactive voice-response system (IVRS) used for randomisation: 18 in the dapagliflozin 5 mg group and 37 in the dapagliflozin 10 mg group. §One additional patient was randomly assigned in error (the site randomly assigned the patient before confirming eligibility); this patient did not receive any treatment and was excluded from the full analysis set and the safety analysis set. ¶Lack of efficacy (n=1), lost to follow up (n=2), poor or non-compliance (n=2), pregnancy (n=1), change of injection method from multiple daily injections to pump (n=1), patient unwilling to attend future visits, phone calls, or allow any contact with their personal physician, or allow review of medical records for health status (n=1), and investigator request for patient discontinuation owing to non-compliance with glycaemic control (n=1). ||Lost to follow-up (n=2), pregnancy (n=2), patient no longer meeting study criteria (n=2), relocation of patient (n=1), and previous diabetic ketoacidosis event that the study centre was unaware of (n=1). **Lack of efficacy (n=1), lost to follow up (n=2), poor or non-compliance (n=2), pregnancy (n=1), patient no longer wanted to be in the study (n=2), and relocation of patient (n=1).

glucose readings obtained from continuous glucose monitoring (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[18]); change in the percentage of 24 h glucose readings obtained from continuous glucose monitoring that fall within the target range of greater than 70 mg/dL (3·9 mmol/L) to 180 mg/dL (10·0 mmol/L); and the proportion of patients achieving an HbA_{1c} decrease of at least 0·5% without severe hypoglycaemia events. In a post-hoc analysis, adjusted mean percentage change in total daily insulin was also adjusted for bodyweight reduction at week 24.

	Dapagliflozin 5 mg plus insulin (n=259)	Dapagliflozin 10 mg plus insulin (n=259)	Placebo plus insulin (n=260)
Sex			
Men	111 (43%)	130 (50%)	132 (51%)
Women	148 (57%)	129 (50%)	128 (49%)
Age (years)	41·9 (14·1)	42·7 (14·1)	42·7 (13·6)
Bodyweight (kg)	80·8 (18·2)	82·0 (17·3)	84·3 (18·3)
BMI (kg/m²)	28·3 (5·8)	28·1 (5·1)	28·6 (5·2)
Ethnic origin			
White	248 (96%)	247 (95%)	249 (96%)
Black or African-American	5 (2%)	7 (3%)	3 (1%)
Asian	0	0	1 (<1%)
Other	6 (2%)	5 (2%)	7 (3%)
Geographical region			
North America	68 (26%)	72 (28%)	70 (27%)
Latin America	30 (12%)	24 (9%)	25 (10%)
Europe	146 (56%)	154 (59%)	161 (62%)
Asia-Pacific	15 (6%)	9 (3%)	4 (2%)
Duration of type 1 diabetes (years)	19·7 (12·0)	19·9 (11·1)	21·2 (12·2)
HbA_{1c} (%)	8·53% (0·71)	8·52% (0·64)	8·53% (0·67)
HbA_{1c} (mmol/mol)	69·7 (7·8)	69·6 (7·0)	69·7 (7·3)
Total baseline insulin dose			
Dose (IU)	62·1 (44·2)	59·4 (28·2)	63·1 (29·3)
Dose/weight (IU/kg)	0·76 (0·52)	0·71 (0·26)	0·74 (0·25)
Method of insulin administration			
MDI	162 (63%)	165 (64%)	165 (63%)
CSII	97 (37%)	94 (36%)	95 (37%)
Use of CGM	85 (33%)	86 (33%)	86 (33%)
HbA_{1c} range at randomisation			
≥7·5% to <9·0% (≥58·5 to <74·9 mmol/mol)	194 (75%)	198 (76%)	194 (75%)
≥9·0% to ≤10·5% (≥74·9 to ≤91·3 mmol/mol)	65 (25%)	61 (24%)	66 (25%)

Data are n (%) or mean (SD). MDI=multiple daily injections. CSII=continuous subcutaneous insulin infusion. CGM=continuous glucose monitoring.

Table 1: **Demographic and baseline characteristics**

Safety and tolerability were assessed in the safety analysis set, which consisted of all patients who took at least one dose of double-blind study medication during the 24 week, double-blind treatment period. It included the 55 incorrectly ransomly assigned patients that were excluded from the full analysis set. Safety and tolerability were assessed throughout the study period by assessment of adverse events, serious adverse events, vital signs, physical examination findings, electrocardiogram, and laboratory values. The proportion of patients with hypoglycaemia events and the frequency of hypoglycaemic events were also assessed. Adverse events of special interest were hypoglycaemia, diabetic ketoacidosis, hepatobiliary events, genital infections, urinary tract infections, volume depletion, fractures, worsening renal function, hypersensitivity reactions based on prespecified standardised MedDRA queries (SMQ) for hypersensitivity reactions (narrow definition), and cardiovascular adverse events.

Hypoglycaemia was classified in accordance with the American Diabetes Association (ADA) classification criteria.[19] Severe hypoglycaemia required assistance of another person to raise glucose levels and promote neurological recovery. Documented symptomatic hypoglycaemia featured typical hypoglycaemia symptoms and a plasma glucose concentration of 70 mg/dL (3·9 mmol/L) or lower. Asymptomatic hypoglycaemia was unaccompanied by typical hypoglycaemia symptoms, but plasma glucose was 70 mg/dL (3·9 mmol/L) or lower. Probable symptomatic hypoglycaemia had typical hypoglycaemia symptoms but without a plasma glucose determination. Pseudohypoglycaemia (or relative hypoglycaemia) was defined as patient-reported hypoglycaemia symptoms with plasma glucose higher than 70 mg/dL (3·9 mmol/L) but approaching that level.

The investigators identified any events that could be consistent with potential diabetic ketoacidosis on the basis of symptoms, diagnoses, or home ketone values. Additionally, the investigators were queried to review any adverse event satisfying an extensive list of preferred terms (customised standard MedDRA query) that could indicate diabetic ketoacidosis. Laboratory criteria for assessing diabetic ketoacidosis were based on the lowest threshold that would satisfy the ADA criteria and included a venous pH of less than 7·3 and serum bicarbonate of 18 mEq/L or lower.[20] Ketone measurements alone were not intended to satisfy the requirement for a definite diabetic ketoacidosis diagnosis because of the emerging evidence of SGLT2 inhibitor-induced (insulin-independent) ketogenesis in type 2 diabetes. In the absence of SGLT2 inhibitor data in type 1 diabetes, whether SGLT2 inhibition could lead to disproportionate (from prevailing insulin levels) increases in ketones was unknown. As such, it was decided to rely predominantly on clinical presentation, pH, and bicarbonate levels. In practice, participant data used for adjudication typically also included ketone values, either self-monitored or

from medical facilities. Because raised glucose is not a criterion for diabetic ketoacidosis, and to avoid missing any potential euglycaemic diabetic ketoacidosis events, raised glucose was not a criterion in classification and was not included in the assessment of whether a potential event should be sent for adjudication. An independent diabetic ketoacidosis adjudication committee (masked to study group assignment) adjudicated all potential diabetic ketoacidosis events. Adjudicated events were classified as definite, possible, or unlikely. No set criteria were used to define possible or unlikely diabetic ketoacidosis, and these terms were used at the committee's discretion. An external data monitoring committee periodically assessed all data for hypoglycaemia, diabetic ketoacidosis, laboratory measurements, and safety findings.

Statistical analysis

To detect a difference in mean HbA_{1c} of 0·35% between each dapagliflozin treatment group and placebo at the two-sided significance level of 0·0262 (based on Dunnett and Tamhane step-up procedure), with an SD of 1·1%, 243 patients were required in each treatment group to provide around 90% power. Assuming that 5% of patients would not have a post-baseline assessment, 768 patients (256 patients per treatment group) were planned to be randomly assigned. A global randomisation procedure with a block size of three was used.

Efficacy analyses were done for the full analysis set, which consisted of all randomly assigned patients who received at least one dose of study drug during the 24 week treatment period (excluding the first 55 randomly assigned patients, who were affected by an error with the interactive voice response randomisation system). The analyses were based on measurements recorded while patients were still on randomised treatments (ie, any measurements made after discontinuation of randomised treatments were treated as missing). Treatment effects were determined through pairwise comparisons between each dapagliflozin group and placebo.

For an overall type I error rate of 5% for the primary endpoint, a Dunnett and Tamhane step-up procedure was used, allowing for the correlation of 0·5 between the standard normal deviate for each comparison. Thus, 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 significance would be declared for the latter comparison. Statistical analyses for secondary efficacy endpoints were only done if there was a significant difference in the primary endpoint for both pairwise comparisons (ie, dapagliflozin 5 mg *vs* placebo, and dapagliflozin 10 mg *vs* placebo), using the Dunnett and Tamhane step-up procedure.

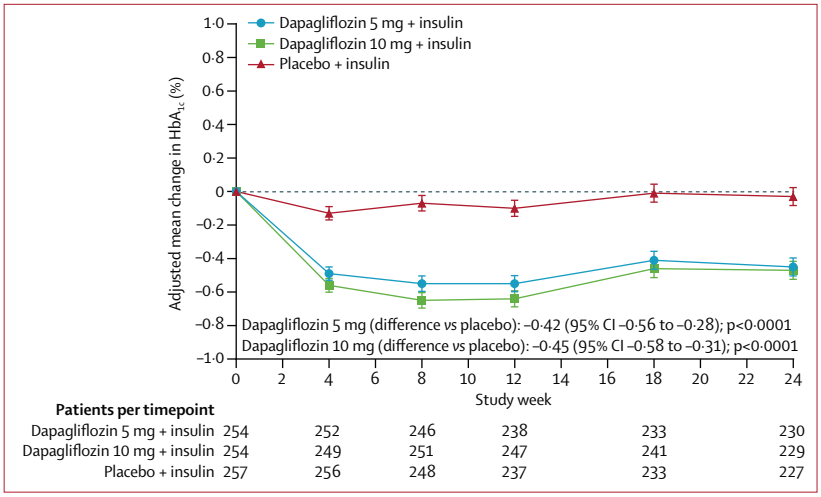

Figure 2: **Change in HbA_{1c} over 24 weeks**

Bars show standard error of the mean. Data are for all patients in full analysis set with non-missing baseline and at least one post-baseline HbA_{1c} measurement. Dapagliflozin 5 mg plus insulin (n=259): mean baseline HbA_{1c} was 8·52% (SD 0·72) and mean week 24 HbA_{1c} was 8·04% (SD 0·90); adjusted mean change, −0·45% (SE 0·05). Dapagliflozin 10 mg plus insulin (n=259): mean baseline HbA_{1c} was 8·50% (SD 0·62) and mean week 24 HbA_{1c} was 8·04% (SD 0·83); adjusted mean change, −0·47% (SE 0·05). Placebo plus insulin (n=260): mean baseline HbA_{1c} was 8·50% (SD 0·67) and mean week 24 HbA_{1c} was 8·43% (SD 0·92); adjusted mean change, −0·03% (SE 0·05).

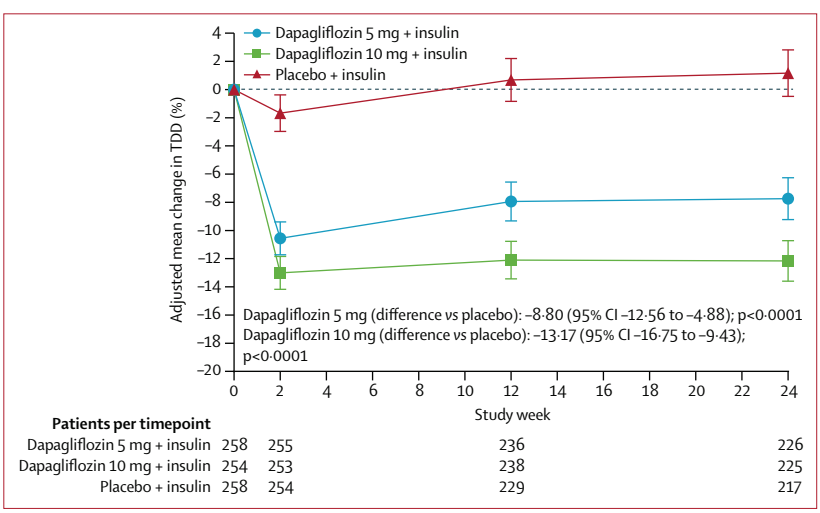

Figure 3: **Change in total daily dose of insulin**

Bars show standard error of the mean. Data are for all patients in full analysis set with non-missing baseline and at least one post-baseline measurement of total daily insulin dose. Dapagliflozin 5 mg plus insulin (n=259): mean baseline total daily insulin dose was 62·91 IU (SD 46·16) and mean week 24 total daily insulin dose was 56·12 IU (SD 30·75); adjusted mean change, −7·74% (SE 1·49). Dapagliflozin 10 mg plus insulin (n=259): mean baseline total daily insulin dose was 59·59 IU (SD 28·20) and mean week 24 total daily insulin dose was 52·35 IU (SD 27·38); adjusted mean change, −12·16% (SE 1·43). Placebo plus insulin (n=260): mean baseline total daily insulin dose was 61·74 IU (SD 26·56) and mean week 24 total daily insulin dose was 62·13 IU (SD 27·41); adjusted mean change, 1·16% (SE 1·66). TDD=total daily insulin dose.

The primary analysis of the change in HbA_{1c} from baseline to week 24 was based on a longitudinal repeated-measures analysis with a model of the fixed categorical effects of treatment, week, randomisation stratification factor (ie, one term for each combination of all stratification factors), treatment-by-week interaction, and the continuous fixed covariates of baseline

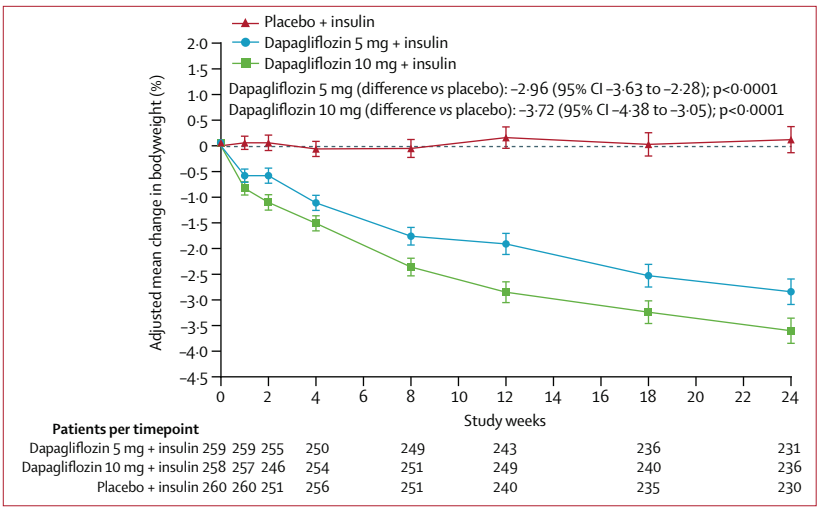

Figure 4: **Change in total bodyweight**
Bars show standard error of the mean. Data are for all patients in full analysis set with non-missing baseline and at least one post-baseline measurement of bodyweight. Dapagliflozin 5 mg plus insulin (n=259): mean baseline bodyweight was 81·67 kg (SD 18·40) and mean week 24 bodyweight was 79·38 kg (SD 18·15); adjusted mean change, −2·84% (SE 0·25). Dapagliflozin 10 mg plus insulin (n=259): mean baseline bodyweight was 81·70 kg (SD 16·40) and mean week 24 bodyweight was 78·72 kg (SD 15·91); adjusted mean change, −3·60% (SE 0·25). Placebo plus insulin (n=260): mean baseline bodyweight was 84·36 kg (SD 18·45) and mean week 24 bodyweight was 84·50 kg (SD 18·75); adjusted mean change, 0·12% (SE 0·26).

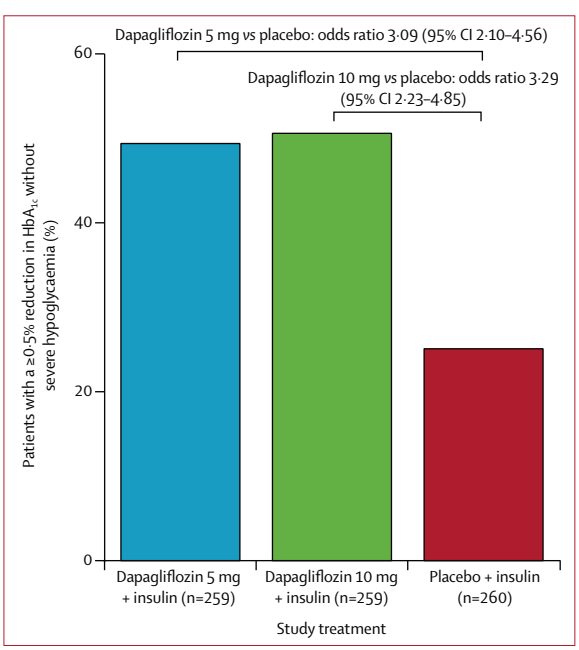

Figure 5: **Change in proportion of patients achieving an HbA_{1c} reduction of 0·5% or more without severe hypoglycaemia events**

measurement and baseline measurement-by-week interaction. This approach has the effect of estimating treatment effects as if treatments for all patients had been continued until week 24.

The percentage changes (using logarithmic transformation for the endpoint in the model) from baseline at week 24 in total daily insulin dose and total bodyweight, the change from baseline at week 24 in the mean value of 24 h glucose readings obtained from continuous glucose monitoring, mean amplitude of glucose excursion of 24 h glucose readings obtained from continuous glucose monitoring, and the percentage of 24 h glucose readings obtained from continuous glucose monitoring that fell within the range of higher than 70 mg/dL (3·9 mmol/L) to 180 mg/dL (10·0 mmol/L) were analysed using a longitudinal repeated-measures analysis, similar to the model used for the primary efficacy analysis. The proportion of patients achieving an HbA_{1c} reduction from baseline to week 24 (last on-treatment value was carried forward for patients who discontinued early) of 0·5% or higher without severe hypoglycaemia events was analysed using a logistic regression model, with adjustment for randomisation stratification factor (ie, one term for each combination of all stratification factors) and baseline values.

Three prespecified sensitivity analyses were done. First, the effect of insulin uptitration on the primary endpoint was examined in the same way as the primary analysis, using a longitudinal repeated-measures analysis with a model of the fixed categorical effects of treatment, week, randomisation stratification factor (ie, one term for each combination of all stratification factors), treatment-by-week interaction, and the continuous fixed covariates of baseline measurement and baseline measurement-by-week interaction. A second sensitivity analysis estimated the intention-to-treat estimand (ie, treatment difference at week 24 irrespective of treatment discontinuation). This analysis included measurements made after withdrawal of randomised treatments. The change in HbA_{1c} from baseline to week 24 was analysed with the same method as was used for the primary analysis. Finally, a sensitivity analysis for estimation of a de-facto intention-to-treat estimand was done irrespective of premature discontinuation. The missing data at week 24 were imputed on the basis of placebo data only, using a multiple-imputation approach. Instead of a longitudinal repeated-measures analysis, the change from baseline to week 24 in HbA_{1c} was analysed directly using an ANCOVA model with factors of treatment group and randomisation stratification factor (ie, one term for each combination of all stratification factors) and covariate for baseline HbA_{1c}. SAS version 9.2 or higher was used for all analyses.

This study was registered with ClinicalTrials.gov, number NCT02268214.

Role of the funding source

The funders of the study contributed to all aspects of the study, including study design, data collection, data analysis, data interpretation, and writing of the report. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between Nov 11, 2014, and April 16, 2016, 1605 participants were enrolled in the study, of whom 834 were randomly assigned to a study group (dapagliflozin 5 mg [n=277] *vs* dapagliflozin 10 mg [n=296] *vs* placebo [n=260]; figure 1). Final data collection for the 24 week treatment period was completed on Jan 4, 2017. 758 (91%) randomly assigned patients completed the 24 week treatment period. The most common reasons for not completing the study were occurrence of adverse events (n=23) and patient request for treatment discontinuation (n=15; figure 1). One ineligible patient was incorrectly randomly assigned to a group but did not receive any treatment and was excluded from the full analysis set and the safety analysis set. Additionally, the first 55 participants were incorrectly, non-randomly allocated by the interactive voice response system to only dapagliflozin treatment groups and were replaced. These 55 participants were excluded from the efficacy analyses (n=778) but were included in the safety analysis (n=833).

Overall, baseline characteristics and demographics were balanced among all three treatment groups (table 1) with the exception that there were more females than males randomised to dapagliflozin 5 mg (57% *vs* 43%). Most participants were white and from Europe. The mean age was 42·5 years (SD 13·9) and the mean time since type 1 diabetes diagnosis was 20·3 years (SD 11·8). Mean baseline HbA_{1c} was 8·53% (SD 0·67; 70 mmol/mol, SD 7·3), mean baseline bodyweight was 82·4 kg (SD 18·0), and mean baseline BMI was 28·3 kg/m² (5·4). The mean total daily insulin dose was 61·6 IU (34·6); of 778 patients included in the efficacy analysis, 492 (63%) received insulin via multiple daily injections and 286 (37%) via continuous subcutaneous insulin infusion; 257 (33%) patients used continuous glucose monitoring.

During the lead-in period, HbA_{1c} improved from a mean of 8·82% (SD 0·87) at screening to 8·53% (0·71) at baseline (representing mean improvements of –0·29% [0·59]) in the dapagliflozin 5 mg group, from 8·76% (0·79) to 8·52% (0·64; improvement –0·24% [0·54]) in the dapagliflozin 10 mg group, and from 8·79% (0·81) to 8·53% (0·67; improvement –0·26% [0·65]) in the placebo group. The absolute HbA_{1c} values measured at the screening visit and throughout the study are reported in the appendix. Compared with placebo, dapagliflozin at both doses produced significant and clinically relevant reductions from baseline in HbA_{1c} at week 24. Mean difference in HbA_{1c} from baseline to week 24 for dapagliflozin 5 mg versus placebo was –0·42% (95% CI –0·56 to –0·28; p<0·0001), and for dapagliflozin 10 mg versus placebo was –0·45% (–0·58 to –0·31; p<0·0001; figure 2). HbA_{1c} reduction with dapagliflozin occurred over the first 4 weeks, with the effect maintained for the study duration. Results of the three sensitivity analyses showed the robustness of the primary analysis of change in HbA_{1c} from baseline to week 24 compared with placebo (appendix).

Compared with placebo, dapagliflozin at both doses led to significant reductions in total daily insulin dose from baseline to week 24 (figure 3). Mean difference in total daily insulin dose from baseline to week 24 was –8·8% (95% CI –12·6 to –4·9; p<0·0001) for dapagliflozin 5 mg versus placebo –13·2% (–16·8 to –9·4; p<0·0001) for dapagliflozin 10 mg versus placebo. Adjusting for bodyweight reductions, the adjusted mean percentage changes in total daily insulin dose per kilogram of bodyweight at week 24 were –4·6% (SE 1·5) for dapagliflozin 5 mg, –9·0% (1·4) for dapagliflozin 10 mg, and 0·9% (1·6) for placebo. Mean difference in total daily insulin dose per kilogram of bodyweight at week 24 for dapagliflozin 5 mg versus placebo was –5·5% (95% CI –9·2 to –1·6; p=0·0064), and for dapagliflozin 10 mg versus placebo was –9·8 % (–13·4 to –6·1; p<0·0001). Reductions in total daily insulin dose occurred in the first 2 weeks of treatment and were maintained for the study duration. The proportional reductions seen for basal and bolus insulin doses individually were similar to the proportional reduction in total insulin dose (for basal insulin, adjusted mean changes from baseline after 24 weeks were –11·6% [SE 1·3] for dapagliflozin 5 mg, –13·7% [1·3] for dapagliflozin 10 mg, and –0·6% [1·5] for placebo; for bolus insulin, adjusted mean changes from baseline after 24 weeks were –14·3% [2·1], –18·0% [2·1],

	Dapagliflozin 5 mg plus insulin (n=259)	Dapagliflozin 10 mg plus insulin (n=259)	Placebo plus insulin (n=260)
CGM mean value (mg/dL)			
N*	238	239	234
Baseline mean (SD)	192·9 (29·9)	189·4 (27·3)	191·4 (29·6)
Week 24 mean (SD)	178·3 (31·8)	173·6 (26·7)	192·9 (34·2)
Adjusted mean change from baseline (SE)	–10·3 (1·9)	–13·0 (1·9)	5·1 (1·9)
Difference from placebo (95% CI)	–15·3 (–20·2 to –10·5)	–18·0 (–23·0 to –13·1)	NA
p value†	<0·0001	<0·0001	NA
CGM MAGE (mg/dL)			
N*	238	239	234
Baseline mean (SD)	170·7 (31·1)	171·0 (31·4)	169·1 (34·3)
Week 24 mean (SD)	152·2 (34·5)	150·5 (32·8)	168·1 (34·9)
Adjusted mean change from baseline (SE)	–14·9 (2·0)	–16·6 (2·0)	2·4 (2·0)
Difference from placebo (95% CI)	–17·3 (–22·5 to –12·1)	–18·9 (–24·1 to –13·7)	NA
p value†	<0·0001	<0·0001	NA
24 h CGM values within >70 mg/dL to ≤180 mg/dL			
N*	238	239	234
Baseline mean (SD)	43·2 (12·4)	44·6 (12·4)	44·4 (12·9)
Week 24 mean (SD)	52·3 (14·8)	54·6 (13·1)	43·8 (14·7)
Adjusted mean change from baseline (SE)	7·0 (0·9)	8·5 (0·9)	–2·1 (0·9)
Difference from placebo (95% CI)	9·1 (6·8 to 11·4)	10·7 (8·4 to 12·9)	NA
p value†	<0·0001	<0·0001	NA

CGM=continuous glucose monitoring. NA=not applicable. MAGE=mean amplitude of glucose excursion. *N is the number of participants in the full-analysis set with no missing baseline data and at least one post-baseline value. †Nominal p value.

Table 2: **Changes in CGM values (interstitial glucose) at week 24**

	Dapagliflozin 5 mg plus insulin (n=277)*	Dapagliflozin 10 mg plus insulin (n=296)*	Placebo plus insulin (n=260)
Adverse events			
One or more adverse events	187 (68%)	207 (70%)	160 (62%)
One or more adverse events related to the study drug	79 (29%)	82 (28%)	31 (12%)
Adverse event leading to study discontinuation	6 (2%)	8 (3%)	9 (3%)
Adverse events of special interest			
Genital infection	34 (12%)	33 (11%)	7 (3%)
Urinary tract infection	19 (7%)	11 (4%)	13 (5%)
Renal impairment or failure†	4 (1%)	2 (1%)	0
Fractures	4 (1%)	3 (1%)	3 (1%)
Hypotension, dehydration, or hypovolaemia	0	1 (<1%)	2 (1%)
Hypersensitivity‡	12 (4%)	13 (4%)	2 (1%)
Cardiovascular events	1 (<1%)§	2 (1%)¶	0
Serious adverse events			
One or more serious adverse events	19 (7%)	24 (8%)	15 (6%)
One or more serious adverse events related to the study drug	5 (2%)	9 (3%)	1 (<1%)
Serious adverse event leading to study discontinuation	3 (1%)	4 (1%)	3 (1%)
Hypoglycaemia			
At least one serious adverse event of hypoglycaemia	1 (<1%)	2 (1%)	1 (<1%)
Hypoglycaemia leading to study discontinuation	1 (<1%)	0	1 (<1%)
Ketone-related events			
One or more ketone-related serious adverse events	5 (2%)	8 (3%)	2 (1%)
DKA leading to study discontinuation	1 (<1%)	5 (2%)	0
Death	0	0	1 (<1%)

Table includes non-serious adverse events with onset on or after the first date and time of assigned treatment and on or before the last day of the 24 week treatment period plus 4 days, or up to the start date of the 28 week extension period, if earlier. Table includes serious adverse events with onset on or after the first date and time of assigned treatment and on or before the last day of the 24 week treatment period plus 30 days, or up to the start date of the 28 week extension period, if earlier. Only hypoglycaemia and DKA reported by the investigator as serious adverse events are included in the categories of adverse events, drug-related adverse events, serious adverse events, drug-related serious adverse events, and adverse events leading to discontinuation. All reported hypoglycaemia events and events sent for DKA adjudication with onset within 4 days of last day of treatment are included in the categories of hypoglycaemia and events sent for DKA adjudication, respectively. DKA leading to study discontinuation refers to investigator diagnosis, not the adjudication result. DKA=diabetic ketoacidosis. *Includes 55 patients who were excluded from the efficacy analysis because of a randomisation error. †Few adverse events of renal impairment or failure; of the six events, four were blood creatinine increase, and one each were obstructive uropathy and renal impairment (this impairment was assessed as mild in intensity and no treatment was required). There were no discontinuations due to renal impairment or failure. ‡Adverse events of hypersensitivity were investigated on the basis of a prespecified list of preferred terms: rash, rhinitis allergic, rash macular, dermatitis allergic, dermatitis contact, eye allergy, eyelid oedema, hypersensitivity, urticaria, circulatory collapse, conjunctivitis allergic, drug eruption, eczema, face oedema, hand dermatitis. §Angina pectoris. ¶Myocardial infarction and thrombosis.

Table 3: **Safety summary**

and –4·6% [2·4], respectively). The placebo group had only small changes in insulin dose that did not change at each measured timepoint, including week 2, suggesting a rapid return to baseline doses after the initial reduction on study day 1.

Compared with placebo, dapagliflozin at both doses produced significant reductions in bodyweight from baseline to week 24 (figure 4). Mean difference in bodyweight from baseline to week 24 for dapagliflozin 5 mg versus placebo was –2·96% (95% CI –3·63 to –2·28; p<0·0001), and for dapagliflozin 10 mg versus placebo was –3·72% (–4·38 to –3·05; p<0·0001). Reduction in bodyweight mostly occurred in the first 8 weeks, after which the rate of reduction was slower though consistent for the 24 week study period, without plateauing.

At week 24, 127 (50%) of 256 participants given dapagliflozin 5 mg and 129 (51%) of 254 participants given dapagliflozin 10 mg achieved a reduction of HbA_{1c} of 0·5% or more without having a severe hypoglycaemic event, compared with 65 (25%) of 257 participants given placebo (patients with only baseline HbA_{1c} were excluded; p<0·0001 for both; figure 5).

The adjusted mean changes in mean daily glucose (24 h continuous glucose monitoring mean) and glycaemic stability (mean amplitude of glucose excursion) readings from baseline to week 24 were significantly greater with dapagliflozin at both doses than with placebo (table 2). In the dapagliflozin 5 mg group, the mean percentage of continuous glucose monitoring values in the target glucose range (>70 mg/dL [>3·9 mmol/L] to ≤180 mg/dL [≤10·0 mmol/L]) increased from 43·2% (SD 12·4) at baseline to 52·3% (14·8) at week 24 (an absolute increase of 9·1% [13·5] and a relative increase of 21·1%); in the dapagliflozin 10 mg group, the percentage of continuous glucose monitoring readings within range increased from 44·6% (12·4) to 54·6% (13·1; an absolute increase of 10·1% [14·2] and a relative increase of 22·6%); and in the placebo group the percentage of readings within range was unchanged (from 44·4% [12·9] at baseline to 43·8% [14·7] at week 24).

Most adverse events reported during the study were of mild or moderate intensity (table 3). Discontinuations due to adverse events occurred in six (2%) participants in the dapagliflozin 5 mg group, eight (3%) in the dapagliflozin 10 mg group, and nine (3%) in the placebo group (table 3). One patient in the placebo group and none in the dapagliflozin groups died during the study. A summary of serious adverse events is reported in the appendix.

The overall adverse event profile was similar to clinical study experience with dapagliflozin in patients with type 2 diabetes. Among patients in the dapagliflozin 5 mg (n=277), dapagliflozin 10 mg (n=296), and placebo (n=260) groups, the most common adverse events were nasopharyngitis (38 [14%], 36 [12%], and 39 [15%], respectively), urinary tract infection (19 [7%], 11 [4%], and 13 [5%]), upper respiratory tract infection (15 [5%], 15 [5%], and 11 [4%]), and headache (12 [4%], 17 [6%], and 11 [4%]); few cardiovascular (one [<1%], two [1%], and zero) or hepatic (two [1%], three [1%], and three [1%]) events occurred. More adverse events of genital infection were reported in the dapagliflozin treatment groups than in the placebo groups. Genital infection adverse events were more common in women than men (dapagliflozin 5 mg: 25 [16%] of 158 women *vs* nine [8%] of 119 men; dapagliflozin 10 mg: 23 [16%] of 144 women *vs* ten [7%] of 152 men; placebo: seven [6%] of 128 women *vs* none of 132 men). No genital infection serious adverse events were reported in any of the treatment groups.

Occurrence of hypoglycaemia and severe hypoglycaemia was not increased in the dapagliflozin treatment groups compared with placebo (table 4). Only two patients, one in the dapagliflozin 5 mg group and one in the placebo group, discontinued study drug due to hypoglycaemia (table 3).

Similar numbers of patients in each group had definite diabetic ketoacidosis events (table 5). Of the 12 adjudicated definite events of diabetic ketoacidosis, ten were also reported as serious adverse events, with eight being given conventional diabetic ketoacidosis treatment using intravenous fluids and insulin. Missed insulin dose and insulin pump failure were the most common primary causes of diabetic ketoacidosis. In only one case was no primary cause identified, which occurred in a patient receiving dapagliflozin 5 mg. Of the adjudicated investigator-reported events, a higher number of possible or unlikely diabetic ketoacidosis events occurred in the dapagliflozin treatment groups than in the placebo group. Of 18 patients with possible events, only four visited a medical facility; two of these patients had laboratory values definitely not meeting the criteria for diabetic ketoacidosis, and the other two did not have these laboratory values of pH or bicarbonate available. Only two of these four patients (the two with laboratory values) received intravenous fluids and insulin. Half of the patients with possible events had no data specifying treatment (other than self-managed). Possible diabetic ketoacidosis was recorded as a result of positive ketone values measured at home. In many instances, the positive value was noted when the investigator reviewed the diary for ketone values at the next scheduled visit.

	Dapagliflozin 5 mg plus insulin (n=277; 121·6 patient-years)	Dapagliflozin 10 mg plus insulin (n=296; 132·1 patient-years)	Placebo plus insulin (n=260; 113·7 patient-years)
Number of hypoglycaemic events	4187	4776	4272
Number of patients with one or more hypoglycaemic event*	220 (79%)	235 (79%)	207 (80%)
Exposure-adjusted incidence rate†	3443·3	3615·0	3756·3
ADA categorisation			
Severe hypoglycaemia			
Number of events‡	31 (1%)	39 (1%)	54 (1%)
Number of patients with one or more event*	21 (8%)	19 (6%)	19 (7%)
Exposure-adjusted incidence rate†	25·5	29·5	47·8
Documented symptomatic hypoglycaemia			
Number of events‡	3343 (80%)	3758 (79%)	3314 (78%)
Number of patients with one or more event*	204 (74%)	218 (74%)	194 (75%)
Exposure-adjusted incidence rate†	2749·2	2844·5	2913·9
Asymptomatic hypoglycaemia			
Number of events‡	655 (16%)	797 (17%)	723 (17%)
Number of patients with one or more event*	99 (36%)	114 (39%)	90 (35%)
Exposure-adjusted incidence rate†	538·7	603·3	635·7
Probable symptomatic hypoglycaemia			
Number of events‡	67 (2%)	68 (1%)	113 (3%)
Number of patients with one or more event*	40 (14%)	30 (10%)	38 (15%)
Exposure-adjusted incidence rate†	55·1	51·5	99·4
Relative hypoglycaemia			
Number of events‡	77 (2%)	99 (2%)	59 (1%)
Number of patients with one or more event*	31 (11%)	31 (10%)	25 (10%)
Exposure-adjusted incidence rate†	63·3	74·9	51·9
Other hypoglycaemia			
Number of events‡	14 (<1%)	15 (<1%)	9 (<1%)
Number of patients with one or more event*	7 (3%)	11 (4%)	8 (3%)
Exposure-adjusted incidence rate†	11·5	11·4	7·9

Data are n (%), unless otherwise stated. Table includes hypoglycaemia events with onset on or after the first date and time of assigned treatment and on or before the last day of the 24 week treatment period plus 4 days, or up to the start of the 28 week extension period, if earlier. ADA=American Diabetes Association. *Percentages are based on the total number of patients in the safety analysis set. †Exposure-adjusted incidence rate per 100 person-years (events/100 person-years), including recurrences. ‡Percentages are based on the total number of events.

Table 4: **Summary of recurrent hypoglycaemic events**

Discussion

Type 1 diabetes is a chronic disease requiring continuous insulin treatment from the time of diagnosis. As in type 2 diabetes, microvascular and macrovascular complications are important features of type 1 diabetes. However, these sequelae occur earlier in the disease process in type 1 diabetes. The DCCT and follow-up EDIC studies first established the basis for tight glycaemic control to prevent microvascular and macrovascular complications in type 1 diabetes.[1] However, the intensification of insulin therapy necessary to achieve tight glycaemic control is often associated with hypoglycaemia. Insulin therapy also does not address other important abnormalities in type 1 diabetes, such as glucagon imbalances and increased rate of gastric emptying (resulting in rapid and large postprandial glucose excursions).[21] Furthermore, insulin therapy itself is linked to weight gain and associated blood pressure increases.[22] As such, there is a need for an adjunct treatment that provides sustained improvement across key parameters including HbA_{1c}, time in glycaemic range, bodyweight, and risk of hypoglycaemia.

Pramlintide is the only non-insulin therapy licensed for use with insulin in patients with type 1 diabetes (in the USA only). However, this drug has inconvenient preprandial dosing and has been associated with nausea, limiting its use in clinical practice. Several other non-insulin therapies have been used off-label or tested in clinical trials.[21] Metformin is a generic and inexpensive drug sometimes used off-label as adjunct therapy in type 1 diabetes, but studies have shown that although this drug reduces insulin requirement and bodyweight, it does not improve HbA_{1c} in the long run.[23,24] Furthermore, a recent 3-year randomised placebo-controlled clinical trial[25] of metformin as adjunct to insulin in 493 patients with type 1 diabetes and increased risk of cardiovascular disease found no benefits of metformin on atherosclerosis (as measured by carotid artery intima-media thickness). Glucagon-like peptide-1 receptor agonists have shown

	Dapagliflozin 5 mg plus insulin (n=277)	Dapagliflozin 10 mg plus insulin (n=296)	Placebo plus insulin (n=260)
Number of patients with event sent for DKA adjudication	16 (6%)	19 (6%)	6 (2%)
Number of patients with definite DKA	4 (1%)	5 (2%)	3 (1%)
Number of events of definite DKA	4	5	3
Incidence rate per 100 patient-years	3·29	3·78	2·64
Severity of events as adjudicated			
Mild	2	1	1
Moderate	1	3	1
Severe	1	1	1
Number of events of euglycaemic* DKA	0	2	0
Primary cause for adjudicated definite DKA events			
Insulin pump failure	2	1	1
Missed insulin dose	1	3	1
Severe illness	0	0	0
Not identified	1	0	0
Other	0	1†	1‡
Mean percent insulin total daily dose (IU) reduction compared with baseline for week before DKA event§	−8·9	−25·3	−7·8
Mean percent insulin total daily dose (IU) reduction compared with baseline at end of 24 week treatment period§	−11·0	−21·6	30·8
Events adjudicated as not DKA			
Number of patients with possible DKA	5 (2%)	7 (2%)	1 (<1%)
Number of events of possible DKA	7	8	3
Number of patients with unlikely DKA	8 (3%)	8 (3%)	3 (1%)
Number of events of unlikely DKA	15	10	8

Data reported are for 24 week treatment period and include all patients with an onset from day 1 of the 24 week treatment period up to and including 4 days after the last dose date in this period, or up to the start date of the 28 week extension period, whichever came first. DKA=diabetic ketoacidosis. *Self-monitored blood glucose of less than 250 mg/dL (13·9 mmol/L). †Reason was excessive alcohol intake. ‡Reason was stress. §Means apply for patients with definite DKA.

Table 5: **Summary of events sent for diabetic ketoacidosis adjudication**

efficacy in terms of weight loss and insulin-dose reduction, but inconsistent efficacy on HbA_{1c} reduction, glycaemic variability, and risk of hypoglycaemia.[21] Very little clinical research has been done to investigate the use of DPP4 inhibitors in patients with type 1 diabetes, although existing evidence has suggested that they have no durable effect on HbA_{1c} or other parameters.[21]

Inhibition of SGLT2, the major sodium–glucose cotransporter in the kidney, directly reduces hyperglycaemia, bodyweight, and blood pressure through an insulin-independent mechanism and could provide new possibilities for patients with type 1 diabetes. SGLT2 inhibitors are the first class of antihyperglycaemic drugs to show the potential for cardiovascular and renal benefit (even before manifestation of renal disease) in patients with type 2 diabetes.[26,27] This effect might be partly related to a reduction in renal hyperfiltration, which is of particular importance in type 1 diabetes, especially considering the younger age of presentation compared with type 2 diabetes. Therefore, if SGLT2 inhibitors are proven safe and efficacious as adjunct treatment to insulin, they should also be considered good candidates for bringing long-term cardiovascular and renal benefits to patients with type 1 diabetes.[28]

Studies reporting the use of either dual SGLT1/SGLT2 inhibitors[29] or selective SGLT2 inhibitors[30] in patients with type 1 diabetes have been limited in patient numbers and short in duration or are currently ongoing. DEPICT-1 is the first phase 3 clinical trial of a selective SGLT2 inhibitor as an add-on to insulin in a type 1 diabetes population to be reported. Dapagliflozin as an adjunct to insulin in type 1 diabetes was shown to provide significant and clinically relevant benefits in terms of improved overall glycaemic control (HbA_{1c}, mean daily glucose, time within target blood glucose range, and mean amplitude of glucose excursion), sustained weight loss (which had not yet plateaued by the end of the 24 week period), and a reduction in insulin dose, without any associated increases in the risk of hypoglycaemia or diabetic ketoacidosis. Although the differences in glycaemic parameters between the dapagliflozin 10 mg and 5 mg groups were limited, the dapagliflozin 10 mg group had slightly greater insulin dose reduction and slightly more weight loss. Because insulin-dose reductions have a negative effect on the glycaemic effect of dapagliflozin,[17] dapagliflozin 10 mg could be more potent than 5 mg at equal insulin doses or reductions.

Diabetic ketoacidosis is a recognised risk in type 1 diabetes, and reductions in insulin dose associated with the use of SGLT2 inhibitors have been linked to diabetic ketoacidosis.[31,32] The suggested maximum 20% reduction in insulin dose in the present study was based on findings from a phase 2 study of dapagliflozin in patients with type 1 diabetes.[15,17] This level of dose reduction is believed to have restricted hypoglycaemia risk, while also reducing the potential for diabetic ketoacidosis.[17] In DEPICT-1, dapagliflozin treatment did not increase the risk of adjudicated events of definite diabetic ketoacidosis. Insulin pump failure and missed insulin doses were the most frequent risk factors for definite diabetic ketoacidosis in the placebo and dapagliflozin groups. Events classified as possible diabetic ketoacidosis were more frequent in the dapagliflozin groups than in the placebo group, but these events were of some diagnostic uncertainty (none fulfilled the criteria for diabetic ketoacidosis and most cases were only ketone values measured at home). In a small study[31] reported in 2016 assessing triple therapy with insulin, liraglutide, and dapagliflozin in patients with type 1 diabetes, two patients had diabetic ketoacidosis. Both patients had reductions in insulin dose greater than 20% and both events occurred within 48 h of an increase in the dose of dapagliflozin from 5 mg per day to 10 mg per day; additionally, one of the patients had missed meals and had consumed a large amount of alcohol and then had euglycaemic ketoacidosis. This report also shows that although patients on dapagliflozin had slight increases in plasma and urinary concentrations of acetoacetate and β-hydroxybutyrate, the patients who had

diabetic ketoacidosis had extreme increases with acidosis. Some data[17] have been published showing that ketogenesis induced by dapagliflozin is dose dependent. Because diabetic ketoacidosis is a common concern in type 1 diabetes, patients, their physicians, and caregivers will be familiar with its detection and management. As such, we believe that events of diabetic ketoacidosis seen in patients treated with dapagliflozin can be managed with standard of care.

Hypoglycaemia risk is also of great importance in type 1 diabetes, being the single greatest fear of patients with type 1 diabetes and the top disease management challenge of caregivers.[33] The insulin-independent, glucose-dependent mechanism of action of dapagliflozin is reflected in the reduced glucose variability and reduced risk of severe hypoglycaemia seen in the present study among patients who reduced their HbA_{1c} by 0·5% or more. Notably, by contrast with the ADJUNCT trials with liraglutide—which, per protocol, did not exclude patients with recent events of severe hypoglycaemia and might be more reflective of the real-world situation[34,35]—in the DEPICT-1 study, patients with an event of severe hypoglycaemia within 1 month before screening were excluded per protocol. In practice, however, no patients ended up being excluded from DEPICT-1 by this criterion.

The present study has several limitations. First, the 24 week duration does not provide long-term evidence of therapeutic benefit. Second, the primary estimand for the primary endpoint is treatment difference at week 24 if patients did not discontinue randomly assigned treatment. The estimand was estimated using a longitudinal repeated-measures analysis with an assumption that patients who discontinued their randomly assigned treatment did so randomly and that the off-treatment effect of those who did discontinue would be the same as that of patients who completed 24 weeks of their randomly assigned treatment. Therefore, outcomes from sensitivity analyses need to be taken into account when considering overall efficacy. Third, the present study excluded patients with common comorbidities to limit confounding factors that could affect results. Fourth, the real-world study design without a protocol-mandated insulin titration algorithm, chosen to allow for study results that would be more relevant to clinical practice, might not fully reveal the glycaemic potential of adding SGLT2 inhibition to insulin therapy. As such, patients might be tempted to reduce insulin dose at the expense of HbA_{1c} improvement. Exploratory analyses do suggest that insulin dose reductions negatively affect glycaemic improvements when adding dapagliflozin to insulin in patients with type 1 diabetes.[17] Finally, the findings were obtained in the context of a clinical trial, with patients who might have a greater interest in their diabetes management (including carbohydrate counting) and with strict guidelines on action steps when diabetic ketoacidosis-predisposing events occur. These measures would need to find their way into clinical practice and educational programmes if patients with type 1 diabetes are to use SGLT2 inhibitors as an adjunct to insulin therapy outside of the trial setting.

In conclusion, dapagliflozin is the first oral adjunct to insulin therapy for the treatment of type 1 diabetes to show improvement in HbA_{1c} and weight loss, with a lower risk of hypoglycaemia. At week 24, both doses of dapagliflozin (5 mg and 10 mg) showed significant and clinically relevant benefits as add-on to adjustable insulin compared with placebo in patients with inadequately controlled type 1 diabetes. Overall, similarly to studies in type 2 diabetes, dapagliflozin was well tolerated when used as an add-on to adjustable insulin, with no new safety signals identified. Our results suggest that dapagliflozin is a promising adjunct treatment to insulin in patients with type 1 diabetes.

Contributors

PD, CM, MP, SCG, DT, FT, and AML contributed to the development of the study concept, scientific literature review, study design, interpretation, and writing of the report. LH contributed to the study design, data collection, data analysis, data interpretation, and writing of the report. JX contributed to the data analysis and interpretation and to the writing of the report.

Declaration of interests

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. 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. 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. LH is an employee and shareholder of Bristol-Myers Squibb. DT has served on advisory boards for AstraZeneca, Amgen, Eli Lilly, Novo Nordisk and Servier; has given lectures for AstraZeneca, Bayer, Eli Lilly, Novo Nordisk, Novartis, Sanofi, and Servier; and has received research grants from AstraZeneca, Bayer, Eli Lilly, Novo Nordisk, Novartis, and Sanofi. FT is an employee of AstraZeneca. JX and AML are employees and shareholders of AstraZeneca. SCG declares no competing interests.

Acknowledgments

This study was funded by AstraZeneca and Bristol-Myers Squibb. Writing support was provided by Parita Sheth and Mark Davies (inScience Communications, Springer Healthcare, London, UK), funded by AstraZeneca.

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