The glucose-lowering effect of dapagliflozin and saxagliptin and the effect of dapagliflozin alone and in combination with saxagliptin on albuminuria in patients with type 2 diabetes and chronic kidney disease (DELIGHT): a randomised controlled trial

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Background: We assessed the effects of the SGLT2 inhibitor dapagliflozin alone and in combination with the DPP4 inhibitor saxagliptin on albuminuria and HbA1c in patients with type 2 diabetes and chronic kidney disease in a double-blind placebo-controlled multicentre multinational study (DELIGHT study; clinicaltrials.gov, NCT02547935).

Methods: After a 4-week single-blind placebo lead-in period, 448 participants were randomised (1:1:1; using computer-generated codes) to dapagliflozin 10 mg (n=145), dapagliflozin 10 mg and saxagliptin 2.5 mg (n=155) or placebo (n=148) once daily for 24 weeks. Inclusion criteria included urinary albumin-to-creatinine ratio (U_{ACR}) 30–3500 mg/g, eGFR 25–75 mL/min/1·73 m^2, HbA1c 7–11% (53–97 mmol/mol) and stable doses of ACEi/ARB and glucose lowering treatment for ≥12 weeks. Primary endpoints were change from baseline in U_{ACR} (dapagliflozin and dapagliflozin/saxagliptin) and HbA1C (dapagliflozin/saxagliptin) at Week 24.

Findings: Dapagliflozin and dapagliflozin/saxagliptin significantly reduced U_{ACR} versus placebo. This effect was sustained over the study period; at Week 24, change in U_{ACR} was −21·0% (95% CI, −34·1, −5·2; p=0·011) for dapagliflozin (n=132) and −38·0% (−48·2, −25·8; p<0·001) for dapagliflozin/saxagliptin (n=139) compared with placebo (n=134). HbA1c was reduced with dapagliflozin/saxagliptin (n=137) compared with placebo (n=118) (Week 24; −0·58% [−0·80 to −0·37; p<0·001]). The proportion of patients with adverse events (79/145 [54·5%], 104/152 [68·4%] and 81/148 [54·7%]) or serious adverse events (12/145 [8·3%], 12/152 [7·9%] and 16/148 [10·8%]) was similar across groups. There were no new drug-related safety signals.

Interpretation: Dapagliflozin alone and dapagliflozin/saxagliptin conferred significant improvements in albuminuria in these patients; dapagliflozin/saxagliptin conferred a clinically significant reduction in both albuminuria and HbA1c at Week 24.

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Research in context

Evidence before this study

Search criteria: We searched PubMed from January 1, 1990, to December 30, 2018 for all English-language publications with the search terms ‘SGLT2’, ‘SGLT2 inhibitor’, ‘DPP4’, ‘DPP4 inhibitor’, ‘albuminuria’, ‘kidney disease’, ‘nephropathy’, ‘HbA1c’, and ‘glycaemic control’.

Sodium glucose cotransporter 2 (SGLT2) inhibitors have been associated with reductions in albuminuria in experimental diabetes and in secondary analyses of clinical trials involving patients with type 2 diabetes (T2D) of whom a minority had kidney disease. Secondary and exploratory data from long-term cardiovascular outcome trials (CVOTs), which assessed the cardiac safety of SGLT2 inhibitors in patients with T2D at risk of or with established cardiovascular disease (EMPA-REG Outcome, CANVAS Programme and DECLARE), suggested that agents from this class reduce the onset or progression of albuminuria, possibly independently of glucose lowering. Dipeptidyl peptidase 4 (DPP4) inhibitors have also been associated with modest reductions in albuminuria in experimental diabetes. A post-hoc analysis from the SAVOR-TIMI trial suggested that the DPP4 inhibitor saxagliptin reduces the onset and progression of albuminuria, although a prospective clinical trial designed to assess the albuminuria lowering effect of the DPP4 inhibitor linagliptin failed to demonstrate benefit. As SGLT2 and DPP4 inhibitors act through different but complementary mechanisms, the combination of both agents may synergistically impact on glycaemic control and albuminuria.

Added value of this study

We describe the results of a randomised, double-blind, placebo-controlled, phase 2/3 trial designed to study the efficacy of either dapagliflozin or a dapagliflozin/saxagliptin combination as an adjunct to angiotensin converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB) therapy, for reducing albuminuria and haemoglobin A1c (HbA1c) in patients with type 2 diabetes and chronic kidney disease. To our knowledge, this is the first prospective clinical trial to assess the efficacy and safety of SGLT2 inhibitors alone and in combination with DPP4 inhibitors on albuminuria and glycaemic control in this patient population. Compared with placebo, dapagliflozin lowered albuminuria after 24 weeks follow-up by 21%. The combination of dapagliflozin and saxagliptin conferred a clinically significant reduction in albuminuria (38%) and robust reduction in HbA1c (0.58%) after 24 weeks of follow-up, compared with placebo. Dapagliflozin and saxagliptin were well tolerated with no unexpected drug-related adverse events reported.

Implications of all the available evidence

On the basis of all available evidence, SGLT2 inhibitors including dapagliflozin decrease albuminuria in patients with T2D and chronic kidney disease. Combining dapagliflozin with saxagliptin confers a clinically relevant reduction in both albuminuria and HbA1c. To ascertain whether this effect translates into improved kidney outcomes remains uncertain and requires dedicated outcome trials with longer follow-up.

Introduction

Poor metabolic control and elevated albuminuria are risk markers for progressive kidney function loss.[1-3] Intensive glucose control has been shown to be renoprotective in a broad range of patients with type 2 diabetes.[4,5] Treatments that lower albuminuria have also been associated with slowing the deterioration in kidney function.[6] Yet, in patients with established type 2 diabetes and chronic kidney disease (CKD), optimising glycaemic control and albuminuria lowering with currently available treatments are insufficient to prevent progressive loss of kidney function.

Sodium glucose co-transporter 2 (SGLT2) and dipeptidyl peptidase 4 (DPP4) inhibitors are now established therapies for the treatment of hyperglycaemia in patients with type 2 diabetes. They improve glycaemic control through different mechanisms. SGLT2 inhibitors limit the physiological reabsorption of glucose by the kidney, resulting in glycosuria and lowering of blood glucose independently of the action of insulin.[7] SGLT2 inhibitors have also been shown to reduce body weight and blood pressure. DPP4 inhibitors lower glucose by inhibiting the breakdown of glucagon-like peptide-1 (GLP-1).[8] The haemoglobin A1c (HbA1c) lowering ability of SGLT2 inhibitors is attenuated at lower kidney function, while the effect on other cardiovascular risk markers such as body weight and blood pressure appear to be independent of kidney function.[9,10] In contrast, the HbA1c lowering efficacy of DPP4 inhibitors does not depend on kidney function. Accordingly, the combination of SGLT2 and DPP4 inhibitors is logical in patients with type 2 diabetes and CKD as these two classes of agents have complementary metabolic effects.

SGLT2 and DPP4 inhibitors may also have direct beneficial effects on kidney function. Cardiovascular outcomes trials have suggested that SGLT2 inhibitors decrease albuminuria and slow the progressive loss of kidney function over time.[11-14] These effects appear to be independent of improvements in glycaemic control.[10,15,16] DPP4 inhibitors have also been shown to significantly decrease albuminuria in secondary analyses of cardiovascular safety trials,[17,18] although a study designed to assess the effects of the DPP4 inhibitor linagliptin on albuminuria failed to detect significant albuminuria reduction.[19]

As there are complementary benefits of SGLT2 and DPP4 inhibitors that may synergistically impact on glucose lowering and improve kidney function, the DELIGHT study was designed to

assess the efficacy of dapagliflozin alone and in combination with saxagliptin in patients with type 2 diabetes and CKD.

Methods

Study design

The DELIGHT trial was a randomised, double-blind, multicentre, multinational, placebo-controlled, clinical trial conducted in patients with type 2 diabetes and CKD. The study was conducted at 112 research centres that enrolled patients in Australia, Canada, Japan, Republic of Korea, Mexico, South Africa, Spain, Taiwan and the United States of America. The study is registered with clinicaltrials.gov (NCT02547935).

Following a screening visit, eligible patients proceeded to a 4-week, single-blind, placebo run-in period in which patients were given dietary advice but had no changes in prescription of glucose-lowering or anti-hypertensive medication. After 4 weeks, eligible patients were randomly assigned to oral once-daily treatment with dapagliflozin 10 mg, or dapagliflozin 10 mg and saxagliptin 2·5 mg or matched placebo for 24 weeks. Efficacy and safety parameters including adverse events were monitored at Weeks 1, 4, 8, 12, 16, 20 and 24. After either completing the treatment period or stopping study medication prematurely, patients entered a 3-week follow-up period to evaluate changes in physical findings, symptoms and laboratory measurements after discontinuation of the study medication. Antihypertensive treatments were to be kept stable throughout the entire study from start of run-in until end of follow-up.

The study was designed and conducted in accordance with the Declaration of Helsinki (version amended October 2000) and in compliance with the ethical principles of Good Clinical Practice. Ethics committees or institutional review boards approved the research protocol. All patients gave their written, informed consent before any study-related procedure commenced.

Population

Eligible patients were ≥18 years old with a known history of type 2 diabetes for more than 12 months. They had elevated albuminuria (U_{ACR} 30 to 3500 mg/g), an estimated glomerular filtration rate (eGFR) between 25 and 75 mL/min/1·73 m^2 and HbA1c between 7.0 and 11.0% (53 and 97 mmol/mol). Patients were receiving stable glucose-lowering and anti-hypertensive treatment including angiotensin converting enzyme inhibitors (ACEi) or angiotensin II receptor

blockers (ARBs) at a clinically appropriate dose for at least 12 weeks prior to study randomisation.

Patients were excluded if they had type 1 diabetes, known non-diabetic kidney disease, severe cardiovascular disease, two or more major hypoglycaemia events within 12 weeks prior to screening, haemoglobin <9 g/dL (or 5·6 mmol/L) or evidence of hepatic disease. Patients were also excluded if they had poorly controlled blood pressure (systolic blood pressure ≥180 mmHg and/or diastolic blood pressure ≥110mHg). Additional exclusion criteria were current use of SGLT2 inhibitors, GLP1 receptor agonists (GLP1-RA) or DPP4 inhibitors and long-term treatment with glucocorticoids. Supplementary Table 1 contains the full list of inclusion and exclusion criteria.

Randomisation and masking

After the run-in period, patients were stratified according to the following pre-enrolment glucose lowering therapies: insulin, metformin, sulphonylurea derivative, thiazolidinedione or other treatment-based regimens. Subsequently, patients were randomly assigned (1:1:1) to receive dapagliflozin 10 mg, dapagliflozin 10 mg and saxagliptin 2·5 mg or matched placebo orally once daily for 24 weeks according to a non-centre-specific randomisation scheme. Stratification and randomisation were performed centrally at AstraZeneca R&D via an interactive voice/web response system. The randomisation scheme was produced by a computer software tool, AZrand (global randomisation system, AstraZeneca), prior to the inclusion of the first patient. The investigators at the study centres assigned each patient according to an identification number provided by the interactive voice/web response system.

The study employed a double-blind and double-dummy design. There was no difference in appearance between the medications for each treatment group. In each phase, medication for each treatment group was supplied in identical bottles, labelled appropriately in order to maintain blinding within the study. All study personnel (except personnel analysing pharmacokinetic data) were unaware of the randomised treatment.

Procedures

Before the randomisation visit and at Weeks 4, 8, 12, 16, 20, 24 and 27, patients collected first morning void urine samples on three separate days for assessment of U_{ACR}. Vital signs were recorded and biochemical laboratory parameters were measured at each study visit. Serum creatinine was monitored at each study visit, and was used to calculate eGFR with the

Modification of Diet in Renal Disease (MDRD) equation.[20] Adapted MDRD formulae were used for Japanese and Taiwanese subjects.[21,22] A 24-hour urine sample was collected at baseline and Week 24 for assessment of 24-hour urinary albumin and glucose excretion. HbA1c and urinary glucose were blinded over the duration of the trial. Analyses of all laboratory samples, including first morning-void urines, were performed at central laboratories (Covance Laboratories, Indianapolis, Indiana; and Geneva, Switzerland).

Safety was monitored at baseline and at Weeks 1, 4, 8, 12, 16, 20, 24 and 27 by assessing adverse events and laboratory data. Reported adverse events were recorded during the trial and analysed with a standard coding dictionary (MedDRA, version 21·0) to classify adverse event terms.

Outcomes

The primary efficacy endpoint for the dapagliflozin treatment arm was percentage change from randomisation in U_{ACR} at Week 24. For the dapagliflozin and saxagliptin combined treatment arm, percentage change from baseline in HbA1c at Week 24 and percentage change from randomisation in U_{ACR} at Week 24 were the co-primary endpoints. Since the HbA1c-lowering effect of dapagliflozin attenuates in patients with kidney impairment, change in HbA1c was not a co-primary endpoint, but a secondary endpoint in the dapagliflozin treatment arm. Secondary endpoints were change from baseline in body weight, systolic blood pressure and fasting plasma glucose at Week 24, proportion of patients achieving a >30% reduction in U_{ACR} and proportion of patients achieving a reduction in HbA1c to <7.0% at Week 24. Pre-specified exploratory outcomes were change from baseline in 24-hour urinary glucose excretion, 24-hour urinary albumin excretion, LDL cholesterol, HDL cholesterol, uric acid, haematocrit, and the proportion of patients achieving a clinical benefit endpoint defined as a ≥0·3% reduction in HbA1c, ≥3% reduction in body weight and ≥3 mmHg reduction in seated systolic blood pressure. A post-hoc analysis of change in UACR for patients achieving or not achieving each individual component of the clinical benefit endpoint was also conducted. Safety endpoints included the change from baseline in eGFR at Week 24 and at Week 27 (3 weeks after treatment completion), and the proportion of patients who discontinued study medication due to a sustained increase in serum creatinine ≥1.5 times from baseline level.

Statistical analyses

The sample size was based on the required improvement in HbA1c and U_{ACR} at Week 24 for dapagliflozin and saxagliptin versus placebo at a multiplicity-adjusted two-sided Type I error level of 0·025, which allowed separate claims for each active treatment. More than 90% power to detect a 35% difference in U_{ACR} assuming a standard deviation of 80% was achieved by including 142 patients per group. The estimated sample size provided 90% power to detect a difference of 0·42% in mean change from baseline in HbA1c assuming a standard deviation in HbA1c of 1·0%. If superiority to placebo was achieved by the dapagliflozin group for the primary endpoint of U_{ACR} and/or superiority to placebo was achieved by the dapagliflozin/saxagliptin group for both HbA1c and U_{ACR} (co-primary), then secondary comparisons would follow a pre-specified order of testing. For each active treatment, hypothesis testing of secondary endpoints proceeded conditional on rejection of a primary hypothesis (hypotheses), and stopped at the first instance when superiority to placebo could not be claimed. Comparisons of dapagliflozin/saxagliptin with placebo were pre-specified as: mean (percentage) change in body weight, mean change in fasting plasma glucose, proportion of patients with >30% U_{ACR} reduction, and proportion of patients achieving an HbA1c <7·0% (<53 mmol/mol), mean change in seated systolic blood pressure. Comparisons of dapagliflozin with placebo were pre-specified as mean (percentage) change in body weight, proportion of patients with >30% U_{ACR} reduction, mean change in seated systolic blood pressure, mean change in HbA1c, mean change in fasting plasma glucose, and proportion of patients achieving an HbA1c <7·0% (<53 mmol/mol).

Continuous primary and secondary endpoint analyses as well as safety analyses of eGFR were performed using a mixed model for repeated measures (MMRM) with a direct likelihood approach, an unstructured model of within-subject correlations, and a Kenward-Roger method to estimate degrees of freedom (SAS®, version 9·4). Values after treatment discontinuation were excluded from each analysis from the full analysis set (FAS; values after rescue were also omitted from analyses of glycaemic parameters). Change from baseline (Week[t]) – baseline or log(Week[t]) – log(baseline) was modelled with terms for randomisation strata, treatment, visit, treatment-by-visit interaction and covariates for baseline (or log[baseline]) and baseline (or log[baseline]) -by-visit interaction. Adjusted mean changes or mean percentage change (derived from exponentiation of adjusted estimates) were reported. Subgroup analyses included terms added for subgroup*visit, subgroup*treatment, and subgroup*treatment*visit, and adjusted estimates (or percentages) and differences were not reported for any subgroup with less than 10 patients for any treatment. Proportions of patients achieving HbA1c <7·0% (<53 mmol/mol) and U_{ACR} ≥30·0% were analysed by logistic regression, and (percent) changes in lipid

parameters and 24-hour urine parameters were analysed by ANCOVA. These models had terms for randomisation strata, treatment and baseline as a covariate, and used a last observation carried forward approach for missing data.

Role of the funding source

The study was overseen by academic advisors, including members from the sponsor. The sponsor was involved in the design of the study, in the collection and analysis of the data and in writing the report. All authors had access to the study results, and the lead author vouches for the accuracy and completeness of the data reported. The lead author and the advisory committee had the final decision to submit the publication.

Results

This study was conducted between September 2015 (first patient enrolled) until June 2018. A total of 1187 patients were screened of whom 461 were randomised. Thirteen randomised patients (five in the placebo, six in the dapagliflozin and two in the dapagliflozin/saxagliptin groups) from one clinical site were excluded from the FAS set because of site-specific issues with data integrity. Therefore, 448 patients were included in the analyses, of whom 148 were assigned to placebo, 145 to dapagliflozin 10 mg/day and 155 to dapagliflozin 10 mg/day and saxagliptin 2·5 mg/day (Supplementary Figure 1). Primary endpoint data were available in 436 (97·3%) patients for HbA1c analyses and in 435 (97·1%) patients for U_{ACR} analyses. Baseline demographic, clinical and biochemical characteristics as well as concomitant medication were similar between the treatment groups (Table 1).

Figure 1 shows the albuminuria changes over time. In the placebo group, U_{ACR} remained fairly stable over time. Patients receiving dapagliflozin alone had a median (25^{th} – 75^{th} percentile) U_{ACR} of 270 (69 – 751) mg/g at baseline. Compared with placebo, mean percentage change in U_{ACR} was −28·3% (95% confidence interval [CI], −36·8 to −18·7; p<0.001) at Week 4. This reduction in U_{ACR} was sustained through to Week 24 at which point the mean percentage change in U_{ACR} was −21·0% (95% CI, −34·1 to −5·2; p=0·011) compared with placebo. In the dapagliflozin/saxagliptin group, median U_{ACR} at baseline was 218·4 (74 – 936) mg/g. Compared with placebo, mean percentage change in U_{ACR} was −34·5% (95% CI, −42·1 to −25·9; p<0.001) at Week 4. This effect was sustained until Week 24 (compared with the placebo group mean percentage change in U_{ACR} was −38·0% [95% CI, −48·2 to −25·8; p<0·001). Three weeks after

the discontinuation of dapagliflozin or dapagliflozin/saxagliptin, U_{ACR} increased and no differences among the treatment groups were observed (Figure 1).

The proportion of patients with a 30% reduction in U_{ACR} at Week 24 in the placebo, dapagliflozin and dapagliflozin/saxagliptin groups was 31·3%, 45·0% (odds ratio [OR} versus placebo, 1·9 [95% CI, 1·1 to 3·0]) and 57·0% (OR versus placebo, 3 ·0 [95% CI, 1·8 to 4·8]), respectively. Compared with placebo, the mean percentage change in 24-h urinary albumin excretion at Week 24 was −19·9% (95% CI, −35·6 to −0·3; p=0.47) with dapagliflozin and −39·7% (95% CI, −51·5 to −24·9; p<0.001) with dapagliflozin/saxagliptin compared with placebo at Week 24 (Table 2). To assess whether the albuminuria lowering effect of dapagliflozin/saxagliptin was mediated by changes in glycaemic or systemic haemodynamic factors after 24 weeks of treatment, the main analysis was repeated with adjustments for concomitant changes in HbA1c, systolic blood pressure, eGFR and uric acid. Compared with placebo, percentage change in U_{ACR} at Week 24 was −15·2% (95% CI, –28·5 to 0·5; p=0·057) with dapagliflozin and −33·6% (95% CI, −44·4, −20·7; p<0·001) with dapagliflozin/saxagliptin, suggesting that the albuminuria-lowering effect was to a large effect independent of these covariates.

Mean baseline (SD) HbA1c was 8·6% (1·2), 8·4% (1·0) and 8·2% (1·1) in the placebo, dapagliflozin and dapagliflozin/saxagliptin groups, respectively (70, 68 and 66 mmol/mol). Compared with placebo, mean change in HbA1c at Week 24 was −0·2% (95% CI, −0·4 to 0·1; p=0·142) in the dapagliflozin group and −0·6% (95% CI, −0·8 to −0·4; p<0·001) in the dapagliflozin/saxagliptin group (Figure 1). The proportion of patients who achieved HbA1c <7% (<53 mmol/mol) at Week 24 was 10·0%, 15·0% (OR vs. placebo, 1·7 [95% CI, 0·8 to 3·8]) and 35·1% (OR vs placebo 5·4 [95 %CI, 2·6 to 11·2]) in the placebo, dapagliflozin and dapagliflozin/saxagliptin groups, respectively·

Mean (SD) baseline eGFR was 47·7 (14), 50·2 (13), and 49·0 (13) mL/min/1·73 m^2 in the placebo, dapagliflozin and dapagliflozin/saxagliptin groups, respectively. An initial decrease in eGFR was observed in the dapagliflozin and dapagliflozin/saxagliptin groups (Figure 2). At Week 1, mean eGFR (mL/min/1·73 m^2) change from baseline versus placebo was −4·8 (95% CI, –6·3 to –3·3) in the dapagliflozin group, and −4·6 (95% CI, –6·0 to –3·1) in the dapagliflozin/saxagliptin group. eGFR remained lower in both the dapagliflozin and dapagliflozin/saxagliptin groups during the 24-week follow-up, with a difference from placebo in mean values at Week 24 of –2·4 mL/min/1·73 m^2 (95% CI, –4·2 to –0·5; p=0·011) and –2·4

mL/min/1·73 m^2 (95% CI, –4·2 to –0·7; p=0·007), respectively. The reduction in eGFR in the dapagliflozin and dapagliflozin/saxagliptin groups was completely reversible after treatment discontinuation and did not differ from randomisation or placebo.

Dapagliflozin and dapagliflozin/saxagliptin treatment resulted in a decrease in body weight (%) at Week 4 which was sustained until Week 16 but which was non-significant at Week 24 (dapagliflozin [mean percentage difference vs placebo (95% CI)]: −0·9% [−2·2 to 0·4%]), p=0·193; dapagliflozin/saxagliptin: −0·0% [−1·3 to 1·3%], p=0·953; Figure 2). Superiority for the first secondary endpoint (body weight) for dapagliflozin/saxagliptin was thus not shown in the testing sequence. As a result, hypothesis testing for other secondary endpoints was discontinued. Compared with placebo, the difference in mean fasting plasma glucose (mmol/L) decreased in both dapagliflozin and dapagliflozin/saxagliptin groups; however this effect was no longer observed at the Week 24 study visit (dapagliflozin: −0·11 [95% CI, −0·76 to 0·54];; dapagliflozin/saxagliptin: −0·34 [95% CI, −0·97 to 0·30]). The mean difference for systolic blood pressure (mmHg) remained lower versus placebo in the dapagliflozin/saxagliptin group at Week 24 (dapagliflozin: −2·8 [95% CI, −6·4 to 0·8] ; dapagliflozin/saxagliptin: −4·8 [95% CI −8·3 to −1·2]) (Figure 2). Changes in uric acid, 24-h urinary glucose excretion, haematocrit and low- and high-density lipoprotein (LDL; HDL) compared with placebo after 24-weeks treatment are shown in Table 2. The proportion of patients that achieved the pre-specified responder criteria of ≥0·3% reduction in HbA1c, ≥3% reduction in body weight and ≥3 mmHg reduction in seated systolic blood pressure was 4·1% in the placebo group, 14·0% in the dapagliflozin group (OR versus placebo, 3·8 [95% CI, 1·5 to 9·9]) and 17·4% in the dapagliflozin/saxagliptin group (OR versus placebo, 4·9 [95% CI, 1·9 to 12·5]).

Subgroup analysis demonstrated that the HbA1c responses to dapagliflozin/saxagliptin and the U_{ACR} responses to both dapagliflozin and dapagliflozin/saxagliptin were generally consistent across subgroups (Figure 3 and Supplementary figure 2).A post-hoc analysis showed that changes in U_{ACR} from baseline during dapagliflozin or dapagliflozin/saxagliptin treatment were consistent regardless of achieving the individual components of the pre-specified responder criteria in HbA1c, body weight and systolic blood pressure (Table 3).

Adverse events are described in Table 4. Overall, the pattern of adverse events in this patient population with type 2 diabetes and CKD was consistent with those observed in dapagliflozin and saxagliptin clinical study programmes. As expected, there was an increase in minor

hypoglycaemia in the dapagliflozin/saxagliptin combination arm, but no increase in major hypoglycaemia. Overall, one (0·7%) patient in the placebo group and three (2·0%) patients in the dapagliflozin/saxagliptin discontinued from study medication due to sustained serum creatinine elevations of >1·5 times the baseline value. Complications potentially related to volume depletion and impaired kidney function were not different in patients treated with dapagliflozin, but were numerically higher in patients randomised to dapagliflozin/saxagliptin therapy. One event of diabetic ketoacidosis occurred in a patient from the dapagliflozin alone group. The study medication was discontinued 10 days prior to the development of ketoacidosis.

Discussion

This study demonstrates that in patients with type 2 diabetes and moderate to severe CKD, once-daily treatment with dapagliflozin in addition to ACEi or ARB treatment reduces albuminuria. The combination of dapagliflozin and saxagliptin produces a robust and clinically meaningful reduction in both HbA1c and albuminuria. Both dapagliflozin and dapagliflozin/saxagliptin were generally well tolerated in this population of patients with type 2 diabetes and CKD.

Although originally developed as glucose-lowering agents, recent studies have shown that SGLT2 inhibitors lower albuminuria.[11-13,15,16] However, these trials were primarily designed to assess effects of treatment on HbA1c, blood pressure or cardiovascular outcomes and included few patients with significant albuminuria or impaired kidney function. Although the reduction in albuminuria with dapagliflozin alone in this trial was somewhat smaller than those in previous secondary analyses,[11-13,15,16] the confidence interval did not exclude the possibility of effects sizes of a similar magnitude as previously observed. Results of the DELIGHT study therefore strongly support the importance of SGLT2 inhibitors in lowering albuminuria in patients with type 2 diabetes and CKD in addition to guideline recommended treatment.

The efficacy and safety of the combination of SGLT2 and DPP4 inhibitors in improving glycaemic control has been shown in patients with type 2 diabetes and preserved kidney function.[23,24] However, the potential of this combination in improving glycaemic control and lowering albuminuria in patients with type 2 diabetes and CKD was hitherto unknown. To our knowledge, the DELIGHT study is the first, prospective, multi-centre, clinical trial demonstrating that a combination of SGLT2 and DPP4 inhibitors can be safely used in patients with type 2

diabetes and CKD and has beneficial effects on glycaemic control and albuminuria. The reduction in Hba1c when saxagliptinis added to dapagliflozin is clinically relevant in patients with kidney impairment since the glycaemic effects of SGLT2 inhibitors attenuate when kidney function declines. The magnitude of the reduction in albuminuria when saxagliptin is combined with dapagliflozin was similar when compared with the reduction in albuminuria achieved with the DPP4 inhibitor linagliptin in patients at high risk of cardiovascular disease of whom the majority had micro- or macroalbuminuria.[18] Secondary analyses of outcome trials in patients with diabetic kidney disease have shown a robust relationship between the magnitude of albuminuria reductions and delay of progression in kidney function decline. This supports the possibility of a long-term kidney protective effect of combined therapy with dapagliflozin and saxagliptin.[6]

The mechanism of potential renoprotection in patients treated with dapagliflozin/saxagliptin can be inferred from preclinical studies. Clearly glycaemic control is optimised, and blood pressure and weight loss are more likely to be positively influenced with these classes of glucose-lowering therapies. However, this study demonstrates benefit that is independent of glycaemic control, reduction in blood pressure and weight loss. SGLT2 inhibitors are thought to exert renoprotection via haemodynamic, metabolic and cytoprotective mechanisms.[7] Specifically, the natriuretic effect of SGLT2 inhibitors activates tubuloglomerular feedback, reducing glomerular hypertension and hyperfiltration to limit kidney damage. In this study, the activation of tubuloglomerular feedback is reflected in a reduction in eGFR as demonstrated at Week 1, with the effect being reversed within three weeks of cessation of study mediation at Week 27, consistent with a haemodynamic effect. Although investigation of additional renoprotective mechanisms are beyond the scope of this study, other proposed beneficial effects of SGLT2 inhibitors include an increase in fat oxidation and ketone body production. These catabolic changes might help provide a more efficient energy substrate to limit cellular hypoxia as well as to normalise diurnal metabolic autophagy and mitophagy patterns, improving mitochondria function[25,26] Reduced sodium transport in the proximal tubule might also contribute to reduced energy demands and thereby ameliorate functional and structural changes in diabetic kidney disease.[27] Furthermore, a reduced glucotoxicity in tubular cells could limit the conversion from the latent to the active form of transforming growth factor beta-1, a known intrarenal cytokine associated with progressive kidney failure.[25]

Both dapagliflozin and saxagliptin were generally well tolerated in this population, which included patients with an eGFR as low as 25 mL/min/1·73m^2. An earlier study with dapagliflozin in patients with type 2 diabetes and CKD suggested increased risk of fractures.[28] However, this was neither observed in the current study nor in a recent dapagliflozin clinical trial in patients with diabetes and impaired kidney function;[29] furthermore, no increase in fractures was observed in the DECLARE trial.[14] The SGLT2 inhibitor canagliflozin has been associated with a higher rate of amputation,[30] but this was not observed with dapagliflozin or dapagliflozin/saxagliptin treatment in this study. Through their mode of action, neither SGLT2 nor DPP4 inhibitors are directly associated with increased risks of hypoglycaemia. However, increased rates of hypoglycaemic events have been observed with these agents when combined with insulin or insulin secretagogues.[31] It is therefore encouraging that only the incidence of minor hypoglycaemic events showed a clear difference from placebo in this vulnerable population with a high proportion of insulin and sulphonylurea users when treated with dapagliflozin/saxagliptin. There were numerically more adverse events related to kidney function with combined dapagliflozin/saxagliptin mainly due to increases in serum creatinine. However, this was an expected finding given dapagliflozin's mode of action. Importantly, none of these events were classified as serious adverse events. Overall, this study confirmed the beneficial safety profile of dapagliflozin and saxagliptin in patients with type 2 diabetes and CKD.

The limitations of the study include the lack of inclusion of a patient population treated with saxagliptin alone to determine the albuminuria lowering efficacy of saxagliptin alone, and to more robustly assess whether the combination of dapagliflozin/saxagliptin confers additive effects compared with dapagliflozin or saxagliptin alone. In addition, the study was not powered to compare the albuminuria-lowering effects of dapagliflozin versus dapagliflozin/saxagliptin combination. As a result of the short follow-up study period, inferences regarding long-term outcomes are guarded. However, the long-term kidney benefits of dapagliflozin in patients with type 2 diabetes and established or at risk of atherosclerotic cardiovascular disease and preserved kidney function were demonstrated in the DECLARE trial.[14] Whether dapagliflozin delays the progression to end-stage kidney disease in patients with CKD is currently being investigated in the DAPA-CKD trial (NCT03036150). Finally, albuminuria was measured in a single spot urine sample at screening to determine trial eligibility. Some patients with albuminuria levels in the required range did not have elevated albuminuria at the randomisation visit when albuminuria was assessed in three consecutive first morning void samples. This may

have diluted the observed treatment effects. For future trials, multiple urine samples for albumin measurement are recommended to properly determine trial eligibility.

In conclusion, the SGLT2 inhibitor dapagliflozin lowers albuminuria when administered in combination with ACEi or ARB treatment. A combination of dapagliflozin and saxagliptin can be used to achieve the dual objectives of effective lowering of blood glucose and urinary albumin excretion in patients with type 2 diabetes and chronic kidney disease. This beneficial profile makes the combination of these agents a potentially attractive option to slow progression of kidney and cardiovascular disease.

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Author contributions:

CP, BS, CDS, AML, DR were involved in the design of the study and the collection of data. CP and HJLH wrote the first draft of the article. All authors were involved in data analysis and interpretation, and in drafting and critically revising the article. All authors had access to study results, and the lead author and corresponding author take responsibility for the integrity of the data and accuracy of the data reported. All authors reviewed and approved the final version of article for submission

Conflicts of interests:

CP sits on the steering committee for CREDENCE (sponsored by Janssen-Cilag) and is an advisor to Boehringer-Ingleheim, Merck Sharp and Dohme, AstraZeneca, Otsuka, Novartis, Vifor.
BS, DR, CDS and AML are employees of AstraZeneca and may hold stocks in AstraZeneca
PR receives research funding and is a consultant for Novo Nordisk, and AstraZeneca, and is a consultant for AbbVie, Astellas, Bayer, Boehringer Ingelheim, Mundi and Merck (all honoraria are paid to employer; Steno Diabetes Center Copenhagen), and has stocks in Novo Nordisk.

DCW has received honoraria from AstraZeneca, Amgen, Boehringer Ingelheim, Janssen, GlaxoSmithKline, Mitsubishi, Mundipharma, Napp and Vifor Fresenius.
HJLH received research funding and is a consultant for Abbvie, AstraZeneca, Boehringer Ingelheim and Janssen and is a consultant for Astellas, Fresenius, Gilead, Merck, and Mitshibushi Tanabe.

References:

1. Emerging Risk Factors Collaboration, Sarwar N, Gao P, Seshasai SR, Gobin R, Kaptoge S, et al. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. *Lancet*. 2010; **375**: 2215-22.
2. Coutinho M, Gerstein HC, Wang Y, Yusuf S. The relationship between glucose and incident cardiovascular events. A metaregression analysis of published data from 20 studies of 95,783 individuals followed for 12.4 years. *Diabetes Care*. 1999; **22**: 233-40.
3. Fox CS, Matsushita K, Woodward M, Bilo HJ, Chalmers J, Heerspink HJ, et al. Associations of kidney disease measures with mortality and end-stage renal disease in individuals with and without diabetes: a meta-analysis. *Lancet*. 2013; **380**: 1662-73.
4. Perkovic V, Heerspink HL, Chalmers J, Woodward M, Jun M, Li Q, et al. Intensive glucose control improves kidney outcomes in patients with type 2 diabetes. *Kidney Int*. 2013; **83**: 517-23.
5. Zoungas S, Arima H, Gerstein HC, Holman RR, Woodward M, Reaven P, et al. Effects of intensive glucose control on microvascular outcomes in patients with type 2 diabetes: a meta-analysis of individual participant data from randomised controlled trials. *Lancet Diabetes Endocrinol*. 2017; **5**: 431-7.
6. Heerspink HJ, Greene T, tighiouart H, Gansevoort R, Coresh J, Simon AW, et al. Change in albuminuria as a surrogate end point for kidney disease progression in clinical trials: a meta-analysis of treatment effects of 41 randomized trials. *Lancet Diabetes Endocrinol*. 2019.
7. Heerspink HJ, Perkins BA, Fitchett D, Husain M, Cherney D. Sodium Glucose Cotransporter 2 Inhibitors in the Treatment of Diabetes: Cardiovascular and Kidney Effects, Potential Mechanisms and Clinical Applications. *Circulation*. 2016; **134**: 752-72.
8. Muskiet MHA, Tonneijck L, Smits MM, van Baar MJB, Kramer MHH, Hoorn EJ, et al. GLP-1 and the kidney: from physiology to pharmacology and outcomes in diabetes. *Nat Rev Nephrol*. 2017; **13**: 605-28.
9. Petrykiv S, Sjostrom CD, Greasley PJ, Xu J, Persson F, Heerspink HJL. Differential effects of dapagliflozin on cardiovascular risk factors at varying degrees of renal function. *Clin J Am Soc Nephrol*. 2017; **12**: 751-9.
10. Dekkers CCJ, Wheeler DC, Sjostrom CD, Stefansson BV, Cain V, Heerspink HJL. Effects of the sodium-glucose co-transporter 2 inhibitor dapagliflozin in patients with type 2 diabetes and Stages 3b-4 chronic kidney disease. *Nephrol Dial Transplant*. 2018; **33**: 2005-11.
11. Perkovic V, de Zeeuw D, Mahaffey KW, Fulcher G, Erondu N, Shaw W, et al. Canagliflozin and renal outcomes in type 2 diabetes: results from the CANVAS Program randomised clinical trials. *Lancet Diabetes Endocrinol*. 2018; **6**: 691-704.
12. Fioretto P, Stefansson BV, Johnsson E, Cain VA, Sjostrom CD. Dapagliflozin reduces albuminuria over 2 years in patients with type 2 diabetes mellitus and renal impairment. *Diabetologia*. 2016; **59**: 2036-9.
13. Cherney DZI, Zinman B, Inzucchi SE, Koitka-Weber A, Mattheus M, von Eynatten M, et al. Effects of empagliflozin on the urinary albumin-to-creatinine ratio in patients with type 2 diabetes and established cardiovascular disease: an exploratory analysis from the EMPA-REG OUTCOME randomised, placebo-controlled trial. *Lancet Diabetes Endocrinol*. 2017; **5**: 610-21.
14. Wiviott SD, Raz I, Bonaca MP, Mosenzon O, Kato ET, Cahn A, et al. Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes. *N Engl J Med*. 2019; **380**: 347-57.

15. Heerspink HJ, Desai M, Jardine M, Balis D, Meininger G, Perkovic V. Canagliflozin slows progression of renal function decline independently of glycemic effects. *J Am Soc Nephrol*. 2017; **28**: 368-75.
16. Heerspink HJ, Johnsson E, Gause-Nilsson I, Cain VA, Sjostrom CD. Dapagliflozin reduces albuminuria in patients with diabetes and hypertension receiving renin-angiotensin blockers. *Diabetes Obes Metab*. 2016; **18**: 590-7.
17. Mosenzon O, Leibowitz G, Bhatt DL, Cahn A, Hirshberg B, Wei C, et al. Effect of saxagliptin on renal outcomes in the SAVOR-TIMI 53 Trial. *Diabetes Care*. 2017; **40**: 69-76.
18. Rosenstock J, Perkovic V, Johansen OE, Cooper ME, Kahn SE, Marx N, et al. Effect of linagliptin vs placebo on major cardiovascular events in adults With type 2 diabetes and high cardiovascular and renal risk: the CARMELINA randomized clinical trial. *JAMA*. 2018. ePub.
19. Groop PH, Cooper ME, Perkovic V, Hocher B, Kanasaki K, Haneda M, et al. Linagliptin and its effects on hyperglycaemia and albuminuria in patients with type 2 diabetes and renal dysfunction: the randomized MARLINA-T2D trial. *Diabetes Obes Metab*. 2017; **19**: 1610-9.
20. Levey AS, Coresh J, Greene T, Marsh J, Stevens LA, Kusek JW, et al. Expressing the Modification of Diet in Renal Disease Study equation for estimating glomerular filtration rate with standardized serum creatinine values. *Clin Chem*. 2007; **53**: 766-72.
21. Matsuo S, Imai E, Horio M, Yasuda Y, Tomita K, Nitta K, et al. Revised equations for estimated GFR from serum creatinine in Japan. *Am J Kidney Dis*. 2009; **53**: 982-92.
22. Chen LI, Guh JY, Wu KD, Chen YM, Kuo MC, Hwang SJ, et al. Modification of diet in renal disease (MDRD) study and CKD epidemiology collaboration (CKD-EPI) equations for Taiwanese adults. *PLoS One*. 2014; **9**: e99645.
23. Rosenstock J, Hansen L, Zee P, Li Y, Cook W, Hirshberg B, et al. Dual add-on therapy in type 2 diabetes poorly controlled with metformin monotherapy: a randomized double-blind trial of saxagliptin plus dapagliflozin addition versus single addition of saxagliptin or dapagliflozin to metformin. *Diabetes Care*. 2015; **38**: 376-83.
24. Mathieu C, Ranetti AE, Li D, Ekholm E, Cook W, Hirshberg B, et al. Randomized, double-blind, phase 3 trial of triple therapy with dapagliflozin add-on to saxagliptin plus metformin in type 2 diabetes. *Diabetes Care*. 2015; **38**: 2009-17.
25. Panchapakesan U, Pegg K, Gross S, Komala MG, Mudaliar H, Forbes J, et al. Effects of SGLT2 inhibition in human kidney proximal tubular cells--renoprotection in diabetic nephropathy? *PLoS One*. 2013; **8**: e54442.
26. Esterline RL, Vaag A, Oscarsson J, Vora J. MECHANISMS IN ENDOCRINOLOGY: SGLT2 inhibitors: clinical benefits by restoration of normal diurnal metabolism? *Eur J Endocrinol*. 2018; **178**: R113-R25.
27. Gilbert RE. SGLT2 inhibitors: beta blockers for the kidney? *Lancet Diabetes Endocrinol*. 2016; **4**: 814.
28. Kohan DE, Fioretto P, List JF, Tang W. Efficacy and safety of dapagliflozin in patients with type 2 diabetes and moderate renal impairment. American Society of Nephrology Philadelphia; 2011.
29. Fioretto P, Del Prato S, Buse JB, Goldenberg R, Giorgino F, Reyner D, et al. Efficacy and safety of dapagliflozin in patients with type 2 diabetes and moderate renal impairment (chronic kidney disease stage 3A): The DERIVE Study. *Diabetes Obes Metab*. 2018; **20**: 2532-40.

30. Neal B, Perkovic V, Mahaffey KW, de Zeeuw D, Fulcher G, Erondu N, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med*. 2017; **377**: 644-57.
31. Jabbour S, Seufert J, Scheen A, Bailey CJ, Karup C, Langkilde AM. Dapagliflozin in patients with type 2 diabetes mellitus: A pooled analysis of safety data from phase IIb/III clinical trials. *Diabetes Obes Metab*. 2018; **20**: 620-8.

Table 1. Demographics and baseline characteristics of the intent-to-treat population

	Placebo (n=148)	Dapagliflozin (n=145)	Dapagliflozin / Saxagliptin (n=155)
Age, years	64·7 (8·5)	64·7 (8·6)	64·0 (9·2)
Gender			
Male	105 (70·9)	102 (70·3)	110 (71·0)
Female	43 (29·1)	43 (29·7)	45 (29·0)
Race			
White	64 (43·2)	55 (37·9)	77 (49·7)
Black	11 (7·4)	7 (4·8)	8 (5·2)
Asian	53 (35·8)	67 (46·2)	57 (36·8)
Other	20 (13·5)	16 (11·0)	13 (8·4)
Body Mass Index, kg/m^2	30·34 (5·6)	30·19 (5·3)	30·81 (5·4)
HbA1c, %	8·57 (1·2)	8·44 (1·0)	8·20 (1·0)
eGFR, mL/min/1·73 m^2	47·7 (13·5)	50·2 (13·0)	49·0 (13·0)
eGFR ≤ 45 mL/min/1·73 m^2, n/%	65 (41·9)	53 (36·6)	70 (47·3)
eGFR > 45 mL/min/1·73 m^2, n/%	90 (58·1)	92 (63·4)	78 (52·7)
Known duration of diabetes, years	17·71 (9·5)	17·55 (7·7)	18·43 (8·1)
Blood pressure			
Systolic, mm Hg*	140·2 (18·6)	138·0 (16·5)	139·6 (18·1)
Diastolic, mm Hg*	75·7 (11·5)	76·9 (9·5)	77·3 (10·7)
Serum creatinine, mg/dL*	1·4 (0·4)	1·4 (0·3)	1·4 (0·4)
Haemoglobin, g/L*	129·2 (17·7)	133·8 (16·4)	132·8 (17·6)
Total cholesterol, mmol/L*	4·5 (1·1)	4·6 (1·2)	4·5 (1·1)
LDL cholesterol, mmol/L*	2·3 (0·9)	2·3 (0·9)	2·3 (1·0)
HDL cholesterol, mmol/L*	1·2 (0·4)	1·2 (0·3)	1·2 (0·4)
Serum potassium, mmol/L*	4·5 (0·5)	4·4 (0·5)	4·5 (0·5)
U_{ACR}, median (quartile 1 to quartile 3), mg/g creatinine	257·5 (80–949)	270·0 (69–751)	218·4 (74–936)
Normoalbuminuria,[†] n/%	11 (7·4)	10 (6·9)	12 (7·7)
Microalbuminuria,[‡] n/%	65 (43·9)	64 (44·1)	73 (47·1)
Macroalbuminuria,[§] n/%	72 (48·7)	71 (49·0)	70 (45·1)
Diabetic retinopathy, n/%	62 (41·9)	56 (38·6)	64 (41·3)
Cardiovascular disease history			
Cardiac disorders	41 (27·7)	58 (40·0)	53 (34·2)
Vascular disorders	23 (15·5)	20 (13·8)	26 (16·8)
Concomitant medications			
Glucose-lowering therapies			
Insulin	107 (72·3)	104 (71·7)	107 (70·4)
Metformin	79 (53·4)	86 (59·3)	92 (60·5)
Sulphonylurea	58 (39·2)	39 (26·9)	49 (32·2)
RAS inhibitors	147 (99·3)	143 (98·6)	152 (100·0)
Diuretics			
Loop diuretics	46 (31·1)	26 (17·9)	36 (23·7)
Thiazides	31 (20·9)	39 (26·9)	40 (26·3)
Statins	111 (75·0)	105 (72·4)	106 (69·7)

Data are reported as mean (SD) unless otherwise noted. *Treated subjects from the intent-to-treat population. [†]Normoalbuminuria defined as U_{ACR} <30 mg/g. [‡]Microalbuminuria defined as U_{ACR} ≥30–≤300 mg/g, [§]Macroalbuminuria defined as U_{ACR} >300–≥3500 mg/g.
HbA1c, haemoglobin A1c; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; RAS, renin-angiotensin system

Table 2. Changes in exploratory biochemical parameters induced by placebo, dapagliflozin, or dapagliflozin/saxagliptin at different time points

	Placebo	Dapagliflozin	Dapagliflozin / Saxagliptin
24-h urinary glucose excretion			
n	92	113	105
Baseline mean, g/24h (SD)	11·4 (21·7)	11·2 (21·4)	10·3 (31.0)
Week 24 mean, g/24h (SD)	1.0 (18·6)	55·1 (32·7)	47·1 (29·7)
Adjusted mean percent change from baseline, % (95% CI)	−0·9 (−10·7, 8·8)	44.0 (34·5, 53·5)	36·5 (27·4, 45·5)
Difference in mean percent change vs placebo, % (95% CI)	-	44·9 (37·5, 52·3)	37·4 (29·8, 44·9)
p-value	-	<0·001	<0·001
24-h urinary albumin excretion			
n	99	108	107
Baseline median, g/day (min, max)	0·34 (0·02, 8·6)	0·41 (0·01, 5·5]	0·30 (0·01, 9·2)
Week 24 median, g/day (min, max)	0·39 (0·01, 7·2)	0·30 (0.01, 8·2)	0·17 (0.01, 5·5)
Adjusted mean percent change from baseline, % (95% CI)	−0·9 (−22·9, 27.6)	−20·6 (−38·9, 3.2)	−40·2 (−53·3, −23·4)
Difference in mean percent change vs placebo, % (95% CI)	-	−19·9 (−35·6, −0·3)	−39·7 (−51·5, −24·9)
p-value	-	0·047	<0·001
LDL cholesterol			
n	123	118	132
Baseline mean, mmol/L (SD)	2·3 (0·9)	2·3 (0·9)	2·3 (1.0)
Week 24 mean, mmol/L (SD)	2·3 (1·2)	2·4 (1·0)	2·2 (1·0)
Mean percent change from baseline, % (95% CI)	−0·4 (−9·3, 9·5)	4·8 (−4·7, 15·1)	−0·4 (−9·0, 9·1)
Difference in mean percent change vs placebo, % (95% CI)	-	5·1 (−3·7, 14·4)	0·0 (−7·9, 8·5)
p-value	-	0·243	0·992
HDL cholesterol			
n	135	131	141
Baseline mean, mmol/L (SD)	1·3 (0·4)	1·2 (0·3)	1·2 (0·4)
Week 24 mean, mmol/L (SD)	1·2 (0·4)	1·2 (0·3)	1·2 (0·4)
Adjusted mean percent change from baseline, % (95% CI)	−0·4 (−4·7, 4·0)	4.0 (−0·5, 8·6)	0·3 (−3·9, 4·7)
Difference in adjusted mean percent change vs placebo, % (95% CI)	-	4·41 (0·5, 8·5)	0·77 (−3.0, 4·7)
p-value	-	0·029	0·689
Uric acid			
n	147	144	152
Baseline mean, umol/L (SD)	414·9 (92·6)	399·4 (98·9)	424·9 (102·8)
Week 24 mean, umol/L (SD)	433·6 (109·9)	417·1 (108·0)	411·5 (92·3)
Adjusted mean change from baseline, % (95% CI)	4·7 (−15·6, 25·1)	−0·6 (−21·0, 19·9)	−24·3 (−44·2, −4·3)
Difference in adjusted mean change vs placebo, % (95% CI)	-	−5·3 (−22·8, 12·2)	−29·0 (−46·3, −11·7)
p-value	-	0·553	0·001
Haematocrit ratio			
n	148	145	152
Baseline mean, % (SD)	0·39 (0·05)	0·41 (0·05)	0·40 (0·05)

Week 24 mean, % (SD)	0·39 (0·05)	0·43 (0·05)	0·43 (0·06)
Mean change from baseline, % (95% CI)	−0·00 (0·03)	0·02 (0·03)	0·02 (0·03)
Difference in mean change vs placebo, % (95% CI)	-	0·03 (0·02, 0·04)	0.03 (0·02, 0·04)
p-value		<0·001	<0·001

CI, confidence interval; HDL, high-density lipoprotein; LDL, low-density lipoprotein, SD, standard deviation

Table 3: Changes in U_{ACR} from baseline with dapagliflozin or dapagliflozin/saxagliptin in HbA1c, body weight and systolic blood pressure responders and non-responders*

	Change in U_{ACR} (%)	
	Dapagliflozin	Dapagliflozin/Saxagliptin
HbA1c		
≥0.3% reduction	−22·1 (−36·5 to −4·3)	−37·2 (−47·6 to −24·8)
<0.3% reduction	−23·6 (−38·7 to −4·7)	−44·7 (−57·4 to −28·1)
Body Weight		
≥3% reduction	−26·7 (−43·3 to −5·2)	−42·7 (−55·7 to −25·9)
<3% reduction	−20·3 (−34·1 to −3·7)	−37·5 (−48·0 to −24·9)
Systolic Blood Pressure		
≥3% reduction	−28·8 (−42·1 to −12·6)	−43·0 (−52·5 to −31·5)
<3% reduction	−13·3 (−30·2 to 7·6)	−29·8 (−44·8 to −10·7)

*Response was defined as ≥0·3% reduction in HbA1c, ≥3% reduction in body weight and ≥3 mmHg reduction in seated systolic blood pressure.

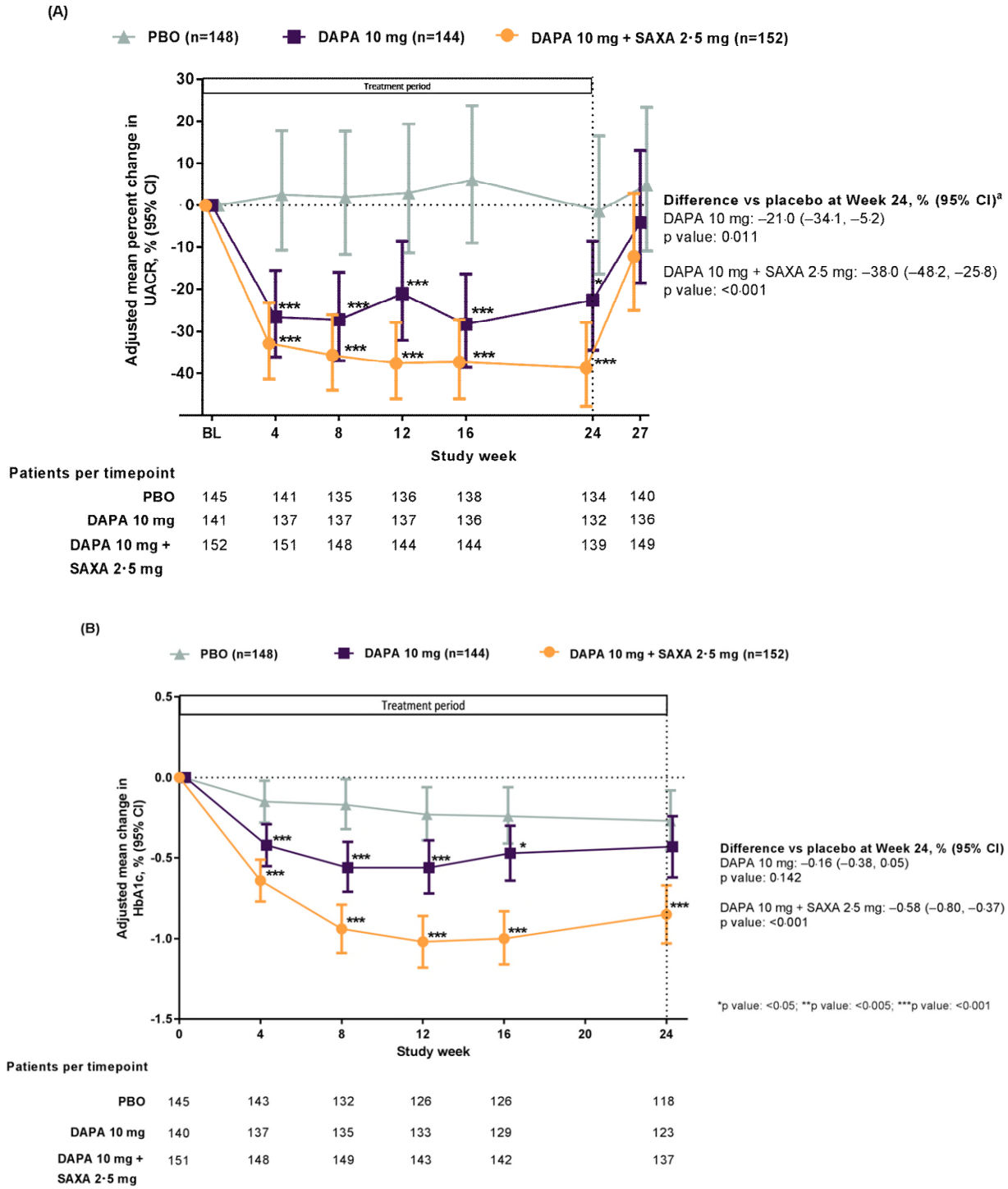
Table 4. Summary of adverse events

		Placebo (n=148)	Dapagliflozin (n=145)	Dapagliflozin/Saxagliptin (n=152)
Any AE		81 (54·7)	79 (54·5)	104 (68·4)
AE leading to discontinuation of study drug		8 (5·4)	4 (2·8)	7 (4·6)
Any serious AE		16 (10·8)	12 (8·3)	12 (7·9)
Serious AE leading to discontinuation of study drug		6 (4·1)	1 (0·7)	1 (0·7)
Hypoglycaemia				
Any AE of hypoglycaemia		1 (0·7)	0 (0·0)	2 (1·3)
Hypoglycaemia leading to study discontinuation		1 (0·7)	0 (0·0)	0 (0·0)
Types of hypoglycaemia	Major	0 (0·0)	0 (0·0)	1 (0·7)
	Minor	29 (19·6)	35 (24·1)	50 (32·9)
	Other	16 (10·8)	19 (13·1)	19 (12·5)
AE of special interest				
Kidney AEs		6 (4·1)	4 (2·8)	10 (6·6)
Sustained >1·5× increase in serum creatinine		1 (0·7)	0 (0·0)	3 (2·0)
Urinary tract infection		4 (2·7)	5 (3·4)	7 (4·6)
Genital infection		0 (0·0)	4 (2·8)	4 (2·6)
Volume depletion		4 (2·7)	4 (2·8)	8 (5·3)
Amputations		0 (0·0)	1 (0·7)	1 (0·7)
Fractures		2 (1·4)	1 (0·7)	0 (0·0)
DKA		0 (0·0)	1 (0·7)	0 (0·0)
Death		0 (0·0)	1 (0·7)	1 (0·7)

Data indicated as number of patients (%).

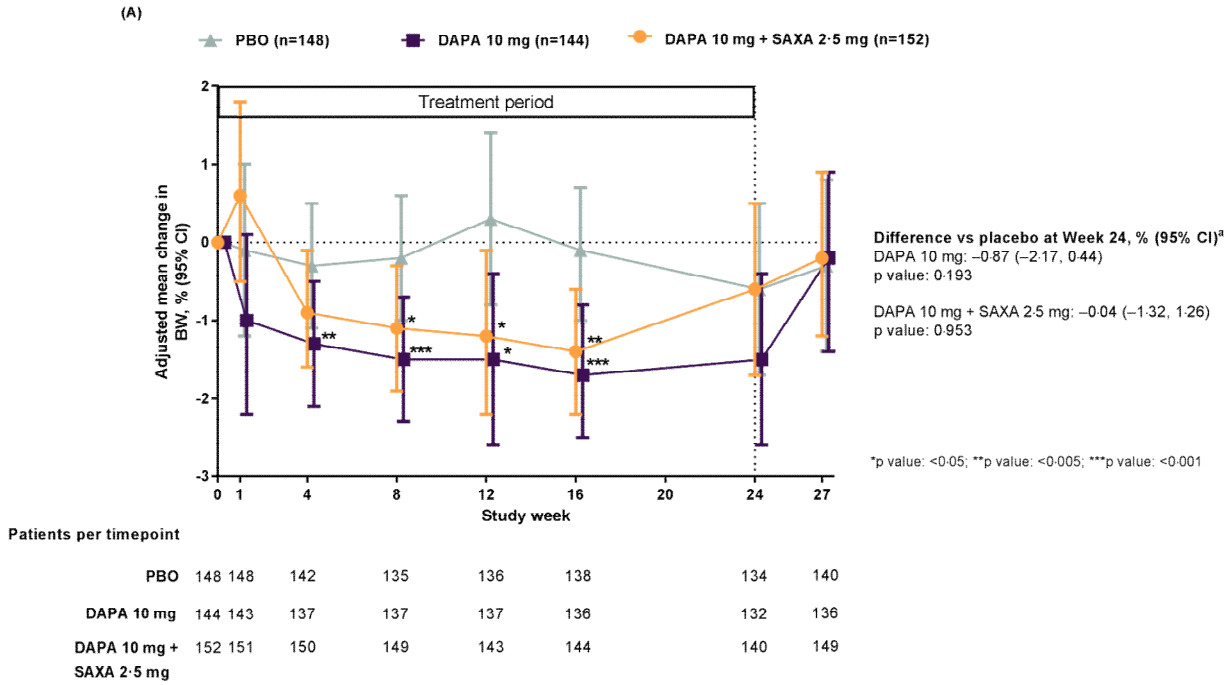
AE, adverse event; DKA, diabetic ketoacidosis

Figure 1: Effect of dapagliflozin and dapagliflozin/saxagliptin on the primary study outcomes over time (A) Change from baseline in U_{ACR} in the placebo, dapagliflozin and dapagliflozin/saxagliptin treatment arms (B) Change from baseline in HbA1c in the three treatment arms over time



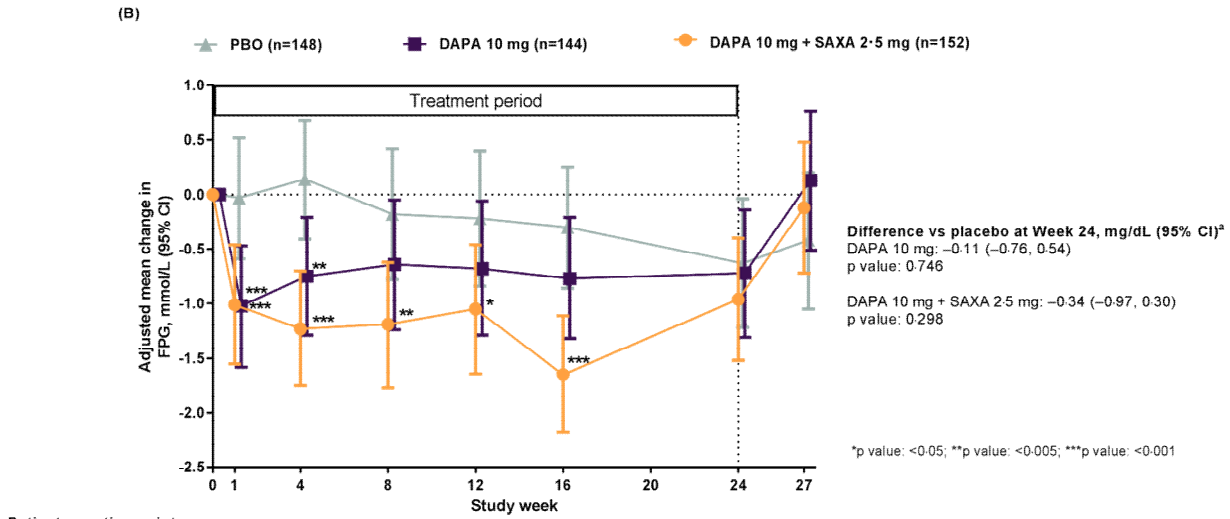
[a]Values (differences and p value) reported here and in the manuscript are based on the Week 24 dataset, in line with the primary endpoint. Patients ceased active drug at 24 weeks. Data plotted in the above graph comprise values from Week 27 dataset (24-week treatment period plus 3 week follow-up period allowing for drug washout).
BL, baseline; CI, confidence interval; DAPA, dapagliflozin; HbA1c, haemoglobin A1c; PBO, placebo; SAXA, saxagliptin; U_{ACR}, urinary albumin-to-creatinine ratio

Figure 2: Effect of dapagliflozin and dapagliflozin/saxagliptin on secondary and safety outcomes over time (A) Change in body weight (B) Change in FPG (C) Change in SBP (D) Change in eGFR



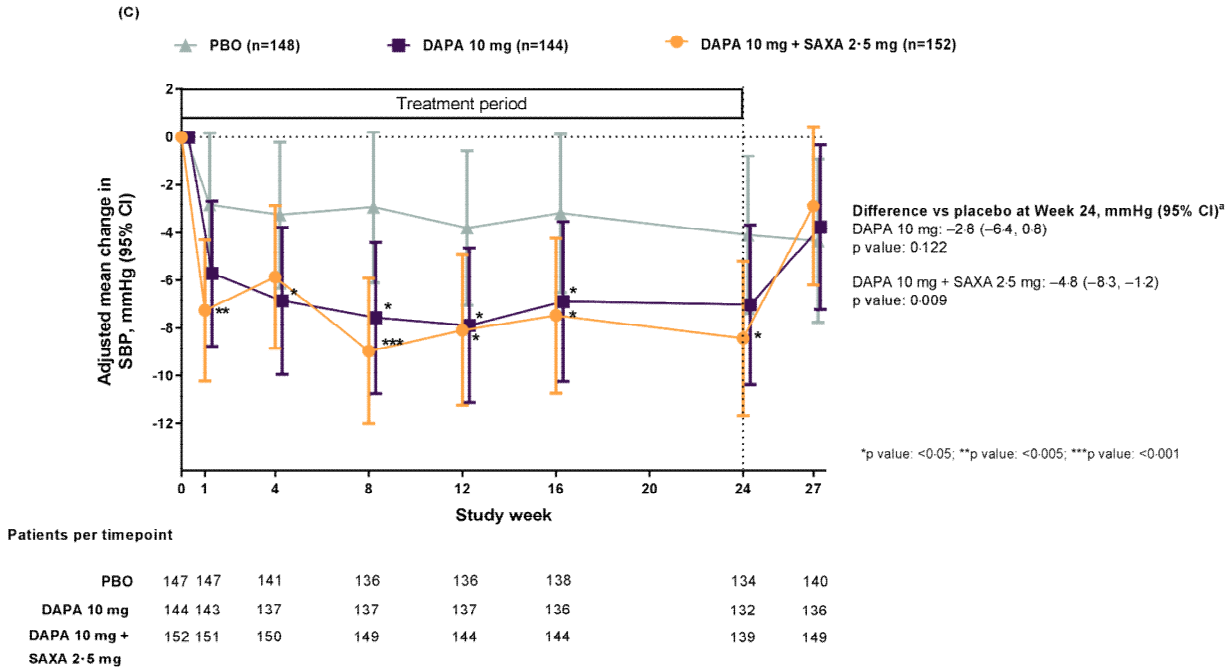
Patients per timepoint

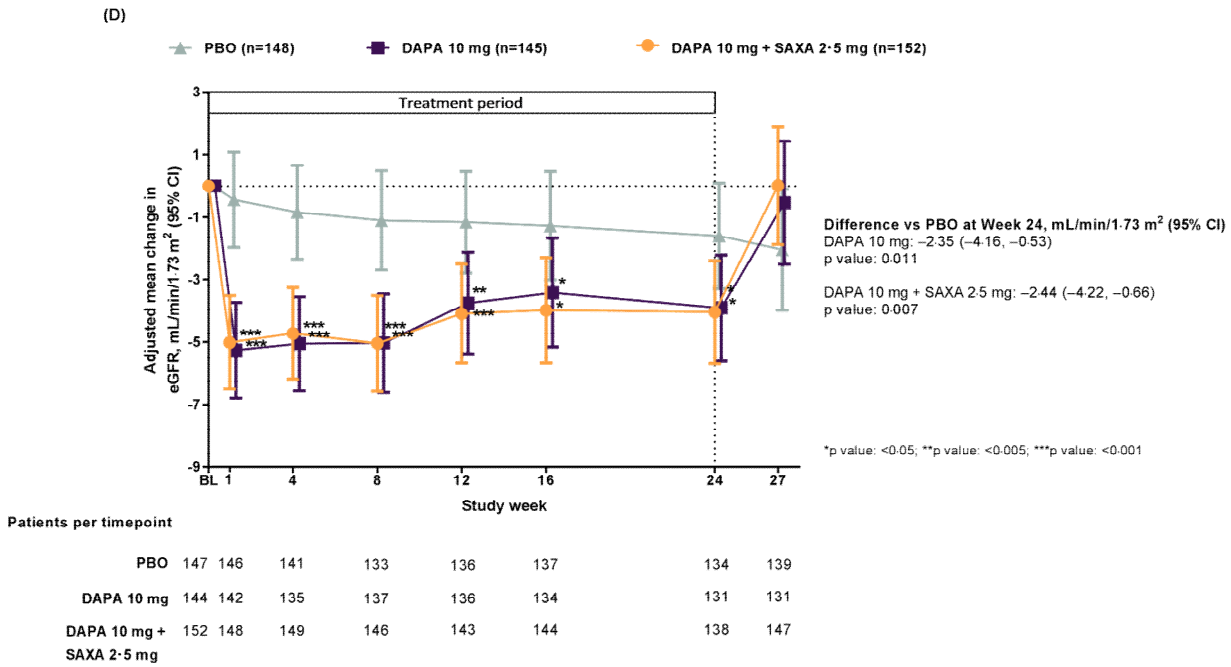
PBO	148	148	142	135	136	138	134	140
DAPA 10 mg	144	143	137	137	137	136	132	136
DAPA 10 mg + SAXA 2·5 mg	152	151	150	149	143	144	140	149



Patients per timepoint

PBO	147	145	136	132	128	126	116	139
DAPA 10 mg	144	143	135	134	133	130	123	132
DAPA 10 mg + SAXA 2·5 mg	152	149	147	147	142	142	136	146



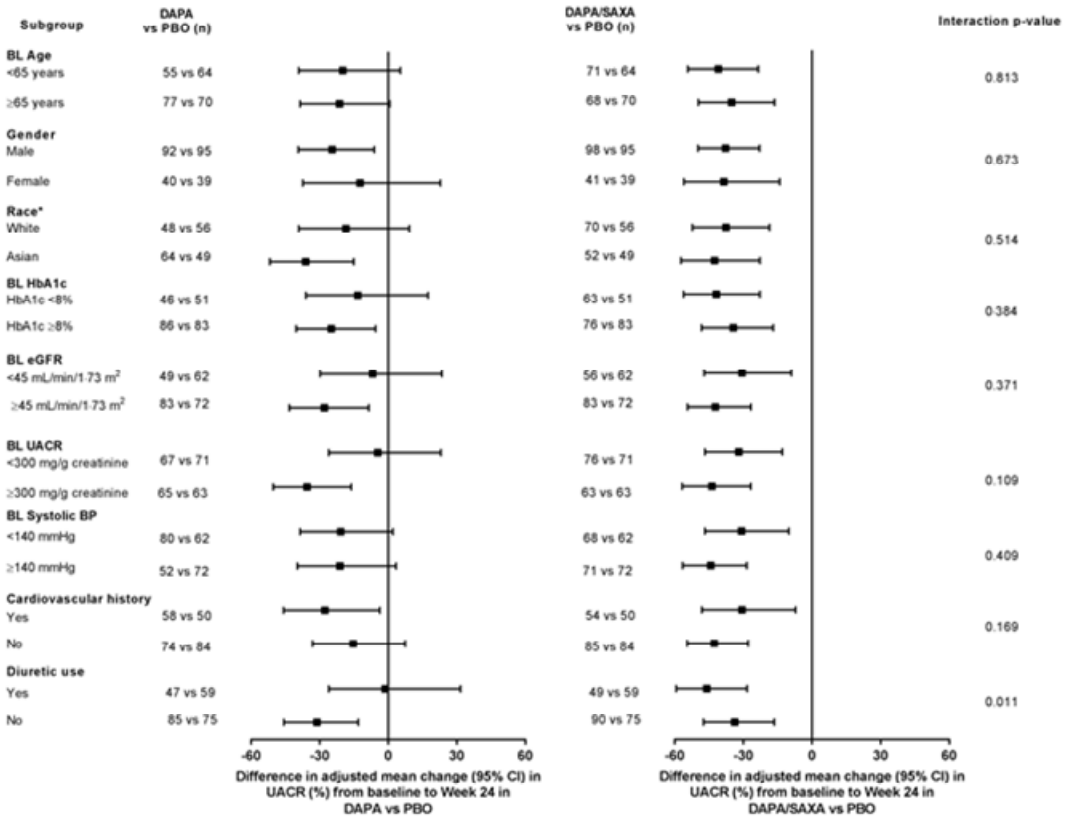


[a]Values (differences and p value) reported here and in the manuscript are based on the Week 24 dataset, in line with the primary endpoint. Patients ceased active drug at 24 weeks. Data plotted in the above graph comprise values from Week 27 dataset (24-week treatment period plus 3 week follow-up period allowing for drug washout).

BL, baseline; BW, body weight; CI, confidence interval; DAPA, dapagliflozin; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; HbA1c, haemoglobin A1c; PBO, placebo; SAXA, saxagliptin; SBP, systolic blood pressure; U_{ACR}, urinary albumin-to-creatinine ratio

Figure 3:

Effects of dapagliflozin and dapagliflozin/saxagliptin on U_{ACR} in participant subgroups



*Race subgroup analysis based on only prominent races within this study population has been indicated here.

eGFR and HbA1c subgroups were pre-specified (Hba1c >/< 8%; eGFR >/< 45 mL/min/1·73 m^2)

BL, baseline; BP, blood pressure; CI, confidence interval; Dapa, dapagliflozin; eGFR, estimated glomerular filtration rate; HbA1c, haemoglobin A1c; PBO, placebo; U_{ACR}, urinary albumin-to-creatinine ratio