A randomized phase 2b trial examined the effects of the glucagon-like peptide-1 and glucagon receptor agonist cotadutide on kidney outcomes in patients with diabetic kidney disease

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Cotadutide is a glucagon-like peptide-1 (GLP-1) and glucagon receptor agonist that may improve kidney function in patients with type 2 diabetes (T2D) and chronic kidney disease (CKD). In this phase 2b study, patients with T2D and CKD (estimated glomerular filtration rate [eGFR] of 20 or more and under 90 mL/min per 1.73 m^2 and urinary albumin-to-creatinine ratio [UACR] over 50 mg/g) were randomized 1:1:1:1:1 to 26 weeks' treatment with standard of care plus subcutaneous cotadutide uptitrated to 100, 300, or 600 μg, or placebo daily (double-blind), or the GLP-1 agonist semaglutide 1 mg once weekly (open-label).The co-primary endpoints were absolute and percentage change versus placebo in UACR from baseline to the end of week 14. Among 248 randomized patients, mean age 67.1 years, 19% were female, mean eGFR was 55.3 mL/min per 1.73 m^2, geometric mean was UACR 205.5 mg/g (coefficient of variation 270.0), and 46.8% were receiving concomitant sodium–glucose co-transporter 2 inhibitors. Cotadutide dose-dependently reduced UACR from baseline to the end of week 14, reaching significance at 300 μg (–43.9% [95% confidence interval −54.7 to −30.6]) and 600 μg (−49.9% [−59.3 to −38.4]) versus placebo; with effects sustained at week 26. Serious adverse events were balanced across arms. Safety and tolerability of cotadutide 600 μg were comparable to semaglutide. Thus, our study shows that in patients with T2D and CKD, cotadutide significantly reduced UACR on top of standard of care with an acceptable tolerability profile, suggesting kidney protective benefits that need confirmation in a larger study.

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Lay Summary

Type 2 diabetes mellitus (T2D) is the main cause of chronic kidney disease (CKD). We conducted a phase 2 study in 248 patients with T2D and CKD who had albumin in their urine, an indicator of kidney damage. We wanted to learn whether cotadutide, a drug that stimulates the hormones (glucagon-like peptide-1 [GLP-1] and glucagon), reduces the amount of urine albumin. Patients were treated with cotadutide at doses 100, 300, or 600 μg, or placebo daily (where the treatment given was undisclosed), or a drug that simulates GLP-1 only (semaglutide) 1 mg once weekly. Treatment was known for the semaglutide group. Cotadutide was seen to reduce albumin in proportion to the dose given, by up to around 50%. Cotadutide was seen to be as safe and tolerable as semaglutide. Our study supports the possibility that cotadutide provides benefits in patients with T2D and CKD. This needs to be confirmed in a larger study.

Type 2 diabetes mellitus (T2D) is the leading cause of chronic kidney disease (CKD) and kidney failure.[1] The increasing incidence of CKD in patients with T2D parallels the ongoing pandemic of T2D and obesity.[2,3] Treatment of T2D and CKD is aimed at optimizing glycemic control, slowing the progressive loss of kidney function, and reducing the high risk of cardiovascular outcomes. Lifestyle interventions targeting weight, lipid, and blood pressure control, with the provision of lipid-lowering agents and angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers, are standard management strategies.[4] Sodium-glucose cotransporter 2 (SGLT2) inhibitors and the nonsteroidal mineralocorticoid receptor antagonist finerenone have shown clinical benefits on top of angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers.[4] Although these treatment strategies have markedly improved outcomes, there remains a sizeable residual risk of kidney and cardiovascular events. This residual risk is closely associated with albuminuria, a strong risk factor for adverse kidney and cardiovascular outcomes.[5,6]

Glucagon-like peptide-1 receptor agonists (GLP-1RAs) have emerged as another drug class with potential kidney protective effects. GLP-1RAs are approved for T2D and weight management, and some have a proven cardiovascular benefit. *Post hoc* analyses of cardiovascular outcome trials have suggested that GLP-1RAs delay the onset of new macroalbuminuria, reduce glomerular filtration rate (GFR) decline, and may reduce the risk of kidney outcomes.[7–11] A dedicated DKD outcome study with GLP-1RA semaglutide has recently shown a 24% reduction in the composite kidney endpoint with significant reductions in CV death, all-cause mortality, time to 50% decline in estimated eGFR (eGFR), and change in total eGFR slope.[12]

Cotadutide is a dual GLP-1 and glucagon receptor agonist with a predicted ratio of GLP-1 to glucagon receptor agonist activity of 5:1. Combining GLP-1 and glucagon receptor agonism is expected to achieve greater clinical effects than GLP-1 receptor agonism alone because of the complementary effects of glucagon in appetite suppression, hepatic lipid oxidation, and augmenting energy expenditure. Furthermore, glucagon receptors are highly expressed in the kidney, especially in the thick ascending loop of Henle and distal tubules.[13] In a *post hoc* analysis of a phase 2 study in 18 patients with T2D and elevated albuminuria, cotadutide reduced albuminuria by 51% (90% CI: 27.7%, 88.4%; $P = 0.0504$) compared with placebo after 32 days of therapy.[14] Because of the small sample size and uncertainty of the phase 2 trial data, a phase 2b dose-finding study was designed to assess the dose-response relationships between cotadutide and urinary albumin-to-creatinine ratio (UACR) to inform the design of a clinical outcome trial. Here, we report the results of the phase 2b trial.

METHODS

Study design and participants

This was a randomized, double-blind, placebo-controlled with open-label comparator, phase 2b study to evaluate the efficacy, safety, tolerability, and pharmacokinetic profile of daily cotadutide 100–600 μg in patients with T2D and CKD. The primary objective was to assess the effect of cotadutide versus placebo on the UACR after 14 weeks of treatment. Secondary objectives were to assess changes in UACR at week 26, glycemic control, body weight, and safety and tolerability.

This study is registered on ClinicalTrials.gov (NCT04515849); it was conducted in accordance with the Declaration of Helsinki and the Council for International Organizations of Medical Sciences International Ethical Guidelines and was reviewed by independent ethics committees. All participants provided written informed consent.

Eligible patients were aged 18–79 years, had a body mass index of ≥25 kg/m^2 (>23 kg/m^2 for patients enrolled in Japan), had confirmed T2D (glycated hemoglobin [HbA1c] of 6.5%–12.5%, with glucose control managed with any insulin and/or oral combination therapy with no major recent dose changes) and CKD (eGFR ≥20 and <90 ml/min per 1.73 m^2), and had a UACR of >50 mg/ml or >5.7 mg/mmol. Patients were receiving standard of care treatments for kidney disease and/or T2D, including an angiotensin-converting enzyme inhibitor or an angiotensin II receptor blocker at the maximally tolerated dose (stable for ≥3 months before screening; although patients unable to tolerate angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers could be enrolled at the investigator's discretion). Exclusion criteria included requirement for kidney replacement therapy or kidney transplant; treatment with a GLP-1RA in the 30 days or 5 half-lives of the drug before the run-in period; recent acute or subacute kidney function deterioration; poorly controlled hypertension (systolic blood pressure >180 mm Hg and diastolic blood pressure ≥90 mm Hg); unstable angina pectoris, myocardial infarction,

transient ischemic attack, or stroke in the 3 months before screening; and basal calcitonin >50 ng/l.

Randomization

Patients were randomized 1:1:1:1:1 to receive daily cotadutide 100 μg, 300 μg, or 600 μg (double-blind), matched placebo (double-blind) or weekly semaglutide 1 mg (open-label) via subcutaneous injection. Randomization was stratified by region (Japan vs. other regions) and use of SGLT2 inhibitor therapy at screening.

Procedures

Patients in the cotadutide arms received cotadutide once daily for 26 weeks, following a titration regimen to reach the target dose. Doses started at 50 μg and were uptitrated every 2 or 4 weeks to a final dose of 100, 300, or 600 μg. Patients in the semaglutide arm received semaglutide once weekly, starting at 0.25 mg and uptitrated every 4 weeks to a final dose of 1.0 mg.

UACR was measured at a central laboratory using first morning void urine (average of 3 samples). Albumin and creatinine levels were measured in urine samples. Blood samples were collected for the measurement of fasting glucose, fasting lipid profile, HbA1c, N-terminal-pro–B-type natriuretic peptide, cystatin C, and uric acid. eGFR was calculated using the CKD Epidemiology Collaboration equation. Continuous glucose monitoring was performed with a FreeStyle Libre Pro or FreeStyle Libre Flash CGM device (Abbott). Patient-reported outcomes were recorded with the Kidney Disease Quality of Life-36 survey, EuroQol-5 Dimension scale, and Diabetes Treatment Satisfaction Questionnaire.

Urinary immunoglobulin analyses were conducted by liquid chromatography–tandem mass spectrometry (see page 2 in the Supplementary Material).

Outcomes

The primary efficacy outcome was absolute and percentage changes in UACR versus placebo from baseline to the end of week 14. Change from baseline versus placebo in UACR at week 26 was a secondary efficacy outcome. Other secondary efficacy outcomes were change from baseline to the end of week 14 and week 26 in HbA1c; fasting glucose; time spent in hyperglycemia (>10 mmol/l), target range (3.9–10 mmol/l), hypoglycemia (<3.9 mmol/l), and clinically significant hypoglycemia (<3.0 mmol/l) over 10 days as measured by continuous glucose monitoring; and body weight. The proportion of patients achieving at least 5% and at least 10% body weight loss versus placebo from baseline to the end of week 14 and week 26 was also a secondary outcome. Levels of antidrug antibodies during cotadutide titration and during follow-up were measured to assess immunogenicity. Safety outcomes were the incidences of adverse events and serious adverse events, vital signs, and electrocardiogram and clinical laboratory assessments. A full list of exploratory outcomes can be found in page 1 of the Supplementary Material.

Statistical analysis

A sample size of 225 (n = 45 per arm) was determined to provide 90% power to detect a 40% relative reduction in UACR for any one dose of cotadutide versus placebo with a 2-sided type 1 error rate of 0.05, assuming an SD of 0.74 and a discontinuation rate of 20%.

The primary analysis was carried out after the completion of 14 weeks of dosing for all patients, and the final analysis was carried out after completion of 26 weeks of dosing and safety follow-up for all patients.

The primary efficacy analysis was performed in the intent-to-treat population with a last postbaseline observation carried forward approach. An analysis of covariance model with a 2-sided significance level of 0.05, including treatment as a fixed effect and the baseline value and stratification factors as covariates, was used to estimate changes from baseline for all continuous outcomes. Lognormal distributed variables (e.g., UACR) were first log-transformed and analyzed on the log scale; results were then transformed back to the original scale to estimate geometric least-squares mean percentage changes from baseline. Absolute changes from baseline in UACR are expressed as median and interquartile range. For categorical outcomes, a logistic regression model was used, including treatment as a fixed effect and the baseline measurement as a covariate. A mixed effects model was used for the analysis of the eGFR slope. The model included an intercept, treatment, time, stratification factors (whether the patient was from a Japan site vs. other regions and whether they were using SGLT2 inhibitors or not), time-by-treatment interaction as fixed effects, and random intercepts and slopes to account for variation of patients over time. The safety analysis was performed in the as-treated population.

Descriptive statistics were used to summarize baseline characteristics and patient-reported outcomes.

RESULTS

Patient disposition and baseline characteristics

Of 416 patients screened between August 2020 and April 2022, 247 were randomized to receive cotadutide (100 μg: n = 52, 300 μg: n = 48, or 600 μg: n = 51), placebo (n = 51), or semaglutide (n = 45; Supplementary Figure S1). One patient in the cotadutide 300 μg arm did not receive treatment. Overall, 235 patients (94.8%) completed the study. Thirty-eight patients did not complete treatment. Reasons for treatment discontinuation included adverse events (29 patients: 2 in the cotadutide 100 μg arm, 3 in the cotadutide 300 μg arm, 12 in the cotadutide 600 μg arm, 5 in the placebo arm, and 7 in the semaglutide arm), noncompliance with the study drug (1 patient in the semaglutide arm), death (2 patients in the cotadutide 100 μg arm), and other reasons (6 patients; Supplementary Figure S1).

Baseline demographics and patient characteristics were generally well balanced among treatment arms (Table 1). Among 248 enrolled patients, the median age was 68.0 years (SD: 7.8 years), 47 (19.0%) were female, and 190 (76.6%) were White. The geometric mean UACR was 205.5 mg/g

Table 1 | Baseline demographics and patient characteristics

Characteristic	Cotadutide			Semaglutide		
	100 μg (n = 52)	300 μg (n = 49)	600 μg (n = 51)	Placebo (n = 51)	1 mg (n = 45)	Total (N = 248)
Age, mean (SD), yr	67.2 (7.3)	65.7 (8.8)	66.1 (7.4)	69.5 (7.3)	67.0 (7.8)	67.1 (7.8)
Male, sex, n (%)	43 (82.7)	46 (93.9)	41 (80.4)	38 (74.5)	33 (73.3)	201 (81.0)
Race, n (%)						
Asian	10 (19.2)	10 (20.4)	13 (25.5)	10 (19.6)	2 (4.4)	45 (18.1)
Black or African American	2 (3.8)	0	0	1 (2.0)	2 (4.4)	5 (2.0)
Native Hawaiian or other Pacific Islander	2 (3.8)	0	1 (2.0)	1 (2.0)	0	4 (1.6)
White	38 (73.1)	36 (73.5)	36 (70.6)	39 (76.5)	41 (91.1)	190 (76.6)
Other	0	3 (6.1)	1 (2.0)	0	0	4 (1.6)
Body weight, mean (SD), kg	93.79 (17.94)	94.01 (18.79)	93.69 (22.66)	93.15 (19.28)	97.52 (19.45)	94.36 (19.59)
BMI, mean (SD), kg/m^2	32.15 (5.22)	32.26 (5.76)	32.14 (5.65)	32.33 (6.05)	34.41 (6.54)	32.62 (5.86)
UACR, geometric mean (CV), mg/g	263.1 (272.5)	293.1 (310.5)	148.4 (324.6)	195.7 (210.9)	160.2 (241.8)	205.5 (270.0)
HbA1c, mean (SD), %	8.00 (1.07)	7.91 (1.10)	8.10 (1.12)	7.84 (0.81)	8.04 (1.18)	7.98 (1.06)
eGFR, mean (SD), ml/min per 1.73 m^2	53.1 (20.8)	57.0 (19.7)	57.9 (16.7)	55.1 (19.2)	53.2 (17.7)	55.3 (18.9)
Concomitant medications						
SGLT2 inhibitor, n (%)	24 (46.2)	24 (49.0)	23 (45.1)	25 (49.0)	20 (44.4)	116 (46.8)
Insulin, mean (SD), units	71.15 (133.30)	80.78 (57.61)	81.19 (58.91)	72.42 (59.07)	71.61 (44.62)	75.4 (70.7)
RAASi, n (%)[a]	49 (94.2)	49 (100)	48 (94)	51 (100)	44 (97.8)	241 (97.1)
T2DM duration, mean (SD), yr	17.4 (7.6)	18.8 (8.5)	19.5 (9.9)	17.5 (9.6)	16.7 (7.5)	18.0 (8.7)
DKD, n (%)	47 (90.4)	43 (87.8)	47 (92.2)	46 (90.2)	44 (97.8)	232 (93.5)
Retinopathy, n (%)	18 (39.1)	24 (53.3)	26 (55.3)	16 (35.6)	13 (28.9)	97 (39.1)
Neuropathy, n (%)	14 (30.4)	25 (55.6)	17 (36.2)	20 (44.4)	14 (31.1)	90 (36.2)

BMI, body mass index; CV, coefficient of variation; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; RAASi, Renin-angiotensin-aldosterone system inhibitors; SGLT2, sodium-glucose cotransporter 2; T2DM, type 2 diabetes mellitus; UACR, urinary albumin-to-creatinine ratio.
[a]Mean daily doses for most frequently prescribed RAASi at screening were candesartan 19 mg (n = 30), irbesartan 214 mg (n = 26), losartan 70.5 mg (n = 22), ramipril 7.5 mg (n = 36), telmisartan 62 mg (n = 21), and valsartan 132 mg (n = 23).

(coefficient of variation 270.0) and was lower in the cotadutide 600 μg and semaglutide arms than in the other arms (Table 1). The mean eGFR was 55.3 (SD: 18.9) ml/min per 1.73 m^2, mean body mass index was 32.6 (SD: 5.9) kg/m^2, and 116 of 248 patients (46.8%) were receiving an SGLT2 inhibitor at baseline (Table 1).

Effects on UACR

Treatment with cotadutide led to dose-dependent percentage reductions in UACR from baseline to the end of week 14, which were statistically significant for cotadutide 300 μg (−43.9% [95% CI: −54.7 to −30.6]; $P = 0.001$) and cotadutide 600 μg (−49.9% [−59.3 to −38.4]; $P < 0.001$) versus placebo (−12.9% [−29.3 to 7.2]; Figure 1a). Treatment ratios versus placebo were 0.64 (95% CI: 0.50–0.84) for cotadutide 300 μg and 0.58 (0.45–0.74) for cotadutide 600 μg, and these effects were sustained at week 26 (Figure 1b). Absolute changes from baseline in UACR to the end of week 14 and week 26 are detailed in Supplementary Table S1. Semaglutide reduced UACR from baseline by 35.6% (95% CI: –50.5 to –16.2). The reduction in UACR was larger with cotadutide 300 and 600 μg with the corresponding ratios for percentage change from baseline in UACR of 0.93 ($P = 0.658$) and 0.84 ($P = 0.24$). Among the subgroup of patients who were receiving SGLT2 inhibitors at baseline, there were dose-dependent reductions in UACR with cotadutide, which reached statistical significance in the 300 μg and 600 μg arms at week 26 versus placebo (Figure 1c and Appendix, page 4). Significant reductions in UACR were also observed in patients who were not receiving SGLT2 inhibitors at baseline (Supplementary Table S2). Patients with an eGFR of less than 60 ml/min per 1.73 m^2 and a UACR of more than 300 mg/g experienced significant reductions in UACR from baseline to week 26 with cotadutide 300 μg (−45.9% [95% CI: −70.5 to −0.9]; $P = 0.01$) and 600 μg (−65.2% [−80.4 to −38.2]; $P < 0.001$) versus placebo (Figure 1d).

Between baseline and week 26, significantly more patients regressed from microalbuminuria to normoalbuminuria in the cotadutide 300 μg arm (21.1%) than in the placebo arm (10.0%; $P = 0.028$; Figure 1e). In the same period, significantly more patients regressed from macroalbuminuria to microalbuminuria or normoalbuminuria status in the cotadutide 600 μg arm (50.0%) than in either the placebo (10.0%; $P = 0.006$) or semaglutide (8.3%; $P = 0.035$) arm (Figure 1f).

Effects on eGFR, HbA1c, body weight, and blood pressure

There was no difference between treatment arms in eGFR change from baseline to the end of week 14 (Figure 1g). Similar results were observed for cystatin C eGFR in all treatment arms (Table 2). Changes from baseline to week 26

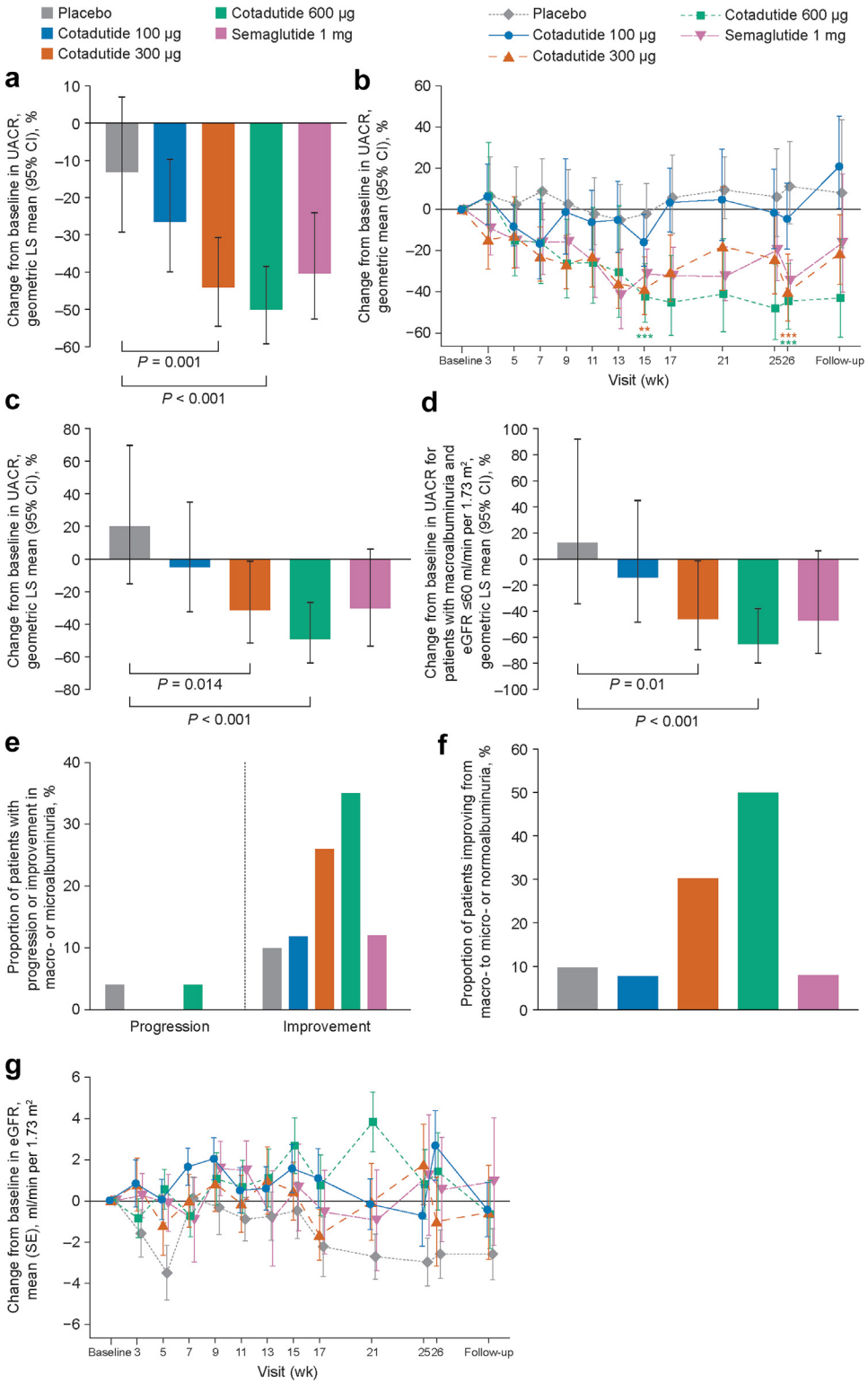

Figure 1 | Effect of cotadutide on kidney function. (**a**) Percentage change in urinary albumin-to-creatinine ratio (UACR) from baseline to the end of week 14 for all patients, (**b**) percentage change in UACR over 26 weeks of dosing for all patients, (**c**) percentage change in UACR from baseline to week 26 among patients receiving sodium-glucose cotransporter 2 inhibitors at baseline, (**d**) percentage change from baseline to week 26 in UACR among patients with macroalbuminuria and estimated glomerular filtration rate (eGFR) ≤60 ml/min per 1.73 m^2 at baseline, (**e**) proportion of patients with progression or improvement in macro- or microalbuminuria from baseline to week 26, (**f**) proportion of patients improving from macro- to micro- or normoalbuminuria from baseline to week 26 among those with macro- or microalbuminuria at baseline, and (**g**) change in eGFR from baseline over 26 weeks of dosing. $^{**}P < 0.01$ versus placebo and $^{***}P < 0.001$ versus placebo. CI, confidence interval; LS, least squares; SE, standard error.

Table 2 | eGFR slope and change from baseline in cystatin C eGFR at week 26

Variables	Cotadutide 100 μg (n = 52)	Cotadutide 300 μg (n = 49)	Cotadutide 600 μg (n = 51)	Placebo (n = 51)	Semaglutide 1 mg (n = 45)
eGFR slope, estimate (SE)	−2.0 (2.9)	1.4 (3.1)	7.3 (3.1)	−2.9 (2.9)	6.0 (3.3)
Versus placebo	$P = 0.810$	$P = 0.301$	$P = 0.016$		
Versus semaglutide	$P = 0.075$	$P = 0.320$	$P = 0.771$		
Cystatin C eGFR, geometric mean (CV), % change from baseline	2.58 (14.83)	1.33 (21.70)	3.13 (20.87)	−1.76 (17.51)	5.69 (10.98)
Versus placebo	$P = 0.566$	$P = 0.809$	$P = 0.057$		
Versus semaglutide	$P = 0.124$	$P = 0.072$	$P = 0.731$		

CV, coefficient of variation; eGFR, estimated glomerular filtration rate; SE, standard error.

in other markers of kidney function are detailed in Supplementary Table S3.

There were significant reductions in HbA1c from baseline to the end of week 14 and week 26 across all cotadutide dose levels (week 26: 100 μg, −0.9% [standard error (SE): 0.1]; 300 μg, −0.9% [0.1]; 600 μg, −0.9% [0.1]) compared with placebo (−0.3% [0.1]; all $P < 0.001$). The largest reduction in HbA1c was observed in the semaglutide arm (−1.2% [SE: 0.1]; $P = 0.034$ vs. cotadutide 600 μg; Figure 2a). There were reductions in fasting glucose from baseline to week 26 with cotadutide versus placebo (cotadutide 100 μg, −1.78 mmol/l [$P = 0.021$]; 300 μg, −1.76 mmol/l [$P = 0.025$]; 600 μg, −1.57 mmol/l [$P = 0.076$]). There were also reductions in continuous glucose monitoring measures of glycemic control to the end of week 14 and week 26 with cotadutide versus placebo (Figure 2b and c). There was no significant increase in the time spent in hypoglycemia

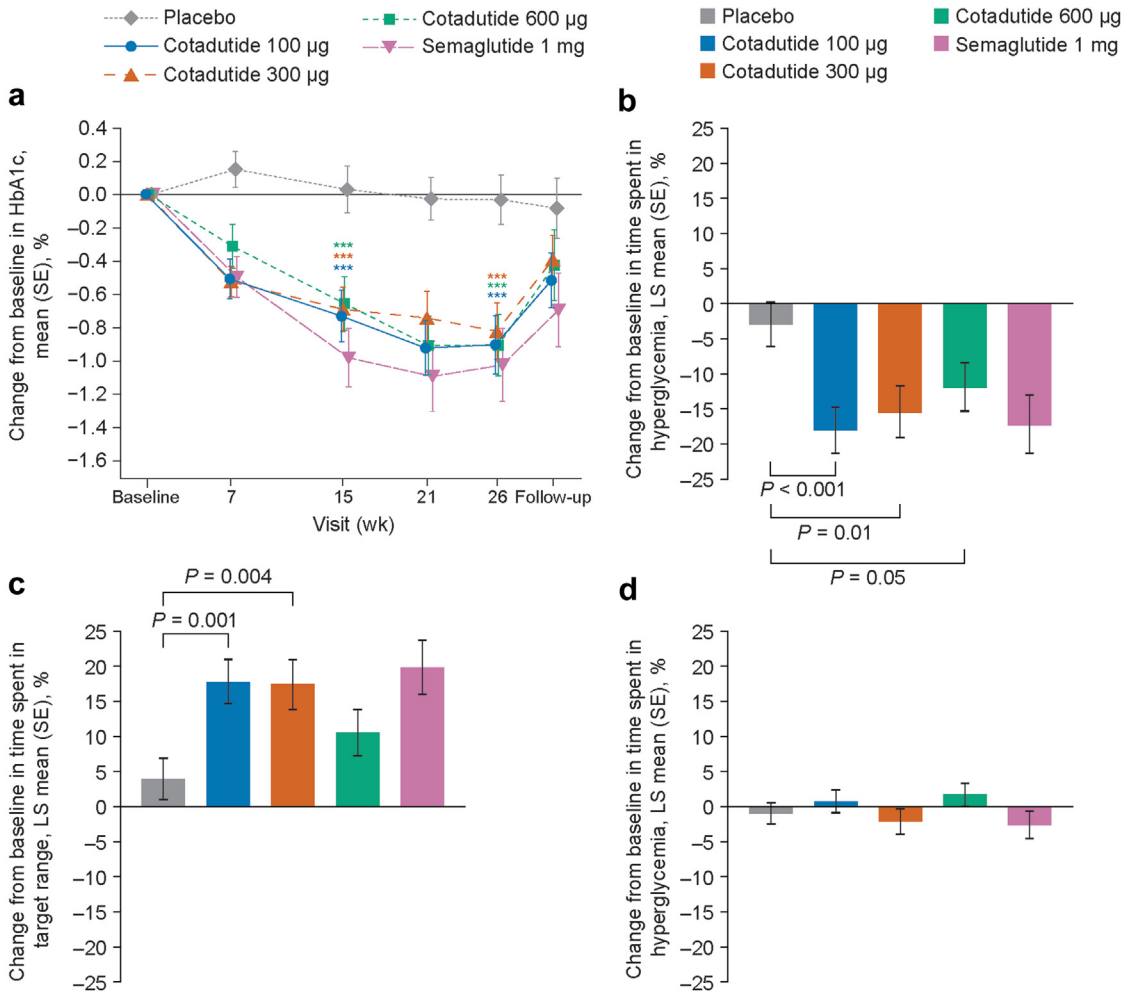

Figure 2 | Effect of cotadutide on glycemic control. Change from baseline to week 26 in (**a**) glycated hemoglobin (HbA1c), and time spent in (**b**) hyperglycemia, (**c**) target glucose range, and (**d**) hypoglycemia. ***$P < 0.001$ versus placebo. LS, least squares; SE, standard error.

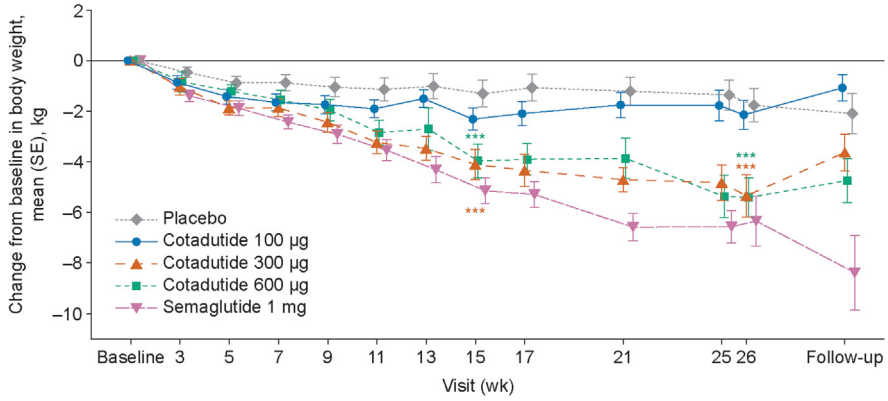

Figure 3 | Effect of cotadutide on body weight. ***$P < 0.001$ versus placebo. SE, standard error.

(Figure 2d). No statistically significant differences were observed between cotadutide and semaglutide.

Cotadutide promoted dose-dependent reductions in body weight from baseline to the end of week 14 versus placebo, which were sustained to week 26 (cotadutide 300 µg, −6.0% [SE: 0.7]; 600 µg, −6.5% [0.7]; placebo, −2.1% [0.7]; both $P < 0.001$) and into follow-up. Reductions in body weight with cotadutide 300 µg and 600 µg were not significant versus semaglutide (week 26: −7.0% [SE: 0.8]; Figure 3). To avoid hypoglycemia, insulin dose could be titrated throughout the study. Significant insulin dose reductions were observed in the cotadutide 300 µg arm from baseline to the end of week 14 and week 26 (week 26: −26.9 units [SE: 6.4]; placebo, −7.9 [6.2]; $P = 0.010$), but not in the other cotadutide dose arms. The largest numerical reductions in insulin dose were in the semaglutide arm (Supplementary Figure S2). After adjustment for changes in insulin dose, reductions from baseline to week 26 in body weight were clinically and statistically significantly (Supplementary Figure S3).

Treatment with cotadutide 600 µg promoted significant reductions from baseline to week 26 in systolic blood pressure (−9.4 mm Hg [SE: 3.0]) vs. placebo (+2.3 mm Hg [3.1]; $P = 0.002$) when measured by ambulatory blood pressure monitoring (Supplementary Table S4; changes in blood pressure by office-based measurements are shown in Supplementary Figure S4). Significant increases in pulse rate were observed in all active arms: +2.7 bpm (SD: 1.6), +6.7 bpm (SD: 1.6), and +4.8 bpm (SD: 1.6) in the cotadutide 100, 300, and 600 µg arms, versus −2.1 bpm (SD: 1.6) in the placebo arm. Pulse rate changes did not appear to be dose-dependent and were similar to those observed in the semaglutide arm +6.5 bpm (SD: 1.8; Supplementary Table S4). Reductions from baseline to week 26 in triglycerides and total cholesterol levels were numerically greater with all doses of cotadutide than with placebo or semaglutide; reductions in low-density and high-density lipoprotein levels were numerically greater with cotadutide 300 µg and 600 µg than with placebo (Supplementary Table S4).

Quality of life

Improvements in Kidney Disease Quality of Life-36 scores from baseline to week 26 versus placebo were observed across all cotadutide dose levels (Supplementary Figure S5A–C). There was a clinically significant improvement in the Kidney Disease Quality of Life-36 burden of kidney disease scale score from baseline to week 26 with cotadutide 600 µg versus placebo and semaglutide (Supplementary Figure S5A). Diabetes Treatment Satisfaction Questionnaire scores were improved in the cotadutide 300 µg and 600 µg arms versus placebo but were comparable to those in the semaglutide arm (Supplementary Figure S5D).

Exploratory outcomes

Additional prespecified analyses of the primary outcome were performed to assess the robustness of the findings. Given that changes in body weight may influence changes in muscle mass and therefore urine creatinine levels,[15] we analyzed the urine albumin and creatinine fractions in 3 first morning void samples to minimize the impact of variability of UACR measurements on the primary outcome. Treatment with cotadutide resulted in significant reductions in urine albumin from baseline to week 26 at 300 µg (−37.8% [95% CI: −51.9 to −19.6]) and 600 µg (−45.0% [−57.2 to −29.3]) dose levels versus placebo (+13.8% [−11.4 to 46.3]; both $P < 0.001$; Figure 4a). Reductions were also significant with cotadutide 600 µg versus semaglutide (−21.1% [−40.8 to 5.2]; $P = 0.028$). There were no notable changes in urine creatinine in any of the cotadutide dose arms versus placebo (Figure 4b). Semaglutide significantly increased urine creatinine from baseline to week 26 versus placebo (ratio 1.18; $P = 0.01$). To determine whether reductions in UACR with cotadutide or semaglutide could be explained by concomitant reductions in HbA1c, systolic blood pressure, or body weight, the primary outcome analyses were repeated with adjustment for these covariates, and similar results were observed (Supplementary Figure S6). *Post hoc* statistical analyses of urinary immunoglobulins were also performed to investigate further (pages 7–11 in the Supplementary Material).

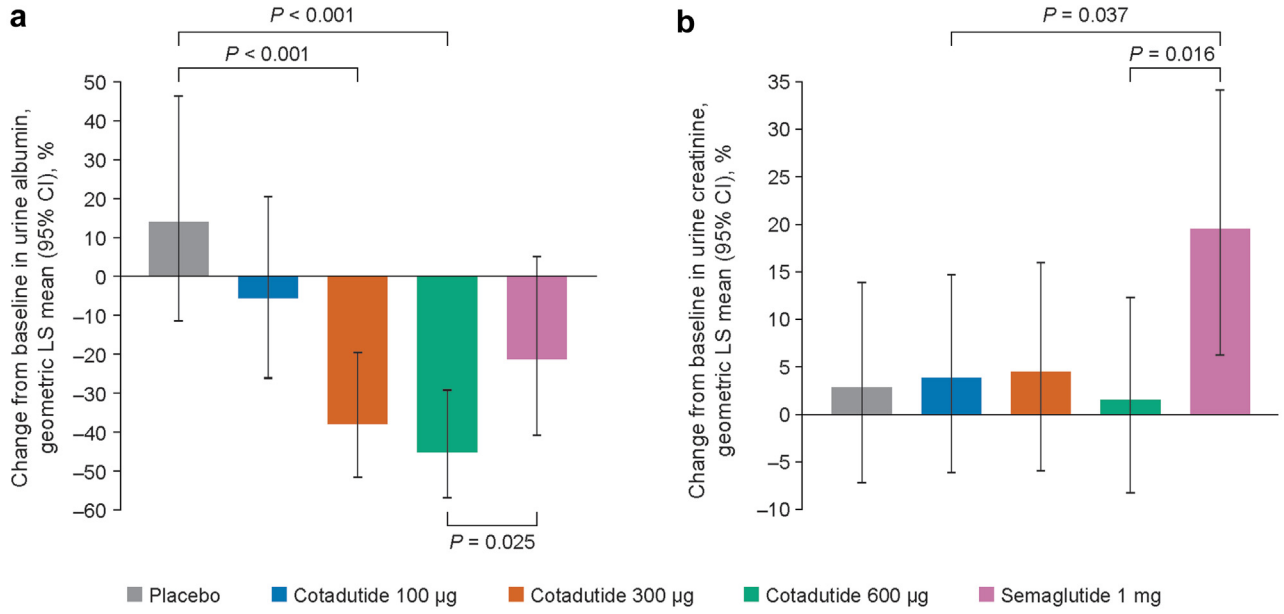

Figure 4| Percentage change from baseline to week 26 in (a) urine albumin and (b) urine creatinine. CI, confidence interval; LS, least squares.

Pharmacokinetic profiles did not differ in patients with kidney impairment, and dose-response analyses confirmed that cotadutide promoted dose-dependent reductions in UACR and albuminuria.

Safety

Safety and tolerability findings with cotadutide 600 µg were comparable to semaglutide and consistent with previous studies of cotadutide.[14,16] Similar proportions of patients in the cotadutide 600 µg and semaglutide arms had serious adverse events (5 of 48 patients [10.4%] and 4 of 45 patients [8.9%], respectively) or adverse events leading to discontinuation of study drug (10 of 48 patients [20.8%] and 7 of 45 patients [15.6%], respectively). Cotadutide 100 µg and 300 µg were better tolerated than semaglutide 1 mg, and there were fewer treatment discontinuations owing to adverse events in the cotadutide 100 µg and 300 µg arms than in the placebo arm (Table 3). Gastrointestinal adverse events were the most frequent class of events recorded. Two deaths were observed in the cotadutide 100 µg arm (acute myocardial infarction and suspected suicide); neither was deemed related to cotadutide. Hypoglycemia was frequently reported, with the highest event rates of hypoglycemia occurring in the placebo arm and one event of severe hypoglycemia recorded in the cotadutide 100 µg arm. One event of acute kidney injury was recorded in the placebo arm (Table 3).

DISCUSSION

We assessed the treatment effects of cotadutide in adults with T2D and CKD. This represents the first study of a dual GLP-1 and glucagon receptor agonist in direct comparison with semaglutide with the primary objective of evaluating kidney parameters. Given that semaglutide has recently been proven to confer kidney protection in patients with DKD,[12] this study is of importance for understanding whether dual GLP-1/glucagon receptor agonists hold potential to deliver additional benefit for patients with DKD. We observed that cotadutide led to marked dose-dependent reductions in albuminuria compared with placebo at the end of week 14, which were sustained at week 26. These effects were present regardless of whether patients were using SGLT2 inhibitors and were numerically greater than those observed with semaglutide. A reduction in albuminuria is recognized to be a valid surrogate endpoint for evaluating kidney disease progression.[17] This finding, alongside clinically significant improvements in glycemic control, body weight, and systolic blood pressure compared with placebo, and the acceptable safety and tolerability profile, suggests that cotadutide may possess kidney protective properties.[18]

Developing new therapies for diabetic kidney disease remains a priority despite recent progress. Clear benefits have been demonstrated for SGLT2 inhibitors[19–21] and finerenone,[22] but patients receiving these therapies in clinical trials still had significant rates of progression to kidney failure and had steeper rates of eGFR decline relative to healthy populations. This high risk is associated with high residual albuminuria even when patients are treated with SGLT2 inhibitors and/or finerenone.[23,24] Additional therapies that further reduce albuminuria on top of standard of care may augment kidney protection and reduce eGFR decline. In this study, the highest dose of cotadutide led to a larger reduction in urine albumin (uncorrected for creatinine) versus semaglutide (–21.1%, $P = 0.028$). In addition, patients were 14 times more likely to experience resolution of macroalbuminuria to microalbuminuria, despite comparable reductions in glucose, body weight, and blood pressure between

Table 3 | Summary of adverse events

Variables	Cotadutide			Placebo	Semaglutide 1 mg
	100 μg	300 μg	600 μg		
All patients, n	55	48	48	51	45
Any AE, n (%)	45 (81.8)	38 (79.2)	39 (81.3)	39 (76.5)	39 (86.7)
Any SAE, n (%)	5 (9.1)	5 (10.4)	5 (10.4)	5 (9.8)	4 (8.9)
Death, n (%)	2 (3.6)	0	0	0	0
Any AE leading to discontinuation of study drug, n (%)	2 (3.6)	2 (4.2)	10 (20.8)	4 (7.8)	7 (15.6)
Any AE leading to withdrawal from study, n (%)	0	0	0	0	2 (4.4)
AEs occurring with > 5% frequency and possibly related to study drug, n (%)					
Nausea	6 (10.9)	6 (12.5)	13 (27.1)	2 (3.9)	11 (24.4)
Hypoglycemia	8 (14.5)	9 (18.8)	13 (27.1)	10 (19.6)	3 (6.7)
Vomiting	2 (3.6)	2 (4.2)	7 (14.6)	1 (2.0)	6 (13.3)
Diarrhea	4 (7.3)	4 (8.3)	3 (6.3)	2 (3.9)	6 (13.3)
Constipation	2 (3.6)	2 (4.2)	4 (8.3)	2 (3.9)	2 (4.4)
Decreased appetite	0	2 (4.2)	5 (10.4)	1 (2.0)	8 (17.8)
Gastroesophageal reflux disease	1 (1.8)	2 (4.2)	3 (6.3)	0	2 (4.4)
Dyspepsia	1 (1.8)	3 (6.3)	0	0	0
AKI as AE, n (%)	0	0	0	1 (2.0)	0
Patients with baseline eGFR <45 ml/min per 1.73 m^2, n	21	11	12	15	16
Any AE, n (%)	19 (90.5)	9 (81.8)	11 (91.7)	11 (73.3)	14 (87.5)
Any SAE, n (%)	3 (14.3)	0	2 (16.7)	1 (6.7)	2 (12.5)
Death, n (%)	1 (4.8)	0	0	0	0
Any AE leading to discontinuation of study drug, n (%)	0	0	2 (16.7)	1 (6.7)	3 (18.8)
Any AE leading to withdrawal from study, n (%)	0	0	0	0	1 (6.3)
Patients with baseline eGFR ≥45 ml/min per 1.73 m^2, n	34	37	36	36	29
Any AE, n (%)	26 (76.5)	29 (78.4)	28 (77.8)	28 (77.8)	25 (86.2)
Any SAE, n (%)	2 (5.9)	5 (13.5)	3 (8.3)	4 (11.1)	2 (6.9)
Death, n (%)	1 (2.9)	0	0	0	0
Any AE leading to discontinuation of study drug, n (%)	2 (5.9)	2 (5.4)	8 (22.2)	3 (8.3)	4 (13.8)
Any AE leading to withdrawal from study, n (%)	0	0	0	0	1 (3.4)

AE, adverse event; AKI, acute kidney injury; eGFR, estimated glomerular filtration rate; SAE, serious adverse event.

the treatment and semaglutide arms. These benefits were achieved on top of standard of care and are complementary to findings of meta-analyses that have demonstrated additive effects of GLP-1RAs and SGLT2 inhibitors on kidney outcomes.[25] The reduction in UACR with cotadutide 600 μg versus placebo is clinically relevant and, based on a meta-analysis of multiple clinical trials, provides more than 95% confidence that cotadutide may also reduce the risk of clinical kidney outcomes.[26]

At the highest dose of cotadutide (with the greatest degree of glucagon receptor agonism), modest differences in urinary albumin were observed in comparison with semaglutide. These observations are limited as the study was not formally powered to ascertain differences in these endpoints; however, their identification raises questions as to whether the glucagon receptor agonist component has a differential effect in the kidney. We have previously demonstrated that cotadutide engages the glucagon receptor in humans via induction of hepatic glycogenolysis[27]; however, the underlying mechanism for how glucagon receptor agonism might impact albuminuria is unclear. It is unlikely that reductions in HbA1c, systolic blood pressure, or body weight contributed to a reduction in albuminuria because reductions in these parameters were numerically larger or the same with semaglutide and did not correlate with albuminuria reductions in the cotadutide treatment arms. Direct effects of glucagon receptor agonism on albumin filtration and reabsorption in the kidney may be involved. Increased urine albumin leakage is the result of increased glomerular albumin filtration and impaired tubular reabsorption in the proximal convoluted tubule. Protein reabsorption in the proximal convoluted tubule is an energy-intensive process,[28] which falters in CKD as proximal convoluted tubule cells undergo important switches in fuel supply and utilization.[29–31] These metabolic alterations (impairments in fatty acid oxidation, gluconeogenesis suppression, and bias toward glycolysis) are known to be modifiable by glucagon when they occur in the liver.[32,33] Yet, the distribution of glucagon receptors in the distal rather than the proximal tubule of the kidney[13] implies that any potential effects of glucagon receptor agonism on these processes could only be indirect. A recent preclinical study exploring kidney-selective glucagon receptor (*Gcgr*) knockout mice showed that

Gcgr deficiency leads to hypertension and profound metabolic defects in the kidney, including kidney lipid deposition, inflammation, and fibrosis, ultimately contributing to CKD.[34] The observations in our study are limited by their exploratory nature and lack of quantification. However, further investigation of the effects of glucagon receptor agonism in humans is warranted.

The reductions in HbA1c, systolic blood pressure, and body weight observed with cotadutide are clinically relevant and might contribute to potential long-term kidney and cardiovascular protective effects, especially because these metabolic risk markers are associated with progressive kidney function loss and cardiovascular complications. These results confirm and extend previous studies of GLP-1RAs in patients with diabetic kidney disease.[10,35] CKD is associated with significant morbidity and mortality and can negatively affect many aspects of life, health, and well-being.[36] Improvements were reported across several measures of quality of life with cotadutide versus placebo over a short time frame, suggestive of perceived improvements in disease burden and diabetes treatment satisfaction despite patients being required to administer injections once daily.

Creatinine is a key biomarker for estimating GFR and correcting for variability of albumin concentrations in urine in kidney disease. Creatinine is a by-product of creatinine phosphokinase metabolism in muscle, and it is well established that changes in muscle mass in association with weight loss can influence the interpretation of creatinine-based measures. Semaglutide treatment led to significant increases in first morning void urine creatinine concentrations in comparison with placebo and cotadutide in this study. This was also observed in a preclinical rodent model of hypertensive diabetic kidney disease.[37] We hypothesized that this may be because of enhanced muscle turnover in association with body weight loss given that muscle catabolism predominates overnight.[38] In support of this hypothesis, daytime plasma creatinine levels were numerically lower with semaglutide, and other clinical studies of semaglutide in T2D and obesity have shown reductions in fat-free mass of up to 40%, suggestive of lean mass loss.[39,40] It is also possible that potent anti-hyperglycemic effects led to reduced glucosuria, resulting in a decrease in osmotic diuresis and an increase in urine creatinine concentrations. However, the effect was not observed with cotadutide in this study, despite comparable HbA1c and body weight loss. The reason for this discrepancy is not entirely clear and warrants further investigation.

This study has several limitations including underrepresentation of Black and female patients and lack of data on patient preference for a once daily subcutaneous formulation as compared with competitor products. In addition, 24-hour urine samples were not collected to assess effects on urinary albumin and creatinine excretion. Further studies are required to more comprehensively determine the effects of weight loss interventions on urinary albumin and creatinine excretion.

Overall, our findings suggest that cotadutide has the potential to be a beneficial therapy in CKD with T2D, driving improvements in albuminuria alongside holistic effects, including improvements in glycemic control, blood pressure, body weight, and insulin dose reduction versus placebo. Furthermore, despite daily injections, patients reported improvements in measures of quality of life with cotadutide versus placebo. We believe that the results indicate an added kidney benefit of combining GLP-1 and glucagon receptor agonism versus GLP-1 receptor agonism alone. However, larger studies with longer follow-up are needed to confirm the benefits for kidney outcomes.

DISCLOSURE

VS, DR, LH, LJ, KS, AC, JS, Y-TC, HY, JP, AK, HSC, SH, and VERP are employees and stockholders at AstraZeneca. RD has received research support from Abbott, Arrowhead, AstraZeneca, Eli Lilly, Medtronic, and Novo Nordisk. AL has participated in advisory boards, conferences, and clinical trials promoted by AstraZeneca; and has received grants for sponsored investigator research. K-MD has received speaker and/or personal fees from AstraZeneca, Boehringer Ingelheim, Eli Lilly, and Novo Nordisk. CM has acted as investigator in clinical trials sponsored by Abbott, AstraZeneca, Boehringer Ingelheim, Eli Lilly, Fundacion Progreso y Salud, Hanmi, Janssen, Lexicon, Merck, Novartis, Novo Nordisk, Pfizer, Sanofi, and TheracosBio; and has acted as an advisor for Abbott, AstraZeneca, Boehringer Ingelheim, Eli Lilly, Merck, Novo Nordisk, and Sanofi. RG has received research support and/or personal fees from AstraZeneca, Bayer, Boehringer Ingelheim, Eli Lilly, Janssen, Merck, Novo Nordisk, and Sanofi. HJLH is a consultant for Alexion, AstraZeneca, Bayer, Boehringer Ingelheim, CSL Behring, Dimerix, Eli Lilly, Janssen, Novartis, Novo Nordisk, Travere Therapeutics, and Vifor Pharma; and has received research support for clinical trials from AstraZeneca, Bayer, Boehringer Ingelheim, Janssen, and Novartis. All the other authors declared no competing interests.

DATA STATEMENT

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

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AUTHOR CONTRIBUTIONS

VS contributed to the methodology, project administration, resources, supervision, validation, visualization, writing the original draft, and reviewing and editing. DR contributed to the concept, funding acquisition, the methodology, project administration, resources, supervision, visualization, writing the original draft, reviewing, and editing. LH contributed to the concept, funding acquisition, the methodology, project administration, visualization, and writing, reviewing, and editing. LJ contributed to funding acquisition, visualization, writing, reviewing, and editing. KS and AC contributed to the methodology, project administration, writing, reviewing, and editing. JS contributed to data curation, formal analysis, validation, writing, reviewing, and editing. Y-TC, HY, and JP contributed to data curation, formal analysis, software, validation, writing, reviewing, and

editing. AK, HSC, and SH contributed to formal analysis, software, validation, writing, reviewing, and editing. RD, TD, SJ, TGE, JB, AL, K-MD, RS, CM, CP, and RG contributed to the investigation, project administration, supervision, writing, reviewing, and editing. VERP contributed to the concept, funding acquisition, the methodology, project administration, resources, software, supervision, validation, visualization, writing the original draft, reviewing, and editing. HJLH contributed to the concept, resources, software, visualization, writing the original draft, reviewing, and editing. This study was funded by AstraZeneca.

Supplementary material is available online at www.kidney-international.org.

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