ORIGINAL RESEARCH ARTICLE

Pharmacokinetics and Safety of Cotadutide, a GLP-1 and Glucagon Receptor Dual Agonist, in Individuals with Renal Impairment: A Single-Dose, Phase I, Bridging Study

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Abstract

Background and Objective Cotadutide is a balanced glucagon-like peptide-1 and glucagon receptor dual agonist under development for the treatment of non-alcoholic steatohepatitis and type 2 diabetes with chronic kidney disease. We evaluated the pharmacokinetics (PK), safety and immunogenicity of a single dose of cotadutide in individuals with varying degrees of renal impairment.

Methods In this phase I bridging study, individuals 18–85 years of age, with a body mass index of 17–40 kg/m^2 and varying degrees of renal function {end-stage renal disease (ESRD; creatinine clearance [CrCl] < 20 mL/min); severe renal impairment (CrCl ≥ 20 to < 30 mL/min); lower moderate renal impairment (CrCl ≥ 30 to < 44 mL/min); upper moderate renal impairment (CrCl ≥ 45 to < 60 mL/min); normal renal function (CrCl ≥ 90 mL/min)} were treated with a single dose of subcutaneous cotadutide 100 µg under fasted conditions in the lower abdomen. The co-primary endpoints were area under the plasma concentration–time curve from time zero to 48 h (AUC$_{48}$) and the maximum observed plasma concentration (C_{max}) for cotadutide. Safety and immunogenicity were secondary endpoints. This trial is registered with ClinicalTrials.gov (NCT03235375).

Results A total of 37 individuals were enrolled in the study (only three enrolled in the ESRD group, therefore this group was excluded from the primary PK analysis). AUC$_{48}$ and C_{max} values for cotadutide were similar across all renal function groups {severe renal impairment vs. normal renal function: AUC$_{48}$ geometric mean ratio (GMR) 0.99 (90% confidence interval [CI] 0.76–1.29); lower moderate renal impairment versus normal renal function: AUC$_{48}$ GMR 1.01 (90% CI 0.79–1.30); upper moderate renal impairment versus normal renal function: AUC$_{48}$ GMR 1.09 (90% CI 0.82–1.43)}. A sensitivity analysis that combined the ESRD and severe renal impairment groups did not show notable changes in the AUC$_{48}$ and C_{max} GMRs. The incidences of treatment-emergent adverse events (TEAE) ranged from 42.9 to 72.7% across all groups and were mostly mild to moderate in severity. Only one patient had a grade III or worse TEAE during the study period. No positive antidrug antibody results were observed.

Conclusions These results suggest that the PK and tolerability of cotadutide are unaffected by renal function and that dose adjustments may not be required in individuals with renal impairment.

1 Introduction

Type 2 diabetes (T2D) is the leading cause of renal impairment and accounts for approximately 44% of all new cases of end-stage renal disease (ESRD) in the United States (US). About half of all patients with T2D develop chronic kidney disease (CKD), which is clinically defined as impaired renal function or elevated urinary albumin excretion, or both [1, 2]. The presence of CKD with T2D increases the risk of major adverse cardiovascular events and all-cause mortality, placing considerable burden on healthcare systems, patients and carers [3]. The development of CKD in patients with T2D is multifactorial, with hyperglycemia, hypertension, obesity and oxidative stress all playing a role [2, 4]. Controlling glucose, blood pressure and weight is seen as the cornerstone of disease management in patients with CKD and T2D [2, 5].

Some established treatments for T2D have shown benefit beyond glucose-lowering, by delaying progression of renal disease or macroalbuminuria in patients with T2D; however, the use of these agents is restricted in patients with more

Extended author information available on the last page of the article

Key Points

Cotadutide is a medication being developed for the treatment of non-alcoholic steatohepatitis and type 2 diabetes mellitus with chronic kidney disease.

Our study shows that exposure to cotadutide and associated drug tolerability after administration of a single therapeutic dose were unaffected by worsening renal function.

These results suggest that dose adjustments due to renal impairment are not required and that dosing in patients with type 2 diabetes mellitus with chronic kidney disease may be performed in future clinical studies.

severe renal impairment, and an unmet need remains in this patient population [6–11].

There is evidence that sodium-glucose cotransporter-2 (SGLT2) inhibitors delay the progression of renal disease in patients with and without T2D [8, 12, 13]. Diabetes management guidelines now recommend the use of an SGLT2 inhibitor in patients with T2D and CKD, particularly in those with a urine albumin-to-creatinine ratio of more than 300 mg/g, to reduce the risk of CKD progression and cardiovascular events, regardless of glycemic control [14]. The glucagon-like peptide-1 (GLP-1) receptor agonist liraglutide has also been shown to delay progression to macroalbuminuria in patients with T2D, including in subsets of patients with an estimated glomerular filtration rate (eGFR) of <60 mL/min/1.73 m^2. However, progression to ESRD has not been investigated in patients with severe renal impairment, with dose adjustments currently required because of tolerability concerns [9, 15].

Cotadutide is a balanced GLP-1 and glucagon receptor dual agonist, with positive effects on glucose control, weight management, lipid profile and liver function [16–18]. It is being investigated for the treatment of non-alcoholic steatohepatitis and T2D with CKD [16, 18, 19].

A recent phase IIa study of patients with T2D and stage 3 CKD (eGFR 30–59 mL/min/1.73 m^2) demonstrated that 32-day treatment with cotadutide 50–300 µg reduced urine albumin-to-creatinine ratio in patients with micro- and macroalbuminuria, compared with placebo [20]. Potential benefits of cotadutide towards kidney function support further evaluation in larger, longer-term clinical trials, and in patients with more severe renal impairment. It is known that renal impairment alters the pharmacokinetics (PK) of many drugs, and that defective clearance can adversely impact safety and tolerability. Although there is reason to believe that cotadutide is not metabolized through the kidneys because it has a different kidney-specific peptide cleavage

site to exenatide [21, 22], the possible accumulation of uremic factors that inhibit or suppress metabolizing enzymes and transport proteins in individuals with more severe renal impairment necessitates PK and safety evaluation of cotadutide in a population with an eGFR of < 30 mL/min/1.73 m^2.

We report results from an open-label, phase I bridging study evaluating the PK, safety and immunogenicity of a single dose of cotadutide in individuals with varying degrees of renal impairment compared with those with normal renal function, to confirm whether dose adjustments are required in individuals with more severely impaired renal function.

2 Methods

2.1 Trial Design and Participants

This open-label, single-dose, parallel-group, phase I study to evaluate the PK, safety, tolerability and immunogenicity of a single dose of cotadutide in individuals with varying stages of renal impairment was performed at four study sites in Germany and New Zealand. The primary objective was to compare the PK profile of a single dose of cotadutide in individuals with varying stages of renal impairment with that of healthy individuals with normal renal function. Secondary objectives were to characterize the safety profile and antidrug antibody (ADA) response of cotadutide.

Eligible participants were men and women 18–85 years of age, with a body mass index (BMI) of 17–40 kg/m^2 and varying degrees of renal function by which they were split into parallel groups: Group 1, ESRD, not yet on dialysis (estimated creatinine clearance [CrCl; calculated by the Cockcroft–Gault method] < 20 mL/min); Group 2, severe renal impairment (CrCl ≥ 20 to < 30 mL/min); Group 3, normal renal function (CrCl ≥ 90 mL/min); and Group 4, moderate renal impairment (CrCl ≥ 30 to < 60 mL/min). Group 4 was split into two subgroups; 4a, lower moderate renal impairment (CrCl ≥ 30 to < 45 mL/min) and 4b, upper moderate renal impairment (CrCl ≥ 45 to < 60 mL/min). Individuals who were undergoing or had undergone dialysis within 1 month of screening or had received a kidney transplant were excluded. Other key exclusion criteria included use of a GLP-1 receptor agonist or other investigation drug 30 days before screening; clinical suspicion of acute or subacute renal function deterioration; acute or chronic pancreatitis; and history of cancer in the past 5 years. Full eligibility criteria are available at www.ClinicalTrials.gov/NCT03235375.

Future pivotal studies of cotadutide in patients with T2D would probably involve patients progressing to ESRD being exposed to this treatment. Therefore, investigators were encouraged to enrol individuals with a CrCl of < 15 mL/min. As practically possible, patients

enrolled into the normal renal function group were matched with the renal impairment groups for age (± 10 years), sex and BMI (± 20%). This study was open-label, and both investigators and patients were aware of treatment.

2.2 Treatment and Assessments

All participants received a single dose of cotadutide 100 μg by subcutaneous administration, under fasted conditions (no food for a minimum of 8 h before treatment and 4 h after treatment), in the lower abdomen. No fluids were allowed 1 h before and 2 h after treatment.

A single-dose design for PK evaluation was based on the previously demonstrated linear and time-independent PK profile in the 5–300 μg dose range. Therefore, multiple-dose PK could be accurately predicted from single-dose analysis. A single dose of cotadutide has been shown to be well tolerated up to 150 μg. A lower dose of 100 μg was used because of the unknown exposure–response relationship in patients with renal impairment; this was the highest dose not associated with any clinically relevant vomiting events in a previous single-ascending dose study [23].

PK and safety (adverse events, vital signs, electrocardiogram [ECG], cardiac telemetry, urinalysis, hematology and blood chemistry) were assessed in an inpatient setting at study sites for 72 h after treatment administration. Outpatient safety and immunogenicity follow-up occurred at 7 ± 1 days and 28 ± 2 days after treatment.

2.3 Endpoints

The co-primary endpoints were the PK parameters of area under the plasma concentration–time curve from time zero to 48 h (AUC_{48}) and the maximum observed plasma concentration (C_{max}) for cotadutide. Secondary PK endpoints were time to maximum observed concentration (t_{max}), apparent clearance (CL/F), AUC from time zero to infinity (AUC_∞) and the elimination half-life ($t_{1/2}$). Safety was a secondary endpoint, which was evaluated by the incidence of treatment-emergent adverse events (TEAEs; as defined in the Medical Dictionary for Regulatory Activities [MedDRA] version 21.0), laboratory results and vital signs up to 28 days after treatment. Immunogenicity, a secondary endpoint, was evaluated by incidence of treatment-emergent ADA titer at baseline and at 7 and 28 days after treatment (or at early study discontinuation). The incidence of treatment-emergent ADAs was defined as the sum of treatment-induced ADAs and treatment-boosted ADAs.

2.4 Pharmacokinetic Analyses

Blood was collected for PK evaluation before treatment administration and at 1, 2, 4, 6, 8, 10, 12, 16, 24, 36, 48 and 72 h after treatment (± 15 min for the first 2 h; ± 30 min for time points up to 48 h; and ± 12 h for the 72-h time point). The PK of cotadutide in plasma were measured using validated liquid chromatography–tandem mass spectrometry, with a 0.4–400 ng/mL calibration range. The method was validated per HA expectations. Sampling outside the specified time point window was not considered a protocol deviation. PK parameters were analyzed using standard non-compartmental analysis (NCA) on actual timepoints and on total plasma concentrations using Phoenix WinNonlin 6.3 (or higher) software. Plasma concentrations that were below the limit of quantification (BLQ) prior to administration of the first dose, up to the first measurable concentration and before the C_{max} were entered as zero. Any other time points were entered as missing and were hence excluded from the NCA. If two or more BLQ plasma concentrations were followed by a quantifiable concentration in the terminal portion of the concentration curve, the quantifiable values were excluded from the NCA analysis.

The C_{max} and the corresponding t_{max} (defined as the first occurrence of the C_{max} and the time at which C_{max} is observed) were identified from the observed data. The terminal phase rate constant (l_z) was estimated by linear regression analysis of the log-transformed concentration–time data using the best fit method on at least three data points in the terminal portion of the concentration–time profile and R-sq adjusted value of at least 0.85. AUC_{48} and AUC_{last} (defined as AUC from the time of dosing to 48 h, or to the time of the last measurable concentration [T_{last}], respectively) were calculated using the linear up/log down trapezoidal rule. AUC_∞ was calculated as the sum of AUC from time zero to t and $C_{t/z}$, where C_t is the observed plasma concentration obtained from the log-linear regression analysis of the last quantifiable time point and z is the terminal phase rate constant. The percentage of AUC_∞ due to extrapolation from T_{last} to infinity was calculated as [(AUC_∞–AUC_{last}/AUC_∞)*100]. CL/F was determined by dose/AUC_∞, and $t_{1/2}$ was calculated as $0.693/l_z$. Other PK parameters such as volume of distribution were calculated but not reported as Cl was considered more descriptive to characterize the PK difference in the different segments of renally impaired patients.

2.5 Statistical Analyses

The sample size of eight participants per group was empirically determined to obtain adequate information to assess the effects of renal impairment on the PK of cotadutide, while limiting the number of individuals exposed to treatment.

Eight evaluable participants per group would provide an 80% probability of achieving a relative precision of 1.8 (ratio between the upper and lower 90% confidence intervals [CIs]), based on the assumption that interparticipant coefficient of variation was 30%.

The PK analysis was performed in the PK population, defined as all subjects receiving the dose of investigational product and having at least one post-dose PK measurement. The primary PK endpoints analysis (AUC_{48} and C_{max}) were performed in the per protocol (PP) population, defined as all subjects in the PK population who have PK measurements up to at least 24 h post-dose and have a percentage of extrapolation on AUC lower than 50%.

Subjects who did not have PK measurements up to at least 24 h post-dose or who had a percentage of extrapolation on AUC > 50%, were to be identified by the Clinical Pharmacokineticist after database lock, after deriving the PK parameters in the PK population. As no such subjects were identified during the course of the PK analysis, the PP population was the same as the PK population. Therefore, the statistical analysis on primary PK endpoints as well as any other analyses planned on the PP population were ultimately conducted in the PK population.

Each renal impairment group with at least six participants was compared with the normal renal function group. The ESRD group was excluded from the primary PK analyses because of insufficient enrolment ($n = 3$) and early study termination. For comparisons, the geometric mean ratio (GMR) and 90% CI for the primary endpoints were derived from analysis of variance (ANOVA) and least-squares mean difference on log-transformed values, with group serving as the fixed classification effect. Sensitivity analyses of the primary PK endpoints using the same ANOVA model were performed combining ESRD and severe renal impairment groups, as well as both moderate renal impairment groups, for comparisons with the control group. Data analyses were conducted using SAS® version 9.3 or higher (SAS Institute Inc., Cary, NC, USA).

Summary or descriptive statistics were generated for secondary PK endpoints with no formal statistical testing performed. Safety was evaluated in all patients who received treatment. TEAEs were recorded from the start of treatment until the last day on study. The type, incidence, severity and relationship to cotadutide of TEAEs were summarized by MedDRA System Organ Class and Preferred Term. Multiple occurrences of specific TEAEs were counted once for summary statistics, with the highest level of severity reported. Immunogenicity was evaluated in all participants who received treatment with reported ADA readings (ADA positive or ADA negative; titer; cross-reactivity to GLP-1: positive or negative; cross-reactivity to glucagon: positive vs. negative).

3 Results

3.1 Study Participants

Of 45 individuals screened across four sites in Germany and New Zealand, 37 were enrolled into the study between 27 October 2017 and 23 April 2018. All participants received a single dose of cotadutide 100 μg, were evaluable for PK analyses, and completed the study as planned (electronic supplementary Fig. S1). No participants withdrew from the study or were lost to follow-up. Renal function groups enrolled were ESRD ($n = 3$), severe renal impairment ($n = 8$), lower moderate renal impairment (CrCl ≥ 30 to < 45 mL/min [$n = 11$], upper moderate renal impairment (CrCl ≥ 45 to < 60 mL/min) [$n = 7$], and normal renal function ($n = 8$).

The mean age of participants was 66.6 (standard deviation [SD] 10.4) years. Almost equal numbers of men and women participated in the study. Mean BMI was 27.4 (SD 5.3) kg/m². Seven of 37 participants (18.9%), all in the renal impairment groups, had a history of diabetes. Mean CrCl in each group was: ESRD group, 14.9 mL/min; severe renal impairment group, 23.6 mL/min; lower moderate renal impairment group, 38.3 mL/min; upper moderate renal impairment group, 51.4 mL/min; and normal renal function group, 110.0 mL/min. Other demographics and baseline characteristics were generally similar across all groups (Table 1).

3.2 Pharmacokinetics

In the primary PK analysis, the estimated GMRs demonstrated that AUC_{48} and C_{max} values for cotadutide in individuals with moderate or severe renal impairment were similar to those in individuals with normal renal function (Table 2; severe renal impairment vs. normal renal function: AUC_{48} GMR 0.99 [90% CI 0.76–1.29]; moderate renal impairment [CrCl ≥ 30 to < 45 mL/min] vs. normal renal function: AUC_{48} GMR 1.01 [90% CI 0.79–1.30]; moderate renal impairment [CrCl ≥ 45 to < 60 mL/min] vs. normal renal function: AUC_{48} GMR 1.09 [90% CI 0.82–1.43]). An additional sensitivity analysis that combined ESRD and severe renal impairment groups, as well as both moderate renal impairment groups, showed similar results, in which the inclusion of three patients with ESRD did not dramatically alter the GMR (Table 3).

Table 1 Demographic and baseline characteristics

	Group 1 [n = 3]	Group 2 [n = 8]	Group 4a [n = 11]	Group 4b [n = 7]	Group 3 [n = 8]	Overall [N = 37]
Age, years [mean (SD)]	66.7 (17.0)	63.5 (13.2)	68.2 (10.6)	70.3 (7.8)	64.4 (7.0)	66.6 (10.4)
Sex [n (%)]						
Female	1 (33.3)	5 (62.5)	5 (45.5)	4 (57.1)	4 (50.0)	19 (51.4)
Male	2 (66.7)	3 (37.5)	6 (54.5)	3 (42.9)	4 (50.0)	18 (48.6)
Race [n (%)]						
White	1 (33.3)	7 (87.5)	9 (81.8)	6 (85.7)	7 (87.5)	30 (81.1)
Native Hawaiian or Pacific Islander	1 (33.3)	1 (12.5)	1 (9.1)	1 (14.3)	0	4 (10.8)
Black or African American	0	0	0	0	1 (12.5)	1 (2.7)
Other	1 (33.3)	0	1 (9.1)	0	0	2 (5.4)
Body mass index, kg/m^2 [mean (SD)]	29.8 (7.9)	26.7 (7.2)	28.8 (5.2)	24.9 (3.0)	27.5 (3.9)	27.4 (5.3)
History of diabetes [n (%)]	2 (66.7)	1 (12.5)	3 (27.3)	1 (14.3)	0	7 (18.9)
Serum creatinine, mg/dL [mean (SD)]	5.5 (2.2)	2.8 (1.3)	2.0 (0.6)	1.1 (0.2)	0.8 (0.1)	2.0 (1.5)
Cystatin C, mg/L [mean (SD)]	4.2 (0.6)	2.9 (0.8)	2.2 (0.6)	1.3 (0.2)	0.9 (0.2)	2.1 (1.1)
Hemoglobin, g/dL [mean (SD)]	9.9 (1.7)	11.3 (1.3)	13.3 (2.2)	13.0 (1.6)	14.3 (1.5)	12.8 (2.1)

SD standard deviation

Table 2 Primary endpoints: estimated GMR of AUC$_{48}$ and C$_{max}$ for cotadutide in groups with renal impairment versus healthy controls

Primary endpoints, GMRs (90% CI)[a]	Group 2 CrCl ≥20 to <30 mL/min [n = 8]	Group 4a CrCl ≥30 to <45 mL/min [n = 11]	Group 4b CrCl ≥45 to <60 mL/min [n = 7]
AUC$_{48}$	0.99 (0.76–1.29)	1.01 (0.79–1.30)	1.09 (0.82–1.43)
C_{max}	1.17 (0.78–1.74)	0.95 (0.65–1.37)	1.12 (0.74–1.70)

ANOVA analysis of variance, *AUC$_{48}$* area under the plasma concentration–time curve from time zero to 48 h, *CI* confidence interval, *C$_{max}$* maximum observed plasma concentration, *CrCl* creatinine clearance, *GMR* geometric mean ratio

[a]Derived from ANOVA and least-squares mean difference on log-transformed values, with group serving as the fixed classification effect

Table 3 Sensitivity analyses of the primary endpoints: estimated GMR of AUC$_{48}$ and C_{max} for cotadutide in combined groups with renal impairment versus healthy controls

Primary endpoints, GMRs (90% CI)[a]	Groups 1 and 2 CrCl < 30 mL/min [n = 11]	Group 4 CrCl ≥ 30 to < 60 mL/min [n = 18]
AUC$_{48}$	0.94 (0.75–1.19)	1.04 (0.84–1.29)
C_{max}	1.13 (0.80–1.58)	1.01 (0.74–1.38)

ANOVA analysis of variance, *AUC$_{48}$* area under the plasma concentration–time curve from time zero to 48 h, *CI* confidence interval, *C$_{max}$* maximum observed plasma concentration, *CrCl* creatinine clearance, *GMR* geometric mean ratio

[a]Derived from ANOVA and least-squares mean difference on log-transformed values, with group serving as the fixed classification effect

All PK parameters for cotadutide, including $t_{1/2}$ and C_{max}, were similar among groups (Table 4). The mean values of AUC$_\infty$ and C_{max} for cotadutide were similar across all groups and showed no consistent trends with decreasing renal function, confirming that the elimination phase was similar across all groups (Fig. 1). The individual overall exposure (AUC$_\infty$) derived was carrying only a minimal (< 20%) extrapolation. The mean exposure ranged from 101.98 ng h/mL in the ESRD group to 135.01 ng h/mL in the upper moderate renal impairment group. Mean C_{max} ranged from 5.44 ng/mL in the lower moderate renal impairment group to 6.73 ng/mL in the severe renal impairment group. Mean $t_{1/2}$ ranged from a minimum of 8.5 h in the severe renal impairment group to 10.8 h in the normal renal function group. The mean CL/F ranged from a minimum of 0.74 L/h in the upper moderate renal impairment group to a maximum of 0.98 L/h in the ESRD group.

3.3 Safety and Immunogenicity

In total, 22 of 37 patients (59.5%) had a TEAE during the study (Table 5). Incidences ranged from 42.9% (3 of 7 patients) in the upper moderate renal impairment group to 72.7% (8 of 11 patients) in the lower moderate renal impairment group. Events were mostly mild to moderate in severity. Only one patient had a grade 3 or worse TEAE during the study period (grade 3 nausea in the lower moderate renal impairment group). There were no deaths or other serious

**Table 4** Secondary PK endpoints: PK parameters for cotadutide across groups

Parameter	Group 1 CrCl < 20 mL/min [n = 3]	Group 2 CrCl ≥20 to <30 mL/min [n = 8]	Group 4a CrCl ≥30 to <45 mL/min [n = 11]	Group 4b CrCl ≥45 to <60 mL/min [n = 7]	Group 3 CrCl ≥90 mL/min [n = 8]
C_{max}, ng/mL	5.89 (3.69–8.71)	6.73 (3.69–11.80)	5.44 (3.14–8.57)	6.47 (3.27–13.00)	5.75 (4.08–8.17)
t_{max}, h [median (range)]	4.0 (4.0–8.0)	6.0 (2.0–10.0)	6.0 (4.0–12.0)	6.0 (4.0–10.0)	8.0 (2.0–10.0)
AUC_{48}, ng h/mL	98.65 (69.66–143.09)	116.38 (92.45–182.72)	119.68 (67.89–172.57)	128.16 (83.75–173.92)	118.04 (89.63–143.51)
AUC_∞, ng h/mL	101.98 (73.12–147.59)	120.40 (96.74–188.72)	124.85[a] (74.64–180.23)	135.01 (90.87–180.97)	126.60 (92.28–156.83)
$t_{1/2}$, h	9.2 (8.3–10.1)	8.5 (5.6–11.8)	10.5[a] (6.3–13.9)	9.6 (5.4–13.3)	10.8 (8.1–15.5)
CL/F, L/h	0.98 (0.68–1.37)	0.83 (0.53–1.03)	0.80[a] (0.55–1.34)	0.74 (0.55–1.10)	0.79 (0.64–1.08)

Data are expressed as geometric means (range), unless specified otherwise

AUC_{48} area under the plasma concentration–time curve from time zero to 48 h, AUC_∞ area under the plasma concentration–time curve from time zero to infinity, *CL/F* apparent clearance, C_{max} maximum observed plasma concentration, *CrCl* creatinine clearance, *PK* pharmacokinetic, $t_{1/2}$ elimination half-life, t_{max} time to maximum observed concentration

[a]$n = 10$

Fig. 1 Plasma concentration profiles of cotadutide across groups. (**a**) Linear scale; (**b**) semi-log scale. [a]Severe renal impairment or end-stage renal disease. [b]Severe renal impairment. [c]Moderate renal impairment. [d]Normal renal function. *CrCl* creatinine clearance, *SE* standard error (for clarity, only upper SE has been represented)
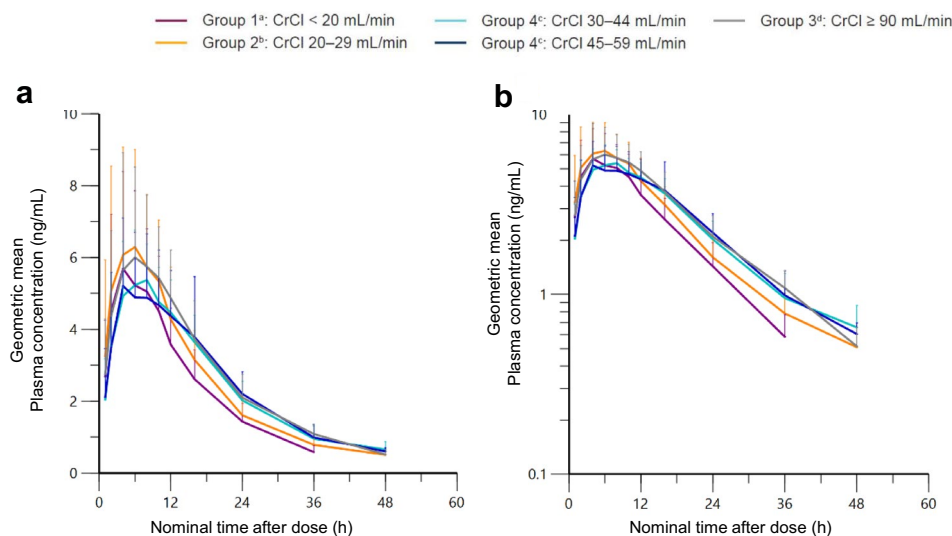
TEAEs during the study period. The gastrointestinal events of nausea and vomiting were the most frequently reported TEAEs across all groups. Vomiting was reported in 13 of 37 individuals (35.1%) and nausea in 12 of 37 individuals (32.4%). These events occurred at similar rates in the renal impairment groups (vomiting, 18–50%; nausea, 29–38%) and the normal renal function group (both 38%). Headache was the third most common TEAE, occurring in 10 of 37 individuals (27.0%) and at similar rates across groups.

Most TEAEs were deemed by investigators to be related to cotadutide (Table 5, electronic supplementary Table S1). Two individuals, one in the upper moderate renal impairment group and one in the normal renal function group, had grade 1 treatment-related injection site reactions. One patient in the lower moderate renal impairment group had grade 2 hypoglycemia the day after treatment administration, which resolved the following day. Two individuals with renal impairment had treatment-related cardiac events; these were the only clinically significant abnormal ECG findings during the study period. One individual in the severe renal impairment group had abnormal sinus rhythm 4 h after treatment administration, which was diagnosed as tachycardia (grade 1) and resolved the following day. One individual in the lower moderate renal impairment group had abnormal sinus rhythm (grade 2 tachycardia) 4, 6 and 8 h after treatment administration and atrial fibrillation (grade 2) on the day of treatment, which both resolved on the same day. This individual was referred to a cardiologist to investigate potential underlying causes of these cardiac events.

There were no clinically meaningful trends or mean shifts from baseline in hematology, serum chemistry, or urinalysis parameters in any of the renal impairment groups or the normal renal function group. No confirmed positive ADA results were observed during the study period.

Table 5 Treatment-emergent adverse events during the study

Parameter [n (%)]	Group 1 CrCl <20 mL/min [n = 3]	Group 2 CrCl ≥20 to <30 mL/min [n = 8]	Group 4a CrCl ≥30 to <45 mL/min [n = 11]	Group 4b CrCl ≥45 to <60 mL/min [n = 7]	Group 3 CrCl ≥90 mL/min [n = 8]	Overall [N = 37]
Any TEAE	2 (66.7)	4 (50.0)	8 (72.7)	3 (42.9)	5 (62.5)	22 (59.5)
Treatment-related	1 (33.3)	4 (50.0)	8 (72.7)	3 (42.9)	4 (50.0)	20 (54.1)
Grade 3 or higher TEAE	0	0	1 (9.1)[a]	0	0	1 (2.7)
Serious TEAE	0	0	0	0	0	0
Deaths	0	0	0	0	0	0
TEAEs occurring at a frequency of ≥ 10% in any group						
Vomiting	1 (33.3)	4 (50.0)	2 (18.2)	3 (42.9)	3 (37.5)	13 (35.1)
Nausea	1 (33.3)	3 (37.5)	3 (27.3)	2 (28.6))	3 (37.5)	12 (32.4)
Headache	1 (33.3)	3 (37.5)	2 (18.2)	0	4 (50.0)	10 (27.0)
Abdominal distension	0	0	1 (9.1)	0	1 (12.5)	2 (5.4)
Decreased appetite	0	0	2 (18.2)	0	0	2 (5.4)
Dizziness	1 (33.3)	0	0	1 (14.3)	0	2 (5.4)
Rhinitis	0	0	2 (18.2)	0	0	2 (5.4)
Tachycardia	0	1 (12.5)	1 (9.1)	0	0	2 (5.4)
Arthralgia	1 (33.3)	0	0	0	0	1 (2.7)
Catheter site bruise	0	0	0	1 (14.3)	0	1 (2.7)
Catheter site swelling	0	0	0	0	1 (12.5)	1 (2.7)
Constipation	1 (33.3)	0	0	0	0	1 (2.7)
Dyspepsia	0	0	0	0	1 (12.5)	1 (2.7)
Injection site bruising	0	0	0	1 (14.3)	0	1 (2.7)
Injection site erythema	0	0	0	0	1 (12.5)	1 (2.7)
Presyncope	0	1 (12.5)	0	0	0	1 (2.7)
Toothache	0	1 (12.5)	0	0	0	1 (2.7)

Serious TEAE criteria: death, life-threatening, required inpatient hospitalization, prolongation of existing hospitalization, persistent or significant disability/incapacity, important medical event, congenital anomaly/birth defect (in the offspring of the patient)

CrCl creatinine clearance, *TEAE* treatment-emergent adverse event

[a]Nausea (grade 3; non-serious)

4 Discussion

In this single-dose, phase I study to evaluate the PK, safety and immunogenicity of cotadutide in individuals with renal impairment, PK parameters were similar across all renal function groups and there was only a slight variation in incidences of generally mild and moderate TEAEs. There were no deaths, other serious TEAEs, or TEAEs leading to discontinuation in this study. Until now, the impact of severe renal impairment or ESRD on the PK of cotadutide has remained largely unknown. These data provide evidence that the PK and tolerability of cotadutide are largely unaffected by severe renal impairment. Multiple-dose PK may be extrapolated from single-dose results, based on the known linear and time-independent PK of cotadutide, confirming that it may be safely administered in patients with T2D and severely impaired renal function, with no need for dose adjustments.

The study design was adequate to describe the PK of cotadutide across a spectrum of renal impairment.

Individuals with impaired renal function had features typical of this population, such as higher mean systolic blood pressure, mean serum creatinine and mean cystatin C at baseline than individuals with normal renal function. There was no clear trend for change in the PK of cotadutide in individuals with increasing renal impairment. The overall safety profile in the renal impairment groups was acceptable and consistent with previous studies of dual glucagon and GLP-1 receptor agonists and mono GLP-1 receptor agonists [24]. Findings in individuals with moderately impaired renal function corroborate safety and tolerability results of the multidose phase IIa study of cotadutide in patients with T2D and an eGFR of 30–59 mL/min/1.73 m[2] [20]. Overall, safety and tolerability were also comparable with that previously observed in studies of cotadutide in obese and overweight patients with T2D without CKD [16, 19].

These data also support results from a pooled population PK analysis that included patients from an ongoing phase IIb study (NCT04515849), in which non-linear mixed-effects modeling demonstrated consistent absorption and

elimination of cotadutide in patients with T2D and three renal function statuses (normal renal function, mild renal impairment, and moderate renal impairment). Renal function was also confirmed as a non-statistically significant baseline covariate on clearance in subjects with T2D [25].

The panel of classical in vitro drug–drug interaction (DDI) assays typical for analysing small molecule interactions with metabolism enzymes and transporters have not been conducted for cotadutide. The DDI potential of cotadutide with metabolism enzymes and transporters is expected to be low, consistent with other cotadutide peptides such as liraglutide and semaglutide [26]. Additionally, the reliability and application of these in vitro assays designed for small molecules are unknown and are not always predictable clinically for peptides [27].

Furthermore, it is unprecedented for linear peptides to produce half maximal inhibitory concentration (IC_{50}) values that present a risk for interaction with drug transporters or metabolizing enzymes. The average C_{max} of cotadutide is about 10 nM at steady state following daily subcutaneous administration of 600 μg of cotadutide. The most potent small molecule inhibitors are typically characterized with in vitro IC_{50} values of 0.1 μM or above and their systemic exposure levels are well above the $C_{max,ss}$ expected for cotadutide. Therefore, the inhibition potential of CYP enzymes and transporters by cotadutide are expected to be minimal.

Previous studies with the GLP-1 receptor agonist exenatide (exendin-4) in subjects with different stages of renal impairment showed tolerability and PK changes that were considered clinically acceptable in mild-to-moderate renally impaired subjects, without dose adjustment needed. However, in severe renally impaired and ESRD subjects, exenatide showed poor tolerability and significant changes in PK [28] and is not recommended for use by patients with severe renal impairment or ESRD. In vitro studies have shown that exenatide is metabolized specifically in the kidney and the primary cleavage sites were after amino acids (AA)-21 and -22 [21]. As cotadutide does not share sequence homology with exenatide in that position, there is reason to believe that the kidney is not a primary site for metabolism of cotadutide and that the PK in severe renally impaired/ESRD subjects will not be different from healthy subjects. More recently, single-dose PK/safety studies with other GLP-1 agonists liraglutide and albiglutide were performed in subjects with renal impairment, with similar conclusions of no need for adjusting dose even in severe renal impairment or ESRD.

These considerations support assumptions that cotadutide is not metabolized through the kidneys, and suggest that the PK of cotadutide are not impacted by any potential suppression of metabolizing enzymes and transport proteins in individuals with severely impaired renal function or ESRD.

A limitation of this study is that safety data were obtained from a small sample of individuals with renal impairment after only a single dose of cotadutide. However, in a randomized, double-blind, placebo-controlled, phase IIa study in patients with moderate renal impairment and T2D, treatment with multiple doses of once-daily cotadutide titrated to 50–300 μg for 32 days was associated with an acceptable safety and tolerability profile, with the majority of TEAEs being mild or moderate and only one 1 of 21 participants (4.8%) having a serious TEAE deemed related to cotadutide [20]. A further limitation is that the small number of participants with ESRD precludes robust conclusions for this subgroup. Evaluation of the longer-term risks of cotadutide in a population with renal impairment is needed in larger, longer-term studies. Importantly, this study allows this exploration of dosing in larger phase IIb and III clinical studies in individuals with impaired renal function.

5 Conclusion

This study demonstrated that cotadutide was well tolerated and showed no change in PK profile in individuals with impaired renal function after a single 100 μg dose. However, caution may still be required in patients with ESRD owing to the small number of patients with this degree of impairment evaluated. These results were anticipated based on evidence that cotadutide is not metabolized through the kidneys and the safety profile associated with multiple doses of cotadutide in patients with moderate renal impairment and T2D in a randomized phase IIa study [20], and confirm that dosing in patients with CKD and T2D may be performed in future, longer-term, pivotal clinical studies.

Declarations

Author contributions GK, MP, YY, TH, LH and AF conceived and designed the study; GK, TH, SH and AF collected the data; MP, YY, TH, LH and AF analyzed the data; MP carried out the PK analysis; and SH and AF supervised the project. All authors contributed to writing of the manuscript and approved the final manuscript for submission.

Ethics approval This study was conducted in accordance with the principles of the Declaration of Helsinki, the International Council for Harmonisation Guidance for Good Clinical Practice, and with any applicable laws and conditions required by relevant regulatory authorities. The study protocol and informed consent documents were approved by the relevant Independent Ethics Committee of the Technical University of Munich.

Consent All participants provided written informed consent before study entry.

Data availability 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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