Clinical Study Report Synopsis	
Drug Substance	Cotadutide
Study Code	D5676C00001
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A Phase 2b, Multicentre, Randomised, Double-blind, Placebo-controlled, and Open-label Comparator Study of Cotadutide in Participants Who Have Chronic Kidney Disease with Type 2 Diabetes Mellitus

Study dates:

First subject enrolled: *31 August 2020*
Last subject last visit: *08 March 2022*

Phase of development:

Therapeutic exploratory (II)

[redacted]

This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents.

Study centre(s)

The study was conducted at 63 study sites across 8 countries: Australia (9 sites), Canada (11 sites), Germany (11 sites), Japan (7 sites), New Zealand (6 sites), Poland (6 sites), Spain (12 sites), and the UK (1 site).

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Table S1 Objectives and Endpoints

Objectives	Endpoints
Primary	
• To assess the effects of cotadutide at different dose levels compared to placebo on UACR after 14 weeks	• Change and percentage change in UACR versus placebo from baseline to the end of 14 weeks of dosing
Secondary	
• To assess the effects of cotadutide at different dose levels compared to placebo on UACR after 26 weeks	• Change and percentage change in UACR versus placebo from baseline to the end of 26 weeks of dosing
• To assess the effects of cotadutide at different dose levels compared to placebo on HbA1c and fasting glucose	• Change in HbA1c versus placebo from baseline to the end of 14 and 26 weeks of dosing • Change in fasting glucose from baseline versus placebo after 14 and 26 weeks of dosing
• To assess the effects of cotadutide at different dose levels compared to placebo on glucose levels as measured by CGM	• Change in 10-day average glucose levels as measured by CGM versus placebo from baseline to the end of 14 and 26 weeks of dosing • Change in percentage time spent in hyperglycaemia (> 10 mmol/L), target range (3.9 – 10 mmol/L), hypoglycaemia (< 3.9 mmol/L), and clinically significant hypoglycaemia (< 3.0 mmol/L) over 10 days as measured by CGM versus placebo from baseline to the end of 14 and 26 weeks of dosing

Table S1 Objectives and Endpoints

• To assess the effects of cotadutide at different dose levels compared to placebo on body weight	• Change and percentage change in body weight versus placebo from baseline to the end of 14 and 26 weeks of dosing • Proportion of participants achieving ≥ 5% and ≥ 10% body weight loss versus placebo from baseline to the end of 14 and 26 weeks of dosing
• To evaluate the immunogenicity profile of cotadutide compared to placebo	• ADAs during the titration treatment period and follow-up period
Safety	
• To evaluate the safety and tolerability of cotadutide compared to placebo	• TEAEs and TESAEs • Vital signs • ECG • Clinical laboratory assessments

ADA = anti-drug antibody; CGM = continuous glucose monitoring; ECG = electrocardiogram; HbA1c = haemoglobin A1c; TEAE = treatment-emergent adverse event; TESAE = treatment-emergent serious adverse event; UACR = urine albumin to creatinine ratio

Study design

Study D5676C00001 was a randomised, double-blind, placebo-controlled Phase IIb study with an open-label comparator (semaglutide) group, designed to evaluate the efficacy, safety, tolerability and pharmacokinetic (PK) profile of cotadutide (100, 300, and 600 µg) in participants with chronic kidney disease (CKD) and type 2 diabetes mellitus (T2DM). Eligible participants were randomly assigned (ratio 1:1:1:1:1) to treatment groups; Japanese participants were not randomised to the semaglutide treatment group. The study had a 14-day run-in period, 26-week treatment period, and 28-day follow-up period. [redacted]

Target subject population and sample size

Participants aged ≥ 18 years and ≤ 79 years, with a diagnosis of CKD as defined by an estimated glomerular filtration rate (eGFR) of ≥ 20 to < 90 mL/min/1.73m^2, and micro- or macroalbuminuria (ie, urine albumin to creatinine ratio [UACR] > 50 mg/g or 5.7 mg/mmol), with haemoglobin A1c (HbA1c) between 6.5% and 12.5% at screening, and who were receiving glucose control therapy for T2DM were to be enrolled in the study. Treatment with

glucagon-like peptide 1 (GLP-1) analogues within 30 days (or 5 half-lives) of Visit 2 was not permitted.

A total of 248 participants were randomised into the study: cotadutide 100 µg (52), cotadutide 300 µg (49), cotadutide 600 µg (51), placebo (51), and semaglutide (45). Anticipating a 20% discontinuation rate, the planned sample size of 225 participants was calculated to provide 90% power to detect a 40% reduction in UACR for cotadutide versus placebo, under the assumption of a standard deviation of 0.74, and a two-sided type I error rate of 0.05.

[redacted]

Duration of treatment

26 weeks.

[redacted]

Efficacy and safety endpoints were summarised by treatment group and at each visit using descriptive statistics. Continuous efficacy variables were summarised for the observed values, the change from baseline and the percent change from baseline, including the number of participants (n), mean, standard deviation, median, minimum and maximum. Geometric mean and geometric coefficient of variation were included for percent change.

Analyses of Primary Endpoint

The primary efficacy endpoint (UACR) was analysed using an analysis of covariance (ANCOVA) model with a two-sided significance level of 0.05. Urine albumin to creatinine ratio data was log-transformed for the model analyses and the results were then transformed back for interpretation. Treatment was included as fixed effect, with baseline value and stratification factors (whether a participant was from a site in Japan and whether a participant was using sodium-glucose cotransporter 2 [SGLT2] inhibitor therapy at screening or not) as covariates. Last observation carried forward method, using post-baseline scheduled

measurements, was applied to handle missing data. Analyses were based on the intent-to-treat population.

[redacted]

Immunogenicity

Immunogenicity results were based on the immunogenicity population. Anti-drug antibodies (ADAs) were summarised as categorical variables, with the number and percentage of participants with a positive result at the specific visit. For ADA positive tests, ADA titre was summarised descriptively as a continuous variable, with median, interquartile range, minimum, and maximum, at each analysis visit.

Analyses of Safety Endpoints

Adverse event (AE) tables were based on the as-treated population. AEs and serious AEs (SAEs) were coded by the Medical Dictionary for Regulatory Activities (MedDRA) version 24.1, and the type, incidence, severity, and relationship to investigational product was summarised by MedDRA System Organ Class and Preferred Term and by treatment. Specific AEs were counted once for each participant for calculating percentages. If the same AE occurred multiple times within a particular participant, the highest severity and level of relationship observed was reported. Clinical safety laboratory results, vital signs, and electrocardiogram parameters were summarised for each visit and for change from baseline. Shifts from baseline to maximum and minimum value were presented for laboratory results, and shifts from baseline to maximum value were presented for vital signs. The number and

percentage of participants within each QTcF interval classes were reported together with the number and percentage of participants within QTcF increase classes at any time.

Study population

A total of 416 participants participated in the study between 31 August 2020 (date first participant enrolled) and 08 March 2022 (date of last participant last visit); 248 were randomised, and 247 treated. Overall, 38 (15.3%) participants discontinued study treatment, with a higher proportion in the cotadutide 600 µg [redacted], and comparable discontinuations across the cotadutide 100 and 300 ug groups and placebo treatment groups, and 235 (94.8%) participants completed the study. Demographic and baseline characteristics were balanced across the treatment groups and representative of the target population.

Summary of efficacy results

In the analysis of the primary endpoint, geometric least squares (GeoLS) mean percent reductions in UACR after 14 weeks' treatment with cotadutide were clinically relevant and statistically significantly greater with cotadutide 300 and 600 µg compared with placebo: -43.88 (95% Confidence Interval [CI]: -54.65, -30.56; p = 0.001) and -49.91 (95% CI: -59.30, -38.35; p < 0.001), respectively. Results in the non-Japanese sub-population were similar to that of all participants, and consistent results were observed from sensitivity analysis of the primary endpoint and no significant treatment interactions were noted.

Secondary endpoints: significant reductions in UACR were sustained after 26 weeks' treatment with cotadutide 300 and 600 µg compared with placebo; significant reductions in body weight were observed with cotadutide 300 and 600 µg compared with placebo; and treatment with cotadutide compared with placebo resulted in significant glycaemic control as seen by reductions in HbA1c and glucose levels, and increased time spent within target glucose range, with the cotadutide 100 and 300 µg doses being more effective at glucose lowering after 26 weeks' treatment than the cotadutide 600 µg dose.

[redacted]

Summary of safety results

The mean duration of actual exposure to IP was comparable across all treatment groups (range: 159.6 to 174.7 days) and the majority of participants in each treatment group had a cumulative actual exposure of ≥ 169 days.

The proportion of participants who experienced at least one AE was higher in the cotadutide total than placebo treatment group [redacted]. The same pattern was observed for AEs considered by investigator as possibly related to IP. Two deaths occurred in the study, both in cotadutide-treated participants, but were not considered by the investigator to be related to IP. Twenty-eight SAEs were reported by 24 participants, with the proportion of participants experiencing SAEs being balanced across the treatment groups. Three SAEs were assessed by investigator as possibly related to IP but occurred in the placebo [redacted] groups, and four led to discontinuation of IP (two in cotadutide-treated participants). The most common AEs in the cotadutide total treatment group were hypoglycaemia (28.5%), nausea (17.9%), and diarrhoea (11.9%). The frequency of participants experiencing hypoglycaemia was comparable across the cotadutide and placebo treatment groups [redacted] the event rate of hypoglycaemia was highest in the placebo treatment group. Data from continuous glucose monitoring (CGM), conducted across 26 weeks, showed no significant increase in time spent in hypoglycaemic or clinically significant hypoglycaemic ranges in cotadutide treatment groups. Most AEs were mild or moderate in intensity. Nausea and vomiting events were experienced by a higher percentage of participants in the cotadutide total versus placebo treatment group [redacted] Nausea and vomiting events increased with increasing dose of cotadutide [redacted]. Injection site reactions were experienced by a similar proportion of participants in the cotadutide total and placebo treatment groups; [redacted] All injection site reactions were mild and non-serious, though one (cotadutide 100 µg group) led to discontinuation of IP. One AE of obstructive pancreatitis was reported in a cotadutide-treated participant but assessed by investigator as not related to IP. No cases meeting potential Hy's Law or Hy's Law criteria were reported during the study. After 14 and 26 weeks' treatment, statistically significant reductions in systolic blood pressure (SBP), via ambulatory blood pressure monitoring (ABPM), were noted with cotadutide 600 µg compared with placebo, and statistically significant increases in pulse rate were noted on ABPM and office-based measures with cotadutide compared with placebo, [redacted].

Overall, the safety profile of cotadutide was similar to that of marketed GLP-1 agonists.

Conclusion(s)

- The primary endpoint was met for the cotadutide 300 and 600 µg dose levels, with significantly greater reductions in UACR from baseline being observed compared with placebo after 14 weeks' treatment. Secondary endpoints were also met, with sustained reductions in UACR compared with placebo after 26 weeks' treatment, significant reductions in body weight, and significant glycaemic control compared with placebo; the greater efficacy of the cotadutide 100 and 300 µg doses compared with the 600 µg dose in glucose lowering suggests increasing engagement of the glucagon receptor at the highest cotadutide dose.
- Overall, cotadutide administered SC once daily, titrated to doses of 100, 300, and 600 µg was well-tolerated; the cotadutide 600 µg dose level was less well tolerated than the 100 and 300 µg dose levels [redacted] Safety and tolerability data were consistent with previous cotadutide studies at 600 ug; cotadutide 100 and 300 ug doses were better tolerated in this study than in other cotadutide studies.
- Overall, efficacy and safety results for the cotadutide 300 and 600 µg dose demonstrate a positive benefit/risk profile in patients with CKD with T2DM, with results suggesting the optimal dose level may reside between ≥ 300 and ≤ 600 µg.