STUDY REPORT SYNOPSIS

DISCOVER CKD (D1843R00291)

An observational study collecting real-world data on patients with chronic kidney disease to assess: early treatment experience, treatment patterns, treatment effectiveness, patient outcomes and patient quality of life through prospective and retrospective data capture

Milestones:	Final protocol (v7.0): 07 November 2022 First patient in: 11 September 2019 Interim analysis: 04 November 2022 Last patient in: 30 June 2022 Last patient last visit (LPLV): 30 June 2023 Database Lock: 29 August 2023 Final study results: 09 October 2023 Final study report: 22 December 2023
Phase of development:	Not applicable
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This study was performed in compliance with Good Clinical Practice (GCP) and Good Pharmacoepidemiology Practice (GPP), including the archiving of essential documents.

Background/rationale: Chronic kidney disease (CKD) is a global health burden associated with adverse clinical consequences, some of which include cardiovascular disease, hyperkalaemia (HK), anaemia, hyperphosphataemia, increased cardiovascular mortality, oedema, and progression to end stage renal disease (ESRD) resulting in high healthcare costs and reduced health-related quality of life (HRQoL). As per Global Burden of Disease 2020, hypertension, impaired fasting plasma glucose, high body mass index (BMI), and a diet high

in sodium were quantified as the major risk factors for CKD. Risk for CKD also increases with age.

Chronic kidney disease describes abnormal kidney function and/or structure. It is classified into 5 stages. Global prevalence of CKD has been reported at 3.5%, 3.9%, 7.6%, 0.4%, and 0.1% for stages 1 to 5, respectively, but data relevant to the patient journey including HRQoL and diet on a global scale remain scarce.

The high prevalence and the extensive existing evidence that intervention is effective in reducing cardiovascular events demonstrates a need for initiatives that may slow the progression to ESRD and reduce cardiovascular-related events in CKD patients.

Currently, real-world data on the patient journey, including treatment patterns, HRQoL, and diet in CKD patients with anaemia or HK are limited. There is a need to fill this gap as well as understand the early experience of sodium zirconium cyclosilicate (Lokelma®), and dapagliflozin (Forxiga®) in a real-world CKD setting (including patient characteristics and changes in patient-reported information before and after therapy initiation), building data of interest across the AstraZeneca (AZ) portfolio and across key markets in order to facilitate the appropriate and effective treatment of patients.

Collecting/extracting patient data from several countries provided regional insights into the real-world practice patterns and clinical management of CKD patients in participating countries.

Objectives:

Primary Objective: The primary objective was to construct a multinational longitudinal cohort of patients with CKD that can be used for the generation of retrospective and prospective real-world data over 3 years to provide insight into the epidemiology of CKD by describing patient characteristics, disease progression, clinical outcomes, patient journey, practice patterns, and clinical management of CKD.

Secondary Objectives: Secondary objectives were related to country-specific descriptions of CKD (Stages 2, 3A, 3B, 4, 5, and ESRD), HK, anaemia, and diabetes status, as follows:

- Describe baseline (index) patient characteristics and comorbidities
- Describe clinical treatment practice, patterns, medications, and adherence
- Describe disease progression
- Describe clinical outcomes, hospitalisation, and mortality
- Describe patient-reported outcomes (PROs) including HRQoL, diet, physical activity, and other patient-reported outcomes (including set of questions to collect patient symptoms)
- Describe healthcare resource utilisation (HCRU) and cost (cost for retrospective data only)

- Describe and compare early treatment experiences by country, upon launch of roxadustat (Evrenzo™), sodium zirconium cyclosilicate (Lokelma), and dapagliflozin (Forxiga) (including patient characteristics and changes in patient-reported information before and after therapy), as well as effectiveness
  - Effectiveness examples: Does treatment with of roxadustat (Evrenzo™) improve and adequately control haemoglobin compared to therapies used as standard of care (SOC) in current practice, for example iron therapy? Does treatment with sodium zirconium cyclosilicate (Lokelma), adequately reduce and maintain normal potassium (K+) compared to therapies used as SOC in current practice, for example sodium polystyrene sulfonate?

Exploratory objectives: Exploratory objectives included utilising data captured to understand:

- Laboratory value (eg, haemoglobin and K+) monitoring and trajectories in CKD patients and how this differs between, for example, dialysis, non-dialysis, HK, anaemic, and diabetic status
- Risk factors (covariates captured at baseline and time-varying) associated with CKD progression, dialysis initiation, HK, anaemia, diabetes, and clinical outcomes (in dialysis and non-dialysis patients) in CKD patients
- The assessment (frequency [N] and percentages [%]) of patients using a mobile phone/tablet application and evaluating compliance (questionnaire completion)

Study design: DISCOVER CKD was an international, observational cohort study in CKD patients, comprising both prospective and retrospective patient cohorts. This study collected real-world data on patients with CKD from multiple countries including the United Kingdom (UK), Italy, United States (US), Sweden, Spain and Japan. This clinical study report describes only the prospective data collection and analysis in detail. Detailed results from the retrospective analyses were reported separately.

This study was largely descriptive in nature and utilised data collected under conditions of routine clinical care and did not test any specific *a priori* hypothesis. No additional invasive clinical tests or procedures were mandated per the study protocol. All data collected/extracted was based solely on observations of disease management and treatment decisions made between the treating physicians and their patients. Patients did not receive any intervention (experimental intervention or experimental treatment) as a result of participating in this study.

The current study report was developed using the umbrella protocol for the DISCOVER CKD study and the master statistical analysis plan (SAP). Targeted SAPs with specified tables, figures, listings, and statistical programming were developed for each specific objective described in the umbrella protocol. Within these targeted SAPs, the country/region was specified. Specific SAPs/protocol amendments were made and reviewed appropriately before activities were initiated.

Data source: Key prospective data were collected under conditions of routine clinical care.

Prospective data were collected/extracted through healthcare providers (HCPs) via manual health record extraction and also directly from patients.

Prospective data collection/extraction were performed as follows:

- The HCPs in the clinics used an electronic case report form (eCRF) to enter patients' data after their routine clinical visit using a web-based data capture (WBDC) system.
- Patient-reported outcomes (PROs), eg, HRQoL, were collected via completion of questionnaires (paper or electronic version) primarily via a mobile phone/tablet application. Patients could complete PRO assessments at home, or sometimes at the clinic during their visits, whatever was more convenient for them during the appropriate time window.
- Semi-structured qualitative interviews were conducted in a subset of patients (approximately 100 patients) to obtain in-depth CKD patient-specific information, including diagnosis journey, symptoms and impact, and treatment and experience of care and other patient-reported information. Detailed methods and results from these interviews were reported separately.

Given the non-interventional nature of the study, the HCPs were not required to perform all the tests or procedures reported in the eCRF but, only the ones done by the site as part of their routine clinical practice. No additional examination not considered as site's standard of care were performed specifically for the study. Therefore, there could have been fields in the eCRF that the sites were not able to complete, if it was not a part of their routine clinical practice and it differed between the sites.

Study population: For prospective data collection/extraction, the targeted sample size was approximately 1000 (no set maximum) CKD patients until the decision to stop the study was taken, with the possibility of prospective follow-up for a minimum of 1 year up to a maximum of approximately 3 years. A minimum of 100 patients (± 10%) were planned to be enrolled per country.

For prospective data collection/extraction, all individuals with CKD fulfilling the study inclusion criteria but none of the exclusion criteria were considered.

Inclusion criteria: For inclusion in the study, patients had to fulfil all the following criteria:

1 For all countries, except Japan: Male or female patients aged 18 years and over
For Japan: Male or female patients aged 20 years and over.

2 First documented diagnostic code (eg, ICD-10) of CKD (Stages 3A, 3B, 4, 5, or ESRD) or 2 measures of estimated glomerular filtration rate (eGFR) of < 75 mL/min/1.73 m^2 recorded at least 90 days apart on or after 1 January 2008, or a code for chronic renal replacement therapy (RRT) (eg, haemodialysis and peritoneal dialysis), whichever came first.

3 Provision of written informed consent – specific for prospective data capture

Exclusion criteria: Patients meeting any of the following criteria were not eligible to participate in the study:

1 Concurrent participation in any interventional trial at baseline (index) (prospective only). Note: Implemented based on local regulatory requirements
2 Patients undergoing treatment for active cancer, except for non-melanoma skin cancer (prospective only)
3 Patients with a life expectancy of less than 12 months (prospective only)
4 Diagnosis of cancer on or within the 1 year prior to index (retrospective only)
5 Less than 1-year registration/medical history (pre-index) (retrospective only)

Statistical methods: Statistical analysis plans with specified tables, figures, and listings, detailed statistical approaches and high-level description of analytical dataset were developed for each specific objective described in the protocol. Within these SAPs, the country/region was specified. The SAPs were prepared for individual research objectives prior to interim reports and final database lock. For all analytical datasets, details were described in a Data Management Plan. Publications (abstracts and manuscripts) were delivered periodically. After database lock, a full study report was delivered.

Different statistical and data processing software were used depending on what was better suited to the task at hand.

Summary statistics for continuous variables included the number of patients, mean, median, standard deviation (SD), 25^{th} and 75^{th} percentile values, and minimum and maximum values. For categorical variables, frequencies and percentages were provided. For time-to-event endpoints, Kaplan-Meier risk (%) curves, incidence rate, and all-events rate (per 100 person-years) were calculated, as appropriate. Missingness in variables and distribution of follow-up duration was presented. Estimates were accompanied by a 95% confidence interval (CI) as appropriate.

Results: A total of 1052 patients participated in the study. Overall, 78.8% of patients completed the study. The majority (63.1%) of patients were male and median age was 65 years. The majority of patients (81.9%) had public/governmental health insurance. Only 11.2% of patients were current smokers, while most patients (59.5%) were current alcohol drinkers. BMI was missing for many patients (37.4%). Among those with BMI available, 45.7% were in the obese category (BMI $\geq$ 30 kg/m^2). Overall, 12.5% of patients had history of HK, 33.3% of anaemia, 43.0% of diabetes, and 7.0% of heart failure; 72.4% of patients reported medical history of hypertension. The most common CKD aetiologies were type II diabetic nephropathy (23.4%), ischaemic/hypertensive nephropathy (19.1%) and immunoglobulin A (IgA) nephropathy (6.3%).

The majority of patients were in early-stage CKD (Stage 2-3), except in the UK where 50.8% were in advanced-stage CKD (Stage 4-5). Only 8.4% of patients were receiving dialysis at baseline. The median eGFR, which was 39.3 mL/min/1.73m^2 overall, was markedly lower in patients with advanced CKD (17.4 [advanced-stage] versus 45.9 [early-stage]). Overall, 58.7% of patients were on at least one renin-angiotensin-aldosterone system inhibitor (RAASi) at baseline, which varied by country from 41.7% in the US to 81.1% in Sweden. Over half of patients received at least one anti-lipid therapy at baseline. Other common classes of medications included antihypertensive (other than RAASi), anti-acidic, anti-diabetic, and antiplatelet therapies. Sodium-glucose cotransporter-2 inhibitors were among the most common anti-diabetic therapies with 14.0% of patients receiving at least one at baseline. Only [redacted] patients received roxadustat and [redacted] received sodium zirconium cyclosilicate (at Month 12).

Nearly one-fourth (23.5%) of patients experienced CKD progression by Month 12. Patients with early-stage CKD were found to be at lower risk of all-cause mortality (HR 0.26, 95% CI 0.10 to 0.61, p = 0.003) than patients with advanced-stage CKD. Additionally, patients with early-stage CKD were found to be at a lower risk of new initiation of dialysis (HR 0.04, 95% CI 0.01 to 0.16, p < 0.001) than patients with advanced-stage CKD. In general, HCRU was higher in patients with advanced-stage CKD compared to patients with early-stage CKD.

For all PROs, data were missing for more than half of patients at baseline and around three-fourths of patients at Month 12. Where data were available, patients with advanced-stage CKD reported greater work productivity impairment, less physical activity, worse HRQoL, and greater symptom burden compared to patients with early-stage CKD.

Interpretation of both the retrospective and qualitative patient interview results is reported separately.

Conclusion: DISCOVER CKD provided a comprehensive examination of the epidemiology and treatment of CKD and furthered understanding of the burden of the disease on patients and healthcare systems. The study highlighted the disparate effects of CKD depending on demographics, healthcare systems, and comorbidities.

Publications:

- Pollock C, Sanchez JJG, Carrero JJ, Kumar S, Pecoits-Filho R, Lam CSP, Chen H, Kanda E, Lainscak M, Wheeler DC. Glucose-lowering treatment pathways of individuals with chronic kidney disease and type 2 diabetes according to the Kidney Disease: Improving Global Outcomes 2012 risk classification. Diabet Med. 2023 Aug 14:e15200. Doi: 10.1111/dme.15200. Epub ahead of print. PMID: 37578188.
- Kumar S, Arnold M, James G, Padman R. Developing a common data model approach for DISCOVER CKD: A retrospective, global cohort of real-world patients with chronic kidney disease. PLoS One. 2022 Sep 29;17(9):e0274131. doi: 10.1371/journal.pone.0274131. PMID: 36173958; PMCID: PMC9521926.

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- Pollock C, James G, Garcia Sanchez JJ, Carrero JJ, Arnold M, Lam CSP, Chen HT, Nolan S, Pecoits-Filho R, Wheeler DC. Healthcare resource utilisation and related costs of patients with CKD from the UK: a report from the DISCOVER CKD retrospective cohort. Clin Kidney J. 2022 Jul 26;15(11):2124-2134. doi: 10.1093/ckj/sfac168. PMID: 36325010; PMCID: PMC9613420.
- Garcia Sanchez JJ, James G, Carrero JJ, Arnold M, Lam CSP, Pollock C, Chen HT, Nolan S, Wheeler DC, Pecoits-Filho R. Health Care Resource Utilization and Related Costs of Patients With CKD From the United States: A Report From the DISCOVER CKD Retrospective Cohort. Kidney Int Rep. 2023 Feb 3;8(4):785-795. doi: 10.1016/j.ekir.2023.01.037. PMID: 37069994; PMCID: PMC10105052.