NHS National Institute for Health Research

NIHR Innovation Observatory
Evidence Briefing: May 2018

Roxadustat for renal anaemia in chronic kidney disease

NIHRIO (HSRIC) ID: 8576 NICE ID: 8380

LAY SUMMARY

One develops anaemia when their circulating level of red blood cells are low, meaning inadequate oxygen is delivered to the various tissues in the body. Anaemia is caused by multiple factors. However, the shortage of iron is the most common. Anaemia of chronic kidney disease (CKD) is caused either by low levels of a hormone principally produced in the kidneys called erythropoietin (EPO for short), or by the disease process causing less iron from the gut to be available for use by the body. EPO, when released by the kidney, stimulates the bone marrow in the body to produce red blood cells. In CKD, low levels of EPO cause poor functioning of this pathway, often thereby causing anaemia. Possible adverse effects of anaemia include fatigue, increased cardiac output, heart failure, reduced cognition and concentration, reduced libido and reduced immune responsiveness.

Roxadustat is a product in development that can be taken orally as a tablet. It has the potential to stimulate the growth of red blood cells by increasing the body's own production of EPO in patients with CKD who may be on dialysis or pre-dialysis. If approved for the treatment of anaemia in this population, roxadustat will provide an alternative treatment option that offers a likely reduction in the need for supplemental iron as an advantage.

This briefing reflects the evidence available at the time of writing. A version of the briefing was sent to the company for a factual accuracy check. The company was available to provide comment. It is not intended to be a definitive statement on the safety, efficacy or effectiveness of the health technology covered and should not be used for commercial purposes or commissioning without additional information.

This briefing presents independent research funded by the National Institute for Health Research (NIHR). The views expressed are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health.

TARGET GROUP

Renal anaemia associated with chronic kidney disease in patients not on dialysis and on dialysis.

TECHNOLOGY

DESCRIPTION

Roxadustat (ASP1517; FG4592) is a hypoxia-inducible factor prolyl hydroxylase inhibitor (HIF-PHI), with potential to increase endogenous EPO stores and therefore treat anaemia. Upon administration, roxadustat binds to and inhibits HIF-PHI, an enzyme responsible for the degradation of transcription factors in the HIF family, under normal oxygen conditions. This prevents HIF breakdown and promotes HIF activity. Increased HIF activity leads to an increase in endogenous erythropoietin production, thereby enhancing erythropoiesis. It also reduces the expression of the peptide hormone hepcidin, thereby improving iron bioavailability and boosting haemoglobin (Hb) levels. HIF regulates the expression of a number of genes in response to reduced oxygen levels, including genes required for erythropoiesis and iron metabolism.[1, 2]

Roxadustat monotherapy is administered orally and is under development for the treatment of anaemia associated with chronic kidney disease (CKD) in both patients requiring and not requiring dialysis. Currently, there are a number of concurrently ongoing phase III trials involving dialysis and non-dialysis patients, with the dose of administration in these trials varying according to participant characteristics. The treatment schedule in the phase III trials are detailed in the clinical trial data tables ('efficacy and safety' section) of this report.

Roxadustat does not currently have Marketing Authorisation in the EU for any indication. A paediatric investigation plan has been agreed by the European Medicines Agency for the treatment of anaemia due to chronic disorders in children aged 6 months to 18 years.[3]

INNOVATION and/or ADVANTAGES

If licenced, roxadustat will offer an additional treatment option for people with CKD that experience anaemia and may or may not have dialysis for their kidney disease. Preclinical studies show that roxadustat increases production of endogenous EPO, increases iron mobilization and utilization, and overcomes the suppressive effects of inflammation on red blood cell production.[1] Furthermore, treatment with roxadustat would likely result in reduced need for supplemental iron.[4]

DEVELOPER

Astellas Pharma Ltd

PATIENT GROUP

BACKGROUND

Red blood cells carry oxygen using a protein called Haemoglobin (Hb). A person develops anaemia when their levels of red blood cells are low and not enough oxygen gets to the tissues. Symptoms of anaemia include feeling tired and shortness of breath. Anaemia is often caused by a shortage of iron

(called iron deficiency) because iron is used to make red blood cells.[5] Anaemia is a common complication of chronic kidney disease (CKD). It is associated with left ventricular dysfunction and heart failure, in addition to a reduction in exercise capacity and quality of life.[6]

CKD, also known as chronic renal failure, is defined by either a pathological abnormality of the kidney, such as haematuria and/or proteinuria, or a reduction in the glomerular filtration rate (GFR) to <60 mL/minute/1.73 m^2 for ≥3 months' duration.[7] It is divided into five stages which increase in severity. Stages 3 to 5 are classified as moderate to severe CKD and stage 5 may require renal replacement therapy (RRT).[8] It is common, frequently unrecognised and often exists together with other conditions, for example, cardio vascular disease (CVD) and diabetes.[9]

Anaemia in CKD is mainly caused by low levels of a hormone called erythropoietin (EPO). The kidneys synthesize EPO, which stimulates the production of red blood cells. EPO levels can be low in patients with CKD resulting in anaemia.[5]

Possible adverse effects of anaemia include fatigue, increased cardiac output, left ventricular hypertrophy, reduced cognition and concentration, reduced libido and reduced immune responsiveness.[10]

A reduced health-related quality of life and increased mortality rates are associated with the evolution of CKD.[11] In particular, negative mental health, e.g. depression, high psychological distress and psychiatric disorders are prevalent amongst CKD patients.[11]

CLINICAL NEED and BURDEN OF DISEASE

CKD is recognised as a global public health problem.[8] In the UK, stage 3-5 CKD, an eGFR less than 60 mL/min/1.73 m^2, has been widely used in prevalence estimates. The Health Survey for England (HSE) 2009 reported a prevalence of CKD in the general adult population of 14% in males and 13% in females.[8]

For CKD stage 3-5, the HSE 2010 report estimated that 6% of men and 7% of women (aged ≥16 years) based on eGFR levels. This was a nationally representative, population-based study on the prevalence of CKD in England using laboratory measures calibrated to allow use of Modification of Diet in Renal Disease (MDRD) to estimate GFR. By applying the HSE prevalence estimate to the 2016 population of England, as recorded by the Office for National Statistics (ONS), there are a total of 2,647,278 men in England with stage 3-5 CKD and 3,088,491 women.[12]

In the US, the National Health and Nutrition Examination Survey (NHANES) III study showed that the prevalence of anaemia increases as eGFR falls. Data collected in 2007-2010 showed that anaemia was twice as prevalent in people with CKD (15.4%) as it was in the general population (7.6%). The prevalence increased with the stage of CKD, from 8.4% at stage 1 to 53.4% at stage 5.[13]

Prevalence data for anaemia in CKD patients not on dialysis for England has not been identified. However, a recently published cross-sectional survey in clinical settings across five European countries, including the UK, suggested that out of 1,993 patients diagnosed with stage 3-4 CKD that didn't need dialysis, anaemia treatment was prescribed in 35% of the patients and those patients tended to be older and more likely to be male.[14]

The UK Renal Registry 19th annual edition reported the median Hb of patients at the time of starting dialysis in the UK in 2015 was 98 g/L; the median Hb of prevalent patients on haemodialysis (HD) was

110 g/L (IQR 101–119) and 112 g/L (IQR 103–120) in patients receiving peritoneal dialysis (PD).[15] According to this report, in England, the estimated percentage of HD patients that received ESA treatment was 88% (~16,290) and 69% (~1,694) in PD patients.[15]

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE guideline. Chronic kidney disease: managing anaemia (NG8). June 2015.
- NICE clinical guideline. Chronic kidney disease in adults: assessment and management (CG182). July 2014.
- NICE quality standard. Chronic kidney disease in adults (QS5). March 2011.

NHS ENGLAND and POLICY GUIDANCE

- NHS England. 2013/14 NHS Standard Contract for Specialised Services for Haemoglobinopathy care (All Ages). B08/S/a.

OTHER GUIDANCE

- Kerr, Marion. Chronic kidney disease in England: The human and financial cost. NHS: Kidney Care.[16]
- KDIGO: Kidney Disease Improving Global Outcomes. August 2012.[17]

CURRENT TREATMENT OPTIONS

In England, NICE guidelines recommend the initiation of ESA (erythropoietic stimulating agent) in combination with iron supplementation in people with CKD and anaemia. NICE establishes that, in this population group, the serum ferritin levels should not rise above 800 micrograms/litre.[10]

There are a number of different ESA treatment available such as epoetin alfa and darbepoetin alfa, NICE recommends to discuss the choice of ESA with the person with anaemia of CKD when initiating treatment and at subsequent review, taking into consideration the patient's dialysis status, the route of administration and the local availability of ESAs.

There is no evidence to distinguish between ESAs in terms of efficacy.[10] Intravenous or subcutaneous forms of administrations may be recommended depending on the CKD stage and whether the patients are receiving hemofiltration or hemodiafiltration therapy.[17]

EFFICACY and SAFETY

Trial	**ALPS, NCT01887600; phase III, roxadustat *versus* placebo**
Sponsor	Astellas Pharma
Status	Complete, unpublished
Source of Information	Trial registry[18, 19]
Location	EU (inc. UK), South America, Russia, South Africa
Design	Randomised; placebo-controlled
Participants	n= 597; aged 18 and older; diagnosis of chronic kidney disease, with Kidney Disease Outcomes Quality Initiative (KDOQI) Stage 3, 4 or 5, not receiving dialysis; three most recent Hb values during the Screening period, obtained at least 4 days apart, must be less than or equal to 10.0 g/dL; ferritin level greater than or equal to 30 ng/mL (greater than or equal to 67.4 pmol/L) at screening.
Schedule	Randomised to Roxadustat dosed three times weekly during correction period and three times weekly during the maintenance period. Dose adjustments will be made during the study; or, placebo three times weekly during correction period and three times weekly during the maintenance period.
Follow-up	Active treatment for 52 weeks up to a maximum of 104 weeks, follow-up period of 4 weeks.
Primary Outcomes	• Haemoglobin (Hb) response to treatment with Roxadustat without the use of rescue therapy [Time Frame: Up to week 24] • Change in Hb from Baseline (BL) to the average level regardless of rescue therapy [Time Frame: Baseline and week 28 to week 52]
Secondary Outcomes	• Hb maintenance: Hb maintenance: Hb change from BL to the average Hb, without having received rescue therapy within 6 weeks prior to and during the 8-week evaluation period (weeks 28 to 36) [Time Frame: Baseline and weeks 28 to 36] • Change from BL in low-density lipoprotein (LDL) cholesterol to the average value of LDL cholesterol [Time Frame: Baseline and weeks 12 to 28] • Use of rescue therapy [Time Frame: Up to 24 weeks] • Time to use of rescue therapy [Time Frame: Up to 24 weeks] • Change from BL in Short Form (SF)-36 Physical Functioning (PF) sub-score to the average SF-36 PF sub-score [Time Frame: Baseline and weeks 12 to 28] • Change from BL in SF-36 Vitality (VT) sub-score to the average SF-36 VT sub-score [Time Frame: Baseline and weeks 12 to 28] • Change from BL in Mean Arterial Pressure (MAP) to the average MAP [Time Frame: Baseline and weeks 20 to 28] • Occurrence of hypertension [Time Frame: Up to week 108] • Time to occurrence of hypertension [Time Frame: Up to week 108] • Hb averaged over weeks 28-36, without use of rescue therapy within 6 weeks prior to and during the evaluation period [Time Frame: Up to week 36]

	• Time to achieve the first Hb response as defined by primary endpoint [Time Frame: Up to week 24] • Hb change from BL to each post-dosing time point [Time Frame: Baseline up to End of Study (EOS) (Up to week 108)] • Hb level averaged over weeks 44-52, without use of rescue therapy within 6 weeks prior to and during the evaluation period [Time Frame: Up to week 52] • Hb change from BL to the average Hb value, regardless of the use of rescue therapy [Time Frame: Baseline, week 28 to week 36 and week 44 to week 52] • Proportion of Hb values within 10.0-12.0 g/dL in weeks 28-36, without use of rescue therapy within 6 weeks prior to and during the 8-week evaluation period [Time Frame: Up to week 36] • Occurrence of hospitalization [Time Frame: Up to End of Treatment (EOT) (Up to week 104)] • Number of days of hospitalization [Time Frame: Up to End of Treatment (EOT) (Up to week 104)] • Number of subjects having received RBC transfusions [Time Frame: Up to End of Treatment (EOT) (Up to week 104)] • Number of RBC packs per subject [Time Frame: Up to End of Treatment (EOT) (Up to week 104)] • Volume of RBC transfused per subject [Time Frame: Up to End of Treatment (EOT) (Up to week 104)] • Number of subjects having received IV iron therapy [Time Frame: Up to End of Treatment (EOT) (Up to week 104)] • Number of Erythropoiesis-Stimulating Agent (ESA)-week dose per subject [Time Frame: Up to End of Treatment (EOT) (Up to week 104)] • Change from BL to each post-dosing visit in total cholesterol [Time Frame: Baseline up to End of Study (EOS) (Up to week 108)] • Change from BL to each post-dosing visit in low density lipoprotein (LDL)/high-density lipoprotein (HDL) ratio [Time Frame: Baseline up to End of Study (EOS) (Up to week 108)] • Change from BL to each post-dosing visit in non-HDL cholesterol [Time Frame: Baseline up to End of Study (EOS) (Up to week 108)] • Occurrence of mean LDL cholesterol < 100 mg/dLdL (mean LDL calculated over weeks 12-28 of treatment) [Time Frame: Up to week 28] • Occurrence of achieved antihypertensive treatment goal in CKD subjects (SBP < 130 mmHg and DBP < 80 mmHg) based on the mean SBP and mean DBP calculated over weeks 12-28 of treatment with study drug [Time Frame: Up to week 28] • Change from BL to the average value in Physical Component Score of SF-36 [Time Frame: Baseline and weeks 12 to 28] • Change from BL to the average value in Anaemia Subscale ("Additional Concerns") of Functional Assessment of Cancer Therapy-Anaemia (FACT-An) Score [Time Frame: Baseline and weeks 12 to 28] • Change from BL to the average value in Total FACT-An Score [Time Frame: Baseline and weeks 12 to 28]

	• Change from BL to the average value in Health Related Quality of Life Questionnaire consisting of Five Levels (EQ-5D 5) visual analogue scale (VAS) Score [Time Frame: Baseline and weeks 12 to 28] • Patients' Global Impression of Change (PGIC) [Time Frame: Up to End of Treatment (EOT) (Up to week 104)] • Changes from BL to each study visit in hepcidin [Time Frame: Baseline up to End of Study (EOS) (Up to week 108)] • Changes from BL to each study visit in HbA1c [Time Frame: Baseline up to End of Study (EOS) (Up to week 108)] • Time to first occurrence of serum Cr having doubled during study [Time Frame: Up to End of Study (EOS) (Up to week 108)] • Occurrence of ESRD [Time Frame: Up to End of Study (EOS) (Up to week 108)] • Safety assessed by nature, frequency, and severity of Adverse Events (AEs) [Time Frame: Up to End of Study (EOS) (Up to week 108)] • Safety assessed by nature, frequency, and severity of Serious Adverse Events (SAEs) [Time Frame: Up to End of Study (EOS) (Up to week 108)] • Number of participants with vital signs abnormalities and/or adverse events related to treatment [Time Frame: Up to End of Study (EOS) (Up to week 108)] • Safety assessed by 12- lead electrocardiogram (ECG) [Time Frame: Up to End of Study (EOS) (Up to week 108)] • Number of participants with laboratory value abnormalities and/or adverse events related to treatment [Time Frame: Up to End of Study (EOS) (Up to week 108)] • Changes from BL to each study visit in serum ferritin [Time Frame: Baseline up to End of Study (EOS) (Up to week 108)] • Changes from BL to each study visit in Transferrin Saturation (TSAT) [Time Frame: Baseline up to End of Study (EOS) (Up to week 108)] • Changes from BL to each study visit in estimated Glomerular Filtration Rate (eGFR), including eGFR slope over time [Time Frame: Baseline up to End of Study (EOS) (Up to week 108)] • Changes from BL to each study visit in urine albumin/Creatinine (Cr) ratio [Time Frame: Baseline up to End of Study (EOS) (Up to week 108)] • Changes from BL to each study visit in fasting blood glucose [Time Frame: Baseline up to End of Study (EOS) (Up to week 108)] • Change from BL to each post-dosing visit in Apolipoproteins (Apo) A1 [Time Frame: Baseline up to End of Study (EOS) (Up to week 108)] • Change from BL to each post-dosing visit in Apolipoproteins B (ApoB) [Time Frame: Baseline up to End of Study (EOS) (Up to week 108)] • Change from BL to each post-dosing visit in ApoB/ApoA1 ratio [Time Frame: Baseline up to End of Study (EOS) (Up to week 108)]

Key Results	Not reported
Adverse effects (AEs)	Not reported
Expected reporting date	Study completion date previously reported as Nov 2017

Trial	**NCT01750190; phase III, roxadustat *versus* placebo**
Sponsor	FibroGen
Status	Active, not recruiting
Source of Information	Trial registry[19, 20]
Location	USA, South East Asia, South America, Australia
Design	Randomised; placebo-controlled
Participants	n= 922 (planned); aged 18 and older; Chronic kidney disease, Stage 3, 4, or 5, not receiving dialysis; anaemia qualified by measurements of haemoglobin values during screening.
Schedule	Randomised to Roxadustat weight-based starting doses of 70mg or 100mg; dose adjustments to haemoglobin levels are allowed during the study; or, placebo weight-based starting doses of 70mg or 100mg; dose adjustments to haemoglobin levels are allowed during the study.
Follow-up	Active treatment may be for less than 52 weeks with a maximum treatment duration up to 156 weeks, follow-up period of 4 weeks.
Primary Outcomes	• Efficacy of roxadustat (FG-4592) for the treatment of anaemia correction and maintenance. [Time Frame: 52 weeks] • Efficacy of roxadustat (FG-4592) in achieving haemoglobin correction and maintenance (as defined in protocol) in CKD subjects not on dialysis
Secondary Outcomes	• Change in low-density lipoprotein (LDL) cholesterol • Health-related quality of life benefits, as measured by the SF-36 • Proportion of patients who received rescue therapy (composite of RBC transfusion, ESA use, and IV iron) • Change in mean arterial pressure and effect on reducing hypertension • Adverse events, serious adverse events, vital signs, electrocardiograms and physical exams
Key Results	Not reported
Adverse effects (AEs)	Not reported
Expected reporting date	Study completion date reported as March 2018

Trial	DOLOMITES, NCT02021318; phase III, roxadustat *versus* darbepoetin alfa
Sponsor	Astellas Pharma
Status	Active, not recruiting
Source of Information	Trial registry[19, 21]

Location	EU (inc. UK) and Russia
Design	Randomised; active-controlled
Participants	n= 616 (planned); aged 18 and older; Chronic kidney disease, Stage 3, 4, or 5, not receiving dialysis; with an Estimated Glomerular Filtration Rate (eGFR) <60 mL/min/1.73 m^2 estimated using the abbreviated 4-variable Modification of Diet in Renal Disease (MDRD) equation; Hb values during the screening period, obtained at least 4 days apart, must be less than or equal to 10.5 g/dL.
Schedule	Randomised to Roxadustat dosed three times weekly (TIW) during correction period, and TIW during the maintenance period. Dose adjustments are allowed during the study; or, darbepoetin alfa subcutaneous or intravenous injection dosed per European Summary of Product Characteristics (SmPC)
Follow-up	Active treatment for 104 weeks, follow-up period of 4 weeks.
Primary Outcomes	• Haemoglobin (Hb) response to treatment [Time Frame: Up to week 24]
Secondary Outcomes	• Hb change from baseline (BL) to the average Hb, without having received rescue therapy within 6 weeks prior to and during this 8-week evaluation period [Time Frame: Baseline and weeks 28 to 36] • Change from BL in Low Density Lipoprotein (LDL) cholesterol to the average LDL cholesterol [Time Frame: Baseline and weeks 12 to 28] • Mean monthly intravenous(ly) (IV) iron (mg) use per subject [Time Frame: Up to week 36] • Monthly is defined as a period of 4 weeks • Change from BL in Short Form 36 (SF-36) Physical Functioning (PF) sub-score to the average PF sub-score [Time Frame: Baseline and weeks 12 to 28] • Change from BL in SF-36 Vitality (VT) sub-score to the average VT sub-score [Time Frame: Baseline and weeks 12 to 28] • Change from BL in mean arterial pressure (MAP) to the average MAP value [Time Frame: Baseline and weeks 20 to 28] • Occurrence of hypertension [Time Frame: Up to week 36] • Defined as either Systolic Blood Pressure (SBP) >170 mmHg and an increase from BL of greater than or equal to 20 mmHg SBP or Diastolic Blood Pressure (DBP) >110 mmHg and an increase from BL of greater than or equal to 15 mmHg DBP on 2 consecutive visits • Time to occurrence of hypertension [Time Frame: Up to week 36] • Hb change from BL to the average Hb value regardless of rescue therapy [Time Frame: Baseline and weeks 28 to 52] • Time (weeks) to achieve the first Hb response as defined by primary endpoint [Time Frame: Up to week 24] • Hb response [Time Frame: Up to week 24] • Hb response defined as: Hb greater than or equal to 11.0 g/dL and a Hb increase from BL Hb by greater than or equal to 1.0 g/dL in any subject with BL Hb > 8.0 g/dL, or an increase from BL Hb by greater than or equal to 2.0 g/dL in any subject with BL Hb less than or equal to 8.0 g/dL as measured at 2 consecutive visits separated by at least 5 days, during the first 24 weeks of treatment regardless of administration of rescue therapy prior to Hb response • Hb averaged over weeks 28 to 36, 44 to 52, 72 to 80, 96 to 104, without use of rescue therapy within 6 weeks prior to and during this evaluation period [Time Frame: Up to week 104]

	• Hb value to each post-dosing time point [Time Frame: Up to End of Study (EOS) (Up to week 108)] • Hb change from BL to each post-dosing time point [Time Frame: Baseline up to End of Study (EOS) (Up to week 108)] • Hb change from BL to the average Hb value regardless of the use of rescue therapy [Time Frame: Baseline, weeks 28 to 36, weeks 44 to 52, weeks 72 to 80, weeks 96 to 104] • Proportion of Hb values within 10.0 to 12.0 g/dL in weeks 28 to 36, 44 to 52, 72 to 80, 96 to 104, without use of rescue therapy within 6 weeks prior to and during the 8-week evaluation period [Time Frame: Up to week 104] • Occurrence (number) of hospitalization(s) [Time Frame: Up to End of Treatment (EOT) (Up to week 104)] • Number of days of hospitalization [Time Frame: Up to End of Treatment (EOT) (Up to week 104)] • Number of subjects having received rescue therapy (composite of red blood cell (RBC) transfusions (all subjects) and darbepoetin alfa use (roxadustat treated subjects only) [Time Frame: Up to End of Treatment (EOT) (Up to week 104)] • Number of subjects having received RBC transfusions [Time Frame: Up to End of Treatment (EOT) (Up to week 104)] • Number of RBC packs per subject [Time Frame: Up to End of Treatment (EOT) (Up to week 104)] • Volume of RBC transfused per subject [Time Frame: Up to End of Treatment (EOT) (Up to week 104)] • Change from BL to each scheduled measurement in total cholesterol [Time Frame: Baseline up to End of Study (EOS) (Up to week 108)] • Change from BL to each scheduled measurement in low density lipoprotein (LDL)/high-density lipoprotein (HDL) ratio [Time Frame: Baseline up to End of Study (EOS) (up to week 108)] • Change from BL to each scheduled measurement in non-HDL cholesterol [Time Frame: Baseline up to End of Study (EOS) (Up to week 108)] • Change from BL to each scheduled measurement in Apolipoproteins (Apo) A1 [Time Frame: Baseline up to End of Study (EOS) (Up to week 108)] • Change from BL to each scheduled measurement in Apolipoproteins B (ApoB) [Time Frame: Baseline up to End of Study (EOS) (Up to week 108)] • Change from BL to each scheduled measurement in ApoB/ApoA1 ratio [Time Frame: Baseline up to End of Study (EOS) (Up to week 108)] • Occurrence of mean LDL cholesterol < 100 mg/dL (mean LDL calculated over weeks 12 to 28, and weeks 36 to 52 of treatment) [Time Frame: Up to week 52] • Occurrence of achieved anti-hypertensive treatment goal (SBP < 130 mmHg and DBP< 80 mmHg) based on the mean SBP and mean DBP calculated over weeks 12 to 28 and 36 to 52 of treatment with study drug [Time Frame: Up to week 52] • Change from BL to the average value in Physical Component Score (PCS) of SF-36 [Time Frame: Baseline, weeks 12 to 28 and weeks 36 to 52]

	• Change from BL to the average value in Anaemia Subscale ("Additional Concerns") of Functional Assessment of Cancer Therapy-Anaemia (FACT-An) Score [Time Frame: Baseline, weeks 12 to 28 and weeks 36 to 52] • Change from BL to the average value in Total FACT-An Score [Time Frame: Baseline, weeks 12 to 28 and weeks 36 to 52] • Change from BL to the average value in Health Related Quality of Life Questionnaire consisting of Five Levels (EQ-5D 5) visual analogue scale (VAS) Score [Time Frame: Baseline, weeks 12 to 28 and weeks 36 to 52] • Change from BL to the average value in Work Productivity and Activity Impairment-Anaemic Symptoms (WPAI:ANS) score [Time Frame: Baseline, weeks 12 to 28 and weeks 36 to 52] • Patients' Global Impression of Change (PGIC) [Time Frame: Up to End of Treatment (EOT) (up to Week 104)] • Change from BL to each scheduled measurement serum ferritin [Time Frame: Baseline up to End of Study (EOS) (Up to week 108)] • Change from BL to each scheduled measurement in Transferrin Saturation (TSAT) [Time Frame: Baseline up to End of Study (EOS) (Up to week 108)] • Change from BL to each scheduled measurement in HbA1c [Time Frame: Baseline up to End of Study (EOS) (Up to week 108)] • Haemoglobin A1c glycated haemoglobin (HbA1c) level • Change from BL to each scheduled measurement in fasting blood glucose [Time Frame: Baseline up to End of Study (EOS) (Up to week 108)] • Change from BL to each scheduled measurement in Estimated Glomerular Filtration Rate (eGFR), including eGFR slope over time [Time Frame: Baseline up to End of Study (EOS) (Up to week 108)] • Change from BL to each scheduled measurement in Urine albumin/creatinine ratio (UACR) [Time Frame: Baseline up to End of Study (EOS) (Up to week 108)] • Time to first of occurrence of serum creatinine having doubled during study in comparison with baseline [Time Frame: Up to End of Study (EOS) (Up to week 108)] • Occurrence of ESRD [Time Frame: Up to End of Study (EOS) (Up to week 108)] • End Stage Renal Disease (ESRD) • Safety assessed by nature, frequency, and severity of Treatment Emergent AEs (TEAEs) [Time Frame: Up to End of Study (EOS) (Up to week 108)] • Number of participants with laboratory value abnormalities and/or adverse events related to treatment [Time Frame: Up to End of Study (EOS) (Up to week 108)] • Number of participants with vital signs abnormalities and/or adverse events related to treatment [Time Frame: Up to End of Study (EOS) (Up to week 108)] • Safety assessed by 12- lead electrocardiogram (ECG) [Time Frame: Up to End of Study (EOS) (Up to week 108)] • Local 12-lead ECGs will be performed on all subjects at specific time points

	• Occurrence of prespecified adjudicated cardiovascular events [Time Frame: Up to End of Study (EOS) (Up to week 108)] • Occurrence of prespecified adjudicated cerebrovascular events [Time Frame: Up to End of Study (EOS) (Up to week 108)]
Key Results	Not reported
Adverse effects (AEs)	Not reported
Expected reporting date	Study completion date reported as October 2018

Trial	**OLYMPUS, NCT02174627; phase III, roxadustat *versus* placebo**
Sponsor	AstraZeneca
Status	Active, not recruiting
Source of Information	Trial registry[19, 22]
Location	North America, South America, Europe (not inc. UK), South Asia, Russia
Design	Randomised; placebo-controlled
Participants	n= 2700 (planned); aged 18 and older; Chronic kidney disease, Stage 3, 4, or 5, not receiving dialysis; with an Estimated Glomerular Filtration Rate (eGFR) <60 mL/min/1.73 m^2 estimated using the abbreviated 4-variable Modification of Diet in Renal Disease (MDRD) equation; Mean of 2 most recent central laboratory haemoglobin (Hb) values during the screening period, obtained at least 7 days apart, must be <10.0 g/dL.- Ferritin ≥50 ng/mL at randomization.
Schedule	Randomised to Roxadustat 70 mg three times a week (TIW). The dose is subsequently adjusted to achieve and maintain Hb 11±1 g/dL.; or, placebo 70 mg three times a week (TIW). The dose is subsequently adjusted to achieve and maintain Hb 11±1 g/dL.
Follow-up	N/R
Primary Outcomes	• Major adverse cardiovascular (CV) events (MACE) • The number from randomization to the first occurrence of any of the components of the primary composite endpoints.
Secondary Outcomes	• Mean change in Haemoglobin (Hb) from baseline to the end of treatment period • Proportion of total time of Hb measurements within the interval of 11±1 g/dL • MACE+: Time to first occurrence of all-cause mortality or non-fatal myocardial infarction (MI) or non-fatal stroke, heart failure requiring hospitalization or unstable angina leading to hospitalization. • Time to first occurrence of all-cause mortality or MI, stroke or heart failure requiring hospitalization, unstable angina leading to hospitalization, deep vein thrombosis, pulmonary embolism, vascular access thrombosis or hypertensive emergency • Time-to-first instance of receiving intravenous (IV) iron, red blood cell (RBC) transfusions or erythropoietin analogue as rescue therapy • Change in estimated glomerular filtration rate (eGFR) • Changes in anaemia symptoms and four disease-specific Health Related Quality of Life (HRQoL) domains as measured by the FACT-An. • Changes in generic HRQoL as measured by the Short Form 36 (SF-36)

	• Changes in self-reported health status as measured by the EuroQol Health Utility Index-5-dimensional-5-level (EQ-5D-5L) and Patients' Global Impression of Change (PGIC) • Adverse events (AEs), serious adverse events (SAEs) and changes in vital signs, electrocardiogram (ECG) and laboratory values.
Key Results	Not reported
Adverse effects (AEs)	Not reported
Expected reporting date	Study completion date reported as Sep 2018

Trial	**HIMALAYAS, NCT02052310; phase III, roxadustat *versus* epoetin alfa**
Sponsor	FibroGen
Status	Ongoing, recruiting
Source of Information	Trial registry[19, 23]
Location	UK, Eastern Europe, Western Europe, North America, South America, and Asia
Design	Randomised; active-controlled
Participants	n= 900 (planned); aged 18 and older; Patients who are new to dialysis, defined by receiving hemodialysis or peritoneal dialysis for end-stage renal disease for a minimum of 2 weeks and a maximum of 4 months, can be included in this study. Patients are excluded if they have received erythropoiesis-stimulating agent treatment within 12 weeks prior to participating in the study.
Schedule	Randomised to roxadustat dosed orally three times a week; or, epoetin alfa dispensed per the package insert or the country-specific product labelling.
Follow-up	Screening period of up to 6 weeks, active treatment period of a minimum of 52 weeks and a maximum of approximately up to 3 years after last patient is randomized, and a post-treatment follow-up period of 4 weeks.
Primary Outcomes	• U.S.A.: Mean Haemoglobin (Hb) change from baseline to average levels from Week 28 to Week 52. • Ex-U.S.A.: Proportion of subjects who achieve a Hb response during the first 24 weeks of treatment. [Time Frame: Minimum of 52 weeks and maximum of up to 3 years after last subject is randomized]
Secondary Outcomes	• U.S.A.: Proportion of subjects who achieve a Haemoglobin (Hb) response • Ex-U.S.A.: Mean Hb change from baseline to average levels oA Hb response is defined as: Hb ≥11.0g/dL and an Hb increase from baseline by ≥1.0g/dL in subjects whose baseline Hb >8.0g/dL, or Increase in Hb ≥2.0g/dL in subjects whose baseline Hb ≤8.0g/dL. • Average monthly IV iron use per subject during the Treatment Period. • Mean change in low-density lipoprotein (LDL) cholesterol. • Proportions of patients with exacerbation of hypertension, meeting at least one of the following criteria: oAn increase from baseline in sBP of ≥ 20 mm Hg and sBP >170 mmHg, or an increase from baseline in dBP of ≥ 15 mm Hg and dBP>100 mmHg • Time to achieve first Hb response as defined by the primary endpoint (ex-U.S.A.) and secondary endpoint (U.S.A).
Key Results	Not reported

Adverse effects (AEs)	Not reported
Expected reporting date	Study completion date previously reported as March 2018

Trial	**SIERRAS, NCT02273726; phase III, roxadustat *versus* epoetin alfa**
Sponsor	FibroGen.
Status	Ongoing, recruiting
Source of Information	Trial registry[19, 24]
Location	North America
Design	Randomised; active-controlled; open-label
Participants	n= 820 (planned); aged 18 and older; patients are receiving adequate dialysis using the same modality of dialysis for end-stage renal disease and have been for greater than 3 months are eligible to be included in this study. Patients must be receiving IV or SC ESA for ≥ 8 weeks prior to screening and on a stable ESA (≤30% change) dose during 4 weeks (8 weeks if on Mircera) prior to randomization. Approximately 150 incident dialysis subjects will be randomized to either roxadustat or epoetin alfa (active control) as part of the Amendment number 1 to this study as recorded in ClinicalTrials.gov.
Schedule	Randomised to roxadustat dosed orally three times a week.; or, epoetin alfa dispensed per the package insert or the country-specific product labelling.
Follow-up	Screening period of up to 6 weeks, active treatment period of a minimum of 52 weeks and a maximum of approximately up to 3 years after last patient is randomized, and a post-treatment follow-up period of 4 weeks.
Primary Outcomes	• U.S.A.: Hemoglobin (Hb) change from baseline to the average Hb level during weeks 28 to 52 • Ex-U.S.A.: Hb change from baseline to the average Hb level during weeks 28 to 36
Secondary Outcomes	• U.S.A. : The proportion of subjects with a mean Hb level ≥10.0 g/dL during the evaluation • Ex-U.S.A.: Hemoglobin response (mean Hb 10.0 to 12.0 g/dL) without having received rescue therapy • Average monthly IV Iron use • Change from baseline in low density lipoprotein (LDL • Change from baseline in SF-36 Physical Functioning (PF) sub-score • Change from baseline in SF-36 Vitality (VT) sub-score • Effect on pre-dialysis blood pressure (BP)
Key Results	Not reported
Adverse effects (AEs)	Not reported
Expected reporting date	Study completion date previously reported as March 2018

Trial	**PYRENEES, NCT02278341; phase III, roxadustat *versus* epoetin alfa or darbepoetin alfa**
Sponsor	Astellas Pharma

Status	Active, not recruiting
Source of Information	Trial registry[19, 25]
Location	UK, Eastern Europe, Western Europe
Design	Randomised; active-controlled; open label
Participants	n= 838 (planned); aged 18 and older; patients on stable hemodialysis (HD), hemodiafiltration (HDF) or peritoneal dialysis (PD) treatment with the same mode of dialysis for ≥4 months prior to randomization. Additionally, patients are on IV or SC epoetin or IV or SC darbepoetin alfa treatment for ≥8 weeks prior to randomization with stable weekly doses
Schedule	Randomised to roxadustat dosed orally three times a week.; or, epoetin alfa dispensed per the package insert or the country-specific product labelling.
Follow-up	Screening period of up to 6 weeks, active treatment period of a minimum of 52 weeks and a maximum of approximately up to 3 years after last patient is randomized, and a post-treatment follow-up period of 4 weeks.
Primary Outcomes	• Haemoglobin (Hb) change from baseline to the average Hb of weeks 28 to 36
Secondary Outcomes	• Hb response without having received rescue • Change from baseline in Low Density Lipoprotein (LDL) cholesterol to the average LDL cholesterol • Mean monthly intravenous (IV) iron use (mg) • Change from baseline in mean arterial pressure (MAP) to the average MAP value • Time to an increase in blood pressure • Change from baseline in SF-36 Physical Functioning (PF) sub-score to the average PF sub-score • Change from baseline in SF-36 Vitality (VT) sub-score to the average VT sub-score
Key Results	Not reported
Adverse effects (AEs)	Not reported
Expected reporting date	Study completion date reported as July 2018

Trial	**ROCKIES, NCT02174731; phase III, roxadustat *versus* epoetin alfa**
Sponsor	AstraZeneca and FibroGen
Status	Ongoing, recruiting
Source of Information	Trial registry[19, 26]
Location	North America, South America, Asia, Africa, Australia, Oceania
Design	Randomised; active-controlled; open label
Participants	n= 2070 (planned); aged 18 and older; patients receiving or initiating hemodialysis or peritoneal dialysis for treatment of native kidney end-stage renal disease at least 30 days prior to visit 1. Two central laboratory hemoglobin values during the screening period, obtained at least 7 days apart, must be <12 g/dL in patients currently treated with an erythropoietin analogue or <10 g/dL in patients not currently treated with an erythropoietin analogue.

Schedule	Randomised to roxadustat administered orally three times a week to achieve an Hb level of 11 g/dL and maintain a Hb level of 11±1 g/dL; or, epoetin alfa administered three time a week consistent with approved prescribing information for epoetin alfa to achieve an Hb level of 11 g/dL and maintain a Hb level of 11±1 g/dL.
Follow-up	N/S
Primary Outcomes	• Major adverse cardiovascular (CV) events (MACE): Time to first occurrence of death from any cause, non-fatal myocardial infarction or non-fatal stroke. • Mean change from baseline in Hb averaged over week 28 to week 52. [Time Frame: From baseline to end of study (event-driven, anticipate up to 4 years).]
Secondary Outcomes	• Proportion of total time of Hb measurements within the interval of 11±1 g/dL from week 28 until end of treatment visit • Major adverse CV events+ (MACE+): Time to first occurrence of death from any cause, non-fatal myocardial infarction (MI), non-fatal stroke, heart failure requiring hospitalization or unstable angina leading to hospitalization. • Time to first occurrence of death from any cause, MI, stroke, heart failure requiring hospitalization, unstable angina leading to hospitalization, vascular access thrombosis, deep vein thrombosis, pulmonary embolism or hypertensive emergency. • Time to first rescue therapy (composite of erythropoietin analogue therapy [for roxadustat-allocated patients only] or RBC transfusion) • Changes in self-reported health status as measured by the EuroQol Health Utility Index 5-dimensional-5-level (EQ-5D-5L) during roxadustat or epoetin alfa treatment • Adverse events (AEs), serious adverse events (SAEs) Changes in vital signs, electrocardiogram (ECG) and laboratory values.
Key Results	Not reported
Adverse effects (AEs)	Not reported
Expected reporting date	Study completion date reported as Sept 2018

ESTIMATED COST and IMPACT

COST

The cost of roxadustat is not yet known.

Current comparators include erythropoiesis stimulating agents (ESAs) such as epoetin and darbepoetin alfa that are delivered as injectable. Current comparators require iron supplementation whereas roxadustat use would likely reduce the need for supplemental ironiron.[19,28]

Drug	Dose	NHS Indicative price
Epoetin alfa[27]	Eprex 1,000units/0.5ml solution for injection (2,000units/1 ml); 6	£33.18

	pre-filled disposable injection (POM)	
Darbepoetin alfa[28]	Aranesp 10micrograms/0.4ml solution (25 microgram per 1 ml) for injection pre-filled syringes; 4 pre-filled disposable injection (POM)	£58.72

IMPACT – SPECULATIVE

IMPACT ON PATIENTS AND CARERS

☐ Reduced mortality/increased length of survival

☒ Reduced symptoms or disability

☒ Other: *improved quality of life*

☐ No impact identified

IMPACT ON HEALTH and SOCIAL CARE SERVICES

☐ Increased use of existing services

☒ Decreased use of existing services

☐ Re-organisation of existing services

☐ Need for new services

☐ Other

☐ None identified

IMPACT ON COSTS and OTHER RESOURCE USE

☐ Increased drug treatment costs

☐ Reduced drug treatment costs

☐ Other increase in costs

☒ Other reduction in costs

☒ Other: *uncertain unit cost compared to existing treatments*

☐ None identified

OTHER ISSUES

☒ Clinical uncertainty or other research question identified: *trials still ongoing*

☐ None identified

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