Assessment report

Evrenzo

International non-proprietary name: roxadustat

Procedure No. EMEA/H/C/004871/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

ADME	absorption/distribution/metabolism/excretion
ADR	adverse drug reactions
AE	adverse event
AESI	adverse event of special interest
AUC	area under the concentration-time curve
AUC_{inf}	area under the concentration-time curve from the time of dosing extrapolated to time infinity
BCRP	breast cancer resistance protein
CI	confidence interval
CKD	chronic kidney disease
CL/F	apparent clearance
C_{max}	maximum concentration
CMC	chemistry, manufacturing and controls
CNS	central nervous system
CrCl	creatinine clearance
CSR	clinical study report
CV	cardiovascular
CYP	cytochrome P450
DA	darbepoetin alfa
DD	dialysis-dependent
DDI	drug-drug interaction
DVT	deep vein thrombosis
ECG	electrocardiogram
eGFR	estimated glomerular filtration rate
EPO	epoetin
ESA	erythropoiesis-stimulating agent
ESRD	end stage renal disease
FAS	full analysis set
Hb	haemoglobin
Hct	haematocrit
HD	haemodialysis
HDL	high density lipoprotein
HIF-PH	hypoxia-inducible factor prolyl hydroxylase
HRQoL	health-related quality of life
hs-CRP	high sensitivity C-reactive protein
ID	incident
ID DD	incident dialysis-dependent
IERC	Independent Event Review Committee
IR	incidence rate
ISE	Integrated Summary of Efficacy
ISS	Integrated Summary of Safety
KDIGO	Kidney Disease: Improving Global Outcomes
LDL	low density lipoprotein
MACE	major adverse cardiovascular events (death, non-fatal myocardial infarction and/or stroke)
MACE+	major adverse cardiovascular events including hospitalisations for either unstable angina and/or chronic heart failure
MI	myocardial infarction
NDD	non-dialysis-dependent
NDD	non-dialysis-dependent – dialysis initiation censored
OAT	organic anion transporter
OATP	organic anion transporter polypeptide
OT	on-treatment
OT-7	events which occurred during the treatment period and within/up to 7 days of the last dose of study medication
OT-28	events which occurred during the treatment period and within/up to 28 days of the last dose of study medication
PCS	potentially clinically significant
PD	peritoneal dialysis
PE	pulmonary embolism
PIP	paediatric investigation plan

PND	postnatal day
popPK	population pharmacokinetics
PPS	per protocol set
PRO	patient-reported outcome
PY	patient years
QoL	quality of life
QTc	corrected QT interval
RBC	red blood cell
RMP	risk management plan
SAE	serious adverse events
SF-36	Short Form 36
SmPC	Summary of Product Characteristics
SMQ	Standardised MedDRA Query
$t_{1/2}$	terminal elimination half-life
TEAE	treatment-emergent adverse event
tiw	3 times weekly
t_{max}	time of the maximum concentration
TQT	thorough QT
UGT	uridine diphosphate-glucuronosyl-transferase
ULN	upper limit of normal
VAT	vascular access thrombosis

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Astellas Pharma Europe B.V. submitted on 12 April 2020 an application for marketing authorisation to the European Medicines Agency (EMA) for Evrenzo, through the centralised procedure under Article 3 (2) (a) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 20 July 2017.

The applicant applied for the following indication:

Evrenzo is indicated for treatment of anaemia in adult patients with chronic kidney disease (CKD)

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain tests or studies

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0160/2020 on the agreement of a pediatric investigation plan (PIP).

The PIP is not completed currently and therefore no opinion on compliance is issued yet. A positive partial compliance check EMEA-C2-001557-PIP01-13-M04 was completed in April 2020.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

New active Substance status

The applicant requested the active substance roxadustat contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

Scientific advice

The applicant received the following Scientific advice on the development relevant for the indication subject to the present application:

Date	Reference	SAWP co-ordinators
23 January 2014	EMEA/H/SA/2684/1/2013/II	Prof. Minne Casteels, Dr Kolbeinn Gudmundsson
26 June 2014	EMEA/H/SA/2684/2/2014/I	Dr Hans Ovelgoenne, Dr David Brown
28 January 2016	EMEA/H/SA/2684/2/FU/1/2015/I	Prof Dieter Deforce, Dr Kolbeinn Gudmundsson

The applicant received Scientific Advice on three occasions as mentioned in the table above for the development of Roxadustat for treatment of anaemia associated with chronic kidney disease (CKD) in adults. The Scientific Advice pertained to the following Quality and Clinical aspects:

- Designation of starting materials
- Strategy for controlling impurities in the drug substance and assessment of genotoxic impurities
- Test methods and proposed specifications for the drug substance, particle size distribution specification limit, need to include Microbial Limit testing
- Dissolution method for release and stability testing
- Bridging strategy for demonstration of drug substance equivalence for change in manufacturing process
- Test methods and specifications for drug product characterisation
- Degradation products control strategy
- Tablet strength differentiation by tablet size and embossing
- General clinical development strategy

- Characterisation of cardiovascular (CV) safety: adjudicated CV safety endpoints, adequacy of envisaged patient exposure to evaluate CV safety, analytical approach

In Europe, 3 National Scientific Advice meetings and 2 subsequent follow-up meetings were held in Sweden, Finland and the United Kingdom. Primary discussion topics included absorption/distribution/metabolism/ excretion (ADME), clinical pharmacology and modelling and simulation and clinical efficacy and safety. In addition, 2 EMA Scientific Advice meetings were held, with 1 subsequent follow-up meeting. Primary discussion topics included clinical, statistical and chemistry, manufacturing and controls (CMC)-related questions. EU scientific advice interactions included:

EMA (EMEA/H/SA/2684/1/2013/II), 23 Jan 2014:
- Feedback provided requested special attention to be paid to the statistical power of the NDD studies.

- The agency agreed with the sponsor's proposed patient exposure at the time of the MAA and the proposed composite safety endpoint approach, with a requirement to improve endpoint justification and analysis strategy.

- The agency provided clarification of the possible risk of induction of renal cell carcinomas and that the testing hypothesis was specified.

EMA (EMEA/H/SA/2684/2/2014/I), 26 Jun 2014

- Feedback provided requested:
  - Redefinition of the regulatory starting material to an earlier point in the synthesis
  - Further investigation of the potential degradation pathways of the drug substance
  - Justification of why any potential differences between coated and uncoated tablets for all the proposed strengths were not significant for the assessment of the dissolution method for the final product
  - More information at the time of the MAA submission regarding test methods and specification

- The agency agreed with the sponsor's strategy for not including the microbiological quality test but noted that it depended on the outcome of the microbial limit testing.

- The agency agreed with the sponsor's proposed strategy for controlling impurities, analytical procedures for testing the drug substance and the drug product differentiation strategy.

1. Follow-up EMA Scientific Advice

EMA (EMEA/H/SA/2684/2/FU/1/2015/I), 28 Jan 2016

- Feedback provided requested redefinition of the regulatory starting material to an earlier point in the synthesis.

The main change in the programme following receipt of Scientific Advice in 2014 was the addition of 2 large efficacy and safety studies in NDD and DD patients (Studies D5740C00001 and D5740C00002). The purpose of these studies was to increase the number of major adverse cardiovascular events (death, non-fatal myocardial infarction and/or stroke) (MACE)/ MACE including hospitalisations for either unstable angina and/or chronic heart failure (MACE+) cases, particularly in support of the development in the US. This change in the programme was thought to enhance the robustness of conclusions to be drawn from analyses of CV events and therefore follow-up advice was not deemed required.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Johann Lodewijk Hillege   Co-Rapporteur: Ondřej Slanař

CHMP Peer reviewer(s): Elita Poplavska

The application was received by the EMA on	12 April 2020
The procedure started on	21 May 2020
The Rapporteur's first Assessment Report was circulated to all CHMP members on	10 August 2020
The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	10 August 2020
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	24 August 2020

The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	04 September 2020
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	17 September 2020
The applicant submitted the responses to the CHMP consolidated List of Questions on	23 December 2020
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	01 February 2021
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	11 February 2021
The CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on	25 February 2021
The applicant submitted the responses to the CHMP List of Outstanding Issues on	20 April 2021
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	06 May 2021
The CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on	20 May 2021
The applicant submitted the responses to the CHMP List of Outstanding Issues on	27 May 2021
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	09 June 2021
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Evrenzo on	24 June 2021

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Treatment of anaemia in adult patients with chronic kidney disease (CKD).

2.1.2. Epidemiology and risk factors, screening tools

CKD is a growing worldwide public health challenge characterised by the progressive loss of kidney function, resulting in premature death or need for renal replacement therapy (kidney transplant or dialysis). In Europe, the average prevalence of CKD regardless of age lies between 5% and 11% [Zoccali et al., 2010]. CKD affects 14.8% of the US adult population, and its prevalence is growing rapidly [the United States Renal Data System, 2018]. All-cause mortality risk increases exponentially [Tonelli et al., 2006] and health-related quality of life (HRQoL) decreases [Mujais et al., 2009] as CKD stages advance.

Anaemia is an important complication experienced by patients with CKD that requires careful management with the aim to prevent or delay the severe clinical consequences associated with prolonged low haemoglobin (Hb) levels. The prevalence of anaemia depends on its definition, but it increases in frequency and severity in the more advanced stages of CKD. Studying adult patients at Boston health clinics, [Hsu et al., 2001] described that mean haematocrit (Hct) values decreased with creatinine clearance (CrCl) < 60 mL/min in men and < 40 mL/min in women. More severe anaemia was common among patients with an estimated glomerular filtration rate (eGFR) < 20 mL/min/1.73 m^2 in men and < 30 mL/min/1.73 m^2 in women. [Hsu et al., 2002] published another study based on National Health and Nutrition Examination Survey (NHANES III, 1988 to 1994) data and analysed 15971 adults who had a serum creatinine, Hb and iron profile. Among these 15971 adults, anaemia, defined as Hb concentration < 12 g/dL in men and postmenopausal women and < 11 g/dL in premenopausal women, was more common with CrCl < 70 mL/min in men and < 50 mL/min in women. In comparison with subjects with CrCl > 80 mL/min, the decrease in Hb for subjects with CrCl of 20 to 30 mL/min was 1.4 g/dL in men and 1.0 g/dL in women.

Various studies have reported a high prevalence of anaemia among patients with CKD. The Nadir-3 study reported that 12.4% of patients developed anaemia (women: Hb < 11.5 g/dL; men aged > 70 years: < 12.0 g/dL: men aged ≦ 70 years: < 13.5 g/dL) in the first year following diagnosis of stage 3 CKD [Portoles et al., 2009]. A further cross-sectional survey of nephrologists in western Europe reported that among non-dialysis-dependent (NDD) patients with CKD (stage 3 and 4), the prevalence of moderate to severe anaemia (Hb < 10 g/dL) was 67% and prevalence of severe anaemia (Hb < 8 g/dL) was 11% [Wiecek et al., 2013]. Over 90% of patients on dialysis are anaemic (Hb < 13.0 g/dL in males and < 12.0 g/dL in females) [Nakhoul & Simon, 2016]. In a cross-sectional survey of CKD patients under the care of a nephrologist, conducted between Jun and Sep 2012 in France, Germany, Italy, Spain and the UK, [Eriksson et al., 2016] reported a high prevalence of anaemia that worsened with the progression of kidney disease: CKD stage 3: 44%, CKD stage 4: 76%, and CKD stage 5: 87%. Similar rates were observed by [Wong et al., 2019] in the prospective CKD Outcomes and Practice Patterns Study. A total of 6766 participants with CKD stages 3a to 5ND from nephrology clinics in Brazil, France, Germany and the US were included. Anaemia (Hb < 10 g/dL) was most prevalent in patients with stages 4 and 5 CKD (stage 4: Brazil: 51%, France: 44%, Germany: 86% and US: 50%; stage 5: Brazil: 45%, France: 18%, Germany: 2% and US: 34%) than stage 3 CKD (Brazil: 4%, France: 38%, Germany: 12% and US: 16%).

2.1.3. Aetiology and pathogenesis

Although the pathogenesis of anaemia is multifactorial, as CKD progresses, there is a potential deficit in the oxygen-sensing mechanism in the kidney that may contribute to insufficient production of erythropoietin, a hormone produced primarily in the kidneys; this is considered an important etiologic factor [Fishbane & Spinowitz, 2018; Babitt & Lin, 2012; Peyssonnaux et al., 2008; Nangaku & Eckardt, 2006]. The impaired ability of the body to absorb and use stored iron, the shorter life span of red blood cells (RBCs), the decrease in erythropoietin responses in hematopoietic cells due to inflammation and nutritional deficiency and the blood loss associated with haemodialysis (HD) are also considered contributing factors.

2.1.4. Clinical presentation, diagnosis and stage/prognosis

Anaemia contributes to excess morbidity and mortality in CKD patients [Foley et al., 1996]. Anaemia in patients with CKD is also associated with symptoms such as fatigue, reduced oxygen use, shortness of breath, increased cardiac output, left ventricular hypertrophy, insomnia, lethargy, headaches, dizziness, lack of concentration and reduced cognitive functioning, reduced libido and reduced immune responsiveness (National Institute for Health and Care Excellence, Chronic kidney disease: managing anaemia, Jun 2015) [Fishbane & Spinowitz, 2018; Eriksson et al., 2016; Hirakata et al., 2010]. Patients with the lowest Hb have worse outcomes [Unger et al., 2010]. In patients with CKD, the severity of anaemia correlates directly with the risk of hospitalisation, cardiovascular (CV) disease and death [Thorp et al., 2009]. The severity of anaemia in patients with CKD on dialysis is also strongly associated with increased CV disease, hospitalisation and mortality [Collins et al., 1998]. CKD patients on dialysis with Hct < 30% and Hb < 11.0 g/dL have an increased associated risk for death (18% to 40% higher), whereas patients with higher Hct (33% to 36%) had a lower associated risk of death (7% lower) [Collins et al.,1998]. Symptoms of anaemia in patients with CKD also reduce their quality of life (QoL) and increase healthcare system burden [Akizawa et al., 2018; Fishbane & Spinowitz, 2018; Covic et al., 2017; Eriksson et al., 2016].

2.1.5. Management

Treatment for anaemia associated with NDD or dialysis-dependent (DD) patients with CKD includes iron supplementation, RBC transfusions and/or treatment with erythropoiesis-stimulating agents (ESA) [Kidney Disease: Improving Global Outcomes (KDIGO), 2012].

Iron supplements alone are rarely sufficient to resolve anaemia in patients with CKD, and many patients with advanced CKD require additional treatment to raise Hb levels sufficiently to alleviate symptoms. Although iron supplementation can be effective to treat iron deficiency and reduce the need for blood transfusions or ESA therapy in CKD patients with anaemia, oral iron therapy is associated with variable absorption in the intestines and gastrointestinal side effects that may limit patient adherence. Furthermore, treatment with intravenous iron can potentially cause severe adverse reactions [Fishbane & Spinowitz, 2018; KDIGO, 2012]. Acute hypersensitivity reactions can occur during intravenous iron infusions, and even though these reactions are rare, they can be life-threatening [Gómez-Ramírez et al., 2019; Rampton et al., 2014]. Intravenous iron injections also add to the healthcare burden as iron should be given in an environment where resuscitation facilities are available and caution should be exercised for every dose of intravenous iron that is given, even if previous administrations have been well-tolerated (New Recommendations to Manage Risk of Allergic Reactions with Intravenous Iron-containing Medicines; CHMP, 28 Jun 2013).

There are no Hb thresholds specified for when to initiate RBC transfusion in CKD patients with anaemia; however, guidelines suggest initiation of RBC transfusion for immediate correction of

anaemia or chronic anaemia in the absence of symptoms should be started when Hb < 7.0 g/dL [Kliger et al., 2013; KDIGO, 2012]. Blood transfusions are associated with a risk of allosensitisation, which decrease the availability of obtaining matching organs for patients eligible for kidney transplantation. Blood transfusions are also associated with the risk of introducing pathogens, hyperkalemia, volume overload and immunologic sensitisation [Obrador & Macdougall, 2013], with a longer-term risk of a decreased probability of receiving an immunologically-matching kidney transplant and a longer waiting time for patients on the waiting list for a kidney transplant [Brenner et al., 2019; Gill et al., 2013]. Given the need to reserve blood transfusions as a last-resort therapy mainly for cases of severe blood loss, the only current option for these patients is ESAs.

Since their first approval in 1988, treatment with ESA has been effective in managing anaemia in patients with CKD, with a range of options now available such as the short-acting epoetin (EPO)-alfa or the long-acting darbepoetin alfa (DA) [Fishbane & Spinowitz, 2018; Babitt & Lin, 2012]. Treatment of anaemia with ESAs is standard of care in CKD [Fishbane & Spinowitz, 2018]. According to the Summary of Product Characteristics (SmPC) for the ESAs, iron status should be evaluated for all patients prior to and during treatment and iron supplementation is recommended when serum ferritin values are < 100 µg/L or transferrin saturation is < 20% [Aranesp SmPC, Dec 2019; Eprex SmPC, Apr 2019]. To date, there is no robust evidence to suggest that ESA is superior to another in terms of patient outcomes and it is considered that differences in clinical outcomes among different ESAs are low [KDIGO, 2012]. A review of efficacy, safety and other outcomes in clinical studies with ESAs also established that there is no current evidence to support the superiority of one ESA over another in terms of outcomes relating to economy, efficacy, QoL and safety [Arantes et al., 2018].

There have been safety concerns regarding the use of ESAs to achieve a high Hb target of 13.0 to 15.0 g/dL, which is effective in the treatment of anaemia, and the resultant increase in the risk of CV adverse events (AEs), all-cause mortality, myocardial infarction (MI) and stroke [Unger et al., 2010; Pfeffer et al., 2009; Szczech et al., 2008; Drüeke et al., 2006; Singh et al., 2006; Zhang et al., 2004; Besarab et al., 1998]. Data from 3 randomised controlled trials (The Normal Hematocrit Study, Correction of Hemoglobin and Outcomes in Renal Insufficiency [CHOIR] and Trial to Reduce Cardiovascular Events with Aranesp Therapy [TREAT]) identified that use of ESAs to achieve Hb targets of 12.5 to 14.0 g/dL caused a substantial increase in the incidence of fatal and nonfatal stroke and thromboembolic events [Unger et al., 2010; Weiner & Miskulin, 2010]. While these studies showed that there was an overall improvement of QoL with ESA treatment, there was no convincing evidence of any additional clinical or QoL benefits from targeting a high Hb level of 13.0 to 15.0 g/dL that were considered to outweigh the increased risk for nonfatal MI, nonfatal stroke and death.

All ESAs are administered either intravenously or subcutaneously. Dosing schedules for intravenous and subcutaneous formulations are generally complex and resource-intensive, which can have a major impact on patients and caregivers.

Despite the successful use of ESAs in treating CKD anaemia, optimal Hb targets are yet to be established [Unger et al., 2010]. Additionally, there is a subset of patients who are classified as poor responders, including those with inflammation [Santos et al., 2018; Solak et al., 2016; Icardi et al., 2013; Johnson et al., 2007]. These patients have a suboptimal response to ESA therapy, evidenced by a lack of increase in Hb while on therapy or a requirement of increased ESA dose to maintain a stable Hb level [KDIGO, 2012]. Hb variability, as well as ESA poor responsiveness or non-responsiveness (causing low Hb levels), is associated with an increased risk of mortality compared with patients with stable Hb levels [Kainz et al., 2010].

About the product

Roxadustat is an oral medication with the potential to manage CKD-related anaemia by correcting and/or maintaining target Hb levels. It stimulates endogenous erythropoietin production without the need for producing the supraphysiologic levels of circulating erythropoietin associated with parenteral ESA treatment. Roxadustat transiently stabilises hypoxia-inducible factor alfa subunits, leading to a response mimicking the natural erythropoietic response to hypoxia [Bernhardt et al., 2010]. Its ability to stimulate erythropoiesis makes it a candidate for the treatment of anaemia. Roxadustat is claimed to suppress hepcidin and activate the genes involved in iron homeostasis and therefore being effective at creating less need for iron supplementation [Maxwell & Eckardt, 2016].

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented in film-coated tablets containing 20, 50, 70, 100 and 150 mg of roxadustat as active substance.

Other ingredients are:

Tablet core: lactose monohydrate, microcrystalline cellulose (E460 (i)), croscarmellose sodium (E468), povidone (E1201), and magnesium stearate (E470b)

Film-coating: poly vinyl alcohol (E1203), talc (E553b), macrogol (E1521), allura red AC aluminium lake (E129), titanium dioxide (E171), and lecithin (soya) (E322)

The product is available in perforated PVC/aluminium blisters in a carton as described in section 6.5 of the SmPC.

2.2.2. Active Substance

General information

The chemical name of the active substance is [[(4-hydroxy-1-methyl-7-phenoxyisoquinolin-3-yl) carbonyl] amino]] acetic acid corresponding to the molecular formula $C_{19}H_{16}N_2O_5$. It has a relative molecular mass of 352.34 and the following structure:
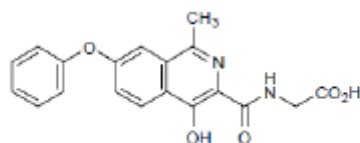
Figure 1: Active substance structure

The chemical structure of the active substance was elucidated by elemental analysis and various spectroscopic techniques: NMR (^{1}H, ^{13}C, and two-dimensional NMR), FTIR, UV-Vis and high-resolution mass spectrometry. The solid-state properties of the active substance were measured by X-ray crystallographic analysis.

The active substance is a non-hygroscopic white to yellow powder.

The active substance does not exhibit stereoisomerism due to the absence of chiral centres. Extensive polymorph screens on the active substance produced only one crystal form.

Manufacture, characterisation and process controls

The active substance is manufactured according to a single manufacturing process.

The active substance is synthesised using commercially available well-defined starting materials with acceptable specifications. Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented and are considered acceptable.
The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances. Actual organic impurities, potential degradants, and potential process related impurities have been adequately discussed. Potential and actual impurities were well discussed with regards to their origin and characterised.

The active substance manufacturing process has been developed using a combination of scientific knowledge, process understanding and manufacturing data, leading to defined operating ranges for process parameters. The proposed control strategy has been developed through an understanding of those process parameters and unit operations with the potential to introduce process variability and impact critical quality attributes (CQAs). The CQAs identified are typical for a non-sterile active substance and are provided as part of a summary of the control strategy.

The active substance is packaged in double low-density polyethylene (LDPE) bags, inside a laminated aluminium foil outer liner, which is inside a rigid container which complies with the EC directive 2002/72/EC and EC 10/2011 as amended on plastic materials and articles intended to come into contact with food.

Specification

The active substance specification includes tests for: appearance (visual), identity (FTIR, HPLC), assay (HPLC), impurities (HPLC), sulfated ash (Ph. Eur.), and particle size distribution (Laser Diffraction).

The absence of tests for microbial enumeration, residual palladium, residual solvents, residual compounds from the sysnthesys route, elemental impurities, polymorphic form, and water content has been adequately justified.

The acceptance criteria for impurities are set according to ICH Q3A. Based on a maximum daily dose of ≤400 mg for roxadustat. Process impurities observed at reportable levels in the active substance have been specified and all other impurities are controlled as unspecified impurities.

Impurities present at higher level than the qualification threshold according to ICH Q3A were qualified by toxicological and clinical studies and appropriate specifications have been set.

The analytical methods used have been adequately described and (non-compendial methods) appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for testing of identification, assay and related substances has been provided.

Batch analysis data of several batches of the active substance are provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data from 3 pilot scale batches of active substance from the proposed manufacturer stored in the intended commercial packaging for up to 36 months under long term conditions (30±2°C/65±5%RH) and for up to 6 months under accelerated conditions (40±2°C/75±5%RH) according to the ICH guidelines were provided.

The following parameters were tested: appearance, assay, impurities, water content, particle size distribution (PSD), X-ray powder diffraction and microbial limits.

All tested parameters under long term and accelerated conditions were within the specifications.

In addition to the primary stability, one pilot scale batch of the active substance was tested after storage at 60°C for one month. In addition, a humidity stressing study was performed using one pilot scale batch of the active substance after storage at 30°C/65% RH (close bottle) and 40°C/75%RH (open bottle) for one month. Roxadustat showed no change under these temperature and humidity conditions.

Photostability testing following the ICH guideline Q1B performed on one pilot scale batch exposed to ICH Q1B option 2 showed susceptibility to photo-degradation. The results demonstrate that the active substance is sensitive to light and the commercial pack configuration is appropriate to protect the active substance from photodegradation and maintain its quality.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period and storage condition 'Store protected from light' in the proposed container.

2.2.3. Finished Medicinal Product

Description of the product and Pharmaceutical development

The finished product is presented as biconvex, film-coated, red coloured, immediate release (IR) tablets. Each tablet shape is oval (20 mg tablets (approximately 8 mm × 4 mm), 50 mg (approximately 11 mm × 6 mm), 100 mg (approximately 14 mm × 7 mm)), round (70 mg (approximately 9 mm)) and almond shaped (150 mg (approximately 14 mm × 9 mm)). Strengths are differentiated by size, shape, and debossing code (i.e., '20', '50', '70', '100', or '150') on one side.

The composition is summarised in 2.2.1. Introduction.

By integrating knowledge gained from preclinical, clinical, formulation and process development studies, clinical trial material manufacture, and stability studies, a Quality Target Product Profile (QTPP) for the finished product was defined as film-coated immediate release tablets for oral administration containing 20 mg, 50 mg, 70 mg, 100 mg and 150 mg of roxadustat, stable for at least 3 years and packed in polyvinyl chloride blisters with aluminum foil, and CQAs are defined as appearance, assay, dissolution, uniformity of dosage units and related substances.

This QTPP was used to guide pharmaceutical development studies and to arrive to the to-be-marketed formulation.

Compatibility of the active substance with the excipients of the core tablets was shown in binary mixtures and in a mock formulation stored at elevated temperature and humidity. Compatibility with excipients was additionally inferred from the results of the stability studies.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards except the coating agent which has an in-house specification. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.2.1 of this report.

Hard gelatine and hypromellose capsules were used in Phase 1 and 2, and a film-coated immediate-release tablet formulation was developed in Phase 3. Inmediate release tablet was developed to meet the demand for a wide range of dosage strengths. A bioequivalence study was carried out for the 150 mg strength of the Phase 3 formulation and the proposed commercial product, and a biowaiver is

requested for the lower strengths. The provided comparative dissolution data support the biowaiver of strengths.

The core tablets have to fulfil appropriate parameters to be coated to reach film-coated tablets in order to protect the photolabile active substance. The coating agent was selected based on its photoprotective and aesthetical attributes, as well as its resistance to bleaching or colour changes upon exposure to ICH Q1B Option 1 lighting conditions. Photostability study results using ICH Q1B Option 2 lighting conditions confirmed that to-be-marketed tablet strengths are photostable in absence of packaging and do not require protection against light under intended use conditions. Therefore, the film-coated tablets are to be swallowed whole and are not to be chewed, broken or crushed in order to maintain protection of the light sensitive tablet core against photodegradation.
The coating was also confirmed to have no effect on the dissolution rate of the finished product.

The primary packaging consists of PVC/aluminium blisters. The material complies with Ph.Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The manufacturing process consists of pre-blending, granulation, delumping, drying, milling, lubrication, compression, film-coating, and packaging. The process is considered to be a standard manufacturing process.

A process validation scheme has been provided. All relevant manufacturing process steps will be validated before commercial launch. This is considered acceptable for a standard process.

The in-process controls are adequate for this type of manufacturing process.

Product specification

The finished product release and shelf life specifications shown in include appropriate tests for this kind of dosage form: appearance (visual), identification (HPLC, UV), assay (HPLC), degradants (HPLC), uniformity of dosage units (HPLC) and dissolution (Ph. Eur.).

All degradants greater than the reporting threshold are summed and reported as total degradants. The limit for total degradants at release was set taking the historical batch data into account and to allow for both specified degradants and a small amount of unspecified degradants.

The absence of tests for water content, residual solvents, and microbial limits in the specifications of the finished product has been adequately justified.

The potential presence of elemental impurities in the finished product has been assessed using a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Batch analysis data on 8 batches of finished product using a validated ICP-MS method were provided, demonstrating that each relevant elemental impurity was not detected above 30% of the respective PDE.

During the procedure, a MO requesting to provide a risk evaluation concerning the presence of nitrosamine impurities in the finished product applying the principles outlined in the notice "Information on nitrosamines for marketing authorisation holders (EMA/189634/2019)" was raised. A risk evaluation regarding the presence of nitrosamines addressing all potential sources listed in the EMA Q&A document was carried out. The risk evaluation was considered acceptable. As no risk was identified, confirmatory testing was considered not needed.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used has been presented.

Batch analysis results are provided for several pilot and commercial scale batches of 20 mg, 50 mg, 70 mg, 100 mg, and 150 mg confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

The finished product is released on the market based on the above release specifications.

Stability of the product

Stability data from 3 finished product pilot scale batches from each strength stored for up to 48 months under long term conditions (30 ± 2°C/75 ± 5%RH) and for up to 6 months under accelerated conditions (40 ± 2°C/75 ± 5%RH) according to the ICH guidelines were provided. The batches of medicinal product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

The analytical methods used were the same as for release and were stability indicating.

A protocol design that employs matrixing of the batches within each dose strength is used. The matrix is based on ICH Guideline Q1D with the addition of full testing at 12 and 24 months to help support initial shelf-life claims. Matrixing only applies to the 30°C/75%RH condition. All batches were tested at all timepoints for the 40°C/75%RH condition. This was considered satisfactory.

All results passed the proposed commercial acceptance criteria. Little or no change were observed after 48 months of storage at 30°C/75%RH, after 6 months of storage at 40°C/75%RH.

In addition, one pilot scale batch of the 20 mg, 70 mg and 150 mg film coated tablets were exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. A dark control was added consisting of tablets in quartz dishes wrapped in aluminium foil. The tablets were shown to be photostable under ICH Q1B conditions.

A bulk hold study (registration bulk hold study) was performed. Samples from two batches each of 20 mg, 70 mg, and 150 mg strength from registration batches were evaluated. Results are considered applicable to the bracketed dose strengths 50 mg and 100 mg as all tablets are made from a common blend. Samples were tested after storage at 30°C/75%RH for up 24 months and 40°C/75%RH for up 6 moths, and controlled room temperature (CRT) and ambient RH (CRT; i.e., normal working conditions of 20°C-25°C with excursions of 15°C-30°C allowed as long as the mean kinetic temperature is calculated to be not more than 25°C). No change was seen in appearance, assay and degradants. Only small changes were observed in water content and dissolution profiles. All results passed the proposed commercial specifications.

Samples from one batch of each 20 mg and 150 mg strength were manufactured as part of the cumulative bulk holding study.

Based on available stability data, the proposed shelf-life of 4 years and without storage conditions as stated in the SmPC (section 6.3) are acceptable.

Adventitious agents

It is confirmed that the lactose is produced from milk from healthy animals in the same condition as those used to collect milk for human consumption and that the lactose has been prepared without the use of ruminant material other than calf rennet according to the Note for Guidance on Minimising the

Risk of Transmitting Animal Spongiform Encephalopathy Agents Via Human and veterinary medicinal products.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

Two MOs were raised by CHMP during the evaluation: to define one of the reagents as an additional starting material in the synthesis of the active substance, and to provide a risk evaluation concerning the presence of nitrosamine impurities in the finished product. All the issues were resolved satisfactorily.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

2.2.6. Recommendation(s) for future quality development

No applicable

2.3. Non-clinical aspects

2.3.1. Introduction

In order to support the oral administration of roxadustat in CKD patients with anaemia, the nonclinical studies investigated the pharmacology, pharmacokinetics (PK), and toxicity of roxadustat in animals dosed by the oral route. Pivotal nonclinical studies described in this section were conducted in accordance with accepted practice for these study types and and selected toxicity and safety pharmacology studies were conducted in general agreement with the principles of Good Laboratory Practice (GLP).

2.3.2. Pharmacology

Primary pharmacodynamic studies

The mechanism of action of roxadustat was evaluated using *in vitro* enzyme assays (Study 301_05_3010_056 AMNDII), by testing the inhibitory potential of roxadustat for all three isoforms of the HIF-PH prolyl hydroxylase domain (PHD) enzymes PHD1, PHD2 and PHD3, and collagen prolyl-4-hydroxylase (CP4H). Another regulator of HIF activity, factor inhibiting HIF (FIH) was also tested. All five enzymes are ketoglutaric acid-dependent non-heme iron hydroxylases. It was shown that roxadustat inhibited PHD1, PHD2, PHD3 and CP4H with high affinity and competitively to alpha-ketoglutaric acid. Roxadustat IC50 values were 1.8, 2.5, 0.19 and 0.2 µM, and Ki values were 0.10, 0.084, 0.36 and 0.33 µM for PHD1, PHD2, PHD3 and CP4H respectively. The IC50 and Ki value for FIH could not be determined, indicating a low affinity for this enzyme.

Cellular responses to roxadustat treatment were evaluated in Hep3B cells (Study 301_05_3040_057), or a clonal derivative of this cell line, 1G6. Treatment up to 30µM roxadustat resulted in dose-dependent increases in HIF-α. A reporter gene, secreted alkaline phosphatase (SEAP), under control of the HIF Response Element (HRE) present in the transfected cell lines showed a dose-dependent increased expression of up 155-fold. Expression of Erythropoietin (EPO) was increased similarly up to 34-fold. The increased expression of EPO was still apparent, albeit at a lower fold change of 6.6, in the presence of EPO inhibiting factors TNF-α and IL-1β. A synergistic effect on SEAP and EPO expression was seen when cells were treated with roxadustat in the presence of IL-6.

The effect of roxadustat on EPO production and erythropoiesis was studied in healthy mice (*Studies 301_05_3510_048 and 301_05_3510_049*) and rats (*Study 301_05_3510_037*). EPO production was increased from a single dose of 6 mg/kg in mice. Erythropoiesis, as shown by increased Hb, Hct and reticulocytes, was increased in a dose, time and frequency-dependent manner in mice and rats. Although Hb was increased after 3 doses in one week of 6 mg/kg in mice, a more robust response was seen after the highest dose of 60 kg/mg when also Hct and reticulocytes were increased. After 4 weeks of dosing in rats, a dose of 30 mg/kg/week was sufficient to elicit a response on erythropoiesis, which became stronger with a higher dose of 60 mg/kg and more frequent dosing of twice or three times per week.

In a rat model of anaemia (*Study 301_07_3510_121_A01*), two weeks treatment with 40 mg/kg three times a week (TIW) roxadustat resulted in increased erythropoiesis (increased Hb, Hct, RBC, RETI), reduction of microcytosis (increased MCV, MCH) and hypochromia (increased MCHC). However, this treatment regime was not sufficient to normalise the decreased iron levels in the anaemic animals. The expression of the gene encoding iron transporter DMT1 was only upregulated in non-anaemic sham-treated animals, while iron regulator hepcidin was also decreased to normal levels in anaemic animals.

Similar results were obtained when the animals were treated for 4 weeks at 30 mg/kg TIW (*Study 301_05_3510_047_A01)*. However, in contrast to 2-week treatment, plasma iron levels were increased after 4 weeks of treatment, as well as expression of iron transporters DMT1 and Dcytb indicating a delayed effect on iron levels, as this is time-dependent and will not occur within a short time period.

In the 5/6 nephrectomy rat model of anaemia (*Study 301_06_3510_071_A01)*, one-week dosing TIW followed by one week twice a week (BIW) of 20 or 40 mg/kg normalised Hb, Hct and RBC, without affecting serum iron levels, again indicating dosing of more than 2 weeks is required to normalise serum iron levels.

Secondary pharmacodynamic studies

In the secondary pharmacology general receptor and enzyme screen, no other targets were identified that were inhibited by roxadustat at concentrations up to 10 µM (Studies *301_13_3010_009A2 and 301_04_3010_010)*. The clinical Cmax at the maximum dose of 3 mg/kg TIW is 41.8 µM. However, taking into account protein binding which is 99%, then for a free fraction of 1% Cmax corresponds to 0.41 µM, indicating that secondary binding is not an issue.

Study 301_16_3040_187 showed that roxadustat can bind to the thyroid receptor (TR) at relevant concentrations (IC50 of 0.13 µM), although with much lower affinity than the natural ligand triiodothyronine (T3) and the TR agonist sobetirome. In an activity assay (*Study 301_16_3040_185*) using a luciferase construct, it was shown that binding of roxadustat to TRα, and β did not lead to significant activity of the receptors, as activation reached only 1% of the reference compound T3 when tested up to 300 µM, while sobetirome reached an activity of 64% of T3. At 10 µM concentration of roxadustat activity was only 0.3% of the T3 activity. In a second reporter assay (*Study 301_16_3040_186*) using HEK293T cells with a beta-lactamase reporter gene, a maximal activity at

TRβ of 36-39% of the reference compound was already reached at a roxadustat concentration of 3 μM. The activity was less pronounced at TRα, where a maximum of 15% was reached at a concentration of 300 μM. Results show that binding to TR does not result in agonistic activity at the TR at clinically relevant concentrations.

Since a reduction in glucose was seen in the toxicology studies in rats and monkeys (see toxicology section), a glucose tolerance test was performed in rats (*Study 3510-10-047*). A dose-dependent reduction in glucose tolerance was observed, with decreased glucose levels and increased insulin levels after a glucose challenge, from the lowest dose tested of 12.5 mg/kg TIW for 2 weeks.

The mechanism behind the decreases in serum LDL, HDL and total cholesterol that were seen in toxicology studies was also investigated *in vitro* (*Study 3510-12-005*). Roxadustat administered intermittently lowered fasting serum total cholesterol, HDL and LDL, and increased fasting serum triglycerides compared to vehicle in a dose-dependent manner. These changes were observed after the first dose administration and were maintained after 2 and 4 weeks of dosing. The LDL/HDL ratio also tended to be lower after treatment with roxadustat. Roxadustat had no effect on fasting serum glucose compared to vehicle at any time point. Roxadustat increased erythropoiesis in a dose-dependent manner in agreement with stimulation of the HIF pathway by roxadustat.

In order to investigate the mechanism of action of the *in vivo* cholesterol lowering effects of roxadustat, *in vitro* studies were carried out to determine effects on the rate-limiting enzyme in the cholesterol biosynthetic pathway, HMGCR (*Studies 301_16_3040_184 and 350_15_3040_001*). Roxadustat had no effect on HMGCR activity, the enzyme involved in cholesterol biosynthesis. However, a HIF-dependent effect was evident on HMGCR protein levels, which were reduced after treatment of cells with roxadustat. This was in turn dependent on increased Insig-2 expression. Results show that the reduction seen in serum LDL and HDL, which are also seen in the clinic, are likely due to a secondary effect of roxadustat on HIF and HMGCR protein levels.

Safety pharmacology programme

Cardiovascular system *(Studies 301_05_3510_038, 301_05_3510_025, 3510-09-090, 3510-10-014, 3510-10-063, 3510-15-009, 3510-15-064, BE001764-07, 352016002)*

When tested in the *in vitro* hERG channel assay, roxadustat at 93.2 μM caused 16.8% inhibition, indicating a low potential for repolarisation abnormalities or prolonged QT at clinical doses.

In the cardiovascular (CV) assessment, cynomolgus monkeys treated with a single oral dose of roxadustat at 100 mg/kg showed up to 55% increase in heart rate (HR), from approximately 7 to 24 hours post-dose as compared to vehicle control, while no increase in HR was observed at doses ≤ 30 mg/kg. There were no measurable effects on BP in the cynomolgus monkey.

Conscious rats treated with roxadustat either by iv bolus injection (30 and 60 mg/kg), or by oral gavage (30 and 60 mg/kg) showed an increase in HR alongside a simultaneous decrease in blood pressure (BP). Co-treatment with the β₁-adrenergic receptor antagonist metoprolol indicated a role for β₁-adrenergic receptors in the increase in HR, but there was no effect of metoprolol on the roxadustat-induced decrease in BP. A cardiac function study in anesthetised rats treated orally with 60 mg/kg roxadustat showed cardiovascular changes, including increased HR, stroke volume, end-diastolic volume, and decreased systemic BP and total peripheral resistance (TPR), consistent with a reflex response to vasodilation. In an isolated rat heart Langendorff preparation study, roxadustat decreased coronary artery pressure and resistance, but did not exert direct cardiac effects on HR or cardiac contractility at up to 10 μg/mL (free roxadustat 1.7 μg/mL at 20 mg/kg oral dose in rats). In an *in vivo* assessment of rat regional haemodynamics, conscious rats administered 30 mg/kg iv displayed a rapid increase in HR and a biphasic BP response, with an early transient elevation in mean BP followed by a

prolonged decrease. The observed effects were accompanied by an early short-lived reduction in blood flow followed by a more sustained vasodilation in the renal, mesenteric and hindquarters vascular beds. In a 28-day repeat TIW dose CV study in rats, the increase in HR observed after the initial oral administration of 20 or 40 mg/kg on day 1 was less pronounced after repeated administration on days 15 and 26. There was also a decrease in BP at the 40 mg/kg dose which was variable, with significant decreases of similar magnitude observed at days 1 and 26, but not day 15.

In human healthy volunteers treated with roxadustat increases in heart rate have been observed, which were more prominent in higher dose ranges (doses greater than 2 mg/kg). In roxadustat clinical studies, no clinically significant differences in vital signs were observed between treatment arms in DD-CKD and NDD-CKD pooled patient populations.

In consideration of the mechanism of action of HR increase, evaluation of the *in vitro* selectivity profile of roxadustat did not reveal potential mechanisms that might contribute to the change in HR observed. The measured IC_{50} values for NE and DA transporters were ≥15 µM, which were higher than the highest estimated free concentration of roxadustat achieved in cardiovascular studies (10 µM, following dosing of 30 mg/kg iv in the regional blood flow study.

These data suggested that a transient increase in HR was at least in part mediated by a reflex response to the transient decrease in BP. It appears that there is no direct effect of roxadustat on heart tissue that impacted HR, but the associated reduced total peripheral resistance (TPR) may result in an increase in HR as a reflex response. This mechanism is also supported by data indicating reduced TPR, and increased hemodynamic flow observed in regional tissues with roxadustat treatment. Reduced TPR is a recognised response to acute hypoxia as a physiological mechanism to optimize oxygen delivery and maintain tissue metabolism [Kuwahira et al, 1993]. What is currently unknown is the mechanism of roxadustat-induced reduction in TPR in the absence of a plausible role for off-target secondary pharmacology targets. HIF target genes can be related to vasodilation, such as adrenomedullin, heme oxygenase or nitric oxide synthase [Hu et al, 2003; Umbrello et al, 2013]. In summary, roxadustat has the ability to increase heart rate in a dose dependent manner in nonclinical studies.

Respiratory system *(Study 301_05_3510_023):*

The effect of a single iv dose of roxadustat on pulmonary function in anesthetised rats 30 min following administration of up to 100 mg/kg showed increased respiratory rates at ≥ 30 mg/kg. Minute volume increased in female rats at ≥ 30 mg/kg and in males at 100 mg/kg. At 100 mg/kg, there were significantly increased tidal volumes in male rats only.

Increased respiratory rate is reported as a response to hypoxia, with implication of the carotid body regulation of breathing rate and role of both HIF-1α and HIF-2α activation in the carotid body or adrenal medulla [Yuan et al, 2013]. Also, the Chuvash population with von Hippel-Lindau (VHL) pathway disruption and increased HIF activation have increased respiratory response to hypoxia compared to non-Chuvash normal VHL function [Smith et al, 2006], a finding that has been reproduced in a mouse model of polycythemia [Slingo et al, 2014].

Central nervous system *(Study 301_05_3510_022*): No effects were seen on CNS parameters in rats when dosed up to 300 mg/kg single dose.

Renal system *(Study 301_05_3510_024)*

A renal function study in conscious rats showed that oral roxadustat at doses ≥ 30 mg/kg increased urine volumes, and urine pH was significantly higher in females at all dose levels and males at doses ≥ 100 mg/kg. Urinary potassium (K^+) concentration was significantly higher at ≥ 100 mg/kg, with K^+ excretion ratios increased in females at all doses and in males at doses ≥ 100 mg/kg. Excretion ratios

for sodium (Na^+) and chloride (Cl^-) were increased in males at all dose level, and in females at 30 and 100 mg/kg roxadustat.

Adverse effects in the kidney were also observed in the repeated dose toxicology studies, mainly related to congestion or linked to thromboembolic lesions of the kidney, and are therefore considered secondary to exaggerated pharmacology of roxadustat in healthy animals.

Pharmacodynamic drug interactions

No pharmacodynamic drug interaction studies were conducted with roxadustat.

2.3.3. Pharmacokinetics

To define absorption, distribution, metabolism, and excretion (ADME) characteristics of roxadustat, a series of *in vivo* studies were conducted in mice, rats, rabbits, cynomolgus monkeys, and humans; as well as *in vitro* studies using human and animal biomaterials. The animal species used in these ADME/Pharmacokinetic (PK) studies included those used in the nonclinical pharmacology and toxicology studies. *In vivo* studies used either oral or intravenous administration, with oral dosing being the same route of administration as in pharmacology and toxicology studies and in clinical trials.

Analytical Methods

The analytical methods developed for the analysis of roxadustat with LC-MS/MS in plasma from mouse, rat, rabbit and monkey were validated with satisfactory accuracy, precision, LLOQ, dilution integrity, matrix effect and stability. The lower limit of quantification (LLOQ) was 0.000977 to 0.01 µg/mL using 0.05 mL plasma of mice, rats, rabbits, and cynomolgus monkeys by LC-MS/MS, 0.1 µg/mL using 0.02 mL plasma of rats by LC-MS/MS, and 0.1 µg/mL using 0.05 mL plasma of rabbits by HPLC-UV. Radioactive metabolite components (drug-related material) were profiled by HPLC with radiometric detection for selected samples to elucidate the metabolism of roxadustat. The estimates of quantitation were made by radioactivity and/or reference standards (when available), while the structure identification was based on LC/MS, LC-MS^n or NMR analysis.

Permeability and transport

Two *in vitro* studies in Caco-2 cell monolayers suggest that roxadustat is highly permeable. Roxadustat is a substrate for the efflux transporter BCRP. No evidence of the involvement of P-gp, BSEP or MRP2 in roxadustat intestinal transport was found in *in vitro* studies.

Single dose pharmacokinetics

The single-dose pharmacokinetics of roxadustat after oral and intravenous administration was investigated in rats (males), rabbits (females) and in cynomolgus monkeys (males, females). Following intravenous administration of roxadustat in rats (20 mg/kg) and rabbits (30 mg/kg), the plasma clearance approximated the hepatic blood flow. In cynomolgus monkeys, plasma clearance decreased with dose and approached at the highest dose (30 mg/kg) the hepatic blood flow (43.6 ml/min/kg). The values for Volume of distribution at steady state (Vss) were higher than the plasma volume (44.8 mL/kg) or approached the volume of total body water (693 mL/kg), suggesting is distribution outside of the circulation.

Orally administered roxadustat was rapidly absorbed with a short tmax (≤2 h), a moderate bioavailability in rabbits (37%), and a high oral bioavailability in rats (86%–100%) and monkeys (40%–83%). Cmax and AUC-values increased approximately dose-proportionally (rats) or more than

dose-proportionally (rabbits, cynomolgus monkeys). No apparent gender-related difference was observed in oral bioavailability or other PK parameters, as found in cynomolgus monkeys.

Repeated dose pharmacokinetics

The toxicokinetics of roxadustat were investigated in mice, rats and cynomolgus monkeys as a part of the toxicology studies for once-daily dosing used in early, 4 week studies and intermittent dosing regimen of three times per week used in the longer-term studies, including the 13-week study (mice), the 2-years carcinogenicity studies (mice, rats), and the 22-week and 52 studies (cynomolgus monkeys).

The intermittent dosing regimen demonstrated rapid oral absorption in all three species (t_{max} generally < 2 h). C_{max} and AUC values increased approximately dose-proportional in mice and rats and more than dose-proportional in cynomolgus monkeys. There were no marked gender differences for C_{max} and AUC values or other pharmacokinetic parameters. The plasma concentrations declined with a mean half-life of 3 to 4 hours in mice, 3 to 6 hours and rats and 7 to 11 hours in cynomolgus monkeys. All three species showed no signs of drug accumulation or change in half-life.

Plasma protein binding

Roxadustat is extensively bound to plasma proteins. The *in vitro* plasma protein binding ratios were 90-95% in mice, 95-99% in rats, 92-98% in guinea pigs, 97-99% in rabbits, 98-99% in cynomolgus monkeys and 99% in human. No clear concentration dependency was observed in the range of 2 to 40 µg/mL in mice, rats, guinea pigs, rabbits, and humans, and in the range of 2 to 400 µg/mL in monkeys. In human plasma, roxadustat was mainly bound to albumin with less than 1% free drug in the circulation.

There was a concentration-dependent increase in the free fraction in the concentration range of 10 to 400 µg/mL in plasma from juvenile rats aged 15, 22, 29 and 57 ±7 days. The highest level of free fraction was observed in the youngest rat plasma; aged 15 days (up to 2.69%), across the roxadustat concentration range, and the overall lowest free fraction was observed in the eldest rat plasma; aged 57 ±7 day (0.21%).

Distribution to red blood cells

In vitro blood cell transfer of ^{14}C -roxadustat in mice, rats, rabbits, cynomolgus monkeys, and humans were investigated. Results show that Roxadustat does not significantly distribute to red blood cells. The blood/plasma ratio in rats, rabbits and cynomolgus monkeys (0.6-0.7) was in the same range of that in humans (0.6), but was somewhat higher in mice (0.8-1.1).

Tissue distribution

Following oral administration of ^{14}C-roxadustat in pigmented (Long Evans) rats, radioactivity was widely distributed and almost all the tissues had maximum concentrations at 1-hour post-dose.

No clear gender difference was apparent. Radioactivity was mainly presented in the gastrointestinal tract and excretory organs. Excluding the gastrointestinal tract, the tissues with the highest concentrations of radioactivity were the renal cortex, kidney, liver, renal medulla and lungs. The high levels in bile reflected that roxadustat-related material is excreted into the bile. The tissues with the lowest concentrations were seminal vesicle, medulla, spinal cord, cerebrum, bone, and eye.

Elimination of radioactivity was complete by 48 hours post-dose, with the exception of gastrointestinal tract, liver, and skin. There was no preferential binding of radioactivity to the skin or the uveal tract, indicating that roxadustat does not bind to melanin.

Placenta transfer and transfer to milk

In the prenatal and postnatal development study in rats, roxadustat was detected in fetal plasma, suggesting transfer to fetus via the placenta. Plasma concentrations of roxadustat were detected in pups, suggesting that roxadustat was excreted in milk, and absorbed into the pups via milk intake. On day 10 of lactation, milk concentrations of roxadustat increased with dose and the milk to plasma concentration ratios were considerably higher than concurrent plasma concentrations and (milk: plasma ratio = 1.4 to 4.4).

Metabolism

***In-vitro* studies**

In-vitro metabolic stability studies with liver microsomes and hepatocytes showed that roxadustat is nearly unchanged (microsomes) or remained as a major component across the tested species (humans, mice, rats and cynomolgus monkeys).

In human hepatocyte incubations, the largest metabolite by radiometric detection was C10 (~3%), estimated to be hydroxy roxadustat (MET4). C10 was also detected in hepatocytes from mice (~1%), rats (~2%), and cynomolgus monkeys (~2%). In mouse and monkey hepatocyte incubations, the major metabolites by radiometric detection were C4 (~18.5 and 5.2%, respectively) and C5 (~12.5 and 3.9%, respectively), proposed as glucuronide metabolites of roxadustat. Among the minor metabolites observed, no human-specific metabolite was detected.

(a)	(b)	(c)
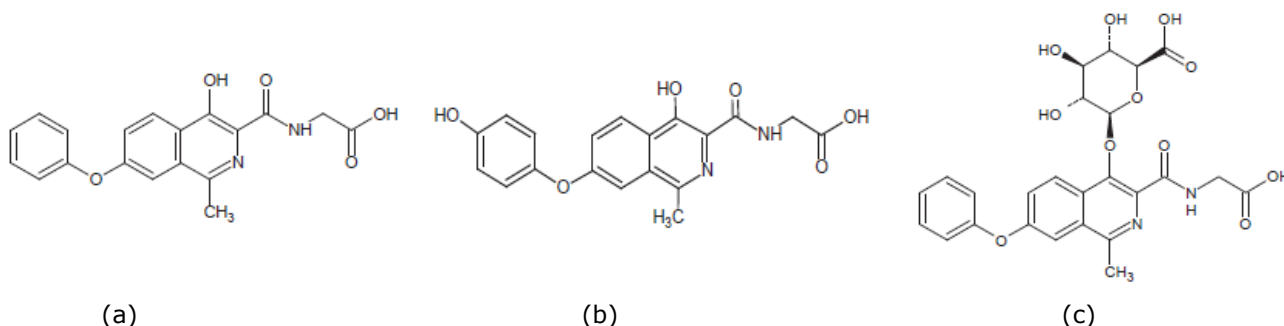
Figure 2: Structure of a) Roxadustat, b) 4'-Hydroxy Roxadustat MET4, c) Glucuronide metabolite of Roxadustat MET1

In-vitro CYP Identification studies with human liver microsomes and recombinant human enzymes showed that roxadustat is primarily converted in Phase I to MET4 by CYP2C8 (CLint was 0.0125 μL/min/pmol P450) and in Phase II to MET1 by UGT1A9 (CLint was 2.29 μL/min/mg).

***In-vivo* studies**

Unchanged roxadustat was the major component in plasma (as determined in rat, cynomolgus monkey and human), but was a minor component in urine (as determined in rat and cynomolgus monkey), bile (as determined in cynomolgus monkeys) and faeces (as determined in rat).

In rats and cynomolgus monkeys, the metabolic pathways of roxadustat were glucuronidation (MET1, MET5), glucosidation (MET2), hydroxylation/oxidation (MET4, MET11-1 [=MET17], MET11-1

[=MET19]), dealkylation (MET6, MET7), sulfation (MET3, MET9, MET10, MET12, MET13) and desphenylation (M8).

In bile duct-cannulated cynomolgus monkeys, roxadustat-related material accounted for 42.9% of the oral dose in the bile up to 24 h after administration of roxadustat. Constituents included roxadustat (4.3%), the metabolites MET3 (17.6%), MET1 (22.4%), MET2 (0.9%), MET8 (0.7%) and an unidentified metabolite MP7 (1.3%).
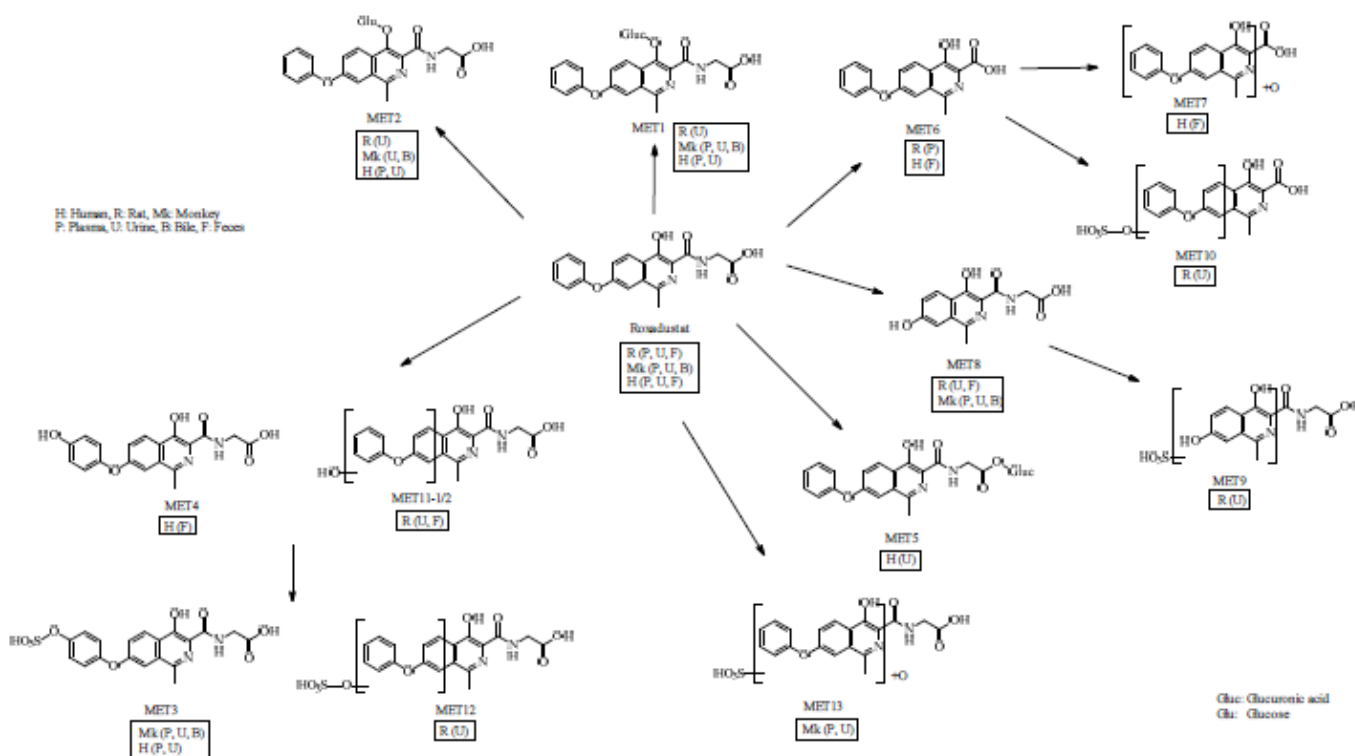
Source: [Studies 301_06_3510_093; 1517-ME-0028; 1517-ME-0026; 1517-ME-0025; 1517-ME-0201; 1517-ME-0051; 352007004; 1517-CL-0508; 1517-CL-0532; 1517-CL-0543].

Figure 3: Postulated, in-Vivo Metabolic Pathways of Roxadustat

Glucuronidation (MET1), glucosidation (MET2), and hydroxylation followed by sulfation (MET3) were the major metabolic pathways in human. About 50% of the oral dose roxadustat was excreted in human faeces. Constituents included roxadustat (28.3%), the metabolites MET4 (17.2%), MET6 (1.1%), and MET7 (2.6%). MET4 was a significant metabolite in human faeces. However, MET4 was not detected in human plasma nor in animal plasma, urine, faeces (rat) or bile (cynomolgus monkey). MET4 in human feces is most likely generated in the intestine from MET3, which is expected to be excreted into bile as it is in cynomolgus monkeys. In addition, comparable results of the product ion patterns between MET4 and MET11-1/2 (found in rat faeces) and the retention times between MET4 and C10, indicated that one of MET11-1/2 is likely to be MET4. Therefore, it can be concluded that MET4 is not a human-specific metabolite.

Excretion

After a single oral dose of ^{14}C-roxadustat to rats or cynomolgus monkeys, the majority of roxadustat-related radioactivity was excreted in faeces (77%–79% in rats, 74% in cynomolgus monkeys), while a minor amount was recovered in urine (16%–17% in rats, 25% in cynomolgus monkeys). In contrast, the excretion of drug-related radioactivity in urine and faeces were nearly equal in humans (46% in

urine and 50% in faeces), suggesting differences in the primary route of elimination pathway following oral administration between animals and humans.

Pharmacokinetic drug interactions

No relevant studies were performed in animal models. *In vitro* study results regarding potential involvement of roxadustat in drug interaction can be found in the clinical pharmacology sections.

2.3.4. Toxicology

Single-dose toxicity

Single-dose toxicity studies were performed in rat and cynomolgus monkey. Results are summarised in Table 1 below:

Table 1: Single dose toxicity studies

Study ID	Species/ Sex/Number/ Group	Dose (mg/kg) /Route	Observed max non-lethal dose	Major findings
301_05_3 510_018 GLP	Rat, Crl:CD (SD) M+F/5	0, 30, 100, 200, 300 2 week recovery Oral	200 (M) 100 (F)	≥30: abs. reticulocyte count ↑, RBC count↑, haemoglobin ↑, Hct↑ (M) ≥100: bw, fc↓, monocytes↑, blood urea nitrogen↑, total protein↑, triglycerides↑, bilirubin↑, K+↓, cholesterol↓ 200: mortality (n=1 F), lymphocytes ↑ 300: mortality all animals (day 4), hunched posture, thinness, laboured and/or irregular respiration, cold to touch, rough haircoat and hypoactivity, WBC count ↑ Recovery: ≥100: reticulocytes↓, platelets ↓(F) 200: platelets↓
301_05_3 510_020 Non-GLP	Cynomolgus Monkey M+F/1	0, 3, 30, 60, 100 Oral or I.V.	100	≥3: plasma EPO ↑

Repeat-dose toxicity

Rat

Repeat-dose toxicity studies were performed in rat for a duration of one month (daily dosing) and six months (dosing three times a week). The six-month study was performed twice in different strains, namely in Sprague Dawley (SD) rats and in Fischer (F344) rats. Results are summarised in Table 2 below:

Table 2: Repeat-dose toxicity studies

Study ID	Species/Sex/ Number/Group	Dose/ Route	Duration	NOAEL (mg/kg /day)	Major findings
301_05_35 10_019 GLP	Rat SD M+F/15	0, 2, 20, 60 Recovery: 0, 2, 20 Oral, daily	One month One-month recovery	2	≥20:bw↓(M, day 22-28), RBC↑, Haemoglobin↑, Haematocrit↑, MCV↑, MCH↑, MCHC↓, platelet count↓, reticulocytes↑, ALAT↑(M), ASAT↑(M), albumin↑, bilirubin↑, triglyceride↑, unsaturated and total iron binding capacity↑, liver weight↑ (M), spleen weight↑, pale liver(M), enlarged spleen(M), black foci in stomach (M), bone marrow hyperplasia (sternum), heart: chronic inflammation of valve, Haematopoiesis in spleen, polychromasia (F), 60: mortality (3F, 5F + 11 TK animals), moribund animals showed activity↓, thin body condition, laboured breathing, black tail tip, skin turgor, red stained nose/mouth, all remaining high dose animals sacrificed after 3 weeks, bw↓(F), dark kidney, pale liver, enlarged spleen, dark kidney, enlarged spleen, femur bone hyperostosis, myelofibrosis, thrombosis, <u>heart</u>: inflammation, chronic, endocardium, papillary muscle, cardiomyopathy;

Study ID	Species/Sex/ Number/Group	Dose/ Route	Duration	NOAEL (mg/kg /day)	Major findings
					Kidney: chronic progressive nephropathy, hyaline accumulation in tubule, tubular pigmentation; Liver haematopoiesis, hepatocyte hypertrophy Lung: chronic inflammation Lymph node: haemorrhage Stomach: glandular erosion, ulceration, and inflammation Testes: germinal epithelium atrophy ALP↑, polychromasia, anisocytosis, Recovery 2: chronic inflammation of heart valve (M 1/5) 20: RBC↓(F), Haemoglobin↑(M). mean corpuscular volume and haemoglobin↑. MCHC↑, reticulocytes↑(M), Bilirubin↑, Iron↑, chronic inflammation of heart valve (F, n=3/5)
301_06_3510_088 GLP	Rat SD M+F 15 Recovery M+F/5	0, 5, 15, 30, 40 M+F40 group terminated on d61 and d98, respectively M30 group terminated on d131 Oral, TIW	Half year One-month recovery	M<5 F 5	≥5: reddened extremities (slight al low doses, moderate/marked at high dose), ≥15: RBC↑, reticulocyte count↑, Hb↑, Hct↑, MCV↑, MCH↑, platelet count↓, serum glucose↑, cholesterol↑, urine volume↓ (M), leukocytes in urine(M), erythropoiesis, hypercellularity of bone marrow, extramedullary haematopoiesis in spleen 30: mortality (10M; spleen size↑, pale/red kidney, liver, lung, intestines, thymus ovaries, uterus, thrombosis of aorta), bw↓, hunched posture, neutrophils and basophils ↑ (F), AST↑, bilirubin↑, serum calcium↑, serum potassium ↓(M), BUN↓(M), triglycerides↑(M), total protein↑(F), blood in urine (M), spleen (F) size↑, pale kidney(F), heart size↑ (F), splenic hemosiderin, hemosiderin deposits in renal tubular epithelium, Valvulopathy (including AV and aortic valves), valvular thrombosis, thromboembolism, valvular lesions, renal infarcts, basophilia of tubular epithelium in infarcted regions, inflammation, haemorrhage, and necrosis in the gastrointestinal tract, hippocampus (1F, focal region with missing neurons, necrosis, minimal gliosis) 40: mortality (5M 9F; adhesion and red discoloration cecum, watery yellow content in ilium, increased heart weight (F),), fc↓, Hb pigment in renal tubules Recovery: 5: valvulopathy (1M/5) ≥15: reticulocyte counts↓, spleen weight↑, valvulopathy without valvular thrombosis, haemorrhage, necrosis, inflammation of cecum, ≥30: atrophy, scarring, pale kidneys, heart weight↑(F), valvulopathy with valvular thrombosis
352007004 GLP	Rat (F344) M+F/15 Recovery M+F/5	0, 5, 15, 30, 40 Oral TIW	Half year 6 weeks recovery	15	≥5: iron↑, TIBC↑, femur and sternum: bone marrow erythroid hyperplasia, congestion, ≥15: RBC↑, haemoglobin↑(M), haematocrit↑(M), MCH↑(M), reticulocytes↑, platelet counts↑,

Study ID	Species/Sex/ Number/Group	Dose/ Route	Duration	NOAEL (mg/kg /day)	Major findings
		M+F40 terminated at day119			eosinophils↓, cholesterol↓, AST↑(M), spleen weight↑(M), 30: mortality (2M; hypoactivity, hunched posture, labored breathing, audible respirations, thin body condition, haircoat staining, rough haircoat, limited use of hind leg(s), recumbency, and/or general debilitation, increased red cell mass, valvulopathy in the heart, thromboembolic lesions), haemoglobin↑, haematocrit↑, MSV↑, MCH↑, basophils↑, prothrombin time↑, serum glucose↓, serum urea nitrogen↑, serum creatinine↑, total protein↑, albumin↑, AST↑(M), ALT↑(M), Urine occult blood, large spleen, large kidney, discoloured stomach, Testis: mottled, small, soft; heart weight↑, kidney weight↑, spleen weight↑, epididymis weight↓, testis weight↓, femur: bone marrow necrosis/fibrosis, sternum marrow congestion/haemorrhage, spleen: extramedullary haematopoiesis, heart: valvulopathy and thrombus of the A-V/aortic valves, kidney: necrosis, congestion, brain: Hippocampus Ammon's horn neuronal necrosis, pyramidal neuron degeneration, stomach: glandular necrosis and neutrophil infiltrate, ilium and cecum: necrosis (1M), testis: infarct with mineralisation, bilateral atrophy/degeneration 40: mortality (6M/4F, as with 30 mg/kg + 1M severe renal dysfunction (increased urea nitrogen, creatinine, and inorganic phosphorus), WBC↑(F), Urine bilirubin, kidney: thrombus, Ilium and cecum: necrosis, thrombosis, Recovery: ≥15: RBC↓(M), MCV↑(M), MCH↑(M), reticulocytes↑(M) 30: RBC↓, haemoglobin↓, haematocrit↓, MCV↑, MCH↑, reticulocytes↑, spleen weight↑
301_05_3510_020 Non-GLP	Cynomolgus Monkey M+F/1	0, 6, 20, 60 Oral	One Week	20	≥6: Hb↑, Hct↑, MCV↑, red cell distribution width↑ ≥20: total iron↑(M), erythropoietin levels↑ 60: inappetence, hunched posture, emesis
301_05_3510_021 GLP	Cynomolgus Monkey M+F/5 (0, 30) M+F/3 (1, 10) Recovery M+F/2 (0, 30)	0, 1, 10, 30 Oral	One month One-month recovery	30	≥10: RBC↑, Hb↑, Hct↑, reticulocytes↑, MCHC↓, WBC↓, lymphocytes↑, total cholesterol↓ 30: EPO levels↑ (peak 8-12h after dosing) bone marrow erythroid production↑, serum iron↓, UIBC↑, TIBC↑, glucose↓ Recovery: 30: Hct↑, Hb↑, reticulocyte count↓, glucose slightly↓, cholesterol↓(M)

Study ID	Species/Sex/Number/Group	Dose/Route	Duration	NOAEL (mg/kg/day)	Major findings
301_06_3510_082 GLP	Cynomolgus Monkey M+F/3 Recovery M+F/2	0, 1, 10, 30, 40 Three times weekly Oral	Five months Six weeks recovery	30 M 40 F	≥1: erythroid hyperplasia in sternal bone marrow, ≥10: anisocytosis, macrocytosis, polychromatophilia ≥30: red oral mucosa and gingivae, RBC↑, Hb↑, Hct↑ anisocytosis, macrocytosis, polychromatophilia, prolonged prothrombin and activated partial thromboplastin times, total bilirubin↑, total iron↓, cholesterol↓(F), red discolored adipose gastric tissue, bone marrow, thymus, uterus, congestion, slight haemorrhage, 40: 2 male monkeys: circulatory collapse/disturbance (with normal blood pressure), convulsions, twitching faintness, reddish discoloration of mucosa, hypoactivity, mortality (1M, with signs above and lying position, foamy saliva, apathy, red tongue, red gingiva and body temperature↓, erythroid hyperplasia in sternal bone marrow; animal had pre-existing cardiac instability before study initiation: bradycardia and grade 1 AV block prior to study initiation), AST↑, transferrin↑, glucose↓, pulmonary thrombi (2M), <u>Recovery</u> 30+40: red gastric discolored foci with minimal/slight gastric haemorrhage
301_06_3520_092 GLP	Cynomolgus Monkey M+F/5 Recovery M+F2	0, 3, 10, 20, 30 Three times weekly Oral	One year Two months recovery	30	≥20: RBC↑, Hb↑, Hct↑, absolute reticulocyte count↑, MCV↑, MCH↑, cholesterol↓
301_06_3510_078 GLP	Mouse Crl:CD-1(ICR) M+F/15 control M+F/10 treated	0, 10, 30, 60, 80(45 from day 3 onwards) Oral, three times weekly (TIW)	Three months	60	≥30: MCV↑, MCH↑, WBC↑ (F), lymphocytes↑ (F), total cholesterol↓ 60: spleen weight↑, extramedullary haematopoiesis in spleen↑

Study ID	Species/Sex/Number/Group	Dose/Route	Duration	NOAEL (mg/kg/day)	Major findings
301_06_3510_083 Non-GLP	Mouse CD-1 M+F/10	0, 60, 100, 150 Oral, three times weekly (TIW)	Three months	60	≥60: haemoglobin↑, haematocrit↑, MCV↑, MCH↑, spleen weight↑, splenic extramedullary haematopoiesis↑ ≥100: discoloration of feet, tails, ventral skin, and tongue, RBC↑, MCHC↑, congestion of adrenal gland and bone marrow, enlarged spleen 150: 2 M sacrificed with preceding clinical signs of (hunched posture, weight loss, scruffy hair coat), generalised organ congestion, hyperplastic bone marrow, total bilirubin, monocytes↑

Genotoxicity

Roxadustat was not found to be genotoxic in the reverse mutation test, chromosome aberration test and the *in vivo* micronucleus test.

Carcinogenicity

Roxadustat's potential for induction of carcinogenicity was assessed in rat and mouse in long-term 2-year studies. (See Table 3 below)

Table 3: Carcinogenicity studies

Study ID /GLP	Dose mg/kg TIW/Route	Exposure (AUC0-24h, µg.h/mL)	Species/No. of animals	Major findings
352010016 GLP	0, 15, 30, 60 Saline and vehicle control Oral	60 mg/kg 434 M 633 F	Mouse CD-1 72 M/F Tox 24 M/F PK	All tumour incidence findings either no dose response, within historical control within CRO (across testing facilities), not significantly different, or no dose response -Hepatocellular Adenoma (M) -Bronchioloalveoral adenoma (M) -Bronchioloalveoral carcinoma (M) -Malignant hemolymphoreticular lymphoma (F) -Mammary adenocarcinoma (F)
352010015 GLP	0, 2.5, 5, 10 Saline and vehicle control Oral	10 mg/kg 372 M 337 F	Rat SD 75 M/F Tox 24 M/F PK	-mammary gland adenomas (F), significantly elevated at mid dose, outside of historical control but no dose response ≥2.5: bone marrow hypercellularity in femur and sternum, hepatocellular vacuolation (F) ≥5: red cell distribution width ↑ 10: atrial/aortic thrombosis (M), 12 months: RBC↑, Hb↑ Hct↑

A series of exploratory non-GLP tumour studies were conducted in xenograft, syngeneic and transgenic mouse models in order to investigate the potential effects of roxadustat on tumour promotion, progression, incidence and metastasis formation. No effect of tumour progression was observed at pharmacologically active roxadustat doses in any of the xenografted or syngeneic models tested.

Reproductive toxicity

Table 4: Pivotal developmental and reproductive toxicity studies:

Study type/ Study ID / GLP	Species; Number Female/ group	Route & dose	Dosing period	Major findings	NOAEL mg/kg AUC µg.h/mL
Male fertility 352012001 GLP	Rat M/25	0, 5, 15, 30 TIW Oral	2 weeks prior to mating with untreated females Until 44-47 days after study initiation	≥15: enlarged spleen 30: mortality (n=1, all lung lobes dark red), epididymis and seminal vesicle weight↓, spleen weight↑, dark red liver (N=1)	General toxicity 5 Fertility 30 AUC0-24 779 Exposure margin: 4.0 total 9.1 unbound
Female fertility 352012001 GLP	Rat F/25	0, 5, 15, 30 TIW Oral	2 weeks prior to mating with untreated males until GD7	≥15: bw gain↑, 30: mean number/percentage of viable embryos↓, postimplantation loss↑, embryo mortality↑, dark red liver (n=2), white area on spleen (n=1), liver weight↑	General toxicity 5 Fertility 15 AUC0-24 429 Exposure margin: 2.2 total 5.0 unbound
Embryo-fetal development 352010001 GLP	Rat F/25	0, 5, 15, 30 daily Oral	GD 7-17	F0 ≥5: Platelet counts ↓ 30: bw gain↓, fc ↓, placental weight↑, RBC ↑, Hb↑, Hct↑, reticulocytes↑, MCV↑, MCHC↓ F1 30: fetal bw↓, 7th rib, edema and limb/digit malformations (n=1, within historical control)	F0 15 F1 15 AUC0-24 418 Exposure margin: 2.1 total 4.9 unbound
Embryo-fetal development 352010002 GLP	Rabbit F/20	0, 15, 35, 100 daily Oral	GD7-19	F0 35: abortion (n=1) 100: Bw↓, fc↓, soft, liquid, scant faeces, abortion (n=2), RBC↑, Hb↑, Hct↑, reticulocytes↑, MCV↑ F1 No findings	F0 35 F1 100 100mg/kg AUC0-24h 604 Exposure margin 3.0 total 5.6 unbound

Study type/ Study ID / GLP	Species; Number Female/ group	Route & dose	Dosing period	Major findings	NOAEL mg/kg AUC µg.h/mL
Pre- & postnatal 352013012 GLP	Rat F0/25 F1/25 (control, low and mid dose)	0, 5, 10, 20 daily	GD7-LD20	F0 ≥10: Hct↑(LD21) 20: bw↑ (GD7-18), bw↓ (GD18-20; LD14-17), fc↓, dying pups in litter (12/24 dams), Hct↑ (GD20), spleen weight↑ F1 5: bw↓(LD21), post-weaning bw gain ↓ PND22-36, fc ↓ PND22-43, preputial sparation delayed, vaginal patency delayed, epididymis and testis weight ↑, 10: mortality (4%, LD5-21), bw↓(LD7-21), % no milk in stomach↑ Post-weaning Bw gain↓, fc↓PND22-50, passive avoidance (latency trial 1 response↓) 20: mortality (75% LD5-21), lactation index↓, bw↓(LD1-21), early eye opening and incissor eruption, delayed acoustic startle, (no post-weaning F1 included in study due to high preweaning mortality rate), haematocrit↓	F0 10 F1 <5
Pre- & postnatal with cross-fostering 20097164 GLP	Rat F0/25 (GD7-20) F0/29-31 (cross fostering)	0, 15 daily	GD7-GD20 (Dams euthanised GD21) LD1-LD20 (Dams euthanised LD21) GD7-LD20 (Dams euthanised LD21)	GD7-GD20 F1 Postnatal Bw (gain)↓, Viability Index (PNDs 1-4)↓, mean plasma iron↓ LD1-LD20 F1 Lactation Index (PNDs 4-21)↓, post-natal mortality↑↑, Dehydration, not nesting/nursing, number of pups with no milk in stomach, post-natal bw gain↓, mean plasma iron↓, Hct↑ GD7-LD20 F1 post-natal bw gain↓, Viability Index (PNDs 1-4)↓, lactation index (PNDs 4-21)↓, mean plasma iron↓, Hct↑	All treatment groups <15

bw= body weight; fc = food consumption

Juvenile toxicity

Dose range finding studies in juvenile animals have been performed to support future paediatric development of roxadustat. These preliminary studies showed that PND 15 rats are less tolerable to roxadustat than PND22/29 and adult rats. This resulted in a dose-dependent effect on mortality and growth in rats treated from PND15 onwards, whereas this was not observed in PND22 and older rats. The free fraction plasma concentration in PND15 rats was also higher compared to PND22 and older rats.

Impurities

Impurity was negative in the bacterial reverse mutation assay.

Phototoxicity

Roxadustat did not show phototoxic potential in the Balb/c 3T3 neutral red uptake assay.

No dedicated studies were provided in local tolerance, antigenicity, immunotoxicity, dependence, metabolites toxicity.

2.3.5. Ecotoxicity/environmental risk assessment

Table 5: Summary of main study results

Substance (INN/Invented Name): roxadustat			
CAS-number (if available): 808118-40-3			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	log D_{ow} 3.4 at pH 4 log D_{ow} 0.71 at pH 7 log D_{ow} 0.17 at pH 9 Ion correction not possible	Potential PBT: No
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	log D_{ow} 3.4 at pH 4 log D_{ow} 0.71 at pH 7 log D_{ow} 0.17 at pH 9 Ion correction not possible	not B
	DegT50	$T_{50, water}$ (dissipation) = 10.8/17.2 d (l/l) DegT50$_{system}$ >10 000/>10 000 d (l/l) Sediment shifting 47-70% at day 14, increasing thereafter.	l=lake DT$_{50}$ values corrected to 12°C. Conclusion: vP
Toxicity	EC$_{10}$ algae EC$_{10}$ crust. EC$_{10}$ fish	>0.797 >2.40 >2.7	not T
	CMR	not investigated	potentially T
PBT-statement:	Roxadustat is not considered as PBT nor vPvB		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$, refined (treatment regime)	0.86	µg/L	> 0.01 threshold: Yes
Other concerns (e.g. chemical class)	-	-	
Phase II Physical-chemical properties and fate			

Study type	Test protocol	Results	Remarks
Adsorption-Desorption	OECD 106	$K_{oc\ sludge}$ 1560 L/kg (domestic), 1980 L/kg (domestic $K_{oc\ soil}$ 2360 L/kg (sandy loam), 626 L/kg (sandy clay loam), 990 L/kg (clay loam)	Geometric mean for sludge: 1757 L/kg Geometric mean for soil: 1135 L/kg
Ready Biodegradability Test	OECD 301	not available	not required
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	$DT_{50\ water}$ 5.1, 8.1 d (l/l) DegT50 $_{system}$ >10 000, >10 000 d (l/l) Sediment shifting 47-70% at day 14, increasing thereafter.	Not required if readily biodegradable l=lake DT_{50} values at 20°C; Significant shifting to sediment observed.

Phase IIa Effect studies

Study type	Test protocol	Endpoint	value	Unit	Remarks
Algae, Growth Inhibition Test/*Pseudokirchneriella subcapitata*	OECD 201	EC10	>797	mg/L	growth rate
Daphnia sp. Reproduction Test	OECD 211	EC10	>2.4	mg/L	mortality, time to 1st brood, reproduction and length
Fish, Early Life Stage Toxicity Test/*Pimephales promelas*	OECD 210	EC10	>2.7	mg/L	hatching, survival and body length
Activated Sludge, Respiration Inhibition Test	OECD 209	EC10	61	mg/L	respiration

Phase IIb Studies

Study type	Test protocol	Endpoint	value	Unit	Remarks
Sediment dwelling organism/*Chironomus riparius*	OECD 2218	EC10	>3014	mg/kg	normalised to 10% o.c.

2.3.6. Discussion on non-clinical aspects

Pharmacodynamics

The pharmacology studies provided by the applicant in general provide sufficient evidence for a proof of concept for roxadustat. *In vitro* results indicate that roxadustat inhibits all isoforms of the HIF-PH enzyme with high affinity, which results in accumulation of HIF-α and leads to increased expression of EPO. Several *in vivo* rat models of anaemia show increased EPO production and iron transport which provide sufficient evidence that treatment with roxadustat can be beneficial in patients suffering from anaemia.

Within *in vitro* inhibited HIF-PH enzymes was also collagen prolyl 4 hydrolase detected. This inhibition does not translate to an observable effect *in vivo* in animals within nonclinical studies, suggesting that roxadustat would have little or no effect on collagen synthesis in patients.

It should be noted that the *in vitro* studies were conducted under normal oxygen conditions, which will not be the case in patients suffering from anaemia.

Claimed increases in HIF-2α levels in the PD section which are responsible for erythropoiesis also play an important role in tumour progression and metastasis (Carroll VA, Ashcroft M., 2006). According to the analysis submitted by the applicant (results of nonclinical studies and cumulative clinical observations in a substantial number of patients) it could be concluded that roxadustat did not promote tumour formation.

Accumulation of HIF-1α and HIF-2α increase the expression of key enzymes for glycolysis (incl. increase IRS2 expression, which would lead to an increase in insulin secretion), leading to the increase in glucose consumption and a potential decrease in plasma glucose. Some statistically significant changes in blood glucose were observed in the 26-week intermittent dose studies in SD rats or F344 rats. However, these changes were transient or mild-to-moderate changes that were not associated with histopathologically relevant changes, suggesting that they were not biologically or toxicologically meaningful. No effects on glucose parameters were seen in the clinical studies. Therefore, this effect is likely not relevant for humans.

Also, vasodilation via HIF stimulation (targeting gens such as iNOS) is considered to be commonly conserved among animal species (incl. human), the sufficient safety margin between findings in rats and monkey to human exposure exist and in the clinical phase 3 programme, there was no overt signal of a hypotensive effect attributable to Roxadustat. It is expected that sufficient safety margin within animal to human exposure for vasodilatory findings exist.

An *in vitro* pharmacodynamic study (301-05-3010-056) revealed that inhibition of HIF-PHs is independent of iron concentration. Although erythropoiesis is iron dependent, the basal levels of iron on hematopoiesis in administration of roxadustat in animal model or in clinical trials did not impact the initial erythropoietic effect of roxadustat. In the absence of clear evidence that iron supplementation enhances the erythropoietic effect of roxadustat, a decision on recommending iron supplementation would depend on multiple clinical factors including benefit risk analysis for the patient.

In safety pharmacology studies, mainly effects that can be related to the pharmacological action of roxadustat were observed. Roxadustat had an effect on heart rate (HR) in monkeys, where it increased HR by 55% at the highest dose of 100 mg/kg tested. The mechanism behind this effect on cardiac function is not fully clear, but a pharmacology-related mechanism seems likely, since these effects are associated with acute hypoxia in order to increase the amount of oxygen circulated throughout the body, and could thus be in response to the increases in HIFα. This is further substantiated by the fact that increases in HR were seen in healthy volunteers given roxadustat, but no such effect was seen in patients that already have the physiological response to decreased oxygen concentration, and therefore the added effect of roxadustat is less pronounced than in healthy volunteers. Additionally, a renal function study in conscious rats showed that oral roxadustat increased urine volumes, and urine pH was significantly higher and increases in potassium (K+), sodium (Na+) and chloride (Cl-) were seen. The effect was only seen at higher doses, with a safety margin of 1.8-fold, and appear to be rat-specific as no effects were seen in the monkey studies. Moreover, no adverse effects on the urinary system were reported in patients with decreased renal function. A clinical relevance of the renal findings in rats for patients is therefore unlikely.

Pharmacokinetics

Regarding the pharmacokinetics section, the applicant was requested to further discuss whether the safety of the metabolite MET4 in human has been sufficiently covered in the animal studies, regarding potential effects as the result of enterohepatic circulation of and/or drug interactions via transporter proteins. MET4 was a significant metabolite in human faeces. However, MET4 was not detected in human plasma nor in animal plasma, urine, faeces (rat) or bile (cynomolgus monkey). It is assumed that in monkeys, MET 3 is deconjugated in faeces by intestinal bacteria, similar to troglitazone, for which the sulfate position is the same as with MET3. In addition, one of MET11-1/2 (found in rat feces) is likely to be MET4, based on comparable results of the product ion patterns between MET4 and MET11-1 and the retention times between MET4 and C10.

No pharmacokinetic parameters were submitted for the animal model of disease. However, as Roxadustat is extensively metabolised and excreted only in minor amount (as parent compound) into the urine, the PK characteristics of animal model of disease and healthy animal are expected to be very similar.

The results from HPLC-LSC method to measure plasma roxadustat concentrations in selected samples are considered as sufficiently reliable to conclude that no metabolites were present at more than 10% of the total drug-related material.

The trend test for onset rate of fibrosarcoma in skin/subcutis fibrosarcoma was statistically significant. Roxadustat is distributed to skin. However, no clear dose-response relationship of fibrosarcoma was demonstrated across groups. In addition, the incidence is in a range for historical control for female mice. The results therefore do not suggest any compound-related increase over the basal levels of skin/subcutis fibrosarcoma.

Toxicology

Further discussion on clinical relevance of the myelofibrosis observed in the 4-week study in SD rats (ISN: 301_05_3510_019) and the possible mode of action was requested. The applicant clarified that myelofibrosis observed in the 4-week repeat-dose study in SD rats occurred in conjunction with bone marrow thrombosis. It is agreed that myelofibrosis observed in rats is not relevant for patients as these are clinically controlled to avoid the exaggerated pharmacological effect of roxadustat due excessive erythropoiesis.

The applicant provided literature data [Haschek et al, 2010] to justify that occurrence of stomach ulcer is a well-known effect of response to stress. Thrombus was not recorded in the gastrointestinal tract in the 4-week study in SD rats, therefore the ulcer and erosion were considered as less likely to be related to thromboembolism in this study. As microscopic examination showed stress-related cortical atrophy in the thymus and since gastric ulcer or erosion occurred only in animals at moribund state at high dose, these effects do not raise further concern for patients.

In the repeat dose studies (in SD Rats and F344 rats) mortality was related to severe exaggerated pharmacology effects related to erythropoiesis. In addition, other target organs were the heart, which was enlarged, and valvulopathy and valvular legions were observed in combination with thromboembolisms in multiple animals. Also, severe effects on the kidney were observed including kidney infarcts, multiple histological changes and leukocytes and blood in the urine. After one month of recovery, valvulopathy was observed at all dose groups. At higher doses which did not induce mortality, valvulopathy was observed in the absence of thrombosis. In addition, reticulocyte counts were decreased, spleen weight was increased, necrosis and inflammation of the cecum was observed. Also, at the doses inducing mortality, atrophy, scarring and pale kidney were observed, heart weight was increased in females and valvulopathy together with valvular thrombosis was observed.

The six-month repeat-dose toxicity study was performed twice in different rat strains the applicant justified repeating the study in a second strain to confirm that valvulopathy was not a strain-specific finding. The discussion provided by the applicant was considered sufficient. However, in this specific case it was commented that it would have been preferable if the applicant had applied for scientific advice at a regulatory authority to discuss the need to perform such a study before start of the study.

In the rat, valvulopathy has been associated with excessive erythropoiesis in literature with other ESA's. This effect was not observed in the cynomolgus monkey. The applicant argued that this is a rat specific effect due to increased shear stress on cardiac valves due to increased cell mass, increased blood viscosity and enhanced chance of thrombosis. The applicant discussed literature data (Elangbam et al, 2002) and historical data for the CRO of concern for the incidence of valvulopathy in long-term studies [Covance, 2020a; Covance, 2020b].   It is agreed that the incidence of valvulopathies observed in the low-dose group of SD rats fall within both the historical and literature incidence range and, as such could be a background finding. Based on Covance data, SD rats suffer for significantly higher incidence of age-related spontaneous valvulopathy than F344 rats. Minimal valvulopahy observed in one male at low dose necropsied on D210 (study 301_06_3510_088) thus does not raise a further concern. It is however of note that dose-related (mid and high dose) chronic inflammation of heart valves was also observed in a repeat-dose one-month study (301_05_3510_019) next to the spontaneous incidence for SD rats clearly demonstrating drug-related effects.

Across all studies, decreased cholesterol and glucose levels were observed. The mechanism behind roxadustat related decreases in cholesterol and glucose have been discussed in the non-clinical pharmacodynamics section.

In conclusion, in rat, next to the expected pharmacological adverse effects related to erythropoiesis, the main target organs of roxadustat in the repeat-dose toxicity studies are the heart and kidney. Effects in these organs were only in part reversible and observed at dose levels not inducing mortality and at an exposure level slightly higher than exposure at MRHD.

It is acknowledged that clinically excessive erythropoiesis can be managed by controlling rate of Hb rise and by setting maximum target Hb levels. However, in case of inadvertent higher Hb levels, in between the Hb control measurements, safety issues observed in the rat may be relevant for human. In addition, due to the relatively low exposure margin at which these adverse effects are observed in rat, and the long-term treatment with roxadustat in the clinic, the adverse findings in rat heart (including valvulopathy and thrombi), brain (hippocampal necrosis) and kidney (ischaemia, infarction), and infarctions in general can theoretically be considered a cause of concern for the clinical situation. Therefore, the applicant was requested to discuss the following findings in more detail in SmPC section 5.3: Findings of 1) the valvulopathy in rat, 2) findings of necrosis in the hippocampus in rat, and 3) the ischaemic effects in kidney and heart in rat 4) general increased risk of infractions in rat.

For the pivotal carcinogenicity and reproductive toxicology animal studies, AUC0-24h was measured. For human AUC0-48h is provided. The human profile shows a high exposure during the first 24 hours and a much less exposure during the next 48 hours. However, in animals, the intended pharmacodynamic effect and related toxicity was shown to be delayed by up to 3 days, and therefore not directly related or comparable to the exposure to roxadustat. Further, the difference in AUC calculation between animals and humans has little numerical effect. In addition, as after three days roxadustat would have been completely cleared, specific toxicity effects are not considered to be induced by direct presence of the roxadustat. Therefore, the effects observed are considered to be induced by upstream regulation induced by roxadustat. Furthermore, the applicant states that high doses were selected based on MTD. As more frequent administration of roxadustat would not have been feasible for such a long study, it is acceptable that under the circumstances this was an optimal dosing strategy.

Regarding the mammary tumours in mouse and rat, there is not a dose-response in either species, although there are increased exposures overdose. Also findings in a xenograft mouse model for human breast cancer showed increased VEGF levels systemically, but no increase in VEGF expression, a marker for increased angiogenesis, in the xenografted breast cancer tumour tissue. The mammary tumours seen in the mouse and rat carcinogenicity studies are likely not roxadustat induced and from the xenograft model it can be concluded that roxadustat did not have a pro-survival effect on breast cancer tumour and did not induce tumour growth. The applicant provided additional historical incidence data. Although the incidence for the 15 mg/kg per day dose group was outside the historical incidence range of this tumour in CD-1 male mice at the testing facility (0 - 16.7%), all groups were within the incidence reported for CD-1 male mice at other facilities (1.4% - 20.0%). It is agreed that bronchioloalveolar adenoma or carcinoma in the lung in mice are considered not to be roxadustat-induced and there is no risk to humans. Haemorrhage and inflammation in the lung in the 4- and 26-week SD rat studies is likely drug-related due to the dose-proportionality, but these were considered to be secondary effects of thrombus in the heart.

In addition, in a scientific advice, CHMP raised a concern that the HIF pathway has been implicated in renal tumour biology, especially renal cell carcinoma. The applicant was asked to carefully examine signs of renal cancer during the long-term and carcinogenicity study. In mice, no renal tumours were observed. In rat, one case of renal tubular cell adenoma (mid-dose) and one animal with multiple renal carcinomas (high dose) were observed. The renal adenoma finding was within historical control range of the facility; however, the incidence of renal carcinoma was outside of the test facility and CRO's combined test facility historical control range. However, as there was only one animal with renal carcinoma's, there is not enough evidence to relate the finding to treatment with roxadustat. Furthermore, in a 786-O human renal tumour xenograft 26-day nu/nu Mouse model study showed no significant roxadustat induced effects on tumour growth, tumour tissue vascular density or circulating VEGF protein.

In the FEED Study 352012001 in rats, enlarged spleens were observed which correlated with significantly higher spleen weights at 30 mg/kg on day 13 of gestation. These findings can be considered as reflections of the intended pharmacological activity. In another study after a 4-week recovery period with enhanced extramedullary hematopoiesis in the spleen, hematological parameters were not fully recovered showing prolonged pharmacodynamic effects of roxadustat. It is agreed that based on (healthy) animal data there is no direct effect of roxadustat on foetal lethality.

As increased mortality was specifically observed with roxadustat exposure during the lactation period at relatively low maternal plasma exposure levels, a contraindication breastfeeding based on animal data as proposed by the applicant is agreed.

The applicant also provided literature data to clarify that possible cause of the early achievement of criterion for eye opening and incisor eruption observed in the PPND study could be due to the downstream effects of roxadustat's action on the HIF pathway via exposure of the pup to breast milk. EGF is one of the genes thought to be controlled by hypoxia inducible factor (HIF) [Rabinowitz, 2013], suggesting that HIF accumulation resulting from HIF prolyl hydroxylase inhibition by roxadustat leads to an increase in EGF.

In the non-clinical overview, the applicant discussed the effects of low maternal plasma cholesterol levels on the fetus. LDL cholesterol plasma changes in patients treated with roxadustat were lowered with approximately 0.5 mmol/L. Reference plasma levels of LDL cholesterol are less than 2.59 mmol/L in non-pregnant women, between 1.55-3.96 during the first trimester, between 1.99-4.77 in the second trimester and 2.62-5.8 during the third trimester[1]. However, this may not exactly apply to the current diseased CKD population in whom higher LDL-cholesterol levels may be expected in a

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[1] (http://perinatology.com/Reference/Reference%20Ranges/Cholesterol,LDL.htm, accessed 2020 July 09).

considerable proportion of the patients. Based on the limited decrease of LDL cholesterol by roxadustat and the expected increased LDL cholesterol in patients indicated for roxadustat therapy it is not considered likely that roxadustat induced decreases in LDL-cholesterol will have an adverse effect on pregnancy.

Regarding the ecotoxicity/environmental risk assessment, roxadustat is not persistent, bioaccumulative and toxic (PBT), nor vPvB. Based on the prescribed use and considering the available data, roxadustat is not expected to pose a risk to the environment.

2.3.7. Conclusion on the non-clinical aspects

Overall, the non-clinical documentation submitted was considered adequate. The relevant information has been included in the SmPC (sections 4.6, 5.1 and 5.3).

2.4. Clinical aspects

2.4.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Table 6: Clinical pharmacology studies of roxadustat

Type	Region/ Country	Study No.	n	Population	Doses Evaluated	Study Description
Biopharmaceutics †	EU	1517-CL-0545	24	Healthy Subjects	150 mg	BE of TBM vs Phase 3 Tablet
	US	FGCL-4592-066	24	Healthy Subjects	100 mg	RBA; Food Effect
	Japan	1517-CL-0202	16	Healthy Male Subjects	100 mg	Food Effect with Japan TBM tablet
	US	FGCL-4592-027	12	Healthy Male Subjects	2 mg/kg	Pilot Food Effect
Pharmacokinetics in Healthy Subjects	EU	FGCL-SM4592-016	145	Healthy Male Subjects	0.3 to 4.0 mg/kg	Single and Multiple-dose Pharmacokinetics
	Japan	1517-CL-0201	100	Healthy Male Subjects	0.3 to 4.0 mg/kg	Single and Multiple-dose Pharmacokinetics in Japanese Subjects
	China	FGCL-4592-043	40	Healthy Subjects	40 to 200 mg	Single-dose Pharmacokinetics in Chinese Subjects
	China	FGCL-4592-044	45	Healthy Subjects	40 to 200 mg	Multiple-dose Pharmacokinetics in Chinese Subjects
	EU	1517-CL-0525	50	Healthy Subjects	50 to 200 mg	Dose Proportionality, Age/Sex
	US	FGCL-4592-058	6	Healthy Male Subjects	200 mg	Mass Balance, Metabolic Profile
Pharmacokinetics in Patients with CKD	US	FGCL-4592-039	17	ESRD Patients	1.0 and 2.0 mg/kg	Single-dose Pharmacokinetics in CKD
	Japan	1517-CL-0203	12	ESRD Patients	1.0 and 2.0 mg/kg	Single-dose Pharmacokinetics; Effect of Dialysis; Metabolic Profile
	EU	1517-CL-0543	34	Patients with severe RI or ESRD; healthy subjects	100 mg	Pharmacokinetics and Metabolic Profile, Effect of Dialysis
Intrinsic Factors	EU	1517-CL-0513	16	Patients with Liver Disease (Child-Pugh B); healthy subjects	100 mg	Moderate Hepatic Impairment
Drug-drug Interactions Roxadustat as Victim	EU	1517-CL-0526	84	Healthy Subjects	200 mg	Sevelamer Carbonate and Calcium Acetate (Phosphate Binders)
	Japan	1517-CL-0205	18	Healthy Male Subjects	100 mg	Lanthanum Carbonate Hydrate (Phosphate Binder)
	Japan	1517-CL-0204	34	Healthy Male Subjects	100 mg	Kremezin (Adsorptive Charcoal)
	EU	1517-CL-0527	18	Healthy Subjects	100 mg	Omeprazole (PPI)
	EU	1517-CL-0508	18	Healthy Subjects	100 mg	Gemfibrozil (CYP2C8 and OATP1B1 Inhibitor)
	EU	1517-CL-0532	18	Healthy Subjects	100 mg	Probenecid (UGT and OAT1/3 Inhibitor)

Table continued on next page

Type	Region/ Country	Study No.	n	Population	Doses Evaluated	Study Description
Drug-drug Interactions Roxadustat as Perpetrator	US	FGCL-4592-037	20	Healthy Male Subjects	150 mg	Rosiglitazone (CYP2C8)
	EU	1517-CL-0509	22	Healthy Subjects	200 mg	Warfarin (CYP2C9)
	EU	1517-CL-0531	24	Healthy Subjects	200 mg	Bupropion (CYP2B6)
	EU	1517-CL-0537	28	Healthy Subjects	200 mg	Simvastatin, Rosuvastatin (BCRP and OATP1B1)
	EU	1517-CL-0538	24	Healthy Subjects	200 mg	Atorvastatin (BCRP and OATP1B1)
	EU	1517-CL-0541	24	Healthy Subjects	200 mg	Simvastatin Dose Separation (BCRP and OATP1B1)
Thorough QT	US	FGCL-4592-065	45	Healthy Subjects	2.75 and 5 mg/kg	TQT

2.4.2. Pharmacokinetics

Various characteristics of roxadustat were investigated in healthy subjects, such as mass balance, dose proportionality, accumulation, age/sex, formulation comparisons, QT prolongation and DDIs, and in subjects with renal or hepatic impairment. A total of 28 phase 1 clinical studies (27 clinical pharmacology studies [Table 6] and 1 additional bioavailability study in China [not listed]) were performed and provide a characterisation of the clinical pharmacology of roxadustat. Additionally, a population pharmacokinetic analysis of roxadustat in NDD and DD patients (phase 3) supports the pharmacokinetic characterisation of roxadustat.

Several bioanalytical assays have been used throughout the development programme. The bioanalytical methods for the quantification of roxadustat have been validated and results were extensively presented (results not shown in this report). Noncompartmental analysis was used to estimate pharmacokinetic parameters in the phase 1 studies. Analyses were conducted using actual sampling times. The primary pharmacokinetic parameters were AUC_{inf} and C_{max}.

Absorption

Roxadustat is a relatively high permeability compound with low solubility. Maximum plasma concentrations are observed at 2h post administration. The absorption of roxadustat from the gastrointestinal tract is at least 60%.

Bioequivalence was concluded between the to-be-marketed and phase 3 tablets. Additionally, a justification was given for waiving additional *in vivo* bioequivalence studies for the lower strengths between the to-be-marketed and phase 3 tablets. It has sufficiently been supported that differences between the formulations used in the clinical studies do not hamper conclusions drawn from these studies and use of the to-be-marketed is accepted.

The influence of food on the bioavailability of roxadustat was studied it can be estimated that the AUC is reduced by 6-11% under the influence of food. The C_{max} is estimated to be reduced by 20-35% under the influence of food. The influence of food has not been investigated with the to-be-marketed tablets, which differ from the phase 3 tablets.

Distribution

Distribution of roxadustat has been characterised in several *in vivo* and *in vitro* investigations. The compound is highly bound to human plasma proteins (~99%), predominantly to albumin and

independent of the concentration. Distribution into RBCs is low. The estimated apparent volume of distribution, at steady state, is approximately 24 L in patients with CKD.

Metabolism

The metabolism of roxadustat has been characterised in several *in vivo* and *in vitro* investigations. Unchanged roxadustat is the predominant circulating compound in plasma. Based on urinary and faecal samples, the majority of roxadustat metabolism occurred through hydroxylation/oxidation followed by sulfation (MET4 and MET3, together 20% of the dose) and o-glucuronidation (MET1, 28% of the dose). CYP2C8 appears to be the major CYP enzyme responsible for the conversion of roxadustat to MET4. UGT1A9 appears to be the major contributor in the glucuronidation to MET1 in human liver. UGT1A7 and UGT1A8 may be involved in the extrahepatic formation of MET1. Minor metabolic routes included glucosidation (MET2, 8.1% of the dose), acyl glucuronidation (MET5, 0.6% of the dose), and demethylation (MET7 and MET6, together ~3.6% of the dose). No metabolite detected in human plasma constituted more than 10% of total drug-related material exposure and no human specific metabolites were observed.

Pharmacokinetic characteristics of the main metabolites have adequately been characterised. None of the metabolites are present at plasma concentrations higher than 10% of the total roxadustat dose, in healthy subjects, or patients. It is therefore agreed with the applicant that further evaluation of the metabolites is not a requirement. MET1 was the predominant component in urine and the main urinary metabolite, consisting of 28% of the radiolabeled dose. In plasma, MET1 is circulating at very low concentrations, between 0.2 and 0.7% of the parent. UGT1A9 is a major contributor in the glucuronidation of roxadustat to its O-glucuronide in human liver, with possible contributions of UGT1A7 and UGT1A8. MET3 is the primary metabolite in plasma and a sulfate conjugate of MET4. MET4 itself has no systemic exposure but was the main metabolite in faeces of healthy subjects accounting for 17% of the radiolabeled dose. Hydroxylation of roxadustat is mediated primarily by CYP2C8, although metabolism by CYP1A1 was also detected. Glucosidation to MET2 is a minor route of elimination for roxadustat, plasma concentrations were 0.1% to 0.4% of the parent. A total of 8.1% of a radiolabeled dose was recovered in urine as MET2.

Elimination

Approximately 50% of a total oral radiolabeled dose in healthy subjects is excreted in faeces, of which 28% represented unchanged roxadustat. Approximately 46% of the total oral radiolabeled dose in healthy subjects is excreted in the urine, primarily as metabolites. Less than 2% of the dose was recovered in urine as unchanged roxadustat. Urinary excretion of unchanged roxadustat plays a minor role in the overall excretion.

Polymorphism

Roxadustat is a substrate for the polymorphic enzymes (CYP2C8 and UGT1A9), which are estimated to be responsible for 20% and 28%, respectively, of the clearance of roxadustat in healthy subjects. It is expected that polymorphisms of CYP2C8 and UGT1A9 will only influence clearance of roxadustat to a minor extent. Further, the impact of genetic variance on roxadustat pharmacokinetics is fully mitigated by the titration of the dosing regimen, which is based on the patient's haemoglobin response.

Dose proportionality and time dependencies

Using a power model approach, the predicted increase in AUC_{inf} was 2.08-fold with a predicted increase in C_{max} of 1.95-fold for every 2-fold increase in dose within the range of 50 to 200 mg. The

pharmacokinetics of roxadustat behave in a dose proportional manner, over the dose range of 50 to 200 mg.

Roxadustat pharmacokinetics do not change over time. Results from studies 1517-CL-0201, FGCL-SM4592-016 and 1517-CL-0541 demonstrate an accumulation ratio of roxadustat between 1.06 and 1.14, and other pharmacokinetic parameters were comparable after single and multiple doses of 200 mg roxadustat.
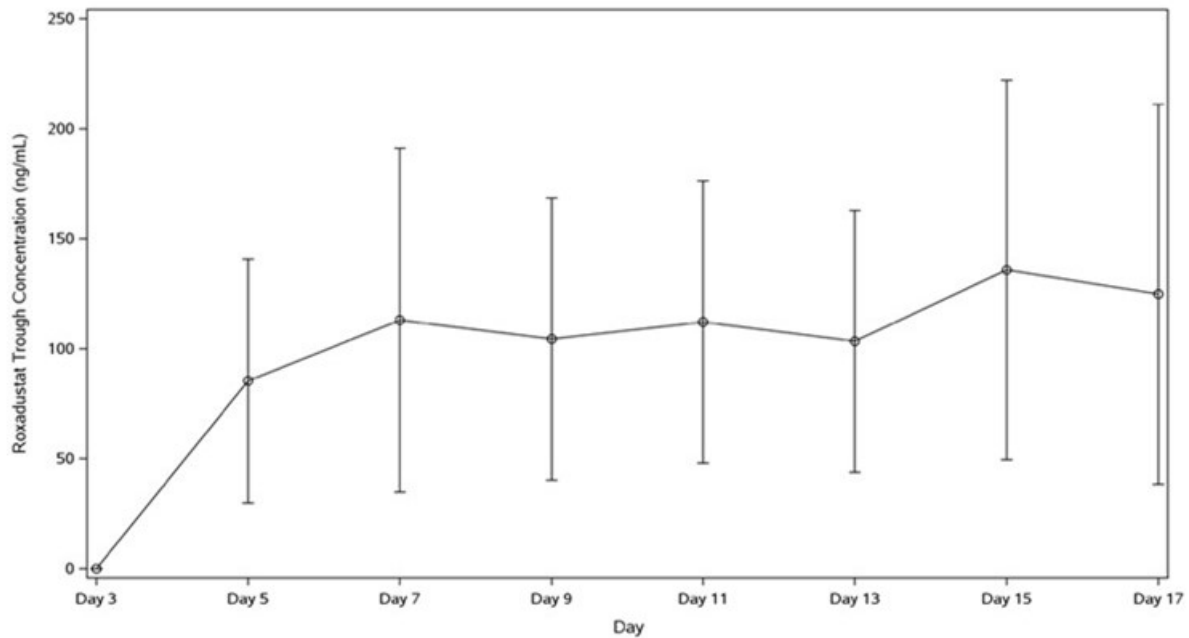
Figure 4: Mean trough plasma concentration-time profile of roxadustat after 200 mg dosed every other day
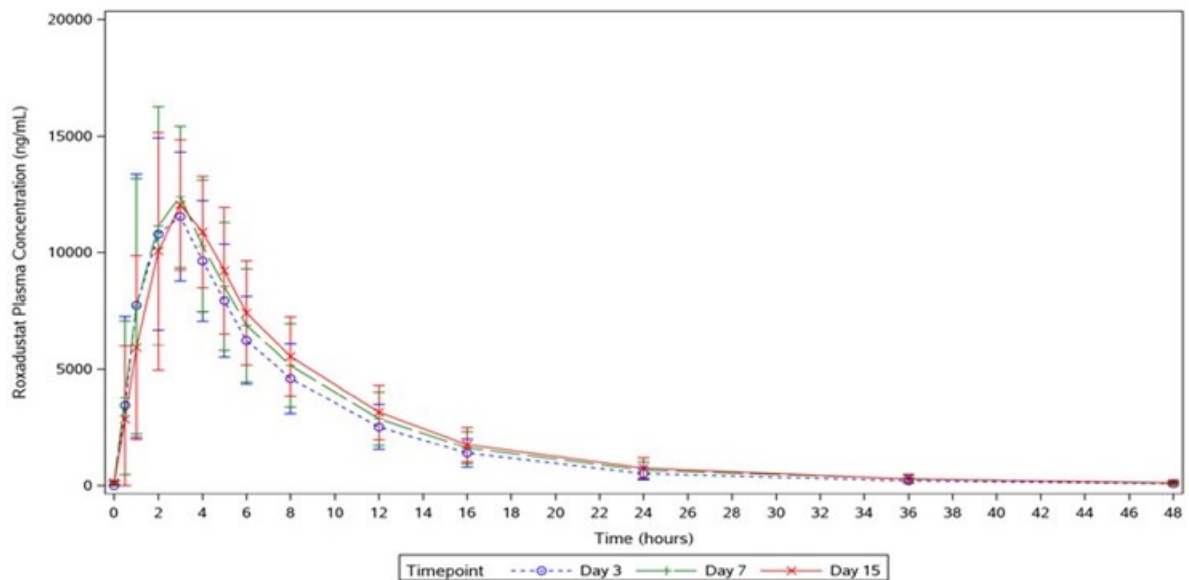
Figure 5: Mean roxadustat plasma concentration-time profiles after administration of 200 mg every other day

Intra- and inter-individual variability

Inter-subject variability for roxadustat C_{max} and AUC_{inf} was estimated to be approximately 20% to 40% in phase 1 studies and is, based on the phase 3 patient population, estimated to be 69.5% for AUC. Intra-subject variability was estimated to be 17.2% for C_{max} and 9.9% for AUC.

Pharmacokinetics in target population

Renal disease and on haemodialysis are the two main determinants of the patient population. Population pharmacokinetic analysis based on sampling during the phase 3 studies support conclusions drawn in the renal impairment studies. Roxadustat AUC is approximately 2.2-fold higher in patients with severe renal impairment and 1.9-fold higher in patients with end stage renal disease (ESRD) on dialysis than in healthy subjects, but C_{max} is comparable. Haemodialysis did not have a significant effect on roxadustat pharmacokinetic parameters, in line with the high plasma protein binding.
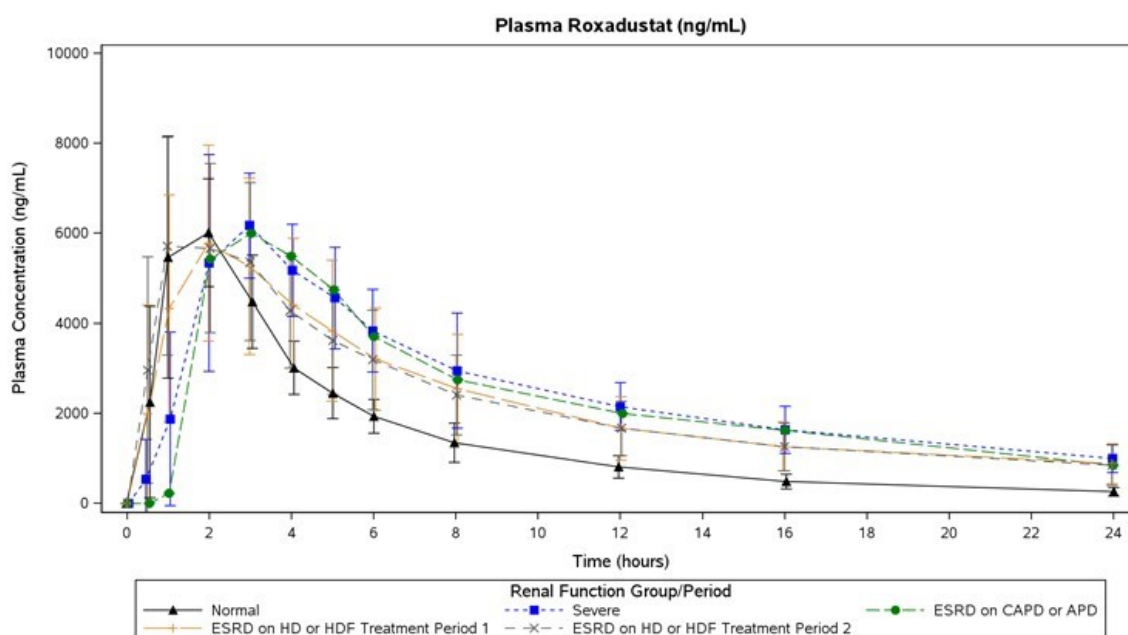
Figure 6: Mean roxadustat plasma concentration-time profiles (up to 24 hours) after a single 100-mg dose of roxadustat in healthy subjects and patients with renal impairment

Table 7: Summary of key roxadustat pharmacokinetic parameters after a single 100-mg dose of roxadustat in healthy subjects and patients with renal impairment

Population	n	C_{max} (ng/mL)	t_{max} (h)	AUC_{inf} (ng•h/mL)	$t_{1/2}$ (h)	CL/F (L/h)	Geometric Mean Ratio (%) (90% CI)†	
							C_{max}	AUC_{inf}
Healthy subjects	12	6780 (21.6)	1.00 (0.983-3.00)	39800 (22.1)	16.0 (42.3)	2.62 (20.4)	NA	NA
Severe renal impairment	9	6730 (19.5)	3.00 (1.00-4.00)	82500 (22.2)	18.5 (23.8)	1.26 (21.2)	107.37 (86.88, 132.69)	222.59 (184.83, 268.05)
ESRD on HD or HDF; 2 h after dialysis	12	6950 (26.6)	2.00 (0.967-5.00)	77400 (38.1)	17.2 (40.4)	1.45 (32.6)	101.67 (84.30, 122.63)	194.54 (165.03, 229.34)
ESRD on HD or HDF; 2 h before dialysis	12	6910 (18.6)	1.00 (0.967-4.00)	76600 (36.9)	16.8 (33.0)	1.47 (34.7)	NA	NA
ESRD on CAPD	1	6010	3.00	74900	12.5	1.34	NA	NA

Values are mean (%CV); median (minimum-maximum) for t_{max}.

Special populations

For the characterisation of roxadustat pharmacokinetic characteristics in special populations, several studies have been performed. Dedicated studies were performed to investigate the effect of renal impairment (study 1517-CL-0543), hepatic impairment (study 1517-CL-0513), and the effect of gender and age (study 1517-CL-0525).

A population pharmacokinetic analysis was performed to aid in the characterisation of these factors, as well as race and body weight. The conclusions drawn regarding the effects of race and body weight on the pharmacokinetics of roxadustat were solely based on the population pharmacokinetics analysis.

Urinary excretion and renal clearance of roxadustat and metabolites was decreased in subjects with severe renal impairment or ESRD on dialysis. Roxadustat AUC is approximately 2.2-fold higher in patients with severe renal impairment and 1.9-fold higher in patients with end stage renal disease (ESRD) on dialysis than in healthy subjects, but C_{max} is comparable.

For subjects with moderate hepatic impairment (Child-Pugh Class B) and normal renal function, roxadustat AUC was increased by 23% and C_{max} decreased by 16% and unbound roxadustat AUC_{inf} was increased by app. 70% relative to healthy subjects. Starting dose is to be reduced by half when initiating treatment in patients with moderate hepatic impairment (Child-Pugh class B). No data were presented for patients with severe hepatic impairment (Child Pugh class C).

In the investigation into the influence of gender on the pharmacokinetics of roxadustat, weight-normalised AUC_{inf} and C_{max} were only increased to a minor extent (9% and 2% respectively) for the female, compared to the male subjects. These increases are not clinically relevant

Body weight has been investigated in the population pharmacokinetic analysis, in which it was identified as a statistically significant covariate on CL/F, with 13-18 % changes of AUC and C_{max} when comparing 50 kg individuals to 70 kg patients, and 70 kg to 100 kg patients. Clinically relevant body weight subgroups between 46-118 kg were included in the simulations and this demonstrated that the expected effect on the roxadustat exposure is limited.

Increases of the AUC were estimated for Asian, Black, American Indian/Alaskan native and 'other' included patients, in the range of 12-26%. A clear cause for these differences has not been identified but is more likely to be found in genetic polymorphisms and/or pharmacokinetic variability.

In study 1517-CL-0525, elderly subjects (65-80 years) exhibited approximately 23% higher AUC_{inf} and 15% higher C_{max} of roxadustat than the younger subjects (21-44 years). Phase 3 studies were largely conducted with sufficient inclusion of elderly patients. It can therefore be accepted that a small difference of pharmacokinetics between the younger and older groups exist.

Table 8: Number of Elderly Subjects in Pharmacokinetic Studies Stratified by Age (65-74, 75-84 and ≥ 85 years)

Pharmacokinetic Studies	Age 65-74 (Older subjects number /total number)	Age 75-84 (Older subjects number /total number)	Age 85+ (Older subjects number /total number)
Phase 1 Pharmacokinetic Studies			
1517-CL-0203	5/12	0/12	0/12
1517-CL-0513	3/16	0/16	0/16
1517-CL-0525	15/50	9/50	0/50
FGCL-4592-039	3/17	1/17	0/17
1517-CL-0543	9/34	2/34	0/34
Total	35/129	12/129	0/129
Phase 2&3 Pharmacokinetic Studies			
1517-CL-0302	26/56	5/56	1/56
1517-CL-0303	61/107	0/107	0/107
1517-CL-0304	59/129	0/129	0/129
1517-CL-0307	115/302	54/302	4/302
1517-CL-0308	21/75	23/75	2/75
1517-CL-0310	112/332	115/332	17/332
1517-CL-0312	49/163	27/163	1/163
1517-CL-0314	36/99	27/99	6/99
1517-CL-0608	163/594	86/594	10/594
1517-CL-0610	168/616	181/616	30/616
1517-CL-0613	229/834	131/834	23/834
D5740C00001	671/2760	466/2760	98/2760
D5740C00002	351/2101	148/2101	24/2101
FGCL-4592-017	42/116	19/116	0/116
FGCL-4592-040	37/161	8/161	0/161
FGCL-4592-041	63/145	21/145	0/145
FGCL-4592-048	12/96	0/96	0/96
FGCL-4592-806	24/304	0/304	0/304
FGCL-4592-808	51/195	0/195	0/195
Total	2290/9185	1311/9185	216/9185

Pharmacokinetic interaction studies

Roxadustat is a substrate of BCRP, OATP1B1, OAT1 and OAT3, but not of P-gp, MRP2, OATP1B3, OCT1, OCT2, BSEP, and MATE1.

Based on *in vitro* studies, roxadustat may be a clinically relevant inhibitor of CYP2C8 (Ki = 16 µM) at maximal systemic concentrations. Roxadustat is not an inhibitor of other CYPs at maximal systemic concentrations and not of CYP3A4 at maximal intestinal concentrations. Roxadustat is an inhibitor of UGT1A1 ($IC_{50}/2$ = 29 µM) at maximal intestinal concentrations. However, roxadustat is not an inhibitor of UGT1A1, 1A3, 1A4, 1A6, 1A9 and 2B7 at maximal systemic concentrations. Transporters were also identified to be inhibited by roxadustat; BCRP at relevant intestinal and systemic concentrations, OATP1B1 at relevant portal vein concentrations, and OATP1B1, OAT1, and OAT3 at relevant systemic concentrations.

In vivo studies were performed for the potential for roxadustat as a victim for phosphate binders, adsorptive charcoal and omeprazole and with gemfibrozil (CYP2C8 and OATP1B1 inhibitor) and probenecid (UGT and OAT inhibitor). Studies for roxadustat as perpetrator have been performed for roxadustat's potential to inhibit CYP enzymes (CYP2B6, CYP2C8 and CYP2C9) or transporters (BCRP and OATP1B1).

Roxadustat as victim

Absorption-based interactions were investigated. Concomitant administration of roxadustat and sevelamer carbonate or calcium acetate results in a lower roxadustat plasma exposure, by approximately 67% and 46% (AUC) and 66% and 52% (C_{max}). The interaction is presumably a result of formation of insoluble chelation complexes in the gastrointestinal tract that inhibit roxadustat absorption. The reduction of roxadustat plasma exposure by concomitant administration of sevelamer carbonate or calcium acetate should be extrapolated to multivalent cation-containing drugs or products. Other absorption-based interactions are not expected, as no interaction was observed upon administration of roxadustat with proton pump inhibitor omeprazole, or an oral adsorptive charcoal.

Co-administration with gemfibrozil (CYP2C8 and OATP1B1 inhibitor) or probenecid (UGT and OAT inhibitor) in healthy subjects resulted in an increase in roxadustat exposure. With gemfibrozil by approximately 2.3-fold (AUC) and 1.4-fold (C_{max}), and with probenecid also by 2.3-fold (AUC) and 1.4-fold (C_{max}). A clinically relevant interaction with clopidogrel is not expected, based on the lower interaction potential of clopidogrel compared to gemfibrozil, clopidogrel was not identified as a significant factor on roxadustat pharmacokinetics in patients with chronic kidney disease by the population modeling analyses and the overall decreased metabolic and transporter function in the CKD population.

Roxadustat as perpetrator

In vivo DDI studies were performed with simvastatin, rosuvastatin and atorvastatin, as these are probe substrates for BCRP and OATP1B1 transporters. Clinically relevant increases in plasma exposure of simvastatin, simvastatin acid, rosuvastatin and atorvastatin with simultaneous administration of roxadustat were identified. Simvastatin acid (OATP1B1 substrate) increased by 1.8 (AUC) and 1.9-fold (Cmax), rosuvastatin (BCRP and OATP1B1 substrate) by 2.9 (AUC) and 4.5-fold (Cmax), and atorvastatin (OATP1B1 substrate) increased by 2.0 (AUC) and 1.3-fold (Cmax). Time-separated administration of simvastatin and roxadustat did not reduce the interaction observed with simultaneous administration.

Furthermore, *in vivo* DDI studies were performed with substrates for CYP2B6 (bupropion), CYP2C8 (rosiglitazone) or CYP2C9 (S-warfarin) and confirmed that roxadustat does not affect the

pharmacokinetics of medicinal products that are substrates of these CYP enzymes. However, rosiglitazone is categorised as a moderate sensitive substrate for CYP2C8 by the FDA and not a sensitive substrate. A qualified PBPK model (SIMCYP® version 20) was used to confirm that roxadustat is not an inhibitor of CYP2C8. Roxadustat has no inhibitory effects on sensitive CYP2C8 substrate repaglinide following dosing with 300 mg roxadustat every other day (maximal clinical dose in patients that are not on dialysis). Therefore, it can be concluded that roxadustat is unlikely to be a clinically relevant inhibitor of CYP2C8 at roxadustat doses of up to 300 mg.

Clopidogrel is a mechanism-based inhibitor of CYP2C8 and OATP1B1 via its glucuronide metabolite, like gemfibrozil. A specific study to assess a possible interaction of roxadustat with clopidogrel has not been conducted, but some clinical data on the combination of roxadustat with clopidogrel were available. Out of the 2855 patients with CKD included in the population pharmacokinetic analysis, 189 had roxadustat pharmacokinetic samples collected while on concomitant clopidogrel. In the population pharmacokinetic analysis, it was concluded that concomitant administration of clopidogrel did not change roxadustat AUC and C_{max} statistically significant.

No clinical DDI study was conducted with roxadustat as intestinal UGT1A1 inhibitor

2.4.3. Pharmacodynamics

Mechanism of action

Hypoxia-inducible factor (HIF) is a transcription factor that regulates the expression of genes involved in erythropoiesis. Activation of the HIF pathway is important in the adaptative response to hypoxia to increase red blood cell production.

Roxadustat mimics the body's natural response to hypoxia by reversibly inhibiting HIF-prolyl hydroxylases (PH) enzymes that target HIFs for degradation under normal oxygen conditions.

Through the inhibition of HIF-PH, roxadustat stimulates a coordinated erythropoietic response that includes the increase of endogenous plasma erythropoietin (EPO) levels, regulation of iron transporter proteins and reduction of hepcidin. This results in improved iron bioavailability increased haemoglobin production and increased red cell mass.

Primary and Secondary pharmacology

Several studies (10 phase I studies, 8 phase 2 studies, 13 phase 3 studies (6 global, one US, 2 China, 4 Japan) have evaluated several pharmacodynamics parameters including EPO, Reticulocytes, CHr, Hepcidin, Serum Iron, TSAT, sTfR, and VEGF in healthy subjects and in patients with CKD.

Erythropoietin

Plasma EPO pharmacodynamic data after single and intermittent administration of roxadustat (once, twice or 3 times a week) were obtained across the phase 1 programme and in 5 phase 2 studies. Single and repeated intermittent administration of roxadustat resulted in transient increases in EPO, which returned to baseline at approximately 48 h post-dose. Mean maximum EPO levels increased more than proportionally with dose and were generally achieved approximately 8 to 12 h post-dose. There was no evidence of a substantial change in EPO profiles with repeated intermittent dosing compared with single doses (FGCL-4592-044). This is consistent with the absence of time-dependent pharmacokinetics, and the transient duration of the effect of roxadustat on EPO.
Baseline-corrected maximum EPO values were higher (by < 15%) under fed conditions, but the difference was not statistically significant.

In DD patients (1517-CL-0543), baseline-corrected maximum EPO values were higher than in healthy subjects (see table and figure below).
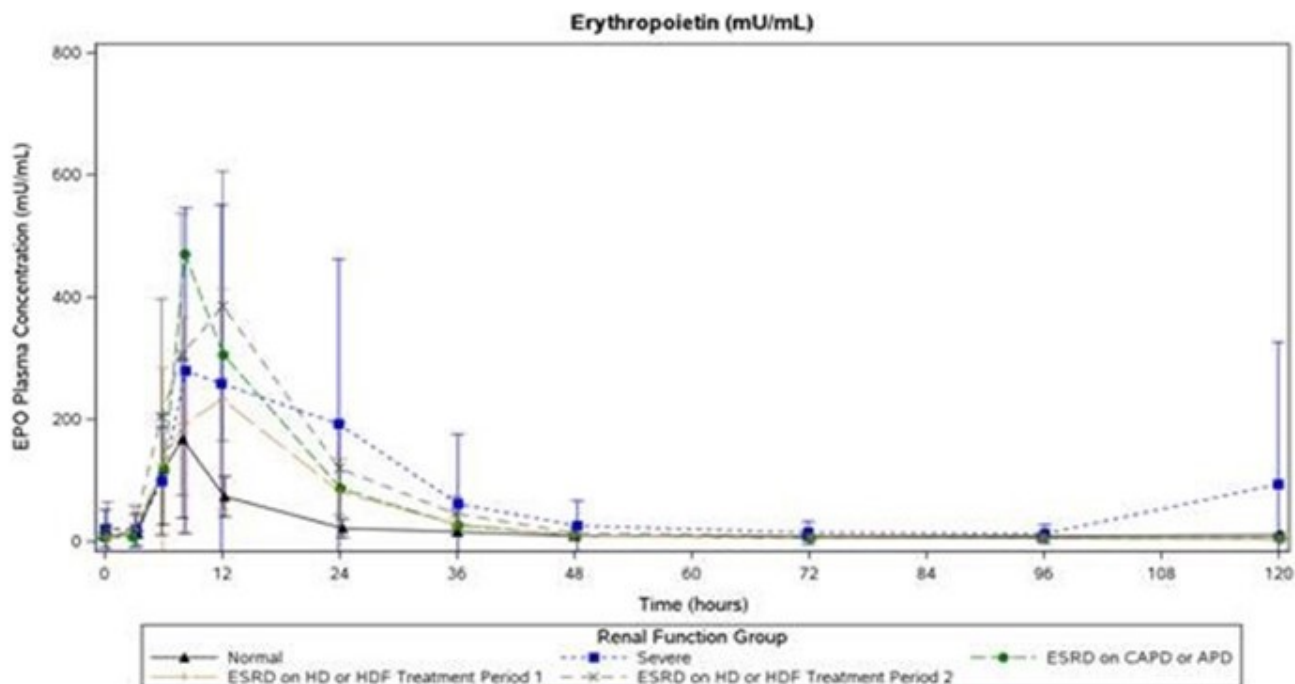
Figure 7: Mean Plasma Concentration-time Profiles of Erythropoietin after a Single 100-mg Dose of Roxadustat in Healthy Subjects and Subjects with Renal Impairment (Study 1517-CL-0543)

Table 9: Mean maximum erythropoietin levels and erythropoietin change from baseline after roxadustat administration in healthy subjects and patients with CKD

Population	Study *All Phase 1 Total patients in study**	Dosing Regimen	Absolute Dose Range (mg)	Mean (SD) EPO$_{max}$, mIU/mL	Mean (SD) Delta EPO$_{max}$, mIU/mL†
Healthy Subjects	1517-CL-0525 *Germany n=50 (age, sex)*	50 mg	50	34.7 (18.0)	25.3 (16.8)
		100 mg	100	102 (76.6)	92.5 (76.8)
		200 mg	200	609 (633)	599 (634)
	1517-CL-0513 *Bulgaria n=16 (HI)*	100 mg	100	114 (104)	103 (101)
	FGCL-4592-066 *USA n=24 (food effect)*	100 mg	100	212 (259)	205 (258)
	FGCL-4592-027 *USA n=12 (food effect)*	2 mg/kg	140-180	361 (318)	354 (318)
	FGCL-4592-043 *China n=40*	100 mg	100	119 (54)	-
		200 mg	200	2110 (1342)	-
	1517-CL-0543 *Germany / UK (n=12)*	100 mg	100	**170 (128)**	161 (128)
	1517-CL-0201 *Japan n=100*	1 mg/kg day 1 1 mg/kg tiw day 12	60	59.6 (15.2) 70.2 (24.4)	40.3 (14.8) 50.9 (24.4)
		3 mg/kg day 1 3 mg/kg tiw day 12	160-200	923 (575) 620 (361)	905 (571) 602 (359)
		2 mg/kg day 1 2 mg/kg tiw day 26	120-200	451 (310) 326 (197)	443 (309) 319 (196)

Population	Study *All Phase 1 Total patients in study**	Dosing Regimen	Absolute Dose Range (mg)	Mean (SD) EPO$_{max}$, mIU/mL	Mean (SD) Delta EPO$_{max}$, mIU/mL†
	FGCL-SM4592-016 *UK n=145*	3 mg/kg day 1 3 mg/kg tiw day 26	NR	933 (555) 848 (345)	927 (554) 841 (344)
Severe RI Patients	**1517-CL-0543** *Germany / UK (n=9)*	100 mg	100	**337 (324)**	316 (307)
DD Patients	**1517-CL-0543** *Germany / UK (n=13)*	100 mg	100	**260 (200)**	253 (201)
	FGCL-4592-039 *USA n=17*	1 mg/kg 2 mg/kg	NR NR	84.0 (60.0) 508 (522)	75.2 (59.2) 467 (541)
	1517-CL-0203 *Japan n=12*	1 mg/kg 2 mg/kg	40-60 80-120	141 (55.3) 559 (340)	123 (52.2) 546 (339)

Effect of Intrinsic Factors on Erythropoietin concentration

Age and Sex: In healthy subjects receiving single dose of 200 mg, mean baseline- and placebo-corrected EPO concentrations were higher in elderly than in young subjects, and higher in women than in men (1517-CL-0525) (figure below).
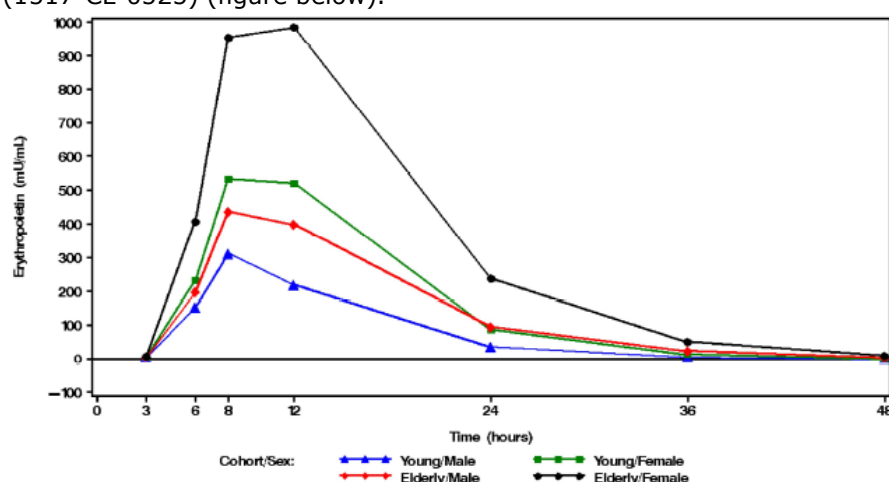
Figure 8: Mean Concentration (Linear Scale Plot) of Baseline-corrected, Placebo-corrected Erythropoietin by Age Cohort and Sex (Pharmacodynamic Analysis Set - Study 1517-CL-0525)). Dose 200 mg FG-4592

Ethnicity: No marked differences in EPO response were observed between Chinese, Japanese, and Caucasian healthy subjects.

Hepatic Impairment: In subjects with moderate HI, the baseline-corrected EPO AUC and maximum EPO levels were respectively 31% and 48% lower than in healthy control subjects (1517-CL-0513). The mean (s.d.) maximum EPO baseline-corrected concentrations were 141 (66) mU/mL in healthy control subjects with normal hepatic function and 103 (101) mU/mL in subjects with moderate hepatic impairment.

Before or after dialysis session: Administration of 100 mg roxadustat before dialysis (2 hours prior to the start of HD on day 1 of treatment period 2) resulted in higher mean (SD) (IU/mL) EPO levels (409 (225), n =8) than administration after dialysis (260 (200), n = 8) (2 hours after completion of HD on day 1 of treatment period 1) (1517-CL-0543).

Reticulocyte Hb Content

In patients with NDD and in patients with DD, the mean (SD) baseline CHr was approximately 31.0 (2.0) pg in each treatment arm.

In patients with NDD, mean CHr (haemoglobin content in reticulocytes) initially decreased up to week 6 in the roxadustat arm and then gradually increased up to week 52, while CHr remained approximately constant in the placebo arm (FGCL-4592-060). CHr values by the end of the study were similar between treatment arms. For roxadustat and placebo respectively, the mean (SD) changes (pg) from baseline were -0.51 (1.65) [n=550] and -0.01 (1.00) [n=274] at week 8; 0.35 (1.68) [n=504] and 0.17 (1.43) [n=214] at week 28; and 0.51 (1.76) [n=451] and 0.24 (1.60) [n=164] at week 52.

In patients with DD, after an initial decrease up to weeks 6 to 8, CHr increased from baseline in roxadustat and epoetin alfa treatment arms through week 52 (FGCL-4592-063). For roxadustat and epoetin alfa respectively, the mean (SD) changes (pg) from baseline were -0.41 (1.73) [n=474] and −0.33 (1.52) [n=466] at week 8; 0.46 (1.87) [n=415] and 0.12 (1.86) [n=417] at week 28; and 0.76 (2.04) [n=340] and 0.53 (2.01) [n=345] at week 52.

Hepcidin

The effect of roxadustat on hepcidin was studied in 6 phase 1 studies and the phase 2 and phase 3 studies in patients with CKD. In healthy subjects, there was an initial increase in hepcidin from baseline in all dose groups including placebo, followed by a decrease in subjects receiving roxadustat: The mean baseline-corrected E_{min} (i.e. decrease in hepcidin concentration relative to baseline) was -2.9 (3.3) -3.1 (2.9) -4.0 (4.1) and -5.8 (4.5) ng/mL for placebo, 50, 100 and 200 mg doses; the decreases were small and variable but appeared to be dose-dependent (1517-CL-0525).

Serum Iron Markers

In the main phase 3 studies, effects on iron utilisation were assessed with the following indices of iron status: serum iron, ferritin, TSAT and soluble transferrin receptor. The data from these studies were obtained with a proportion of patients using concomitant iron products. See efficacy part for the results.

Secondary Pharmacology

HR and Blood Pressure

Roxadustat treatment produces a dose-dependent increase in HR in healthy subjects at doses > 2 mg/kg [1517-CL-0201, 1517-CL-0525, FGCL-4592-065]. The TQT study, FGCL-4592-065, demonstrated a placebo-corrected HR increase up to 9 to 10 bpm at 8 to 12 h post-dose for a therapeutic dose of 2.75 mg/kg and 15 to 18 bpm at 6 to 12 h post-dose for a supratherapeutic dose of 5.0 mg/kg. No adverse events were related to the increase in HR developed in the combined phase 3 studies. An effect of roxadustat on blood pressure in humans has not been observed [1517-CL-0201, 1517-CL-0525].

QT interval prolongation

Based on data from a TQT study, concentration-effect modelling showed no significant relationship between plasma levels of roxadustat and ΔΔQTcI *(QTcI = QT interval corrected for heart rate using an individual correction)* with an intercept of -2.37 ms and slope of 0.3481 x 10^{-4} ms per ng/mL (90% CI: -0.2254, 0.9215; p = NS). The predicted effect on ΔΔQTcI at the geometric mean peak plasma

concentrations was -1.84 ms (90% CI: -3.11, -0.58) and -1.37 ms (-2.80, 0.06) after dosing roxadustat at 2.75 mg/kg and 5 mg/kg, respectively.

VEGF

VEGF (vascular endothelial growth factor) expression is directly induced by HIF-1a. VEGF is a signaling molecule that stimulates vasculogenesis and angiogenesis in response to decreases in oxygen levels and as such is one element of a response to restore the oxygen supply to tissues in hypoxic conditions.

VEGF was evaluated as an exploratory marker in 3 Phase 1 placebo-controlled, healthy subject studies (FGCL-SM4592-016, 1517-CL-0201, 1517-CL-0525) and a Phase 1 study in DD patients (1517-CL-0203). Single and repeated intermittent administration of roxadustat doses of 100 and 200 mg and 3.0, 3.75, and 4.0 mg/kg resulted in transient increases in VEGF, with high inter-subject variability. At lower doses, VEGF concentrations were similar to those in placebo subjects or to pre-dose levels. Mean VEGF concentrations peaked at approximately 8 to 12 h post-dose and generally returned to pre-dose values by 48 h post-dose. Change from baseline (pg/mL) was 62.8 (47.5) (n=17) for the 2 mg/kg dose, 58.1 (32.7) (n=10) and 40.2 (23.9) (n=6) for the 3 mg/kg dose, 112.6 (164.9) (n=5) and 180.3 (103.6) (n=6) for the 4 mg/kg dose, 15.0 (10.1) (n=48), 28.6 (34.20) (n=48) and 40.8 (27.5) (n=49) for the 50, 100 and 200 mg doses. In DD patients (n=6) it was 142.3 (74.7) for the 3 mg/kg dose.

Pharmacodynamic interactions with other medicinal products or substances

No information was provided on PD interactions with other medicinal products.

Genetic differences in PD response

No information was provided on potential genetic differences in PD response

2.4.4. Discussion on clinical pharmacology

Pharmacokinetics

Overall, pharmacokinetic characteristics of roxadustat have adequately been characterised. The fragmented development of this product is evidenced by different clinical study locations, different CROs, methodologies and use of multiple drug product formulations. However, this did not hamper assessment of the pharmacokinetics and the totality of evidence is sufficient.

It is accepted that the influence of food on the bioavailability of roxadustat for the to-be-marketed will not be different from the estimated effect on the 3 studied formulations. Therefore, proposed labelling (roxadustat can be taken with or without food, as was the method of administration during the phase 3 studies) is supported.

Regarding the pharmacokinetic characteristics of roxadustat in special populations, the applicant concluded that no dose adjustments are required for the administration of roxadustat. Roxadustat is not recommended for use in patients with severe hepatic impairment (Child Pugh class C) due to the absence of data in this population.

PK differences in gender and race were not considered clinically relevant taking also into account that roxadustat is dosed based on titration based on the patient's haemoglobin response.

Safety and efficacy of roxadustat in pediatric patients under 18 years of age have not been established, which is in line with the pediatric investigation plan.

No clinical DDI study was conducted with roxadustat as intestinal UGT1A1 inhibitor. It can currently not be excluded that roxadustat is a clinically relevant inhibitor of intestinal UGT1A1 and could affect the bioavailability of UGT1A1 substrates (increased exposure). A warning in section 5.2 of the SmPC has been included regarding UGT1A1 inhibition potential in absence of clear recommendations for the prescriber.

Pharmacodynamics

Erythropoietin

EPO is a key driver of erythropoiesis that facilitates the survival of red blood cell (RBC) progenitors and precursors in the bone marrow, allowing their differentiation into RBCs. EPO promotes precursor cell survival by inhibiting apoptosis. EPO is considered one of the main factors causing the rise in Hb concentration.

Phase 1 studies demonstrate that the plasma EPO concentration increases with increasing dose of roxadustat. With doses of 50 mg, 100 mg and 200 mg, the mean maximum baseline-corrected EPO levels in plasma increased more than proportionally with dose. This can be seen in e.g. a 4-fold higher EPO level (mIU/ml, mean (s.d.)) reached with 100 mg (92.5 (76.8)) compared to 50 mg (25.3 (16.8)) in healthy volunteers and a 24 fold higher level reached with 200 mg (599 (634)) compared to 50 mg. It should also be noted that at high roxadustat doses, there is large inter-individual variability in the EPO levels. Further, based on one study with a 100 mg dose, it was observed that mean (SD) maximum baseline-corrected EPO concentration (mIU/mL) was higher in patients with severe renal impairment, non-dialysis dependent (316 (307) or dialysis-dependent (253 (201)), compared to healthy volunteers (161 (128)). Comparable results were obtained in 5 phase 2 studies with various doses ranging from 0.7 mg/kg up to 2.0 mg/kg and 50 mg up to 200 mg. These studies showed a wide range of individual responses in plasma EPO level and EPO levels increasing more than proportionally with dose.

It is noticed that the baseline-corrected EPO concentration after a roxadustat dose of 200 mg is higher in elderly patients and in females than younger patients and male, respectively. Further possible implications of these findings on Hb effects per subgroup are discussed in the efficacy section.

Hepcidin

Hepcidin is a hormone responsible for the regulation of iron mobilisation. There are non-clinical data demonstrating effects on hepcidin and iron parameters. For clinical evaluation, three phase 1 studies in healthy volunteers and 2 phase 1 studies in CKD patients could overall not clearly reveal a substantial effect of a decrease in hepcidin levels with the absence of a clear difference versus placebo or only a small and high variable effect. Hepcidin measurements in the Phase 3 studies showed a significant decrease in hepcidin at 24 weeks in non-dialysis patients treated with roxadustat compared to placebo and in dialysis patients in comparison to ESA therapy (see also efficacy section).

Serum Iron Markers

Transferrin(s) are blood plasma/serum glycoproteins that reversibly bind iron and therefore control the levels of circulating free iron and facilitate iron transport. Transferrin saturation (TSAT) is a measure of the percentage of transferrin that is bound to iron, namely serum iron divided by the total iron binding capacity. Overall, the results of these parameters should be interpreted in the context of concomitant iron treatment during these studies, which may complicate interpretation of the exact PD effect of roxadustat on these parameters. Nevertheless, the initial decrease in serum ferritin and TSAT as observed in the NDD and DD patients may reflect the increased use of iron if increased erythropoiesis is occurring after starting treatment with roxadustat with subsequent increase and stabilisation during further treatment. These data are further discussed in the efficacy section of this report.

The observed changes in reticulocyte Hb content (CHr) could be interpreted as mirroring these changes in serum ferritin and TSAT and may reflect iron utilisation in RBC production. In patients with NDD, mean CHr initially decreased up to week 6 in the roxadustat arm and then gradually increased up to week 52, while CHr remained approximately constant in the placebo arm (FGCL-4592-060). CHr values by the end of the study were similar between treatment arms. Although, CHr increased from baseline in roxadustat and epoetin alfa treatment arms through week 52 in patients with DD (FGCL-4592-063).

QT prolongation

In a thorough QT Study with doses of 2.75 mg/kg [120-280 mg] and 5 mg/kg [230-510 mg] no dose dependent placebo corrected effect on QT prolongation could be observed.

VEGF (vascular endothelial growth factor)

In 3 Phase 1 placebo-controlled healthy subject studies and one Phase 1 study in dialysis patients, 100 and 200 mg and 3.0, 3.75, and 4.0 mg/kg resulted in transient increases in VEGF, with high inter-subject variability, while this was not observed with the lower doses. This is potentially of concern considering that VEGF is a signaling molecule that stimulates vasculogenesis and angiogenesis and can theoretically promote several mechanism including a tumour-promoting effect and a retino-proliferative effect. However, safety data on imbalance in tumour associated effects did not demonstrate any imbalance (see safety section). Further, particular studies 1517-CL-0304 and 1517-CL-0307 examining ophthalmological effects did not show any clinically relevant mean changes from baseline in the total number of retinal haemorrhages or in the proportion of patients with evidence of retinal haemorrhages, hard exudates and cotton wool spots.

2.4.5. Conclusions on clinical pharmacology

Overall, pharmacokinetic and pharmacodynamic characteristics of roxadustat have adequately been characterised throughout this dossier. The relevant information has been included in the SmPC sections 4.2 and 5.2.

2.5. Clinical efficacy

At the time of MAA submission, the phase 2 and phase 3 clinical development programme for roxadustat for the treatment of anaemia in CKD patients consisted of 22 completed studies, 2 ongoing studies (Studies 1517-CL-0610 and 1517-CL-0310) and 1 ongoing extension study (Study FGCL-4592-059). Studies 1517-CL-0610 and 1517-CL-0310 completed during the review period. Results for 1517-CL-0610 within this assessment are based on the 36-week early timepoint analysis results available at the time of dossier submission, unless otherwise noted. Studies are summarised below:

Table 10: Listing of studies supporting the phase 2 and phase 3 clinical development programme for roxadustat

Study Number Status Region Where Studies Were Conducted	Phase	Design and Control Type	Patient Characteristics	Study and Control Drugs Dose‡ and Regimen
Patients with NDD				
Main Phase 3 Studies				
1517-CL-0608 Completed Global	3	double-blind, randomized, placebo-controlled maximum of 104-week treatment	stages 3, 4 or 5 CKD ESA-untreated and Hb ≤ 10.0 g/dL	roxadustat†: 70 or 100 mg tiw placebo: tiw followed by maintenance period once Hb level is corrected
FGCL-4592-060 Completed Global	3	multicenter, double-blind, randomized, placebo-controlled minimum 52-week treatment minimum treatment duration could be shortened	stages 3, 4 or 5 CKD ESA-untreated and Hb ≤ 10.0 g/dL	roxadustat†: 70 or 100 mg tiw placebo: tiw followed by maintenance period once Hb level is corrected 6 treatment arms: *1A* (roxadustat) and *1P* (placebo): tiw then qw for the maintenance period *2A* (roxadustat) and *2P* (placebo): tiw then biw for the maintenance period *3A* (roxadustat) and *3P* (placebo): tiw then tiw for the maintenance period
D5740C00001 Completed Global	3	multicenter, double-blind, randomized, placebo-controlled treatment duration up to 4 years	stages 3, 4 or 5 CKD Hb values obtained at least 7 days apart < 10.0 g/dL	roxadustat: 70 mg tiw placebo: tiw > 4 weeks and until Hb is corrected followed by a maintenance dose once Hb level is corrected
1517-CL-0610 Ongoing Global	3	multicenter, open-label, randomized, active-controlled 104-week treatment	stages 3, 4 or 5 CKD and Hb ≤ 10.5 g/dL	roxadustat†: 70 or 100 mg tiw, followed by maintenance period tiw once Hb level is corrected DA: dosing per EU SmPC
Supportive Studies				
FGCL-4592-017 Completed United States	2a	multicenter, single-blind, randomized, placebo-controlled 4-week treatment	stages 3 or 4 CKD and Hb ≤ 11.0 g/dL	roxadustat: 0.7, 1, 1.5, or 2 mg/kg biw or tiw, 4 weeks placebo: biw or tiw, 4 weeks
FGCL-4592-041 Completed United States	2b	multicenter, open-label, randomized dose titration; 16- or 24-week treatment	stages 3 or 4 CKD mean Hb value obtained at least 7 days apart ≤ 10.5 g/dL (difference of ≤ 1.0 g/dL between the 2 values)	cohorts: roxadustat treatment *A†, B†*: 60, 100, or 140 mg tiw, 16 weeks *C*: 50 mg tiw, 24 weeks *D*: 100 mg tiw, 24 weeks *E†*: 70, 100, or 150 mg biw, 24 weeks *F*: 70 mg tiw, 24 weeks

Study Number Status Region Where Studies Were Conducted	Phase	Design and Control Type	Patient Characteristics	Study and Control Drugs Dose and Regimen
Studies Conducted in Japan and China				
1517-CL-0310 Ongoing Japan	3	multicenter, open-label, partly-randomized, 3-arm parallel, active-controlled, conversion 24 or 52-week treatment	eGFR $\leq$ 89 mL/min/1.73 m^2 and Hb 10.0 to 12.0 g/dL	*patients who used rHuEPO or DA as ESA before conversion randomized to:* roxadustat: 70 or 100 mg tiw, randomization for a treatment duration of 52 weeks – based on dose of rHuEPO or DA DA: 15, 30, 60, 90, 120, or 180 µg, once in 2 weeks, randomization for a treatment duration of 24 weeks *patients who used EBP as ESA before conversion:* roxadustat: 70 or 100 mg tiw, 52 weeks – based on EBP
1517-CL-0314 Completed Japan	3	multicenter, open-label, randomized, 2-arm 24-week treatment period	ESA-untreated, eGFR $\leq$ 89 mL/min/1.73 m^2 and Hb $\leq$ 10.5 g/dL	roxadustat: 50 or 70 mg tiw
FGCL-4592-808 Completed China	3	multicenter, double-blind, randomized, placebo-controlled 26- or 52-week treatment	stages 3, 4, or 5 CKD and Hb $\geq$ 7.0 g/dL and < 10 g/dL	*week 1 to 8 (for all patients):* blinded roxadustat† (70 or 100 mg tiw) or placebo (tiw) *week 9 to 26 (for all patients):* open-label roxadustat *week 26 to 52 (only for patients who were originally randomized to roxadustat):* open-label roxadustat
1517-CL-0303 Completed Japan	2	multicenter, double-blind, randomized, placebo-controlled fixed dose 6-week period followed by 18-week titration period	eGFR $\leq$ 89 mL/min/1.73 m^2 and Hb < 10.0 g/dL	roxadustat: 50, 70 or 100 mg tiw placebo: tiw after 2nd randomization, roxadustat: tiw or qw
FGCL-4592-047 Completed China	2	multicenter, double-blind, randomized, placebo-controlled 8-week, dose-ranging treatment period; sequential enrollment	stages 3 or 4 NDD and Hb < 10.0 g/dL	roxadustat dose cohort: 1†: 70, 90, or 120 mg tiw 2†: 90, 120, or 150 mg tiw placebo
Patients with DD				
Main Phase 3 Studies				
1517-CL-0613 Completed Global	3	multicenter, open-label, randomized, active-controlled Minimum duration: 52 weeks; Maximum duration: 104 weeks	stable hemodialysis or peritoneal dialysis, stable treatment with EPO-α or DA, and Hb $\geq$ 9.5 g/dL and $\leq$ 12.0 g/dL	*roxadustat treatment arm:* roxadustat: 100, 150, or 200 mg tiw – based on dose of EPO-α or DA before randomization *EPO-α or DA treatment arm:* EPO-α: dosing per SmPC; qw, biw or tiw DA: dosing per SmPC; qw or QOW
FGCL-4592-064 Completed US, EU, Canada	3	multicenter, open-label, randomized, active-controlled, conversion minimum treatment duration of 52 weeks and a maximum duration of up to approximately 3 years minimum treatment duration could be shortened	hemodialysis or peritoneal dialysis; stable and incident, treated with an ESA and Hb between $\geq$ 9.0 g/dL and $\leq$ 12.0 g/dL (incident dialysis: Hb between $\geq$ 8.5 g/dL and $\leq$ 12.0 g/dL)	roxadustat: 70, 100, 150, or 200 mg tiw – based on previous ESA dose EPO-α: tiw – based on previous ESA dose
FGCL-4592-063 Completed Global	3	multicenter, open-label, randomized, active-controlled, correction minimum treatment duration of 52 weeks and a maximum duration of up to approximately 3 years minimum treatment duration could be shortened	ESA-naive (incident dialysis) and Hb $\leq$ 10.0 g/dL	roxadustat†: 70 or 100 mg tiw EPO-α: dosing per package insert or SmPC

Study Number Status Region Where Studies Were Conducted	Phase	Design and Control Type	Patient Characteristics	Study and Control Drugs Dose† and Regimen
D5740C00002 Completed Global	3	multicenter, open-label, randomized, active-controlled treatment duration up to 4 years	hemodialysis or peritoneal dialysis; stable and incident dialysis and Hb < 12.0 g/dL (ESA at enrollment) or < 10 g/dL (no ESA at enrollment)	roxadustat treatment arm *patients previously treated with EPO-α:* 70, 100, 150, or 200 mg tiw *patients not previously treated with EPO-α:* 70 or 100 mg tiw† EPO-α treatment arm: *patients previously treated with EPO-α or β:* EPO-α: EPO-α tiw (except for patients who were treated with EPO-α using a less frequent dosing regimen before study entry) DA/Mircera®: EPO-α at doses based on a conversion factor *patients not previously treated with EPO-α:* 50 IU/kg tiw with subsequent dose adjustments

Supportive Studies

Study Number Status Region Where Studies Were Conducted	Phase	Design and Control Type	Patient Characteristics	Study and Control Drugs Dose† and Regimen
FGCL-4592-040 Completed United States	2	multicenter, randomized, active-controlled (open-label), placebo-controlled (single-blind) dose ranging 19-week treatment for patients with ≤ 6 weeks of treatment at the time of protocol amendment 2 (dated Dec 2010); treatment not extended for the other patients proof of concept	stable hemodialysis and *A (normoresponders):* Hb between 9.0 to 13.5 g/dL *B (hyporesponders):* Hb between 8.5 and 13.5 g/dL	group treatment: *A (normoresponders):* roxadustat: 1.0, 1.3, 1.5, 1.8, or 2 mg/kg tiw; 0.7 to 3.0 mg/kg biw, tiw or qw EPO-α: prestudy dose *B (hyporesponders):* 19 weeks roxadustat: 1.5 or 2 mg/kg tiw; 0.7 to 3.0 mg/kg tiw, biw, or qw EPO-α: prestudy dose placebo

Studies Conducted in Japan and China

Study Number Status Region Where Studies Were Conducted	Phase	Design and Control Type	Patient Characteristics	Study and Control Drugs Dose† and Regimen
1517-CL-0302 Completed Japan	3	multicenter, open-label, randomized, non-comparative 24-week treatment	peritoneal dialysis; stable or incident and *patients not receiving ESA* Hb < 10.5 g/dL *patients receiving ESA* Hb ≥ 10.0 g/dL and ≤ 12.0 g/dL	*patients not receiving ESA* roxadustat: 50 or 70 mg tiw *patients receiving ESA* roxadustat: based on previous ESA dose – 70 or 100 mg
1517-CL-0307 Completed Japan	3	multicenter, double-blind, randomized, 2-arm parallel, active-controlled 24-week treatment	stable hemodialysis and Hb between 10.0 and 12.0 g/dL	*roxadustat treatment arm* roxadustat: based on previous rHuEPO dose – 70 or 100 mg tiw *DA treatment arm:* DA: based on previous rHuEPO dose – 10, 15, 20, 30, 40, 50, or 60 μg
1517-CL-0308 Completed Japan	3	multicenter, open-label, randomized, 2-arm 24-week treatment	hemodialysis; stable and incident, ESA-naive and Hb ≤ 10.0 g/dL	roxadustat: 50 or 70 mg
1517-CL-0312 Completed Japan	3	multicenter, open-label, non-comparative, long-term 52-week treatment	stable hemodialysis Hb between 10.0 to 12.0 g/dL	roxadustat: based on previous ESA dose – 70 or 100 mg tiw
FGCL-4592-806 Completed China	3	multicenter, open-label, randomized, active-controlled 52-week roxadustat treatment; 26-week EPO-α treatment	hemodialysis or peritoneal stable dialysis, on stable dose of EPO-α and Hb 9.0 g/dL to 12.0 g/dL	roxadustat†: 100 or 120 mg tiw EPO-α: average dose ≤ 15000 IU/week.

Study Number Status Region Where Studies Were Conducted	Phase	Design and Control Type	Patient Characteristics	Study and Control Drugs Dose‡ and Regimen
1517-CL-0304 Completed Japan	2	multicenter, double-blind (arms 1 to 3), open-label (arm 4), randomized, 4-arm parallel, active-controlled 6-week, fixed dose period; 18-week titration period	stable hemodialysis and Hb < 9.5 g/dL after ESA washout in patients with Hb ≥ 10.0 g/dL	treatment arms: 1: roxadustat 50 mg tiw 2: roxadustat 70 mg tiw 3: roxadustat 100 mg tiw 4: DA 20 µg qw (open-label)
FGCL-4592-048 Completed China	2	multicenter, open-label, randomized, active-controlled 6-week, escalating dosing period	stable hemodialysis and Hb between 9.0 and 12.0 g/dL	roxadustat cohorts cohort 1: 70, 90, or 120 mg tiw cohort 2: 90, 120, or 150 mg tiw cohort 3 (flexible): 90/100, 140/150, or 180/200 mg tiw EPO-α: pre-randomization dose and schedule
Studies Conducted in Russia, US and Hong Kong				
FGCL-4592-053 Completed Russia/US/Hong Kong	2	randomized, open-label, dose-titration 12-week treatment	hemodialysis or peritoneal dialysis; stable or incident dialysis and Hb ≤ 10.0 g/dL	patients on hemodialysis: *arm A*: roxadustat; no iron supplementation *arm B*: roxadustat and oral iron supplementation *arm C*: roxadustat and iv iron supplementation *arm E*: optional, flexible dosing; roxadustat; no iron supplementation patients on peritoneal dialysis: *arm D*: roxadustat and received oral iron supplementation roxadustat starting doses‡: 60, 100, or 140 mg tiw oral iron supplement: 50 to 195 mg daily iv iron supplement: 60 mg qw
Extension Study				
FGCL-4592-059 Ongoing United States	2	multicenter, open-label, extension, long-term maintenance 8-year treatment period prior to amendment 2 1-year treatment period from amendment 2 onwards	NDD and DD (hemodialysis or peritoneal dialysis; stable or incident dialysis)	patients on roxadustat in the previous Studies FGCL-4592-040 and FGCL 4592 041: initial dose of roxadustat at the same dose and frequency optional treatment group: patients on placebo in the previous Studies FGCL-4592-040 and FGCL-4592-041 roxadustat: *DD patients*: 2.0 mg/kg tiw *NDD patients*†: 70, 100, or 150 mg

Stable dialysis comprises the initiation of dialysis > 4 months at the time of randomization. Incident dialysis comprises the initiation of dialysis ≥ 2 weeks but ≤ 4 months at the time of randomization.

CKD: chronic kidney disease; DA: darbepoetin alfa; DD: dialysis-dependent; EBP: epoetin beta pegol; EPO-α: epoetin alfa; eGFR: estimated glomerular filtration rate; ESA: erythropoiesis-stimulating agent; Hb: hemoglobin; ISE: Integrated Summary of Efficacy; IU: internal unit; NDD: non-dialysis-dependent; QOW: once every other week; rHuEPO: recombinant human epoetin; SmPC: Summary of Product Characteristics.

† Weight-dependent doses.

‡ Starting doses are presented; where applicable, individualized dosing approach based upon Hb was performed.

2.5.1. Dose response study(ies)

The following phase 2 studies were used to investigate dose response and conclude on starting dose for phase 3 studies: Study No. FGCL-SM4592-016, Study No. FGCL-SM4592-017, Study No. FGCL-4592-041 Study No. FGCL-4592-040 Study No. FGCL-4592-053 Study No. FGCL-4592-047 Study No. 1517-CL-0304 Study No. FGCL-4592-048. (results not shown).

Roxadustat dosing is governed by haemoglobin (Hb) response. The aim of starting dose selection and dose adjustment rules for treatment with roxadustat is to achieve and maintain Hb within 10 to 12 g/dL. As Hb response is variable and a single dose level cannot achieve the target Hb range for all patients, individualised dose adjustment is required following initiation of treatment with a defined starting dose setting. The details are summarised below.

<u>Starting doses</u>

Different starting doses of roxadustat were studied in the phase 2 programme: using a tiered weight-based approach where a patient's starting dose was selected based on categorizing the patient's body weight as low or high, and using an absolute starting dose regardless of body weight. These approaches were also adopted in the main phase 3 studies based on the efficacy and safety results from the phase 2 studies.

<u>Patients previously untreated with ESA</u>

A tiered weight-based approach for starting doses of roxadustat (70 or 100 mg 3 times weekly with 70 kg as a cut-off point) was chosen in all except one of the studies in patients previously untreated with ESA. This approach was thought to provide the best opportunity for managing the controlled individualised correction to target Hb values by achieving a steady Hb increase associated with moderate rates of Hb overshoots.

Absolute dosing was used for ESA-untreated patients in Study D5740C00001, and all patients started at a dose of 70 mg 3 times weekly in an attempt to simplify the setting of the starting dose.

<u>Patients previously treated with ESA</u>

Starting doses for the patients previously treated with ESA were chosen based on the patient's average prescribed weekly ESA dose within 4 weeks prior to randomisation. Based on dose data and Hb data from earlier studies in DD patients, a simplified dosing guide for conversion from 3 or 4 different dose ranges of ESA at baseline for Hb maintenance was developed.

<u>Maximum dose</u>

The maximum allowed dose for the patients not on dialysis was 3.0 mg/kg or 300 mg per administration, whichever was lower, a maximum weekly dose of 300 mg 3 times weekly (maximum of 900 mg per week). For patients on dialysis, the maximum dose step (level) was 3.0 mg/kg or 400 mg per administration, whichever was lower.

2.5.2. Main study(ies)

Eight of the studies presented above are submitted as the main clinical phase 3 studies in support of this application. Four of them were conducted on non-dialysis dependent (NDD) patients and four were conducted on dialysis dependent (DD) patients. The summary of the studies is presented in the tables below.

Table 11: Overview on roxadustat phase 3 development programme in anaemia with CKD

Studies in non-dialysis-dependent patients				
	Placebo-controlled studies (NDD pool)			**ESA-control (Darbepoetin alfa)**
Setting	Hb correction			
Study	ALPS (1517-CL-0608)	ANDES (FGCL-4592-060)	OLYMPUS (D5740C 00001)	DOLOMITES (1517-CL-0610)
Randomised (roxadustat/comparator)	594 (391/203)	916 (611/305)	2760 (1384/1376)	616 (323/293)
Studies in dialysis-dependent patients				
	ESA-controlled studies (DD pool) (Epoetin alfa or Darbepoetin alfa)			
Setting	ESA conversion		Hb correction	ESA conversion and Hb correction
Study	PYRENEES (1517-CL-0613)	SIERRAS (FGCL-4592-064)	HIMALAYAS (FGCL-4592-063)	ROCKIES (D5740C00002)
Randomised (roxadustat/comparator)	834 (414/420)	740 (370/370)	1039 (522/517)	2101 (1048/1053)

DD: dialysis dependent; ESA: erythropoiesis-stimulating agent; Hb: haemoglobin; NDD: non-dialysis dependent.

Methods

Table 12: Overview of key design features; main phase 3 NDD studies

Design Feature	Placebo-controlled, NDD Studies			ESA-controlled, NDD Study
	1517-CL-0608	**FGCL-4592-060**	**D5740C00001**	**1517-CL-0610**
Study name	ALPS	ANDES	OLYMPUS	DOLOMITES
Region	Global	Global	Global	Europe
Randomisation ratio	2:1	2:1	1:1	2:1 or 1:1 †
Open-label	-	-	-	X
Double-blind	X	X	X	-
Control	Placebo	Placebo	Placebo	ESA (DA)
Number of patients enrolled	594	922	2761	616
Stage 3 - 5 CKD	X	X	X	X
eGFR (mL/min/1.73 m^2)	< 60	< 60	< 60	< 60
Hb at baseline (g/dL)	≤ 10.0	≤ 10.0	< 10.0	≤ 10.5 ‡
Hb correction setting	X	X	X	X
Correction period with specific dose adjustment rules	X	X	-	X
Hb target (g/dL) – Correction Period	≥ 11.0 and ≥ 1.0 from baseline	≥ 11.0 and ≥ 1.0 from baseline	11.0 ± 1.0	≥ 11.0 and ≥ 1.0 from baseline
Hb target (g/dL) – Maintenance Period	10.0 - 12.0	10.0 - 12.0	10.0 - 12.0	10.0 - 12.0

CKD: chronic kidney disease; DA: darbepoetin alfa; eGFR: estimated glomerular filtration rate; ESA: erythropoiesis-stimulating agent; Hb: haemoglobin; NDD: non-dialysis-dependent.
† Original clinical study protocol: 2:1 ratio to receive roxadustat: DA. Protocol v2.0 onwards: 1:1 ratio to receive roxadustat or DA.
‡ Original clinical study protocol Hb at baseline ≤ 10.0 g/dL. Protocol v2.0 onwards: Hb at baseline ≤ 10.5 g/dL

Table 13: Overview of key design features; main phase 3 DD studies

Design Feature	ESA-controlled DD Studies			
	1517-CL-0613	**FGCL-4592-064**	**FGCL-4592-063**	**D5740C00002**
Study name	PYRENEES	SIERRA	HIMALAYA	ROCKIES
Region	Europe	Global†	Global	Global
Randomisation ratio	1:1	1:1	1:1	1:1
Open-label	X	X	X	X
Control	ESA (EPO-α or DA)	ESA (EPO-α)	ESA (EPO-α)	ESA (EPO-α)
Number of patients enrolled	836	741	1043	2106
HD/PD	X	X	X	X
Hb at baseline (g/dL)	≥ 9.5 to ≤ 12.0	≥ 9.0‡ to ≤ 12.0	≤ 10.0	< 10.0§, < 12.0
Hb correction setting	-	-	X	X
ESA conversion setting	X	X	-	X
Hb target (g/dL) – maintenance period	10.0 - 12.0	10.0 - 12.0¶	10.0 - 12.0¶	10.0 - 12.0¶

Stable dialysis comprises the initiation of dialysis > 4 months at the time of randomisation. ID DD comprises the initiation of dialysis ≥ 2 weeks and ≤ 4 months at the time of randomisation.
DA: darbepoetin alfa; DD: dialysis-dependent; EPO-α: epoetin alfa; ESA: erythropoiesis-stimulating agent; Hb: hemoglobin; HD: haemodialysis; ID: incident; PD: peritoneal dialysis.
† Study FGCL-4592-064 planned to recruit patients from centers globally, however all patients who actually took part in the study were from the US region only.
‡ ≥ 8.5 g/dL for ID DD patients.
§ For patients not on ESA treatment.
¶ Hb maintenance target in ESA-treated patients followed the local label.

Randomisation Stratification Factors

Most patients were stratified by region due to known variations in clinical practice between regions except for Studies D5740C00001 (NDD) and D5740C00002 (DD), in which patients were stratified by country only. Most studies were stratified by screening Hb value: ≤ 8 g/dL vs > 8 g/dL (Hb correction Studies NDD 1517-CL-0608, FGCL-4592-060, 1517-CL-0610 and DD FGCL-4592-063), ≤ 10.5 g/dL vs > 10.5 g/dL (ESA conversion Study FGCL-4592-064) and ≤ 11 g/dL vs > 11 g/dL (ESA conversion Study 1517-CL-0613). In addition, NDD studies were stratified by screening estimated glomerular filtration rate (eGFR). Patients in ESA conversion DD Studies 1517-CL-0613 and FGCL-4592-064 were stratified by previous average weekly ESA dose and previous ESA treatment (Study 1517-CL-0613 only).

Efficacy Assessment Schedule

For the evaluation of Hb efficacy endpoints, all studies used central laboratory Hb assessments. The timepoints of Hb assessments for the main phase 3 NDD and DD studies were generally every 2 weeks until week 24 to 36 and every 4 weeks after that. Assessments undertaken for the analysis of other efficacy endpoints were generally similar across all main phase 3 studies. See also results tables for differences in endpoints.

Study periods

All main phase 3 studies had a minimum duration of 52 weeks. Studies FGCL-4592-060 before amendment 2 (NDD), and FGCL-4592-064 and FGCL-4592-063 after amendments 1 (DD studies) and all patients randomised into Studies D5740C00001 and D5740C00002 were scheduled to run until a common time point to observe the requisite number of patients with adjudicated CV endpoint events in the phase 3 study programme. Studies 1517-CL-0608 (NDD), 1517-CL-0610 (NDD), and 1517-CL-0613 (DD) had a protocol-defined maximum treatment duration of 104 weeks.

Safety evaluation

A Data Safety Monitoring Board (DSMB) reviewed safety data at least every 6 months or twice per calendar year while the trial was ongoing to ensure subject safety during the study. In general, an Independent Event Review Committee (IERC), blinded to the treatment group, adjudicated prespecified safety events of interest.

Study Participants

Patient were generally included with > 18 years of age, and body weight > 45 and < 160 kg. Patients in the non-dialysis studies were to be CKD stage 3, 4, or 5 (< 60 ml/min/1.73 m2) and not on dialysis. Serum folate levels and vitamin B12 were to be in the normal range. For the Hb correction studies patients were included with Hb < 10 g/dL, while for the ESA conversion studies (0613, 064, partly 002) this was set at Hb > 9 to 9.5 g/dL and < 12.0 g/dL. Ferritin and TSAT levels could be ≥ 30 ng/mL to ≥ 50 ng/mL and ≥ 5% to ≥ 15%, respectively, for the placebo-controlled NDD studies, and ≥ 100 ng/mL and ≥ 20% for the ESA comparator studies. Depending on the dialysis study, patients were to be on dialysis <> 4 months (but > 2 weeks), and ≥ 8 weeks on ESA prior to randomisation. For the non-dialysis Hb correction study 0610 comparing roxadustat with ESA therapy, the patients were eligible for treatment with ESA using the criteria specified in the Kidney Disease Improving Global Outcomes (KDIGO) 2012 recommendation considering the rate of fall of Hb concentration, prior response to iron therapy, the risk of needing a transfusion, the risks related to ESA therapy and the presence of symptoms attributable to anaemia.

Relevant exclusion criteria were ESA therapy within 6 to 12 weeks prior to randomisation (for the Hb correction studies), iv iron use 6 to 12 weeks prior to randomisation (in the NDD studies), iron-chelating agents within 4 weeks before randomisation, RBC transfusion within 8 weeks before randomisation, conditions leading to blood loss (including elective surgery and GI bleeding). Patients with (recent) malignancies were also not allowed in the main studies.

Treatments

Initial dosing

For patients who were not already receiving ESA, the study drug was initially dosed based on either a tiered weight-based approach for patients in NDD Studies 1517-CL-0608, FGCL-4592-060 and 1517-CL-0610 and in DD Studies FGCL-4592-063 and D5740C00002, or on a fixed starting dose approach for patients in NDD Study D5740C00001. In the DD Studies 1517-CL-0613, FGCL-4592-064 and D5740C00002, roxadustat dose for patients already treated with ESA was chosen based on the patient's average prescribed weekly ESA dose within 4 weeks prior to randomisation.

Table 14: Initial phase 3 roxadustat dose for patients previously untreated with ESA

Study Drug (Dose Frequency)	Weight (≥ 45 to ≤ 70 kg)	Weight (> 70 to ≤ 160 kg)
Roxadustat/Placebo (tiw)	70 mg	100 mg

A starting dose of 70 mg was used for all patients in Study D5740C00001. ESA: erythropoiesis-stimulating agent.

Table 15: Initial roxadustat dosing for patients converting from ESA

Epoetin† (IU/week)	DA† (µg/week)	Methoxy Polyethylene Glycol-epoetin Beta‡ (µg/month)	Roxadustat (mg, tiw)
< 5000‡	< 25‡	< 80‡	70‡
5000 to < 8000 §	< 40	80 to 120	100
8000 to 16000	40 to 80	> 120 to 200	150¶
> 16000	> 80	> 200	200††

Dose adjustments

Roxadustat dose adjustment to maintain target Hb levels between 10.0 to 12.0 g/dL were permitted at week 4 and at intervals of every 4 weeks until week 52 and every 8 weeks thereafter. For roxadustat, a dose adjustment algorithm, as summarised in the table below, was used. Dose adjustment by dose step increases and decreases for roxadustat were determined based on current Hb levels (measured locally using the HemoCue® device) as well as on change in Hb level. Roxadustat dose steps were as follows: 20, 40, 50, 70, 100, 150, 200, 250 and 300 mg and for patients on dialysis only, up to 400 mg. When the Hb level was ≥ 13 g/dL at any time, the dose of roxadustat was withheld until the Hb was < 12 g/dL and resumed at a dose that was decreased by 2 dose steps.

Placebo dosing in individual placebo-controlled studies was blinded and thus followed the same monitoring schedule and adjustment instructions as those for roxadustat.

DA dosing in Studies 1517-CL-0610 and 1517-CL-0613 followed centrally approved SmPC and EPO-alfa dosing in Study 1517-CL-0613 followed UK SmPC. Studies FGCL-4592-064 and D5740C00002 followed approved ESA package insert or SmPC and Study FGCL-4592-063 followed the US package insert or SmPC.

Table 16: Roxadustat dose adjustment rules in phase 3 studies

Change in Hb over the previous 4 weeks (g/dL)	Only Until Achievement of Correction (Correction Rule)†	Current Hb < 10.5 g/dL	Current Hb 10.5 to < 12.0 g/dL	Current Hb 12.0 to < 13.0 g/dL	Current Hb ≥ 13 g/dL
Decrease by < -1.0	Increase dose by 1 (or 2) step(s)	Increase dose by 1 step	Increase dose by 1 step	No change	Hold then resume dosing when Hb < 12.0 g/dL at a dose that is reduced by 2 steps
-1.0 to 1.0	Increase dose by 1 step	Increase dose by 1 step	No change	Reduce dose by 1 step	
Increase by > 1.0 to ≤ 2.0	No change	No change	Reduce dose by 1 step		
Increase by > 2.0	Reduce dose by 1 step				

Iron use

For the NDD studies, see rescue therapy.

For DD studies, iron supplementation was permitted in the study with oral iron as the first-line iron supplementation. IV iron was permitted for subjects who did not respond (in the opinion of the investigator) or were not able to tolerate oral iron AND were iron deficient based on central laboratory results of ferritin <100 ng/mL or TSAT <20%. Up to 250 mg of IV iron was administered per administration cycle.

Rescue therapy

In the main phase 3 placebo-controlled NDD studies, rescue therapy included red blood cell (RBC) transfusion, ESA or intravenous iron. In the main phase 3 ESA-controlled NDD Study FGCL-4592-0610 and all main phase 3 DD studies, rescue therapy included RBC transfusion and ESA (roxadustat-treated

patients only). Instructions for initiating these rescue therapies were similar in all main phase 3 studies:

- RBC transfusion was allowed in all patients who needed rapid correction of anaemia due to acute or severe blood loss, patients that had moderate to severe symptoms from their anaemia (e.g., dyspnea at rest or on mild exertion) or the investigator was of the opinion that the blood transfusion was a medical necessity.

- ESA was allowed in patients who met all the following criteria:

  o Hb level that had not sufficiently responded to ≥ 2 dose increases or maximum dose limit of the study drug had been reached.

  o Hb was lower than a prescribed value depending on the study; either < 8 g/dL (placebo-controlled NDD studies), < 8.5 g/dL (Studies FGCL-4592-0613 and FGCL-4592-063) or < 9 g/dL (Studies 1517-CL-0610, FGCL-4592-064 and D5740C00001) on 2 consecutive measurements.

  o Clinical judgement did not suggest iron deficiency or bleeding as a cause of lack of response or rapid decline in Hb.

  o Reducing the risk of alloimmunisation in transplant-eligible patients and/or reduction for other RBC transfusion-related risk was the goal.

  o Rescue ESA was limited to a maximum of 4 weeks (2 courses in placebo-controlled NDD studies, 1 course in ESA-controlled NDD study and 1 course in DD studies).

- In the individual placebo-controlled main phase 3 NDD studies, intravenous iron was initiated (as per local standard of care or a maximum dose of 250 mg once daily) by the investigator if Hb had not responded to ≥ 2 dose increases or the maximum dose (by body weight) of the study drug while taking oral iron (all studies except Study D5740C00001), the patient was unresponsive to or did not tolerate oral iron, and Hb was < 8.5 g/dL and ferritin were < 100 ng/mL or TSAT was < 20% (all studies).

- The need for a third course of rescue therapy automatically led to treatment discontinuation.

Objectives

Placebo-controlled NDD studies

The primary objectives of all placebo-controlled studies in NDD patients were to evaluate the efficacy of roxadustat compared to placebo for the treatment of anaemia in CKD patients, not on dialysis.

ESA controlled ongoing open-label NDD study

The 1517-CL-0610 study evaluated the efficacy of roxadustat compared to DA in the treatment of anaemia in NDD patients in the setting of correction of Hb.

ESA controlled DD studies

Of the 4 studies in DD patients, two had the primary objective to evaluate the efficacy of roxadustat compared with EPO-alfa and/or DA in the maintenance treatment of anaemia in ESRD patients on stable dialysis (1517-CL-0613, FGCL-4592-064) in the setting of conversion of ESA to roxadustat.

In one study the primary objective was to evaluate the efficacy and safety of roxadustat in the treatment of anaemia in ID (initiating dialysis) DD patients compared with active control (FGCL-4592-063) in the setting of correction of low Hb levels.

In one study the primary efficacy objective was to evaluate the efficacy of roxadustat for the treatment of anaemia in CKD patients on dialysis (D5740C00002) both in the setting of conversion of ESA and correction of low Hb levels.

Outcomes/endpoints

The primary and secondary endpoints for all studies are displayed below.

Table 17:Haemoglobin control efficacy endpoints; main phase 3 studies

Hb Control Efficacy Endpoint	Placebo-controlled NDD Studies			ESA-controlled, NDD Study	ESA-controlled DD Studies			
	1517-CL-0608	FGCL-4592-060	D5740C00001	1517-CL-0610	1517-CL-0613	FGCL-4592-064	FGCL-4592-063	D5740C00002
Correction and/or Conversion Studies								
Hb correction	X	X	X	X			X	X
ESA conversion					X	X		X
Key Efficacy Endpoints								
Proportion of patients who achieved an Hb response† at 2 consecutive visits separated by at least 5 days during the first 24 weeks of treatment without rescue therapy prior to Hb response	Primary	Primary	Primary	Primary			Primary	
Proportion of patients with Hb response defined as Hb within the target range of 10.0 - 12.0 g/dL during weeks 28 - 36 without having received rescue therapy within 6 weeks prior to and during this 8-week evaluation period					Secondary	Secondary		
Change from baseline in Hb averaged over weeks 28 - 36, without having received rescue therapy within 6 weeks prior to and during this 8-week evaluation period	Secondary	Secondary		Secondary	Primary	Primary	Secondary	Primary

† Hb response: Hb ≥ 11 g/dL and an Hb increase from baseline by ≥ 1 g/dL in any patients with baseline Hb > 8 g/dL or an increase in Hb by ≥ 2 g/dL in patients whose baseline Hb ≤ 8.0 g/dL.

Other Hb endpoints included Hb rate of rise > 2 g/dL within 4 weeks, the proportion of Hb values ≥ 10 g/dL without the use of rescue therapy within 6 weeks prior to and during the 8-week evaluation periods, Proportion of Hb values within 10 - 12 g/dL without the use of rescue therapy within 6 weeks prior to and during the 8-week evaluation period, Percentage of time with Hb values, Hb change from baseline in patients with baseline hs-CRP > ULN, Time to first Hb response, depending on the study.

Other efficacy endpoints

Table 18: Other efficacy endpoints; main phase 3 studies

Other Efficacy Endpoints	Placebo-controlled, NDD Studies			ESA-controlled, NDD Study	ESA-controlled, DD Studies			
	1517-CL-0608	FGCL-4592-060	D5740C 00001	1517-CL-0610	1517-CL-0613	FGCL-4592-064	FGCL-4592-063	D5740C 00002
Non-haemoglobin Anaemia-related Endpoints								
Time to rescue therapy	X	X	X	X	X	X		X
Time to RBC transfusion	X	X	X	X	X	X	X	X
Mean monthly iv iron use	X (weeks 1 - 36, 37 - 52, 53 - 104)	X (weeks 1 - 52)		X (weeks 1 - 36)	X (day 1 – week 36)	X (weeks 28 - 52)	X (weeks 28 - 52)	X (week 36 - EOS)
Renal Function Endpoints								
eGFR rate of change	X	X	X	X				
Metabolic Changes Endpoints								
LDL cholesterol change from baseline	X (weeks 12 - 28)	X (weeks 12 - 28)	X (week 24)	X (week 12 - 28)	X (weeks 12 - 28)	X (weeks 12 - 28)	X (weeks 12 - 24)	X (week 24)
QoL Endpoints								
SF-36 VT subscore	X	X	X	X	X	X	X	
SF-36 PF subscore	X	X	X	X	X	X	X	

Sample size

In the placebo-controlled NDD studies, a minimum of 450, and up to 600 (1517-cl-0608), 1200 (fgcl-4592-060), 2600 (d5740c00001) patients were planned to be randomised to receive roxadustat or placebo (2:1 with approximately 300 roxadustat versus 150 placebo) in a double-blind manner in order to support the primary endpoint(s) of the study. Three hundred patients for the roxadustat group and 150 patients for the placebo group were needed to achieve at least power of 95% to demonstrate a statistically significant difference with a 5% 2-sided significance level between roxadustat and placebo in the primary endpoint assuming that the proportion of patients with a response in the roxadustat group is at least 65% and in the placebo group is at most 25%.

During the course of the Phase 3 studies, which were being conducted in parallel, up to 600 (1517-cl-0608), 1200 (fgcl-4592-060), 2600 (d5740c00001) subjects might have been enrolled in the studies to support the overall safety evaluation of roxadustat across pooled multiple studies in the Phase 3 programme, including adjudicated composite safety endpoints of interest.

In Study 1517-cl-0610, approximately 570 patients were planned to be randomised to receive roxadustat or darbepoetin alfa as follows:

Table 19: Sample size calculations per treatment arm

Treatment Group	Protocol version 1 (Ratio 2:1)		Protocol versions 2 and 3 (Ratio 1:1)		Total	
	Randomized	PPS	Randomized †	PPS	Randomized	PPS
Roxadustat	100	80	210	168	310	248
Darbepoetin alfa	50	40	210	168	260	208
Total	150	120	420	336	570	456

† The number of patients under protocol v2.0 and v3.0 will depend on the number of patients randomized under protocol v1.

Two hundred and forty-eight (248) patients for the roxadustat group and 208 patients for the darbepoetin alfa group will provide at least 98% test power to demonstrate statistically noninferiority of roxadustat versus darbepoetin alfa in the primary endpoint assuming that the proportion of patients with a response in both groups is at least 80% and a noninferiority margin for the difference of proportions of 15%. The power for the sensitivity analysis of post-amendment 1 data (336 patients) will be at least 93%.

In the ESA controlled DD studies, 300 patients for the roxadustat treatment group and 300 patients for the ESA treatment group would provide 97% power to statistically demonstrate noninferiority of roxadustat versus ESA in the EU primary endpoint in both the total study population and the planned subset population analysis assuming a difference (roxadustat minus ESA) of -0.25 g/dL in the Hb change from baseline and an SD of 1.5 g/dL, following a parametric chain procedure.

During the course of these studies, which were being conducted in parallel, up to 1200 (fgcl-4592-064 and fgcl-4592-063) or 2000 (d5740c00002) subjects were to be enrolled for safety evaluation of roxadustat in comparison to epoetin alfa including prespecified and adjudicated safety events of interest.

For the sample size for cardiovascular safety analysis, a 30% per year study drug discontinuation incidence rate is assumed in estimating the patient-exposed-years (PEYs) for roxadustat and the active control arms, based on data from the peginesatide phase 3 programme. For placebo, the rate of discontinuations is expected to be up to 70% per year. 1500 and 2320 patients are expected to be included for EMA MAA in non-dialysis and dialysis respectively.

Table 20 shows the minimum number of events and test power expected for EMA MAA.

Table 20: Number of events and test power expected for EMA MAA

Population	Comparison	Allocation Ratio	Number of MACE+ events	Test Power #
Non-dialysis	Roxadustat vs Placebo	2:1†	137	90% ‡
Dialysis @	Roxadustat vs Active Control	1:1	151	95%

Test power for HR < 1.8 at a one-sided significance level of 2.5% assuming a true HR=1 calculated by EAST® using the log-rank test. Actual test power may be slightly lower since the inverse of variance approach over the log-transformed hazard ratios will be used for the actual analysis.

@ Dialysis includes both newly-initiated dialysis and stable dialysis subjects.

† Allocation ratio assuming that this analysis is performed using 1517-CL-0608 and FGCL-4592-060 only.

‡ Actual power may be lower since the events ratio may be close to 3:1 due to a higher dropout rate with placebo.

Randomisation

Subjects were randomised using an IWRS and depending on the study at a 1:1 ratio or 2:1 ratio to receive roxadustat or placebo/ comparator. Depending on the study, several stratifications were applied.

Blinding (masking)

Three out of 4 NDD studies were placebo-controlled studies. Placebo tablets were identical to roxadustat tablets in appearance, packaging, and labelling. The storage and dose preparations were also the same as roxadustat. The investigator, study site staff, subject, and the sponsor and designees, were blinded to study drug assignment, but not to the dose. Treatment assignments remained blinded until the completion of the study. When possible and appropriate, the blind was maintained for sponsor personnel responsible for analysis and interpretation of results. Any intentional or unintentional breaking of the blind was reported and documented. Breaking the blind (for a single subject) was considered only when knowledge of the treatment assignment was deemed essential by the investigator for the subject's care. Unplanned unblinding resulted in the discontinuation of subject participation from the study.

For the comparator studies, an open-label design was selected

Statistical methods

Analysis Sets

Across all the main phase 3 studies, the full analysis set (FAS) was primarily used to show superiority and the per-protocol set (PPS) to show non-inferiority of the primary and/or secondary endpoints. The definitions of each population were similar across all main phase 3 studies:

- The intent-to-treat (ITT) analysis set included all randomised/enrolled patients.

- The FAS analysis set consisted of all randomised/enrolled patients who received at least 1 dose of the study drug and had at least 1 non-missing post-dose Hb assessment. In addition, patients in Studies FGCL-4592-060, D5740C00001 and D5740C00002 were also required to have baseline Hb assessment.

- In Studies 1517-CL-0608, 1517-CL-0610 and 1517-CL-0613, the PPS included all FAS patients who received at least 2 weeks (Studies 1517-CL-0608 and 1517-CL-0610) or 12 weeks (Study 1517-CL-0613) of treatment and did not meet any of the reasons to exclude a complete patient from the PPS. In Studies FGCL-4592-060, FGCL-4592-064, FGCL-4592-063, D5740C00001 and D5740C00002, the PPS consisted of all patients in the FAS population who received at least 8 weeks of treatment, had at least 1 valid post-dose Hb assessment and were without any major protocol violations.

Primary efficacy analysis

For the placebo-controlled NDD studies, the proportion of responders in the primary efficacy variable was compared using a Cochran–Mantel–Haenszel (CMH) test adjusting for the region, history of CV, baseline Hb and baseline eGFR, comparing roxadustat to placebo.

Subjects who discontinued or received rescue therapy before or on the date of the second consecutive Hb value that fulfilled the definition of response were classified as non-responders.

For the ESA-controlled NDD and DD correction studies (1517-cl-0610 and fgcl-4592-063), the proportion of responders in the primary efficacy variable were compared using a Miettinen & Nurminen

(MN) approach, adjusting for region, history of CV, baseline Hb and baseline eGFR and comparing roxadustat to darbepoetin alfa.

The Miettinen and Nurminen method was used to calculate the two-sided 95% CI for the difference in rates. If the resulting lower bound of the two-sided 95% CI between roxadustat and darbepoetin alfa was > -0.15, non-inferiority would be concluded.

Subjects who discontinued or received rescue therapy before or on the date of the second consecutive Hb value that fulfils the definition of response were classified as non-responders.

For the DD conversion studies, the change from baseline to the average Hb of weeks 28 to 36, without having received rescue therapy within 6 weeks prior to and during this 8-week period, were computed from the Mixed Model of Repeated Measures method (MMRM). The MMRM model was run for the purpose of implicit imputation of missing data by using all the available information from the observed data via the within-patient correlation structure. The analysis was based on the estimated difference between the two treatment arms overall mean effects throughout the evaluation period (weeks 28 to 36) based on this MMRM model.

The model contained treatment arm, region, CV History, previous ESA treatment, visits and visit by treatment as categorical variables. It also contained baseline Hb and baseline Hb by visit as a continuous variable. The unstructured covariance pattern model was used. If the unstructured covariance pattern did not converge, then heterogeneous Toeplitz, (homogeneous) Toeplitz structure or first-order autoregressive covariance structure would be used to achieve convergence, consecutively.

As a sensitivity analysis, the analysis of the primary endpoint would be repeated using different analysis sets, analysis methods and handling of missing data.

Analysis of secondary endpoints

Binary endpoints were analyzed using the same methods as for the binary primary endpoints.

The analysis of the US primary endpoint change from baseline Hb, and some other continuous endpoints used ANCOVA. The mean value of all change from baseline values available within the pre-specified timeframe was used as the dependent variable, baseline values and stratification factors used in randomisation were included as covariates (baseline values) or fixed effects (other covariates). For the primary efficacy analysis, a multiple imputation ANCOVA method was used, assuming MAR.

For other continues endpoints, the MMRM, as described above, was used.

For time to event variables, treatments were compared using a Cox proportional hazards model. Stratification factors used in randomisation will be used as covariates (baseline values) or fixed effects (other covariates). The Efron method was used for ties. The p-values, hazard ratio (HR) and 95% confidence intervals for the HR were reported. Kaplan-Meier estimates of the cumulative proportion of subjects with events were estimated and plotted, with the number of subjects at risk indicated below the plot at specific time points.

Non-inferiority margins

Non-inferiority margins for the primary endpoints were defined for both the correction (-15%) and the conversion (-0.7.5 g/dl) studies. The margin for the correction studies was accepted in a previous application (Mircera). The margin for conversion studies was based on relatively conservative statistical reasoning, preserving at least 70% of the EPO effect in previous studies, which is close to the natural fluctuation in Hb within patients (0.5%). For quality of life endpoints, the non-inferiority margin was

based on the MCIs in the user's manual, and for blood pressure, a margin of 1mmHg was chosen based on clinical judgement.

Multiplicity

Efficacy parameters were tested sequentially in contributing studies; however, the order as tested was not consistent between studies.

In study 1517-cl-0613, the primary analysis of the EU (EMA) primary efficacy endpoint was tested both in the overall population and in the subset of patients defined as subjects with an average prescribed weekly epoetin or darbepoetin dose within the last four weeks prior to randomisation $\leq$ 200 IU/kg or $\leq$ 1 μ g/kg respectively, following a parametric chain procedure. The information fraction (subjects in the subset population/total study population) was calculated at the time of database hardlock. The overall one-sided significance level (alpha) was fixed at 0.025. If both null hypotheses are rejected, secondary endpoints were assessed on the overall population.

Analysis of cardiovascular safety

An adjudicated event was classified as on-treatment if it occurred on or after Day 1 of study treatment and up to 3, 7 or 28 days after the end of treatment (OT-3, OT-7 and OT-28, respectively).

Post hoc on-study analyses were performed on data from the NDD population.

A summary of the individual adjudicated events, and the composition of MACE categories specified in endpoint definitions is provided in the Table 21 below.

Table 21: Adjudicated events and composite cardiovascular endpoint definitions

Adjudicated Events	Composite Cardiovascular Endpoint			
	MACE	MACE+	CV-MACE	CV-MACE+
Death – any reason (all-cause mortality)	Y	Y	-	-
Cardiovascular death †	-	-	Y	Y
Myocardial infarction	Y	Y	Y	Y
Stroke	Y	Y	Y	Y
Unstable angina that requires hospitalization	-	Y	-	Y
Congestive heart failure that requires hospitalization	-	Y	-	Y
Deep vein thrombosis that requires hospitalization	-	-	-	-
Pulmonary embolism that requires hospitalization	-	-	-	-
Vascular access thrombosis	-	-	-	-
Hypertensive emergency	-	-	-	-

CV: cardiovascular; CV-MACE: CV death, myocardial infarction or stroke; CV-MACE+: CV-MACE including, in addition, hospitalization for either unstable angina and/or congestive heart failure; MACE: major adverse cardiovascular event (death [any reason], non-fatal myocardial infarction, and/or stroke);

MACE+: MACE including, in addition, hospitalization for either unstable angina and/or congestive heart failure; Y: yes.

† Defined as death resulting from an acute myocardial infarction, sudden cardiac death, death due to heart failure, death due to stroke, death due to CV procedures, death due to CV hemorrhage, and death due to other cardiovascular causes.

The primary analysis used the Cox model that would be applied separately for each study and population, analyzing the time to the first occurrence of the event. Patients who had no event during their time in the study would be included as censored observations. Different models were applied for the non-dialysis and the dialysis studies, respectively.

For non-dialysis studies, a very high discontinuation rate is expected after the transition to dialysis, during the trial, especially in subjects treated with placebo. Subjects were also expected to have a higher rate of MACE+ events after dialysis. Both mechanisms would lead to a significant bias should the standard Cox model be applied in this population. Therefore, a Cox model weighted inversely for the probability of censoring was fitted to MACE+ for the non-dialysis studies. In the censoring model, the event of interest was censoring. Time to MACE+/censoring data were merged with the eGFR values at baseline and during the study up to the event of interest and with the date of initiation of dialysis data using a vertical (long format) dataset as used for the counting process formulation of the Cox model. The eGFR/dialysis classes (eGFR >= 30; 15 <= eGFR < 30; 10 <= eGFR < 15; eGFR < =10; or dialysis) were used as a time-dependent covariate, treatment and endpoints as baseline covariates together with baseline log-transformed eGFR and age. Un-stabilised and stabilised IPCW weights for each subject and event time were calculated and a Cox model was fitted on MACE+ using these weights.

Results

Participant flow

Table 22: Patient disposition; main phase 3 NDD studies and NDD pool

Category	Number of Patients (%)									
	Placebo-controlled								**ESA-controlled**	
	Studies						**NDD Pool (SAF)**		**Study**	
	1517-CL-0608 (SAF)		**FGCL-4592-060 (ITT)**		**D5740C00001 (ITT)**				**1517-CL-0610 (SAF)**	
	R	**PB**	**R**	**PB**	**R**	**PB**	**R**	**PB**	**R**	**DA**
Safety Analysis Set Population	391	203	611	305	1384	1376	2386	1884	323	293
Completed†	245 (62.7)	89 (43.8)	349 (56.7)	98 (32.0)	885 (63.9)	575 (41.8)	1485 (62.2)	769 (40.8)	55 (17.0)	34 (11.6)
Ongoing‡	NA		NA		NA		NA		194 (60.1)	201 (68.6)
Study discontinuation†§	119 (30.4)	71 (35.0)	ND		84 (6.1)	130 (9.4)	ND		50 (15.5)	41 (14.0)
Treatment discontinuation¶	146 (37.3)	114 (56.2)	267 (43.3)	208 (68.0)	499 (36.1)	801 (58.2)	901 (37.8)	1115 (59.2)	74 (22.9)	58 (19.8)
Primary reason for treatment discontinuation										
Adverse event††	21 (5.4)	9 (4.4)	47 (7.6)	19 (6.2)	79 (5.7)	52 (3.8)	150 (6.3)	83 (4.4)	14 (4.3)	6 (2.0)
Withdrawal by patient	58 (14.8)	52 (25.6)	83 (13.5)	89 (29.1)	ND		143 (6.0)	143 (7.6)	22 (6.8)	17 (5.8)
Patient decision	ND		ND		250 (18.1)	390 (28.3)	250 (10.5)	390 (20.7)	ND	
Physician decision	7 (1.8)	8 (3.9)	16 (2.6)	17 (5.6)	ND		49 (2.1)	67 (3.6)	6 (1.9)	4 (1.4)
Development of study specific discontinuation criteria	ND		ND		76 (5.5)	252 (18.3)	76 (3.2)	252 (13.4)	ND	
Kidney transplant	ND		8 (1.3)	4 (1.3)	ND		24 (1.0)	9 (0.5)	ND	
Dialysis	ND		22 (3.6)	8 (2.6)	ND		ND	ND	ND	
Dialysis initiation	ND		ND		ND		23 (1.0)	11 (0.6)	ND	

DD pool

Table 23: Patient disposition; main phase 3 DD studies

Category	Number of Patients (%)							
	1517-CL-0613 (SAF)		FGCL-4592-064 (ITT)		FGCL-4592-063 (ITT)		D5740C00002 (ITT)	
	R	ESA†	R	EPO-α	R	EPO-α	R	EPO-α
Safety Analysis Set Population‡	414	420	370	370	522	517	1048	1053
Completed§	249 (60.1)	309 (73.6)	127 (34.3)	183 (49.3)	307 (58.8)	309 (59.3)	696 (66.2)	796 (75.5)
Study discontinuation¶	117 (28.3)	91 (21.7)	ND	ND	ND	ND	69 (6.6)	65 (6.2)
Treatment discontinuation††	165 (39.9)	111 (26.4)	243 (65.7)	188 (50.7)	215 (41.2)	212 (40.7)	352 (33.5)	257 (24.4)
Primary reason for treatment discontinuation								
Randomised/ registered but never received/dispensed study drug	0	0	ND		ND		ND	
Adverse event‡‡	15 (3.6)	6 (1.4)	27 (7.3)	9 (2.4)	29 (5.6)	22 (4.2)	54 (5.1)	22 (2.1)
Death	62 (15.0)	47 (11.2)	70 (18.9)	62 (16.7)	64 (12.3)	54 (10.4)	ND	
Lack of efficacy	7 (1.7)	0	6 (1.6)	1 (0.3)	6 (1.1)	1 (0.2)	ND	
Protocol deviation	0	0	4 (1.1)	0	1 (0.2)	6 (1.2)	ND	
Withdrawal by patient/patient decision	50 (12.1)	26 (6.2)	41 (11.1)	29 (7.8)	37 (7.1)	49 (9.4)	135 (12.8)	88 (8.3)
Physician decision	7 (1.7)	2 (0.5)	30 (8.1)	15 (4.0)	14 (2.7)	7 (1.3)	ND	
Kidney transplant	0	0	31 (8.4)	39 (10.5)	23 (4.4)	29 (5.6)	ND	
Other	1 (0.2)	4 (1.0)	28 (7.6)	30 (8.1)	32 (6.1)	29 (5.6)	125 (11.9)	142 (13.5)

Recruitment

Studies 1517-CL-0613 and 1517-CL-0610 recruited patients from centres in Europe and Study FGCL-4592-064 planned to recruit patients from centres globally, however all patients who actually took part in the study were from the US region only. All other studies recruited patients from centres globally.

Conduct of the studies

Protocol violations: The most common protocol deviations were: receipt of wrong treatment or incorrect doses of the study drug (30.4% of patients on roxadustat; 22.2% on patients on placebo) [Study 1517-CL-0608], prohibited medication deviation (8.9% of patients on roxadustat; 13.7% of patients on placebo) and operational deviation (12.0% of patients on roxadustat; 8.5% of patients on placebo) [Study FGCL-4592-060] and violation of inclusion or exclusion criteria (11.2% of patients on roxadustat; 11.1% of patients on placebo) [Study D5740C00001].

GCP violations: A total of 47 all randomised patients from Studies D5740C00001 and D5740C00002 were excluded from the study ITT populations due to major GCP violations or being phantom subjects due to technical issues.

Baseline data

General patients characteristics, CKD characteristics, and anaemia characteristics are presented below, for the placebo controlled studies and the active ESA comparator study in the NDD pool.

Table 24: Summary of demographics; main phase 3 NDD studies and NDD pool

Category	Placebo-controlled						NDD Pool (SAF)		ESA-controlled Study	
	Studies								1517-CL-0610 (SAF)	
	1517-CL-0608 (SAF)		FGCL-4592-060 (SAF)		D5740C00001 (ITT) †					
	R n = 391	PB n = 203	R n = 611	PB n = 305	R n = 1384	PB n = 1377	R n = 2386	PB n = 1884	R n = 323	DA n = 293
Sex, n (%)										
Male	169 (43.2)	99 (48.8)	240 (39.3)	130 (42.6)	564 (40.8)	603 (43.8)	973 (40.8)	831 (44.1)	145 (44.9)	129 (44.0)
Age (Years)										
Mean (SD)	60.6 (13.5)	61.7 (13.8)	65.0 (12.57)	64.8 (13.20)	60.9 (14.67)	62.4 (14.14)	61.9 (14.09)	62.7 (13.98)	66.8 (13.6)	65.7 (14.4)
Age Range, n (%)										
65 – 74 years	108 (27.6)	55 (27.1)	190 (31.1)	79 (25.9)	321 (23.2)	350 (25.4)	619 (25.9)	484 (25.7)	83 (25.7)	85 (29.0)
≥ 75 years	58 (14.8)	38 (18.7)	152 (24.9)	81 (26.6)	267 (19.3)	297 (21.6)	477 (20.0)	416 (22.1)	113 (35.0)	98 (33.4)
Weight (kg)										
Mean (SD)	73.86 (16.49)	76.50 (16.51)	71.32 (19.44)	71.23 (18.37)	69.9 (18.46)	70.6 (18.84)	70.91 (18.46)	71.32 (18.61)	76.90 (16.33)	78.39 (17.68)
BMI (kg/m²)										
Mean (SD)	27.06 (5.53)	27.63 (5.51)	27.45 (6.33)	27.29 (6.02)	26.68 (6.01) ‡	26.85 (6.12) ‡	26.94 (6.02) ‡	27.01 (6.05) ‡	27.95 (5.76)	28.74 (6.06)
Race, n (%)										
White	335 (85.7)	182 (89.7)	176 (28.8)	99 (32.5)	623 (45.0)	611 (44.4)	1134 (47.5)	892 (47.3)	306 (94.7)	281 (95.9)
Black or African American	10 (2.6)	3 (1.5)	75 (12.3)	28 (9.2)	112 (8.1)	115 (8.4)	197 (8.3)	146 (7.7)	8 (2.5)	2 (0.7)
Asian	9 (2.3)	0	306 (50.1)	150 (49.2)	544 (39.3)	538 (39.1)	859 (36.0)	687 (36.5)	9 (2.8)	10 (3.4)
CKD Stage, n (%)										
Stage 3	83 (21.2)	52 (25.6)	129 (21.1)	65 (21.3)	256 (18.5)	255 (18.5)	428 (17.9)	351 (18.6)	72 (22.3)	62 (21.2)
Stage 4	161 (41.2)	80 (39.4)	292 (47.8)	146 (47.9)	534 (38.6)	520 (37.8)	953 (39.9)	724 (38.4)	155 (48.0)	143 (48.8)
Stage 5	147 (37.6)	71 (35.0)	195 (31.9)	95 (31.1)	591 (42.7)	598 (43.4)	1005 (42.2)	809 (42.9)	96 (29.7)	88 (30.0)
Most Likely CKD Etiology, n (%)										
Diabetic nephropathy	109 (27.9)	66 (32.5)	357 (58.4)	165 (54.1)	614 (44.9)	602 (44.2)	1080 (45.3)	832 (44.2)	109 (33.7)	98 (33.4)
Hypertensive nephropathy‡	116 (29.7)	58 (28.6)	259 (42.4)	131 (43.0)	207 (15.2)	192 (14.1)	582 (24.4)	381 (20.2)	92 (28.5)	87 (29.7)
eGFR (mL/min/1.73 m²)										
Mean (SD)	16.5 (10.2)	17.2 (11.7)	21.84 (11.51)	22.39 (11.43)	19.69 (11.74)	19.95 (11.75)	19.72 (11.55)	20.06 (11.76)	20.31 (11.49)	20.34 (10.73)
hs-CRP, n (%)										
≤ ULN	245 (63.1)	135 (66.8)	453 (74.1)	223 (73.1)	520 (37.6)	497 (36.1)	1218 (51.0)	855 (45.4)	209 (65.3)	177 (60.4)
> ULN	143 (36.9)	67 (33.2)	156 (25.5)	81 (26.6)	227 (16.4)	209 (15.2)	526 (22.0)	357 (18.9)	111 (34.7)	116 (39.6)
Haemoglobin (g/dL)										
Mean (SD)	9.08 (0.76)	9.10 (0.72)	9.09 (0.75)	9.09 (0.69)	9.11 (0.73)	9.10 (0.74)	9.10 (0.74)	9.10 (0.73)	9.55 (0.75)	9.55 (0.69)
Iron Repletion at Baseline, n (%)										
Ferritin ≥ 100 ng/mL and TSAT ≥ 20%	204 (52.2)	109 (53.7)	369 (60.4)	170 (55.7)	809 (58.5)	799 (58.0)	1429 (59.9)	1126 (59.8)	182 (56.3)	152 (51.9)
Ferritin < 100 ng/mL (and) (or) TSAT < 20%	ND		241 (39.4)	134 (43.9)	575 (41.5)	578 (42.0)	956 (40.1)	755 (40.1)	51 (15.8)	64 (21.8)

Category	Placebo-controlled								ESA-controlled	
	Studies						NDD Pool (SAF)		Study	
	1517-CL-0608 (SAF)		FGCL-4592-060 (SAF)		D5740C00001 (ITT) †				1517-CL-0610 (SAF)	
	R n = 391	PB n = 203	R n = 611	PB n = 305	R n = 1384	PB n = 1377	R n = 2386	PB n = 1884	R n = 323	DA n = 293
LDL Cholesterol (mg/dL)										
Mean (SD)	115.4 (49.7)	111.5 (44.2)	97.74 (39.09)	96.39 (40.06)	94.50 (ND)	92.52 (ND)	99.0 (44.2)	95.5 (42.4)	100.6 (40.0)	102.8 (39.8)
Median	108.3	105.2	92.00	89.00	ND		92.0	89.3	94.2	98.4
SF-36 PF										
Mean (SD)	40.1 (9.7)	38.6 (9.8)	41.16 (10.12)	41.35 (10.07)	39.31 (ND)	39.15 (ND)	39.96 (10.12)	39.46 (10.28)	38.5 (10.1)	38.8 (10.6)
SF-36 VT										
Mean (SD)	45.9 (10.2)	44.3 (9.7)	48.19 (10.15)	47.62 (9.77)	46.87 (ND)	47.04 (ND)	47.06 (9.99)	46.86 (10.05)	43.6 (9.2)	44.7 (10.2)
MAP (mmHg)										
Mean (SD)	96.07 (8.82)	96.23 (8.50)	92.16 (8.54)	91.53 (8.08)	94.45 (8.60)	94.56 (8.69)	94.12 (8.70)	94.24 (8.67)	95.64 (9.74)	96.01 (9.16)

DD pool

General patients characteristics, CKD characteristics, and anaemia characteristics are presented below, both for the individual studies as for the pooled data.

Table 25: Summary of demographics; main phase 3 DD studies

Category	1517-CL-0613 (SAF)		FGCL-4592-064 (SAF)		FGCL-4592-063 (SAF)		D5740C00002 (ITT)	
	R n = 414	ESA† n = 420	R n = 370	EPO-α n = 370	R n = 522	EPO-α n = 517	R n = 1051	EPO-α n = 1055
Sex, n (%)								
Male	245 (59.2)	235 (56.0)	187 (50.5)	214 (57.8)	309 (59.2)	306 (59.2)	625 (59.5)	626 (59.3)
Female	169 (40.8)	185 (44.0)	183 (49.5)	156 (42.2)	213 (40.8)	211 (40.8)	426 (40.5)	429 (40.7)
Age (Years)								
Mean (SD)	61.0 (13.8)	61.8 (13.4)	57.6 (13.63)	58.4 (13.34)	53.8 (14.74)	54.3 (14.49)	53.5 (15.30)	54.5 (14.97)
Age Range, n (%)								
< 65 years	222 (53.6)	229 (54.5)	253 (68.4)	246 (66.5)	381 (73.0)	388 (75.0)	798 (75.9)	783 (74.2)
65 - 74 years	114 (27.5)	115 (27.4)	80 (21.6)	76 (20.5)	100 (19.2)	94 (18.2)	174 (16.6)	177 (16.8)
≥ 75 years	78 (18.8)	76 (18.1)	37 (10.0)	48 (13.0)	41 (7.9)	35 (6.8)	79 (7.5)	95 (9.0)
Weight (kg)								
Mean (SD)	76.29 (15.88)	76.18 (17.25)	84.28 (22.30)	86.58 (22.98)	76.01 (18.50)	76.67 (19.10)	75.1 (21.20)	75.1 (19.65)
BMI (kg/m²) ‡								
Mean (SD)	26.87 (4.86)	26.95 (5.59)	30.21 (7.39)	30.51 (7.55)	26.73 (5.84)	26.99 (6.02)	27.01 (6.75)	26.93 (6.36)
Race, n (%)								
White	405 (97.8)	407 (96.9)	165 (44.6)	184 (49.7)	415 (79.5)	396 (76.6)	597 (56.8)	598 (56.7)
Black or African American	6 (1.4)	6 (1.4)	158 (42.7)	156 (42.2)	44 (8.4)	50 (9.7)	148 (14.1)	158 (15.0)
Asian	1 (0.2)	3 (0.7)	21 (5.7)	15 (4.1)	43 (8.2)	51 (9.9)	208 (19.8)	198 (18.8)
American Indian or Alaska Native	0	0	10 (2.7)	7 (1.9)	1 (0.2)	4 (0.8)	50 (4.8)	62 (5.9)
Native Hawaiian or Other Pacific Islander	0	0	1 (0.3)	3 (0.8)	0	0	5 (0.5)	3 (0.3)
Other	2 (0.5)	4 (1.0)	15 (4.1)	5 (1.4)	19 (3.6)	16 (3.1)	43 (4.1)	36 (3.4)
Baseline Dialysis Type, n (%)								

Category	1517-CL-0613 (SAF)		FGCL-4592-064 (SAF)		FGCL-4592-063 (SAF)		D5740C00002 (ITT)	
	R n = 414	ESA† n = 420	R n = 370	EPO-α n = 370	R n = 522	EPO-α n = 517	R n = 1051	EPO-α n = 1055
Haemodialysis	379 (91.5)	405 (96.4)	354 (95.7)	353 (95.4)	469 (89.8)	461 (89.2)	938 (89.4)‡	938 (88.9)
Peritoneal dialysis	35 (8.5)	15 (3.6)	16 (4.3)	17 (4.6)	53 (10.2)	56 (10.8)	111 (10.6)	117 (11.1)
Most Likely CKD Etiology, n (%)§								
Diabetic Nephropathy	74 (17.9)	95 (22.6)	199 (53.8)	222 (60.0)	185 (35.4)	181 (35.0)	342 (32.7)	315 (30.1)
Hypertensive Nephropathy¶‡	124 (30.0)	120 (28.6)	207 (55.9)	205 (55.4)	175 (33.5)	178 (34.4)	179 (17.1)	204 (19.5)
LDL Cholesterol (mg/dL)‡								
n	413	420	369	370	522	513	836	905
Mean (SD)	106.3 (39.4)	102.2 (39.3)	84.53 (34.01)	84.45 (34.12)	109.12 (38.83)	109.22 (35.91)	88.26 (ND)	88.20 (ND)
SF-36 VT‡								
n	408	415	368	369	521	509	ND	
Mean (SD)	49.8 (10.0)	49.2 (10.0)	51.65 (10.11)	51.27 (9.84)	48.44 (10.41)	47.93 (10.68)		
SF-36 PF‡								
n	407	416	368	369	520	509	ND	
Mean (SD)	41.3 (10.3)	41.5 (9.9)	38.55 (11.20)	39.63 (11.37)	40.46 (10.28)	40.49 (10.18)		
MAP (mmHg)								
n	414	420	370	370	521	517	1048	1053
Mean (SD)	95.22 (11.49)	95.14 (11.55)	101.36 (12.62)	100.34 (12.35)	99.33 (10.15)	99.07 (9.94)	99.09 (10.64)	98.80 (10.87)

Table 26: Summary of baseline CKD characteristics (SAF); DD pools

Parameter Category/Statistics	Overall DD Pool		ID DD Subpool		Stable DD Subpool	
	R n = 2354	ESA n = 2360	R n = 760	ESA n = 766	R n = 1594	ESA n = 1594
Baseline Dialysis Type, n (%)						
Haemodialysis	2137 (90.8)	2156 (91.4)	680 (89.5)	674 (88.0)	1457 (91.4)	1482 (93.0)
Peritoneal dialysis	215 (9.1)	204 (8.6)	80 (10.5)	92 (12.0)	135 (8.5)	112 (7.0)
Missing	2	0	0	0	2	0
Time Since Dialysis Initiation, n (%)						
> 6 months	1494 (63.5)	1507 (63.9)	0	0	1103 (93.5)	1111 (94.6)
>4 to ≤ 6 months	99 (4.2)	86 (3.6)	0	0	76 (6.4)	62 (5.3)
≤ 4 months	760 (32.3)	766 (32.5)	760, (100)	766, (100)	0	0
Most Likely CKD Etiology, n (%)						
Diabetic Nephropathy	799 (33.9)	813 (34.4)	275 (36.2)	268 (35.0)	524 (32.9)	545 (34.2)
Hypertensive Nephropathy	684 (29.1)	707 (30.0)	232 (30.5)	241 (31.5)	452 (28.4)	466 (29.2)
Other	1155 (49.1)	1126 (47.7)	395 (52.0)	395 (51.6)	760 (47.7)	731 (45.9)
Haemoglobin (g/dL)						
Mean (SD)	9.83 (1.28)	9.86 (1.28)	8.82 (1.22)	8.86 (1.20)	10.31 (1.00)	10.34 (1.02)
Median	10.05	10.10	8.88	8.87	10.47	10.50
Min, Max	4.3, 12.3	5.0, 12.2	5.3, 12.0	5.0, 12.0	4.3, 12.3	5.4, 12.2
Iron Repletion at Baseline, n (%)						
Ferritin ≥ 100 ng/mL and TSAT ≥ 20%	2042 (86.7)	2052 (86.9)	603 (79.3)	605 (79.0)	1439 (90.3)	1447 (90.8)
Ferritin < 100 ng/mL or TSAT < 20%	305 (13.0)	304 (12.9)	155 (20.4)	161 (21.0)	150 (9.4)	143 (9.0)

Numbers analysed

Numbers analysed

Table 27: Analysis sets; main phase 3 NDD studies and NDD pool

Analysis Set	Number of Patients (%)									
	Placebo-controlled						NDD Pool		ESA-controlled	
	Studies								Study	
	1517-CL-0608		FGCL-4592-060		D5740C00001				1517-CL-0610	
	R	PB	R	PB	R	PB	R	PB	R	DA
Intent to Treat †	391 (100)	203 (100)	616 (100)	306 (100)	1393 (100)	1388 (100)	2391 (100)	1886 (100)	323 (100)	293 (100)
Safety Analysis Set	391 (100)	203 (100)	611 (99.2)	305 (99.7)	1384 (99.4)	1376 (99.1)	2386 (99.8)	1884 (99.9)	323 (100)	293 (100)
Full Analysis Set	389 (99.5)	203 (100)	608 (98.7)	305 (99.7)	1371 (98.4)	1357 (97.8)	2368 (99.0)	1865 (98.9)	322 (99.7)	292 (99.7)
Per Protocol Set	359 (91.8)	183 (90.1)	561 (91.1)	281 (91.8)	1148 (82.4)	1113 (80.2)	2068 (86.5)	1577 (83.6)	286 (88.5)	273 (93.2)

Table 28: Analysis sets; main phase 3 DD studies

Analysis Set	Number of Patients (%)							
	1517-CL-0613		FGCL-4592-064		FGCL-4592-063		D5740C00002	
	R	ESA†	R	EPO-α	R	EPO-α	R	EPO-α
Intent to Treat ‡	415 (100)	421 (100)	370 (100)	371 (100)	522 (100)	521 (100)	1051 (100)	1055 (100)
Safety Analysis Set	414 (99.8)	420 (99.8)	370 (100)	370 (99.7)	522 (100)	517 (99.2)	1048 (99.7)	1053 (99.8)
Full Analysis Set	413 (99.5)	420 (99.8)	369 (99.7)	370 (99.7)	522 (100)	513 (98.5)	1038 (98.8)	1045 (99.1)
Per Protocol Set	386 (93.0)	397 (94.3)	334 (90.3)	352 (94.9)	490 (93.9)	468 (89.8)	842 (80.1)	869 (82.4)

Outcomes and estimation

NDD pool

Table 29: Summary of efficacy results for main phase 3 NDD studies (made by assessor)

Efficacy Endpoint	Placebo-controlled NDD Studies			ESA-controlled, NDD Study
	1517-CL-0608 N=389 vs 203	FGCL-4592-060 N=616 vs 306	D5740C00001 N=1384 vs 1377	1517-CL-0610 N=323 vs 293
Hb effect				
Proportion of patients who achieved an Hb response during the first 24 weeks (%) - difference	[1] 79.2 vs 9.9 69.3 (63.6, 75.1) superiority met	[1] 86.0 vs 6.6 77.6 (44.7, 134.5) superiority met	[1] 77.0 vs 8.5 9.1 (7.6, 10.9) superiority met	[1] 89.5 vs 78.0 11.5 (5.7 vs 17.4) non-inferiority met
Change from baseline in Hb to weeks 28 – 36 (g/dL) - difference	[2] 2.07 vs 0.47 1.6 (1.4, 1.8) superiority met	[2] 2.02 vs 0.20 1.9 (1.7, 2.0) superiority met	NA	[2] 1.85 vs 1.84 0.015 (-0.132, 0.161) non-inferiority met
Change from baseline in Hb to weeks 28 - 52 among patients with baseline hs-CRP > ULN (g/dL) - difference	NA	[3] 2.0 vs 0.18 1.9 (1.7, 2.1) superiority met	[4] 1.75 vs 0.62 1.1 (0.9, 1.4) superiority met	NA
Proportion of patients with Hb ≥ 10 g/dL to weeks 28 – 36 (%) - HR	NA	[4] 76.8 vs 18.4 15.5 (10.8, 22.2) superiority met	NA	NA
Hb maintenance ≥ 10 g/dL by dose frequency (%)	NA	[5] QW 76.0 vs 16.1 24.1 (10.2, 56.6) BIW 90.2 41.6 (12.1, 142.7) TIW 86.6 41.0 (25.9, 65.0) superiority met	NA	NA

| Efficacy Endpoint | Placebo-controlled NDD Studies | | | ESA-controlled, NDD Study |
	1517-CL-0608 N=389 vs 203	FGCL-4592-060 N=616 vs 306	D5740C00001 N=1384 vs 1377	1517-CL-0610 N=323 vs 293
Percentage of time with Hb values ≥ 10 g/dL to weeks 28 - 52	NA	NA	**[2]** 0.82 vs 0.33 0.50 (0.47, 0.52) superiority met	NA
Percentage of time with Hb values within 10 - 12 g/dL to weeks 28 - 52	NA	NA	**[3]** 0.70 vs 0.28 0.42 (0.40, 0.45) superiority met	NA
Effect on cholesterol				
Change from baseline in LDL cholesterol to weeks 12 – 28 (mmol/L) - difference	**[3]** -0.60 vs 0.15 -0.71 (-0.83, -0.57) superiority met	**[6]** -0.48 vs 0.01 -0.48 (-0.53, -0.36) superiority met	**[5]** -0.38 vs - 0.02 -0.36 (-0.42, -0.29) superiority met (24 weeks)	**[3]** -0.35 vs 0.05 -0.40 (-0.51, -0.30) superiority met
Rescue therapy and iv iron use				
Time to rescue therapy (incidence per 100 PY)	**[4]** 14.6 vs 59.6 superiority met	**[7]** 10.2 vs 38.1 0.19 (0.14, 0.28) superiority met	**[6a]** 11.9 vs 39.8 0.26 (0.23, 0.31) superiority met	NA
Time to blood/RBC transfusion	NA	**[10]** 6.4 vs 20.4 0.26 (0.17, 0.41) not formally tested	**[6b]** 8.0 vs 19.6 0.37 (0.30, 0.44) superiority met	NA
Time to iv iron use weeks 1 - 36	NA	NA	NA	**[4]** 9.9 vs 20.6 0.46 (0.27, 0.80) superiority met
Patient reported outcomes				
Change from baseline in SF-36 VT subscore to weeks 12 - 28	**[5]** 2.42 vs 1.69 1.13 (-0.19, 2.4) superiority not met	**[8]** 1.90 vs 1.02 1.22 (0.15, 2.3) superiority met	**[7]** 1.59 vs 1.15 0.44 (-0.11, 0.99) superiority not met	**[6]** 4.09 vs 3.88 -0.42 (-1.6, -0.78) non-inferiority met
Change from baseline in SF-36 PF subscore to weeks 12 – 28 – mean difference	**[6]** 1.41 vs 1.07 0.71 (-0.56, 2.0) not formally tested	**[11]** 0.33 vs -0.27 0.60 (-0.40, 1.60) not formally tested	**[9]** 0.14 vs -0.39 0.52 (0.0, 1.05) not formally tested	**[5]** 0.91 vs 2.06 -1.28 (-2.42, -0.14) non-inferiority met
Effect on blood pressure				
Change from baseline in MAP to weeks 20 – 28 (mmHg)	*[7]* 0.66 vs -0.08 0.84 (-0.40, 2.1) not formally tested (not included in hierarchical testing)	**[12]** 0.02 vs -0.12 0.36 (-0.74, 1.5) not formally tested	NA	**[7]** 0.55 vs 0.59 -0.36 (-1.58, 0.85) non-inferiority met superiority not met
Time to first hypertension (event rate per 100 PY)	*[8]* 13.4 vs 12.1 1.29 (0.77, 2.16) not formally tested (not included in hierarchical testing)	**[13]** 12.3 vs 12.7 1.16 (0.83, 1.62) not formally tested	NA	**[8]** 30.0 vs 34.5 0.83 (0.56, 1.22) non-inferiority met† superiority not formally tested†
Effect on renal function decline				
Rate of change in eGFR over time adjusted by baseline eGFR, censored at chronic dialysis or kidney transplant	*[9]* -2.65 vs -3.24 0.59 (-0.57, 1.75) (not included in the hierarchical testing)	**[9]** ? vs ? 2.53 (0.52, 4.6) superiority not met	**[8]** -3.70 vs -3.19 -0.51 not formally tested	NA

The numbers in parentheses represent the sequence in which the endpoints were tested i.e., **[1]** represents the primary endpoint and **[2]** to **[13]** represent the secondary endpoints that were **formally tested sequentially** in a fixed sequence testing procedure.

Endpoints indicated as 'not formally tested' refer to where the fixed sequential testing procedure was stopped based on pre-specified criteria. Not every efficacy endpoint listed in the table above was evaluated as a primary or secondary endpoint in all of the studies. Therefore, cells containing NA refer to the endpoints that were not formally tested as a primary or secondary endpoint in the studies as per protocol.

eGFR: estimated glomerular filtration rate; Hb: baseline; hs-CRP: high-sensitivity C-reactive protein; LDL: low density lipoprotein; MAP: mean arterial pressure NA: not applicable; NDD: non-dialysis-dependent; PF: physical function; RBC: red blood cell; SF-36: Short Form 36; ULN: upper limit of normal; VT: vitality. † In weeks 1 to 36.

Combined analyses NDD pool (haemoglobin response)

The haemoglobin response during the first 24 weeks of treatment without rescue therapy was 1899 (80.2%) vs 163 (8.7%) for the placebo-controlled studies. The Odds ratio was 40.49 (33.0, 50.0), p<0.0001. The mean Hb level was 11.0 (SD 0.94) vs 9.4 (1.17) during weeks 28 to 36 for the placebo-controlled studies with a LS mean difference of 1.77 g/dL (1.7, 1.8), p <0.001.

Table 30: Percentage of time with haemoglobin values Within 10 to 12 g/dL, > 12 g/dL or > 13 g/dL; main phase 3 NDD studies and NDD pool

Hb Category/ Statistics	Placebo-controlled								ESA-controlled	
	Studies						NDD Pool (FAS)		Study	
	1517-CL-0608 (FAS)		FGCL-4592-060 (FAS)		D5740C00001 (ITT)				1517-CL-0610 (FAS)	
	Efficacy emergent period		Weeks 28 - 36		Weeks 28 - 52		Weeks 28 - 36		Efficacy emergent period	
	R n = 389	PB n = 203	R n = 608	PB n = 305	R n = 1384	PB n = 1377	R n = 2368	PB n = 1865	R n = 322	DA n = 292
10.0 - 12.0 g/Dl										
n	389	203	503	193	1220	1145	1939	1295	322	292
Mean (SD)	58.55 (25.71)	25.48 (31.01)	72.24 (34.82)	24.98 (39.04)	69.4 (28.69)	27.0 (33.44)	71.04 (35.77)	25.51 (38.68)	63.51 (21.48)	63.71 (24.47)
Median	62.97	11.29	89.11	0	76.25	11.05	88.46	0	68.02	67.86
Min, Max	0, 100	0, 98.03	0, 100	0, 100	0, 100	0, 100	0, 100	0, 100	0, 100	0, 100
> 12.0 g/dL										
n	389	203	ND		ND		1939	1295	322	292
Mean (SD)	18.78 (18.48)	1.49 (5.86)					13.94 (27.47)	2.17 (11.91)	23.90 (19.12)	20.34 (21.15)
Median	15.47	0					0	0	21.25	14.42
Min, Max	0, 83.11	0, 50.33					0, 100	0, 100	0, 89.73	0, 98.53
> 13.0 g/dL										
n	389	203	ND		ND		1939	1295	322	292
Mean (SD)	2.63 (5.61)	0.10 (0.49)					1.52 (8.63)	0.40 (4.95)	3.65 (7.47)	2.74 (7.29)
Median	0	0					0	0	0	0
Min, Max	0, 40.39	0, 3.84					0, 100	0, 100	0, 62.70	0, 84.62

The number of patients on dose hold due to Hb > 13g/dL up to week 52 was 306 (12.8%) vs 15 (0.8%)

Exploratory endpoints NDD pool

<u>Rescue therapy overview</u>

Table 31: Use of rescue therapy; main phase 3 NDD studies and NDD pool

Category/ Statistics	Placebo-controlled								ESA-controlled	
	Studies						NDD Pool (FAS)		Study	
	1517-CL-0608 (FAS)		FGCL-4592-060 (FAS)		D5740C00001 (SAF)				1517-CL-0610 (FAS)	
	Efficacy emergent period		During Treatment		OT - 28		Up to Week 52		Efficacy emergent period	
	R n = 389	PB n = 203	R n = 608	PB n = 305	R n = 1384	PB n = 1376	R n = 2368	PB n = 1865	R n = 322	DA n = 292
Number of Patients with	64 (16.5)	93 (45.8)	118 (19.4)	114 (37.4)	254 (18.4)	574 (41.7)	211 (8.9)	580 (31.1)	27 (8.4)	19 (6.5)

Category/ Statistics	Placebo-controlled								ESA-controlled	
	Studies						NDD Pool		Study	
	1517-CL-0608 (FAS)		FGCL-4592-060 (FAS)		D5740C00001 (SAF)		(FAS)		1517-CL-0610 (FAS)	
	Efficacy emergent period		During Treatment		OT - 28		Up to Week 52		Efficacy emergent period	
	R n = 389	PB n = 203	R n = 608	PB n = 305	R n = 1384	PB n = 1376	R n = 2368	PB n = 1865	R n = 322	DA n = 292
Rescue Therapy, n (%)										
RBC Transfusion	31 (8.0)	34 (16.7)	66 (10.9)	64 (21.0)	176 (12.7)	320 (23.3)	118 (5.0)	240 (12.9)	20 (6.2)	19 (6.5)
iv Iron	21 (5.4)	12 (5.9)	47 (7.7)	20 (6.6)	59 (4.3)	108 (7.9)	50 (2.1)	90 (4.8)	ND†	
ESA	12 (3.1)	47 (23.2)	35 (5.8)	69 (22.6)	65 (4.7)	324 (23.6)	48 (2.0)	257 (13.8)	7 (2.2)	0‡
Incidence Rate (per 100 Patient-Years at Risk)	14.6	59.6	10.4	30.2	11.9	39.8	10.4	41.0	8.1	6.4
Hazard Ratio	0.238		0.25		0.26		0.19		1.17	
95% CI	0.17, 0.33		0.19, 0.33		0.23, 0.31		0.16, 0.23		0.65, 2.12	
P value	< 0.001		< 0.0001		< 0.001		< 0.0001		0.597	

Iron parameters

In the NDD pool, mean serum iron increased from baseline to week 52 in the roxadustat group (9.94 [38.47] µg/L); there was no change in the placebo group (1.54 [35.04] µg/L). In the roxadustat group, serum iron initially decreased from baseline to week 8, subsequently increased to above baseline at week 20 and remained relatively stable up to week 52. Serum iron levels in patients in the placebo group remained stable over the course of the study. Patients in the roxadustat group had a greater mean decrease in mean ferritin from baseline to week 52 (-52.09 [253.43] µg/L) than patients in the placebo group (14.59 [204.13] µg/L) [ISE]. This trend was observed over 52 weeks. In the NDD pool, the change from baseline to week 52 in mean transferrin saturation was comparable between treatment groups (0.05 [14.23]% on roxadustat and 0.30 [12.70]% on placebo). In the roxadustat group, mean transferrin saturation initially decreased from baseline to week 8, but then increased to baseline levels and remained stable up to week 52. Transferrin saturation in the placebo group remained similar over the course of the study. In the NDD pool, there was a statistically significant decrease from baseline in serum hepcidin to week 24 compared with the placebo group (LS mean difference: -25.86 µg/L; 95% CI: -33.09, -18.63; P < 0.0001)].

In the comparator study 0610, serum ferritin, TSAT and serum iron were comparable between roxadustat and ESA.

DD pool

Table 32: Summary of efficacy results for main phase 3 DD studies (made by assessor)

Efficacy Endpoint	1517-CL-0613 N= 414 vs 420 ESA conversion study	FGCL-4592-064 N= 370 vs 371 ESA conversion study	FGCL-4592-063 N= 522 vs 521 Correction study	D5740C00002 N=1051 vs 1055 Conversion + correction
Hb effect				
Proportion of patients who achieved an Hb response during the first 24 weeks (%)	NA	NA	**[1]** 88.2 vs 84.4 3.5 (-0.7, 7.7) non-inferiority met	NA
Change from baseline in Hb to weeks 28-36 (g/dL)	**[1]** 0.49 vs 0.21 0.25 (0.14, 0.35) non-inferiority met	**[1]** 0.63 vs 0.09 0.55 (0.40, 0.69) non-inferiority met	NA	**[1]** 0.88 vs 0.74 0.14 (0.03, 0.25) non-inferiority met
Change from baseline in Hb to weeks 28 – 52 (g/dL)			**[2]** 2.62 vs 2.44 0.16 (0.03, 0.30) non-inferiority met	
Percentage of Hb responders with mean Hb within 10 – 12 g/dL to weeks 28 – 36 (%)	**[2]** 84.2 vs 82.4 -0.38 (-0.45, -0.30) non-inferiority met	**[2]** 64.1 vs 60.8 non-inferiority met	NA	NA
Change from baseline in Hb to weeks 18 - 24 among patients with baseline hs-CRP > ULN (g/dL)	NA	**[4]** 0.56 vs -0.15 0.71 (0.52, 0.89) non-inferiority met	**[4]** 2.36 vs 2.54 0.0 (-0.19, -0.02) non-inferiority met (weeks 18 - 24)	**[4]** 0.80 vs 0.59 0.20 (0.04, 0.36) superiority met (weeks 28 - 52)
Percentage of time with Hb ≥ 10 g/dL to weeks 28- 52	NA	NA	NA	0.79 vs 0.76 0.03 (0.0, 0.05) non-inferiority met
Percentage of time with Hb within 10 - 12 g/dL to weeks 28 – 52 (%)	NA	NA	NA	**[2]** 0.65 vs 0.63 0.02 (-0.01, 0.05) non-inferiority met
Effect on cholesterol				
Change from baseline in LDL cholesterol to weeks 12 – 28 (mmol/L)	**[3]** -0.47 vs -0.07 -0.38 (-0.45, -0.30) superiority met	**[3]** -0.32 vs 0.06 -0.38 (-0.46 vs -0.30) superiority met	**[3]** -0.62 vs -0.14 -0.47 (-0.55, -0.39) superiority met (weeks 12 - 24)	**[3]** -0.38 vs -0.05 -0.33 (-0.39, -0.27) superiority met (24 weeks)
Rescue therapy and iv iron use				
Monthly iv iron (mg)	**[4]** 12.0 vs 44.8 -31.9 (-41.4, 22.4) superiority met (day 1 – week 36)	**[5]** 17.1 vs 37.0 HR not provided superiority met (weeks 28 - 52)	**[5]** 59.1 vs 64.0 HR? superiority not met by pre-specified method† (weeks 28 - 52)	**[5]** 58.7 vs 91.3 HR? superiority met (week 36 - end of study)
Time to RBC transfusion (incidence per 100 PY)	NA	**[6]** 7.3 vs 10.2 0.66 (0.46, 0.97) non-inferiority met	**[6]** 4.3 vs 3.5 1.26 (0.79, 2.02) not formally tested (non-inferiority not met even if tested)	**[6]** 41.7 vs 41.7 0.83 (0.64, 1.07) non-inferiority met
Patient reported outcomes				
Change from baseline in SF-36 PF subscore to weeks 12 - 28	**[5]** 41.7 vs 41.7 0.21 (0.65, 1.06) non-inferiority met	NA	NA	NA
Change from baseline in SF-36 VT subscore to weeks 12 - 28	**[6]** 0.96 vs 0.15 0.86 (-0.12, 1.8) non-inferiority met	NA	NA	NA

Efficacy Endpoint	1517-CL-0613 N= 414 vs 420 ESA conversion study	FGCL-4592-064 N= 370 vs 371 ESA conversion study	FGCL-4592-063 N= 522 vs 521 Correction study	D5740C00002 N=1051 vs 1055 Conversion + correction
Effect on blood pressure				
Change from baseline in MAP to weeks 20 – 28 (mmHg)	**[7]** -0.60 vs 0.27 -0.85 (-2.0, -0.27) non-inferiority met superiority not met	**[7]** 0.10 vs -0.59 0.69 (-0.76, 2.14) superiority not met	**[7]** -0.12 vs 1.15 -1.15 (-20.1, -0.20) not formally tested (weeks 8 - 12)	NA
Time to first exacerbation of hypertension to weeks 1 – 36 (incidence per 100 PY)	**[8]** 32.8 vs 37.2 0.92 (0.67, 1.25) non-inferiority met superiority not formally tested	**[8]** 41.0 vs 33.9 1.29 (0.99, 1.68) not formally tested (weeks 28 - 52)	**[8]** 16.9 vs 17.9 0.93 (0.68, 1.28) not formally tested (weeks 28 - 52)	

The numbers in parentheses represent the sequence in which the endpoints were tested i.e., **[1]** represents the primary endpoint and **[2]** to **[8]** represent the secondary endpoints that were **formally tested sequentially** in a fixed sequence testing procedure.

Endpoints indicated as 'not formally tested' refer to where the fixed sequential testing procedure was stopped based on pre-specified criteria. Not every efficacy endpoint listed in the table above was evaluated as a primary or secondary endpoint in all of the studies. Therefore, cells containing NA refer to the endpoints that were not formally tested as a primary or secondary endpoint in the studies as per protocol.

DD: dialysis-dependent; Hb: baseline; hs-CRP: high-sensitivity C-reactive protein; LDL: low density lipoprotein; MAP: mean arterial pressure NA: not applicable; PF: physical function; RBC: red blood cell; SF-36: Short Form 36; ULN: upper limit of normal; VT: vitality.

† While posthoc analysis suggested statistical significance, superiority was not met by the pre-specified method.

Combined analyses DD pool (haemoglobin response)

The mean Hb level was 11.1 (SD 1.05) vs 10.9 (1.06) during weeks 28 to 36 for the ID subpool (initiating dialysis; n=1342) with a LS mean difference of 0.28 g/dL (0.11, 0.45), p =0.013. The mean Hb level was 11.0 (SD 0.87) vs 10.7 (0.97) during weeks 28 to 36 for the DD subpool (stable dialysis; n=2796) with a LS mean difference of 0.30 g/dL (0.23, 0.37), p <0.001.

Haemoglobin response was 59.9% vs 59.6% for the ID subpool and 70.9 vs 67.7% for the DD subpool.

Table 33: Percentage of time with haemoglobin values within 10 to 12 g/dL, ≥ 10 g/dL, > 12 g/dL or > 13 g/dL; main phase 3 DD studies

Hb Category/ Statistics	1517-CL-0613 (FAS)		FGCL-4592-063 (FAS)		D5740C00002 (ITT)‡	
	Efficacy emergent period		Weeks 28 - 52		Weeks 28 - 52	
	R n = 413	ESA† n = 420	R n = 522	EPO-α n = 513	R n = 1051	EPO-α n = 1055
10 - 12 g/dL						
n	413	420	ND		897	942
Mean (SD)	72.54 (19.07)	75.31 (17.41)			65.6 (29.83)	63.4 (31.45)
Median	76.17	78.20			72.11	69.84
Min, Max	0, 100	9.74, 100			0, 100	0, 100
> 12 g/dL						
n	413	420	ND		ND	
Mean (SD)	17.09 (16.50)	9.95 (13.35)				
Median	12.74	6.00				
Min, Max	0, 100	0, 90.26				
> 13 g/dL						
n	413	420	ND		ND	
Mean (SD)	1.86 (4.10)	0.78 (2.64)				
Median	0	0				
Min, Max	0, 30.26	0, 31.64				

The number of patients on dose hold due to haemoglobin > 13 g/dL up to week 52 was 23.8% vs 12.8% in the ID subpool, and 11.7% vs 3.4% in the DD subpool.

Exploratory endpoints DD pool

Iron Parameters

In the stable DD subpool, there was a decrease from baseline in mean serum iron to week 52 in the ESA group (-9.20 [35.82] µg/L); there was no change in the roxadustat group (0.26 [42.70] µg/L).

A greater decrease from baseline in mean ferritin to week 52 than those in the ESA group (-246.24 [332.82] µg/L roxadustat, -165.97 [386.12] µg/L ESA) was observed. Mean transferrin saturation decreased from baseline to week 52 in both treatment groups (-6.00 [16.88] µg/L roxadustat, -5.72 [15.28] µg/L ESA); this trend was observed at different timepoints and was similar between treatment groups. There was a nominally statistically significant decrease from baseline in serum hepcidin to week 24 in the roxadustat group compared with the ESA group (LS mean difference: -17.04 µg/L; 95% CI: -25.59, -8.50; P < 0.0001).

In the ID DD subpool, change from baseline in serum iron, change in ferritin and transferrin saturation was not calculated. There was a nominally statistically significant decrease from baseline in serum hepcidin to week 24 (-63.47 [121.84] µg/L) in the roxadustat group compared with the ESA group

(-34.84 [141.63] µg/L). In the stable DD subpool.

Rescue Therapy

In Studies 1517-CL-0613, FGCL-4592-064 and D5740C00002, the proportion of patients who required the use of rescue therapy was comparable between groups over the efficacy emergent period in Studies 1517-CL-0613 and FGCL-4592-064 or up to 3 days after the EOT in Study D5740C00002. There was no difference between groups in time to first use of rescue therapy.

Table 34: Use of rescue therapy; main phase 3 DD studies

Category/ Statistics	1517-CL-0613 (FAS) Efficacy emergent period		FGCL-4592-064 (FAS) Efficacy emergent period		FGCL-4592-063 (FAS) Efficacy emergent period		D5740C00002 (SAF) OT – 3	
	R n = 413	ESA† n = 420	R n = 369	EPO-α n = 370	R n = 522	EPO n = 513	R n = 1048	EPO-α n = 1053
Number of Patients with Rescue Therapy, n (%)	44 (10.7)	54 (12.9)	59 (16.0)	78 (21.1)	ND		132 (12.6)	139 (13.2)
RBC Transfusion	38 (9.2)	54 (12.9)	46 (12.5)	78 (21.1)			103 (9.8)	139 (13.2)
ESA	6 (1.5)	NA	23 (6.2)	NA			NA	
Incidence Rate (per 100 Patient-Years at Risk)	7.1	7.8	9.4	10.3			7.8	7.2
Hazard Ratio	0.98		0.89				1.07	
95% CI	0.66, 1.46		0.63, 1.25				0.84, 1.36	
P value (nominal)	0.92		0.5044				0.565	

Ancillary analyses

Persistence of efficacy and/or tolerance effects

<u>NDD pool</u>

The initial effect on Hb stabilised after approximately 12 weeks and was maintained during 104 weeks of follow-up.

<u>DD pool</u>

The initial effect on Hb stabilised after approximately 12 weeks and was maintained during 52 weeks in study FGCL-4592-063 and 104 to 200 weeks of follow-up for the stable dialysis pool and initiating dialysis pool, respectively.

Subgroup analyses

<u>NDD pool</u>

Figure 9: Forest Plot of Difference in Proportion of Patients who Achieved Haemoglobin Response During the First 24 Weeks (FAS); NDD Pool

Subgroups/ Value	Roxadustat n/N1 (%)	Placebo n/N1 (%)	Response Rate Difference (95% CI)	
Diabetes Medical History				
Yes	1056 /1323 (79.8)	82 /1081 (7.6)	72.2 (69.56, 74.91)	
No	843 /1045 (80.7)	81 / 784 (10.3)	70.3 (67.13, 73.54)	
Baseline CRP level				
<= ULN	1042 /1213 (85.9)	69 / 854 (8.1)	77.8 (75.14, 80.50)	
> ULN	401 / 523 (76.7)	44 / 355 (12.4)	64.3 (59.29, 69.27)	
Baseline Hb				
<8 g/dL	150 / 199 (75.4)	13 / 162 (8.0)	67.4 (60.05, 74.65)	
>=8 g/dL	1749 /2169 (80.6)	150 /1703 (8.8)	71.8 (69.69, 73.97)	
Body weight				
<70 Kg	1069 /1277 (83.7)	74 / 975 (7.6)	76.1 (73.50, 78.74)	
>=70 - <100 Kg	714 / 926 (77.1)	72 / 747 (9.6)	67.5 (64.03, 70.90)	
>=100 Kg	116 / 165 (70.3)	17 / 143 (11.9)	58.4 (49.65, 67.18)	
Baseline eGFR				
<10 mL/min/1.73 m2	341 / 472 (72.2)	14 / 352 (4.0)	68.3 (63.74, 72.79)	
10 - <15 mL/min/1.73 m2	417 / 523 (79.7)	27 / 448 (6.0)	73.7 (69.62, 77.80)	
15 - <30 mL/min/1.73 m2	793 / 949 (83.6)	69 / 719 (9.6)	74.0 (70.77, 77.16)	
>=30 mL/min/1.73 m2	348 / 424 (82.1)	53 / 346 (15.3)	66.8 (61.49, 72.02)	

95% CI for Response Rate Difference

DD pool

Figure: 10 Forest Plot of Difference in Change from Baseline in Haemoglobin Averaged Over Weeks 28 to 52 (ITT); ID DD Subpool

Subgroups/ Value	Roxadustat n Mean (SD)	Active Control n Mean (SD)	LS Means Difference (95% CI) [1]	P-value [1]
Overall	760 2.12 (1.454)	770 1.91 (1.422)	0.22 (0.047, 0.399)	0.0130
Age Group				
18 - 64	570 2.15 (1.478)	584 1.98 (1.441)	0.21 (-0.014, 0.426)	0.0659
65 - 74	132 2.16 (1.313)	129 1.74 (1.386)	0.42 (0.030, 0.816)	0.0349
>=75	58 1.77 (1.491)	57 1.55 (1.221)	0.05 (-0.404, 0.495)	0.8430
Sex				
Male	461 2.07 (1.427)	464 1.85 (1.390)	0.25 (0.044, 0.459)	0.0177
Female	299 2.20 (1.492)	306 2.01 (1.465)	0.16 (-0.140, 0.467)	0.2904
Race				
Asian	116 1.86 (1.573)	127 1.45 (1.463)	0.39 (0.011, 0.771)	0.0438
Black	67 1.19 (1.275)	67 1.62 (1.214)	-0.06 (-0.492, 0.381)	0.8024
White	508 2.37 (1.380)	505 2.10 (1.395)	0.27 (0.034, 0.500)	0.0248
Other	69 1.59 (1.371)	71 1.65 (1.458)	N/A	N/A
Geographical Region				
US	195 1.25 (1.218)	196 1.12 (1.219)	0.23 (0.011, 0.449)	0.0399
Europe	362 2.68 (1.320)	374 2.41 (1.276)	0.16 (-0.016, 0.343)	0.0744
Other	203 1.96 (1.445)	200 1.75 (1.478)	0.14 (-0.054, 0.339)	0.1557
Iron Status at Baseline				
Ferritin <100.0 or TSAT <20.0%	155 2.23 (1.447)	162 2.13 (1.298)	0.12 (-0.391, 0.632)	0.6444
Ferritin >=100.0 and TSAT >=20.0%	603 2.10 (1.454)	608 1.85 (1.448)	0.24 (0.055, 0.427)	0.0110

95% CI for LS Means Difference [1]

Subgroups/ Value	Roxadustat n Mean (SD)	Active Control n Mean (SD)	LS Means Difference (95% CI) [1]	P-value [1]
Diabetes Medical History				
Yes	322 1.72 (1.361)	314 1.54 (1.374)	0.26 (0.031, 0.480)	0.0261
No	438 2.41 (1.453)	456 2.17 (1.397)	0.19 (-0.104, 0.484)	0.2053
Baseline CRP level				
<= ULN	406 2.21 (1.515)	401 1.90 (1.424)	0.21 (-0.001, 0.426)	0.0509
> ULN	285 2.18 (1.307)	301 2.05 (1.396)	0.32 (0.023, 0.618)	0.0349
Baseline Hb				
<8 g/dL	180 3.68 (1.160)	179 3.29 (1.097)	0.41 (0.076, 0.743)	0.0161
>=8 g/dL	580 1.64 (1.168)	591 1.49 (1.231)	0.20 (0.024, 0.373)	0.0259
Body weight				
<70 Kg	355 2.15 (1.580)	333 2.07 (1.496)	0.18 (-0.105, 0.467)	0.2140
>=70 - <100 Kg	319 2.16 (1.335)	362 1.81 (1.371)	0.27 (-0.000, 0.538)	0.0504
>=100 Kg	86 1.82 (1.301)	75 1.71 (1.259)	0.35 (-0.163, 0.853)	0.1827

95% CI for LS Means Difference [1]

Figure 11: Forest Plot of Difference in Change from Baseline in Haemoglobin Averaged Over Weeks 28 to 36 (FAS); Stable DD Subpool

Subgroups/Value	Roxadustat n Mean (SD)	Active Control n Mean (SD)	LS Means Difference (95% CI) [1]	P-value [1]
Overall	1320 0.63 (1.185)	1442 0.37 (1.244)	0.28 (0.205, 0.349)	<.0001
Age Group				
18 - 64	906 0.74 (1.247)	967 0.48 (1.286)	0.28 (0.187, 0.369)	<.0001
65 - 74	273 0.44 (0.999)	297 0.20 (1.153)	0.27 (0.127, 0.420)	0.0003
>=75	141 0.30 (0.986)	178 0.10 (1.078)	0.21 (0.010, 0.406)	0.0391
Sex				
Male	763 0.59 (1.164)	832 0.40 (1.227)	0.24 (0.144, 0.335)	<.0001
Female	557 0.69 (1.212)	610 0.34 (1.268)	0.32 (0.209, 0.428)	<.0001
Race				
Asian	123 1.03 (1.347)	126 0.85 (1.699)	0.29 (-0.337, 0.909)	0.3664
Black	224 0.35 (1.120)	271 -0.03 (0.950)	0.34 (0.091, 0.582)	0.0074
White	906 0.66 (1.133)	983 0.40 (1.205)	0.30 (0.214, 0.380)	<.0001
Other	67 0.42 (1.491)	62 0.72 (1.408)	0.08 (-0.426, 0.588)	0.7522
Geographical Region				
US	541 0.39 (1.095)	610 0.02 (1.017)	0.38 (0.276, 0.482)	<.0001
Europe	611 0.76 (1.148)	648 0.57 (1.224)	0.13 (0.039, 0.227)	0.0056
Other	168 0.92 (1.438)	184 0.87 (1.626)	0.02 (-0.239, 0.283)	0.8699
Iron Status at Baseline				
Ferritin <100.0 or TSAT <20.0%	119 0.86 (1.293)	127 0.87 (1.276)	-0.21 (-0.569, 0.145)	0.2430
Ferritin >=100.0 and TSAT >=20.0%	1197 0.61 (1.167)	1313 0.33 (1.231)	0.31 (0.236, 0.383)	<.0001

95% CI for LS Means Difference [1]

Subgroups/Value	Roxadustat n Mean (SD)	Active Control n Mean (SD)	LS Means Difference (95% CI) [1]	P-value [1]
Diabetes Medical History				
Yes	558 0.50 (1.119)	648 0.21 (1.131)	0.33 (0.228, 0.440)	<.0001
No	762 0.73 (1.222)	794 0.51 (1.314)	0.22 (0.121, 0.327)	<.0001
Baseline CRP level				
<= ULN	602 0.65 (1.175)	675 0.38 (1.232)	0.25 (0.151, 0.351)	<.0001
> ULN	516 0.64 (1.120)	557 0.30 (1.158)	0.36 (0.253, 0.471)	<.0001
Baseline Hb				
<10 g/dL	386 1.57 (1.222)	412 1.38 (1.288)	0.20 (0.040, 0.363)	0.0147
>=10 g/dL	934 0.24 (0.923)	1030 -0.03 (0.970)	0.28 (0.205, 0.359)	<.0001
Body weight				
<70 Kg	488 0.75 (1.351)	532 0.46 (1.447)	0.25 (0.117, 0.392)	0.0003
>=70 - <100 Kg	634 0.57 (1.092)	704 0.39 (1.137)	0.22 (0.120, 0.312)	<.0001
>=100 Kg	198 0.56 (1.000)	206 0.13 (0.973)	0.49 (0.327, 0.660)	<.0001
Mean Prescribed Baseline ESA Dose*				
0 - <= 150 IU/KG/WEEK	1180 0.67 (1.164)	1247 0.40 (1.225)	0.30 (0.226, 0.376)	<.0001
> 150 IU/KG/WEEK	140 0.29 (1.304)	195 0.19 (1.351)	0.06 (-0.191, 0.305)	0.6523
Dialysis Modality				
Hemodialysis (HD)	1212 0.60 (1.162)	1345 0.37 (1.227)	0.25 (0.180, 0.327)	<.0001
Peritoneal Dialysis (PD)	106 0.99 (1.374)	97 0.47 (1.470)	0.48 (0.151, 0.818)	0.0046

95% CI for LS Means Difference [1]

Cholesterol effect by statin use

In the NDD pool and ID DD and stable DD subpools, approximately 20% of patients in each treatment group were on statin treatment at the start of the study. In the NDD pool, the change from baseline in LDL-C was -0.38 vs 0.13 mmol/L with statin use and -0.46 vs 0.01 mmol/L without statin use. This was -0.52 vs 0.07 mmol/L and -0.60 vs -0.13 mmol/L, respectively, in the ID DD subpool, and -0.31 vs 0.04 mmol/L and -0.40 vs -0.02 mmol/L, respectively, in the stable DD subpool.

Summary of main study(ies)

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Non-Dialysis studies (4 studies)

Table 35

Title: A phase 3 randomized, double-blind, placebo-controlled study of the efficacy and safety of roxadustat for the treatment of anemia in chronic kidney disease patients not on dialysis			
Study identifier	1517-CL-0608		
Design	Phase 3, multicentre, randomised, double-blind, placebo-controlled study in anemic patients with Stage 3, 4 or 5 CKD who were not on dialysis at the time of randomisation. Up to 200 centres were planned worldwide		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		Minimum of 52 weeks up to 6 weeks, maximum up to 104 weeks (double-blind)
Hypothesis	Superiority		
Treatments groups	roxadustat		3 times weekly (TIW) orally; tiered weight-based approach with starting doses of 70 mg given 3 times per week for patients weighing up to 70 kg and 100 mg given 3 times per week for patients weighing more than 70 kg was chosen; ESA treatment within 12 weeks prior to randomisation was an exclusion criteria
	Placebo		Dosing instructions matched to instructions provided for roxadustat
Endpoints and definitions	Primary endpoint	Hb response	Hb ≥ 11.0 g/dL and a Hb increase from baseline by ≥ 1.0 g/dL in any patient with baseline Hb > 8.0 g/dL, OR an increase from baseline by ≥ 2.0 g/dL in any patient with baseline Hb ≤ 8.0 g/dL at 2 consecutive visits separated by at least 5 days during the first 24 weeks of treatment without rescue therapy (i.e., RBC transfusion, ESA, or iv iron) prior to Hb response
	Secondary endpoint	Mean change in Hb	Change in Hb from baseline to the average Hb of Weeks 28 to 36, without having received rescue therapy within 6 weeks prior to and during this evaluation period.
	Secondary	LDL-C change	Change from baseline in low density lipoprotein (LDL) cholesterol to the average LDL cholesterol of Weeks 12 to 28.
	Secondary	Time to first rescue therapy	Occurrence and time to first use of rescue therapy [composite of RBC transfusions, iv iron supplementation and rescue ESA].
		SF-36-VT	Change from baseline in SF-36 Vitality (VT) subscore to the average VT subscore of weeks 12 to 28.
	Secondary	SF-36-PF	Change from baseline in Short Form-36 questionnaire (SF-36) physical functioning (PF) subscore to the average PF subscore of weeks 12 to 28.
	Secondary	Change in MAP	Change from baseline in mean arterial pressure (MAP) to the MAP value averaged over Weeks 20 to 28.
	Secondary	Time to hypertension	Time to first exacerbation of hypertension: An increase from baseline of ≥20 mm systolic blood pressure (sBP) and sBP ≥170 mm Hg or an increase from baseline of ≥15 mm Hg diastolic blood pressure (dBP) and dBP ≥110 mm Hg.
	Secondary	GFR rate	Rate of progression of CKD measured by annualised eGFR slope over time

	Additional endpoints	Others	Hb correction and maintenance, hospitalisations, rescue therapy use, changes in cholesterol levels, blood pressure effect, health-related quality of life, and hepcidin, iron indices, haemoglobin A1c (HbA1c) and CKD progression.
Database lock	21 Mar 2018		

Results and Analysis

Analysis description	Primary Analysis			
Analysis population and time point description	fixed sequence testing endpoints 1 to 5 FAS population			
Descriptive statistics and estimate variability	Treatment group	roxadustat	Placebo	Difference (95%CI, p value)
	Number of subject	389	203	
	Hb response (%)	79.2	9.9	69.3 (63.6 – 75.1) P<0.001
Notes				
Analysis description	Secondary analysis			
Descriptive statistics and estimate variability	Treatment group	roxadustat	Placebo	Difference (95%CI, p value)
	Mean change in Hb (g/dL) (Mean (SD)	2.07 (1.0)	0.47 (1.1)	1.6 (1.4 – 1.8) P<0.001
	LDL-C change (Mean mmol/L (SD))	-0.60 (0.91)	0.15 (0.78)	-0.71 (-0.83 - -0.57) P<0.001
	Time to first rescue therapy (incidence per 100 PY)	14.6	59.6	0.24 (0.17 – 0.33) P<0.001
	SF-36-VT	2.42 (8.8)	1.69 (8.5)	1.13 (-0.19 – 2.4) P=0.093
	SF-36-PF	1.41 (8.2)	1.07 (7.0)	0.71 (-0.56 – 2.0) P=0.270
	Change in MAP (Mean (SD)) PPS	0.66 (7.9)	-0.08 (7.5)	0.84 (-0.40 – 2.1) P=0.182
	Time to increased BP ((event rate per 100 PYE)	13.4	12.1	1.29 (0.77 – 2.16) P=0.334

Title: A phase 3 randomized, double-blind, placebo-controlled study of the efficacy and safety of roxadustat for the treatment of anaemia in chronic kidney disease patients not on dialysis	
Study identifier	FGCL-4592-060
Design	Phase 3, multicentre, randomised, double-blind, placebo-controlled study in anemic patients with Stage 3, 4 or 5 CKD who were not on dialysis at the time of randomisation. Up to 200 centres were planned worldwide
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase: / Minimum of 52 weeks, up to 6 weeks, maximum up to 3 years (double-blind)
Hypothesis	Superiority

Treatments groups	roxadustat		3 times weekly (TIW) orally; tiered weight-based approach with starting doses of 70 mg given 3 times per week for patients weighing 46-60 kg. 100 mg for 60-90 kg, and 150 mg given 3 times per week for patients weighing 90 to 160 kg; after amendment 2 (n=627) 70 mg < 70 kg and 100 mg > 70 kg; Dosing frequency was TIW throughout the study, except in subjects who had already converted to BIW or QW dosing regimens as a result of being enrolled under previous FGCL-4592-060 protocol versions. ESA treatment within 12 weeks prior to randomisation was an exclusion criteria
	Placebo		Dosing instructions matched to instructions provided for roxadustat
Endpoints and definitions	Primary endpoint	Hb response	Hb ≥ 11.0 g/dL and a Hb increase from baseline by ≥ 1.0 g/dL in any patient with baseline Hb > 8.0 g/dL, OR an increase from baseline by ≥ 2.0 g/dL in any patient with baseline Hb ≤ 8.0 g/dL at 2 consecutive visits separated by at least 5 days during the first 24 weeks of treatment without rescue therapy (i.e., RBC transfusion, ESA, or iv iron) prior to Hb response
	Secondary endpoint	Mean change in Hb	Change in Hb from baseline to the average Hb of Weeks 28 to 36, without having received rescue therapy within 6 weeks prior to and during this evaluation period.
	Secondary endpoint	Mean change in Hb when sCRP > ULN	
	Secondary endpoint	Proportion with Hb ≥10 g/dL	
	Secondary	Hb maintenance by dose frequency	
	Secondary	Proportion with Hb ≥10 g/dL by dose frequency	
	Secondary	LDL-C change	Change from baseline in low density lipoprotein (LDL) cholesterol to the average LDL cholesterol of Weeks 12 to 28.
	Secondary	Time to first rescue therapy	Occurrence and time to first use of rescue therapy [composite of RBC transfusions, iv iron supplementation and rescue ESA] in the first 52 weeks of treatment.
	Secondary	SF-36-VT	Change from baseline in SF-36 Vitality (VT) subscore to the average VT subscore of weeks 12 to 28.
	Secondary	Change in MAP	Change from baseline in mean arterial pressure (MAP) to the MAP value averaged over Weeks 20 to 28.
	Secondary	Time to hypertension	Time to first exacerbation of hypertension: An increase from baseline of ≥20 mm systolic blood pressure (sBP) and sBP ≥170 mm Hg or an increase from baseline of ≥15 mm Hg diastolic blood pressure (dBP) and dBP ≥110 mm Hg.
	Secondary	GFR rate	Rate of progression of CKD measured by annualised eGFR slope over time

	Additional endpoints	Others	Hb correction and maintenance, hospitalisations, rescue therapy use, changes in cholesterol levels, blood pressure effect, health-related quality of life, and hepcidin, iron indices, haemoglobin A1c (HbA1c) and CKD progression.
Database lock	11-Dec 2018		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	fixed sequence testing endpoints 1 to 5 FAS population		

Descriptive statistics and estimate variability	Treatment group	roxadustat	Placebo	Difference (95%CI, p value)
	Number of subject	616	306	
	Hb response (%)	86.0	6.6	77.6 (44.7 – 134.5) P<0.001

Notes	

Analysis description	**Secondary analysis**			
Descriptive statistics and estimate variability	Treatment group	roxadustat	Placebo	Difference (95%CI, p value)
	Mean change in Hb (g/dL) (Mean (SD)	2.02 (1.1)	0.20 (1.0)	1.9 (1.7 – 2.0) P<0.0001
	Mean change in Hb when sCRP > ULN	2.0 (0.9)	0.18 (0.9)	1.9 (1.7 – 2.1) P<0.0001
	Proportion with Hb ≥10 g/dL	76.8	18.4	15.5 (10.8 – 22.2) P<0.0001
	Hb maintenance by dose frequency QW BIW TIW	1.8 2.4 2.1	0.18 0.17 0.14	1.64 (1.3 – 1.9) 2.2 (2.0 – 2.5) 1.9 (1.8 – 2.1) All p<0.001
	Proportion with Hb ≥10 g/dL by dose frequency QW BIW TIW	76.0 90.2 86.8	16.1 16.1 16.1	24.1 (10.2 – 56.6) 41.6 (12.1 – 142.7) 41.0 (25.9 – 65.0)
	LDL-C change (Mean mg/dL (SD))	-18.5 (29.6)	0.22 (29.7)	-17.3 (-20.5 - -13.8) P<0.0001
	Time to first rescue therapy (incidence per 100 PY)	10.2	38.1	0.19 (0.14, 0.28) Superiority met
	SF-36-PF	1.90 (8.7)	1.02 (8.3)	1.22 (0.15 – 2.3) P=0.0259
	Change in MAP (Mean (SD)) PPS	0.02 (8.6)	-0.12 (7.6)	0.36 (-0.74 – 1.5) P=0.5180
	Time to increased BP ((event rate per 100 PYE)	12.3	12.7	1.16 (0.83 – 1.62) P=0.3814

	GFR rate	?	?	2.53 (0.52 – 4.6) P=0.0140 during first 6 months

Title: A phase 3 multicenter, randomized, double-blind, placebo-controlled study evaluating the safety and efficacy of roxadustat for the treatment of anaemia in chronic kidney disease patients not on dialysis	
Study identifier	D5740C 00001
Design	Phase 3, multicentre, randomised, double-blind, placebo-controlled study in anemic patients with Stage 3, 4 or 5 CKD who were not on dialysis at the time of randomisation. Up to 385 centres were planned worldwide
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase: — Minimum of 52 weeks / up to 6 weeks, / variable
Hypothesis	Superiority
Treatments groups	roxadustat — 3 times weekly (TIW) 70 mg orally; ESA treatment within 6 weeks prior to randomisation was an exclusion criteria
	Placebo — Dosing instructions matched to instructions provided for roxadustat

Endpoints and definitions			
	Primary endpoint	Hb response	Hb ≥ 11.0 g/dL and a Hb increase from baseline by ≥ 1.0 g/dL in any patient with baseline Hb > 8.0 g/dL, OR an increase from baseline by ≥ 2.0 g/dL in any patient with baseline Hb ≤ 8.0 g/dL at 2 consecutive visits separated by at least 5 days during the first 24 weeks of treatment without rescue therapy (i.e., RBC transfusion, ESA, or iv iron) prior to Hb response
	Secondary endpoint	Proportion of time of Hb within target	Proportion of total time of Hb within the interval of ≥10 g/dL from Week 28 to Week 52. Proportion of total time of Hb within the interval of 10 to 12 g/dL from Week 28 to Week 52.
	Secondary endpoint	Mean change in Hb when sCRP > ULN	Change in Hb from baseline to the average Hb of Weeks 28 to 52 in subjects with baseline hsCRP greater than the ULN.
	Secondary	LDL-C change	Change from baseline in low density lipoprotein (LDL) cholesterol to the average LDL cholesterol of Weeks 12 to 28.
	Secondary	Time to first rescue therapy	Occurrence and time to first use of rescue therapy [composite of RBC transfusions, iv iron supplementation and rescue ESA]. Time-to-first administration of (and proportion of subjects who received) a RBC transfusion as rescue therapy.
	Secondary	SF-36	Changes in generic HRQoL as measured by the SF-36.
	Secondary	GFR rate	Annual rate of eGFR change, calculated as the linear slope of eGFR values (calculated using the 4-variable MDRD equation) prior to initiation of dialysis/kidney transplant
	Additional endpoints	Others	Hb correction and maintenance, hospitalisations, rescue therapy use, changes in cholesterol levels, blood pressure effect, health-related quality of life, and hepcidin, iron indices, haemoglobin A1c (HbA1c) and CKD progression.

Database lock	08 Dec 2018			

Results and Analysis

Analysis description	Primary Analysis			
Analysis population and time point description	fixed sequence testing endpoints 1 to 5 FAS population			

Descriptive statistics and estimate variability	Treatment group	roxadustat	Placebo	Difference (95%CI, p value)
	Number of subject	1384	1377	
	Hb response (%)	77.0	8.5	9.1 (7.6 – 10.9) P<0.001

Notes	

Analysis description	Secondary analysis

Descriptive statistics and estimate variability	Treatment group	roxadustat	placebo	Difference (95%CI, p value)
	Mean change in Hb (g/dL) (LS Mean (SE) when sCRP > ULN	1.75 (0.09)	0.62 (0.09)	1.1 (0.9 – 1.4) P<0.0001
	Proportion of time of Hb with Hb ≥10 g/dL (mean change (SE)) with Hb between 10 and 12 g/dL	0.82 (0.01) 0.70 (0.01)	0.33 (0.01) 0.28 (0.01)	0.50 (0.47 – 0.52) P<0.001 0.42 (0.40 – 0.45) P < 0.001
	LDL-C change (Mean mmol/L (SE))	-0.38 (0.03)	-0.02 (0.03)	-0.36 (-0.42 - -0.29) P<0.001
	Time to first rescue therapy (incidence per 100 PY)	11.9	39.8	0.26 (0.23 – 0.31) P< 0.001
	Time to first RBC (incidence per 100 PY)	8.0	19.6	0.37 (0.30 – 0.44) P<0.001
	SF-36-PF	1.59	1.15	0.44 (-0.11 – 0.99) P=0.120
	GFR rate (ml/min/1.73 m2)	-3.70	-3.19	-0.51 P=0.046 Not formally tested

Title: A phase 3 multicenter, randomized, open-label active-controlled study to evaluate the efficacy and safety of roxadustat in the treatment of anaemia in chronic kidney disease patients not on dialysis	
Study identifier	1517-CL-0610
Design	Open-Label, Randomised, Active-Controlled Study Multicentre study. Up to 200 centres were planned worldwide.

	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		104 weeks up to 6 weeks, Patients were not to receive any ESA treatment within at least 12 weeks, any intravenous iron treatment within at least 6 weeks, or any RBC transfusion within at least 8 weeks prior to randomisation
Hypothesis	Non-inferiority		
Treatments groups	roxadustat		3 times weekly (TIW) orally in strengths in 20 mg, 50 mg, and 100 mg tablets Initial dose of study treatment was based tiered, weightbased dosing scheme starting dose of 70 mg for subjects who weighed 45 to <70 kg or 100 mg for subjects who weighed ≥70 kg to 160 mg; Roxadustat dose adjustments were permitted from Week 4 onwards during the correction phase and maintenance phase (specific rules).
	ESA (darbepoetin alfa)		Subjects randomised to the active control treatment arm were to receive darbepoetin alfa SC or IV according to EU SmPC TIW according to SmPC
Endpoints and definitions	Primary endpoint	Hb response	Hb ≥ 11.0 g/dL and a Hb increase from baseline by ≥ 1.0 g/dL in any patient with baseline Hb > 8.0 g/dL, OR an increase from baseline by ≥ 2.0 g/dL in any patient with baseline Hb ≤ 8.0 g/dL at 2 consecutive visits separated by at least 5 days during the first 24 weeks of treatment without rescue therapy (i.e., RBC transfusion, ESA, or iv iron) prior to Hb response
	Key secondary endpoint	Mean change in Hb	Change in Hb from baseline to the average Hb of Weeks 28 to 36, without having received rescue therapy within 6 weeks prior to and during this evaluation period.
	Secondary	LDL-C change	Change from baseline in low density lipoprotein (LDL) cholesterol to the average LDL cholesterol of Weeks 12 to 28.
	Secondary	Time to IV iron use	Time to first IV iron use during Weeks 1 to 36 (
	Secondary	SF-36 PF	Change from BL in SF-36 PF (physical function) subscore to the average PF subscore in weeks 12 to 28
	Secondary	SF-36-VT	Change from baseline in SF-36 Vitality (VT) subscore to the average VT subscore of weeks 12 to 28.
	Secondary	Change in MAP	Change from baseline in mean arterial pressure (MAP) to the MAP value averaged over Weeks 20 to 28.
	Secondary	Time to hypertension	Time to first exacerbation of hypertension: An increase from baseline of ≥20 mm systolic blood pressure (sBP) and sBP ≥170 mm Hg or an increase from baseline of ≥15 mm Hg diastolic blood pressure (dBP) and dBP ≥110 mm Hg during Weeks 1 to 36.
	Additional endpoints	Others	Hb correction and maintenance, hospitalisations, rescue therapy use, iron supplementation, changes in cholesterol levels, blood pressure effect, health-related quality, iron indices, haemoglobin A1c (HbA1c), and CKD progression
Database lock	19 Jan 2020		

Results and Analysis

Analysis description	Primary Analysis
Analysis population and time point description	Per protocol (PPS), NI (non-inferiority), SUP (superiority for some endpoints), fixed sequence results PPS population 286 (88.5%) vs 273 (93.2%)

Descriptive statistics and estimate variability	Treatment group	roxadustat	ESA (darbepoetin alfa)	Difference (95%CI, p value)
	Number of subject	323	293	
	Hb response (%)	89.5	78.0	11.5 (5.7 – 17.4)
Notes				
Analysis description	**Secondary analysis**			
Descriptive statistics and estimate variability	Treatment group	roxadustat	ESA (epoetin alfa)	Difference (95%CI, p value)
	Mean change in Hb (g/dL) dL (Mean (SD) (PPS analysis)	1.85 (1.08)	1.84 (0.97)	0.015 (-0.132 – 0.161)
	LDL-C change (Mean mmol/L (SD))	-0.35 (0.77)	0.05 (0.71)	-0.40 (-0.51 – -0.30)
	Time to IV iron use (mg) (event rate per 100 PYE)	9.9	20.6	0.46 (0.27 – 0.80) P=0.006
	SF-36 PF Mean change (SD)	0.91 (7.2)	2.06 (7.8)	-1.28 (-2.42 - -0.14)
	SF-36-VT Mean change (SD)	4.09 (8.7)	3.88 (8.8)	-0.42 (-1.6 – 0.78)
	Change in MAP (Mean (SD)) PPS	0.55 (8.6)	0.59 (8.8)	-0.36 (-1.58 – 0.85)
	Time to hypertension exarcerbation ((event rate per 100 PYE)	30.0	34.5	0.83 (0.56 – 1.22)

Dialysis studies (4 studies)

Table 36

Title: A phase 3 randomized, open-label active-controlled study to evaluate the efficacy and safety of roxadustat in the maintenance of anaemia in End Stage Renal Disease patients on stable dialysis	

Study identifier	1517-CL-0613		
Design	Open-Label, Randomised, Active-Controlled Study Global Multicentre study. Up to 150 centres were planned worldwide; mainly located in EU		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		52 weeks up to 42 days, maximum up to 104 weeks Patient was to be on ESA therapy ≥ 8 weeks prior to randomisation with stable weekly doses
Hypothesis	Non-inferiority		
Treatments groups	roxadustat		3 times weekly (TIW) orally in strengths in 20 mg, 50 mg, and 100 mg tablets, if requiring ultra-low levels then < TIW possible; Initial roxadustat dose was based on the conversion table and was determined by the patient's average weekly dose of epoetin or darbepoetin alfa within 4 weeks prior to randomisation. Patients were switched from epoetin or darbepoetin alfa treatment to roxadustat treatment.
	ESA (epoetin alfa, darpepoetin alfa)		Subjects randomised to the active control treatment arm were to continue epoetin alfa or darpepoetin alfa; IV TIW according to SmPC
Endpoints and definitions	Primary endpoint	Mean change in Hb	Change in Hb from baseline to the average Hb of Weeks 28 to 36, without having received rescue therapy within 6 weeks prior to and during this evaluation period.
	Secondary endpoint	Proportion with Hb in target range (Hb response)	Proportion of subjects with Hb response, defined as mean Hb during Weeks 28 to 36 within the target range of 10.0 to 12.0 g/dL without having received rescue therapy within 6 weeks prior to and during this 8-week evaluation period.
	Secondary	LDL-C change	Change from baseline in low density lipoprotein (LDL) cholesterol to the average LDL cholesterol of Weeks 12 to 28.
	Secondary	IV iron use	Average monthly IV iron use during day 1 to week 36 (monthly defined as a period of 4 weeks).
	Secondary	SF-36-PF	Change from baseline in Short Form-36 questionnaire (SF-36) physical functioning (PF) subscore to the average PF subscore of weeks 12 to 28.
	Secondary	SF-36-VT	Change from baseline in SF-36 Vitality (VT) subscore to the average VT subscore of weeks 12 to 28.
	Secondary	Change in MAP	Change from baseline in mean arterial pressure (MAP) to the MAP value averaged over Weeks 20 to 28 and time to increase in BP during week 1 to 36.
	Additional endpoints	Others	
Database lock	19 Sep 2018		
Results and Analysis			

Analysis description	Primary Analysis			
Analysis population and time point description	Per protocol (PPS), NI (non-inferiority), SUP (superiority for some endpoints), fixed sequence results PPS population 386 (93.0%) vs 397 (94.3%)			
Descriptive statistics and estimate variability	Treatment group	roxadustat	ESA (epoetin alfa)	Difference (95%CI, p value)
	Number of subject	414	420	
	Mean change in Hb (g/dL) dL (Mean (SD) (PPS analysis)	0.49	0.21	0.25 (0.14-0.35), P<0.001
Notes				
Analysis description	**Secondary analysis**			
Descriptive statistics and estimate variability	Treatment group	roxadustat	ESA (epoetin alfa)	Difference (95%CI, p value)
	Proportion with Hb in target range (%)	84.2	82.4	2.3 (-2.9 – 7.6) NI met
	LDL-C change (Mean mmol/L (SD))	-0.47 (0.67)	-0.07 (26.1)	-0.38 (-0.45 - -0.30, p<0.001) SUP met
	IV iron use (mg)	12.0 (47.6)	44.8 (88.6)	-31.9 (-41.4 – 22.4), P <0.001 SUP met
	SF-36-PF	41.7 (10.1)	41.7 (9.9)	0.21 (0.65 – 1.06) NI met
	SF-36-VT	0.96 (7.7)	0.15 (7.9)	0.86 (-0.12 – 1.8) NI met
	Change in MAP (Mean (SD)) PPS	-0.60 (9.5)	0.27 (8.79)	-0.85 (-2.0 - 0.27) NI met
	Time to increased BP ((event rate per 100 PYE)	32.8	37.2	0.92 (0.67 – 1.25) NI

Title: A Phase 3, Open-Label, Randomized, Active-Controlled Study of the Efficacy and Safety of Roxadustat (FG-4592) in the Maintenance Treatment of anaemia in Subjects with End Stage Renal Disease (ESRD) on Stable Dialysis			
Study identifier	FGCL-4592-064		
Design	Open-Label, Randomised, Active-Controlled Study Multicentre study conducted **in the U.S**. Up to 200 centres were planned worldwide; however, no ex-U.S. centres enrolled subjects in the study.		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	52 weeks up to 6 weeks, or 8 weeks for subjects who were taking maximum up to 3 years after the last subject was randomised Mircera®	
Hypothesis	Non-inferiority		

Treatments groups	roxadustat		Subjects randomised to roxadustat were to **discontinue prior ESA therapy and initiate roxadustat** therapy; 3 times weekly (TIW) orally in strengths in 20 mg, 50 mg, and 100 mg tablets, if requiring ultra-low levels then < TIW possible;
			initial dose of study treatment was based on the subject's average prescribed ESA dose in the 4 weeks prior to randomisation; Roxadustat dose adjustments were permitted from Week 4 onwards
			370; 334 were enrolled under the original protocol and 36 incident dialysis subjects were enrolled under Amendment 1and 2.
	ESA (epoetin alfa)		Subjects randomised to the active control treatment arm were to receive epoetin alfa irrespective of their prior ESA use 371 epoetin alfa; 337 in were enrolled under the original protocol and
			34 incident dialysis subjects were enrolled under Amendment 1 and 2.
Endpoints and definitions	Primary endpoint	Mean change in Hb	Change in Hb from baseline to the average Hb of Weeks 28 to 36, without having received rescue therapy (i.e., RBC transfusion or rescue ESA therapy) within 6 weeks prior to and 8-week evaluation period during this
	Secondary	Proportion with Hb in target range	Proportion of subjects with Hb response, defined as mean Hb during Weeks 28 to 36 within the target range of 10.0 to 12.0 g/dL without having received rescue therapy within 6 weeks prior to and during this 8-week evaluation period.
	Secondary	LDL-C change	Change from baseline in low density lipoprotein (LDL) cholesterol to the average LDL cholesterol of Weeks 12 to 28.
	Secondary	Mean Hb when hsCRP > ULN	Hb change from baseline to the average level during the Weeks 18 to 24 for subjects with baseline high-sensitivity C-reactive protein (hs-CRP) >ULN.
	Secondary	IV iron use	Average monthly IV iron use per subject during the Treatment Period during Weeks 28 to 52 (monthly defined as a period of 4 weeks).
	Secondary	Time to RBC transfusion	Time to first RBC transfusion during the treatment.
	Secondary	Change in MAP	Change from baseline in mean arterial pressure (MAP) to the MAP value averaged over Weeks 20 to 28.
	Secondary	Time to hypertension	Time to first exacerbation of hypertension: An increase from baseline of ≥20 mm systolic blood pressure (sBP) and sBP ≥170 mm Hg or an increase from baseline of ≥15 mm Hg diastolic blood pressure (dBP) and dBP ≥100 mm Hg during Weeks 28 to 52.
	Additional endpoints	Others	Hb maintenance, iron supplementation, hospitalisations, missed dialysis, rescue therapy use, changes in cholesterol levels, blood pressure effect, vascular access thrombosis, health-related quality of life, and hepcidin, iron indices, and haemoglobin A1c (HbA1c).
Database lock	10 Dec 2018		

Results and Analysis

Analysis description	**Primary Analysis**

Analysis population and time point description	Per protocol (PPS), NI (non-inferiority), SUP (superiority for some endpoints), fixed sequence results			
Descriptive statistics and estimate variability	Treatment group	roxadustat	ESA (epoetin alfa)	Difference (95%CI, p value)
	Number of subjects	370	371	
	Mean change in Hb (mg/dL) dL (LS mean (SEM) (PPS analysis)	0.63 (SEM 0.13)	0.09 (0.13)	0.55 (0.40 – 0.69, p <0.001) NI met
Notes				
Analysis description	**Secondary analysis**			
Descriptive statistics and estimate variability	Treatment group	roxadustat	ESA (epoetin alfa)	Difference (95%CI, p value)
	Proportion with Hb in target range (%)	64.1	60.8	2.7 (-4.3 – 9.7) NI met
	LDL-C change (LS mean mg/dL (SEM)	-12.2 (1.5)	2.4 (1.5)	-14.7 (-17.6 - -11.7, p<0.001) SUP met
	Mean change in Hb when hsCRP > ULN (mg/dL (LS mean (SEM)))	0.56 (0.11)	-0.15 (0.11)	0.71 (0.52 – 0.89, p<0.001), NI
	IV iron use (mg)	17.1 mg	37.0 mg	P = 0.0009
	Time to RBC transfusion (event rate per 100 PYE)	7.3	10.2	HR 0.66 (0.46 – 0.97, p = 0.031), NI
	Change in MAP (LS mean (SEM)) FAS population	0.10 (0.67)	-0.59 (0.65)	0.69 (-0.76 – 2.14, p=0.035), No superiority
	Time to hypertension	41.0	33.9	1.29 (0.99 – 1.68, p = 0.055) Not analysed

Title: A phase 3 multicenter, randomized, open-label active-controlled study of the efficacy and safety of FG4592 in the treatment of anaemia in <u>incident-dialysis patients (dialysis started > 2 weeks and < 4 months prior to randomisation)</u>	
Study identifier	FGCL-4592-063
Design	Open-Label, Randomised, Active-Controlled Study Global Multicentre study. Up to 200 centres were planned worldwide.

	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		52 weeks up to 6 weeks, maximum up to 4 years after the last subject was randomised ESA had to be ≤3 weeks within the preceding 12 weeks from the time informed consent was obtained
Hypothesis	Non-inferiority		
Treatments groups	roxadustat		3 times weekly (TIW) orally in strengths in 20 mg, 50 mg, and 100 mg tablets, if requiring ultra-low levels then < TIW possible; Initial dose of study treatment was based tiered, weightbased dosing scheme starting dose of 70 mg for subjects who weighed <70 kg or 100 mg for subjects who weighed ≥70 kg; Roxadustat dose adjustments were permitted from Week 4 onwards during the correction phase and maintenance phase (specific rules).
	ESA (epoetin alfa)		Subjects randomised to the active control treatment arm were to receive epoetin alfa; IV TIW according to SmPC
Endpoints and definitions	Primary endpoint	Proportion with Hb in target range	Proportion of subjects with Hb response at 2 consecutive visits at least 5 days apart during the first 24 weeks. HB response was defined as Hb within the target range of Hb ≥11.0 g/dL and Hb increase from baseline by ≥1.0 g/dL in subjects whose baseline Hb >8.0 g/dL OR an increase in Hb ≥2.0 g/dL in subjects whose baseline Hb was ≤8.0 g/dL.
	Key secondary endpoint	Mean change in Hb	Change in Hb from baseline to the average Hb of Weeks 28 to 52, without having received rescue therapy within 6 weeks prior to and during this evaluation period.
	Secondary	LDL-C change	Change from baseline in low density lipoprotein (LDL) cholesterol to the average LDL cholesterol of Weeks 12 to 24.
	Secondary	Mean Hb when hsCRP > ULN	Hb change from baseline to the average level during the Weeks 18 to 24 for subjects with baseline high-sensitivity C-reactive protein (hs-CRP) >ULN.
	Secondary	IV iron use	Average monthly IV iron use per subject during the Treatment Period during Weeks 28 to 52 (monthly defined as a period of 4 weeks).
	Secondary	Time to RBC transfusion	Time to first RBC transfusion during the treatment.
	Secondary	Change in MAP	Change from baseline in mean arterial pressure (MAP) to the MAP value averaged over Weeks 8 to 12.
	Secondary	Time to hypertension	Time to first exacerbation of hypertension: An increase from baseline of ≥20 mm systolic blood pressure (sBP) and sBP ≥170 mm Hg or an increase from baseline of ≥15 mm Hg diastolic blood pressure (dBP) and dBP ≥110 mm Hg during Weeks 28 to 52.
	Additional endpoints	Others	Hb correction and maintenance, hospitalisations, missed dialysis sessions, rescue therapy use, changes in cholesterol levels, blood pressure effect, health-related quality of life (HRQoL) and European Quality of Life Questionnaire in 5 Dimensions, 5 Levels (EQ-5D-5L) benefits of anaemia therapy; and hepcidin, iron indices, and haemoglobin A1c (HbA1c).
Database lock	10 Dec 2018		

Results and Analysis

Analysis description	Primary Analysis			
Analysis population and time point description	Per protocol (PPS), NI (non-inferiority), SUP (superiority for some endpoints), fixed sequence results PPS population 490 (93.9%) vs 468 (89.8%)			
Descriptive statistics and estimate variability	Treatment group	roxadustat	ESA (epoetin alfa)	Difference (95%CI, p value)
	Number of subject	522	521	
	Proportion with Hb in target range (%)	88.2	84.4	3.5 (-0.7 – 7.7) NI met
Notes				
Analysis description	**Secondary analysis**			
Descriptive statistics and estimate variability	Treatment group	roxadustat	ESA (epoetin alfa)	Difference (95%CI, p value)
	Mean change in Hb (g/dL) dL (Mean (SD) (PPS analysis)	2.62 (1.3)	2.44 (1.2)	0.16 (0.03 – 0.30, P=0.00148) NI met
	LDL-C change (Mean mg/dL (SD))	-23.8 (30.0)	-5.39 (26.1)	-18.3 (-21.4 - -15.2, p<0.001) SUP met
	Mean change in Hb when hsCRP > ULN (mg/dL (Mean (SD)))	2.36	2.54	0.0 (-0.19 – 0.020, p<0.976), NI
	IV iron use (mg)	59.1 mg	64.0 mg	P = 0.00028
	Time to RBC transfusion (event rate per 100 PYE)	4.3	3.5	HR 1.26 (0.79 – 2.02, p = 0.328), NI not met
	Change in MAP (Mean (SD)) FAS population	-0.12 (8.0)	1.15 (8.7)	-1.15 (-20.1 - -0.20,) Not assessed
	Time to hypertension exarcerbation ((event rate per 100 PYE)	16.9	17.9	0.93 (0.68 – 1.28) Not analysed

Title: A phase 3 multicenter randomized, open-label active-controlled study of the safety and efficacy of roxadustat in the treatment of anaemia in dialysis patients	
Study identifier	D5740C00002
Design	Open-Label, Randomised, Active-Controlled Study Global Multicentre study. Up to 250 centres were planned worldwide
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	52 weeks up to 6 weeks, maximum up to 4 years No specific requirement with regard to ESA therapy
Hypothesis	Non-inferiority

Treatments groups	roxadustat		3 times weekly (TIW) orally in strengths in 20 mg, 50 mg, and 100 mg tablets, if requiring ultra-low levels then < TIW possible. Initial roxadustat dose was based on a tiered, weight-based dosing scheme for patients not treated with an ESA. For patients on ESA, conversion was based on ESA dose.
	ESA (epoetin alfa)		Subjects randomised to the active control treatment arm were to continue epoetin alfa; IV TIW according to SmPC. For patients not on ESA dose, initial dose was 50 IU/kg TIW
Endpoints and definitions	Primary endpoint	Mean change in Hb	Change in Hb from baseline to the average Hb of Weeks 28 to 36, without having received rescue therapy within 6 weeks prior to and during this evaluation period.
	Secondary endpoint	Proportion of time with Hb in target range	Proportion of total time of Hb response within the target range of 10 to 12 g/dL from Week 28 to 52.
	Secondary	LDL-C change	Change from baseline in low density lipoprotein (LDL) cholesterol from baseline to Weeks 24.
	Secondary	Mean change in Hb when hsCRP > ULN	Mean change in Hb from baseline to the subjects' mean level between Week 28 to Week 52 in subjects with baseline hsCRP greater than the ULN.
	Secondary	IV iron use	Mean monthly IV iron use
	Secondary	Time to RBC rescue	Time-to-first administration of (and proportion of subjects who received) RBC transfusion as rescue therapy.
	Additional endpoints		
Database lock	08 Dec 2018		

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	Per protocol (PPS), NI (non-inferiority), SUP (superiority for some endpoints), fixed sequence results PPS population 842 vs 869			
Descriptive statistics and estimate variability	Treatment group	roxadustat	ESA (epoetin alfa)	Difference (95%CI, p value)
	Number of subject	1051	1055	
	Mean change in Hb (g/dL) dL (Mean (PPS analysis))	0.88	0.74	0.14 (0.03-0.25), P<0.001 NI met
Notes				
Analysis description	**Secondary analysis**			
Descriptive statistics and estimate variability	Treatment group	roxadustat	ESA (epoetin alfa)	Difference (95%CI, p value)
	Time Hb in target range	0.65	0.63	0.02 (-0.01 – 0.05) P<0.001 NI met
	LDL-C change (Mean mmol/L (SE))	-0.38 (0.03)	-0.05 (0.03)	-0.33 (-0.39 - -0.27, p<0.001) SUP met

Mean change in Hb when hsCRP > ULN (g/dL)	0.80	0.59	0.20 (0.04 – 0.36) P=0.012 NI met
IV iron use (mg)	58.7	91.3	P <0.001
Time to RBC rescue	41.7 (10.1)	41.7 (9.9)	HR 0.83 (0.64 – 1.07) P=0.151 NI met

Analysis performed across trials (pooled analyses and meta-analysis)

See efficacy section.

Clinical studies in special populations

See for efficacy according to age, ancillary subgroup analyses above (*Ancillary analyses*).

Table 37: Number of patients above 65 participated in controlled and non-controlled trials

	Age 65-74 (Older subjects number /total number)	Age 75-84 (Older subjects number /total number)	Age 85+ (Older subjects number /total number)
Controlled Trials	1388/6124	667/6124	101/6124
Non Controlled Trials	222/1114	107/1114	10/1114

Supportive study(ies)

Several phase 2 and 3 studies have been performed in the US, Japan, and China, some as part of the registration of the product for China and Japan. Studies were generally smaller and with shorter follow-up than the main studies for this EU application. Two US phase 2 studies in NDD patients showed a dose-dependent Hb effect versus placebo and one phase 2 study showed conversion of ESA to roxadustat with maintaining of Hb effect. Further, one phase 2 and two phase 3 studies in NDD patients in Japan showed a dose-dependent effect on Hb versus placebo and/or possible conversion from ESA therapy. One phase 2 and four phase 3 studies in dialysis Japanese patients showed possible correction, maintenance and/or comparable Hb effect compared to ESA with different doses or dose regimens of roxadustat. One phase 2 study with different dose cohorts and one phase 3 study showed correction of Hb versus placebo in a study in Chinese NDD patients. One phase 2 and one phase 3 study showed a comparable or improved Hb effect versus ESA therapy in Chinese dialysis patients. Further, one phase 2 Hb correction study in starting dialysis patients and one very small long-term study in dialysis and non-dialysis patients showed correction of Hb and maintenance of Hb conducted in US/Hong Kong/Russia.

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The overall design was considered acceptable. The selection of an open label design for the comparator studies although not optimal was attributed to challenges due to different administration route (would need multiple additional injections or infusions), and potentially identifiable difference in iron supplementation requirements which was acceptable.

The primary endpoint for the main NDD phase 3 studies defined as the proportion of patients who achieved a Hb response at 2 consecutive visits during the first 24 weeks of treatment without rescue therapy is considered appropriate to evaluate the correction of Hb during a sufficient period of time. Response defined as Hb ≥ 11.0 g/dL and a Hb increase from baseline by ≥ 1.0 g/dL, or increase from baseline by ≥ 2.0 g/dL in any patient with baseline Hb ≤ 8.0 g/dL, is considered of clinical relevance. Although this endpoint should also be interpreted in conjunction with the endpoint of mean change in Hb during the study in week 28 to 36 (without rescue medication), used as secondary endpoints in these studies. Moreover, the other Hb related endpoints, including percentage of time within a certain Hb level range are of support as well to sufficiently understand the full Hb treatment effect. Further, the proportion of patients above a certain threshold Hb level is of interest for the risk of overshooting and in potentially in relation to safety aspects.

For study FGCL-4592-063, a Hb correction study, a similar endpoint of proportion of patients who achieved a Hb response was used as for the NDD studies (all correction studies), which is acceptable. For 3 out of 4 DD studies, where DD patients were already on ESA therapy at thus more at or close(r) to appropriate Hb levels, the use of mean change in Hb during the study in week 28 to 36 as primary endpoint provides the most efficient use of the Hb data for evaluation, which is considered appropriate. Hb response as a key secondary endpoint in these studies is acceptable. These endpoints should be evaluated in conjunction with the other secondary Hb control endpoints to sufficiently understand the entire Hb treatment effect.

All studies included secondary objectives which were analysed in sequential order. These included safety evaluation, the effect on LDL-cholesterol, Hb response, need for iv iron and need for RBC transfusion which are particularly useful in comparison to existing ESA therapy to provide further insight and nuance to potential advantages of roxadustat versus ESA.

Hb response in the setting of increased CRP (hsCRP > ULN) as a secondary endpoint was defined in 2 NDD studies (FGCL-4592-060, D5740C00001) and 3 of the DD studies (FGCL-4592-064, FGCL-4592-06, D5740C00002), as Hb response may be less in the setting of inflammation, and thus could likely demonstrate that the effect of roxadustat would also be present in the setting of inflammation. In this context, though, inflammation defined by > ULN in hsCRP may be somewhat imprecise due to the lack in specificity of this marker.

The relevance of evaluation of LDL-C cholesterol change in the context of treatment of anaemia was also discussed. In the literature, it has been described that this appears to be a drug class effect, as HIF activation increases lipoprotein uptake and has been shown to promote the degradation of HMG-CoA reductase reducing cholesterol synthesis (Sanghani 2019).

The definitions of the analysis sets are acceptable. Of note, for non-inferiority comparisons, both the per-protocol and the full analysis set are considered of importance and should lead to similar conclusions. These were provided as sensitivity analyses. Missing data after discontinuations is discussed below

Efficacy data and additional analyses

Non-dialysis pool (NDD pool)

Placebo-controlled NDD studies

During the placebo-controlled studies in the NDD pool, a large proportion of patients discontinued treatment. This was lower in the roxadustat group (901 [37.8%]) than in the placebo group (1115 [59.2%]). Reasons for discontinuation are not well understood as a large proportion of patients discontinued due to patient decision (10.5% vs 20.7%), development of study-specific discontinuation

criteria (3.2% vs 13.4%), and withdrawal by patient (6.0% vs 7.6%) without further clear details on these categories. A clear understanding of these factors is important as such high proportion and difference in discontinuation may likely impact efficacy evaluation likely in the advantage of roxadustat. Discontinuations due to adverse events were higher for roxadustat than for placebo (6.3% vs 4.4%), but apparently not a major contributor to patients discontinuing therapy. A lower eGFR as one reason of earlier discontinuation has been presented.

In the NDD pool, patients were generally representative of a CKD population not on dialysis with anaemia. Most patients had CKD stage 4 and 5 (38%, 43%), with a mean eGFR of 20 mL/min/1.73 m^2 and a mean Hb level of 9.1 g/dL. A representative number of patients > 65 years of age was included (47%) and sufficient patients from Europe were included (25%). Approximately 40% had iron depletion (according to criteria of ferritin < 100 ng/ml and or TSAT <20%). Most pronounced reasons for CKD were diabetic or hypertensive nephropathy.

For the 3 placebo-controlled studies in the NDD pool, the primary endpoint of patients who achieved Hb response during the first 24 weeks without rescue medication was higher for roxadustat (80.2%) than for placebo (8.7%)(OR 40.5% (95%CI 33 -50, p< 0.0001), and was consistent across the different studies. The difference in the correction of Hb between was maintained over time during 104 weeks of treatment. Mean weekly dose of roxadustat was relatively stable over time (approximately 3.2 mg/kg) during this period. Other Hb endpoints were consistent with the primary Hb endpoint. However, the proportion of patients with levels > 12 g/dL and > 13 g/dL was higher for roxadustat than placebo (in study 1517-CL-0608; 23.4% vs 3.65%, and 5.6% vs 0.5%, respectively). The need for dose adjustments was in line with these observations (12.8% vs 0.8% on dose hold due to Hb > 13 mg/dL). Despite improvement in Hb, the effect of roxadustat on the improvement of patient-reported outcome measures at week 12 has not been clearly demonstrated, especially since superiority for the SF-36 PF (physical function) component (in contrast to the VT component) could not be met in study 001 (HR 0.44 (-0.11, 0.99), while not formally tested in the other studies.

Based on the difference in Hb effect, a lower proportion of patients required rescue therapy (difference in incidence rate per 100 patient-years at risk 0.19; 95% CI: 0.16, 0.23; P < 0.0001). Although the the time to RBC transfusion was only formally tested and showed a significantly lower risk (HR 0.37 (0.30, 0.44)), with no formal testing for ESA use and i.v. iron use. In line with the mechanism of action initial decline (to week 8) with subsequent reversibility to baseline (week 20) was observed in iron need, expect for transferrin saturation where no difference was observed (0.05 [14.23]% vs 0.30 [12.70]%). A decrease of hepcidin was also seen up to week 24 (LS mean difference: -25.86 µg/L; 95% CI: -33.09, -18.63; P < 0.0001), although the exact clinical meaning in terms of iron responsiveness is not clear (Batchelor, JASN, 2020).

A significant larger reduction in LDL-C cholesterol was found with treatment of roxadustat (-17.35 vs 2.1%; difference LS mean: -19.83; 95% CI: -22.16, -17.51; P < 0.0001) during week 12-28 (week 24 in study D5740C00001) from a baseline level of 2.56 mmol/L. However, a counteracting effect on HDL-C was observed, with a difference of -4.1 mg/dL (0.11 mmol/L) (-5.0 - -3.3), p <0.0001 for roxadustat vs placebo from a mean baseline of 47 mg/dL (1.22 mmol/L). Therefore, the clinical implications of this finding in the context of treatment for anaemia and in relation to the observed increased CV risk are unclear.

There was no clinically relevant difference in an increase in blood pressure as evaluated by mean arterial pressure (MAP) and time to blood pressure increase in studies 608 (0.66 vs -0.08 mmHg; 13.4 vs 12.1 event rate per 100 PY, respectively), and 060 (0.02 vs -0.12 mmHg; 12.3 vs 12.7 event rate per 100 PY, respectively).

The renal function (eGFR) appears to remain stable during the first 12 weeks of treatment with roxadustat and appears to decline in a similar rate for both groups afterwards (not formally tested),

with some difference between studies ((0.59, -0.65 and -0.51 ml/min/1.73m^2 for the 3 placebo-controlled studies).

For the NDD placebo-controlled studies some differences in effect across subgroups appear, although no p for interaction has been provided. Especially the lower response for lower ferritin/TSAT status and baseline, CRP > ULN, and higher body weight, are of interest due to claims being made, and dosing according to weight as proposed. Although, the effect according to hsCRP level <> ULN was part of the sequential testing in study 060, where the effect according to this subgroup appeared comparable to the overall effect.

Subgroup data according to age have been presented for age groups of <65, 65 to 75, 75 to 85 and >85 years in the ancillary subgroup analyses (see ancillary analysis) and do not suggest any difference in effect.

Any effect on HbA1c has not been observed.

ESA controlled open label NDD study

For the ESA controlled open-label study (0610), study discontinuation is comparable (15.5% roxadustat, 14.0% DA). Also, for this study, patients were generally representative of a CKD population not on dialysis with anaemia. The main difference is that fewer patients than in the placebo-controlled studies had iron depletion (15.8% vs 21.8%, according to criteria of ferritin < 100 ng/ml and or TSAT <20%), likely due to the different inclusion requirement. Patients characteristics were fairly similar between both treatment groups.

The proportion of patients who achieved Hb response in the first 24 weeks was similar between the roxadustat (89.5%), and DA (78.0%) groups and non-inferiority was achieved (difference 11.5% (95%CI 5.7 – 17.4)) with a NI margin of -15%. Other Hb endpoints were consistent with these findings with maintenance of effect. However, the time percentage of time with haemoglobin values > 12 g/dL was higher with roxadustat than with darbepoetin ESA (23.9% vs 20.3%) and for > 13 g/dL (3.7% vs 2.7%) during the efficacy period. It is not clear whether this may be associated with potentially less accurate oral dosing steps of roxadustat versus sc or iv dosing with ESA. In line with the Hb effect, the need for rescue therapy (exploratory) showed to be comparable between treatment arms (RBC transfusions (6.2% vs 6.6%) and only 2.2% in the roxadustat needed ESA), and comparable improvements in SF-36-PF (difference in mean change -1.28 (-2.4 - -0.1) and SF-36-VT (-0.42 (-1.6 - -0.8) were observed.

Time to iv iron use was significantly improved for roxadustat versus ESA (HR 0.46 (0.27, 0.80)) and iron was less used for roxadustat (6.2%) than for darbepoetin ESA (12.3%) (not rescue therapy), while iron parameters (ferritin, TSAT and serum iron) were comparable between treatment groups. As with the placebo-controlled studies, a significantly larger reduction in LDL-C cholesterol was found with treatment of roxadustat difference. No difference in blood pressure or time to blood pressure increase versus ESA was observed (MAP difference from baseline 0.55 vs 0.59 mmHg; 30.0 vs 34.5 events rate per 100 PY). No substantial differences were observed for subgroup analyses of the primary endpoint of responders and the key secondary endpoint of mean Hb change between roxadustat and ESA therapy.

ESA controlled DD studies

For the DD pool, more patients discontinued the study and treatment for roxadustat than ESA treatment (28.3% vs 21.7%; 41.2% vs 32.4%, respectively), which could be of concern. This was consistent across the studies, except for the Hb correction study 063 (41.2 vs 40.7% treatment discontinuation). Main reasons for treatment discontinuation were death (8.6% vs 7.5%), discontinuation due to AEs (6.3% vs 3.6%), patient decision (5.7% vs 3.7%), and withdrawal by

patient (5.4% vs 4.4%). Except for AEs, these categories could not be clearly further specified. Comparison for the ID (incident dialysis) DD population versus the stable DD population has also been provided. The ID DD population consists of all patients from study FGCL-4592-063 (n= 1042), 36 patients from study FGCL-4592-064 and 411 patients from study D5740C00002.

For the DD pool, the per-protocol set (PPS) is important for the assessment of the non-inferiority for the primary endpoint and several of the secondary endpoints. The PPS population was 80 to 95% of the intention to treat the population with some slight differences between treatment groups for each study, although acceptable.

In all 4 DD studies, non-inferiority for roxadustat in comparison to ESA therapy on the primary endpoint of change from baseline in Hb without the use of rescue therapy up to weeks 28 to 36 was demonstrated with a Hb difference of approximately 0.30 g/dL. For the Hb correction study FGCL-4592-063, non-inferiority was evaluated based on the endpoint of patients who achieved haemoglobin response during the first 24 weeks, which showed NI was confirmed (difference of proportion 3.5 (95%CI -0.7 – 7.7), which is well within the lower bound of the 2-sided 95% CI of > -15%). For the ESA conversion studies, comparable results were obtained. The effect on Hb could be maintained during long term follow-up. Mean dose level remained relatively stable between 3.2 and 4.0 mg/kg during this period. Also for the ESA group, Hb was maintained and mean dose level remained relatively stable between 136.7 and 11.3 IU/kg (ID DD subpool) and 118 to 175 IU/kg (stable DD subpool). However, the proportion out of Hb range was higher with roxadustat (percentage of time > 12 g/dL was 17.1 (16.5) vs 10.0 (13.4)) and > 13 g/dL was 1.9 (4.1) vs 0.78 (2.6)). In line with these observations, more patients needed a dose withheld due to Hb >13 mg/dL (23.8% vs 12.8% ID DD and 11.7% vs 3.4% in DD DD pool). In line with comparable Hb effect, rescue therapy in terms of the incidence rate of RBC transfusions or ESA therapy was comparable between roxadustat and ESA therapy (HR 0.98 (0.66-1.46); 0.89 (0.63 – 1.25) and 1.07 (0.84 – 1.36) for studies 0613, 0645 and 002, respectively), and quality of life indicators (SF-36-PF (physical function) 41.7 (10.1) vs 41.7 (9.9) and SF-36-VT (vitality) 41.7 (10.1) vs 41.7 (9.9), as only formally tested in study 0613.

The mean IV iron use was lower in all studies (12-59 mg vs 37-88 mg based on different evaluation periods), with some more decrease in mean ferritin levels and stable transferrin saturation. A decrease of hepcidin was also seen up to week 24, which would comply with the proposed mechanism of action, although the exact clinical meaning is not clear.

A change of -0.37 to -0.47 mmol/L was observed in LDL-C to week 12-28, 12-24 or to 24 weeks for roxadustat versus ESA which was significant in all 4 individual studies (from a baseline level of 2.28 to 2.92 mmol/L. HDL-C was changed over week 12 to 28 with a difference of -0.10 mmol/L.

There was no clinical relevant difference in any increase in blood pressure as evaluated by mean arterial pressure (MAP) and time to blood pressure increase in studies 0613 (-0.60 vs 0.27 mmHg; 32.8 vs 37.2 event rate per 100 PY), 064 (0.10 vs -0.59; 41.0 vs 33.9 event rate per 100 PY), and 063 (-0.12 vs 1.15; 16.9 vs 17.9 event rate per 100 PY).

Subgroup analyses for the DD pool were presented according to the ID (incident dialysis) DD subpool and the stable dialysis DD subpool. In the IDD subpool, no substantial differences appear across subgroups for the mean change in Hb from week 28 to 52. For the stable DD subpool, roxadustat appears to do slightly better for US vs Europe and others. Further, a lower ferritin/TSAT status showed a lower effect for roxadustat vs ESA for mean Hb levels, which may not be expected if roxadustat would improve iron availability, however no p for interaction has been provided. For the endpoint of proportion of responders no differences appear in de DD pool, although confidence intervals were wide.

2.5.4. Conclusions on the clinical efficacy

Non-dialysis pool

Treatment with roxadustat shows a clear improvement in efficacy for correction and maintaining Hb levels versus placebo; however this was not clearly associated with a significant improvement in patient-reported outcomes of SF-36 VT and PF. A clear lower need for rescue therapy (RBC transfusion, iv iron use, ESA therapy) was observed for roxadustat vs placebo. The proportion of overshooting (> 12 and >13 g/dL) was higher with roxadustat. Any effect on a delay of renal function decline could not be shown. In comparison to ESA, comparable efficacy for correction and maintaining Hb levels was observed with comparable improvement in QoL and a lower need for iv iron use.

Roxadustat treatment is associated with a slight lowering of LDL-C; however, in relation to the increased CV risk (see safety), the clinical meaning is unclear.

Dialysis pool

Treatment with roxadustat shows comparable efficacy for correcting and maintaining Hb levels versus ESA therapy and was maintained over time in both groups. The proportion of overshooting (> 12 and >13 g/dL) was higher with roxadustat. Roxadustat treatment is associated with a slight lowering of LDL-C, however, in relation to the increased CV risk (see safety), the clinical meaning is unclear. Monthly iv iron use was lower with roxadustat than with ESA in 3 of the 4 studies. Time to rescue therapy (in particular RBC transfusions) was comparable to ESA therapy. Patient-reported outcomes have only been formally tested in one study and showed to be comparable to ESA therapy. Effects on blood pressure/hypertension appear to be comparable between roxadustat and ESA therapy.

2.6. Clinical safety

Patient exposure

Overall

A total of 12,048 patients were treated in phase 2 and phase 3 studies of the clinical development programme, 5985 of whom were NDD patients, and 6063 of whom were DD patients. A total of 3542 NDD patients were treated with roxadustat, 2020 patients with placebo, and 423 patients with darbepoetin alfa (DA). A total of 3353 DD patients were treated with roxadustat, 4 patients with placebo, and 2706 patients with erythropoiesis-stimulating agent (ESA).

NDD pool

Placebo controlled studies

The median duration of treatment was substantially longer for the roxadustat groups than placebo groups for the NDD pool (87.1 vs 57.1 weeks), with a less pronounced difference in the NDD NDD (patients censored for dialysis) pool (62.0 vs 51.3 weeks). This was due to fewer patients discontinuing treatment in the roxadustat groups than placebo.

For the NDD pool, greater percentages of patients in the roxadustat than placebo groups were on study drug for > 52 to 104 weeks (37.0% vs 32.3%), > 104 to 156 weeks (26.8% vs 18.9%), and > 156 weeks (7.2% vs 2.2%). The same trend was observed for the NDD NDD pool.

Active comparator study

In Study 1517-CL-0610, the median durations of treatment were similar for the roxadustat group

(50.3 weeks) and DA group (48.1 weeks).

The mean and median doses of roxadustat decreased in the period following start of treatment, with subsequent stabilisation.

DD pool

The DD pool consisted of 4715 patients and was further examined in 2 further subpools of ID DD and stable DD. The safety analysis set for the ID DD subpool consisted of 1526 patients, including 1039 from Study FGCL-4592-063, 71 from Study FGCL-4592-064, and 416 from Study D5740C00002; 760 patients were in the roxadustat group, and 766 patients were in the ESA group. The safety analysis set for the stable DD subpool consisted of 3188 patients, including 834 from Study 1517-CL-0613, 669 from Study FGCL-4592-064, and 1685 from Study D5740C00002; 1594 patients each were in the roxadustat and ESA groups.

The median duration of treatment was slightly longer for the ESA group than the roxadustat group for the DD pool (103.1 vs 94.1 weeks) and for the ID DD subpool (59.9 vs 54.6 weeks). For the stable DD subpool, the median duration of exposure was similar for roxadustat (103.7 weeks) and ESA (103.9 weeks). In the DD pool, duration of exposure of > 104 to 156 weeks was 550 (23.4%) vs 636 (26.9%) and > 156 weeks was 302 (12.8%) vs 385 (16.3%).

In conversion Studies 1517-CL-0613 and FGCL-4592-064, the mean and median doses of roxadustat decreased in the period following start of treatment with subsequent stabilisation, but the mean and median doses of ESA increased during the course of treatment. In Hb correction Study FGCL-4592-063, the mean and median doses of roxadustat and ESA remained stable over the course of treatment following a small decline after the start of treatment.

Adverse events

An overview of observed adverse events, commonly observed adverse events, special pre-defined adverse events of special interest, and post-hoc analysis of adverse events of special interest, in the non-dialysis and dialysis pool is provided below.

Adverse events overview

Table 38 Incidence of treatment-emergent adverse events; main phase 3 studies (SAF)

Category	NDD Pool				DD Pool	
	NDD Pool		1517-CL-0610			
	R n = 2386	PB n = 1884	R n = 323	DA n = 293	R n = 2354	ESA n = 2360
All TEAEs						
n (%) IR	301 (12.6) 8.3	153 (8.1) 6.6	70 (21.7)	58 (19.8)	2039 (86.6) 51.6	2030 (86.0) 45.5
Drug-related TEAEs						
n (%) IR	301 (12.6) 8.3	153 (8.1) 6.6	70 (21.7)	58 (19.8)	289 (12.3) 7.3	143 (6.1) 3.2
Serious TEAEs						
n (%) IR	1308 (54.8) 45.9	845 (44.9) 43.9	171 (52.9)	140 (47.8)	1288 (54.7) 32.6	1260 (53.4) 28.2
Drug-related Serious TEAEs						
n (%) IR	55 (2.3) 1.9	18 (1.0) 0.9	17 (5.3)	6 (2.0)	70 (3.0) 1.8	38 (1.6) 0.9
TEAEs Leading to Discontinuation of Study Drug or Study†						
n (%) IR	157 (6.6) 3.9	92 (4.9) 3.8	17 (5.3)	9 (3.1)	253 (10.7) 6.4	175 (7.4) 3.9
Drug-related TEAEs Leading to Discontinuation of Study Drug or Study†						
n (%) IR	34 (1.4) 0.8	13 (0.7) 0.5	4 (1.2)	0	46 (2.0) 1.2	9 (0.4) 0.2

Percentages were calculated based on the total number of patients in the treatment group. The IR is patients/100 patient years.

Common observed adverse events

Table 39: Incidence of common treatment-emergent adverse events (≥ 5% of patients in either treatment group of the main phase 3 NDD and DD studies (SAF)

Category	NDD Pool				DD Pool	
	NDD Pool		1517-CL-0610			
	R n = 2386	PB n = 1884	R n = 323	DA n = 293	R n = 2354	ESA n = 2360
Overall						
n (%) IR	2132 (89.4) 222.6	1608 (85.4) 211.5	277 (85.8)	248 (84.6)	2039 (86.6%) 51.6	2030 (86.0%) 45.5
Cardiac Disorders						
n (%) IR	-	-	-	-	567 (24.1) 14.3	567 (24.1) 14.3

Category	NDD Pool				DD Pool	
	NDD Pool		1517-CL-0610			
	R n = 2386	PB n = 1884	R n = 323	DA n = 293	R n = 2354	ESA n = 2360
Atrial fibrillation						
n (%) IR	-	-	-	-	79 (3.4) 2.0	79 (3.4) 2.0
Blood and Lymphatic System Disorders						
n (%) IR	123 (5.2) 3.1	141 (7.5) 6.0	16 (5.0)	15 (5.1)	-	-
Anaemia						
n (%) IR	51 (2.1) 1.3	101 (5.4) 4.2	7 (2.2)	7 (2.4)	-	-
Gastrointestinal Disorders						
n (%) IR	974 (40.8) 34.9	582 (30.9) 30.3	105 (32.5)	90 (30.7)	914 (38.8) 23.1	848 (35.9) 19.0
Constipation						
n (%) IR	209 (8.8) 5.5	102 (5.4) 4.3	19 (5.9)	11 (3.8)	127 (5.4) 3.2	114 (4.8) 2.6
Diarrhoea						
n (%) IR	248 (10.4) 6.6	129 (6.8) 5.5	24 (7.4)	25 (8.5)	278 (11.8) 7.0	250 (10.6) 5.6
Nausea						
n (%) IR	243 (10.2) 6.5	119 (6.3) 5.1	26 (8.0)	17 (5.8)	198 (8.4) 5.0	163 (6.9) 3.7
Vomiting						
n (%) IR	148 (6.2) 3.8	76 (4.0) 3.2	18 (5.6)	14 (4.8)	169 (7.2) 4.3	139 (5.9) 3.1
General Disorders and Administration Site Conditions						
n (%) IR	725 (30.4) 22.6	472 (25.1) 22.9	82 (25.4)	71 (24.2)	614 (26.1) 15.5	563 (23.9) 12.6
Pyrexia						
n (%) IR	-	-	-	-	118 (5.0) 3.0	118 (5.0) 3.0
Oedema peripheral						
n (%) IR	279 (11.7) 7.6	143 (7.6) 6.1	36 (11.1)	31 (10.6)	-	-
Infections and Infestations						
n (%) IR	1255 (52.6) 51.3	798 (42.4) 47.4	124 (38.4)	121 (41.3)	1157 (49.2) 29.3	1166 (49.4) 26.1
Pneumonia						
n (%) IR	212 (8.9) 5.5	118 (6.3) 4.9	19 (5.9)	15 (5.1)	-	-
Urinary tract infection						
n (%) IR	248 (10.4) 6.6	120 (6.4) 5.1	14 (4.3)	19 (6.5)	112 (4.8) 2.8	118 (5.0) 2.6
Upper respiratory tract infection						
n (%) IR	187 (7.8) 5.0	110 (5.8) 4.7	9 (2.8)	6 (2.0)	150 (6.4) 3.8	136 (5.8) 3.0

Category	NDD Pool				DD Pool	
	NDD Pool		**1517-CL-0610**			
	R **n = 2386**	**PB** **n = 1884**	**R** **n = 323**	**DA** **n = 293**	**R** **n = 2354**	**ESA** **n = 2360**
Viral upper respiratory tract infection						
n (%) IR	228 (9.6) 6.2	137 (7.3) 6.0	22 (6.8)	21 (7.2)	122 (5.2) 3.1	138 (5.8) 3.1
Injury, Poisoning and Procedural Complications						
n (%) IR	-	-	-	-	883 (37.5) 22.3	866 (36.7) 19.4
Arteriovenous fistula site complication						
n (%) IR	-	-	-	-	169 (7.2) 4.3	173 (7.3) 3.9
Arteriovenous fistula thrombosis						
n (%) IR	-	-	-	-	224 (9.5) 5.7	176 (7.5) 3.9
Metabolism and Nutrition Disorders						
n (%) IR	869 (36.4) 29.2	536 (28.5) 27.0	113 (35.0)	103 (35.2)	607 (25.8) 15.4	632 (26.8) 14.2
Fluid overload						
n (%) IR	-	-	-	-	126 (5.4) 3.2	136 (5.8) 3.0
Hyperkalaemia						
n (%) IR	261 (10.9) 7.0	133 (7.1) 5.7	33 (10.2)	29 (9.9)	153 (6.5) 3.9	152 (6.4) 3.4
Musculoskeletal and Connective Tissue Disorders						
n (%) IR	590 (24.7) 18.3	360 (19.1) 17.3	75 (23.2)	56 (19.1)	557 (23.7) 14.1	607 (25.7) 13.6
Nervous System Disorders						
n (%) IR	585 (24.5) 17.7	369 (19.6) 17.3	66 (20.4)	56 (19.1)	673 (28.6) 17.0	590 (25.0) 13.2
Headache						
n (%) IR	178 (7.5) 4.7	103 (5.5) 4.4	18 (5.6)	10 (3.4)	217 (9.2) 5.5	170 (7.2) 3.8
Psychiatric Disorders						
n (%) IR	227 (9.5) 6.0	91 (4.8) 3.8	23 (7.1)	23 (7.8)	-	-
Renal and Urinary Disorders						
n (%) IR	817 (34.2) 25.0	498 (26.4) 22.9	102 (31.6)	95 (32.4)	-	-
End stage renal disease						
n (%) IR	473 (19.8) 13.0	282 (15.0) 12.1	88 (27.2)	77 (26.3)	-	-
Acute kidney injury						
n (%) IR	121 (5.1) 3.1	53 (2.8) 2.2	6 (1.9)	6 (2.0)	-	-
Respiratory, Thoracic and Mediastinal Disorders						
n (%) IR	573 (24.0) 16.9	393 (20.9) 18.4	49 (15.2)	46 (15.7)	595 (25.3) 15.1	625 (26.5) 14.0

Category	NDD Pool				DD Pool	
	NDD Pool		1517-CL-0610			
	R n = 2386	PB n = 1884	R n = 323	DA n = 293	R n = 2354	ESA n = 2360
Cough						
n (%) IR	170 (7.1) 4.5	90 (4.8) 3.8	9 (2.8)	11 (3.8)	153 (6.5) 3.9	169 (7.2) 3.8
Dyspnoea						
n (%) IR	124 (5.2) 3.2	90 (4.8) 3.8	17 (5.3)	7 (2.4)	138 (5.9) 3.5	153 (6.5) 3.4
Skin and Subcutaneous Tissue Disorders						
n (%) IR	433 (18.1) 12.3	239 (12.7) 10.7	60 (18.6)	39 (13.3)	-	-
Pruritus						
n (%) IR	138 (5.8) 3.6	86 (4.6) 3.6	16 (5.0)	11 (3.8)	-	-
Vascular Disorders						
n (%) IR	581 (24.4) 17.1	333 (17.7) 15.3	105 (32.5)	104 (35.5)	745 (31.6) 18.8	726 (30.8) 16.3
Hypertension						
n (%) IR	329 (13.8) 9.0	153 (8.1) 6.6	78 (24.1)	82 (28.0)	327 (13.9) 8.3	308 (13.1) 6.9
Hypotension						
n (%) IR	-	-	-	-	203 (8.6) 5.1	174 (7.4) 3.9

Percentages were calculated based on the total number of patients in the treatment group. The IR is patients/100 patient years.

Adverse events of special interest

Table 40: Incidence of predefined treatment-emergent adverse events of special interest; main phase 3 NDD and DD pools (SAF)

SMQ or Preferred Term	NDD Pool		DD Pools	
	R n = 2386	PB n = 1884	R n = 2354	ESA n = 2360
Acute pancreatitis SMQ				
n (%) IR	17 (0.7) 0.4	7 (0.4) 0.3	23 (1.0) 0.6	22 (0.9) 0.5
Drug related hepatic disorders SMQ (severe events)				
n (%) IR	50 (2.1) 1.2	23 (1.2) 0.9	57 (2.4) 1.4	58 (2.5) 1.3
Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions SMQ (severe events)				
n (%) IR	34 (1.4) 0.8	20 (1.1) 0.8	47 (2.0) 1.2	43 (1.8) 1.0
Hepatitis, non-infectious SMQ (severe events)				
n (%) IR	11 (0.5) 0.3	2 (0.1) 0.1	7 (0.3) 0.2	16 (0.7) 0.4
Liver neoplasms, benign (incl cysts and polyps) SMQ (severe events)				
n (%) IR	8 (0.3) 0.2	1 (0.1) 0.0	6 (0.3) 0.2	4 (0.2) 0.1
Liver neoplasms, malignant and unspecified SMQ (severe events)				
n (%) IR	1 (0.0) 0.0	1 (0.1) 0.0	0	0
Liver related investigations, signs and symptoms SMQ (severe events)				
n (%) IR	88 (3.7) 2.2	50 (2.7) 2.1	105 (4.5) 2.7	78 (3.3) 1.7
Malignant tumours SMQ				
n (%) IR	47 (2.0) 1.2	35 (1.9) 1.4	58 (2.5) 1.5	51 (2.2) 1.1
Haematological malignant tumours SMQ				
n (%) IR	4 (0.2) 0.1	6 (0.3) 0.2	6 (0.3) 0.2	5 (0.2) 0.1
Non-haematological malignant tumours SMQ				
n (%) IR	43 (1.8) 1.1	29 (1.5) 1.2	52 (2.2) 1.3	47 (2.0) 1.0
Rhabdomyolysis/myopathy SMQ				
n (%) IR	7 (0.3) 0.2	7 (0.4) 0.3	8 (0.3) 0.2	2 (0.1) 0.0
Retinal disorders SMQ				
n (%) IR	75 (3.1) 1.9	42 (2.2) 1.7	38 (1.6) 1.0	37 (1.6) 0.8

Percentages were calculated based on the total number of patients in the treatment group.
The IR is patients/100 patient years.

- Ophtalmological effects (retinal disorders)

As specifically evaluated during a 24 weeks phase 3 study, no clinically meaningful changes from week 0 in the proportion of patients with the evidence of retinal haemorrhages, hard exudates and cotton wool spots were found in either the roxadustat or darbepoetin alfa group. The proportion of patients with new or worsening retinal haemorrhages during the treatment period was 32.4% (46/142 patients) and 36.6% (53/145 patients), respectively. No difference in retinal thickness was observed (change from baseline (-4.93 vs 1.64 (right eye) and -1.07 vs -0.31 um (left eye) at 24 weeks for roxadustat vs ESA).

Post-hoc analysis of adverse events

Imbalances in certain specific adverse events and laboratory measures were noted during the review of safety data from the NDD and DD pools. These TEAEs were identified using 3 methods:

- TEAEs were identified that had either a ≥ 1% difference between roxadustat and comparator group or were double the incidence in 1 group and were at least 1% in either group and also had a difference in IR between treatment of > 1.

- TEAEs were identified that had statistically significant increases in HR for roxadustat in the adjudicated event analysis.

- TEAEs were identified based on known risks for ESAs.

These events are presented as post-hoc TEAEs and SAEs of special interest in and are individually discussed in the sections below.

A focus of the assessments was to determine whether there was conclusive evidence for a causal relationship between the occurrence of the event and the use of roxadustat. Decisions on whether a causal relationship existed were based on clinical judgment and factors such as: frequency, severity, seriousness, event incidence exceeding comparator incidence, whether the event occurred in both the NDD and DD populations, the extent to which the event was consistent with the pharmacology and non-clinical data of the drug.

Table 41: Incidence of post-hoc treatment-emergent adverse events of special interest; main phase 3 NDD and DD pools (SAF)

SMQ, SOC or Preferred Term	NDD Pool		DD Pool	
	R n = 2386	PB n = 1884	R n = 2354	ESA n = 2360
Acute kidney injury, preferred term				
n	121	53	1	1
(%)	(5.1)	(2.8)	(0.0)	(0.0)
IR	3.1	2.2	0.0	0.0
Convulsions SMQ				
n	26	4	47	37
(%)	(1.1)	(0.2)	(2.0)	(1.6)
IR	0.6	0.2	1.2	0.8
Seizure (preferred term)				
n	18	3	38	30
(%)	(0.8)	(0.2)	(1.6)	(1.3)
IR	0.4	0.1	1.0	0.7
Gastrointestinal haemorrhage SMQ				
n	109	55	134	160
(%)	(4.6)	(2.9)	(5.7)	(6.8)
IR	2.8	2.3	3.4	3.6
Hyperbilirubinaemia SMQ				
n	72	32	82	65
(%)	(3.0)	(1.7)	(3.5)	(2.8)
IR	1.8	1.3	2.1	1.5
Hyperkalemia SMQ				

SMQ, SOC or Preferred Term	NDD Pool		DD Pool	
	R n = 2386	PB n = 1884	R n = 2354	ESA n = 2360
n (%) IR	276 (11.6) 7.4	139 (7.4) 6.0	160 (6.8) 4.0	167 (7.1) 3.7
Hypertension SMQ				
n (%) IR	426 (17.9) 12.1	235 (12.5) 10.4	458 (19.5) 11.6	459 (19.4) 10.3
Infection Death SMQ (assessed by adjudication)				
n (%) IR	55 (2.3) 1.4	16 (0.8) 0.7	59 (2.5) 1.5	57 (2.4) 1.3
Infections and Infestations SOC				
n (%) IR	1255 (52.6) 51.3	798 (42.4) 47.4	1157 (49.2) 29.3	1166 (49.4) 26.1
Infections and infestations SOC (fatal)				
n (%) IR	71 (3.0) 1.8	18 (1.0) 0.7	66 (2.8) 1.7	59 (2.5) 1.3
Sepsis SMQ				
n (%) IR	127 (5.3) 3.2	39 (2.1) 1.6	204 (8.7) 5.2	191 (8.1) 4.3
Sepsis SMQ (fatal)				
n (%) IR	49 (2.1) 1.2	9 (0.5) 0.4	54 (2.3) 1.4	42 (1.8) 0.9
Nausea, preferred term				
n (%) IR	243 (10.2) 6.5	119 (6.3) 5.1	198 (8.4) 5.0	163 (6.9) 3.7
Pulmonary embolism or deep vein thrombosis (adjudicated positive)				
n (%) IR	32 (1.3) 0.8	6 (0.3) 0.2	40 (1.7) 1.0	18 (0.8) 0.4
Deep vein thrombosis (adjudicated positive)				
n (%) IR	25 (1.0) 0.6	4 (0.2) 0.2	31 (1.3) 0.8	6 (0.3) 0.1
Pulmonary embolism (adjudicated positive)				
n (%) IR	10 (0.4) 0.2	3 (0.2) 0.1	13 (0.6) 0.3	12 (0.5) 0.3
Severe cutaneous adverse reactions SMQ (narrow)				
n (%) IR	10 (0.4) 0.2	1 (0.1) 0.0	6 (0.3) 0.2	6 (0.3) 0.1
Vascular access thrombosis (adjudicated positive)				
n (%) IR	58 (2.4) 1.5	7 (0.4) 0.3	301 (12.8) 7.6	240 (10.2) 5.4

Percentages were calculated based on the total number of patients in the treatment group.
The IR is patients/100 patient years.

Serious adverse event/deaths/other significant events

Serious adverse events

Serious adverse events are provided below for the main phase 3 studies.

Table 42: Serious treatment-emergent adverse events (≥ 1% of patients in either treatment group of the main phase 3 NDD and DD studies (SAF)

Category	NDD Pool				DD Pool	
	NDD Pool		1517-CL-0610			
	R n = 2386	PB n = 1884	R n = 323	DA n = 293	R n = 2354	ESA n = 2360
Overall						
n (%) IR	1308 (54.8) 45.9	845 (44.9) 43.9	171 (52.9)	140 (47.8)	1288 (54.7) 32.6	1260 (53.4) 28.2
Blood and Lymphatic System Disorders						
n (%) IR	-	-	-	-	40 (1.7) 1.0	54 (2.3) 1.2
Anaemia						
n (%) IR	-	-	-	-	25 (1.1) 0.6	33 (1.4) 0.7
Cardiac Disorders						
n (%) IR	240 (10.1) 6.2	144 (7.6) 6.0	35 (10.8)	34 (11.6)	338 (14.4) 8.6	389 (16.5) 8.7
Acute myocardial infarction						
n (%) IR	35 (1.5) 0.9	27 (1.4) 1.1	4 (1.2)	8 (2.7)	85 (3.6) 2.2	89 (3.8) 2.0
Atrial fibrillation						
n (%) IR	-	-	-	-	35 (1.5) 0.9	42 (1.8) 0.9
Cardiac arrest						
n (%) IR	-	-	-	-	30 (1.3) 0.8	43 (1.8) 1.0
Cardiac failure						
n (%) IR	26 (1.1) 0.6	25 (1.3) 1.0	11 (3.4)	9 (3.1)	24 (1.0) 0.6	22 (0.9) 0.5
Cardiac failure congestive						
n (%) IR	53 (2.2) 1.3	25 (1.3) 1.0	1 (0.3)	10 (3.4)	57 (2.4) 1.4	60 (2.5) 1.3
Coronary artery disease						
n (%) IR	-	-	-	-	34 (1.4) 0.9	35 (1.5) 0.8
Myocardial infarction						
n (%) IR	26 (1.1) 0.6	9 (0.5) 0.4	3 (0.9)	0	25 (1.1) 0.6	17 (0.7) 0.4
Gastrointestinal disorders						
n (%) IR	184 (7.7) 4.7	87 (4.6) 3.6	20 (6.2)	15 (5.1)	208 (8.8) 5.3	233 (9.9) 5.2
General Disorders and Administration Site Conditions						
n (%) IR	106 (4.4) 2.7	65 (3.5) 2.7	10 (3.1)	8 (2.7)	160 (6.8) 4.0	137 (5.8) 3.1
Death						
n (%) IR	32 (1.3) 0.8	9 (0.5) 0.4	2 (0.6)	0	30 (1.3) 0.8	37 (1.6) 0.8
Non-cardiac chest pain						
n (%) IR	-	-	-	-	30 (1.3) 0.8	21 (0.9) 0.5

Category	NDD Pool				DD Pool	
	NDD Pool		1517-CL-0610			
	R n = 2386	PB n = 1884	R n = 323	DA n = 293	R n = 2354	ESA n = 2360
Infections and Infestations						
n (%) IR	452 (18.9) 12.4	243 (12.9) 10.6	48 (14.9)	33 (11.3)	555 (23.6) 14.0	543 (23.0) 12.2
Sepsis						
n (%) IR	57 (2.4) 1.4	7 (0.4) 0.3	3 (0.9)	8 (2.7)	79 (3.4) 2.0	80 (3.4) 1.8
Septic shock						
n (%) IR	-	-	-	-	30 (1.3) 0.8	25 (1.1) 0.6
Injury, Poisoning and Procedural Complications						
n (%) IR	132 (5.5) 3.4	55 (2.9) 2.3	20 (6.2)	14 (4.8)	322 (13.7) 8.1	287 (12.2) 6.4
Arteriovenous fistula site complication						
n (%) IR	-	-	-	-	28 (1.2) 0.7	13 (0.6) 0.3
Arteriovenous fistula thrombosis						
n (%) IR	30 (1.3) 0.7	5 (0.3) 0.2	7 (2.2)	2 (0.7)	116 (4.9) 2.9	78 (3.3) 1.7
Metabolism and Nutrition Disorders						
n (%) IR	222 (9.3) 5.8	135 (7.2) 5.7	19 (5.9)	16 (5.5)	190 (8.1) 4.8	174 (7.4) 3.9
Fluid overload						
n (%) IR	27 (1.1) 0.7	24 (1.3) 1.0	3 (0.9)	1 (0.3)	66 (2.8) 1.7	70 (3.0) 1.6
Hyperkalaemia						
n (%) IR	57 (2.4) 1.4	26 (1.4) 1.1	7 (2.2)	3 (1.0)	59 (2.5) 1.5	55 (2.3) 1.2
Nervous System Disorders						
n (%) IR	-	-	-	-	195 (8.3) 4.9	196 (8.3) 4.4
Respiratory, Thoracic, and Mediastinal Disorders						
n (%) IR	-	-	-	-	166 (7.1) 4.2	212 (9.0) 4.7
Renal and Urinary Disorders						
n (%) IR	543 (22.8) 15.1	322 (17.1) 14.0	93 (28.8)	83 (28.3)	-	-
Acute kidney injury						
n (%) IR	81 (3.4) 2.0	36 (1.9) 1.5	6 (1.9)	6 (2.0)	-	-
Azotaemia						
n (%) IR	78 (3.3) 2.0	63 (3.3) 2.6	1 (0.3)	0	-	-
Chronic kidney disease						
n (%) IR	33 (1.4) 0.8	12 (0.6) 0.5	1 (0.3)	0	-	-
End stage renal disease						
n (%) IR	358 (15.0) 9.5	206 (10.6) 8.7	88 (27.2)	77 (26.3)	-	-

Category	NDD Pool				DD Pool	
	NDD Pool		**1517-CL-0610**			
	R **n = 2386**	**PB** **n = 1884**	**R** **n = 323**	**DA** **n = 293**	**R** **n = 2354**	**ESA** **n = 2360**
Vascular Disorders						
n (%) IR	134 (5.6) 3.4	84 (4.5) 3.5	27 (8.4)	17 (5.8)	607 (25.8) 15.4	632 (26.8) 14.2
Deep vein thrombosis						

n
  (%)
  IR
	-	-	-	-	28
					(1.2)
					0.7
						7
						(0.3)
						0.2

Hypertension						

n
  (%)
  IR
	-	-	-	-	32
					(1.4)
					0.8
						24
						(1.0)
						0.5

Hypertensive crisis						

n
  (%)
  IR
	34
	(1.4)
	0.8
		24
		(1.3)
		1.0
			4
			(1.2)
				4
				(1.4)
					39
					(1.7)
					1.0
						54
						(2.3)
						1.2

Hypertensive emergency						

n
  (%)
  IR
	-	-	-	-	28
					(1.2)
					0.7
						37
						(1.6)
						0.8

Hypotension						

n
  (%)
  IR
	-	-	-	-	46
					(2.0)
					1.2
						41
						(1.7)
						0.9

Percentages were calculated based on the total number of patients in the treatment group. The IR is patients/100 patient years.

A post-hoc analysis was performed by the applicant, which yielded the information as provided below.

Table 43: Incidence of post-hoc treatment-emergent serious adverse events of special interest; main phase 3 NDD and DD pools (SAF)

SMQ, SOC or Preferred Term	NDD Pool		DD Pool	
	R n = 2386	PB n = 1884	R n = 2354	ESA n = 2360
Acute kidney injury, preferred term				
n	81	36		1
(%)	(3.4)	(1.9)	0	(0.0)
IR	2.0	1.5		0.0
Convulsions SMQ				
n	10	1	27	23
(%)	(0.4)	(0.1)	(1.1)	(1.0)
IR	0.2	0.0	0.7	0.5
Seizure (preferred term)				
n	4	1	22	19
(%)	(0.2)	(0.1)	(0.9)	(0.8)
IR	0.1	0.0	0.6	0.4
Gastrointestinal haemorrhage SMQ				
n	63	33	77	95
(%)	(2.6)	(1.8)	(3.3)	(4.0)
IR	1.6	1.4	1.9	2.1
Hyperbilirubinaemia SMQ				
n	23	7	26	27
(%)	(1.0)	(0.4)	(1.1)	(1.1)
IR	0.6	0.3	0.7	0.6
Hyperkalemia SMQ				
n	57	26	60	57
(%)	(2.4)	(1.4)	(2.5)	(2.4)
IR	1.4	1.1	1.5	1.3
Hypertension SMQ				
n	79	49	102	120
(%)	(3.3)	(2.6)	(4.3)	(5.1)
IR	2.0	2.0	2.6	2.7
Infection Death SMQ (assessed by adjudication)				
n	55	16	59	57
(%)	(2.3)	(0.8)	(2.5)	(2.4)
IR	1.4	0.7	1.5	1.3
Infections and Infestations SOC				
n	452	243	555	543
(%)	(18.9)	(12.9)	(23.6)	(23.0)
IR	12.4	10.6	14.0	12.2
Infections and infestations SOC (fatal)				
n	71	18	66	59
(%)	(3.0)	(1.0)	(2.8)	(2.5)
IR	1.8	0.7	1.7	1.3
Sepsis SMQ				
n	110	31	172	159
(%)	(4.6)	(1.6)	(7.3)	(6.7)
IR	2.8	1.3	4.4	3.6
Sepsis SMQ (fatal)				
n	49	9	54	42
(%)	(2.1)	(0.5)	(2.3)	(1.8)
IR	1.2	0.4	1.4	0.9
Nausea, preferred term				
n	5		3	2
(%)	(0.2)	0	(0.1)	(0.1)
IR	0.1		0.1	0.0
Pulmonary embolism or deep vein thrombosis (adjudicated positive)				
n	32	6	40	18
(%)	(1.3)	(0.3)	(1.7)	(0.8)
IR	0.8	0.2	1.0	0.4
Deep vein thrombosis (adjudicated positive)				
n	25	4	31	6
(%)	(1.0)	(0.2)	(1.3)	(0.3)
IR	0.6	0.2	0.8	0.1
Pulmonary embolism (adjudicated positive)				

SMQ, SOC or Preferred Term	NDD Pool		DD Pool	
	R n = 2386	PB n = 1884	R n = 2354	ESA n = 2360
n	10	3	13	12
(%)	(0.4)	(0.2)	(0.6)	(0.5)
IR	0.2	0.1	0.3	0.3
Severe cutaneous adverse reactions SMQ (narrow)				
n	4		5	3
(%)	(0.2)	0	(0.2)	(0.1)
IR	0.1		0.1	0.1
Vascular access thrombosis (adjudicated positive)				
n	58	7	301	240
(%)	(2.4)	(0.4)	(12.8)	(10.2)
IR	1.5	0.3	7.6	5.4

Percentages were calculated based on the total number of patients in the treatment group. The IR is patients/100 patient years.

Cardiovascular Safety and Overall Deaths

NDD pool placebo comparison

Analyses of on-treatment and ITT CV and mortality rate have been provided below.

Table 44: Analysis of Time to MACE, MACE+ and ACM for Events Classified as OT-28 (Original and Simplified IPCW Cox Models) NDD Studies and Pool

Category	NDD Pool					
	MACE		MACE+		ACM	
	Roxadustat n = 2386	Placebo n = 1884	Roxadustat n = 2386	Placebo n = 1884	Roxadustat n = 2386	Placebo n = 1884
On-treatment Cox model (OT-28)						
Number of events/PY/FAIR/100 PY †						
All studies	344/3962.1/8.7	166/2431.4/6.8	448/3860.4/11.6	242/2384.3/10.1	260/4037.6/6.4	122/2460.4/5.0
FGCL-4592-060	56/1156.4/4.8	15/399.2/3.8	86/1125.4/7.6	28/394.6/7.1	38/1179.8/3.2	11/400.1/2.7
1517-CL-0608	52/489.4/10.6	20/211.1/9.5	61/487.2/12.5	23/207.9/11.1	37/500.4/7.4	16/212.7/7.5
D5740C00001	236/2316.4/10.2	131/1821.1/7.2	301/2247.7/13.4	191/1781.7/10.7	185/2357.3/7.8	95/1847.6/5.1
Original IPCW Cox regression, HR (95% CI)						
All studies ‡	1.26 (1.02, 1.55)		1.17 (0.99, 1.40)		1.16 (0.90, 1.50)	
FGCL-4592-060 §	1.04 (0.63, 1.71)		0.93 (0.62, 1.42)		0.75 (0.41, 1.39)	
1517-CL-0608 §	1.05 (0.62, 1.78)		1.06 (0.65, 1.73)		0.91 (0.50, 1.66)	
D5740C00001 §	1.38 (1.07, 1.79)		1.26 (1.03, 1.56)		1.40 (1.02, 1.91)	

For the ITT MACE analyses this was 480 (20.1%) vs 350 (18.6%) with IR 10.6 vs 10.3 and HR 1.10 (0.96, 1.27). For studies 060, 0608 and 001 this was 0.89 (0.60, 1.30), 1.23 (0.76, 1.99) and 1.13 (0.96, 1.32), respectively. For MACE+ ITT this was 578 (24.2%) vs 432 (22.9%); IR 13.2 vs 13.2; HR 1.07 (0.94, 1.21).

For the ITT mortality analyses this was 400 vs 301 with IR 8.3 vs 8.1 and HR 1.08 (0.93, 1.26). For studies 060, 0608, and 001 this was HR 0.75 (0.50, 1.13), HR 1.11 (0.65, 1.90), and HR 1.15 (0.97, 1.37), respectively.

Fatal events occurred in 276 (11.6%) vs 134 (7.1%) with IR 6.9 vs 5.5. This was mainly observed in cardiac disorders (IR 1.3 vs 1.5), infections and infestations (IR 1.8 vs 0.7) with sepsis (IR 0.6 vs 0.1), renal and urinary tract disorders (IR 1.1 vs 0.9) and general disorders and administration site conditions (IR 1.0 vs 0.7). For other fatal AE SOC categories, IRs were below 1.

Hb correction studies in NDD and DD

Analyses of on-treatment CV and mortality rate in the pool of Hb correction studies, both including studies in NDD (study 0610) and patients studied in DD patients (study 063, 10% of study 064 and 20% of study 002). Note that the MACE, MACE+ and ACM results for Study 1517-CL-0610 within the Hb correction pool are based on final data.

Table 45: Analysis of time to MACE, MACE+ and ACM for events classified as OT-7 (Cox Model) Hb correction pool

Category	Hb Correction Pool					
	MACE		MACE+		ACM	
	Roxadustat n = 1083	ESA n = 1059	Roxadustat n = 1083	ESA n = 1059	Roxadustat n = 1083	ESA n = 1059
On-treatment Cox model (OT-7)						
Number of events/PEY/ IR /100 PEY †						
All Studies	105/1617.5/6.5	136/1662/8.2	134/1617.5/8.3	171/1662/10.3	74/1617.5/4.6	99/1662/6.0
Study FGCL-4592-063	57/890.7/6.4	66/951.6/6.9	62/890.7/7.0	84/951.6/8.8	41/890.7/4.6	47/951.6/4.9
Study FGCL-4592-064 ID-DD	2/23.1/8.6	6/21.7/27.6	6/23.1/25.9	7/21.7/32.2	1/23.1/4.3	4/21.7/18.4
Study 1517-CL-0610	31/519.3/6.0	39/472.5/8.3	46/519.3/8.9	50/472.5/10.6	22/519.3/4.2	29/472.5/6.1
Study D5740C00002 ID-DD	15/184.4/8.1	25/216.2/11.6	20/184.4/10.8	30/216.2/13.9	10/184.4/5.4	19/216.2/8.8
Cox regression, HR (95% CI)						
All Studies ‡	0.79 (0.61, 1.02)		0.78 (0.62, 0.98)		0.78 (0.57, 1.05)	
Study FGCL-4592-063 §	0.93 (0.65, 1.33)		0.79 (0.57, 1.09)		0.97 (0.64, 1.48)	
Study FGCL-4592-064 ID-DD §	0.23 (0.04, 1.28)		0.55 (0.16, 1.86)		0.20 (0.02, 1.93)	
Study 1517-CL-0610 §	0.70 (0.44, 1.12)		0.81 (0.54, 1.22)		0.67 (0.39, 1.17)	
Study D5740C00002 ID-DD §	0.66 (0.34, 1.29)		0.73 (0.41, 1.32)		0.56 (0.26, 1.23)	

Hb correction pool (All patients from Studies FGCL-4592-063 and 1517-CL-0610 and only patients who initiated dialysis < 4 months (≤ 121 days) prior to randomisation for Studies FGCL-4592-064 and D5740C00002).

OT-7: events that occurred during the treatment period and within 7 days of the last dose of study medication.

Active control was epoetin alfa (Studies D5740C00002, FGCL-4592-063 and FGCL-4592-064) and darbepoetin alfa (Study 1517-CL-0610).

MACE is a composite of ACM, myocardial infarction and stroke and MACE+ is a composite including all components of MACE as well as hospitalisation for either unstable angina or congestive heart failure.

ACM: all-cause mortality; BL: baseline; CI: confidence interval; CV: cardiovascular; eGFR: estimated glomerular filtration rate; ESA: erythropoiesis-stimulating agent; Hb: haemoglobin; HR: hazard ratio; ID-DD: incident dependent-dialysis; IR: incident rate; MACE: major adverse CV event; PEY: patient exposure years.

† PEY for each patient = (last dose date - first dose date + 1) / 365.25. IR/100 PEY = 100 x number of subjects with events / PEY.

‡ HR comparing roxadustat to active control was derived using a meta-analysis method which combines individual study log-HRs with weights inversely proportional to the variance of the study-specific log-HRs

§ HR in Study 1517-CL-0610 was obtained using a single Cox model stratified by region (Central and Eastern Europe vs Western Europe and Israel) and CV history (yes vs no), and adjusted on age, BL Hb and log-transformed eGFR as continuous covariates with treatment as a fixed effect. HR in Studies FGCL-4592-063 / FGCL-4592-064 and D5740C00002 was obtained using a Cox model adjusting for age, history of CV, cerebrovascular or thromboembolic diseases (yes vs no), and other study-specific stratification factors, which are, for Study FGCL-4592-063: region (US vs ex-US) and screening Hb values (≤ 8 vs .> 8 g/dL); for Study FGCL-4592-064: mean

qualifying screening Hb (≤ 10.5 vs > 10.5 g/dL) and mean prescribed weekly BL epoetin alfa dose (or, equivalent epoetin dose for non-epoetin patients) in 4 weeks prior to randomisation (≤ 150 vs > 150 IU/kg/week); for Study D5740C00002, region (US vs ex-US) and BL Hb (≤ 10.5 vs > 10.5 g/dL)

DD pool (overall, conversion from ESA subpool)

Overall

MACE was increased in the a-priori defined OT-7 on-treatment analysis (7 days after last dose; HR of 1.09 (0.95 – 1.26) (371 (15.8%) vs 398 (16.9%)).

The mortality rate was also higher for roxadustat than for ESA therapy (IR of 6.7 vs 6.2 per 100PY; HR 1.13 [95% CI: 0.95, 1.34]) during treatment (OT-7; follow-up to 7 days after the last dose), despite a lower total number of deaths for roxadustat (11.2% vs 11.7%).

Fatal events occurred in 359 (15.3%) vs 359 (15.2%) with IR 9.1 vs 8.0. This was mainly observed in cardiac disorders (IR 3.0 vs 2.7), infections and infestations (IR 1.7 vs 1.3) with sepsis (IR 1.0 vs 0.8), and general disorders and administration site conditions (IR 1.7 vs 1.4). For other fatal AE SOC categories, IRs were below 1.

Conversion from ESA

Analyses of on-treatment CV and mortality risk have been provided below for conversion from ESA including studies 064 (90% of the patients), 0613, and 002 (80% of the patients).

Table 46: Analysis of time to MACE, MACE+ and ACM for rvents classified as OT-7 and OT-28 (Cox Model) ESA conversion studies and pool

Category	ESA Conversion Pool (Stable DD)					
	MACE		MACE+		ACM	
	Roxadustat n = 1594	ESA n = 1594	Roxadustat n = 1594	ESA n = 1594	Roxadustat n = 1594	ESA n = 1594
Cox model (OT-7)						
Number of events/PEY/IR/100 PEY †						
All studies	297/2854.2/10.4	301/3273.8/9.2	357/2854.2/12.5	403/3273.8/12.3	212/2854.2/7.4	207/3273.8/6.3
FGCL-4592-064	66/601.4/11.0	70/737.5/9.5	88/601.4/14.6	106/737.5/14.4	39/601.4/6.5	35/737.5/4.7
1517-CL-0613	65/637.2/10.2	59/719.7/8.2	72/637.2/11.3	66/719.7/9.2	57/637.2/8.9	45/719.7/6.3
D5740C00002	166/1615.7/10.3	172/1816.5/9.5	197/1615.7/12.2	231/1816.5/12.7	116/1615.7/7.2	127/1816.5/7.0
Cox regression, HR (95% CI)						
All studies ‡	1.18 (1.00, 1.38)		1.03 (0.90, 1.19)		1.23 (1.02, 1.49)	
FGCL-4592-064 §	1.18 (0.84, 1.66)		0.99 (0.74, 1.31)		1.46 (0.92, 2.32)	
1517-CL-0613 §	1.37 (0.96, 1.96)		1.36 (0.97, 1.90)		1.64 (1.10, 2.43)	
D5740C00002 §	1.11 (0.90, 1.37)		0.97 (0.80, 1.17)		1.04 (0.81, 1.34)	
Cox model (OT-28)						
Number of events/PEY/IR/100 PEY †						
All studies	347/2854.2/12.2	341/3273.8/10.4	408/2854.2/14.3	439/3273.8/13.4	269/2854.2/9.4	260/3273.8/7.9
FGCL-4592-064	82/601.4/13.6	79/737.5/10.7	103/601.4/17.1	114/737.5/15.5	58/601.4/9.6	49/737.5/6.6
1517-CL-0613	73/637.2/11.5	63/719.7/8.8	80/637.2/12.6	70/719.7/9.7	65/637.2/10.2	52/719.7/7.2
D5740C00002	192/1615.7/11.9	199/1816.5/11.0	225/1615.7/13.9	255/1816.5/14.0	146/1615.7/9.0	159/1816.5/8.8
Cox regression, HR (95% CI)						
All studies ‡	1.21 (1.04, 1.41)		1.08 (0.94, 1.24)		1.24 (1.05, 1.48)	
FGCL-4592-064 §	1.30 (0.95, 1.77)		1.07 (0.82, 1.40)		1.53 (1.04, 2.25)	
1517-CL-0613 §	1.44 (1.02, 2.02)		1.42 (1.03, 1.96)		1.62 (1.12, 2.34)	
D5740C00002 §	1.11 (0.91, 1.35)		1.00 (0.84, 1.20)		1.05 (0.84, 1.32)	

Stable DD subpool: Studies D5740C00002, FGCL-4592-064 and 1517-CL-0613 patients who had been on dialysis at least 4 months (> 121 days) prior to randomization.
OT-7/28: events that occurred during the treatment period and within 7/28 days of the last dose of study medication.

No clear differences were observed for subgroups of hyperkalemia status or hypertension exarcerbation status. Analysis according to ESA dose <> 7000 IU/week showed an increased risk for higher ESA dose (MACE HR 1.49 (1.13, 1.97) and mortality (1.45 (1.04, 2.01) for baseline ESA of > 7000 IU/week group vs HR 1.06 (0.86, 1.29) and 1.17 (0.92, 1.48) in the baseline ESA of ≤ 7000 IU/week group).

CV and mortality risk in hyporesponsiveness

In both the non-dialysis and dialysis pool a lack of sufficient response of remaining Hb levels below 10 g/dL have been observed. Hb levels before the event have been displayed in the table below. Increased event rates for MACE and ACM were observed in the below 10 g/dL category for roxadustat vs placebo.

Table 47: MACE+, MACE and ACM event rates by Hb category (OT-7)

Pool/Study	< 10 g/dL		10 - < 12 g/dL		12 - < 13 g/dL		≥ 13 g/dL	
	R	Comp.	R	Comp.	R	Comp.	R	Comp.
NDD †								
MACE+	24.2	11.2	7.4	6.0	7.9	8.8	11.0	0.0
MACE	17.1	6.2	5.1	4.6	5.4	7.1	6.4	0.0
ACM	13.0	4.1	3.0	2.5	2.9	3.5	0.9	0.0
1517-CL-0610 ‡								
MACE+	31.8	21.9	8.4	11.9	3.6	11.2	4.8	0.0
MACE	20.6	14.1	4.8	8.6	2.7	7.9	4.8	0.0
ACM	15.0	9.4	3.0	6.3	2.7	4.5	4.8	0.0
ID-DD §								
MACE+	22.0	22.0	5.8	7.8	3.1	1.5	6.2	11.1
MACE	17.8	15.9	4.9	6.2	3.1	1.5	6.2	7.4
ACM	12.6	12.6	2.5	4.0	3.1	0.0	6.2	7.4
Stable DD ¶								
MACE+	29.8	23.9	11.3	11.1	9.3	8.7	5.8	7.2
MACE	22.5	15.7	9.2	7.9	5.6	7.3	5.8	3.6
ACM	17.2	10.7	5.7	5.0	3.5	4.7	4.3	1.8

OT-7: events that occurred during the treatment period and within 7 days of the last dose of study medication. MACE is a composite of ACM, myocardial infarction and stroke and MACE+ is a composite including all components of MACE as well as hospitalization for either unstable angina or congestive heart failure.

ACM: all-cause mortality; Comp: comparator (either placebo or ESA); DD: dialysis-dependent; ESA: erythropoiesis-stimulating agent; Hb: hemoglobin; ID: incident; ISS: Integrated Summary of Safety; MACE: major adverse CV event; ISS: Integrated Summary of Safety; NDD: non-dialysis-dependent; OT: on-treatment; PEY: patient exposure years; R: roxadustat

Incidence rate/100 PEY = 100 x number of patients with events / PEY. PEY for each patient = (last dose date - first dose date + 1) / 365.25. Patients with > 1 event in a category are counted only once for that category.

† Randomized patients who took any dose of study medication in the NDD Studies D5740C00001, FGCL-4592-060 and 1517-CL-0608. Comparator was placebo.

‡ NDD Study 1517-CL-0610 randomized patients. Active control was darbepoetin alfa.

§ Study FGCL-4592-063 and ID-DD dataset from Study D5740C00002. ID-DD1 (Studies FGCL-4592-063 and the ID-DD dataset of Study D5740C00002): DD patients who initiated dialysis < 4 months (≤ 121 days) prior to randomization. Active control was epoetin alfa.

¶ Stable DD (Studies D5740C00002, FGCL-4592-064, 1517-CL-0613): DD (Studies D5740C00002, FGCL-4592-064, 1517-CL-0613) patients who have been on dialysis at least 4 months (> 121 days) prior to randomization. Active control was epoetin alfa (Studies D5740C00002 and FGCL-4592-064) and either epoetin alfa or darbepoetin alfa (Study 1517-CL-0613).

Laboratory findings

NDD pool

An overview of haematology, renal parameters, liver enzymes, lipid parameters and vital signs are provided below.

Hematology

Mean change from baseline in haematocrit was 7.3% vs 0.78%, erythrocytes 0.67 vs 0.08 10^{12}/L, leukocytes 0.16 vs 0.10 10^9/L, lymphocytes -0.02 vs -0.02 10^9/L, neutrophils 0.13 vs 0.02 10^9/L, platelets -8.5 vs -4.3 for roxadustat vs placebo.

Mean change from baseline in haematocrit was 6.0% vs 5.6%, erythrocytes 0.59 vs 0.63 10^{12}/L, leukocytes 0.19 vs -0.08 10^9/L, lymphocytes 0.03 vs -0.03 10^9/L, neutrophils 0.12 vs -0.12 10^9/L, platelets -6.8 vs -17.0 for roxadustat vs ESA in study 0610.

Renal values

Differences in potential significant renal values were for creatinine >1.5x baseline was 27.6 vs 30.6 (incidence rates per 100 patients years), blood urea nitrogen > 1.5 × baseline 27.9 vs 31.5, calcium < 0.8 × LLN 5.0 vs 4.7, calcium > 1.2 × ULN 0.3 vs 0.2, sodium < 0.9 × LLN 1.1 vs 1.1, sodium > 1.1 × ULN 0 vs 0, protein < 0.9 × LLN 9.9 vs 7.2, protein > 1.1 × ULN 0.5 vs 0.4 for roxadustat vs placebo.

Differences in potential significant renal values were for creatinine >1.5x baseline was 28.0 vs 30.1 (%), blood urea nitrogen > 1.5 × baseline 30.2 vs 37.0, calcium < 0.8 × LLN 4.4 vs 4.2, calcium > 1.2 × ULN 0 vs 1.0, sodium < 0.9 × LLN 0 vs 0.7, sodium > 1.1 × ULN 0 vs 0, protein < 0.9 × LLN 917.0 vs 13.8, protein > 1.1 × ULN 0.6 vs 0 for roxadustat vs ESA.

Effects on potassium by baseline eGFR category are displayed below.

Table 48: Patients with potentially clinically significant potassium values by baseline eGFR category; main phase 3 NDD NDD pool (censored for dialysis) (SAF)

Parameter Statistic	NDD NDD Pool							
	Roxadustat				Placebo			
	< 10 mL/min/ 1.73 m² n = 481	≥ 10 - < 15 mL/min/ 1.73 m² n = 524	≥ 15 - < 30 mL/min/ 1.73 m² n = 953	≥ 30 mL/min/ 1.73 m² n = 428	< 10 mL/min/ 1.73 m² n = 358	≥ 10 - < 15 mL/min/ 1.73 m² n = 451	≥ 15 - < 30 mL/min/ 1.73 m² n = 724	≥ 30 mL/min/ 1.73 m² n = 351
Potassium < 0.75 × LLN								
n/N (%) IR	3/429 (0.7) 0.9	4/502 (0.8) 0.6	5/932 (0.5) 0.3	2/412 (0.5) 0.3	0/318 (0.0) 0	0/429 (0.0) 0	3/693 (0.4) 0.3	2/341 (0.6) 0.4
Potassium > 1.2 × ULN								
n/N (%) IR	80/411 (19.5) 23.5	91/494 (18.4) 14.6	136/915 (14.9) 9.4	43/403 (10.7) 6.2	38/299 (12.7) 17.9	33/419 (7.9) 7.6	63/677 (9.3) 6.9	17/335 (5.1) 3.4

The IR is patients/100 patient years.

Liver enzymes

Effects on liver enzymes were ALT > 3 × ULN 1.2 vs 2.2, AST > 3 × ULN 1.8 vs 1.9 and total bilirubin > 2 x ULN 0.8 vs 0.3 for roxadustat vs placebo. Patients with elevated ALT, AST, and total bilirubin values are discussed below for each individual study in the NDD pool. No case of Hy's law was observed in any study.

Study 1517-CL-0608

Only 1 patient in the roxadustat group had an ALT and/or AST level > 3 × ULN and total bilirubin > 2 × ULN; this patient recorded values of ALT: 108 U/L, AST: 113 U/L, and bilirubin: 59.1 µmol/L at Week 2. The patient died on Day 15 due to pyelonephritis chronic and multiple organ dysfunction syndrome, which were considered unrelated to treatment by the investigator. The increases in liver enzymes were thought to be due to the multiorgan failure.

Study FGCL-4592-060

One subject in the placebo group met potential Hy's law criteria (ALT 220 U/L, AST 295 U/L, and bilirubin 2.46 mg/dL) at Week 60; however, these elevations were preceded by non-serious TEAEs of bile duct stone and biliary colic.

Study D5740C00001

Twelve patients (6 in the roxadustat group and 6 in the placebo group) met the laboratory criteria for potential Hy's law cases (ALT ≥ 3 × ULN or AST ≥ 3 × ULN and total bilirubin ≥ 2 × ULN). The elevations in ALT/AST and total bilirubin were independent of time and therefore may not have occurred concurrently. All cases had a plausible alternative etiology for the elevated liver function tests and did not meet Hy's law criteria. Three roxadustat-treated patients had an observed AST level ≥ 1000 U/L and were noted to have documented etiologies (i.e., acute hepatitis B, associated acute infection and ischemic hepatopathy, and alcoholic hepatitis). Narratives for these patients are provided in [Module 5.3.5.3, D5740C00001, Section 11.4].

Study 1517-CL-0610

Effects on liver enzymes were ALT > 3 × ULN 0.3 vs 1.0, AST > 3 × ULN 2.5 vs 1.4 and total bilirubin > 2 x ULN 0.9 vs 0 for roxadustat vs ESA. No patients in either treatment group were recorded with ALT and/or AST > 3 × ULN and total bilirubin > 2 × ULN.

Lipid parameters

Change from baseline in LDL-C was -0.54 vs 0.08, HDL-C -0.13 vs -0.01, Triglycerides -0.16 vs 0.09 mmol/L for roxadustat vs placebo.

Change from baseline in LDL-C was -0.39 vs 0.11, HDL-C -0.08 vs 0.04, Triglycerides -0.18 vs -0.09 mmol/L for roxadustat vs ESA.

Vital signs

A systolic blood pressure of ≥ 170 and increase of ≥ 20 was 11.7 vs 11.1 (incidence rate per 100 PY), systolic BP ≤ 90 and decrease of ≥ 20 4.1 vs 3.8, diastolic BP ≥ 110 and increase of ≥ 15 1.3 vs 1.2, diastolic BP ≤ 50 and decrease of ≥ 15 4.1 vs 4.6, pulse rate ≥ 120 and increase of ≥ 20 1.9 vs 2.3, pulse rate ≤ 50 and decrease of ≥ 20 0.7 vs 0.9 for roxadustat vs placebo.

A systolic blood pressure of ≥ 170 and increase of ≥ 20 was 19.3 vs 20.9 (%), systolic BP ≤ 90 and decrease of ≥ 20 3.1 vs 1.4, diastolic BP ≥ 110 and increase of ≥ 15 1.6 vs 1.7, diastolic BP ≤ 50 and decrease of ≥ 15 0.9 vs 3.1, pulse rate ≥ 120 and increase of ≥ 20 0.6 vs 0.3, pulse rate ≤ 50 and decrease of ≥ 20 2.5 vs 1.4 for roxadustat vs ESA.

DD pool

An overview of haematology, renal parameters, liver enzymes, lipid parameters and vital signs are provided below.

Haematology

Mean change from baseline in haematocrit was 3.2% vs 3.4%, erythrocytes 0.30 vs 0.29 10^{12}/L, leukocytes -0.03 vs -0.15 10^9/L, lymphocytes -0.11 vs -0.17 10^9/L, neutrophils 0.08 vs -0.01 10^9/L, platelets -0.6 vs -5.2 for roxadustat vs ESA.

Liver enzymes

Effects on liver enzymes were ALT > 3 × ULN 1.5 vs 1.6 (incidence rate per 100 PY), AST > 3 × ULN 1.5 vs 1.8 and total bilirubin > 2 x ULN 1.4 vs 0.4 for roxadustat vs ESA. Patients with elevated ALT, AST, and total bilirubin values are discussed below for each individual study in the DD pool.

Study 1517-CL-0613

A total of 2 (0.5%) patients in the roxadustat group and 2 (0.5%) patients in the ESA group had ALT and/or AST > 3 x ULN and total bilirubin > 2 x ULN at any point during the study. The majority of patients' values returned toward baseline by the end of the patients' participation in the study, and the investigator considered there to be plausible reasons for the elevated liver values other than a relationship with study drug.

Study FGCL-4592-063

A total of 5 patients (2 in the roxadustat group and 3 in the EPO-alfa group) had ALT and/or AST > 3 x ULN and total bilirubin > 2 x ULN. All 5 cases had established or suspected etiologies for the increases and, therefore, did not meet Hy's law criteria.

Study FGCL-4592-064

One patient in the EPO-alfa group had concurrent elevations of AST ≥ 3 x ULN and total bilirubin > 2 x ULN. The patient was discontinued from study drug and permanently withdrawn from the study due to an AE of cholangiocarcinoma. Given an identifiable cause for the liver function transaminase elevations, the patient was not considered to have met Hy's law.

Study D5740C00002

Twelve patients (4 in the roxadustat group and 8 in the ESA group) had ALT or AST ≥ 3×ULN and total bilirubin ≥ 2×ULN). The elevations in liver function values were independent of time and, therefore, may not have occurred concurrently. For all 12 patients, there was an alternative explanation for the elevation in liver biochemistry other than a relationship with study drug.

Lipid parameters

Change from baseline in LDL-C was -0.22 vs -0.19, HDL-C -0.006 vs -0.009, triglycerides -0.18 vs -0.12 mmol/L for roxadustat vs ESA.

Vital signs

A systolic blood pressure of ≥ 170 and increase of ≥ 20 was 21.3 vs 20.0 (incidence rate per 100 PY), systolic BP ≤ 90 and decrease of ≥ 20 3.9 vs 3.2, diastolic BP ≥ 110 and increase of ≥ 15 4.6 vs 4.5, diastolic BP ≤ 50 and decrease of ≥ 15 5.8 vs 5.1, pulse rate ≥ 120 and increase of ≥ 20 1.9 vs 1.7, pulse rate ≤ 50 and decrease of ≥ 20 1.0 vs 0.9 for roxadustat vs ESA.

Safety in special populations

Table 49: Treatment-emergent adverse events of special interest by age; main phase 3 NDD and DD pools (SAF)

MedDRA Preferred Term	NDD Pool				DD Pool				ID DD Subpool			
	Roxadustat		Placebo		Roxadustat		ESA		Roxadustat		ESA	
	< 65 yrs n = 1290	≥ 65 yrs n= 1096	< 65 yrs n = 984	≥ 65 yrs n = 900	< 65 yrs n = 1652	≥ 65 yrs n = 702	< 65 yrs n = 1645	≥ 65 yrs n = 715	< 65 yrs n = 570	≥ 65 yrs n = 190	< 65 yrs n = 581	≥ 65 yrs n = 185
Arteriovenous fistula thrombosis												
n	40	10	8	2	147	77	122	54	54	19	46	9
(%)	(3.1)	(0.9)	(0.8)	(0.2)	(8.9)	(11.0)	(7.4)	(7.6)	(9.5)	(10.0)	(7.9)	(4.9)
IR	1.9	0.5	0.7	0.2	5.2	6.8	3.9	4.1	6.5	7.2	5.1	3.1
Deep vein thrombosis												
n	10	18	3	3	22	14	10	9	1	3	4	1
(%)	(0.8)	(1.6)	(0.3)	(0.3)	(1.3)	(2.0)	(0.6)	(1.3)	(0.2)	(1.6)	(0.7)	(0.5)
IR	0.5	1.0	0.2	0.2	0.8	1.2	0.3	0.7	0.1	1.1	0.4	0.3
Nausea												
n	142	101	70	49	137	61	108	55	36	16	22	13
(%)	(11.0)	(9.2)	(7.1)	(5.4)	(8.3)	(8.7)	(6.6)	(7.7)	(6.3)	(8.4)	(3.8)	(7.0)
IR	7.1	5.9	6.0	4.1	4.8	5.4	3.4	4.2	4.3	6.1	2.4	4.5
Seizure												
n	11	7	2	1	30	8	24	6	6	3	7	1
(%)	(0.9)	(0.6)	(0.2)	(0.1)	(1.8)	(1.1)	(1.5)	(0.8)	(1.1)	(1.6)	(1.2)	(0.5)
IR	0.5	0.4	0.2	0.1	1.1	0.7	0.8	0.5	0.7	1.1	0.8	0.3

Table 50: Treatment-emergent adverse events of special interest by age; main phase 3 NDD and DD pools (SAF)

MedDRA Preferred Term	NDD Pool				DD Pool				ID DD Subpool			
	Roxadustat		Placebo		Roxadustat		ESA		Roxadustat		ESA	
	< 75 yrs n = 1909	≥ 75 yrs n= 477	< 75 yrs n = 1468	≥ 75 yrs n = 416	< 75 yrs n = 2120	≥ 75 yrs n = 234	< 75 yrs n = 2107	≥ 75 yrs n = 253	< 75 yrs n = 702	≥ 75 yrs n = 58	< 75 yrs n = 710	≥ 75 yrs n = 56
Arteriovenous fistula thrombosis												
n	49	1	9	1	198	26	159	17	67	6	52	3
(%)	(2.6)	(0.2)	(0.6)	(0.2)	(9.3)	(11.1)	(7.5)	(6.7)	(9.5)	(10.3)	(7.3)	(5.4)
IR	1.5	0.1	0.5	0.2	5.5	7.1	4.0	3.6	6.6	7.3	4.7	3.4
Deep vein thrombosis												
n	19	9	6	0	33	3	16	3	3	1	4	1
(%)	(1.0)	(1.9)	(0.4)		(1.6)	(1.3)	(0.8)	(1.2)	(0.4)	(1.7)	(0.6)	(1.8)
IR	0.6	1.1	0.3		0.9	0.8	0.4	0.6	0.3	1.2	0.4	1.1
Nausea												
n	202	41	98	21	184	14	144	19	48	4	31	4
(%)	(10.6)	(8.6)	(6.7)	(5.0)	(8.7)	(6.0)	(6.8)	(7.5)	(6.8)	(6.9)	(4.4)	(7.1)
IR	6.8	5.6	5.4	3.9	5.1	3.8	3.6	4.1	4.7	4.8	2.8	4.5
Seizure												
n	15	3	2	1	37	1	28	2	9	0	7	1
(%)	(0.8)	(0.6)	(0.1)	(0.2)	(1.7)	(0.4)	(1.3)	(0.8)	(1.3)		(1.0)	(1.8)
IR	0.5	0.4	0.1	0.2	1.0	0.3	0.7	0.4	0.9		0.6	1.1

Safety related to drug-drug interactions and other interactions

Drug-drug interactions (DDI) with statins: In Phase 1 studies, roxadustat increased the C_{max} and AUC_{inf} of the active metabolite of simvastatin 40 mg 1.9-fold and 1.75-fold, respectively; of rosuvastatin 10 mg 4.5-fold and 2.9-fold, respectively; and of atorvastatin 40 mg 1.3-fold and 2.0-fold, respectively. Roxadustat pharmacokinetics (PK) was unaffected. These DDI are well-characterised and described in the product label. In addition, the incidence and adjusted incidence rate of combined

rhabdomyolysis/myopathy events, with or without concomitant use of statins, was similar in the NDD-CKD safety pool between roxadustat, 0.3% (0.2/100 PY) and placebo, 0.4% (0.3/100 PY). In the DD-CKD safety pool, the incidence and incidence rates were also low in both treatment groups, 0.3% (0.2/100 PY) for roxadustat and 0.1% (0.1/100 PY) for active comparators. Myopathy related adverse drug reactions (e.g., rhabdomyolysis), are known to be associated with statins, and it is routine health clinical practice to monitor patients taking statins for these events and to manage statin therapy when prescribing concomitant medications that interact with statins. Therefore, there is no expected clinically significant impact on the benefit-risk balance of roxadustat due to drug-drug interactions with statins and this risk is not considered a safety concern for roxadustat.

Discontinuation due to adverse events

NDD pool

An overview of discontinuations due to adverse events is provided below.

Table 51: Treatment-emergent adverse events (≥ 2 patients in any treatment group) that led to discontinuation of study drug or study; main phase 3 NDD studies and DD pools (SAF)

Category	NDD Pool				DD Pool	
	NDD Pool		1517-CL-0610			
	R n = 2386	PB n = 1884	R n = 323	DA n = 293	R n = 2354	ESA n = 2360
Overall						Overall
n (%) IR	157 (6.6) 3.9	92 (4.9) 3.8	17 (5.3)	9 (3.1)	253 (10.7) 6.4	175 (7.4) 3.9
Blood and Lymphatic System Disorders						
n (%) IR	3 (0.1) 0.1	9 (0.5) 0.4	0	0	4 (0.2) 0.1	2 (0.1) 0.0
Cardiac Disorders						
n (%) IR	18 (0.8) 0.4	15 (0.8) 0.6	1 (0.3)	0	66 (2.8) 1.7	58 (2.5) 1.3
Gastrointestinal Disorders						
n (%) IR	12 (0.5) 0.3	4 (0.2) 0.2	1 (0.3)	0	26 (1.1) 0.7	5 (0.2) 0.1
General Disorders and Administration Site Conditions						
n (%) IR	3 (0.1) 0.1	15 (0.8) 0.6	0	0	28 (1.2) 0.7	20 (0.8) 0.4
Hepatobiliary Disorders						
n (%) IR	4 (0.2) 0.1	1 (0.1) 0.0	0	0	11 (0.5) 0.3	2 (0.1) 0.0
Infections and Infestations						
n (%) IR	27 (1.1) 0.7	8 (0.4) 0.3	4 (1.2)	2 (0.7)	51 (2.2) 1.3	29 (1.2) 0.6
Injury, Poisoning and Procedural Complications						
n (%) IR	6 (0.3) 0.1	0	0	0	8 (0.3) 0.2	6 (0.3) 0.1
Investigations						
n (%) IR	5 (0.2) 0.1	6 (0.3) 0.2	1 (0.3)	1 (0.3)	8 (0.3) 0.2	4 (0.2) 0.1
Metabolism and Nutrition Disorders						
n (%)	7 (0.3)	6 (0.3)	0	0	-	-

Category	NDD Pool				DD Pool	
	NDD Pool		1517-CL-0610			
	R n = 2386	PB n = 1884	R n = 323	DA n = 293	R n = 2354	ESA n = 2360
IR	0.2	0.2				
Neoplasms Benign, Malignant and Unspecified (Incl Cysts and Polyps)						
n	16	6	5	5	-	-
(%)	(0.7)	(0.3)	(1.5)	(1.7)		
IR	0.4	0.2				
Nervous System Disorders						
n	17	10	1	0	13	21
(%)	(0.7)	(0.5)	(0.3)		(0.6)	(0.9)
IR	0.4	0.4			0.3	0.5
Psychiatric Disorders						
n	2	1	0	0	4	0
(%)	(0.1)	(0.1)			(0.2)	
IR	0.0	0.0			0.1	
Renal and Urinary Disorders						
n	38	14	2	2	8	3
(%)	(1.6)	(0.7)	(0.6)	(0.7)	(0.3)	(0.1)
IR	0.9	0.6			0.2	0.1
Respiratory, Thoracic and Mediastinal Disorders						
n	9	6	0	1	15	14
(%)	(0.4)	(0.3)		(0.3)	(0.6)	(0.6)
IR	0.2	0.2			0.4	0.3
Skin and Subcutaneous Tissue Disorders						
n	11	5	0	0	5	1
(%)	(0.5)	(0.3)			(0.2)	(0.0)
IR	0.3	0.2			0.1	0.0
Vascular Disorders						
n	6	4	0	0	15	5
(%)	(0.3)	(0.2)			(0.6)	(0.2)
IR	0.1	0.2			0.4	0.1

Percentages were calculated based on the total number of patients in the treatment group.
The IR is patients/100 patient years.

Post marketing experience

Roxadustat received first marketing authorisation in China for treatment of anaemia in DD and NDD on 17 Dec 2018 and 16 Aug 2019, respectively. As of the data cut-off date of 07 Sep 2019, 100 patients were exposed to roxadustat as part of a donation programme in China. The available post-marketing safety data have not suggested any new important risks.

2.6.1. Discussion on clinical safety

A total of 12048 patients (5885 NDD, 6063 DD) have been included in the clinical development programme. For the pivotal NDD (non-dialysis dependent) placebo-controlled studies (NDD pool) there were 2386 on roxadustat and 1884 on placebo, for comparison to ESA in NDD this was however limited to 525 on roxadustat and 423 on ESA. For the pivotal DD (dialysis-dependent) population (DD pool) a substantial number of 2354 on roxadustat versus 2360 on ESA (2197 on epoetin-alfa, 163 on darbepoetin) have been evaluated. Other patients treated with roxadustat were mainly from other phase 2 and 3 supportive studies in the US, Japan and China.

Further, particularly adverse events of interest have been evaluated, including acute pancreatitis, hepatic disorders, malignant tumours, retinal disorders, and rhabdomyolysis/myopathy. Moreover, in line with the EMA reflection paper on assessment of cardiovascular safety profile of medicinal products, MACE events have been adjudicated by an independent committee and evaluated for MACE and MACE+. Due to the increased risk of ESA therapy on CV safety, these analyses are of particular importance. MACE is considered the most relevant analysis, especially since no clear justification has

been provided on the importance of analysing MACE+, and thus is considered only to be supportive. An analysis, including the on-treatment events, is the preferred analysis according to the EMA reflection paper. Also, thromboembolic risk has been reported with ESA, so specific attention for pulmonary embolism (PE) and/or deep vein thrombosis (DVT) that required hospitalisation has been given.

NDD pool placebo-controlled studies: In the NDD pool, roxadustat patients were treated substantially longer than placebo due to increased discontinuation in the placebo group (mean 84.6 vs 64.3 weeks). Long term safety has been evaluated, although more patients were treated for more than 52 weeks in the roxadustat arm than placebo. More adverse events, drug-related AEs, serious AEs, drug related serious AEs and discontinuations due to AEs occurred in the roxadustat versus placebo however this cannot be entirely explained by the longer treatment duration of roxadustat due to higher discontinuation in the placebo group.

NDD comparator study: Adverse events, drug-related AEs, serious AEs, drug-related serious AEs and discontinuations due to AEs occurred consistently higher for roxadustat however, substantial differences for increased frequency for roxadustat vs ESA were not found.

DD pool: For the DD pool, in all studies, roxadustat was compared to ESA therapy, and therefore pooling of data can be considered appropriate despite that differences in study design are present. In the DD pool, the duration of treatment was slightly longer for the ESA group than the roxadustat group (mean 87.6 vs 98.7 weeks). Longer-term treatment data beyond 52 weeks are also present and this was also longer for ESA. Adverse events, drug-related AEs, serious AEs, drug-related serious AEs and discontinuations due to AEs occurred consistently higher for roxadustat versus ESA therapy, especially if calculated based on incidence rate (as treatment period was longer for ESA). This was more pronounced in the stable DD pool than the ID DD pool. However substantial differences for increased frequency for roxadustat vs ESA were not found.

Based on further post-hoc evaluation by the applicant of difference in frequency, hazard ratio, or based on known risk of ESA, adverse events of nausea, deep vein thrombosis, pulmonary embolism (PE), convulsions (seizures), vascular access thrombosis (VAS), hyperkalaemia, hyperbilirubinaemia, hypertensive exacerbation, diarrhoea, headache, peripheral oedema and insomnia have been included as adverse reaction in the labelling. However, for similar reasons constipation and pyrexia should also remain as ADRs in the labelling.

CV and mortality risk evaluation

Hb correction versus placebo (NDD placebo-controlled studies):

A potentially increased CV safety risk with roxadustat versus placebo could not been excluded based on adjudicated MACE events in this pool. Both the MACE and MACE+ primary analyses are suggestive of an increased CV safety risk for treatment with roxadustat with a HR > 1 and with an upper CI outside the 1.3 margin. This strict(er) margin is considered relevant based on the known CV risk with ESA therapy, especially associated with increased levels of Hb, also the pivotal treatment effect for roxadustat. Further sensitivity analyses correcting for possible factors including Hb over time, hyperkalaemia, DVT/PE and hypertension, or a model with simple correction all show comparable increased HRs. Whether this method is able to appropriately correct for any residual confounding remains uncertain. An ITT approach was set a-priori at time of disclosure of the main studies but before unblinding of the adjudicated MACE events and shows a HR of 1.10 (0.96 – 1.27) for MACE and 1.07 (0.94 – 1.21) for MACE+ with upper CI levels just below this margin. However, this method is not preferred due to lower sensitivity, because events will be less likely due to the randomised treatment and more likely due to the background event rate and subsequent therapies (especially due to the possibility of introducing ESA therapy after treatment discontinuation), hence adding noise and possibly introducing new confounders to the treatment comparison.

Further, increased mortality was observed in the roxadustat group versus placebo (10.9% vs 6.5%; IR 6.4 vs 5.0; HR 1.16 [95% CI: 0.90, 1.51]) during treatment. CV mortality was also increased (HR: 1.17 [95% CI: 0.82, 1.67]). The increased fatal events occurring with roxadustat vs placebo (11.6 vs 5.5%; IR 6.9 vs 5.5) was primarily due to cardiac disorders (2.2 vs 2.0%; IR 1.3 vs 1.5), infections and infestations (3.0 vs 1.0%; IR 1.8 vs 0.7), and renal and urinary disorders (1.9 vs 1.2%; IR 1.1 vs 0.9), with sepsis and renal death as most notable individual fatal AEs.

Other possible factors associated with the observed increased CV and mortality risk have also been further explored. Hb overshooting could not clarify on any increased risk, however, non-responders (< 10 g/dL Hb during) during 24 weeks of treatment clearly show an increased CV and mortality risk. A similar observation can be noticed in the DD pool, supporting the notion that this can likely not (only) be attributed to any possible difference in baseline population risk and/or early discontinuation. In this context, it should be noticed that after a decrease from baseline a constant proportion of patients of 10-15% is observed after 12 weeks of treatment for whom Hb levels remain < 10g/dL. This warrants specific dose recommendations for those patients not sufficiently responding on roxadustat treatment, as included in the SmPC.

Hb correction in NDD and DD studies versus ESA

Correction of Hb versus ESA has been evaluated in the NDD study 1517-CL-0610 and the DD study FGCL-4592-063, 20% of the patients in the DD study D5740C00002, (and 10% of the ID-DD patients in study FGCL-4592-064). As baseline characteristics and treatment discontinuation (33.8% vs 31.0%) were approximately comparable in these studies, on-treatment analyses for CV and mortality risk are likely the most reliable of the 3 data pools as presented. These data are not suggestive for an increased CV and mortality risk versus ESA therapy (HR 0.81 (0.62, 1.05) and 0.80 (0.59, 1.08) for OT-7 and 0.93 (0.73, 1.18) and 0.99 (0.76, 1.30) for OT-28 evaluations).

ESA conversion in DD studies in stable dialysis patients (comparison versus ESA)

In addition to the overall DD pool data showing an increase in MACE on-treatment OT-7 of HR of 1.09 (0.95 – 1.26) (371 (15.8%) vs 398 (16.9%)) and mortality risk (IR of 6.7 vs 6.2 per 100PY; HR 1.13 [95% CI: 0.95, 1.34]), data for the conversion from (stabilised) ESA treatment to roxadustat pool has also been evaluated based on studies 1517-CL-0613, FGCL-4592-064 (90%) and D5740C00002 (approximately 80%).

A difference in observed increased CV and mortality risk in this pool (MACE HR 1.21 (1.04, 1.42) and mortality (1.24 (1.05, 1.48)) versus the observed suggestion for absence of CV and mortality risk in the correction pool can be noticed. This has been clarified by the design related issue of the need for switching to roxadustat treatment in one study arm whereas ESA patients could remain on their stabilised dose for maintaining their Hb level in the target range. Fluctuations caused by necessary up- or down-titration of the doses of study treatment, likely increasing the patient burden and inflicting Hb variability, are only seen in the roxadustat-treated patients and could possibly clarify the differences in increased discontinuation for roxadustat (44.7 vs 32.7%) and CV and mortality outcomes compared to the stable ESA therapy. As clarified, such switching strategy for a stable ESA treated patient is not common clinical practice unless there is a valid clinical indication to do so. However, following this reasoning and the imposed possible treatment complications and possible increase in CV and mortality risk should have clear consequences for the switching recommendation as mentioned in posology section of the SmPC.

In line with the increased hazard ratio as evaluated for the meta-analytic approach, slightly more fatal adverse events occurred in the roxadustat vs ESA (15.3 vs 15.2%), primarily due to cardiac disorders (5.0 vs 5.2%; IR 3.0 vs 2.7), general disorders and administration site conditions (2.9 vs 2.6%), and

infections and infestations (2.8 vs 2.5%) for the complete DD pool. Individual adverse events were too limited to identify any clear pattern.

Both the non-dialysis versus placebo pool and the ESA conversion in stable dialysis pool have specific issues that complicate interpretation. As baseline characteristics and treatment discontinuation were approximately comparable in the pool of correction of Hb versus ESA (2), on-treatment analyses for CV and mortality risk are likely the most reliable of the 3 data pools as presented.

Possible (other) factors associated with CV risk

- ESA hyporesponsiveness

Within the DD conversion setting, the applicant has provided the results according to (previous) ESA dose level. First, for the subgroup with baseline ESA of > 7000 IU/week higher roxadustat doses were needed vs baseline ESA of ≤ 7000 IU/week, while dosing adjustments (increases, decreases and holds) were comparable between both subgroups. Also, the proportion of roxadustat patients with Hb levels <10 g/dL during treatment appeared to be slightly lower in the low vs high ESA baseline dose group (data not provided), which could reflect a better response in the lower dose group. Further, the risk for MACE and mortality appears to be higher in the high baseline ESA dose group (MACE HR 1.49 (1.13, 1.97) and mortality (1.45 (1.04, 2.01) for baseline ESA of > 7000 IU/week group vs HR 1.06 (0.86, 1.29) and 1.17 (0.92, 1.48) in the baseline ESA of ≤ 7000 IU/week group).

Further, in both the non-dialysis and dialysis pool a lack of sufficient response of remaining Hb levels below 10 g/dL have been observed to be associated with a possible increased CV and mortality risk, as already presented in previous round based on Hb levels measured prior to the event (MACE for R vs comparator event rates 17.1 vs 6.2 (NDD), 20.6 vs 14.1 (study 0610), 17.8 vs 15.9 (DD Hb correction), 22.5 vs 15.7 (stable DD)). Such results should have clear implications for dose recommendations, as included in the SmPC.

- Hyperkalaemia, exacerbation of hypertension, and baseline Hb level

The applicant has provided subgroup analyses for hyperkalaemia, exacerbation of hypertension and for baseline Hb levels <> 8 g/dL for the correction of Hb study pool and the stable DD study pool. These data do not consistently demonstrate a pattern of increased CV and mortality risk with any of these baseline factors. Unfortunately, no such data have been presented for the NDD pool, where these factors have been integrated in the ICPW analysis model instead.

Finally Fibrogen, Inc. (the development partner for roxadustat in response (to FDA by Fibrogen, Inc., April 6 2021), disclosed that it included post-hoc changes to the stratification factors as applied in the primary cardiovascular safety analyses. It has been formally confirmed that these post-hoc analyses did not substantially differ from the results as presented during the MAA procedure, nor were used in current submission. The correct data have been submitted for completeness and have not impacted the decision making during the MAA procedure.

Other safety aspects

Data according to age category did not identify any clear pattern related to age.

Relevant increases in exposure of statins are observed based on phase I study PK data including 1.9-fold and 1.75 -fold increase in C_{max} and AUC_{inf} for the active metabolite of simvastatin 40 mg, 4.5-fold and 2.9-fold for rosuvastatin 10 mg, and 1.3-fold and 2.0-fold for atorvastatin 40 mg. Despite this increased exposure of statins with roxadustat no clear increased risk of myopathy was observed in both the NDD pool (roxadustat, 0.3% (0.2/100 PY) and placebo, 0.4% (0.3/100 PY)) and the DD pool (0.3% (0.2/100 PY) for roxadustat and 0.1% (0.1/100 PY) for active comparators). Information on the interaction with statins has been included in section 4.5 and 5.2 of the SmPC.

No apparent increase of adverse events **potentially associated with VEGF increase** such as retinal disorders (3.1 vs 2.2% NDD (IR 1.9 vs 1.7); 1.6 vs 1.6% DD) or malignant tumours (2.0 vs 1.9%, IR 1.2 vs 1.4 per 100PY in NDD; 2.5 vs 2.2% DD) were identified

For **liver enzyme evaluation** no apparent differences were observed in ALT > 3 x ULN (2.6% vs 3.0%), and AST > 3 x ULN (2.6% vs 3.5%), while total bilirubin > 2 x ULN was slightly greater for roxadustat (2.4% vs 0.9%; IR 1.4 vs 0.4).

Post marketing data appear to be limited (100 patients in China as of the data cut-off date of 07 Sep 2019) and do not sufficiently contribute to evaluate the safety profile of the product in clinical practice.

2.6.2. Conclusions on the clinical safety

Adverse events, serious AEs and discontinuations due to AEs occurred consistently higher for roxadustat than placebo in the NDD pool and versus ESA therapy in the DD pool. Specific adverse events could be identified based on increased frequency in both pools for roxadustat, including e.g. nausea, deep vein thrombosis, convulsions (seizures), and vascular access thrombosis (VAS).

Further, the CV and mortality risk appear to be at a similar level as for ESA based on data from the correction of Hb study data. Evaluation in other data pools including comparison to placebo and in the stable dialysis pool are associated with methodological and study design issues complicating interpretation. Nevertheless, factors and circumstances can be identified that could increase this risk. These have been included in the product information.

2.7. Risk Management Plan

Safety concerns

Summary of safety concerns

Important identified risks	Thrombotic vascular events
	Seizures
	Sepsis
Important potential risks	Serious infections
Missing information	Data in Pregnant and breastfeeding patients

Pharmacovigilance plan

No additional pharmacovigilance activity.

Risk minimisation measures

Safety concern	Risk minimisation measures
Thrombotic vascular events	Routine risk communication: Special warnings and precautions for use (SmPC section 4.4), and Undesirable effects sections (SmPC section 4.8) Routine risk minimisation activities recommending specific clinical measures to address the risk: Recommendations for haemoglobin monitoring are included in the Special warnings and precautions for use section (SmPC section 4.4).
Seizures	Routine risk communication: Special warnings and precautions for use (SmPC section 4.4); Effects on ability to drive and use machines (SmPC section 4.7) and Undesirable effects sections (SmPC section 4.8). Routine risk minimisation activities recommending specific clinical measures to address the risk: Special warnings and precautions for use (SmPC section 4.4). Use with caution in patients with history of seizures, epilepsy or medical conditions associated with a predisposition to seizure activity such as central nervous system infections.
Sepsis	Routine risk communication: Special warnings and precautions for use (SmPC section 4.4) and Undesirable effects sections (SmPC 4.8). Routine risk minimisation activities recommending specific clinical measures to address the risk: Special warnings and precautions for use (SmPC section 4.4). Recommendation to promptly evaluate for signs and symptoms of sepsis and treat according to standard of care.
Serious infections	Routine risk communication: Special warnings and precautions for use (SmPC section 4.4) Routine risk minimisation activities recommending specific clinical measures to address the risk: Recommendations for monitoring signs and symptoms of infection are included in the Special warnings and precautions for use (SmPC section 4.4).

Safety concern	Risk minimisation measures
Data in pregnant and breastfeeding patients	Risk communication: • Contraindication (SmPC 4.3) • Special warnings and precautions (SmPC section 4.4) • Fertility, pregnancy and lactation (SmPC section 4.6) • Patient leaflet section 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: Women of childbearing potential must use highly effective contraception during treatment and for at least one week after the last dose of roxadustat. If pregnancy occurs while roxadustat is being administered, treatment should be discontinued and switched to alternative treatments (SmPC 4.4 and 4.6). Other routine risk minimisation measures beyond the Product information: None

Conclusion

The CHMP and PRAC considered that the risk management plan version 4.0 is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 17.12.2018. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.9. New Active Substance

The applicant compared the structure of roxadustat with active substances contained in authorised medicinal products in the European Union and declared that it is not a salt, ester, ether, isomer, mixture of isomers, complex or derivative of any of them.

The CHMP, based on the available data, considers roxadustat to be a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.

2.10. Product information

2.10.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.10.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Evrenzo (roxadustat) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Roxadustat is indicated for the treatment of adult patients with symptomatic anaemia associated with chronic kidney disease (CKD).

Anaemia in CKD is caused by insufficient production of erythropoietin or imbalance in oxygen sensing. The prevalence of anaemia increases in frequency and severity in the more advanced stages of CKD. The impaired ability of the body to absorb and use stored iron, the shorter life span of red blood cells (RBCs), the decrease in erythropoietin responses in haematopoietic cells due to inflammation and nutritional deficiency and the blood loss associated with haemodialysis (HD) are contributing factors.

Anaemia contributes to the excess morbidity (risk of hospitalisation, CV risk) and mortality in CKD patients and is associated with symptoms such as fatigue, reduced oxygen use, shortness of breath, increased cardiac output, left ventricular hypertrophy, insomnia, lethargy, headaches, dizziness, lack of concentration and reduced cognitive functioning, reduced libido and reduced immune responsiveness resulting in a reduced quality of life (QoL) and increased healthcare system burden.

3.1.2. Available therapies and unmet medical need

Treatment for anaemia associated with **NDD (non-dialysis) or dialysis-dependent (DD) patients** with CKD includes iron supplementation (oral or iv), treatment with erythropoiesis-stimulating agents (ESA) (sc or iv), and/or RBC transfusions.

Iron supplementation can increase Hb levels to resolve anaemia in patients with CKD, but iron alone is rarely sufficient when CKD disease advances and requires additional treatment to sufficiently raise Hb levels. Oral iron is initially preferred, but responsiveness is variable (variable absorption) and GI effects are common. IV iron use is more potent in the dialysis population (in NDD this is not exactly clear). However, it may be associated with hypotension and dyspnoea and rarely results in potentially life-threatening events of acute hypersensitivity reactions requiring specific precautions upon administration.

Erythropoiesis-stimulating agents (ESAs) have been regarded as the standard of care, depending on the type of patients. Several options include short-acting epoetin (EPO)-alfa or the long-acting darbepoetin alfa (DA). While improvement in QoL has been demonstrated, an increase in the risk of CV adverse events (AEs), all-cause mortality, myocardial infarction (MI), stroke and thromboembolic events is observed when high Hb targets of 13 to 15 g/dL are achieved.

RBC transfusion in CKD patients with anaemia is seen as last resort therapy, mostly effective but can be associated with a risk of allosensitisation, which decreases the availability of obtaining matching

organs for patients eligible for kidney transplantation. Other risks can be introducing pathogens, hyperkalaemia, and volume overload.

3.1.3. Main clinical studies

The clinical package of Evrenzo was primarily supported by eight main clinical studies, of which 4 were performed in non-dialysis dependent patients (NDD) and 4 were performed in dialysis-dependent patients (DD).Three out of 4 studies in NDD patients were randomised, double-blind, placebo-controlled studies to evaluate the efficacy of roxadustat compared to placebo for the treatment (correction) of anaemia in CKD patients not on dialysis. The fourth study was a multicentre, randomised, open-label active-controlled (versus ESA) study to evaluate the efficacy and safety of roxadustat in the treatment (correction) of anaemia in chronic kidney disease patients not on dialysis.

The 4 studies in DD patients were all randomised, open-label active-controlled studies to evaluate the efficacy and safety of roxadustat either in the maintenance treatment of anaemia (conversion of ESA) in CKD patients on stable dialysis, (correction) treatment of anaemia in ID (initiating dialysis) CKD patients compared with active control or both conversion of ESA or correction of anaemia in CKD patients on dialysis.

The primary evaluation was based on evaluation of haemoglobin levels, including responder rates for the correction studies and mean Hb levels for the ESA conversion studies. Several other secondary endpoints were included for sequential testing.

All studies included at least an evaluation period of 52 weeks with extension to 104 weeks or 3 to 4 years for individual cases (versus placebo or active-comparator).The median duration of treatment was substantially longer for the roxadustat groups than placebo groups for the NDD pool (87.1 vs 57.1 weeks), with a less pronounced difference in the NDD (patients censored for dialysis) pool (62.0 vs 51.3 weeks). This was due to fewer patients discontinuing treatment in the roxadustat groups than placebo. For this reason, the safety characteristics expressed in IR per 100 patient-years are more reliable for an unbiased interpretation of the data.

3.2. Favourable effects

NDD pool (non-dialysis dependent pool)

The 3 placebo-controlled studies demonstrated **improvement in haemoglobin levels for roxadustat versus placebo** as demonstrated by achieved Hb response during the first 24 weeks of treatment without rescue medication (80.2% vs 8.7%; OR 40.5% in patients generally representative of a CKD population not on dialysis with anaemia. This effect could be maintained over time during at least 104 weeks of treatment. The effect was consistent across the 3 placebo-controlled studies and consistent with an improvement in mean Hb levels (during week 28 to 36). Mean weekly dose of roxadustat was relatively stable over time (approximately 3.2 mg/kg) during this period. The **correction of haemoglobin levels** was comparable to that obtained with **ESA therapy,** as demonstrated in study 0610. The proportion of patients who achieved Hb response in the first 24 weeks was non-inferior for roxadustat (89.5%) compared to darbepoetin (78.0%) (difference 11.5%; NI margin of -15%) and was maintained during 104 weeks of treatment. Mean Hb levels were also comparable during week 28 to 36.

The need for **rescue therapy** was improved with roxadustat versus placebo as formally tested in all 3 studies (difference in incidence rate per 100 patient-years at risk 0.19;), with the greatest difference in the proportion of patients using RBC transfusions (5.0% vs 13%) and ESA therapy (2.0% vs 14%) and somewhat less for iv iron therapy (2.1% vs 4.8%). As formally tested in study D5740C00001, the need

for RBC transfusion also showed a significantly lower incidence (HR 0.37 (0.30, 0.44)) for roxadustat versus placebo. As also formally tested, the need for **iv iron use** (not defined as rescue therapy in this study) was significantly lower for roxadustat **versus ESA** (HR 0.46 (0.27, 0.80)).

Subgroup data, according to age do not suggest for any difference in effect.

A significant larger reduction in **LDL-C cholesterol** was found with treatment of roxadustat versus placebo (-17.35 vs 2.1%) and ESA therapy (-0.39 mmol/L vs 0.11 mmol/L); during week 12-28 (week 24 in study D5740C00001) from a mean baseline level of 2.56 mmol/L in the placebo-controlled studies and 2.61 mmol/L in the active comparator study.

DD pool (dialysis dependent pool)

A comparable effect on **haemoglobin levels** was observed for roxadustat versus ESA therapy in dialysis patients, as non-inferiority of change from baseline in Hb without the use of rescue therapy up to weeks 28 to 36 as the primary endpoint was demonstrated in 3 ESA conversion studies. All studies excluded the lower bound of the 2-sided 95% CI of > -0.75 g/dL)) of the NI margin. A similar Hb effect was also observed for the primary endpoint of patients who achieved haemoglobin response during the first 24 weeks in correction study FGCL-4592-063 (difference of proportion 3.5 (95%CI -0.7 – 7.7), which was well above the lower bound of the 2-sided 95% CI of > -15%). Comparable results were seen across the studies for these endpoints and the effect was maintained during 104 to 200 weeks of treatment. Mean dose level remained relatively stable between 3.2 and 4.0 mg/kg during this period.

A significant lower mean **IV iron use** (although based on different evaluation periods) was observed in 3 studies (12 (47.6) mg vs 44.8 (88.6) mg and 17.1 (53.4) vs 37.0 (107) mg conversion studies 0613 and 064, respectively; 53.2 (175) vs 87.8 (260) mg correction and Hb maintenance study 002).

Rescue therapy in terms of the **incidence rate of RBC transfusions** was similar (non-inferior) between roxadustat and ESA therapy (HR 0.66 (0.46, 0.97); 0.83 (0.64 – 1.07) for studies 064 and 002, respectively).

A significant larger reduction in **LDL-C cholesterol** was found with the treatment of roxadustat versus ESA (-0.37 to -0.47 mmol/L) from a baseline level of 2.28 to 2.92 mmol/L.

3.3. Uncertainties and limitations about favourable effects

NDD pool (non-dialysis dependent pool)

During the placebo-controlled studies, a large proportion of patients **discontinued treatment**, which was higher for placebo 1115 [59.2%]) than for roxadustat (901 [37.8%]). The reasons for discontinuation were not exactly clear as important discontinuation categories could not be further detailed (patient decision (10.5% vs 20.7%), development of study-specific discontinuation criteria (3.2% vs 13.4%), and withdrawal by the patient (6.0% vs 7.6%)). Further, this could highly impact the primary efficacy evaluation in the advantage of roxadustat. Although, when compared to ESA study treatment discontinuation was slightly larger for roxadustat than ESA ((74 (22.9%) vs 58 (19.8%)) mainly due to unspecified 'withdrawal by the patient' (6.8% vs 5.8%).

The **proportion of patients that achieved too high Hb levels** (*overshooting*) was higher for roxadustat versus placebo ((in study 1517-CL-0608; > 12 g/dL 23.4% vs 3.65%; > 13 g/dL 5.6% vs 0.5%) as well as versus ESA therapy (> 12 g/dL 23.9% vs 20.3%; > 13 g/dL 3.7% vs 2.7%) with an increased proportion of patients in need for a dose hold (12.8% vs 0.8% on dose hold due to Hb > 13 g/dL vs placebo).

The clinical meaning of reduction in **LDL-C cholesterol** is not exactly clear as a counteracting effect on the exploratory endpoint of HDL-C was observed (difference of -4.1 mg/dL (-0.11 mmol/L) (-5.0 - - 3.3), p <0.0001) for roxadustat vs placebo from a mean baseline of 47 mg/dL (1.22 mmol/L) and -0.14 vs -0.005 mmol/L vs ESA) and no improvement in CV benefit has been observed (see safety section).

The effect of roxadustat versus placebo on the improvement of **patient-reported outcomes** has not been clearly demonstrated. Superiority for SF-36 VT (vitality) at week 12 has only been demonstrated in study 001 (HR 0.22 (0.15, 2.3) and not in studies 608 and 060 as part of sequential testing (HR 1.13 (-0.19, 2.4) and 0.44 (-0.1, 0.99)). Further, SF-36 PF (physical function) superiority could not be formally tested in any of the studies. Other exploratory endpoints showed some improvement including FACT-An Total Score (Functional Assessment of Cancer Therapy-Anemia) (mean difference 1.84 (0.56-3.13, p=0.0048)), and EQ-5D-5L VAS Score (EuroQol Questionnaire-5 Dimensions 5 Levels on a visual analogue scale) (mean difference 1.67 (0.73-2.60, p=0.0005)), however, all these endpoints only showed numerical improvement when analysed at week 28. When analysed versus ESA, comparable improvements in SF-36-PF (difference in mean change -1.28 (-2.4 - -0.1) and SF-36-VT (-0.42 (-1.6 - -0.8) were observed.

No superiority in **renal function (eGFR) decline** could be observed for roxadustat versus placebo (difference 2.53 (0.52, 4.6) in study 060), while differences in annual slope estimations were not consistent between studies (0.59, -0.65 and -0.51 ml/min/1.73m^2 for the 3 placebo-controlled studies). Also, discontinuation due to kidney transplant or dialysis initiation was not in favour of roxadustat (24 (1.0%) vs 9 (0.5%) and 23 (1.0%) vs 11 (0.6%), respectively), although data are limited and not formally adjudicated as endpoints. An initial stabilisation in eGFR during the first 12 weeks is observed for roxadustat.

In line with a somewhat lower frequency of iv iron use, an exploratory evaluation showed that **serum iron** initially decreased from baseline to week 8, subsequently increased to above baseline at week 20 and remained relatively stable up to week 52 and was generally higher for roxadustat than for placebo from baseline to week 52 (9.94 [38.47] µg/L vs 1.54 [35.04] µg/L). A decrease in mean ferritin to week 52 was observed (-52.09 [253.43] µg/L vs 14.59 [204.13] µg/L). Any difference in transferrin saturation was not observed (0.05 [14.23]% vs 0.30 [12.70]%). Mean transferrin saturation initially decreased from baseline to week 8, but then increased to baseline levels and remained stable up to week 52. These data may suggest some effect on iron mobilisation with roxadustat. A decrease of hepcidin was also seen up to week 24 (LS mean difference: -25.86 µg/L; 95% CI: -33.09, -18.63; P < 0.0001), which would comply with the proposed mechanism of action, although the exact clinical meaning in terms of iron responsiveness is not clear (Batchelor, JASN, 2020).

Some differences in effect across **subgroups** appear in the placebo-controlled studies, although no p for interaction has been provided. A lower response appears for white and black vs Asian and others, Europe vs the US and others, lower ferritin/TSAT status, baseline CRP > ULN, and higher body weight. However, this was not consistent with subgroup analyses for mean level of Hb response where a lower effect was found for lower ferritin/TSAT level, Hb > 8, and a trend for lower effect with increasing GFR. The effect according to hsCRP level <> ULN was part of the sequential testing in study 060, where the effect according to this subgroup appeared comparable to the overall effect. Based on more limited data from the active-comparator study, no substantial differences in subgroup analyses could be observed.

DD pool (dialysis dependent pool)

All 4 studies comparing the treatment of roxadustat with ESA therapy in dialysis patients were **open-label** which may be subject to bias in particular to endpoints with treatment management decisions

(e.g. rescue therapy, iv iron use) and patient-reported outcomes. Further, ESA conversion study 064 was only performed in the US and maybe less representative for the EU setting.

For the dialysis patients, more patients **discontinued study and treatment** for roxadustat than ESA treatment (28.3% vs 21.7%; 41.2% vs 32.4%, respectively). This was consistent across the studies, except for the Hb correction study 063 (41.2 vs 40.7% treatment discontinuation). Any details for reasons for the patient decision and withdrawal by the patient are missing.

However, the **proportion of patients achieving too high Hb levels** (*overshooting*) was higher for roxadustat versus ESA (> 12 g/dL, 17.1% vs 10.0%; > 13 g/dL, 1.9% vs 0.78% based on study 0613). In line with these observations, more patients needed a dose to be withheld due to Hb >13 mg/dL (23.8% vs 12.8% in patients starting dialysis (ID DD) and 11.7% vs 3.4% in stable dialysis patients (DD pool)).

Regarding the reduction in **LDL-C cholesterol**, a counteracting effect on the exploratory endpoint of HDL-C was observed (difference of -0.10 mmol/L) and no improvement in CV benefit has been observed (see safety section).

No difference (non-inferior) in **patient-reported outcomes** were observed versus ESA therapy as SF-36-PF (physical function) (41.7 (10.1) vs 41.7 (9.9) with LS mean difference 0.21 (0.65 – 1.06)) and SF-36-VT (vitality) (0.96 (7.7) vs 0.15 (7.9) with LS mean difference 0.86 (-0.12 – 1.8)) were non-inferior to ESA therapy in study 0613. Although no substantial differences in other studies were found, these were only exploratory.

For the stable DD subpool (for ID DD subpool this was not measured), exploratory evaluation showed a decrease in mean ferritin to week 52 (-246.24 [332.82] µg/L roxadustat, -165.97 [386.12] µg/L ESA). Any difference in mean transferrin saturation was not observed ((-6.00 [16.88] µg/L roxadustat, -5.72 [15.28] µg/L ESA). A decrease of hepcidin was also seen up to week 24.

Subgroup analyses for the DD pool were presented according to the ID (incident dialysis) DD subpool and the stable dialysis DD subpool. In the IDD subpool, no substantial differences appear across subgroups for the mean change in Hb from week 28 to 52. For the stable DD subpool, roxadustat appears to do slightly better for US vs Europe and others. Further, a lower ferritin/TSAT status showed a lower effect for roxadustat vs ESA for mean Hb levels, which may not be expected if roxadustat would improve iron availability, however, no p for interaction has been provided. For the baseline hsCRP <> ULN, no substantial differences in effect appear. In relation to this, for the sequential testing of the endpoint of change from baseline in Hb to weeks 18 - 24 among patients with baseline hs-CRP > ULN superiority was demonstrated in the 002 study, while NI was demonstrated in the 063 and 064 studies. For the endpoint of proportion of responders, no differences appear in de DD pool, although confidence intervals were wide (no data for the ID DD pool).

3.4. Unfavourable effects

NDD pool

The **exposure to roxadustat** in non-dialysis patients is 2386 patients treated with roxadustat and 1884 with placebo beyond 52 weeks of treatment (> 52 to 104 weeks (37.0% vs 32.3%), > 104 to 156 weeks (26.8% vs 18.9%), and > 156 weeks (7.2% vs 2.2%), although roxadustat patients were treated substantially longer than placebo due to more patients discontinuing treatment in the placebo group (mean 84.6 vs 64.3 weeks).

More adverse events (IR 222 vs 211), drug-related AEs (IR 8.3 vs 6.6), and serious AEs (IR 45.9 vs 43.9), occurred for roxadustat than placebo. The longer treatment duration of roxadustat could not

entirely explain this due to higher discontinuation in the placebo group (incidence rate 222/100 patient-years vs 211/100 PY). Also versus ESA, adverse events (85.8 vs 84.6%), drug-related AEs (21.7 vs 19.8%), serious AEs (52.9 vs 47.8%), drug related serious AEs (5.3% vs 2.0%) occurred consistently higher for roxadustat, although the difference was less outspoken than versus placebo. Discontinuations due to AEs in the roxadustat arm were slightly higher than placebo (6.6 vs 4.9%; IR 3.9 vs 3.8) ESA (5.3 vs 3.1%), although discontinuation due to AEs was relatively limited.

Adverse events of nausea, deep vein thrombosis, convulsions (seizures), vascular access thrombosis (VAS), diarrhoea, nausea, vomiting, hyperkalaemia, hyperbilirubinaemia, headache, cough, peripheral oedema and insomnia are identified as treatment-related AEs. Further, pulmonary embolism (PE) events were limited, but slightly increased for roxadustat vs placebo (10 (0.4%) vs 3 (0.2%); IR 0.2 vs 0.1) and comparable to ESA in the DD pool (13 (0.6%) vs 12 (0.5%); IR 0.3 vs 0.3) and has been included as ADR.

In line with the Hb effects of roxadustat, **haematocrit and erythrocytes** were increased with roxadustat vs placebo (7.27% vs 0.78%; 0.696×10^{12}/L vs 0.078×10^{12}/L) and comparable to ESA therapy 6.01% vs 5.60%; 0.590×10^{12}/L vs 0.628×10^{12}/L).

Hypertension, a known AE associated with ESA therapy, was more observed in the NDD pool (17.9 vs 12.5% NDD; IR 12.1 vs 10.4) and the NDD comparator study (2.8 vs 2.4%; n= 9 vs 7) while being similar versus ESA in the DD pool (19.5 vs 19.4%). However, time to exacerbation of hypertension showed a numerically increased risk with roxadustat versus placebo in studies 608 (13.4 vs 12.1 (HR 1.29 (0.77-1.26)) and 060 (12.3 vs 12.7 (HR 1.16 (0.83-1.62)).

Infection and infestations were more reported for roxadustat in the NDD and DD pool (52.6 vs 42.4%; IR 51.3 vs 47.4 NDD; 49.2 vs 49.4%; IR 29.3 vs 26.1 per 100PY DD pool). Also, more serious and fatal infections and infestations were reported. Compared to placebo, serious AEs of sepsis (2.4 vs 0.4%; IR 1.4 vs 0.3) was most pronounced, but was not increased when compared to ESA in the DD pool (3.4 vs 3.4%)). However, based on sepsis SQM (serious events), serious sepsis incidence was increased (4.6% vs 1.6%; IR 2.8 vs 1.3 NDD pool; IR 7.3% vs 6.7% DD pool). Limited data of comparison to ESA in the NDD revealed a lower frequency for sepsis (0.9 vs 2.7%).

DD pool

The **exposure to roxadustat** for the dialysis-dependent population is 2354 patients treated with roxadustat versus 2360 with ESA (2197 on epoetin-alfa, 163 on darbepoetin) with treatment beyond 52 weeks (> 52 to 104 weeks (29.2% vs 30.1%), > 104 to 156 weeks (23.4% vs 26.9%), and > 156 weeks (12.8% vs 16.3%), although this was slightly shorter for roxadustat than for ESA (mean 87.6 vs 98.7 weeks).

Adverse events of nausea, deep vein thrombosis, convulsions (seizures), vascular access thrombosis (VAS) diarrhoea, nausea, hyperkalaemia, hyperbilirubinaemia, headache, cough, peripheral oedema and insomnia are identified as treatment-related AEs. Most frequently observed **serious adverse events** with a clear higher frequency for roxadustat vs ESA (≥ 1%) were arteriovenous fistula thrombosis (4.9 vs 3.3%) and deep vein thrombosis (1.2 vs 0.3%).

CV and mortality risk estimation

A comparable on-treatment CV and mortality risk estimation (MACE HR 0.79 (0.61, 1.02) and mortality HR 0.78 (0.57, 1.05) for OT-7) has been shown for correction of Hb versus ESA pooled study data (NDD study 1517-CL-0610 and the DD study FGCL-4592-063, 10% of the patients in DD study FGCL-4592-064, 20% of the patients in the DD study D5740C00002).

An increased CV and mortality risk has been observed in patients not demonstrating response to roxadustat treatment (Hb levels < 10 g/dL over time) and for difficult-to-treat patients treated with high doses of ESA (> 7000 IU/week) before converted to roxadustat.

3.5. Uncertainties and limitations about unfavourable effects

NDD pool

Exposure of roxadustat compared to ESA in non-dialysis patients is relatively limited to 525 on roxadustat and 423 on ESA therapy (patient exposure years 383 vs 316).

Evaluation of **CV safety** based on major adverse cardiac events (MACE) assessment and **mortality** have been pre-specified. An a-priori defined inverse probability of censoring weighting (IPCW) on-treatment (OT28; 28 days after treatment discontinuation) method adjusting for informative censoring due to treatment discontinuation was used and showed an on-treatment HR of 1.26 (1.02 - 1.55) for MACE (based on 344 (14.4%) vs 166 (8.8%) events; IR/100 PY 8.7 vs 6.8), mainly attributed to the largest D5740C0001 study (HR 1.26 (1.03 - 1.56)). Whether this method is able to appropriately correct for any residual confounding is uncertain. An ITT approach was set a-priori at time of disclosure of the main studies but before unblinding of the adjudicated MACE events and shows a HR of 1.10 (0.96 – 1.27) for MACE. However, this method is not preferred due to lower sensitivity, because events will be less likely due to the randomised treatment and more likely due to the background event rate and subsequent therapies (especially due to the possibility of introducing ESA therapy after treatment discontinuation), hence adding noise to the treatment comparison, possibly introducing new confounders to the treatment comparison. **Mortality** was also increased with roxadustat vs placebo (10.9% vs 6.5%; IR/100PY 6.4 vs 5.0; HR 1.16 [95% CI: 0.90, 1.51]) during treatment (follow-up to 28 days after treatment) and based on ITT data (400 (16.8%) vs 301 (16.0%); HR: 1.08 [95% CI: 0.93, 1.26] and was primarily increased in the largest study D5740C0001 (on-treatment HR 1.40 (1.02, 1.91)). The increased number of fatal events occurring with roxadustat vs placebo (11.6 vs 5.5%; IR 6.9 vs 5.5) was primarily due to cardiac disorders (2.2 vs 2.0% vs placebo (IR 1.3 vs 1.5) and 3.7 vs 3.1% vs ESA) and infections and infestations (3.0 vs 1.0% (IR 1.8 vs 0.7) and 1.5 vs 2.0% vs ESA).

DD pool

Evaluation of **CV safety** based on major adverse cardiac events (MACE) assessment and **mortality** have been pre-specified in the dialysis patients versus ESA therapy. MACE was increased in the a-priori defined OT-7 on-treatment analysis (7 days after last dose; HR of 1.09 (0.95 – 1.26) (371 (15.8%) vs 398 (16.9%)). The **mortality rate** was also higher for roxadustat than for ESA therapy (IR of 6.7 vs 6.2 per 100PY; HR 1.13 [95% CI: 0.95, 1.34]) during treatment (OT-7; follow-up to 7 days after the last dose), despite a lower total number of deaths for roxadustat (11.2% vs 11.7%), and some heterogeneity across the 4 studies. The increased fatal events occurring with roxadustat vs ESA (15.3 vs 15.2%) were primarily observed for cardiac disorders (5.0 vs 5.2%; IR 3.0 vs 2.7), general disorders and administration site conditions (2.9 vs 2.6%), and infections and infestations (2.8 vs 2.5%). Individual adverse events were too limited to identify any clear differences. Since ESA already has an increased cardiovascular risk compared to placebo, it can be argued that stricter margins than suggested in the Reflection Paper on cardiovascular safety should be set when comparing roxadustat to ESA. The higher MACE risk with roxadustat treatment appears to be driven by the stable DD subpool (HR 1.18 (1.00 – 1.38); 297 (18.6%) vs 301 (18.9%)). This also applies to the mortality risk (HR 1.23 (1.02-1.49)) and is explained by the fluctuations caused by necessary up- or down-titration of the doses of roxadustat study treatment, likely increasing the patient burden and inflicting Hb variability,

which could possibly clarify the differences in increased discontinuation for roxadustat (44.7 vs 32.7%) and CV and mortality outcomes compared to the stable ESA therapy.

Other **adverse events** of arteriovenous fistula thrombosis (9.5 vs 7.5% DD pool) and pyrexia (5.0 vs 4.8% DD pool) have been reported in a higher frequency for the DD pool as known AEs of ESAs; however, any data on this in the NDD pool have not been provided.

3.6. Effects Table

Table 52:Effects table for roxadustat in non-dialysis CKD patients (data cut-off: Aug 2020).

Effect	Short Description	Unit	Roxadustat	Placebo	ESA	Uncertainties/ Strength of evidence	References
Favourable Effects							
Hb response	Proportion of patients who achieved an Hb response during the first 24 weeks	N (%)	1899 (80.2)	163 (8.7)		**SoE:** Consistent across studies Superiority met Supported by mean Hb levels. Lower need for rescue therapy (including RBC transfusion, iv iron use, ESA use) **Unc:** Analysis sufficiently accounting for difference in discontinuation rate? Percentage time > 12 g/dL increased (14.0% vs 2.2%). Proportion with >13 g/dL increased (12.8% vs 0.8%). Patient reported outcome not clearly significantly improved No improvement in renal function decline	0608, 060, 001
			256 (89.5)		213 (78.0)	**SoE:** Supported by mean Hb levels. NI met. Patient reported outcome similar Lower need for iv iron **Unc:** Percentage time > 12 g/dL increased (23.9% vs 20.3%). Percentage time >13 g/dL increased (3.7% vs 2.7%)	0610
LDL-C change	Change from baseline in LDL cholesterol to weeks 12 – 28	mmol/L	-0.54	0.08		**SoE:** Superiority met in all studies **Unc:** HDL- C decreased (-0.14 mmol/L vs PLB). No CV benefit	0608, 060, 001
			-0.39		0.11	**SoE:** Superiority met **Unc:** HDL-C decreased (-0.12 mmol/L vs ESA). No CV benefit	0610
Unfavourable Effects (data displayed are vs placebo)							
Mortality	On-treatment (OT-28)	N (%) IR	260(10.9) 6.4	122(6.5) 5.0		**SoE:** HR 1.16 (95% CI: 0.90, 1.51); Correction of Hb versus ESA based on studies 1517-CL-0610, FGCL-4592-063, and 20% of D5740C00002, with similar baseline characteristics and treatment discontinuation show a comparable CV and mortality risk versus ESA therapy (HR 0.80 (0.59, 1.08) for OT-7 and 0.99 (0.76, 1.30) for OT-28 evaluations).**Unc:** Mainly due to largest D5740C0001 study (HR 1.40 (1.02, 1.91). ITT analysis different outcome - HR 1.08 (0.93, 1.26); 400 (16.8%) vs 301 (16.0%); uncertainty on correction for the large difference in discontinuation rate imposed by patient and study design bias in on-treatment analyses. Introducing noise and new confounding in ITT analyses.	0608, 060, 001
			23(7.1)		20 (6.8)	**Unc**: Data are limited	0610

MACE	Death, MI, stroke On-treatment (OT-28)	N (%) IR	344(14.4) 8.7	166(8.8) 6.8		**SoE:** HR of 1.26 (1.02 -1.55); Correction of Hb versus ESA based on studies 1517-CL-0610, FGCL-4592-063, and 20% of D5740C00002, with similar baseline characteristics and treatment discontinuation show a comparable CV risk versus ESA therapy (HR 0.81 (0.62, 1.05) for OT-7 and 0.93 (0.73, 1.18) for OT-28 evaluations). **Unc:** mainly due to largest D5740C0001 study (HR 1.38 (1.07 - 1.79)) ITT different outcome - HR 1.10 (0.96 – 1.27); 480 (20.1%) vs 350 (18.6%); uncertainty on correction for the large difference in discontinuation rate imposed by patient and study design bias in on-treatment analyses. Introducing noise and new confounding in ITT analyses.	0608, 060, 001
			38(11.8)		41 (14.0)	**Unc:** HR 0.81 (0.52 – 1.25), data are limited	0610
Thrombotic events	deep vein thrombosis	IR %	0.6 1.0	0.2 0.2		**SoE:** Adjudicated DVT/PE OT-28 HR 3.27 (1.29, 8.31)	0608, 060, 001
	vascular access thrombosis	IR %	1.5 2.4	0.3 0.4			0608, 060, 001
	Pulmonary embolism	IR %	0.2 0.4	0.1 0.2		**SoE**: Known AE from ESAs **Unc:** Events are limited. Comparable incidence when compared to ESA	0608, 060, 001
hyperkalemia		IR %	7.0 10.9	5.7 7.1		**SoE:** consistently increased vs placebo for each eGFR category	0608, 060, 001
		%	10.2		9.9		0610
peripheral oedema		IR %	7.6 11.7	6.1 7.6			0608, 060, 001
		%	11.0		10.6		0610

Abbreviations: IR=incidence rate per 100 patient years (PY)
Notes: Overall data as presented have only been formally tested for the primary Hb endpoint. IRs are displayed because of a substantial difference between R and P in treatment discontinuations (38% vs 59%) and study completion (62% vs 41%).

Table 53: Effects table for roxadustat in CKD patients on dialysis (data cut-off: Aug 2020).

Effect	Short Description	Unit	Roxadustat	ESA	Uncertainties/ Strength of evidence	References
Favourable Effects						
Hb response	Change from baseline in Hb to weeks 28-36	g/dL	0.58	0.28	**SOE:** Consistent for each study. Similar patient reported outcome (only study 0613). Similar need for rescue therapy (RBC transfusion). Lower need for iv iron **Unc:** Percentage time > 12 g/dL increased (17.1% vs 10.0%) (study 0613). Percentage time > 13 g/dL increased (1.86% vs 0.78%) (study 0613)	0613, 064, 002 *Data presented are for the stable dialysis pool*
	Proportion of patients who achieved an Hb response during the first 24 weeks	N (%)	88.2	84.4	**SoE:** NI met. Similar findings for the other studies	063
LDL-C change	Change from baseline in LDL cholesterol *Data presented is change to end of study*	mmol /L	-0.22	-0.19	**SoE:** Superiority met in all studies – Difference was -0.36 to -0.47 mmol/L in week 12-28 **Unc:** No CV benefit	0613, 064, 063, 002
Unfavourable Effects						
Mortality	On-treatment (OT-7)	N (%) IR	264(11.2) 6.7	277(11.7) 6.2	**SoE:** HR 1.13 (95% CI: 0.95, 1.34); Correction of Hb versus ESA based on studies 1517-CL-0610, FGCL-4592-063, and 20% of D5740C00002, with similar baseline characteristics and treatment discontinuation show a comparable CV and mortality risk versus ESA therapy (HR 0.80 (0.59, 1.08) for OT-7 and 0.99 (0.76, 1.30) for OT-28 evaluations). **Unc:** The higher mortality risk with roxadustat treatment appears to be driven by the stable DD subpool (HR 1.23 (1.02-1.49))	0613, 064, 063, 002
MACE	Death, MI, stroke On-treatment (OT-7)	N (%) IR	371(15.8) 9.4	398(16.9) 8.9	**SoE**: HR of 1.09 (0.95 – 1.26); Correction of Hb versus ESA based on studies 1517-CL-0610, FGCL-4592-063, and 20% of D5740C00002, with similar baseline characteristics and treatment discontinuation show a comparable CV risk versus ESA therapy (HR 0.81 (0.62, 1.05) for OT-7 and 0.93 (0.73, 1.18) for OT-28 evaluations). **Unc:** The higher MACE risk with roxadustat treatment appears to be driven by the stable DD subpool (HR 1.18 (1.00 – 1.38); 297 (18.6%) vs 301 (18.9%)	
Thrombotic events	Deep vein thrombosis	%	1.3	0.3	**SoE:** Adjudicated DVT/PE OT-7 HR 2.40 (1.35, 4.26). Also increased vs placebo	

Effect	Short Description	Unit	Roxadustat	ESA	Uncertainties/ Strength of evidence	References
	Vascular access thrombosis	%	12.8	10.2	**SoE:** Adjudicated OT-7 HR 1.41 (1.19, 1.68). Also increased vs placebo	
	Pulmonary embolism	%	0.6	0.5	**SoE:** Known AE from ESAs. Also increased vs placebo **Unc:** Events are limited	
hyperkale mia		%	6.5	6.4	**SoE**: IR 3.9 vs 3.4. Also increased vs placebo	

Abbreviations: IR=incidence rate per 100 patient years (PY)
Notes: Overall data as presented have only been formally tested

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Correction and maintaining appropriate haemoglobin levels are considered of clinical relevance as this is generally associated with improvement of quality of life due to alleviation of symptoms such as fatigue, shortness of breath, insomnia, lethargy, headaches, dizziness, lack of concentration/ cognitive functioning, amongst others. Further, Hb correction is believed to result in improvement of CV morbidity and overall mortality eventually. Furthermore, the use of RBC transfusion may be prevented.

In non-dialysis patients, anaemia severity increases with more advanced kidney disease but is generally less dysregulated than in dialysis patients. Managing correction of anaemia is very individualised in these patients, but iron use may be sufficient in a relevant proportion of patients and excludes ESA therapy's general need. In this context, roxadustat demonstrates a clear improvement in Hb correction versus placebo. One would expect that this would be accompanied by a clear improvement in quality of life (QoL) indicators; however, no clear significant improvement in SF-36 assessment could be formally demonstrated versus placebo (although numerical improvements were observed). Due to the clear effect on correction of Hb levels obtained with roxadustat vs placebo, patients were less in need for rescue therapy than placebo as demonstrated by the need for blood transfusion and IV iron use/or ESA therapy. Any effect on the delay of renal function decline could not be shown, but this may be associated with too limited evaluation period to establish any differences on this endpoint. A comparable impact on Hb was seen in the study versus ESA therapy, with a comparable improvement in QoL, although data are limited compared to the data generated for comparison to placebo.

In dialysis patients, ESA therapy is part of standard therapy in a relevant proportion of patients. Roxadustat has shown a comparable effect on Hb correction and maintenance versus ESA therapy. This was associated with comparable effects on QoL indicators, although formally assessed in one study only and based on an open-label design, thus limiting drawing firm conclusions. A potential advantage over ESA therapy could be that some effect of iron mobilisation appears present with roxadustat, as patients were less in need for iv iron use for roxadustat compared to ESA. To a certain extent, this could lower the risk of rare potentially life-threatening severe allergic reactions associated with iv iron use. Although, an appropriate iron status may still be needed for roxadustat to prevent hyporesponsiveness (as known with ESAs with inappropriate iron levels), as a diminished efficacy has been observed in patients with an inappropriate iron status too.

Although the current studies were not specifically designed and powered to evaluate a potential improvement in morbidity and mortality, these aspects have been addressed in terms of safety, in particular as it is known from ESA therapy that too high levels of haemoglobin levels are associated with increased risk for mortality and cardiovascular events.

In the **non-dialysis patients**, an increased risk has been observed for **major adverse cardiac events (MACE)**, and an increased risk appears for **mortality** for roxadustat versus placebo, which compromises/outbalances the observed beneficial hematological effects compared to placebo. However, interpretation of these findings is complicated due to possible patient and study design bias with large difference in discontinuation as a result, for which it is not clear whether applied analysis appropriate correct for or display sufficiently sensitivity to observe the correct roxadustat induced signal. Best available data are those as provided by the haemoglobin correction studies which randomised roxadustat versus ESA both in non-dialysis and dialysis patients, and display similar randomised baseline characteristics and study discontinuation. Overall, these show a comparable MACE

and mortality risk for roxadustat versus ESA therapy. Based on this certainty, it is proposed that treatment with roxadustat should be restricted to those patients that would normally qualify for ESA therapy.

In **dialysis patients** compared to ESA therapy, the observed increase in MACE and mortality risk is driven by the conversion to ESA studies, and can likely explained by dysregulation of ESA stabilised patients with randomisation to roxadustat, likely causing undesirable variability in haemoglobin levels which possibly triggers clinical issues including increased MACE and mortality risk. This increased risk as particularly seen in those difficult-to-treat patients who need high ESA dose may support this hypothesis. Further, non-responsiveness appears a factor likely associated with increased CV and mortality risk. Consequently, such circumstances should appropriately be accounted for in the labelling. Further, overshooting (too high levels of Hb) appears not to be an obvious factor to clarify this possible risk. Notably, any morbidity and mortality effect for the small reduction in LDL-C cholesterol with roxadustat treatment (although associated with a small decrease in HDL-C, which is generally considered disadvantages) could not be observed both compared to placebo and ESA therapy.

Further, an increased tendency of (venous) **thrombosis** appears to be associated with roxadustat treatment based on an increased incidence for adverse events of deep venous thrombosis, vascular access thrombosis and likely increased pulmonary embolism (PE) risk, although events are somewhat limited. This is most pronounced in the non-dialysis patients compared to placebo but also observed for dialysis patients compared to ESA therapy.

Three times a week of **oral administration** of roxadustat provides a benefit and convenience over iv or sc use of ESA therapy, especially for the non-dialysis and peritoneal dialysis patients without standard (arterio-venous) access, although an increased number of gastro-intestinal events was observed with oral administration of roxadustat both when compared to placebo and ESA therapy. Nevertheless, this seems not importantly result in tolerability issues as discontinuation due to AEs was generally limited.

In addition to these safety issues, some **other** typical **adverse events** observed with ESA could also be identified for roxadustat, although not yet all included in the SmPC, which request further explanation (e.g. hyperkalemia, hypertension exacerbation). Further, any increased risk for infections could not be clearly associated with roxadustat treatment likely also due to increased background risk in this type of patients. Further, an increase of statin exposure has been observed with concomitant use of roxadustat, although any effect on typical statin-associated adverse effects of myopathy could not be identified. These issues have currently been addressed in the labelling. Further, any effect on tumour promotion (as potentially observed with ESAs) could potentially be likely for roxadustat as well. However, extensive non-clinical data do not suggest such an effect, while any imbalance on tumour adverse effects during the main clinical studies has not been observed.

3.7.2. Balance of benefits and risks

Correction and maintenance of appropriate haemoglobin levels with (convenient) oral roxadustat have shown to be better versus standard of care in non-dialysis patients and comparable to what can be achieved with sc or iv ESA in non-dialysis and dialysis patients. This is of clinical relevance. Most notably, this resulted in a comparable improvement in the quality of life when compared to ESA therapy; however, an improvement in QoL appears somewhat unclear when compared to placebo in non-dialysis patients. However, this laboratory and (likely) symptomatic improvement accompanied by some suggestion of improved iron mobilisation with roxadustat in anaemic CKD patients does only outweigh the possible safety risk for those patients for whom the CV and mortality risk is sufficiently understood; meaning those patients that would normally qualify for ESA therapy as the risk could be estimated with sufficient confidence and the benefit of ESA therapy outweighs the potential risk.

Accordingly, this should have clear restriction implications for the indication of non-dialysis patients with CKD associated anaemia. Further, several contributing factors have been identified that may impose this risk, including non-responsiveness and converting stable ESA treated dialysis patients; especially those who are already difficult to treat.

3.7.3. Additional considerations on the benefit-risk balance

3.8. Conclusions

The overall B/R of roxadustat is positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Evrenzo is favourable in the following indication:

Evrenzo is indicated for treatment of adult patients with symptomatic anaemia associated with chronic kidney disease (CKD).

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or

as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that roxadustat is a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.