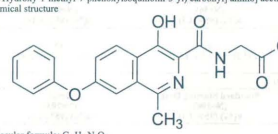
Evrenzo Capsules Package Insert

SP04011 01

Please read this leaflet carefully and use as directed by your physician.

[Drug Names]
Generic Name: Roxadustat Capsules
Brand Name: Evrenzo®, 愛瑞唯®™
English Name: Evrenzo® Capsules
[Composition (Ingredients)]
Active ingredient: roxadustat
Roxadustat Capsules 20mg: Each capsule contains 20mg of roxadustat
Roxadustat Capsules 50mg: Each capsule contains 50mg of roxadustat
Chemical name:
[[(4-Hydroxy-1-methyl-7-phenoxyisoquinolin-3-yl) carbonyl] amino] acetic acid
Chemical structure



Molecular formula: $C_{19}H_{16}N_2O_5$
Molecular weight: 352.34
Excipients:
Capsule contents: Lactose Monohydrate, Microcrystalline Cellulose, Povidone K30, Croscarmellose Sodium, Magnesium Stearate
Capsule shell (20mg): Gelatin, Iron Oxide Yellow, Titanium Dioxide
Capsule shell (50mg): Gelatin, Allura Red AC, Iron Oxide Yellow, Titanium Dioxide
Edible printing ink: Shellac, Ethanol, Isopropanol, Butyl Alcohol, Propylene Glycol, Ammonia Solution, Iron Oxide Black, Potassium Hydroxide
[Description]
Roxadustat Capsules 20 mg: Capsules with opaque yellow cap and body, with "FG20" printed in black on the cap, containing white to yellow powder or granules.
Roxadustat Capsules 50 mg: Capsules with opaque red cap and body, with "FG50" printed in black on the cap, containing white to yellow powder or granules.
[Indications]
The product is indicated for patients with anemia caused by chronic kidney disease (CKD), including dialysis-dependent (DD) and non-dialysis-dependent (NDD) patients.
[Strengths]
(1) 20 mg; (2) 50 mg
[Dosage and Administration]
The treatment with this product must be initiated under the supervision of healthcare professionals.
Recommended dose
The starting dose should be selected based on body weight: 70 mg (45 to < 60 kg) or 100 mg (≥ 60 kg) for dialysis-dependent (DD) chronic kidney disease (CKD) patients with anemia; 50 mg (40 to < 60 kg) or 70 mg (≥ 60 kg) for non-dialysis-dependent (NDD) CKD patients with anemia, administered orally three times per week (TIW). Physicians may adopt an individualized dosing regimen based on patients' specific clinical condition. For example, for stage 5 CKD patients with anemia not on dialysis, the starting dose may be increased to 70 mg (40 to <60 kg) or 100 mg (≥60 kg), administered orally three times per week. The product must not be taken on consecutive days.
Roxadustat treatment should not be continued beyond 24 weeks of therapy if a clinically meaningful increase in hemoglobin (Hb) levels is not achieved. Alternative explanations for an inadequate response should be sought and treated before re-starting roxadustat.
Patients currently treated with erythropoietin with stable hemoglobin levels within the target range may experience fluctuations in Hb levels after converting to roxadustat. Conversion should only be considered based on benefit-risk assessment when there is a valid clinical reason.
Conversion of non-dialysis patients otherwise stable on erythropoiesis-stimulating agent (ESA) treatment has not been investigated. A decision to treat these patients with roxadustat should be based on a benefit-risk consideration for the individual patient.
Research indicates that intake of food will not significantly affect the exposure of roxadustat, therefore the drug can be taken on an empty stomach or with food. For patients undergoing hemodialysis or peritoneal dialysis, roxadustat can be taken at any time before or after dialysis.
If you miss a dose, skip the missed dose and take your next dose at your regularly scheduled time.
Dose Adjustment
The symptoms and outcomes of anemia vary with age, gender, and the overall burden of the disease, assessment should be made in combination with patients' specific clinical condition for physicians. During the initial treatment period, it is recommended to monitor the hemoglobin (Hb) levels every 2 weeks until stabilized, and every 4 weeks thereafter. Roxadustat dose should be adjusted based on Hb levels to achieve and maintain an Hb level of 100 to 120 g/L, while minimizing the need for blood transfusion. The dose can be adjusted every 4 weeks, by taking into account both the current Hb level and the change in Hb level over the past 4 weeks. The recommended dose adjustment rules are shown in Table 1.

Table 1: Roxadustat Dose Adjustment Rules

Change in Hb level over Previous 4 Weeks (g/L)	Hb Level at the Time of Dose Adjustment (g/L)			
	<105	105 to <120	120 to <130	≥130
<-10	↑	↑	No change	Withhold dosing, monitor Hb [level] and resume dosing when Hb level is <120 g/L, at a dose that is reduced by one step.
-10 to 10	↑	No change	↓	
>10	No change	↓	↓	
The dose steps are as follows: 20, 40, 50, 70, 100, 120, 150, and 200 mg. For example, a dose increases at a dose of 70 mg results in 100 mg as the new dose. A dose reduction at a dose of 150 mg results in 120 mg as the new dose.				

Abbreviations: ↑ = dose increase; ↓ = dose reduction
Notes:
Dose Increases and Reductions:
- Dose increases (↑) and reductions (↓) are made according to pre-set dose steps.
- The recommended maximum dose is 2.5 mg/kg.

Dose Adjustment for Rapid Hb Level Increase:
- If Hb level increases by >20 g/L within 2 weeks in a patient whose Hb value is >90 g/L, the dose should be reduced by one step.
- In the event of rapid Hb level increase, it is recommended to reduce the dose only once within a 4-week period.

Special Populations
Geriatric Patients: No starting dose adjustment is necessary for patients aged 65 and above.
Pediatric Patients: The safety and efficacy of roxadustat in pediatric patients under 18 years of age have not been established.
Patients with hepatic impairment: No adjustment of the starting dose level is required in patients with mild hepatic impairment (Child-Pugh Class A). The safety and efficacy of roxadustat have not been studied in patients with moderate or severe hepatic impairment (Child-Pugh Class B or C). It is recommended to closely monitor the hepatic function in these patients and reduce the starting dose.
[Adverse Reactions]
Adverse Reactions from Clinical Trials
This Package Insert summarizes the adverse reactions potentially associated with roxadustat observed in clinical trials and their approximate incidence rates. Because clinical trials are conducted under a wide variety of conditions, the incidence rates of adverse reactions observed in a drug clinical trial cannot be directly compared to those observed in another drug clinical trial and may not reflect the actual incidence rates observed in clinical practice.
Summary of Safety Data
In China, safety data were obtained from two Phase 2 clinical trials and two Phase 3 clinical trials: including one Phase 2 study FGCL-4592-047 (N=91) involving NDD CKD patients with anemia, one Phase 2 study FGCL-4592-048 (N=96) involving DD CKD patient with anemia, one Phase 3 study FGCL-4592-808 (N=154) involving NDD CKD patients with anemia, and one Phase 3 study FGCL-4592-806 (N=305) involving DD CKD patients with anemia. In these clinical trials, a total of 554 subjects were treated with roxadustat, 229 subjects received the drug for >6 months and 102 subjects for ≥1 year. The dose ranged from 1.2-2.5 mg/kg (50-180 mg) TIW in the Phase 2 studies and from 1.2-2.5 mg/kg (20-200 mg) TIW in the Phase 3 studies.
In the global development program of roxadustat, including studies conducted in China, a total of 947 healthy subjects and 12,386 chronic kidney disease patients with anemia were received the study drug. Among the healthy subjects, 863 received roxadustat and 84 received placebo; among the CKD patients with anemia, there were 5,994 NDD patients with anemia and 6,392 DD patients with anemia. Of these, 7,227 patients received roxadustat, while the remaining 5,159 patients received either active comparators (i.e., epoetin alfa, darbepoetin) or placebo.
Adverse Reactions in the Clinical Trials in China
DD CKD patients with anemia
FGCL-4592-806 was a randomized, open-label, active-controlled (epoetin alfa) Phase 3 study evaluating the efficacy and safety of roxadustat for treatment of anemia in patients with dialysis-dependent CKD. Patients were randomized in a 2:1 ratio to receive treatment with either oral roxadustat or epoetin alfa. The study included a 26-week initial treatment period followed by a 26-week extension treatment period (for subjects randomized to the roxadustat group only). Table 2 lists the adverse reactions reported during the 26-week initial treatment period of FGCL-4592-806 with an incidence rate of ≥1% and severity grade of ≥3 (adverse events are coded by MedDRA 19.1 and listed by System Organ Class and Preferred Term). The incidence rate of adverse events related to roxadustat was relatively low (<5%), with most events being of Grades 1-2. These adverse events were consistent with the known complications in CKD patients.

Table 2. Adverse Reactions[a] with the reported incidence rates of ≥1% and Severity Grade of ≥3 during the 26-week Initial Treatment Period of Study FGCL-4592-806

System Organ Class Preferred Term	Roxadustat N=204 N	 %	Epoetin alfa N=100 N	 %
Eye Disorders				
Eyelid Edema	2	1.0%	0	0.0%
Gastrointestinal Disorders				
Abdominal Discomfort	2	1.0%	0	0.0%
Abdominal Distension	2	1.0%	0	0.0%
Dyspepsia	2	1.0%	0	0.0%
Flatulence	2	1.0%	0	0.0%
Gastroesophageal Reflux Disease	2	1.0%	0	0.0%
Nausea	6	2.9%	0	0.0%
Vomiting	4	2.0%	0	0.0%
General Disorders and Administration Site Conditions				
Asthenia	7	3.4%	0	0.0%
Chest Discomfort	2	1.0%	0	0.0%
Immune System Disorders				
Hypersensitivity [b]	1	0.5%	0	0.0%
Infections and Infestations				
Lung Infection [b]	1	0.5%	0	0.0%
Upper Respiratory Tract Infection	2	1.0%	0	0.0%
Investigations				
ALT/AST Increased [c]	2	1.0%	1	1.0%
Blood Glucose Increased	2	1.0%	1	1.0%
Metabolism and Nutrition Disorders				
Decreased Appetite	2	1.0%	0	0.0%
Nervous System Disorders				
Dizziness	3	1.5%	0	0.0%
Respiratory, Thoracic and Mediastinal Disorders				
Hiccups	2	1.0%	0	0.0%
Vascular Disorders				
Hypertension [d]	9	4.4%	7	7.0%

a: An adverse reaction is defined as an adverse event (AE) that is considered to be related or possibly related to study drug by the investigator and the sponsor.
b: Adverse reactions with an incidence rate of <1% and a severity grade of ≥3 (according to CTCAE).
c: ALT/AST with transient elevations.
d: Study sites had different criteria to report hypertension AE. According to the analysis of blood pressure change from the baseline, the mean blood pressure (Mean Arterial Pressure, MAP) did not increase in roxadustat group, also there was no increase in antihypertensive medication use. The causal relationship between the adverse reaction hypertension and roxadustat is unclear.

Of the 111 subjects participated in the extension treatment period (Weeks 27-52) of Study FGCL-4592-806, there were 4 cases of hypertension (3.6%) with adverse reaction incidence rates of≥1%, which were similar to those observed during the 26-week initial treatment period.
NDD CKD patients with anemia
FGCL-4592-808 was a randomized, multicenter, double-blind, placebo-controlled study conducted in the NDD CKD patient with anemia. Patients were randomized in a 2:1 ratio to receive either roxadustat or placebo treatment. The study included a 26-week initial treatment period followed by a 26-week extension treatment period. The initial treatment period comprised an 8-week double-blind treatment period followed by an 18-week open-label treatment period. Table 3 lists all adverse reactions with the reported incidence rates of ≥1% (adverse events are coded by MedDRA 19.1 and listed by System Organ Class and Preferred Term) during the double-blind, placebo-controlled 8-week treatment period of Study FGCL-4592-808.

Table 3. Adverse Reactions[a] with the Reported Incidence Rates being ≥1% during the 8-week Double-Blind Treatment Period of Study FGCL-4592-808

System Organ Class Preferred Term	Roxadustat N=101 N	 %	Placebo N=51 N	 %
Gastrointestinal Disorders				
Nausea	3	3.0%	1	2.0%
Abdominal Pain	1	1.0%	0	0.0%
Gastrointestinal Hemorrhage	1	1.0%	0	0.0%
Gastroesophageal Reflux Disease	1	1.0%	0	0.0%
General Disorders and Administration Site Conditions				
Oedema Peripheral	2	2.0%	1	2.0%
Chest Discomfort	1	1.0%	0	0.0%
Investigations				
ALT/AST Increased [b]	1	1.0%	1	2.0%
Metabolism and Nutrition Disorders				
Decreased Appetite	2	2.0%	0	0.0%
Musculoskeletal and Connective Tissue Disorders				
Muscle Fatigue	2	2.0%	0	0.0%
Myalgia	2	2.0%	0	0.0%
Arthralgia	1	1.0%	0	0.0%
Skin and Subcutaneous Tissue Disorders				
Rash	2	2.0%	0	0.0%
Drug Eruption	1	1.0%	0	0.0%
Vascular Disorders				
Hypertension	1	1.0%	0	0.0%

a: An adverse reaction is defined as an adverse event that is considered to be related or possibly related to study drug by the investigator and the sponsor.
b: Transient ALT/AST elevations in the Roxadustat group
A total of 131 patients (roxadustat group: N=87, placebo group: N=44) entered the open-label initial treatment period to receive roxadustat treatment. During the Week 9-27 initial treatment period of Study FGCL-4592-808, adverse reactions with the reported incidence rate of ≥1% included 4 (3.1%) cases of ALT elevation and 2 (1.6%) cases of AST elevation. Adverse reactions with a reported incidence rate of <1% but with severity of≥3 included cold sweat, hypertension, cerebellar infarction, and blood pressure increased, with each occurring in 1 (0.8%) case. The adverse reactions reported during the 52-week extension treatment period of the study were similar to those observed in the initial treatment period.
Cardiovascular Adverse Events in Completed Trials in China
Erythropoiesis stimulating agents (ESAs) have been reported to potentially increase the risk of cardiovascular events in CKD patients. This section describes cardiovascular adverse events observed in roxadustat clinical trials. The cardiovascular adverse events include myocardial infarction, cardiac failure, cerebrovascular accidents, thrombosis, and severe hypertension, as reported in the study.
Two randomized clinical trials have been conducted with subjects on dialysis. In the Phase 2 Study FGCL-4592-048, 74 subjects received roxadustat treatment; in the Phase 3 Study FGCL-4592-806, 204 subjects received 6 months of initial treatment with roxadustat, with 111 of these subjects continuing treatment for up to 1 year. Two randomized clinical trials have been conducted with subjects not on dialysis. In the Phase 2 Study FGCL-4592-047, 61 subjects received roxadustat treatment, and in the Phase 3 Study FGCL-4592-808, 128 subjects received 6 months of roxadustat treatment. The incidence rates of cardiovascular events in these clinical trials are listed in Table 4.

Table 4. Incident Rates of Cardiovascular Events in Roxadustat-Treated Subjects in China (Phase 2 and 3 Studies)

CV Events	DD CKD Subjects	NDD CKD Subjects
Cardiac Failure	1.5%	2.5%
Myocardial Infarction	0.4%	0.0%
Thrombosis	4.2%	1.2%
Hypertension (severe)	0.4%	1.6%

Adverse Reactions from Global Pivotal Phase 3 Clinical Trials and Post-marketing Experience
In the roxadustat global CKD Anemia development program, a total of 6 pivotal Phase 3 studies have been completed, including 3 studies comparing roxadustat with placebo in NDD CKD patients with anemia (FGCL-4592-060/ANDES, 1517-CL-0608/ALPS, and D5740C00001/OLYMPUS) and 3 studies comparing roxadustat with epoetin alfa in DD CKD patients with anemia (FGCL-4592-063/HIMALAYAS, FGCL-4592-064/SIERRAS, D5740C00002/ROCKIES). These 6 Phase 3 clinical trials included 8150 patients with CKD, of whom 4326 received roxadustat (7185.9 patient exposure years, PEY), 1940 received epoetin alfa (3743.6 PEY), and 1884 received placebo (2323.2 PEY).
DD CKD patients with anemia
Adverse reactions were determined based on pooled data from 3 randomized open-label active-controlled studies (FGCL-4592-063, FGCL-4592-064, D5740C00002), involving 3880 patients. Of these, 1940 patients were treated with roxadustat and 1940 patients were treated with epoetin alfa. The mean duration of exposure for patients receiving roxadustat was 1.71 years, with 63% of patients exposed for > 1 year and 43% of patients exposed for > 2 years. For patients receiving epoetin alfa, the mean duration of exposure was 1.93 years, with 71% of patients exposed for > 1 year and 52% of patients exposed for > 2 years.
In a subgroup analysis of 1526 DD patients who started dialysis within 4 months before receiving their first dose of either roxadustat (N=760) or epoetin alfa (N=766) (incident dialysis [ID] patients), the mean duration of exposure to roxadustat was 1.45 years, with 51% of patients exposed for more than 1 year and 30% of patients exposed for more than 2 years. The mean duration of exposure to epoetin alfa was 1.55 years, with 54% of patients exposed for > 1 year and 34% of patients exposed for > 2 years. The incidence of adverse reactions reported in this subgroup was consistent with that observed in the overall DD patients.
NDD CKD patients with anemia
Adverse reactions were determined based on pooled data from 3 randomized double-blind placebo-controlled studies (FGCL-4592-060, 1517-CL-0608, D5740C00001), including 4270 patients. Among these, 2386 patients were treated with roxadustat and 1884 patients were treated with placebo. The mean duration of exposure for patients receiving roxadustat was 1.62 years, with 71% of patients exposed for > 1 year and 34% of patients exposed for > 2 years. For the placebo group, the mean duration of exposure was 1.23 years, with 53% of patients exposed for > 1 year and 21% of patients exposed for > 2 years.
Adverse Reactions
Adverse Drug Reactions are listed by MedDRA System Organ Class (SOC) and frequency, as detailed in Table 5. Frequency categories are defined as follows: Very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000), and not known (cannot be estimated from the available data).

Table 5. Adverse Reactions

System Organ Class (SOC)	Frequency	Adverse Reaction
Infections and infestations	Common	Sepsis
Endocrine disorders	Not known	Secondary hypothyroidism
Nervous system disorders	Common	Seizures
Vascular disorders	Very common	Hypertension, vascular access thrombosis (VAT)[1]
	Common	Deep vein thrombosis (DVT)
Gastrointestinal disorders	Very common	Nausea, diarrhea
	Common	Constipation
Skin and subcutaneous tissue disorders	Not known	Dermatitis Exfoliative Generalized (DEG)

[1] This adverse reaction is associated with CKD patients who were on dialysis while receiving roxadustat.
Description of Selected Adverse Reactions
Skin Reactions
Dermatitis exfoliative generalized, part of severe cutaneous adverse reactions (SCARs), has been reported during post-marketing surveillance and has shown an association with roxadustat treatment (frequency not known).
[Contraindications]
The use of roxadustat is contraindicated in the following patients:
- Women who are pregnant or breastfeeding
- Patients with known hypersensitivity to the active substance or any of the excipients.

[Precautions]
1. **Hemoglobin level monitoring:** In CKD patients, hemoglobin levels should not exceed the upper limit of the target value recommended for use. Excessively high hemoglobin levels and a rapid increase in hemoglobin may increase the risks of deep vein thrombosis and vascular access thrombosis. During the treatment with this product, the dose of roxadustat should be adjusted based on the Hb level to maintain the Hb level within the range of 100-120 g/L. After starting treatment or adjusting the dose, monitor the Hb level every 2 weeks until it reaches and stabilizes within the target range, after which monitoring can be done every 4 weeks. If the Hb level increases by more than 20 g/L within 4 weeks, necessary actions should be taken, such as reducing the dose or suspending the treatment (see "Dose Adjustment" section in [Dosage and Administration] for details).
2. **Blood pressure monitoring:** Hypertension was observed as an adverse event in clinical trials, though these may be influenced by factors such as underlying disease and dialysis, and the relationship to the drug is not yet clear. The possibility of blood pressure increases during roxadustat treatment for anemia cannot be ruled out. Therefore, blood pressure should be monitored before starting, at the start, and during treatment with roxadustat. Patients with poorly controlled hypertension were excluded from clinical trials, so those with uncontrolled hypertension should use this product with caution.
3. **Patients with moderate to severe hepatic impairment:** The efficacy and safety of this product have not been established in patients with moderate and severe hepatic impairment (Child Pugh Class B and C). For these patients, treatment should only be initiated after a thorough assessment of the patient's risk-benefit. Patients should be closely monitored during dose adjustments, and the starting dose of roxadustat should be appropriately reduced (see "Dose Adjustment" in [Dosage and Administration] for details).
4. **Serious infection:** Serious infections, including fatal ones, have been reported in both DD and NDD CKD patients with anemia treated with roxadustat. The causal relationship between roxadustat and serious infections has not been established. In the study of DD CKD patients with anemia, the incidence of serious infections was similar in patients treated with roxadustat compared to those treated with epoetin alfa (24.4% and 14.3/100 PY with roxadustat versus 24.6% and 12.8/100 PY with epoetin alfa); the most commonly reported serious infections were pneumonia, sepsis, and peritonitis. In the study of NDD CKD patient with anemia, serious infections occurred more frequently but at similar exposure-adjusted rates in patients treated with roxadustat (18.9%, 12.4 patients with events per 100 patient years of exposure [PY]) compared to placebo (12.9%, 10.6 patients with events per 100 PY), with the most common serious infections being pneumonia, sepsis, and urinary tract infection. In DD patients, the incidence of fatal infections was similar between treatment groups (2.4%, 1.4/100 PY with roxadustat versus 2.4%, 1.2/100 PY with epoetin alfa). However, there was a numerical imbalance in the subgroup of patients who started roxadustat within 4 months of beginning dialysis (2.5%, 1.7/100 PY with roxadustat versus 1.4%, 0.9/100 PY with epoetin alfa). In NDD studies, the incidence of fatal infections was higher in the roxadustat group (3.6%, 0.7/100 PY) compared to the placebo group (2.1%, 1.2/100 PY). Fatal infections were most pronounced in severe NDD CKD patients with anemia (e.g. eGFR <10 mL/min/1.73m^2) who were just started roxadustat treatment and in NDD CKD patients with anemia who started dialysis while on roxadustat. Risk-benefit profile should be assessed carefully before starting roxadustat treatment in patients with active severe or serious infections. It is recommended to monitor patients for symptoms and signs of infection during treatment with roxadustat and advise them to contact their doctors if signs or symptoms of infection appear. Suspected infections should be promptly assessed and treated.
5. **Sepsis:** Sepsis was one of the most commonly reported serious infections and included fatal events. Patients with signs and symptoms of sepsis (e.g., an infection that spreads throughout the body with low blood pressure and the potential for organ failure) should be promptly evaluated and treated according to standard of care.
6. **Deep Vein Thrombosis:** In clinical trials involving DD and NDD CKD patients with anemia, those treated with roxadustat had a higher incidence of deep vein thrombosis (DVT) compared to patients receiving placebo or epoetin alfa. Treatment with roxadustat should be considered after a thorough assessment of the patient's risk-benefit profile. Patients should be advised to contact their doctors if they experience signs or symptoms of DVT. DVT should be promptly assessed and treated.
7. **Vascular Access Thrombosis:** In clinical trials involving DD and NDD CKD patients with anemia, those treated with roxadustat had an increased incidence of vascular access thrombosis (VAT) compared to those receiving placebo or epoetin alfa. In studies involving DD CKD patients with anemia, the highest incidence of VAT in roxadustat-treated patients occurred within the first 12 weeks of treatment and when hemoglobin levels increased by more than 20 g/L over 4 weeks. Hemoglobin levels should be closely monitored for the first 12 weeks of treatment. Dose adjustments or discontinuation should be made as needed, following the dose adjustment guidelines (Table 1). Treatment should be started after careful assessment of patient's risk-benefit profile. Patients with VAT should be promptly assessed and treated.
8. **Seizures:** In clinical trials involving DD and NDD CKD patient with anemia, those treated with roxadustat had a higher incidence of seizures compared to those receiving placebo or epoetin alfa. During the initial months of roxadustat treatment, patients should be closely monitored for any premonitory neurologic symptoms. Treatment should be started after careful assessment of patient's risk-benefit profile. Patients should be advised to promptly contact their doctors if they experience new-onset seizures, premonitory symptoms, or an increase in the frequency or severity of seizures.
9. **Secondary hypothyroidism:** Cases of secondary hypothyroidism have been reported with the use of roxadustat. These reactions were reversible upon roxadustat withdrawal. Monitoring of thyroid function is recommended as clinically indicated.
10. Roxadustat should not be co-administered with ESAs.
11. Athletes should use this medication with caution.

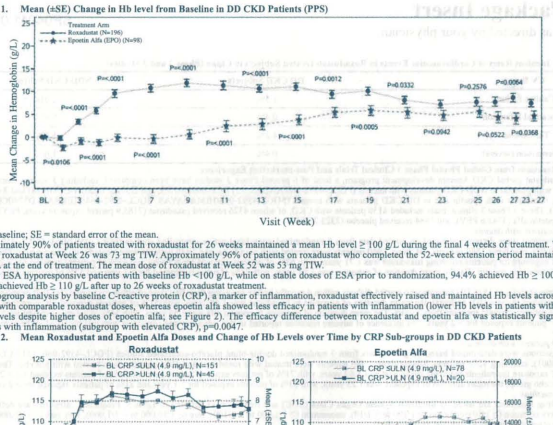
[Use in Pregnant and Lactating Women]
Pregnant Women
Clinical trials with roxadustat have not been conducted in pregnant women. Reproductive toxicity studies in animals demonstrated roxadustat can reduce foetal and pup body weight. Therefore, roxadustat is contraindicated in pregnant women. Women of childbearing age should use highly effective contraceptive methods during treatment and for 7 days after the last dose.
Lactating Women
It is currently unknown whether roxadustat is excreted in human milk. A study in rats has shown excretion of roxadustat in milk, potentially leading to increased mortality, slowed growth, and delayed development in offspring. Consequently, roxadustat is contraindicated in lactating women.
[Use in Children]
The safety and efficacy of roxadustat in pediatric patients under 18 years of age have not been established.
[Use in Geriatric Patients]
No dose adjustment based on age is required for patients over 65 years old. Analyses of hemoglobin levels and roxadustat doses in subjects aged ≥65 and <65 years from Studies FGCL-4592-806 and FGCL-4592-808 showed no significant differences in hemoglobin levels or roxadustat doses between the two age groups.
[Drug Interactions]
Patients with CKD often use multiple medications concurrently. The following are drugs that require caution when used in conjunction with roxadustat:
Phosphate binders, oral iron
Co-administration of roxadustat (200 mg) with sevelamer carbonate (2400 mg) or calcium acetate (1900 mg) decreased roxadustat AUC by 67% and 46% and C_{max} by 66% and 52%, respectively. Roxadustat should be taken at least 1 hour before or after the use of phosphate binders, oral iron, magnesium/aluminum-containing antacids, or other multivalent cation-containing drugs and mineral supplements. This restriction does not apply to lanthanum carbonate, as co-administration with lanthanum carbonate did not result in a clinically meaningful change in roxadustat AUC or C_{max}.
Activated adsorptive charcoal
Co-administration with oral adsorptive charcoal (Kremezin®) does not have a clinically meaningful effect on roxadustat AUC or C_{max}.
Probenecid (UGT and OAT1/OAT3 inhibitor)
Co-administration of roxadustat (100 mg) with probenecid (500 mg, BID) results in a 2.3-fold increase in roxadustat AUC and a 1.4-fold increase in C_{max}. Caution is advised when starting or stopping concurrent treatment with probenecid, other OAT1/OAT3 inhibitors (e.g., teriflunomide), UGT inhibitors (e.g., valproic acid), and UGT inducers (e.g., rifampin). Dose adjustment of roxadustat may be considered if necessary.
Statins
Co-administration of roxadustat (200 mg) with simvastatin (40 mg) increases the AUC and C_{max} of simvastatin by 1.8- and 1.9-fold, respectively, and the AUC and C_{max} of Simvastatin acid (the active metabolite of Simvastatin) by 1.9- and 2.8-fold, respectively. Time-separation of dosing by 2, 4, or 10 hours does not mitigate this interaction.
Co-administration of roxadustat (200 mg) with Rosuvastatin (10 mg) increases the AUC and C_{max} of Rosuvastatin by 2.9- and 4.5-fold, respectively.
Co-administration of roxadustat (200 mg) with Atorvastatin (40 mg) increases the AUC and C_{max} of Atorvastatin by 2.0- and 1.3-fold, respectively.
Interactions are also expected when co-administered with other statins (or an OATP1B1 substrate such as Glyburide).
To avoid statin overdose and potential effects on skeletal muscles (e.g., myalgia, myopathy, and rare rhabdomyolysis), it is recommended to consider reducing the dose of statin and to monitor for adverse reactions when used with roxadustat.
Gemfibrozil (CYP2C8 and OATP1B1 inhibitor)
Co-administration of roxadustat (100 mg) with Gemfibrozil (600 mg BID) increased roxadustat AUC by 2.3-fold and C_{max} by 1.4-fold. Caution is advised when initiating or discontinuing concomitant treatment with Gemfibrozil, other OATP1B1 inhibitors (e.g., cyclosporine), CYP2C8 inhibitors, and CYP2C8 inducers (e.g., Rifampin). Dose adjustment of roxadustat may be considered if necessary.
Increased roxadustat plasma exposure could potentially lead to a rapid rise in Hb levels when roxadustat is used with Gemfibrozil or Probenecid. This risk can be mitigated by regular monitoring of Hb levels and appropriate dose adjustments. For information on the use of Probenecid or Gemfibrozil in patients with CKD, please refer to relevant Package Inserts of these products.
Omeprazole (gastric acid inhibitor)
Co-administration of roxadustat with Omeprazole did not show a clinically meaningful effect on roxadustat AUC or C_{max}. No interactions are anticipated between roxadustat and other proton pump inhibitors.
CYP450 inhibition/induction potential
Co-administration of roxadustat did not show a clinically meaningful effect on the AUC or C_{max} of drugs metabolized byCYP2B6 (bupropion), CYP2C8 (rosiglitazone), or CYP2C9 (S-warfarin) enzyme. No clinically significant interactions (CYP metabolism inhibition) are expected when roxadustat is used with drugs metabolized by CYP enzymes.
Roxadustat has shown no induction of CYP enzymes *in vitro* at clinically relevant concentrations.
In vitro CYP450 enzyme inhibition studies assessing the inhibition of a panel of CYP enzymes (CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, and 3A4/3A5) revealed that roxadustat is a mixed-type inhibitor of CYP2B6, 2C8, and 2C9, with K_i values of 110, 16, and 140 μmol/L, respectively. Roxadustat is a non-competitive inhibitor of CYP2A6 and 3A4/3A5, with K_i values of 340 and 460 μmol/L, respectively. Roxadustat shows minimal direct inhibition of CYP1A2, 2D6, and 2E1 (IC50 > 500 μmol/L). Although the effects of roxadustat on the pharmacokinetics of CYP1A2, 2A6, 2C19, 2D6, 2E1, and 3A4/3A5 substrates have not been assessed in humans, the absence of clinically meaningful drug interactions with CYP2C8, 2C9, and 2B6 probe substrates suggests that inhibition of other CYP enzyme substrates are unlikely.
Clopidogrel
Co-administration of roxadustat with Clopidogrel did not affect roxadustat exposure.
[Overdose]
The maximum tolerable dose of roxadustat in humans has not yet been established. Single supratherapeutic doses of roxadustat 5 mg/kg (up to 510 mg) was administered in healthy subjects, and up to 400 mg TIW in CKD patients with anemia in clinical studies.
Overdose may result in enhanced pharmacodynamic effects, such as a rapid increase in Hb levels or an elevated heart rate, including tachycardia. In the event of an overdose, symptomatic and supportive treatment should be adopted. If Hb levels become excessively high, treatment with roxadustat should be temporarily discontinued. Roxadustat is not significantly removed by haemodialysis.
[Clinical Trials]
Phase 3 Dialysis Study FGCL-4592-806
Study 806 was a randomized, multicenter, open-label, active-controlled study that demonstrated the efficacy and safety of roxadustat in correcting and maintaining Hb levels in CKD patients on dialysis (either hemodialysis or peritoneal dialysis) who had previously been treated with epoetin alfa. A total of 305 CKD patients with baseline Hb levels ranging from 90 to 120 g/L (mean ~104 g/L) were enrolled and randomized in a 2:1 ratio to receive either oral administration of roxadustat capsules (204 patients) or epoetin alfa for injection (101 patients). The initial dose of roxadustat capsules was based on body weight, with starting dose of 100 mg (for patients weighing 45-60 kg) or 120 mg (for patients weighing ≥60 kg), TIW. Patients receiving epoetin alfa continued their previous dose of epoetin alfa for 26 weeks of treatment. Patients in roxadustat group received the medication for a 26-week initial treatment period, followed by a 26-week extension treatment period, totaling 52 weeks.
Baseline characteristics were similar between the two treatment groups, with comparable baseline Hb levels (104.2 g/L in the roxadustat group versus 104.7 g/L in the epoetin alfa group), and similar proportions of patients with baseline Hb <100 g/L. Both groups had a mean CKD history of 9.3 years and had been on dialysis for 4.4 to 4.5 years. Prior to enrollment, both groups had similar weekly doses of epoetin alfa (~7600 IU). Of these patients, 89% of patients were on hemodialysis, and the rest of patients were on peritoneal dialysis. Patients ranged in age from 18 to 74 years, with no significant differences in gender, height, weight, and body mass index between two groups.
The primary efficacy endpoint was the mean change in Hb level from baseline averaged over Weeks 23 to 27. This analysis used Hb values obtained from the central laboratory. Baseline Hb level was defined as the average of the last 3 central laboratory Hb values assessed prior to the first dose of the study drug.
A total of 304 patients were included in the full analysis set (FAS) population (roxadustat group: 204 patients, epoetin alfa group: 100 patients), and 294 patients were included in the per protocol set (PPS) population (roxadustat group: 196 patients, epoetin alfa group: 98 patients).
In the FPS population, roxadustat met both non-inferiority and superiority criteria (p=0.0718). Notably, in patients receiving roxadustat, Hb levels increased significantly higher than in those receiving epoetin alfa (Espo®) as early as Week 2 and continued throughout the study, despite similar baseline Hb levels (~104 g/L) (See Table 6 and Figure 1).
In the PPS population, roxadustat met both non-inferiority and superiority criteria, with Hb level improvements in the roxadustat group being significantly better than in the epoetin alfa group (p=0.037).

Table 6. Mean Hb Value and Change from Baseline Averaged over Weeks 23 to 27 (FAS and PPS)

Hb Averaged over Week 23-27	Roxadustat (N=204)		Epoetin Alfa (N=100)		Treatment Difference (g/L)	p-Value
	Observed Values (g/L)	CFB (g/L)	Observed Value (g/L)	CFB (g/L)		
FAS						
N	164	164	94	94		
Mean (SD)	111.9 (9.63)	7.3 (11.21)	109.3 (8.13)	4.6 (10.12)		
LSMean (SE)		7.4 (0.88)		5.2 (1.01)	2.2 (1.25)	0.072
95% CI		5.7 - 9.1		3.2 - 7.1	-0.2 - 4.7	
PPS						
N	164	164	93	93		
Mean (SD)	112.0 (9.47)	7.5 (11.01)	109.3 (8.16)	4.6 (10.16)		
LSMean (SE)		7.7 (0.86)		5.1 (1.01)	2.6 (1.24)	0.037
95% CI		6.0 - 9.3		3.1 - 7.1	0.2 - 5.0	

CFB = change from baseline; SD = standard deviation; LSMean = least squares mean; SE = standard error of the LSMean , CI = 95% confidence interval

Figure 1. Mean (±SE) Change in Hb level from Baseline in DD CKD Patients (PPS)



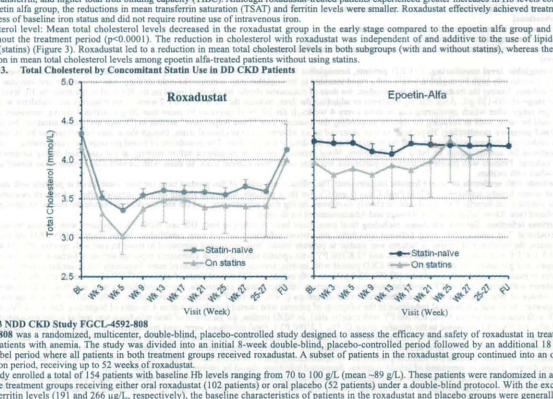
BL = baseline; SE = standard error of the mean.

Approximately 90% of patients treated with roxadustat for 26 weeks maintained a mean Hb level ≥ 100 g/L during the final 4 weeks of treatment. The mean dose of roxadustat at Week 26 was 73 mg TIW. Approximately 96% of patients on roxadustat who completed the 52-week extension period maintained Hb ≥ 100 g/L at the end of treatment. The mean dose of roxadustat at Week 52 was 53 mg TIW.

Among ESA hyporesponsive patients with baseline Hb <100 g/L, while on stable doses of ESA prior to randomization, 94.4% achieved Hb ≥ 100 g/L, and 83.3% achieved Hb ≥ 110 g/L after up to 26 weeks of roxadustat treatment.

In a subgroup analysis by baseline C-reactive protein (CRP), a marker of inflammation, roxadustat effectively raised and maintained Hb levels across all CRP levels, with comparable roxadustat doses, whereas epoetin alfa showed less efficacy in patients with inflammation (lower Hb levels in patients with elevated CRP levels despite higher doses of epoetin alfa; see Figure 2). The efficacy difference between roxadustat and epoetin alfa was statistically significant in patients with inflammation (subgroup with elevated CRP), p=0.0047.

Figure 2. Mean Roxadustat and Epoetin Alfa Doses and Change of Hb Levels over Time by CRP Sub-groups in DD CKD Patients

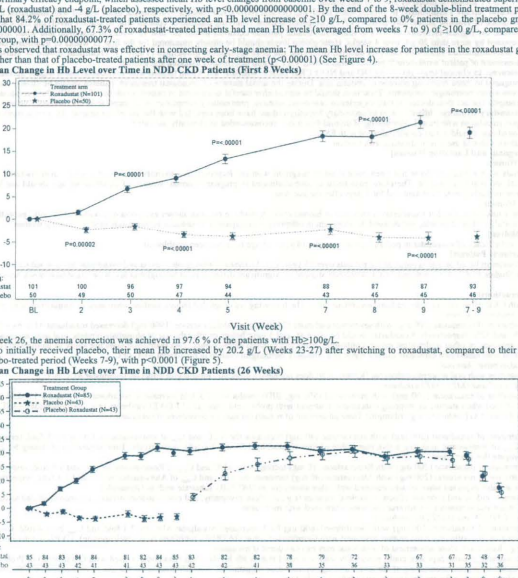


BL = baseline; ULN = upper limit of normal; CRP = C-reactive protein; SE = standard error of the mean

Iron level: Iron utilization improved in roxadustat-treated patients compared to the epoetin alfa group, as indicated by higher mean serum iron levels, higher mean transferrin, and higher total iron binding capacity (TIBC). Although roxadustat-treated patients experienced greater increases in Hb levels compared to the epoetin alfa group, the reductions in mean transferrin saturation (TSAT) and ferritin levels were smaller. Roxadustat effectively achieved treatment goals regardless of baseline iron status and did not require routine use of intravenous iron.

Cholesterol level: Mean total cholesterol levels decreased in the roxadustat group in the early stage compared to the epoetin alfa group and remained throughout the treatment period (p<0.0001). The reduction in cholesterol with roxadustat was independent of and additive to the use of lipid-lowering agents (statins) (Figure 3). Roxadustat led to a reduction in mean total cholesterol levels in both subgroups (with and without statins), whereas there was no reduction in mean total cholesterol levels among epoetin alfa-treated patients without using statins.

Figure 3. Total Cholesterol by Concomitant Statin Use in DD CKD Patients



Phase 3 NDD CKD Study FGCL-4592-808

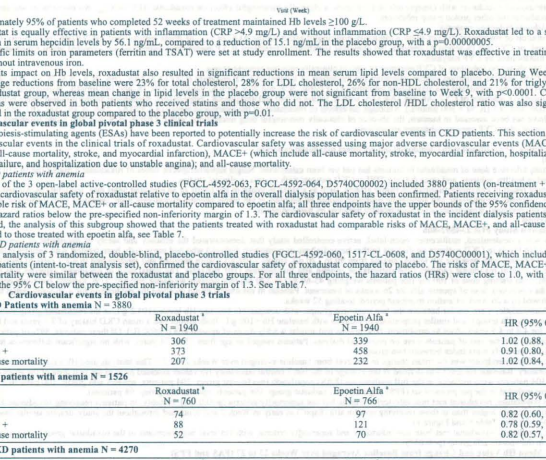
Study 808 was a randomized, multicenter, double-blind, placebo-controlled study designed to assess the efficacy and safety of roxadustat in treating NDD CKD patients with anemia. The study was divided into an initial 8-week double-blind, placebo-controlled period followed by an additional 18 weeks of open-label period where all patients in both treatment groups received roxadustat. A subset of patients in the roxadustat group continued into an open-label extension period, receiving up to 52 weeks of roxadustat.

The study enrolled a total of 154 patients with baseline Hb levels ranging from 70 to 100 g/L (mean ~89 g/L). These patients were randomized in a 2:1 ratio, with the treatment groups receiving either oral roxadustat (102 patients) or oral placebo (52 patients) under a double-blind protocol. With the exception of mean ferritin levels (191 and 266 μg/L, respectively), the baseline characteristics of patients in the roxadustat and placebo groups were generally similar. Both groups had mean baseline Hb levels of 88.7 and 89.3 g/L, respectively. The proportions of patients with baseline Hb levels of ≥80 g/L were comparable, at 83.2% and 86.3%, respectively. Patients in the roxadustat group had slightly longer CKD history (5.3 years) and higher eGFR levels (16.5 mL/min/1.73 m^2) compared to the placebo arm (4.2 years and 14.5 mL/min/1.73 m^2).

In terms of the primary efficacy endpoint, which assessed mean Hb level changes from baseline over weeks 7 to 9, roxadustat demonstrated superiority over placebo at 19 g/L (roxadustat) and -4 g/L (placebo), respectively, with p<0.0000000000000001. By the end of the 8-week double-blind treatment period, the results showed that 84.2% of roxadustat-treated patients experienced an Hb level increase of ≥10 g/L, compared to 0% patients in the placebo group, with p<0.0000000000000001. Additionally, 67.3% of roxadustat-treated patients had mean Hb levels (averaged from weeks 7 to 9) of ≥100 g/L, compared to 6.0% in the placebo group, with p=0.0000000077.

Moreover, it was observed that roxadustat was effective in correcting early-stage anemia: The mean Hb level increase for patients in the roxadustat group was significantly higher than that of placebo-treated patients after one week of treatment (p<0.00001) (See Figure 4).

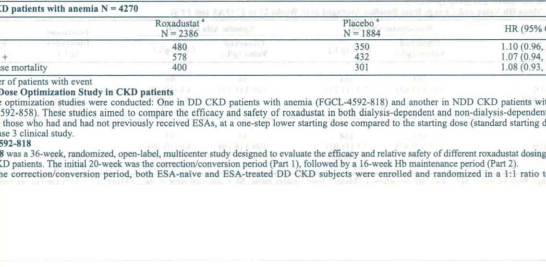
Figure 4. Mean Change in Hb Level over Time in NDD CKD Patients (First 8 Weeks)



By the end of Week 26, the anemia correction was achieved in 97.6 % of the patients with Hb≥100g/L.

For patients who initially received placebo, their mean Hb increased by 20.2 g/L (Weeks 23-27) after switching to roxadustat, compared to their mean Hb during the placebo-treated period (Weeks 7-9), with p<0.0001 (Figure 5).

Figure 5. Mean Change in Hb Level over Time in NDD CKD Patients (26 Weeks)



Approximately 95% of patients who completed 52 weeks of treatment maintained Hb levels ≥100 g/L.

Roxadustat is equally effective in patients with inflammation (CRP >4.9 mg/L) and without inflammation (CRP ≤4.9 mg/L). Roxadustat led to a significant reduction in serum hepcidin levels by 56.1 ng/mL, compared to a reduction of 15.1 ng/mL in the placebo group, with a p=0.00000005.

No specific limits on iron parameters (ferritin and TSAT) were set at study enrollment. The results showed that roxadustat was effective in treating anemia even without intravenous iron.

Beyond its impact on Hb levels, roxadustat also resulted in significant reductions in mean serum lipid levels compared to placebo. During Weeks 7 to 9, the average reductions from baseline were 23% for total cholesterol, 28% for LDL cholesterol, 26% for non-HDL cholesterol, and 21% for triglycerides in the roxadustat group, whereas mean change in lipid levels in the placebo group were not significant from baseline to Week 9, with p<0.001. Cholesterol reductions were observed in both patients who received statins and those who did not. The LDL cholesterol /HDL cholesterol ratio was also significantly improved in the roxadustat group compared to the placebo group, with p=0.01.

Cardiovascular events in global pivotal phase 3 clinical trials

Erythropoiesis-stimulating agents (ESAs) have been reported to potentially increase the risk of cardiovascular events in CKD patients. This section describes cardiovascular events in the clinical trials of roxadustat. Cardiovascular safety was assessed using major adverse cardiovascular events (MACE, which include all-cause mortality, stroke, and myocardial infarction), MACE+ (which include all-cause mortality, stroke, myocardial infarction, hospitalization due to heart failure, and hospitalization due to unstable angina); and all-cause mortality.

DD CKD patients with anemia

The pool of the 3 open-label active-controlled studies (FGCL-4592-063, FGCL-4592-064, D5740C00002) included 3880 patients (on-treatment + 7analysis set). The cardiovascular safety of roxadustat relative to epoetin alfa in the overall dialysis population has been confirmed. Patients receiving roxadustat have a comparable risk of MACE, MACE+ or all-cause mortality compared to epoetin alfa; all three endpoints have the upper bounds of the 95% confidence interval (CI) of hazard ratios below the pre-specified non-inferiority margin of 1.3. The cardiovascular safety of roxadustat in the incident dialysis patients has been confirmed, the analysis of this subgroup showed that the patients treated with roxadustat had comparable risks of MACE, MACE+, and all-cause mortality compared to those treated with epoetin alfa, see Table 7.

NDD CKD patients with anemia

A pooled analysis of 3 randomized, double-blind, placebo-controlled studies (FGCL-4592-060, 1517-CL-0608, and D5740C00001), which included a total of 4270 patients (intent-to-treat analysis set), confirmed the cardiovascular safety of roxadustat compared to placebo. The risks of MACE, MACE+, and all-cause mortality were similar between the roxadustat and placebo groups. For all three endpoints, the hazard ratios (HRs) were close to 1.0, with the upper limits of the 95% CI below the pre-specified non-inferiority margin of 1.3. See Table 7.

Table 7. Cardiovascular events in global pivotal phase 3 trials

DD CKD Patients with anemia N = 3880

	Roxadustat [a] N = 1940	Epoetin Alfa [a] N = 1940	HR (95% CI)
MACE	306	339	1.02 (0.88, 1.20)
MACE +	373	458	0.91 (0.80, 1.05)
All-cause mortality	207	232	1.02 (0.84, 1.23)

ID CKD patients with anemia N = 1526

	Roxadustat [a] N = 760	Epoetin Alfa [a] N = 766	HR (95% CI)
MACE	74	97	0.82 (0.60, 1.11)
MACE +	88	121	0.78 (0.59, 1.02)
All-cause mortality	52	70	0.82 (0.57, 1.18)

NDD CKD patients with anemia N = 4270

	Roxadustat [a] N = 2386	Placebo [a] N = 1884	HR (95% CI)
MACE	480	350	1.10 (0.96, 1.27)
MACE +	578	432	1.07 (0.94, 1.21)
All-cause mortality	400	301	1.08 (0.93, 1.26)

a: Number of patients with event

Phase 4 Dose Optimization Study in CKD patients

Two dose optimization studies were conducted: One in DD CKD patients with anemia (FGCL-4592-818) and another in NDD CKD patients with anemia (FGCL-4592-858). These studies aimed to compare the efficacy and safety of roxadustat in both dialysis-dependent and non-dialysis-dependent patients, including those who had and had not previously received ESAs, at a one-step lower starting dose compared to the starting dose (standard starting dose) used in the phase 3 clinical study.

FGCL-4592-818

Study 818 was a 36-week, randomized, open-label, multicenter study designed to evaluate the efficacy and relative safety of different roxadustat dosing regimens in DD CKD patients. The initial 20-week was the correction/conversion period (Part 1), followed by a 16-week Hb maintenance period (Part 2).

During the correction/conversion period, both ESA-naïve and ESA-treated DD CKD subjects were enrolled and randomized in a 1:1 ratio to receive roxadustat at the following two starting doses: A lower starting dose (70 mg TIW for subjects weighing 45 to <60 kg and 100 mg TIW for subjects weighing ≥60 kg) and a standard starting dose (100 mg TIW for subjects weighing 45 to <60 kg and 120 mg TIW for subjects weighing ≥60 kg). Roxadustat doses were adjusted during correction/conversion period according to the approved dose adjustment guidelines in this Package Insert.

In total, 318 subjects were randomized and entered the correction/conversion period for study treatment. The full analysis set (FAS) consisted of 316 subjects, including 113 ESA-naïve subjects (57 in the lower starting dose group and 56 in the standard starting dose group) and 203 ESA-treated subjects (103 in the lower starting dose group and 100 in the standard starting dose group). The FAS was used for efficacy data analysis.

Overall, baseline characteristics, including age, gender, and CKD duration, were comparable between the two groups. Among both ESA-naïve and ESA-treated patients, the average baseline Hb levels were similar between the two starting dose groups (87.73 g/L and 86.17 g/L in the ESA-naïve group, and 104.81 g/L and 105.47 g/L in the ESA-treated group).

For ESA-naïve subjects, the primary efficacy endpoint (proportion of subjects achieving Hb ≥ 110 g/L in the first 20 weeks) was similar in both lower and standard starting dose groups (77.2% and 73.2%, respectively) (see Table 8). For ESA-treated subjects, the primary efficacy endpoint (proportion of subjects with a mean Hb ≥ 100 g/L from the Week 17 visit to the Week 21 visit) was comparable in both lower and standard starting dose groups (82.5% and 79.0%) (see Table 9).

Table 8. Primary Efficacy Analysis in ESA-naïve Subjects (FAS Population)

	Lower Starting Dose (N=57) n(%) (95% CI)	Standard Starting Dose (N=56) n(%) (95% CI)	Total (N=113) n(%) (95% CI)
Number and proportion of subjects who achieved Hb ≥110 g/L in the first 20 weeks	44 (77.2%) (64.2%, 87.3%)	41 (73.2%) (59.7%, 84.2%)	85 (75.2%) (66.2%, 82.9%)

Table 9. Primary Efficacy Analysis in ESA-Treated Subjects (FAS Population)

	Lower Starting Dose (N=103) n(%) (95% CI)	Standard Starting Dose (N=100) n(%) (95% CI)	Total (N=203) n(%) (95% CI)
Number and proportion of subjects with mean Hb ≥100 g/L over Week 17 visit to Week 21 visit	85 (82.5%) (73.8%, 89.3%)	79 (79.0%) (69.7%, 86.5%)	164 (80.8%) (74.7%, 86.0%)

The lower starting dose of roxadustat also showed similar results in the following secondary efficacy endpoints for correction of anemia compared with the standard starting dose.

In ESA-naïve subjects, the mean change from baseline in Hb levels from Week 17 visit to Week 21 visit was 20.7 (±10.41) g/L in the lower starting dose group and 21.6 (±14.91) g/L in the standard starting dose group; the proportion of subjects with a mean Hb (mean Hb from Week 17 visit to Week 21 visit) ≥100 g/L was slightly higher in the lower starting dose group than in the standard starting dose group (78.9% vs. 67.9%). In ESA-treated subjects, the mean change from baseline in Hb levels from Week 17 visit to Week 21 visit was 4.9 (±11.80) g/L in the lower starting dose group and 6.0 (±12.63) g/L in the standard starting dose group.

Additionally, in ESA-naïve subjects, the mean change from baseline (CFB) in Hb level at Week 5 was slightly lower in the lower starting dose group compared to the standard starting dose group (11.5 g/L vs. 16.8 g/L). From Week 9 onward, Hb CFB remained stable and similar in both groups (19.8 g/L vs. 21.6 g/L at Week 9). This trend was similar to what was observed in ESA-treated subjects (3.3 g/L vs. 8.5 g/L at Week 5; 5.9 g/L vs. 8.2 g/L at Week 9), further supporting the comparable efficacy between the two groups.

FGCL-4592-858

Study 858 was a randomized, controlled, open-label, multicenter study designed to evaluate the efficacy and safety of the lower starting dose of roxadustat in Stage 3-5 CKD subjects with anemia not on dialysis over a 16-week treatment period. The study hypothesized that the primary efficacy endpoint (mean change from baseline in hemoglobin level between Week 12 and Week 16) in the lower starting dose group would be non-inferior to that in the standard starting dose group.

Following screening for eligibility, subjects were stratified by CKD stage (Stage 3, Stage 4, Stage 5) and randomized in a 1:1 ratio to either the lower starting dose group (50 mg TIW for subjects weighing < 60 kg and 70 mg TIW for subjects weighing ≥ 60 kg) or the standard starting dose group (70 mg TIW for subjects weighing < 60 kg and 100 mg TIW for subjects weighing ≥ 60 kg). Roxadustat doses were adjusted during treatment according to the approved dose adjustment guidelines in the Package Insert.

A total of 254 subjects were randomized, of whom 250 subjects (126 in the lower starting dose group and 124 in the standard starting dose group) were treated. Of these, 249 subjects (126 in the lower starting dose group and 123 in the standard starting dose group) were included in the full analysis set (FAS), and 226 subjects (115 in the lower starting dose group and 111 in the standard starting dose group) were included in the per protocol set (PPS).

Baseline characteristics such as age, gender, and CKD duration were generally comparable between the two groups. Baseline Hb levels (89.4 ± 6.96 g/L in the lower starting dose group and 90.4 ± 6.83 g/L in the standard starting dose group) and proportions of subjects in each Hb subgroup (≥ 80 g/L, < 80 g/L) were comparable. Additionally, baseline levels of transferrin, transferrin saturation, serum iron, and total iron-binding capacity were comparable between two groups.

In the PPS, the least squares mean for the primary efficacy endpoint (change from baseline in mean hemoglobin level between Week 12 and Week 16) was 21.57 g/L for subjects in the lower starting dose group and 26.35 g/L for subjects in the standard starting dose group. The difference between groups (2-sided 95% CI) was -4.78 g/L (-7.77, -1.79), with the lower limit being less than the preset non-inferiority margin of -5 g/L (see Table 10). For the secondary efficacy endpoint, the proportion of subjects with mean Hb level in the range of 100-120 g/L between Week 12 and Week 16), the proportions were comparable between the lower starting dose group and the standard starting dose group, at 47.8% (55 subjects) and 47.7% (53 subjects), respectively, with an odds ratio of 1.158 (95% CI: 0.671, 1.996), and the difference was not statistically significant (P = 0.5983) (see Table 11). Other secondary endpoints indicated that the overall magnitude of hemoglobin fluctuation was smaller in the lower starting dose group compared to the standard starting dose group.

Throughout the treatment period, the number and proportion of subjects experiencing an hemoglobin (Hb) rise > 20 g/L over any 4-week period (lower starting dose group vs. standard starting dose group: 51 subjects [40.5%] vs. 72 subjects [58.5%]), the number and proportion of subjects with Hb concentration > 120 g/L (lower starting dose group vs. standard starting dose group: 54 subjects [42.9%] vs. 78 subjects [63.4%]), and the number and proportion of subjects with Hb concentration > 130 g/L (lower starting dose group vs. standard starting dose group: 19 subjects [15.1%] vs. 39 subjects [31.7%]) were lower in the lower starting dose group compared to the standard starting dose group (P < 0.05).

Subgroup analyses based on the primary endpoint showed that in the lower starting dose group, the change from baseline in mean hemoglobin level between Week 12 and Week 16 in Stage 5 CKD subjects with anemia (17.28 g/L) was numerically smaller than that in subjects with Stage 3 (25.41 g/L) and Stage 4 (23.91 g/L) CKD, and this trend was not reflected in the standard starting dose group. These results suggest that the lower starting dose may be more suitable for patients with Stage 3-4 CKD, while the standard starting dose may be more effective for achieving target hemoglobin levels in patients with Stage 5 CKD.

Table 10 Mean Change from Baseline in Mean Hemoglobin Level between Week 12 and Week 16 (PPS Population)

Visit	Statistics	Lower starting dose group N=115	Standard starting dose group N = 111
Baseline [1]	Number of subjects	115	111
	Mean (SD)	89.4 (7.00)	90.6 (6.69)
Mean over Week 12 to Week 16 [2]	Number of subjects	106	108
	Mean (SD)	111.3 (13.38)	117.1 (9.97)
Change from baseline in mean over Week 12 to Week 16 (MMRM)	Least square mean (95% CI)	21.57 (19.25, 23.89)	26.35 (24.44, 28.27)
	Treatment Difference (95% CI)	-4.78 (-7.77, -1.79)	

MMRM = Mixed model for repeated measures, CI = Confidence interval, SE = Standard error. The MMRM model included treatment group, visit, treatment group * visit as fixed effects, baseline hemoglobin value, and baseline estimated glomerular filtration rate as covariates, with the selection of unstructured covariance.

[1] Baseline hemoglobin level is defined as the mean of the last 2 hemoglobin values before the first dose of study drug.

[2] Mean over Week 12 to Week 16 = (hemoglobin level at Week 12 + hemoglobin level at Week 16)/2

Table 11 Proportion of Subjects with Mean Hemoglobin Levels in the Range of 100 to 120 g/L between Week 12 and Week 16 (PPS Population)

Category	Lower starting dose group (N = 115)	Standard starting dose group (N = 111)
Mean hemoglobin (g/L)	111.4	117.1
Mean hemoglobin between 100-120 g/L[1]		
Number of subjects (%)	55 (47.8)	53 (47.7)
Odds ratio (95% CI) [2]		1.158 (0.671, 1.996)
P-value		0.5983

Note: CI = Confidence interval [1] In the logistic regression model, baseline hemoglobin and baseline eGFR were included as covariates. [2] Odds ratio: Number of subjects in the lower starting dose group/number of subjects in the standard starting dose group.

[Pharmacology and Toxicology]

1. Pharmacology

Roxadustat is a hypoxia-inducible factor, prolyl hydroxylase inhibitor. It inhibits prolyl hydroxylases PHD1, PHD2, and PHD3 *in vitro*, leading to the rapid and reversible activation of hypoxia-inducible factor-α (HIF-α) in Hep3B cell line 1G6 cells. This activation induces elevated levels of erythropoietin (EPO) in Hep3B cells. Roxadustat increases hemoglobin and hematocrit levels in normal mice and rats, as well as in rat models of anemia induced by inflammation or nephrectomy.

2. Toxicology

Genotoxicity:

Roxadustat was negative in the Ames test, the chromosome aberration test of human peripheral blood lymphocytes, and the bone marrow micronucleus test in mouse.

Reproductive and Developmental toxicity:

In the rat fertility and early embryo developmental toxicity test, rats were orally administered Roxadustat at doses of 5, 15, and 30 mg/kg. Male rats were given the drug three times a week from 14 days before mating until the end of the study, while female rats were given the drug three times a week from 14 days before mating throughout the mating period, and once daily from day 0 to day 7 of pregnancy. At the 30 mg/kg dose, the weights of the epididymis and seminal vesicles in male rats decreased, but fertility was unaffected. Female fertility was also unaffected, although the number of stillbirths and the post-implantation loss rate increased at the 30 mg/kg dose; at 30 and 15 mg/kg doses, both male and female rats showed enlarged spleens and increases in spleen weight and coefficient, with female rats also showing increased liver weight.

In the rat embryo-fetal toxicity test, rats were orally administered with roxadustat at 5, 15, or 30 mg/kg/day from day 7 to day 17 of pregnancy. In the 30 mg/kg dose group, pregnant rats experienced reduced body weight early in dosing, decreased food intake during the dosing period, and decreased fetal weight. Additionally, the average weight of male fetal placentas increased and the incidence of cervical rib variations increased. In the rabbit embryo-fetal toxicity test, rabbits were orally administered with roxadustat at 15, 35, or 100 mg/kg/day from day 7 to day 17 of pregnancy. At the 35 and 100 mg/kg doses, the miscarriage rate increased, but no significant fetal abnormalities were observed.

In the rat perinatal toxicity study, rats were orally administered with roxadustat at doses of 5, 10, or 20 mg/kg/day from day 7 of pregnancy to day 20 of lactation. The 20 mg/kg dose led to decreased food intake and body weight in the mothers (F0 generation) during lactation period, a significant increase in hematocrit, and increased spleen weight and coefficient. At doses of 10 mg/kg and above, F1 generation offspring showed a dose-dependent increase in mortality and significant abnormal clinical signs. The evaluation of F1 generation after weaning was stopped at the 20 mg/kg dose level due to high mortality. At doses of 5 mg/kg and above, F1 generation offspring experienced reduced food intake and weight gain, delayed reflex development (e.g., righting reflex, auditory startle reflex), delayed sexual maturity, reduced passive avoidance, increased testicular weight and coefficient, and decreased spleen weight and coefficient. At the 10 mg/kg dose level, F1 generation showed decreased body weight and food intake during pregnancy. At doses of 5 and 10 mg/kg, some F2 generation offspring showed visible malformations, though the relevance to the drug remains unclear. Roxadustat can cross the placental barrier and is excreted in milk, with the concentration in milk significantly higher than maternal blood concentrations during the same period.

Carcinogenicity:

Mice were orally administered with roxadustat at doses of 15, 30, or 60 mg/kg, and rats were orally administered with roxadustat at doses of 2.5, 5, or 10 mg/kg, three times a week for two consecutive years. No carcinogenic effects related to roxadustat were observed.

[Pharmacokinetics]

Roxadustat PK data were obtained from a single- and multiple-dose escalation study in Chinese healthy subjects (dose range 40 to 200 mg), as well as from PK subgroup studies in a China phase 2 study (hemodialysis patients) and two China phase 3 studies in China (one in NDD CKD patients and one in CKD patients undergoing peritoneal dialysis). Additionally, PK data were collected from a bioequivalence (BE) study in China and a BE study conducted in Chinese subjects in Singapore. Other PK data concerning dose escalation, drug-drug interactions, human mass balance, food effects, bioequivalence, and *in vitro* pharmacokinetics were obtained from various studies conducted in the US, Europe, and Japan.

Absorption

Roxadustat is rapidly absorbed after oral administration, with median time for reaching the maximum plasma concentration at 2 hours post dose in the fasted state. Roxadustat plasma exposure (C_{max} and AUC) is dose-proportional within the recommended therapeutic dose range. The mean elimination half-life is approximately 8-11 hours in healthy subjects, around 12 hours in NDD CKD patients, and approximately 10-12 hours in DD patients. No significant drug accumulation was observed when roxadustat was administered three times per week at the recommended dose.

After a high-calorie, high-fat breakfast including dairy products, roxadustat AUC remained unchanged, while C_{max} decreased by 25%. Roxadustat can be taken with or without food.

Distribution

Roxadustat is highly bound to human plasma proteins (>98%), predominantly to albumin. Hemodialysis or peritoneal dialysis does not significantly affect the removal of Roxadustat.

Metabolism

Roxadustat is primarily metabolized *in vivo* by UGT1A9 and CYP2C8, with major metabolites including roxadustat-O-glucuronide and hydroxy-roxadustat. *In vitro* studies assessing CYP450 metabolic enzyme phenotyping evaluated a range of common CYP enzymes (CYP1A1, 1A2, 2A6, 1B1, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, 3A4, and 3A5). Results indicated that CYP2C8 is the primary enzyme responsible for converting roxadustat to hydroxy-roxadustat in the human liver.

In vitro UGT metabolic enzyme phenotyping studies assessed a range of common UGT enzymes (UGT1A1, 1A3, 1A4, 1A6, 1A7, 1A8, 1A9, 1A10, 2B4, 2B7, 2B10, 2B15, and 2B17). These studies found that UGT1A9 is the major enzyme responsible for the glucuronidation of roxadustat in the human liver. Additionally, *in vitro* studies showed that O-glucuronidation activity of roxadustat was detectable in both human liver and renal microsomes. Although *in vitro* studies showed that rUGT1A7 and rUGT1A8 play a role in roxadustat metabolism, given that both enzymes were usually outside the liver and their effects could not be verified by correlation analysis of human liver microsomes, it was suggested that these enzymes may be involved in the renal glucuronidation of roxadustat.

Elimination

When radiolabelled roxadustat was administered orally in healthy subjects, the mean recovery rate of radioactivity was approximately 96% (50% in feces, 46% in urine). The majority of radioactivity in plasma (≥83%) was attributed to unchanged roxadustat. No major metabolites were detected in plasma.

Special Population

Geriatrics: In elderly subjects (≥65 years old), roxadustat C_{max} and AUC_{inf} increased by 15% and 23%, respectively, compared to younger subjects (18 to 45 years old); these differences were not clinically significant. Changes in mean Hb from baseline, adverse events, and average roxadustat dose in subjects > 65 years were similar to subjects < 65 years in China Phase 3 clinical trial.

Patients with Hepatic Impairment: Following a single dose of 100 mg roxadustat, mean roxadustat AUC was 23% higher and mean C_{max} was 16% lower in subjects with moderate hepatic impairment (Child-Pugh Class B) and normal renal function compared to subjects with normal hepatic and renal functions. The unbound fraction of roxadustat increased in subjects with moderate hepatic impairment compared to matched healthy subjects (1.1% vs. 0.8%), resulting in a significant increase in mean unbound exposure (70%).

The pharmacokinetics of roxadustat in patients with severe hepatic impairment (Child-Pugh Class C) have not been studied.

Cardiac Electrophysiology:

In a thorough QT interval study in healthy subjects, roxadustat administered at doses of 2.75 mg/kg and 5.0 mg/kg (up to 510 mg) did not result in a prolongation of the QT interval after correction for heart rate.

[Storage]

Protect from light, store below 30°C, seal tight.

[Package Size]

Aluminum/Aluminum blister packaging, 3 capsules/blister; 1 blister/box.

[Shelf Life] 36 months.

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