BMJ Open

Lower starting dose of roxadustat in non-dialysis-dependent chronic kidney disease patients with anaemia: a study protocol for a randomised, multicentre, open-label study

Ping Li ,[1] Xuefeng Sun ,[1] Dinghua Chen,[1] Hong-li Lin,[2] Li Zhang,[1] Yiqing Wu,[3] Shuting Pan,[3] Guangyan Cai ,[1] Xiangmei Chen[1]

To cite: Li P, Sun X, Chen D, *et al*. Lower starting dose of roxadustat in non-dialysis-dependent chronic kidney disease patients with anaemia: a study protocol for a randomised, multicentre, open-label study. *BMJ Open* 2023;**13**:e068864. doi:10.1136/bmjopen-2022-068864

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2022-068864).

PL and XS contributed equally.

Received 02 October 2022
Accepted 16 December 2022

[1]Department of Nephrology, First Medical Center of Chinese PLA General Hospital, Beijing, Beijing, China
[2]Department of Nephrology, The First Affiliated Hospital of Dalian Medical University, Dalian, China
[3]Medical Affairs & Biometrics department, FibroGen, Shanghai, China

Correspondence to
Dr Xiangmei Chen;
xmchen301@126.com

ABSTRACT

Introduction Roxadustat is a first-in-class oral therapy that treats chronic kidney disease (CKD) anaemia with the benefit of a novel mechanism of action that consistently corrects and maintains haemoglobin (Hb) across the spectrum of non-dialysis-dependent (NDD) CKD anaemia with an acceptable safety profile.

Methods and analysis This is a randomised, control, open-label, multicentre trial. About 250 adult Chinese participants with stage 3–5 CKD NDD in approximately 30 centres will be enrolled, randomly assigned in a 1:1 ratio, to receive a 16-week treatment and 4-week follow-up. The interventions for study arm are <60 kg: 50 mg TIW and ≥60 kg: 70 mg TIW; for control arm, <60 kg: 70 mg TIW and ≥60 kg: 100 mg TIW. The primary endpoint is the mean change in haemoglobin level from baseline to average over weeks 12–16. Secondary endpoints are to assess the proportion of subjects achieving an average Hb level of 100 to 120 g/L over weeks 12–16, the Hb variability, the rescue therapy requirement between two groups and the safety in two groups. The exploratory objectives are expected to evaluate the rate and time of Hb response, times of dose adjustment, the proportion of subjects with rapid Hb rise, overshooting during the treatment between two different starting dose groups, and subgroup analyses.

Ethics and dissemination The Medical Ethics Committee of Chinese PLA General Hospital has approved this study (No. S2020-523-05) and will be performed in accordance with the Declaration of Helsinki. Participant consent will be obtained in writing. Results will be disseminated via peer-reviewed publications and conference presentations.

Trial registration number ChiCTR2100045359.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ An RCT design clinical trial ensures two treatment groups are balance to compare and avoiding observable confounding.
⇒ This is the first roxadustat clinical trial that introduce indices to evaluate Hb variability during the first 8 weeks and during the whole treatment period.
⇒ Patients and physician are not blinded to treatment.
⇒ The relationship between Hb variability and hard outcomes cannot be drawn in this study.

INTRODUCTION

CKD-anaemia, a common complication in patients with chronic kidney disease (CKD), may present in the early stages, and its prevalence increases as CKD progresses.[1] Studies showed that CKD-anaemia was present in 17% of patients with late stage 3 disease in America; this increases to 50% in patients with stage 4 disease and 53% in patients with stage 5 CKD who have not yet progressed to dialysis.[1] And in a multicentre, cross-sectional survey of patients with non-dialysis-dependent (NDD) CKD in China, CKD-anaemia occurred up to 90.2% in stage 5 patients.[2] Anaemia was a prevalent condition associated with adverse renal, cardiovascular, hospitalisation outcomes, and reduction of health-related quality of life in patients with CKD.[3 4]

Until now, erythropoiesis-stimulating agents (ESAs) and oral or intravenous iron are the main treatments for NDD patients. In China, most patients need to receive a subcutaneous injection of EPO in a hospital or healthcare centre, and this inconvenience results in a large number of NDD patients being undertreated. Hypoxia-inducible factor (HIF), the critical element in the body's oxygen sensing mechanism, regulates the expression of genes that modulate the acute and chronic responses to hypoxia.[5] HIF acts indirectly at sites of erythropoiesis to enhance the differentiation and proliferation of red blood cell precursors and also induces expression of the erythropoietin (EPO) receptor and proteins that promote iron absorption and recycling.[6] Hypoxia-inducible factor prolyl hydroxylase inhibitor (HIF-PHI), a class of novel, orally active medication, was

developed to tackle this issue for patients with CKD, especially NDD patients and patients on peritoneal dialysis. Roxadustat is a potent and reversible HIF-PHI that leads to a functional HIF transcriptional response that mimics the erythropoietic response associated with exposure of humans to intermittent hypoxia. Thus, roxadustat pharmacologically stimulates erythropoiesis through the HIF pathway and in a manner consistent with the body's normal homeostatic response to anaemia but under normoxic conditions.[7]

Roxadustat was the first-in-class HIF-PHI approved by a regulatory agency to treat anaemia in patients with dialysis-dependent (DD) or NDD CKD in China, Japan, the EU, the UK, South Korea and Chile.[8–10] The label of roxadustat recommends weight-based starting dose of 70/100 mg in NDD population in China.[11] However, the starting dose of phase II and phase III clinical trials on NDD CKD-anaemia in Japan is 50/70 mg.[12 13] Meanwhile, studies showed that the increase of Hb is rapid with the in-label dose during the starting period, leading to the potential overshooting risk.[14 15] Therefore, the purpose of this study is to validate the efficacy and safety of roxadustat at a lower starting dose in stage 3–5 CKD NDD subjects with CKD-anaemia, to explore dose optimisation and provide more clinical evidence of alternative starting dose regimen in Chinese population for roxadustat post-marketing clinical application.

METHODS

Study design

This is a randomised, control, open-label, multicentre non-inferiority trial in stage 3–5 CKD NDD subjects to evaluate the efficacy and safety of roxadustat at a lower starting dose over a 16-week treatment period. The hypothesis is that the efficacy of roxadustat at the lower starting dose is not inferior to the standard starting dose for CKD-NDD patients with CKD-anaemia. Eligible subjects will be randomised on day 1 at a 1:1 ratio, stratified by CKD stage (stage 3 or stage 4, or stage 5) to the standard weight-based starting dose group (control arm) and the one-step lower weight-based starting dose group (study arm). The definition of CKD stages 3–5 is according to the Kidney Disease Outcomes Quality Initiative (KDOQI) 2002 classification system. There will be three study periods: screening period (up to 14 days before day 1), treatment period (16 weeks) and follow-up period (4 weeks). The duration of the screening period is flexible to allow re-testing of subjects and scheduling difficulties. The investigator will decide whether the issue meets the eligibility criteria based on the repeated tests (figure 1). This study meets the SPIRIT reporting guidelines.[16]

Setting and participants

About 250 subjects will be enrolled in approximately 30 study centres in China. The treatment duration is 16 weeks, and 4 weeks of follow-up are performed after the end of the treatment period. Detailed study inclusion and exclusion criteria are shown in box 1. Treatment allocation occurs when the study participant meets all of the inclusion criteria and signs the informed consent form (online supplemental material 1).

Interventions

Study arm: one-step lower weight-based starting dose group: <60 kg: 50 mg three times a week (TIW), ≥60 kg: 70 mg TIW.

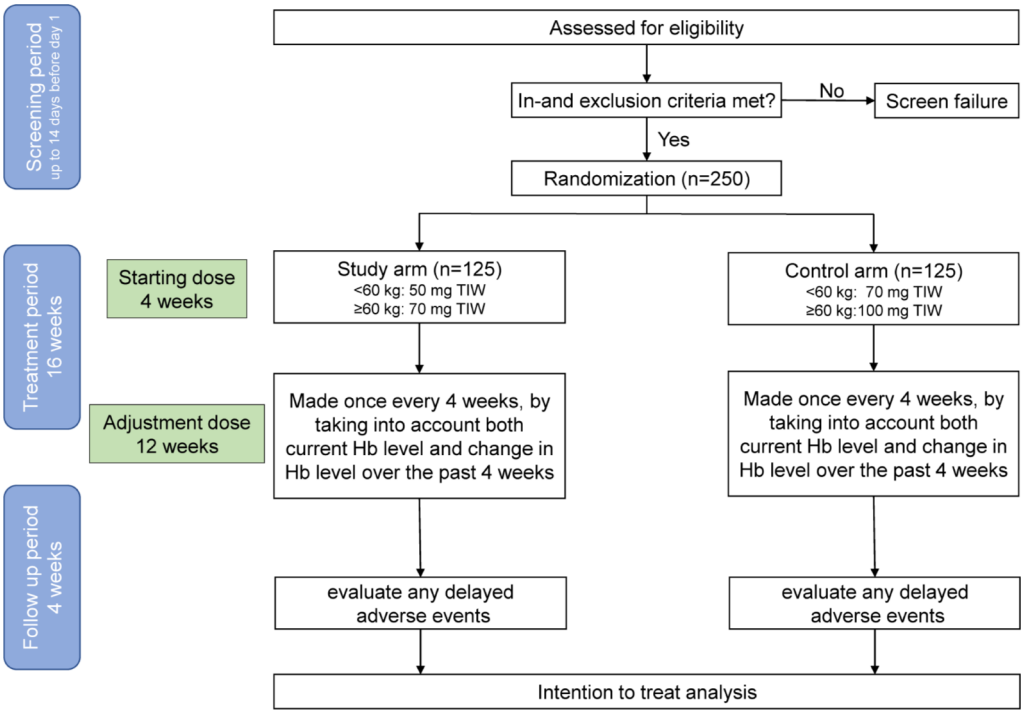

Figure 1 Flow chart of the study. mg, milligram; TIW, three times a week.

Li P, *et al*. *BMJ Open* 2023;**13**:e068864. doi:10.1136/bmjopen-2022-068864

Box 1 Detailed study inclusion and exclusion criteria

Inclusion criteria

1. Ages 18 to 75 years (inclusive);
2. Subject has voluntarily signed and dated an informed consent form, approved by an Ethics Committee, after the nature of the study has been explained and the subject has had the opportunity to ask questions;
3. Diagnosis of chronic kidney disease stage 3–5 patients with an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2 based on the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula, estimated not receiving renal replacement therapy with 6 months;
4. Subject has not been treated with ESA within the previous 4 weeks, the most recent Hb value during the screening period and average Hb value of screening and baseline visit must be ≥70 to <100 g/L;
5. A minimum body weight of 40 kg (inclusive);
6. Subjects agreeing not to start taking any new traditional Chinese medicine (TCM) for anaemia and not to change the dose, schedule or brand of any prescreening TCM for anaemia from the beginning of screening period through the end of trial.

Exclusion criteria

1. New York Heart Association Class III or IV congestive heart failure at screening;
2. Positive for HIV antibody (HIV-Ab), or positive for hepatitis B surface antigen (HBsAg) and HBV NDA level higher than limits of detection, or positive for anti-hepatitis C virus antibody (HCV-Ab) and HCV RNA level higher than limits of detection, or a scheduled anti-virus treatment for HBV and HCV;
3. Myocardial infarction, acute coronary syndrome, stroke, seizure or a thromboembolic event (eg, deep venous thrombosis or pulmonary embolism) within 26 weeks before day 1;
4. History of malignancy except the following: cancers determined to be cured or in remission for ≥5 years, curatively resected basal cell or squamous cell skin cancers, or in situ cancer at any site;
5. Chronic inflammatory disease other than glomerulonephritis that could impact erythropoiesis (eg, systemic lupus erythematosus, rheumatoid arthritis, coeliac disease);
6. Clinically significant active gastrointestinal bleeding (eg, stool occult bleeding test positive for patients without taking oral iron or ≥++ for patients receiving oral iron);
7. Known history of myelodysplastic syndrome, multiple myeloma, hereditary haematological disease such as thalassemia, sickle cell anaemia, pure red cell aplasia or other known causes for anaemia other than CKD, hemosiderosis, hemochromatosis, known coagulation disorder or hypercoagulable condition;
8. Received organ transplant within 6 years or a scheduled organ transplantation;
9. Anticipated elective surgery that could lead to significant blood loss during the study period;
10. Anticipated renal replacement therapy within 6 months by investigator's discretion;
11. Deferoxamine, deferiprone or deferasirox therapy within 12 weeks before day 1 or anticipated use during the treatment period;
12. Life expectancy of <12 months in the judgement of investigators;
13. Blood transfusion within 12 weeks before day 1 or anticipated need for transfusion;
14. Unwilling to withhold intravenous iron during treatment period;
15. Anabolic steroid treatment (eg, androgen) within 12 weeks prior to day 1 or anticipated use during the treatment period;
16. Previous treatment with roxadustat or any HIF-PHI within 12 weeks prior to day 1;
17. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3× upper limit of normal (ULN) or total bilirubin >1.5× ULN at screening and baseline visit except for subjects with known Gilbert's syndrome;
18. Ferritin <100 ng/mL;
19. Use of an investigational medication or treatment, participation in an investigational interventional study within 28 days prior to day 1 or carryover effect of an investigational treatment expected during the study;
20. Women who are pregnant or breast feeding;
21. Women of childbearing potential and men with sexual partners of childbearing potential who are not using adequate contraception;
22. Any medical condition, for example, including active, clinically significant infection, decompensated cirrhosis and so on, that, in the opinion of the investigator, may pose a safety risk to a subject in this study, may confound efficacy or safety assessment, or may interfere with study participation.

Control arm: standard weight-based starting dose group: <60 kg: 70 mg TIW, ≥60 kg: 100 mg TIW.

The starting dose of roxadustat should remain constant as much as possible during the first 4 weeks of the treatment unless a dose reduction is required for excessive hematopoiesis. Dose adjustments should be made once every 4 weeks by considering both the current Hb level and the change in Hb level over the past 4 weeks, as shown in the dose adjustment guideline (online supplemental material 2). Based on Hb level, roxadustat doses may be titrated to achieve and maintain a Hb level of 100 to 120 g/L and to minimise the need for blood transfusion. In the event of excessive hematopoiesis, unscheduled dose adjustment could happen at any time. If a subject requires <20 mg TIW to maintain Hb levels, the dosing frequency could be further reduced in a stepwise fashion, for example, TIW to twice a week (BIW) and BIW to once a week (QW).

Roxadustat (FibroGen (China) Medical Technology Development Company Limited) is formulated in gelatin capsules, stored below 30°C and protected from light. This study uses both 20 mg capsules and 50 mg capsules.

Concomitant medications and rescue therapy

ESAs and new or changes in TCMs (dose or frequency increase) for treating anaemia are not permitted during treatment; other medications that may affect erythropoiesis such as androgens and anabolic steroid, deferoxamine, deferiprone or deferasirox therapy are also prohibited.

Blood transfusions, intravenous iron and ESAs can only be used as rescue therapy during the treatment period. And once subjects receive ESAs as rescue therapy, they should discontinue the study.

Outcome measurements

Efficacy outcomes

The primary efficacy endpoint is the mean change in Hb level from baseline to average over weeks 12–16. The secondary efficacy endpoints are (1) the proportion of subjects achieving an average Hb level of 100 to 120 g/L over weeks 12–16, (2) variability of Hb and (3) the proportion of requirement of rescue therapy (administration of intravenous iron, blood transfusion and ESAs) from 5 weeks on since the first day of treatment, and time to rescue therapy from date of the first dose during study treatment.

The exploratory endpoints are (1) time to first achieving Hb increase by ≥10 g/L from baseline and cumulative proportion of subjects at any time up to and including week 16; (2) number of dose changes (up or down) from treatment initiating up to week 4, and during the treatment period; (3) proportion of subjects having Hb rise >10 g/L or 20 g/L between any 2 weeks in the first 8 weeks, and 4 weeks during the treatment period, and the proportion with Hb above 120 g/L or 130 g/L at any time up to week 16; and (4) differences in efficacy of drugs across subgroups (eg, age, gender, CKD stage, primary diseases, combined with diabetes or not, iron biomarker, proteinuria and inflammation levels).

Safety assessments

We assess the safety through the number (%) of subjects with treatment-emergent adverse events (TEAEs) or serious adverse events (SAEs), and changes from baseline in vital signs, ECG findings and clinical laboratory values.

Participant follow-up

Subjects will undergo an up to 14-day screening period to evaluate eligibility. Eligible participants will be randomised at a 1:1 ratio to the standard starting dose or a one-step lower starting dose arm. After randomisation, subjects will enter the treatment period and receive site visits every 2 weeks in the first 8 weeks and then every 4 weeks until week 16 for efficacy and safety assessment. A routine 4-week follow-up will be performed after the treatment period to capture safety information after study drug dosing is completed. The choice of CKD-anaemia treatment during the follow-up period is up to the investigators' discretion. If the investigators decide to start or resume ESA treatment, the first dose of ESA should be administered at least 3 days after the last dose of roxadustat. This study will not provide ESAs.

Recruitment

Outpatient and inpatient patients diagnosed with CKD stage 3–5 according to KDOQI will be screened according to the inclusion and exclusion criteria. About eight patients will be enrolled in each centre. First patient was enrolled in December 2021 and the planned end date of the study is in May 2023.

Randomisation procedure and allocation concealment

Eligible subjects are randomised in a 1:1 ratio to a standard weight-based starting dose group or lower weight-based starting dose group, respectively, and stratified by CKD stage (stage 3 or stage 4 or stage 5). Randomisation will be performed centrally in sequential order. Once an eligible subject is ready to be randomised, the investigator will contact the randomisation centre to obtain the subject's ID number assigned by the following available ID number from a randomisation schedule. The study treatment will be dispensed as instructed by the randomisation centre. This is an open-label study with investigators and participants unmasked to the information about allocation; any form of population-level summaries of outcome data will be prohibited before the end of the trial.

Data collection and handling

Source documents

Source records are original documents, data and records relevant to the clinical trial. The investigator will prepare and maintain adequate and accurate source documents. Source records must be sufficient to reconstruct all data transcribed onto the case report forms (CRFs) and resolved queries.

Data collection, handling and verification

The clinical investigators from each centre will collect the data and fill in the EDC (electronic data capture) system. Researchers write the medical records at the same time follow-up observations on the patients, and ensure that the data records are timely, complete, accurate and true. Medical records and informed consent as the original datum are archived in the participating centres for at least 5 years after the clinical trials are finished. The General Hospital of PLA and FibroGen China are responsible for CRF development. Authorised site personnel will enter all required data into the EDC. Data will be entered into a validated clinical database compliant with the database requirements of the National Medical Products Administration (NMPA). The database will be a secured, password-protected system with an entire audit trail. Data that appear inconsistent, incomplete or inaccurate will be queried for clarification by the investigator. Medical history, adverse events and concomitant medications will be coded using industry-standard dictionaries (eg, MedDRA and WHO Drug dictionaries). The investigator is responsible for reviewing, verifying and approving all subject data, that is, CRFs and queries before study completion.

Patient and public involvement

There was no patient and public involvement in this protocol.

Statistical analysis

Sample size

About 250 subjects will be enrolled and provide at least 85% power to test the non-inferiority of lower starting dose to standard starting dose in Hb mean change

from baseline averaged over weeks 12 to 16, with a non-inferiority margin of 5 g/L. M1 (margin based on roxadustat standard starting dose) was 19 g/L based on prior China phase III chronic kidney disease study.[11] Also, 5 g/L was chosen as the non-inferiority margin (M2); in this case, the proportion of treatment effect of M1 (f) was approximately 70% which can be deemed an adequate portion of the clinical benefit of roxadustat's standard starting dose to be preserved.

This calculation is based on the t-statistics for a two-sample comparison at a two-sided significance level of 0.05, and the assumption that the difference of mean change from baseline between two arms is 0 g/L and the expected SD is no more than 12 g/L. This calculation also assumes the dropout rate is no more than 30%.

Analysis population

This study will include three analysis sets: the complete analysis set (FAS), the per-protocol analysis set (PPS) and the safety analysis set. The FAS population includes all subjects who receive at least one dose of roxadustat and have at least one non-missing post-baseline Hb value. The PPS population will consist of all FAS patients without significant protocol deviations influencing the primary endpoint evaluation. The safety population consists of all subjects who receive at least one dose of roxadustat. Analyses of the safety data in the study will be based on the safety population.

Subject enrolment and disposition

Enrolment and disposition will be presented for all enrolled subjects. The total number and percentage of patients who completed or discontinued, and the reasons for early discontinuation, will be summarised.

Demographics and baseline characteristics

Demographics (age, ethnicity, sex), baseline characteristics (eg, height, weight) and subject disease characteristics will be summarised for the FAS and safety population. Descriptive statistics will be calculated for continuous variables (age and weight) and frequency counts and percentages will be tabulated for categorical variables (eg, sex, and ethnicity).

Efficacy analyses

Below is the primary hypothesis to be tested for the primary efficacy analysis:

H0: Difference in Hb mean change from baseline to average over weeks 12–16 between two arms (lower starting dose arm − standard starting dose arm) ≤−5 g/L.

vs:

H1: Difference in Hb mean change from baseline to average over weeks 12–16 between two arms (lower starting dose arm − standard starting dose arm) >−5 g/L.

The primary efficacy analysis will test the non-inferiority of the lower starting dose arm compared with standard starting dose arm. The non-inferiority is established if the lower bound of the two-sided 95% CI for the treatment difference in change from baseline Hb (lower starting dose arm − standard starting dose arm) is >−5 g/L. Using repeated measurement mixed model (MMRM) to compare the primary efficacy endpoint with treatment group, visit, treatment group visit as a fixed effect (considering all visit data) and unstructured covariance was adopted, considering the baseline Hb value and eGFR as covariates, and considering the baseline Hb value and eGFR as covariates. The means and differences of the two groups of primary endpoints will be analysed based on the results of the MMRM model to construct their least-squared means (and their 95% intervals). The primary efficacy analysis will be based on the full analysis set (FAS) and the per protocol set (PPS). Haemoglobin results from the local laboratory will be used for all efficacy analyses. Baseline Hb is defined as the mean of the last two Hb values prior to the first dose of study drug.

The FAS population will be used for the primary endpoint and secondary endpoints. The PPS will be used as the primary analysis population for primary and secondary endpoints.

For Hb-related efficacy analyses including primary and secondary endpoints, missing Hb values will not be imputed. A multiple imputation (MI) method will be used for sensitivity analysis. This will be implemented on the raw Hb values, and then the Hb-related endpoints will be derived based on the imputed data (algorithm used for the previous phase III studies). The algorithm for the MI method will be detailed in SAP. For continuous endpoints, changes from baseline will be presented descriptively.

The proportion of responders will be presented descriptively with count and percentages and a 95% CI of the responder rate as deemed applicable. Time to response will be analysed using the Kaplan-Meier method with the KM curve plotted. Additional analysis/endpoints may be detailed with corresponding statistical analysis methods specified in SAP.

Safety analyses

The safety population consists of all subjects who receive at least one dose of roxadustat. Analyses of the safety data in the study will be based on the safety population. All safety assessment data, including laboratory assessments, vital signs, ECGs, AEs, concomitant medications and therapies, will be summarised by time point of collection as appropriate.

Adverse events will be coded using Medical Dictionary for Regulatory Activities (MedDRA). A TEAE is any new or worsening of an existing condition that occurred after the first dose of the study medication and within 28 days after the last dose of the study medication. TEAEs will be tabulated to examine their frequency, severity, organ systems affected and relationship to study treatment. Deaths, TESAEs and TEAEs leading to research or treatment discontinuation will be listed or tabulated separately.

Laboratory tests, vital sign measurements, ECG parameters and baseline changes will be summarised descriptively

Table 1 Schedule of assessments

	Screening period	Treatment period: week							Follow-up period
Visit*	V1	V2 Day 1†	V3 Week 2	V4 Week 4	V5 Week 6	V6 Week 8	V7 Week 12	V8 Week 16/EOT	V9 Week 20
Sign written ICF	X								
Demographics, medical history	X								
Physical examination	X	X						X	X
Height, body weight	X‡	X						X	X
Vital signs	X	X	X	X	X	X	X	X	X
CBC with WBC differential§	X	X¶	X	X	X	X	X	X	X
Serum chemistry††‡‡‡	X	X¶		X		X	X	X	X
Serum iron, ferritin, TIBC, TSAT, transferrin	X**	X				X		X	X
sTfR§		X				X		X	
IL-6§		X				X		X	
12-Lead ECG	X							X	X
Vitamin B_{12}, folate	X								
CRP††		X				X		X	
HIV-Ab, HBsAg, HCV-Ab ‡‡	X								
iPTH††		X						X	
Stool for occult blood§§	X								
Urinary albumin/creatinine ratio		X						X	
Pregnancy test¶¶	X							X	
Evaluate eligibility and randomise eligible subjects***		X							
Dispense study drug		X		X		X	X		
Evaluation for dose adjustment				X		X	X		
Adverse event reporting	X	X	X	X	X	X	X	X	X
Concomitant medication, procedures and non-drug therapies†††	X	X	X	X	X	X	X	X	X

*V1 should be done within 14 days prior to day 1. The visit window for V2–V8 is ±2 days and ±3 days for V9.
†Day 1 is defined as the baseline visit, complete dispensing study drug, patient start taking roxadustat on the day or the second day of dispensing.
‡Height will only be measured at screening visit.
§When testing serum iron studies (serum iron, ferritin, TIBC, TSAT, transferrin and sTfR) and IL-6 during the study period, the collected biological samples will be sent to central laboratory for testing.
¶Laboratory tests completed within 72 hours prior to initial dosing do not need to be tested repeatedly at V2.
**At screening period, only ferritin will be tested at a local laboratory.
††Collect one of alternative results tested in local laboratory for following indicators: blood urea or blood urea nitrogen (BUN), CRP or hs-CRP, iPTH or PTH, bicarbonate/carbon dioxide combining power/total carbon dioxide.
‡‡For subjects with a history of hepatitis B or HBsAg test positive, HBV-DNA level should be tested; for those with a history of hepatitis C or HCV antibody positive, testing for HCV-RNA should be performed.
§§Performed in local laboratory. If positive, document investigator's determination whether the subject has significant gastrointestinal bleeding.
¶¶For female subjects of childbearing potential only.
***Randomisation of eligible subjects occur on day 1.
†††Concomitant medication, procedures and non-drug therapies mentioned in inclusion/exclusion criteria should be recorded strictly following inclusion/exclusion criteria requirements, while those not mentioned in inclusion/exclusion criteria should be recorded within 12 weeks prior to screening period.
‡‡‡Serum chemistry test includes albumin, total protein, alkaline phosphatase, alanine transaminase (ALT), aspartate transaminase (AST), bilirubin (total and direct), bicarbonate/carbon dioxide combining power/total carbon dioxide, blood urea nitrogen (BUN)/blood urea, creatinine, uric acid, calcium, chloride, magnesium, phosphorus, potassium, sodium, glucose, total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL) and triglyceride. At screening period, lipid panel (total cholesterol, LDL, HDL and triglyceride) will not be collected.
CBC, Count of Blood Cell; CRP, C-reativeprotein; ECG, Electrocardiogram; ICF, Informed Consent Form; IL-6, Interleukin-6; iPTH, intact parathyroid hormone; sTfR, soluble Transferrin Receptor; TIBC, Total Iron Binding Capacity; WBC, White Blood Cell.

by assessment time. Clinically significant changes from baseline in these safety parameters will be identified. Shift tables will summarise changes for selected laboratory measures (table 1).

Statistical analysis plan

A detailed statistical analysis plan (SAP) will be finalised prior to the database lock. Any significant changes to the analyses described in this protocol will be highlighted in the SAP. Deviations in comments from the SAP will be detailed in the Clinical Study Report.

Study quality assurance

The study team, composed of the FibroGen China and the clinical research management centre of PLA General Hospital, will be responsible for data reviewing and

monitoring to ensure the study quality during the whole study period.

The investigator must provide direct access to, and allocate sufficient space and time for, the monitor to inspect subject source records, CRFs, queries, collection of local laboratory normal ranges (if applicable), investigational product accountability records, and regulatory documents by Chinese and International Conference on Harmonisation (ICH) E6 Good Clinical Practice (GCP) guidelines.

Authorised representatives of the sponsor, a regulatory authority or an EC may visit the investigator site to perform audits or inspections, including source data verification. The investigator will allow the sponsor auditor, regulatory authority or ethics committee representative to inspect the drug storage area, study drug stocks, drug accountability records, subject charts and study source documents, and other records relative to study conduct.

Safety reporting

The safety reporting period begins after the subject has signed the informed consent and ends 28 days after the last dose of study drug except for pregnancy reporting. SAEs must only be reported following approval and prior to the first dose, while all AEs be reported after that. In the clinical trial process, any serious adverse events must be immediately reported to the principal investigator, the Chinese PLA General Hospital Medical Ethics Committee, the sponsor's drug safety department and the safety supervision of China Food and Drug Administration within the required time. At the same time, the researchers must fill in the record of serious adverse events including the time of serious adverse events, severity, duration, the measures and outcome.

Ethical considerations and dissemination

The Medical Ethics Committee has approved this Chinese PLA General Hospital study (No. S2020-523-05). The trial protocol will need to be approved by an independent ethics committee at each study site. During the implementation in clinical trials, if the protocol needs to be revised, the principal investigator is responsible for revising the plan and re-submitting it to the Ethics Committee for approval after the executive committee for consultation and discussion. The protocol has been amended for several times: the original design (version 1.0, 1 December and version 2.0, 22 March 2021) was a single-arm study evaluating effectiveness and safety of lowering starting dose of roxadustat for CKD 3–4 patients with renal anaemia. The amendment of version 3.0 (18 September 2021) was made before patient enrolment; this version changed study design into an RCT, comparing lower starting dose with standard starting dose of roxadustat for CKD 3–4 anaemia patients. Soon after first patient in, version 3.1 were made and effective to allow the enrolment of CKD 5 NDD anaemia patients, mainly due to feasibility consideration. Investigators in each study centre are responsible for the patient's information and consent. All patient data will be saved according to the assigned serial number and private information will be protected. The principal investigator declares no interest for the overall trial and each study site.

The study will be conducted by NMPA regulations, the ICH E6 Guideline for GCP, the Declaration of Helsinki, any other applicable regulatory requirements and EC requirements. This protocol, the ICF, the investigator's brochure and any information to be given to the subject must be submitted to a properly constituted EC by the investigator for review. No study procedure may be implemented prior to obtaining a signed, written ICF from the subject or the subject's legally authorised representative. The sponsor has purchased insurance to cover for bodily injury or property damage which are results from activities during this trial.

Results of the study will be disseminated via peer-reviewed publications and conference presentations. The release of research results should preserve the privacy of medical information and subject medical information obtained as part of this study is confidential.

DISCUSSION

Roxadustat is a first-in-class, oral therapy that provides treatment of CKD-anaemia with the benefit of a novel mechanism of action that consistently corrects and maintains Hb across the spectrum of non-dialysis-dependent (NDD) CKD-anaemia with an acceptable safety profile. Starting dose of roxadustat based on the weight of NDD subjects were different in trials worldwide.[12 13] These results showed that both high and low starting dose regimens of roxadustat were well tolerated and achieved CKD-anaemia correction with reduced serum hepcidin levels.

As of 30 April 2022, more than 10 000 subjects have been exposed to roxadustat in the clinical development programme, compared with ESAs or placebo. A recent meta-analysis showed that roxadustat could significantly correct renal anaemia in patients with CKD by increasing Hb level and iron metabolism. At the same time, attention must be paid to the risk of SAEs during treatment.[17] Also, a meta-analysis of RCTs showed evidence that after the oral administration of roxadustat, NDD patients' Hb levels were increased effectively and the risk of SAEs was not observed within the short term.[18] The clinical data collected thus far suggest that roxadustat is generally safe and well tolerated in anaemic subjects with CKD on or not on dialysis.[11 12 19–30] Previous phase II and phase III clinical studies in China showed that Hb response got stable after weeks 8,[11 31] so the 16-week treatment duration in this study is considered to be long enough to observe the efficacy with different starting doses in this study. The efficacy of long-time maintenance has been well validated by global phase III clinical studies, and the efficacy of long-time maintenance is not the purpose of this study. Besides treat to Hb targets, minimising Hb variability is also important to decrease adverse outcomes

when treating patients with CKD-anaemia. However, in roxadustat phase III programmes that evaluated efficacy of CKD-anaemia correction and haemoglobin maintenance, few studies assessed Hb variation other than Hb response. In our research, we plan to quantify the degree of haemoglobin variability from inter-patient and intra-patient levels by using measurements such as a sum of absolute value of slope rate of Hb change, slope of linear regression of haemoglobin level during the starting phase and the whole treatment period. By innovatively adopting Hb variability measurements, this study will provide a comprehensive observation and evaluation of the change of haemoglobin over time with each starting-dose arm.

To better explore effective and safe suitable doses, we intend to conduct this randomised study of different initial doses among NDD CKD subjects in China. With approximately 9.1% of the global prevalence of CKD, affecting about 700 million people,[32] further studies are necessary.

Acknowledgements We appreciate Professor Wei Li and Professor Siyan Zhan for their valuable suggestions. No professional medical writers participated in this article.

Contributors Participated in research design: PL, XS, XC, GC, LZ, H-IL, YW and SP. Wrote or contributed to the writing of the manuscript: PL, DC and YW.

Funding Beijing Municipal Science & Technology Commission (Z191100007619054) and FibroGen China co-funded this study. Investigation medication roxadustat is provided by FibroGen China. The study is sponsored by Chinese PLA General Hospital and FibroGen (China) Medical Technology Development Company Limited (FibroGen China). The sponsors were involved in study design, data collection and analysis.

Competing interests YW and SP are employees of FibroGen China Medical Affairs and Clinical Biometrics department.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and the Medical Ethics Committee has approved this Chinese PLA General Hospital study. The trial protocol will need to be approved by an independent ethics committee at each study site. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

ORCID iDs
Ping Li http://orcid.org/0000-0001-5330-1040
Xuefeng Sun http://orcid.org/0000-0003-2984-8905
Guangyan Cai http://orcid.org/0000-0001-8586-6353

REFERENCES

1 Stauffer ME, Fan T. Prevalence of anemia in chronic kidney disease in the United States. *PLoS One* 2014;9:e84943.
2 Li Y, Shi H, Wang W-M, *et al*. Prevalence, awareness, and treatment of anemia in Chinese patients with nondialysis chronic kidney disease: first multicenter, cross-sectional study. *Medicine (Baltimore)* 2016;95:e3872e3872.
3 Lamerato L, James G, van Haalen H, *et al*. Epidemiology and outcomes in patients with anemia of CKD not on dialysis from a large US healthcare system database: a retrospective observational study. *BMC Nephrol* 2022;23:166.
4 Pergola PE, Pecoits-Filho R, Winkelmayer WC, *et al*. Economic burden and health-related quality of life associated with current treatments for anaemia in patients with CKD not on dialysis: a systematic review. *Pharmacoecon Open* 2019;3:463–78.
5 Semenza GL. Hif-1: mediator of physiological and pathophysiological responses to hypoxia. *J Appl Physiol (1985)* 2000;88:1474–80.
6 Peyssonnaux C, Nizet V, Johnson RS. Role of the hypoxia inducible factors HIF in iron metabolism. *Cell Cycle* 2008;7:28–32.
7 Besarab A, Chernyavskaya E, Motylev I, *et al*. Roxadustat (FG-4592): correction of anemia in incident dialysis patients. *J Am Soc Nephrol* 2016;27:1225–33.
8 Dhillon S. Roxadustat: first global approval. *Drugs* 2019;79:563–72.
9 Mima A, Horii Y. Treatment of renal anemia in patients with hemodialysis using hypoxia-inducible factor (HIF) stabilizer, roxadustat: a short-term clinical study. *In Vivo* 2022;36:1785–9.
10 Henry DH, Glaspy J, Harrup R, *et al*. Roxadustat for the treatment of anemia in patients with lower-risk myelodysplastic syndrome: open-label, dose-selection, lead-in stage of a phase 3 study. *Am J Hematol* 2022;97:174–84.
11 Chen N, Hao C, Peng X, *et al*. Roxadustat for anemia in patients with kidney disease not receiving dialysis. *N Engl J Med* 2019;381:1001–10.
12 Akizawa T, Iwasaki M, Otsuka T, *et al*. Roxadustat treatment of chronic kidney disease-associated anemia in Japanese patients not on dialysis: a phase 2, randomized, double-blind, placebo-controlled trial. *Adv Ther* 2019;36:1438–54.
13 Akizawa T, Yamaguchi Y, Otsuka T, *et al*. A phase 3, multicenter, randomized, two-arm, open-label study of intermittent oral dosing of roxadustat for the treatment of anemia in Japanese erythropoiesis-stimulating agent-naïve chronic kidney disease patients not on dialysis. *Nephron* 2020;144:372–82.
14 Provenzano R, Besarab A, Sun CH, *et al*. Oral hypoxia-inducible factor prolyl hydroxylase inhibitor roxadustat (FG-4592) for the treatment of anemia in patients with CKD. *Clin J Am Soc Nephrol* 2016;11:982–91.
15 Provenzano R, Szczech L, Leong R, *et al*. Efficacy and cardiovascular safety of roxadustat for treatment of anemia in patients with non-dialysis-dependent CKD: pooled results of three randomized clinical trials. *Clin J Am Soc Nephrol* 2021;16:1190–200.
16 Chan A-W, Tetzlaff JM, Gøtzsche PC, *et al*. Spirit 2013 explanation and elaboration: guidance for protocols of clinical trials. *BMJ* 2013;346:e7586.
17 Zheng L, Tian J, Liu D, *et al*. Efficacy and safety of roxadustat for anaemia in dialysis-dependent and non-dialysis-dependent chronic kidney disease patients: a systematic review and meta-analysis. *Br J Clin Pharmacol* 2022;88:919–32.
18 Zheng Q, Yang H, Fu X, *et al*. The efficacy and safety of roxadustat for anemia in patients with chronic kidney disease: a meta-analysis. nephrology, dialysis, transplantation: official publication of the European Dialysis and Transplant Association. *European Renal Association* 2021;36:1603–15.
19 Akizawa T, Iwasaki M, Yamaguchi Y, *et al*. Phase 3, randomized, double-blind, active-comparator (darbepoetin alfa) study of oral roxadustat in CKD patients with anemia on hemodialysis in Japan. *J Am Soc Nephrol* 2020;31:1628–39.
20 Charytan C, Manllo-Karim R, Martin ER, *et al*. A randomized trial of roxadustat in anemia of kidney failure: SIERRAS study. *Kidney Int Rep* 2021;6:1829–39.
21 Chen N, Hao C, Liu B-C, *et al*. Roxadustat treatment for anemia in patients undergoing long-term dialysis. *N Engl J Med* 2019;381:1011–22.
22 Akizawa T, Iwasaki M, Otsuka T, *et al*. Phase 3 study of roxadustat to treat anemia in non-dialysis-dependant CKD. *Kidney Int Rep* 2021;6:1810–28.
23 Barratt J, Andric B, Tataradze A, *et al*. Roxadustat for the treatment of anaemia in chronic kidney disease patients not on dialysis: a phase 3, randomized, open-label, active-controlled study (DOLOMITES). *Nephrol Dial Transplant* 2021;36:1616–28.
24 Coyne DW, Roger SD, Shin SK, *et al*. Roxadustat for CKD-related anemia in non-dialysis patients. *Kidney Int Rep* 2021;6:624–35.

25 Csiky B, Schömig M, Esposito C, *et al*. Roxadustat for the maintenance treatment of anemia in patients with end-stage kidney disease on stable dialysis: a European phase 3, randomized, open-label, active-controlled study (Pyrenees). *Adv Ther* 2021;38:5361–80.
26 Fishbane S, El-Shahawy MA, Pecoits-Filho R, *et al*. Roxadustat for treating anemia in patients with CKD not on dialysis: results from a randomized phase 3 study. *J Am Soc Nephrol* 2021;32:737–55.
27 Fishbane S, Pollock CA, El-Shahawy M, *et al*. Roxadustat versus epoetin alfa for treating anemia in patients with chronic kidney disease on dialysis: results from the randomized phase 3 ROCKIES study. *J Am Soc Nephrol* 2022;33:850–66.
28 Hou Y-P, Mao X-Y, Wang C, *et al*. Roxadustat treatment for anemia in peritoneal dialysis patients: a randomized controlled trial. *J Formos Med Assoc* 2022;121:529–38.
29 Provenzano R, Shutov E, Eremeeva L, *et al*. Roxadustat for anemia in patients with end-stage renal disease incident to dialysis. Nephrology, Dialysis, Transplantation: official publication of the European Dialysis and Transplant Association. *European Renal Association* 2021;36:1717–30.
30 Shutov E, Sułowicz W, Esposito C, *et al*. Roxadustat for the treatment of anemia in chronic kidney disease patients not on dialysis: a phase 3, randomized, double-blind, placebo-controlled study (ALPS). *Nephrol Dial Transplant* 2021;36:1629–39.
31 Chen N, Qian J, Chen J, *et al*. Phase 2 studies of oral hypoxia-inducible factor prolyl hydroxylase inhibitor FG-4592 for treatment of anemia in China. *Nephrol Dial Transplant* 2017;32:1373–86.
32 GBD Chronic Kidney Disease Collaboration. Global, regional, and national burden of chronic kidney disease, 1990-2017: a systematic analysis for the global burden of disease study 2017. *Lancet* 2020;395:709–33.