Clinical Study Report Synopsis	
Drug Substance	Roxadustat
Study Code	D5741C00002
Edition Number	1
Date	25 April 2022
NCT Number	NCT04655027

ALTAI: An Open-Label, Randomized, Active-Controlled, Parallel Design, Multicenter Phase IV Study to Investigate the Effect of Roxadustat versus Recombinant Human Erythropoietin (rHuEPO) on Oral Iron Absorption in Chinese Patients with Anemia of Chronic Kidney Disease (CKD)

Study dates: First subject enrolled: 22 February 2021
Last subject last visit: 12 October 2021
The analyses presented in this report are based on a clinical data lock date of 06 December 2021

Phase of development: Therapeutic use (IV)

Co-ordinating Investigator: PPD
PPD
PPD
Beijing, China, 100730

Sponsor's Responsible Medical Officer: PPD
AstraZeneca Gothenburg,
SE-43183 Mölndal, Sweden

This study was performed in compliance with International Council for Harmonisation (ICH) Good Clinical Practice, including the archiving of essential documents.

Study centers

This study was conducted at 8 clinical sites in China, of which 5 sites enrolled patients.

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Table S1 Objectives and Endpoints

Objectives	Endpoints
Primary	
Evaluate the main effect of roxadustat versus rHuEPO on GI iron absorption	The main treatment effect on the difference from baseline (Day 1) to Day 15 in log-transformed [a] AUC of iron absorption from 0-3 hours based on the change in serum iron levels obtained just prior to T0 (time when single dose of oral iron is administered) and over a 3-hour period
Secondary	
Assess the effect and interaction with key baseline variables [b] of roxadustat versus rHuEPO on iron absorption	The main treatment effect and key interaction effects on the difference from baseline (Day 1) to Day 15 in log-transformed [a] AUC of iron absorption from 0-3 hours based on the change in serum iron levels obtained just prior to T0 (time when single dose of oral iron is administered) and over a 3-hour period
Assess the effect and interaction with key baseline variables [b] of roxadustat versus rHuEPO on the indices of iron metabolism (ie, serum iron, ferritin, TIBC, TSAT, transferrin, soluble transferrin receptor) and hepcidin levels	The main treatment effect and key interaction effects on the difference from baseline (Day 1) to Day 15 prior to administration of oral iron in serum iron, ferritin, TIBC, TSAT, transferrin, soluble transferrin receptor and hepcidin levels, log-transformed as appropriate
Safety	
Safety evaluation	Safety assessed by incidence of AEs, and measurement of vital signs (tympanic temperature, BP, pulse, and respiratory rate), and laboratory variables

[a] Log transformation was not appropriate for analysis of the final AUC data received; hence untransformed AUC data were used for this analysis.

[b] Pre-specified key baseline variables analyzed in this study were hs-CRP and hepcidin.

Abbreviations: AE = adverse event; AUC = area under the time-concentration curve; BP = blood pressure; GI = gastrointestinal; hs-CRP = high sensitivity C-reactive protein; rHuEPO = recombinant human erythropoietin; TIBC = total iron binding capacity; TSAT = transferrin saturation.

Study design

This was a Phase IV, randomized, active-controlled, open-label, parallel design, multicenter prospective study conducted in China to evaluate the effect of treatment with roxadustat (oral tablets) versus recombinant human erythropoietin (rHuEPO) (either intravenous [IV] or subcutaneous [SC]) on the gastrointestinal (GI) iron absorption in patients with anemia of Stage 4 and Stage 5 chronic kidney disease (CKD).

An Interactive Voice Response System was used for randomization to study treatments and patient stratification. At randomization, patients were stratified first by dialysis status as dialysis-dependent (DD) or non-dialysis-dependent (NDD); within those strata, DD were stratified by dialysis modality as hemodialysis (HD) or peritoneal dialysis (PD); and NDD were stratified by prior rHuEPO exposure as rHuEPO-users or rHuEPO-naïve as described below:

- Dialysis-dependent patients: patients who had been on stable renal replacement therapy and had been on a stable dose of rHuEPO within 4 weeks prior to screening.
  - DD-HD.
  - DD-PD.
- Non-dialysis-dependent patients: patients with Stage 4 or Stage 5 CKD (glomerular filtration rate [GFR] estimated to be < 30 mL/min/1.73 m^2 by the 2009 Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] equation[1]).
  - NDD-rHuEPO-users.
  - NDD-rHuEPO-naïve.

Patients were also planned to be stratified by high sensitivity C-reactive protein (hs-CRP) levels at screening (≤◦upper limit of normal [ULN] or >◦ULN; ULN = 10.0 mg/mL). However, this stratification was removed per Protocol Amendment 2 because the capping on recruitment based on baseline hs-CRP ULN was removed and the total sample size was reduced.

The study consisted of 3 periods: Screening Period (up to 3 weeks), Treatment Period (2 weeks), and Follow-up Period (4 weeks). Eligible patients were randomized at a 1:1 ratio to receive either roxadustat or rHuEPO for 14 days starting from Day 1.

All patients randomized to rHuEPO group received a uniform brand of short-acting rHuEPO, SEPO, according to the dosage approved in the SEPO China package insert. Patients who

[1] Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF 3rd, Feldman HI, et al; CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration). A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009;150(9):604-12.

were on a rHuEPO prior to screening received a starting SEPO dose that was based on their previous dose of rHuEPO and according to the dosage approved in the SEPO China package insert.

A ferrokinetic study consisting of ferrokinetic measurements (serum iron and total iron binding capacity [TIBC]) on Day 1 and Day 15 was conducted.

Target subject population and sample size

This study included Chinese patients with anemia of CKD.

The study was originally planned to randomize a minimum of 46 patients with anemia of CKD. Per the last protocol amendment, a maximum of 104 patients with anemia of CKD were planned to be screened to achieve a minimum of 20 and a maximum of 60 eligible randomized patients. Twenty-five patients were finally included:

- Roxadustat: 13 patients.
- rHuEPO: 12 patients.

Investigational product and comparator(s): dosage, mode of administration and batch numbers

The study treatments administered to patients included roxadustat (oral doses) or SEPO (by either IV or SC routes).

Roxadustat

The starting dose of roxadustat was calculated as per the China package insert, on the basis of patient's body weight:

- Dialysis-dependent patients: 100 mg (45 to < 60 kg) or 120 mg (≥ 60 kg); patient's weight prior to dialysis, dosing was 3 times per week (TIW).
- Non-dialysis-dependent patients: 70 mg (40 to < 60 kg) or 100 mg (≥ 60 kg), dosing was TIW.

Roxadustat doses were administered at least 2 days apart but no more than 4 days apart. The dose of roxadustat was not adjusted during the study (except for safety reasons as judged by the Investigator).

rHuEPO

Patients randomized to rHuEPO received SEPO according to the dosage approved in the rHuEPO China package insert.

- For patients on once per week dose of rHuEPO of 6000 IU, dosing was twice per week (BIW).
- For patients on once per week dose of rHuEPO of > 6000 IU, dosing was TIW.

The study rHuEPO starting dose depended on the patient's hemoglobin (Hb) levels at screening and could be adjusted on Day 8 during the 2-week Treatment Period, depending on the patient's Hb levels, or could be adjusted at any time for safety reasons as judged by the Investigator.

For DD patients, rHuEPO was administered either IV or SC depending on the route of administration they used before the Treatment Period. For NDD patients, rHuEPO was administered via the SC route.

Oral iron for ferrokinetic study
For the ferrokinetic study on Day 1 and Day 15, patients were administered a single dose of oral iron of 12.5 mL containing 100 mg elemental iron. All patients received the same brand of liquid oral iron containing ferrous sulfate.

Duration of treatment

The length of the treatment period was 2 weeks.

Statistical methods

In the ferrokinetic study, on Day 1 and Day 15, patients were administered a single dose of oral liquid elemental iron (100 mg) at time T0, and serum iron level was determined in samples taken just before T0 and after 1, 2, and 3 hours (timepoints T1, T2, and T3). TIBC was determined in samples taken just before T0. Gastrointestinal iron absorption was assessed as area under the time-concentration curve (AUC) of serum iron from T0 to T3.

The primary endpoint for this study was the change from baseline (Day 1) to Day 15 in GI iron absorption (serum iron AUC) compared between treatment with roxadustat versus rHuEPO.

The difference between Day 1 to Day 15 in AUC of serum iron was analyzed using an ANCOVA model, adjusting for study treatment and baseline hs-CRP ($\leq$ ULN, > ULN; ULN = 10.0 mg/mL) level.

The null hypothesis was that there is no difference in the average change from baseline in the ferrokinetic measurements between rHuEPO and roxadustat treatment.

Multiple imputation was implemented for the primary and secondary analysis to account for missing data. If there were no missing data, then analysis was performed on observed cases. If the primary endpoint results were not significant ($p > 0.05$), then hypothesis testing was to stop and the null hypotheses for the secondary endpoints was to be accepted.

After clinical data lock, it was found that serum iron AUC values were negative for 2 patients, due to which log-transformation of the AUC data was not possible. Consequently, changes were made in the planned analysis and recorded in a Statistical Analysis Modification Requests. Briefly, untransformed AUC data for efficacy analysis were used, wherever applicable. Analysis of log-transformed serum iron AUC data using only the non-negative AUC values was done as a sensitivity analysis on the Sensitivity analysis set.

For the secondary analyses, the relative difference between Day 1 and Day 15 in serum iron AUC and in serum levels was planned to be analyzed using an ANCOVA model similar to primary analysis, adjusting for study treatment, strata (NDD-rHuEPO-users, NDD-rHuEPO-naïve, DD-PD, and DD-HD), baseline variables (hs-CRP and hepcidin), and interactions of these 2 variables with treatment. For the actual analyses, the key change was the removal of strata from the ANCOVA model.

The primary and secondary analysis was performed on the Full analysis set, with additional analysis performed on the Per-protocol analysis set. The following analysis populations were defined:

Population	Description
All-patients analysis set	The all-patients analysis set consisted of all patients who were screened. This analysis set was used for generating listings.
Full analysis set	The FAS was the primary efficacy analysis set and included all randomized patients who completed baseline (Day 1) measurements for any efficacy analysis. The FAS was used for analyses of primary and secondary endpoints, as well as for the presentation of demographic and disposition data.
Per-protocol analysis set	The PP analysis set included all randomized patients who received at least 1 dose of study treatment, had baseline (Day 1) and at least 1 post-baseline iron absorption measurement, and no major protocol violations. The PP analysis set was used for sensitivity analysis of the primary and secondary endpoints.
Safety analysis set	The Safety analysis set included all randomized patients who received at least 1 dose of study treatment, with patients being analyzed as treated, rather than as randomized. The Safety analysis set was used for analysis of the safety endpoints and of the exposure to study treatment.
Sensitivity analysis set [a]	The Sensitivity analysis set included all subjects in the FAS who had positive serum iron AUC iron absorption values at all visits. The Sensitivity analysis set was used for the additional sensitivity analysis of the primary endpoint.

[a] Sensitivity analysis set was not included in the original SAP but was introduced during data analysis as described above.

Abbreviations: AUC = area under the time-concentration curve; FAS = full analysis set; PP = per-protocol; SAP = statistical analysis plan.

Study population

	Roxadustat	rHuEPO	Total
No. of subjects enrolled			51
No. of subjects randomized	13	12	25
Males/females	4/9	5/7	9/16
Mean age (years; range [min-max])	57.3 PPD	52.8 PPD	55.1 PPD
Dialysis-dependent			
HD	5	6	11
PD	6	5	11
Non-dialysis-dependent			
rHuEPO-users	0	0	0
rHuEPO-naïve	2	1	3
No. analyzed for efficacy (FAS)	13	12	25
No. analyzed for efficacy (PP)	12	10	22
No. analyzed for safety	13	12	25
No. withdrawn from study	1[a]	0	1
No. completed the study	12	12	24

[a] In total, 1 patient was withdrawn; the main reason given was failure to meet inclusion/exclusion criteria and secondary due to the global/country COVID-19 situation.

Abbreviations: COVID-19 = Coronavirus Disease of 2019; FAS = full analysis set; HD = hemodialysis; PD = peritoneal dialysis; PP = per-protocol; rHuEPO = recombinant human erythropoietin.

Overall, demographic and baseline characteristics, including disease characteristics, were comparable between the 2 treatment groups. It may be noted that the dialysis vintage (time from first dialysis) was longer in rHuEPO: The mean ± SD time from initial dialysis to randomization was 75.5 ± 58.49 months for the roxadustat group and 91.5 ± 85.33 months for the rHuEPO group, but all had been on dialysis for at least 20 months.

Summary of efficacy results

Efficacy results are summarized as follows:

- The mean ± SD change from baseline (Day 1) to Day 15 in serum iron AUC in the roxadustat group was numerically higher than in the rHuEPO group (11.288 ± 28.1506 g*3hr/dL vs −0.259 ± 9.7369 g*3hr/dL) but this difference was not statistically significant (p = 0.212).
- There was no statistically significant difference (p > 0.05) between roxadustat and rHuEPO treatments for primary analysis using untransformed serum iron AUC data analyzed on the FAS or PP analysis set with multiple imputations, or analyzed on FAS or PP analysis set with observed cases, when excluding the patients with negative serum iron AUC values (1 patient each from each treatment group).
- There was no statistically significant difference (p > 0.05) between roxadustat and rHuEPO treatments for the primary analysis using log-transformed serum iron AUC data.

- Nominally statistically significant differences ($p < 0.05$) were observed between roxadustat and rHuEPO treatments for some of the secondary analyses of the following variables:
  - TIBC.
  - Transferrin.
  - Soluble transferrin receptor.
  - Hepcidin.

However, statistical significance of the secondary endpoints should be viewed with caution and treated as exploratory, because the primary endpoint indicated a lack of statistical significance for the treatment effect of roxadustat compared with rHuEPO.

Subgroup analyses had large uncertainty due to low numbers within each subgroup.

Summary of safety results

Safety results are summarized as follows:

- Overall, 5 (38.5%) patients from the roxadustat group experienced a total of 8 adverse events (AEs), and 2 (16.7%) patients in the rHuEPO group experienced a total of 2 AEs.
- The most frequently reported AE (reported by at least 10% of patients in one treatment group) was hyperkalemia in rHuEPO group, reported in 2 (16.7%) patients. No AE was reported in > 10% of the patients in the roxadustat group.
- All AEs reported in the roxadustat group were considered to be of mild intensity, while all AEs reported in the rHuEPO group were considered of moderate intensity.
- No serious AEs, deaths, or discontinuations of investigational product due to AEs were reported.
- One AE (back pain) that was reported in the roxadustat group was considered possibly related to roxadustat.
- Overall, clinical laboratory evaluations were comparable between treatment groups. No Potential Hy's Law cases were detected.
- No clinically important observations were made regarding vital signs.
- The safety findings observed in this study were consistent with those expected for a population of patients with CKD and anemia, and the known safety profile of roxadustat.

Conclusions

- No statistically significant difference was observed in GI iron absorption assessed as change from baseline of serum iron AUC between roxadustat and rHuEPO.
- No new clinically significant safety concerns were identified in roxadustat or rHuEPO groups.