Clinical Trial/Experimental Study

Medicine

OPEN

Biosimilar erythropoietin in anemia treatment (BEAT)—Efficacy and safety of a 1:1 dose conversion from EPREX® to EPIAO® in patients with end-stage renal disease on hemodialysis

A prospective, randomized, double blind, parallel group study

Bolong Miao, MD[a,*], Alina Nikolaevna Isachkina, MD, PhD[b], Evgeny Viktorovich Shutov, MD, PhD[c], Alexander Alekseevich Selyutin, MD[d], Lyudmila Vladimirovna Kvitkova, MD, PhD[e], Valery Yuryevich Shilo, MD[f], Olga Nikolaevna Vetchinnikova, MD[g], Ilya Vyacheslavovich Alexandrov, MD, PhD[h], Dmitry Vladislavovich Perlin, MD[h], Alexander Vasilievich Zuev, MD[i], Igor Leonidovich Davydkin, MD[i], Tatyana Pavlovna Mironova, MD[i], Olga Mikhailovna Solovyova, MD[k], Alexey Pavlovich Tutin, MD[l], Alexey Mikhailovich Omelchenko, MD[m], Kriengsak Vareesangthip, MD[n], Nadezhda Georgievna Khadikova, MD[o], Man Li, MD[p], Xiang Li, MD[q]

Abstract

Background: EPREX®/ERYPO®/PROCRIT® (epoetin alfa, Janssen-Cilag GmbH) was the first available recombinant human erythropoietin (rHuEPO) and was universally reference product as per the recommendation provided by European Medicines Agency. EPIAO® is a biosimilar formulation of EPREX®, and making it a 1:1 dose conversion from EPREX® according to recommendation of European Medicines Agency. This study evaluated the clinical efficacy and safety of EPIAO® in subjects with end-stage renal disease receiving hemodialysis after intravenous administration.

Methods: This study was a multicenter, prospective, randomized, double-blind, parallel-group, 2-cohort, maintenance phase, therapeutic equivalence study to evaluate a 1:1 dose conversion from EPREX® to EPIAO® in terms of clinical efficacy and safety that was conducted at 20 sites in 2 countries in patients with end-stage renal disease on hemodialysis. Eligible subjects were treated with EPREX® (reference product of epoetin) for a period of at least 3 months before the treatment period, and then were randomly assigned to the group of EPREX® or EPIAO®. Primary endpoints were mean absolute change in hemoglobin level and mean absolute change in weekly epoetin dosage from baseline to 6 months after treatment with EPIAO®/EPREX® in parallel groups.

Results: A total of 200 people received the random intervention and were included in the safety set. After 6, 9, and 12 months of treatment with EPIAO® or EPREX®, there were no significant differences in the hemoglobin levels of the 2 groups compared with baseline. The 95% confidence interval for the treatment difference was within the predetermined acceptable range: ±0.5 g/dL. There were no significant differences in the epoetin dosage of the 2 groups compared with the baseline. The 95% confidence interval for the treatment difference was within the predetermined acceptable range: ± 45 IU/kg. There were no significant differences in the incidence of adverse events between the EPIAO® and EPREX® groups. Most adverse events were mild to moderate and were reverted/resolved.

Conclusion: EPIAO® demonstrated promising effectiveness and manageable safety in patients with end-stage renal disease on hemodialysis.

Abbreviations: AE = adverse event, CKD = chronic kidney disease, CRF = Case Report Form, EPO = erythropoietin, IV = intravenously, rHuEPO = recombinant human erythropoietin, SAE = serious adverse event.

Keywords: biosimilar EPO, chronic kidney disease, EPIAO®, epoetin, erythropoietin

This research is partially funded by National Science and Technology Major Project, Ministry of Science and Technology of the People's Republic of China (No. 2018ZX09303004).

The authors have no conflicts of interest to disclose.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

ClinicalTrials.gov, NCT02947438. Biosimilar Erythropoietin in Anaemia Treatment (Maintenance Phase Study).

Supplemental Digital Content is available for this article.

[a] Medical Department, Shenyang Sunshine Pharmaceutical Co., Ltd., Shenyang Economy & Technology Department Zone, Shenyang, P.R.China, [b] State Educational Government-Financed Institution of Higher Professional Education "North-Western State Medical University named after I.I. Mechnikov" of the Ministry of Health and Social Development of the Russian Federation, Clinical Hospital named after Peter the Great, dialysis department, Saint Petersburg, Russia, [c] State Budgetary Institution of Health Care of the city of Moscow Municipal Clinical Hospital named after S.P. Botkin of the Department of Healthcare of the city of Moscow, Moscow, Russia, [d] State-financed Health Institution "Municipal Clinical Hospital No. 1" of Orenburg, Orenburg City, Russia, [e] Autonomous Public Health Care Institution in the Kemerov region "S.V. Belyaev Kemerovo Regional Clinical Hospital," Kemerovo City, Russia, [f] Limited Liability Company "MEDITSYNSKY TSENTR VYSOKIKH TEKHNOLOGYII POLIKLINIKA No. 1 (Medical Center of High Technologies Policlinic No. 1", Moscow, Russia, [g] State budgetary Healthcare Institution of the Moscow Region "Moscow Regional Research and Clinical Institute n.a. M.F. Vladimirskiy", Surgical Nephrology and Hemocorrection Division, Chronic Hemodialysis Department, Moscow, Russia,

1. Introduction

Chronic kidney disease (CKD) is a clinical syndrome secondary to the definitive change in function and/or structure of the kidney and with characteristics of irreversible and chronic progression.[1] Iron deficiency anemia is a common complication that accompanies the progression of CKD.[2] The decisive cause of anemia due to CKD is insufficient erythropoietin (EPO).[3] Therefore, the therapies include iron supplements, erythropoietin-stimulating agents, and red blood cell transfusion.[4]

The introduction of recombinant human erythropoietin (rHuEPO) into clinical practice in the1980s was a major breakthrough in the treatment of anemia of CKD.[5] It stimulates red blood cell production and replaces the insufficient endogenous EPO production related to CKD progression.[6] Epoetin alfa [EPREX®/ERYPO®/PROCRIT® (Janssen-Cilag GmbH)] was the first available rHuEPO.[7,8] Since then, such biosimilars have been developed. Due to modern pharmaceutical technology assuring high structural similarity between the biosimilar and originator products, it is unnecessary to conduct the same clinical trials as of originator products.[7] However, equivalence and safety trials are still the keys to evaluating the clinical availability of biosimilar EPO.

EPIAO® is a biosimilar formulation of EPREX® and a kind of epoetin-alfa widely used in China and was approved for marketing in China in 1998.[9] Since the marketing approval, it is estimated that about 587,897 domestic and foreign subjects have used EPIAO® for the treatment of anemia. But studies on the efficacy and safety of EPIAO® are limited. Herein, we present the results of this prospective, randomized, double-blind, parallel-group study that compares the efficacy and safety between EPIAO® and EPREX® in the treatment of patients with end-stage renal disease on hemodialysis.

2. Methods

2.1. Study design and sample size

This study was a multicenter, prospective, randomized, double-blind, parallel group, 2-cohort, maintenance phase, therapeutic equivalence study to evaluate a 1:1 dose conversion from EPREX® to EPIAO® in terms of clinical efficacy and safety that was conducted at 20 sites in 2 countries in patients with end-stage renal disease (CKD stage 5) on hemodialysis. Inclusion criteria and exclusion criteria are presented in Table S1, http://links.lww.com/MD/H774. The study was conducted in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki. This study was ethically approved by The Ministry of Health of the Russian Federation Ethics Committee (No. 4018558-20-1/ww). All patients provided written informed consent. This study was registered with ClinicalTrials.gov (https://www.clinicaltrials.gov/), number NCT02947438, with the title "Biosimilar Erythropoietin in Anaemia Treatment (Maintenance Phase Study)."

As shown in Figure 1, eligible subjects were treated with EPREX® (reference product of epoetin) for a period of at least 3 months (titration period) after screening. Patients with hemoglobin levels within the target range of 10 to 12.5 g/dL during the titration period were randomly assigned in a 1:1 ratio to switch to treatment with EPIAO® (investigational product of epoetin) or continue treatment with EPREX®. The dose of EPIAO®/EPREX® was adjusted individually to maintain hemoglobin at a level not exceeding 12 g/dL. Subjects would receive oral iron supplements if transferrin saturation was <20% and would continue on an iron supplement to maintain the transferrin saturation ≥20%. During the treatment period, the subjects were instructed to visit the study facility 1 to 3 times a week, from week 14 to 64. The visit date could be ±2 days from the scheduled date.

The calculation of the sample size showed that 70 cases would be included in each group, and a total of 140 subjects could achieve a degree of more than 80% confidence to prove the equivalence of the 2 synergistic primary endpoints. The expected dropout rate was around 18%, and the total number of randomized subjects was estimated to be 170 (n = 85 subjects per group). The recruitment should be stopped when the total enrollment of at least 170 subjects was achieved.

2.2. Randomization

Subjects would be assigned to either treatment arm A (receiving EPIAO®) or B (receiving EPREX®) in a ratio of 1:1. The randomization schedule was generated by statistical team, using PROC PLAN in SAS, version 9.2 or higher, according to

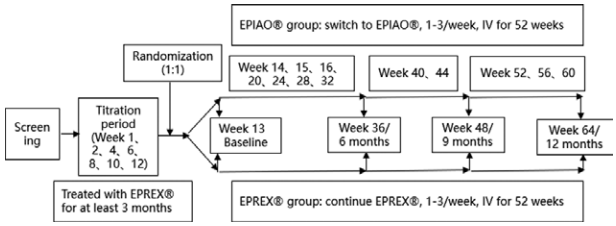

Figure 1. Study design.

[h] Budgetary Public Health Care Institution "Volgograd Regional Center for Urology and Nephrology", Volzhsky City, Russia, [i] State Budgetary Healthcare Institution of the Republic of Karelia "V.A. Baranov Republican Hospital", Petrozavodsk City, Russia, [j] State Educational Government-Financed Institution of Higher Professional Education "Samara State Medical University" of the Ministry of Health and Social Development of the Russian Federation, of the Clinic of the Samara State Medical University, the Clinic and Department of Hospital Therapy, dialysis department, Samara City, Russia, [k] Saint Petersburg State budget institution of healthcare "City hospital of Saint Martyr Elizabeth", Saint Petersburg, Russia, [l] Limited Liability Company "Kupchinski tsentr ambulatornogo dializa", Saint Petersburg, Russia, [m] Saint Petersburg State-financed Health Institution "Municipal Mariinsky Hospital", Dialysis Department, Saint Petersburg, Russia, [n] Renal Division, Department of Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand, [o] St. Petersburg Budgetary Public Health Care Institution "Nikolayevsky Hospital", Konstantinovskaya, Russia, [p] Project Manager, International Department, Shenyang Sunshine Pharmaceutical Co., Ltd., Beijing, P.R. China, [q] Medical Manager, Medical Department, Shenyang Sunshine Pharmaceutical Co., Ltd., Shenyang Economy & Technology Department Zone, Shenyang, P.R. China.

* Correspondence: Bolong Miao, Medical Director, Medical Department, Shenyang Sunshine Pharmaceutical Co., Ltd., No. 3A1, Road 10, Shenyang Economy & Technology Department Zone 110027, P.R. China (e-mail: miaobolong@3sbio.com).

How to cite this article: Miao B, Isachkina AN, Shutov EV, Selyutin AA, Kvitkova LV, Shilo VY, Vetchinnikova ON, Alexandrov IV, Perlin DV, Zuev AV, Davydkin IL, Mironova TP, Solovyova OM, Tutin AP, Omelchenko AM, Vareesangthip K, Khadikova NG, Li M, Li X. Biosimilar erythropoietin in anemia treatment (BEAT)—Efficacy and safety of a 1:1 dose conversion from EPREX® to EPIAO® in patients with end-stage renal disease on hemodialysis: A prospective, randomized, double blind, parallel group study. Medicine 2022;101:47(e31426).

Received: 18 August 2022 / Received in final form: 29 September 2022 / Accepted: 30 September 2022

http://dx.doi.org/10.1097/MD.0000000000031426

standard operating procedures. The randomization allocation was done by the Interactive Voice Response System/Interactive Web Response System for dispensing the test drugs.

2.3. Blinding and unblinding

This was a double blinded and randomized study. All investigators, subjects, site personnel (except the study nurse performing the drug administration and pharmacist), and Contract Research Organization study team (except persons involved in the preparation of the codes, clinical operations team in Russia, and project manager who was responsible for convening the Safety Monitoring Committee meeting) were blinded to the medication codes. A treating physician might request unblinding of study medication on an individual subject, if it was essential for the clinical management of the subject's health.

2.4. Study endpoints

Primary endpoints included mean absolute change in hemoglobin level from baseline to 6 months after treatment with EPIAO®/EPREX® in parallel groups (g/dL). Mean absolute change in weekly epoetin dosage per kg body weight from baseline to 6 months after treatment with EPIAO®/EPREX® in parallel groups (IU/kg/week).

Secondary endpoints included proportion of subjects hemoglobin values are within 10 to 12 g/dL for the last 4 weeks of the period for assessment of treatment efficacy and safety (weeks 32–36). Proportion of subjects with any hemoglobin measurement outside the target range during the double-blind treatment period. Mean hemoglobin and hematocrit levels every 4 weeks within the treatment period (52 weeks). Mean doses of the study products (IU/kg/week) every 4 weeks throughout the study period (52 weeks). Incidence of blood transfusions.

Safety endpoints included incidence and nature of adverse events (AEs). Incidence of drug-related adverse events. Clinically significant changes in the vital signs, and physical and laboratory examination. Number of subjects who prematurely withdrew from the study due to AE and serious adverse event (SAE). Number of subjects with the presence of anti-erythropoietin antibodies (anti-EPO Ab).

2.5. Statistical analysis

The SAS® package (SAS® Institute Inc., and Version 9.2 or higher) was used for statistical analysis. The t-test/rank-sum test was used to compare the quantitative data of patients, and the chi-square test/Fisher's exact probability test was used to compare the categorical variables of patients. The ANCOVA was performed based on the normality of data for mean absolute change in hemoglobin level and mean absolute change in weekly epoetin dosage per kg body weight from baseline to 6, 9, and 12 months in parallel groups. The variables of center, hemoglobin level at baseline and weight were used as covariates. The 95% confidence intervals were calculated for the treatment differences and compared with pre-defined acceptance ranges: ±0.5 g/dL for hemoglobin, ±45 IU/kg/week for dosage. All statistical tests were performed using 2-sided tests. P value <.05 was considered as statistically significant.

3. Results

3.1. Patient disposition and baseline characteristics

Two hundred and seven patients were enrolled in this study between April 2016 and July 2021 (Fig. 2), and 200 of them received randomized intervention and were included in the safety set. The number of patients at 6, 9, and 12 months were 166, 153, and 137, respectively. Primary reasons for subjects' withdrawn including change of residence, change of dialysis center or hospital, renal transplantation, death, loss of contact, and the patient voluntarily giving up continuing to participate in the study. There were no significant differences in age, gender, height, weight, physical examination and other general examinations between parallel groups (Tables 1–5).

3.2. Efficacy

3.2.1. Primary endpoints Results of the main efficacy evaluation were presented in Tables 6 and 7. Mean hemoglobin levels and weekly epoetin dose/kg every 4 weeks within the treatment period (52 weeks) was shown in Figures 3 and 4. The baseline hemoglobin level in the EPIAO® group was 11.19 ± 0.57 g/dL, and it was 11.13 ± 0.89 g/dL at 6 months, with difference of −0.06 ± 1.01 g/dL. In the parallel group of EPREX®, the baseline hemoglobin level was 11.26 ± 0.55 g/dL, and it was 11.11 ± 0.95 g/dL at 6 months, with difference of −0.15 ± 0.97 g/dL. Performing ANCOVA with the center, hemoglobin level and body weight as covariates, after 6 months of treatment with EPIAO® or EPREX®, there was no significant difference in the hemoglobin levels of the 2 groups compared with baseline (P = .71). The difference at 6 months was 0.05 g/dL (95% confidence interval: −0.22, 0.33). It was within the predetermined acceptable range: ±0.5 g/dL (hemoglobin), which indicated equivalent curative effect between 2 groups. The baseline weekly epoetin dose/kg (IU/kg/week) of EPIAO® group was 92.03 ± 55.10, and it was 92.49 ± 70.70 at 6 months, with difference of 0.45 ± 43.64. The baseline weekly epoetin dose/kg (IU/kg/week) of EPREX® group was 109.73 ± 59.12, and it was 94.43 ± 62.56 at 6 months, with the difference of −15.30 ± 54.47. Performing ANCOVA with the center, hemoglobin level, and body weight as covariates, there was no significant difference in the epoetin dosage compared with baseline after treated with EPIAO®/EPREX® for 6 months (P = .08). The difference at 6 months was 12.49 IU/kg/week (95% confidence interval: −1.86, 26.86). It was within the predetermined acceptable range: ±45 IU/kg (dose), which indicated that equivalent efficacy between 2 groups.

3.2.2. Secondary endpoints The secondary efficacy evaluated the difference in hemoglobin levels and epoetin dosage between 2 groups after 9 months and 12 months of treatment with

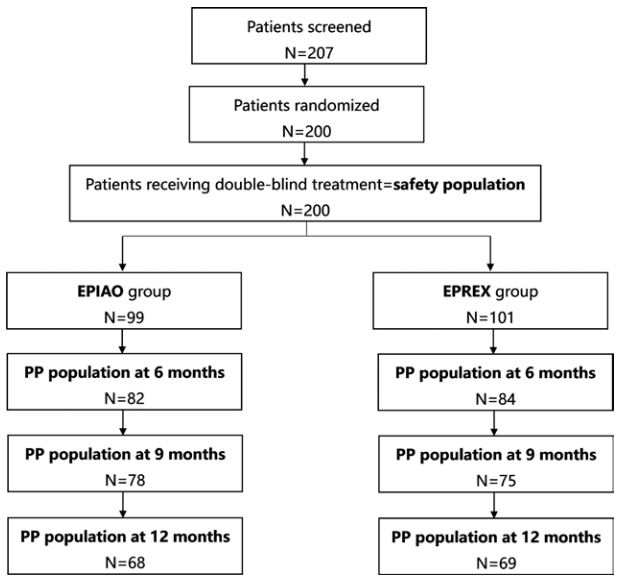

Figure 2. Patient disposition chart.

Table 1

Baseline patient demographics.

Index	EPIAO® (N = 99)	EPREX® (N = 101)	Statistics	*P* value
Age (yrs)			−0.7307	.46
N (Nmiss)	99 (0)	101 (0)		
Mean (SD)	57.55 (11.93)	58.84 (12.92)		
Median (Q1~Q3)	58 (51~67)	60 (52~69)		
Min~Max	26~81	20~80		
Gender, n (%)			0.3129	.57
Male	50 (50.51)	55 (54.46)		
Female	49 (49.49)	46 (45.54)		
Race, n (%)			0.0720	.78
Asian	17 (17.35)	19 (18.81)		
White	81 (82.65)	82 (81.19)		
Height (cm)			0.0198	.98
N (Nmiss)	99 (0)	101 (0)		
Mean (SD)	168.25 (8.99)	168.23 (8.77)		
Median (Q1~Q3)	167 (163~175)	168 (162~175)		
Min~Max	151~191.5	152~189		
Weight (kg)			0.5857	.55
N (Nmiss)	99 (0)	101 (0)		
Mean (SD)	75.72 (16.97)	74.28 (17.73)		
Median (Q1~Q3)	75.5 (63.3~86)	73 (63.1~85)		
Min~Max	44.8~127.7	41.6~146.9		

Table 2

Baseline physical examination.

Index	EPIAO® (N = 99)	EPREX® (N = 101)	Statistics	*P* value
Abdomen, n (%)				
Abnormality had no clinical significance	6 (6.12)	6 (6.00)	-	>.99
Normal	92 (93.88)	94 (94.00)		
ENT, n (%)				
Abnormality had no clinical significance	1 (1.09)	0 (0.00)	-	>.99
Normal	91 (98.91)	100 (100.00)		
Limbs, n (%)				
Abnormality had no clinical significance	1 (1.02)	3 (3.00)	-	>.99
Normal	97 (98.98)	97 (97.00)		
General appearance, n (%)				
Abnormality had no clinical significance	1 (1.02)	1 (1.00)	-	>.99
Normal	97 (98.98)	99 (99.00)		
Head and neck, n (%)				
Abnormality had no clinical significance	1 (1.02)	1 (1.00)	-	>.99
Normal	97 (98.98)	99 (99.00)		
Heart, n (%)				
Abnormality had no clinical significance	29 (29.59)	25 (25.00)	0.5261	.46
Normal	69 (70.41)	75 (75.00)		
Lungs, n (%)				
Abnormality had no clinical significance	12 (12.24)	10 (10.00)	0.2526	.61
Normal	86 (87.76)	90 (90.00)		
Lymph nodes, n (%)				
Abnormality had no clinical significance	0 (0)	0 (0)	-	>.99
Normal	98 (100)	100 (100)		
Muscles and bones, n (%)				
Abnormality had no clinical significance	1 (1.02)	3 (3.00)	-	>.99
Normal	97 (98.98)	97 (97.00)		
Nervous system, n (%)				
Abnormality had no clinical significance	1 (1.02)	3 (3.00)	-	>.99
Normal	97 (98.98)	97 (97.00)		
Skin, n (%)				
Abnormality had no clinical significance	14 (14.29)	14 (14.00)	0.0033	.95
Normal	84 (85.71)	86 (86.00)		

EPIAO®/EPREX® compared with the baseline. As showed in Tables 8–11, there was no significant difference between the 2 groups.

In addition, subjects with hemoglobin within 10 to 12 g/dL (the last 4 weeks of the treatment course) and the occurrence of blood transfusion were also used as secondary efficacy evaluation indicators. As shown in Tables 12 and S2, http://links.lww.com/MD/H775, there was no significant difference between the 2 groups (76.12% of EPIAO® vs 89.96% of EPREX®, $P = .103$; 1.39% of EPIAO® vs 2.60% of EPREX®, $P > .99$).

Table 3

Baseline vital signs.

Index	EPIAO® (N = 99)	EPREX® (N = 101)	Statistics	*P* value
Systolic pressure (mm Hg)			–1.1069	.26
N (Nmiss)	98 (1)	100 (1)		
Mean (SD)	126.31 (17.60)	129.02 (16.76)		
Median (Q1~Q3)	130 (115~140)	129.5 (120~140)		
Min~Max	85~160	89~170		
Abnormality had no clinical significance	18 (18.37)	16 (16.00)	0.1950	.65
Normal	80 (81.63)	84 (84.00)		
Diastolic pressure (mm Hg)			–1.3729	.17
N (Nmiss)	98 (1)	100 (1)		
Mean (SD)	74.93 (10.39)	76.97 (10.41)		
Median (Q1~Q3)	78 (68~82)	80 (70~80)		
Min~Max	40~102	49~104		
Abnormality had no clinical significance	4(4.08)	8(8.00)	1.3348	.24
Normal	94(95.92)	92(92.00)		
Pulse (times/min)			1.9010	.05
N (Nmiss)	98 (1)	100 (1)		
Mean (SD)	72.95 (6.41)	71.15 (6.96)		
Median (Q1~Q3)	72 (69~78)	72 (67.5~76)		
Min~Max	58~90	60~103		
Abnormality had no clinical significance	1 (1.02)	1 (1.00)	-	>.99
Normal	97 (98.98)	99 (99.00)		
Respiration rate (times/min)			–0.3531	.72
N (Nmiss)	98 (1)	100 (1)		
Mean (SD)	16.29 (1.23)	16.36 (1.31)		
Median (Q1~Q3)	16 (16~17)	16 (16~17)		
Min~Max	14~20	13~22		
Abnormality had no clinical significance	0 (0)	1 (1.00)	-	>.99
Normal	98 (100)	99 (99.00)		
Body temperature (ear temperature) (◦C)			1.2842	.20
N (Nmiss)	98 (1)	100 (1)		
Mean (SD)	36.62 (0.13)	36.59 (0.14)		
Median (Q1~Q3)	36.6 (36.6~36.7)	36.6 (36.5~36.6)		
Min~Max	36.2~37.2	36.0~37.1		
Abnormality had no clinical significance	3 (3.06)	3 (3.00)	0.0006	.98
Normal	95 (96.94)	97 (97.00)		

Table 4

Baseline history.

Index	EPIAO® (N = 99)	EPREX® (N = 101)	*P* value
Previous history, n (%)			>.99
None	0 (0)	0 (0)	
Yes	99 (100)	101 (100)	

Table 5

Baseline standard 12-lead ECG examination.

Index	EPIAO® (N = 97)	EPREX® (N = 101)	Statistics	*P* value
ECG, n (%)			0.3503	.55
Abnormality had no clinical significance	70 (72.16)	69 (68.32)		
Normal	27 (27.84)	32 (31.68)		

4. Safety

4.1 Adverse events

After treatment, there was no significant difference in the incidence of AEs between the 2 groups, and the incidence was 51.52% of EPIAO® group and 56.44% of EPREX® group ($P = .485$), respectively, as showed in Table 13. After treatment, AEs of different severity (mild, moderate, severe) were not significantly different between the 2 groups (mild: $P = .84$; moderate: $P = .392$; severe: $P = .116$), as shown in Table 13. The outcomes of most AEs were recovery/solved. The proportion of unrecovered/unresolved was 11.11% and 7.92% in the EPIAO® and EPREX® groups, respectively ($P = .442$). The proportion of AEs unrelated to the treatment measures (EPIAO®/EPREX®) in this study was not significantly different between the 2 groups, and the proportion was 47.47% (EPIAO®) and 53.47% (EPREX®), respectively ($P = .397$), as showed in Tables 14 and 15. Meanwhile, there was no significant difference between the proportions of possibly relevant to definitely relevant between the 2 groups ($P > .99$). The mortality rates were 3.03% (EPIAO® group) and 5.94% (EPREX® group) respectively. However, the outcome of AEs was not significantly different between the 2 groups ($P > .99$).

4.2 Serious adverse event

Regarding serious adverse events, there was no significant difference between the 2 groups, including the incidence of SAEs (27.27% of EPIAO® group vs 27.72% of EPREX® group, $P = .943$) and the incidence of SAEs in different categories, as shown in Table 16. In addition, there was no significant difference between the 2 groups in the number of subjects who withdrew from the study due to AE/SAE ($P > .99$), as shown in Table 16.

Table 6

EPIAO®/EPREX® treatment for 6 mo and baseline hemoglobin level.

	EPIAO® (N = 82)			EPREX® (N = 84)			*P* value	95% CI
Index	**Baseline**	**6 mo**	**Difference**	**Baseline**	**6 mo**	**Difference**		**Confidence interval**
Hemoglobin (g/dL)								
Mean (SD)	11.19 (0.57)	11.13 (0.89)	−0.06 (1.01)	11.26 (0.55)	11.11 (0.95)	−0.15 (0.97)		
Median	11.25	11.10	−0.10	11.25	11.3	−0.1		
(Q1~Q3)	(10.7~11.7)	(10.60~11.72)	(-0.52~0.62)	(10.8~11.8)	(10.52~11.7)	(-0.7~0.6)		
Min~Max	10~12.3	9.4~14.5	−3.1~3.0	10.1~12.4	8.3~13.4	−3~2.2		
Hemoglobin level difference							.71	0.05 (−0.22, 0.33)

Table 7

EPIAO®/EPREX® treatment for 6 mo and baseline wkly epoetin dosage (IU/kg).

	EPIAO® (N = 82)			EPREX® (N = 84)			*P* value	95% CI
Index	**Baseline**	**6 mo**	**Difference**	**Baseline**	**6 mo**	**Difference**		**Confidence interval**
Dosage of wkly epoetin (IU/kg)								
Mean (SD)	92.03 (55.10)	92.49 (70.70)	0.45 (43.64)	109.73 (59.12)	94.43 (62.56)	−15.30 (54.74)		
Median	83.79	68.18	0	98.55	81.56	0		
(Q1~Q3)	(55.99~112.83)	(43.10~68.18)	(−27.77~28.21)	(66.22~98.55)	(38.34~128.20)	(−42.01~8.53)		
Min~Max	18.21~329.67	0~343.14	−105.26~105.18	30.30~333.33	0~227.78	−300~109.36		
Wkly epoetin dosage (IU/kg) difference							.08	12.49 (−1.86, 26.86)

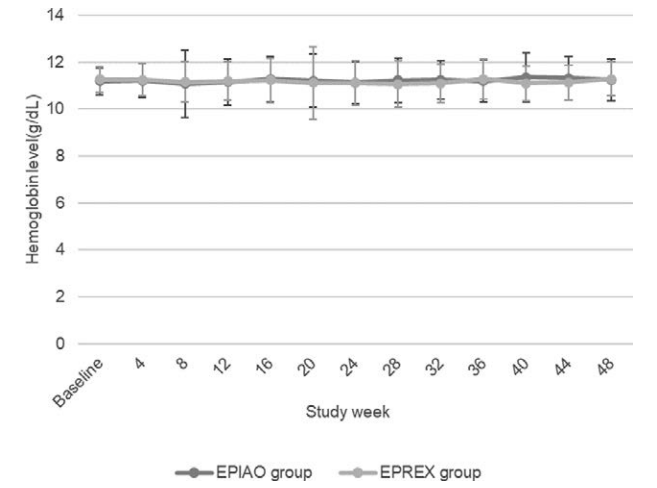

Figure 3. Hemoglobin levels (g/dL).

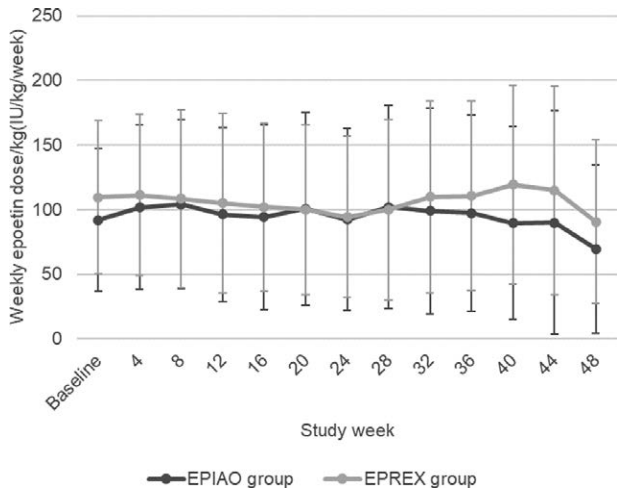

Figure 4. Wkly epoetin dose/kg (IU/kg/wk).

5. Immunogenicity

During the follow-up period of the study, there was no positive immunogenicity in the EPIAO® group. However, 1 case of positive immunogenicity in the EPREX® group. There was no statistical difference between the 2 groups ($P > .99$) (Table 17).

6. Discussion

Anemia caused by CKD is mainly due to an absolute or relative decrease in EPO production by the failing kidney function. Other factors, such as iron and vitamin deficiency, infection, and inadequate dialysis often contribute to anemia development and reduce response to treatment.[10] Thus, the introduction of erythropoietin-stimulating agents has revolutionized the care of anemic patients with CKD and almost eradicated the severe anemia of end-stage renal disease.[10,11] However, few reports around the efficacy and safety of epoetin alfa in clinical application in recent years. Results of the present study showed that EPIAO® was therapeutically equivalent to the reference product EPREX® and had a comparable safety profile in the IV treatment of anemia in patients with CKD.

The Committee for Medicinal Products for Human Use recommends that each therapeutic equivalence study for biosimilar epoetin has 2 pre-specified co-primary endpoints: change in hemoglobin and change in average dose.[12] Epoetin alfa induces erythropoiesis in a dose-dependent manner but does not affect the lifespan of erythrocytes.[13,14] Therefore, the improvement in anemia is not within 2 weeks after application of epoetin alfa, but waits for the erythrocytes to mature and be released into the peripheral blood. This study observed subjects for a sufficiently long period of time (52 weeks). Results showed that during EPIAO® treatment, the hemoglobin levels of EPIAO® group were not significantly different between the baseline and the EPREX® group. Meanwhile, the changes of weekly epoetin dosage were within the predetermined acceptable range: ±45 IU/kg (dose). These suggested EPIAO® was comparable in effectiveness to EPREX® and was effective in treating anemia in end-stage CKD patients. By late 2007, 2 biosimilar epoetins

Table 8

EPIAO®/EPREX® treatment for 9 mo and baseline hemoglobin level.

	EPIAO® (N = 78)			EPREX® (N = 75)			*P* value	95% CI
Index	**Baseline**	**9 mo**	**Difference**	**Baseline**	**9 mo**	**Difference**		**Confidence interval**
Hemoglobin (g/dL)								
Mean (SD)	11.20 (0.58)	11.20 (0.88)	−0.002 (0.95)	11.29 (0.52)	11.28 (0.86)	−0.01 (0.98)		
Median	11.30	11.20	0	11.3	11.4	0		
(Q1~Q3)	(10.7~11.7)	(10.6~11.8)	(−0.7~0.6)	(10.9~11.8)	(10.7~11.8)	(−0.8~0.5)		
Min~Max	10~12.3	9.3~14.4	−2~2.6	10.2~12.3	8.9~14.3	−2.2~2.5		
Hemoglobin level difference							.62	−0.07 (−0.35, 0.21)

Table 9

EPIAO®/EPREX® treatment for 9 mo and baseline wkly epoetin dosage (IU/kg).

	EPIAO® (N = 78)			EPREX® (N = 75)			*P* value	95% CI
Index	**Baseline**	**9 mo**	**Difference**	**Baseline**	**9 mo**	**Difference**		**Confidence interval**
Dosage of wkly epoetin (IU/kg)								
Mean (SD)	93.47 (57.05)	97.37 (75.97)	3.89 (56.7)	111.49 (55.18)	110.66 (73.32)	−0.82 (54.66)		
Median (Q1~Q3)	86.39	75.1	0	100.53	106.76	0		
	(55.85~113.03)	(43.1~130.1)	(−30.41~28.87)	(68.9~139.06)	(48.15~141.72)	(−43.32~31.73)		
Min~Max	18.21~329.67	0~362.64	−105.26~218.45	30.3~277.78	0~363.64	−136.36~158.62		
Wkly epoetin dosage (IU/kg) difference							.73	3.04 (−14.81, 20.91)

Table 10

EPIAO®/EPREX® treatment for 12 mo and baseline hemoglobin level.

	EPIAO® (N = 68)			EPREX® (N = 69)			*P* value	95% CI
Index	**Baseline**	**12 mo**	**Difference**	**Baseline**	**12 mo**	**Difference**		**Confidence interval**
Hemoglobin (g/dL)								
Mean (SD)	11.18 (0.57)	11.24 (0.89)	0.04 (1.11)	11.29 (0.52)	11.28 (0.73)	−0.01 (0.87)		
Median	11.2	11.2	−0.05	11.3	11.3	0.1		
(Q1~Q3)	(10.7~11.7)	(10.7~11.87)	(−0.6~0.9)	(10.9~11.8)	(10.85~11.6)	(−0.6~0.6)		
Min~Max	10~12.3	9.3~13.4	−2.9~2.5	10.2~12.3	9.3~13.5	−1.9~2.4		
Hemoglobin level difference							.85	−0.02 (−0.3, 0.25)

Table 11

EPIAO®/EPREX® treatment for 12 mo and baseline wkly epoetin dosage (IU/kg).

	EPIAO® (N = 68)			EPREX® (N = 69)			*P* value	95% CI
Index	**Baseline**	**12 mo**	**Difference**	**Baseline**	**12 mo**	**Difference**		**Confidence interval**
Dosage of wkly epoetin (IU/kg)								
Mean (SD)	92.17 (54.92)	69.59 (64.91)	−22.57 (59.64)	113.88 (57.45)	90.72 (63.3)	−23.15 (55.85)		
Median (Q1~Q3)	86.25	52.16	−21.3	100.4	81.63	−20.08		
	(55.59~113.43)	(25.85~90.76)	(−44.58~7.34)	(68.66~144.13)	(38.1~120.6)	(−68.05~14.78)		
Min~Max	18.21~329.67	0~351.65	−244.9~202.27	30.3~277.78	0~290.91	−164.63~98.68		
Wkly epoetin dosage (IU/kg) difference							.47	−6.8 (−25.59, 11.98)

(HX575 and SB309) had been approved by the European Medicines Agency.[12] HX575, the medicinal product applied for, has been developed as a biosimilar product to the reference product EPREX®. The active substance is an epoetin of identical primary structure as the endogenous human erythropoietin (EPO) and is produced in Chinese Hamster Ovary (CHO) cells.[15] The applicant has provided efficacy and safety results from 2 double blind, randomized, parallel group, multicenter phase III studies. Study INJ-9 was designed to evaluate a 1:1 dose conversion from EPREX® to HX575 with respect to efficacy based on hemoglobin assessment in chronic renal failure (CRF) patients on hemodialysis.[16] Study INJ-11 was performed on patients receiving chemotherapy for solid tumors.[17] Results of the study INJ-9 showed that the hemoglobin levels and epoetin dosages remained stable throughout the entire study period of 56 weeks.[16] In addition, 2 clinical studies were conducted to compare the therapeutic equivalence of IV administered SB309 and the reference product ERYPO® in patients with anemia due to chronic renal failure.[18,19] In a study of 1 correction phase study of SB309, results suggested that epoetin zeta, administered intravenously, was therapeutically equivalent to epoetin alpha in the correction of low hemoglobin concentration in patients with CKD undergoing hemodialysis.[18] Another study of SB309 was a maintenance phase study, showed the consistency of efficacy between the biosimilar and the reference product.[19] Also, results of the present study were in accordance with previous

Table 12

Subjects with hemoglobin within 10 to 12 g/dL (the last 4 wks of treatment course).

Index	EPIAO® (N = 67)	EPREX® (N = 69)	Statistics	*P* value
HB within 10 to 12 g/dL, n (%)			2.6609	.10
Yes	51 (76.12)	60 (86.96)		
No	16 (23.88)	9 (13.04)		

studies, presented equivalence effectiveness compared with the comparator EPREX®, suggesting EPIAO® clinical availability.

Safety is another critical evaluation of the present study. The results showed that there were no significant differences in the incidence of AEs and SAEs between the EPIAO® and EPREX® groups. Most AEs were mild to moderate, and most AEs were reverted/resolved. Life-threatening and death cases in SAE were only a few cases. In addition, the subjects were patients with end-stage renal disease, and the life crisis may be related to multiple factors. Based on the analysis of the above results, EPIAO® and EPREX® are also similar in safety. Biosimilar epoetin safety has also been reported in the previous studies. Most AEs in study INJ-9 were mild or moderate in intensity and resolved completely. No clear trend in occurrence of particular drug-related AEs was observed.[16] Meanwhile, the majority of SAEs were assessed as unrelated to the study medication and resolved.[16] In study INJ-11, the overall incidence of AEs was comparable for the 2 treatment groups, and the majority of AEs were mild or moderate in intensity.[17] With the exception of 1 SAE (hypertension) in the HX575 group, all other SAEs in both treatment groups were assessed as unrelated to study medication.[17] In study of correction phase study of SB309, there were no SAEs experienced by ≥5% of patients in either treatment group.[18] Analysis of AEs and SAEs revealed no significant differences between the epoetin zeta and epoetin alfa treatment groups.[18] AE profile of SB309 maintenance phase study was similar for both products; the most commonly reported AEs were infections and infestations.[19] Compared with previous studies, the present study showed similar results that the EPIAO® group had similar safety compared with the comparator EPREX®, which would be appropriate for clinical application.

The present study still has certain limitations. Previous study reported that the occurrence of rHuEpo-neutralizing antibodies was rare in patients treated by rHuEPO.[20] Therefore, post-marketing studies and pharmacovigilance program should be critical in this regard.

7. Conclusions

This study met its endpoints by demonstrating that mean absolute change in hemoglobin level from baseline after treatment with EPIAO® was highly similar to patients with EPREX®. Mean absolute change in weekly epoetin dosage per kg body weight from baseline after treatment with EPIAO® was similar to patients with EPREX®. Meanwhile, EPIAO® had no new safety issues compared with EPREX®. This study demonstrated efficacy, typical safety profile and therapeutic equivalence of EPIAO® versus reference product. In summary, EPIAO® was well tolerated and presented good clinical availability.

Acknowledgments

This paper and the research behind it would not have been possible without the exceptional input of Dr Mingyu Zhang. His vision and foresight, knowledge, and enthusiasm has been an inspiration and driving-force for completion of our work. Many thanks to National Science and Technology Major Project, Ministry of Science and Technology of the People's Republic of China for the financial support.

Author contributions

Bolong Miao designed the protocol, drafted the manuscript, and approved the final version of the manuscript. Alina Nikolaevna Isachkina, Evgeny Viktorovich Shutov, Alexander Alekseevich Selyutin, Lyudmila Vladimirovna Kvitkova, Valery Yuryevich Shilo, Olga Nikolaevna Vetchinnikova, Ilya Vyacheslavovich Alexandrov, Dmitry Vladislavovich Perlin, Alexander Vasilievich Zuev, Igor Leonidovich Davydkin, Tatyana Pavlovna Mironova, Olga Mikhailovna Solovyova, Alexey Pavlovich Tutin, Alexey Mikhailovich Omelchenko, Kriengsak Vareesangthip, and Nadezhda Georgievna Khadikova conducted the study and provided intellectual content of critical importance to the work

Table 13

Adverse events after treatment.

	EPIAO® (N = 99)			EPREX® (N = 101)			Statistics	*P* value
	Instance	N	Rate (%)	Instance	N	Rate (%)		
AEs	144	51	51.52	187	57	56.44	0.4873	.48
Mild	74	32	32.32	73	34	33.66	0.0406	.84
Moderate	59	25	25.25	95	31	30.69	0.1915	.39
Severe	10	10	10.10	19	18	17.82	2.4753	.11

Table 14

Correlation between adverse events and treatment.

	EPIAO® (N = 99)			EPREX® (N = 101)			Statistics	*P* value
Relevance to treatment	Instance	N	Rate (%)	Instance	N	Rate (%)		
Irrelevant	118	47	47.47	171	54	53.47	0.7177	.39
May be irrelevant	8	7	7.07	8	8	7.92	-	>.99
May be related	10	9	9.09	4	4	3.96	-	>.99
Probably related	5	3	3.03	3	3	2.97	-	>.99
Definitely related	2	2	2.02	1	1	0.99	-	>.99

Table 15

Outcomes of adverse events.

	EPIAO® (N = 99)			EPREX® (N = 101)			Statistics	*P* value
Outcomes	**Instance**	**N**	**Rate (%)**	**Instance**	**N**	**Rate (%)**		
Unrecovered/unresolved	11	11	11.11	10	8	7.92	0.5919	.44
Recovered/resolved and no sequelae	103	43	43.43	127	50	49.50	0.7406	.38
Recovered/resolved with sequelae	23	13	13.13	43	16	15.84	0.2962	.58
Death	3	3	3.03	6	6	5.94	-	>.99
Unknown	3	3	3.03	1	1	0.99	-	>.99

Table 16

Serious adverse event.

	EPIAO® (N = 99)			EPREX® (N = 101)			Statistics	*P* value
	Instance	**N**	**Rate (%)**	**Instance**	**N**	**Rate (%)**		
SAEs	31	27	27.27	39	28	27.72	0.0051	.94
Need to be hospitalized or extend the current hospital stay	27	23	23.23	30	20	19.80	0.3486	.55
Life threatening	1	1	1.01	3	3	2.97	-	>.99
Lead to death	3	3	3.03	6	6	5.94	-	>.99

Table 17

Occurrence of immunogenicity.

Index	EPIAO® (N = 99)	EPREX® (N = 101)*	*P* value
Immunogenicity, n (%)			>.99
Positive	0 (0.00)	1 (1.00)	
Negative	99 (100.00)	99 (99.00)	

*EPREX® group missing 1 patient.

described. Man Li and Xiang Li analyzed and interpreted the data.

Conceptualization: Bolong Miao.

Data curation: Man Li, Xiang Li.

Formal analysis: Man Li, Xiang Li.

Investigation: Alina Nikolaevna Isachkina, Evgeny Viktorovich Shutov, Alexander Alekseevich Selyutin, Lyudmila Vladimirovna Kvitkova, Valery Yuryevich Shilo, Olga Nikolaevna Vetchinnikova, Ilya Vyacheslavovich Alexandrov, Dmitry Vladislavovich Perlin, Alexander Vasilievich Zuev, Igor Leonidovich Davydkin, Tatyana Pavlovna Mironova, Olga Mikhailovna Solovyova, Alexey Pavlovich Tutin, Alexey Mikhailovich Omelchenko, Kriengsak Vareesangthip, Nadezhda Georgievna Khadikova.

Writing – original draft: Bolong Miao.

Writing – review & editing: Bolong Miao, Xiang Li.

References

[1] Ammirati AL. Chronic kidney disease. Revista da Associacao Medica Brasileira. 2020;66 (Suppl 1):s03–s09.

[2] Gafter-Gvili A, Schechter A, Rozen-Zvi B. Iron deficiency anemia in chronic kidney disease. Acta Haematol. 2019;142:44–50.

[3] Atkinson MA, Warady BA. Anemia in chronic kidney disease. Pediatr Nephrol. 2018;33:227–38.

[4] Chen TK, Knicely DH, Grams ME. Chronic kidney disease diagnosis and management: a review. JAMA. 2019;322:1294–304.

[5] Salamin O, Kuuranne T, Saugy M, et al. Erythropoietin as a performance-enhancing drug: its mechanistic basis, detection, and potential adverse effects. Mol Cell Endocrinol. 2018;464:75–87.

[6] Bahlmann FH, Kielstein JT, Haller H, et al. Erythropoietin and progression of CKD. Kidney Int Suppl. 2007;107:S21–5.

[7] Dingermann T, Scotte F. Biosimilar epoetin zeta: extrapolation of indications and real world utilization experience. Expert Opin Biol Ther. 2016;16:967–74.

[8] McKoy JM, Stonecash RE, Cournoyer D, et al. Epoetin-associated pure red cell aplasia: past, present, and future considerations. Transfusion. 2008;48:1754–62.

[9] Chen L, Ling YS, Lin CH, et al. High dose ESAs are associated with high iPTH Levels in hemodialysis patients with end-stage kidney disease: a retrospective analysis. Front Public Health. 2015;3:258.

[10] Bonomini M, Del Vecchio L, Sirolli V, et al. New treatment approaches for the anemia of CKD. Am J Kidney Dis. 2016;67:133–42.

[11] Winearls CG, Oliver DO, Pippard MJ, et al. Effect of human erythropoietin derived from recombinant DNA on the anaemia of patients maintained by chronic haemodialysis. Lancet. 1986;2:1175–8.

[12] Mikhail A, Farouk M. Epoetin biosimilars in Europe: five years on. Adv Ther. 2013;30:28–40.

[13] Patel S, Patel JB. Epoetin Alfa. Treasure Island (FL): StatPearls; 2022.

[14] Hematologic Growth Factors. LiverTox: clinical and research information on drug-induced liver injury. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases; 2012–. Hematologic Growth Factors. 2012.

[15] Dellanna F, Goldsmith D, Krendyukov A, et al. HX575: established biosimilarity in the treatment of renal anemia and 10 years of clinical experience. Drug Des Devel Ther. 2018;12:9–14.

[16] Haag-Weber M, Vetter A, et al. Therapeutic equivalence, long-term efficacy and safety of HX575 in the treatment of anemia in chronic renal failure patients receiving hemodialysis. Clin Nephrol. 2009;72:380–90.

[17] Weigang-Kohler K, Vetter A, Thyroff-Friesinger U. HX575, recombinant human epoetin alfa, for the treatment of chemotherapy-associated symptomatic anaemia in patients with solid tumours. Onkologie. 2009;32:168–74.

[18] Krivoshiev S, Todorov VV, Manitius J, et al. Comparison of the therapeutic effects of epoetin zeta and epoetin alpha in the correction of renal anaemia. Curr Med Res Opin. 2008;24:1407–15.

[19] Wizemann V, Rutkowski B, Baldamus C, et al. Comparison of the therapeutic effects of epoetin zeta to epoetin alfa in the maintenance phase of renal anaemia treatment. Curr Med Res Opin. 2008;24:625–37.

[20] Praditpornsilpa K, Tiranathanagul K, Kupatawintu P, et al. Biosimilar recombinant human erythropoietin induces the production of neutralizing antibodies. Kidney Int. 2011;80:88–92.