Comparative Study of Recombinant Human Erythropoietin (rhEPO) Products on CKD (Chronic Kidney Disease) Patients

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Keywords
comparative, erythropoietin, CKD, Anemia

received 20.07.2022
accepted 31.07.2022
published online 27.03.2023

Bibliography
Drug Res 2023; 73: 271–278
DOI 10.1055/a-1982-3811
ISSN 2194-9379

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ABSTRACT

Purpose This study was conducted to evaluate whether the efficacy and safety profile of recombinant human erythropoietin (rhEPO) manufactured by Daewoong Pharmaceutical Co., Ltd was similar to biological products approved by the drug safety regulatory authority.

Patients and methods It was an open-label, randomized, comparative, parallel, multi-center study in hemodialysis patients with anemia. The reference product at an individualized dose 3 times a week was given in 4–8 weeks of titration period and hemoglobin (Hb) level was controlled to reach the range of 10–12 g/dL. Then, the subjects were randomly administered with reference or test product with the same dose regimen. The primary endpoints were to demonstrate the Hb level change between baseline and evaluation period in both treatment groups, while the secondary endpoints were the mean change in weekly dosage per kg body weight and the instability rate of Hb level during maintenance and evaluation period. The safety was evaluated based on the adverse events incidence.

Results There was no statistical difference in the change of Hb between test and reference (0.14 g/dL and 0.75 g/dL respectively, with $p > 0.05$), also for the mean changes of weekly dosage between groups (1091.40 IU and 570.15 IU respectively, with $p > 0.05$). The instability rate of Hb in both test and reference was not statistically significantly different as well (26 and 15 % respectively, with $p > 0.05$).

Conclusion This study proves that the efficacy indicated by the change instability of Hb and safety indicated by adverse event incidence of Epodion and the reference product on chronic kidney disease were similar.

Introduction

Clinically, Chronic Kidney Disease (CKD) is defined as kidney damage and/or decreased Glomerular Filtration Rate (GFR) of less than 60 mL/minute/1.73 m^2 for a minimum of 3 months [1]. CKD is a comorbidity of diabetes and hypertension and can indirectly increase the mortality risk of patients with cardiovascular disease, diabetes, hypertension, HIV (Human Immunodeficiency Virus) positive, and malaria [2]. Based on 2015 data by the Global Burden of Disease, 1.2 million deaths are directly correlated with a decrease in glomerular filtration ability. In addition, it is also estimated that 2.3–7.1 million deaths due to difficulty accessing dialysis, 1.7 million deaths from acute kidney failure, and 5–10 million deaths from other kidney diseases [3]. 0.2 % of the adult population in Indonesia was diagnosed with CKD in 2013, making it the second-largest disease with respect to the fund allocated by the national social insurance scheme [4].

People with CKD often also suffer from anemia complications caused by a decrease in kidney function. Anemia diagnosis is given

to adult CKD patients if the Hb concentration is < 13 g/dl in men or < 12 g/dl in women. "A reduction in hemoglobin concentrations in CKD patients is associated with impairment in quality of life and increased mortality [5]. This condition can occur when a decrease in kidney function is up to 50 %. Iron therapy can be performed on CKD patients with anemia who have low iron levels, which is known by conducting laboratory tests for ferritin < 200 ng/L and transferrin saturation < 30 %. In addition, CKD patients with anemia can be given erythropoietin (EPO) therapy to increase levels of red blood cells or erythrocytes in the blood [6].

EPO is a glycoprotein hormone produced by renal erythropoietin-producing cells and has a function in inducing red blood cell production in the red marrow. Recombinant human erythropoietin (rhEPO) has been used successfully to correct the anemia of chronic renal failure for more than 12 years [7]. Today, EPO has been developed on a manufacturing scale using recombinant technology to meet market needs. EPO which is developed using recombinant technology is called recombinant human EPO (rhEPO) [8].

Several rhEPO products that have been globally successful include Epoetin alpha manufactured by Amgen Inc., Procrit by Amgen Inc., and Eprex by Janssen Pharmaceuticals [9].

Epodion is an alpha rhEPO product produced by PT. Daewoong Infion, this product is used in conjunction with other clinical treatments for anemic patients due to chronic kidney failure or due to chemotherapy. Yellowish transparent Epodion injection solution can be injected intravenously (IV) or subcutaneously (SC). Epodion has four products with different EPO content, including 2000 IU, 3000 IU, 4000 IU, and 10000 IU.

Biosimilar products are products that are similar to other biological products whose period of protection has ended. Biosimilar products must have similarities and sequences of amino acids or proteins and protein folding structures that determine their biological activity. In addition, biosimilar products are also not allowed to have different posology and administrative routes unless they produce safety and efficacy. Based on applicable regulations in the European Union, biosimilar producers must be able to show data as proof that the product has been produced to applicable standards and is intended for certain clinical uses. The Indonesian government adopts World Health Organization (WHO) regulations on evaluating biosimilar products [10]. Some requirements include characteristic structure, physicochemical properties, purity, biological activity, product composition, formulation, manufacturing process, and stability of active ingredients and products during storage [11].

Material and methods

Study Design and Subjects

This open-label, randomized, active drug-comparative, parallel-designed, multi-center study was conducted in hemodialysis patients with anemia in Gatot Soebroto Army Hospital, Dr. Esnawan Antariksa Airforce Hospital, and Cempaka Putih Jakarta Islamic Hospital from November 2019 to May 2021. The sample size was calculated using the POWER procedure (Proc Power Procedure) of SAS ver. 9.4 (SAS Institute, Cary, NC, USA). A sample size of 90 subjects was determined with difference 0 g/dL, standard deviation 0.8 g/dL, statistical power 90 %, randomization ratio 1:1 to demonstrate equivalence at 5 % significance level and equivalence margin ± 0.5 g/dL.

Before study commencement, the protocol, patient information, and consent form were approved by the Health Research Ethics Committee of the Faculty of Medicine, University of Indonesia (Reference number of vote: Ket – 1146/UN2.F1/ETIK/PPM.00.02/2019). Written informed consent was obtained from each study subject before the screening. The conduct of the study conformed to the Declaration of Helsinki and Good Clinical Practice (GCP) ICH E6 (R2) standards [12].

The study was implemented on Nov, 7th 2019 until May, 15th 2019, and the study design was registered at Clinicaltrial.gov on July, 12th 2022. Subjects should meet the inclusion criteria of male or female patients ≥ 18 and < 75 years old of age at the time of screening visit, patients with End-Stage Renal Failure (ESRD) who are chronically receiving hemodialysis and have anemia associated with CKD, with mean baseline Hemoglobin (Hb) level ≥ 9 g/dL during the screening period, currently receiving stable maintenance therapy with EPO alfa at least once per week, have adequate iron substitution status (serum ferritin ≥ 100 µg/L (100 ng/mL) or saturated transferrin levels ≥ 20 %) and should understand the information provided to them or their representatives and may provide written consent. The exclusion criteria were patients with contraindication with EPO therapy, documented active bleeding in the last 12 weeks prior to screening period, any blood transfusion within the last 2 weeks prior screening period, have history of malignancy of any organ system within the last 5 years, patients with uncontrolled hypertension (in case the mean value of diastolic blood pressure as measured 4 times during the baseline observation period is 110 mmHg or more), patients hyporesponsive EPO treatment or had medical history of experiencing pure red blood cell forming failure after being administered with EPO products, known bone marrow fibrosis (osteitis fibrosa cystica), patient with serious cardiovascular disorders: myocardial infarction, patients with congestive heart failure (NYHA class III or higher), ischemic vascular disease, patient who received percutaneous coronary intervention (PCI), or coronary artery bypass grafting (CABG) during the last 6 months prior to screening, patients with alanine transaminase (ALT) or aspartate aminotransferase (AST) exceeding the upper limits of the normal level by more than 5-folds, patients whose kidney transplant is expected or already planned for survival, patient with secondary anemia to other causes different to the CKD (aplastic anemia, hemolytic anemia, sickle cell anemia, multiple myeloma, leukemia, myelodysplastic syndrome), patients with the following diseases and who are considered unfit to enroll in the clinical study: mental system disease, mental disease, drug intoxication, epilepsy, lung infarction, cerebral infarction, positive HIV antibody, systemic lupus erythematosus, immunosuppressive condition and general infection, female patients with pregnancy or lactation period, or women of childbearing potential without an effective method of birth control, and patients who were considered unfit for study by investigators. Patients with at least one of those exclusion criteria above were not eligible to be included in the study.

Efficacy

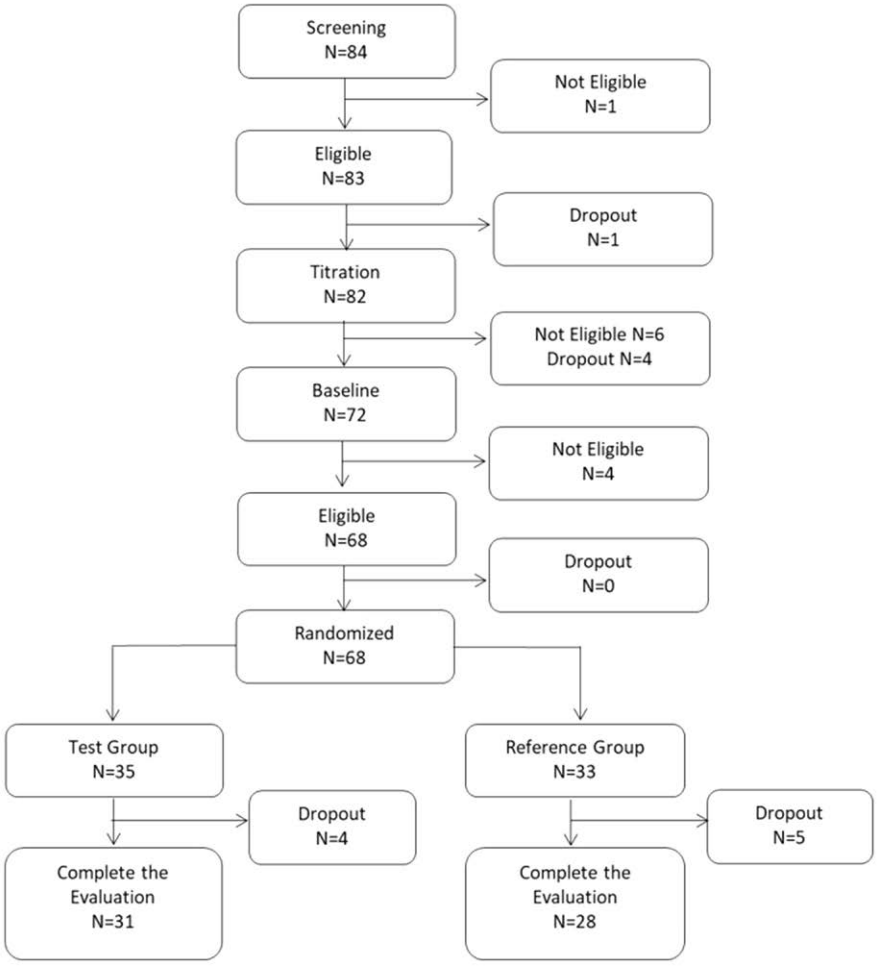
Study Products

The test product, Epodion (Daewoong Pharmaceutical Co., Ltd), and the reference product, Eprex (Janssen), in this study both contain recombinant human erythropoietin alpha. In the maintenance period, each subject was administered the test and reference product according to a random sequence. Since this was an open-label study, both subject and investigator knew whether the subject was given the test or reference product.

Study Treatment

In the titration period, the reference product at an individualized dose 3 times a week through intravenous injection was given and the Hb level of the subject was controlled to reach the target range of 10–12 g/dL. After the titration period, subjects enter the baseline evaluation to get the hemoglobin mean data, and the mean weekly EPO dose was used as an efficacy assessment parameter. Subject inclusion and exclusion criteria in this period were assessed before the subjects received a randomization number and were allocated into a study or control group in the maintenance period. Subjects should have Hb target 10–12 g/dL, had adequate iron substitution status (serum ferritin ≥ 100 µg/L (100 ng/mL) or saturated transferrin levels ≥ 20 %), dry weight less than 5 % during the baseline evaluation period, and should reliable and will willingly cooperate during the maintenance period and observe the restrictions. While subjects with one or more of exclusion criteria of any blood transfusion within the last 2 weeks prior to the screening period, in case the EPO administration dose during the baseline evaluation period (week 9–12/13–16) is increased or decreased by 20 % or more, currently contraindicated with EPO therapy, administered with prohibited drug (cyclosporine, androgen, and chemotherapy agents) and occurrence medical condition which can affect efficacy data during maintenance period judged by investigator could not continue to the maintenance period.

In the maintenance period, administration of the test or reference product was done with the same dose regimen during titration period through intravenous injection. EPO dose may be increased or decreased at an appropriate level according to the condition of the subjects. Subject Hb levels were controlled to reach a range of 10–12 g/dL. Blood collection was carried out once every two weeks for the purposes of a routine hematological test. Adverse events, concomitant medication, and instability rate of Hb



▶ **Fig. 1** Subject Disposition Scheme.

▶ **Table 1** Demographic and Characteristic of Study Subjects.

	N	Test (N = 35)		N	Reference (N = 33)	
		%			%	
Male	19	54 %		17	52 %	
Female	16	46 %		16	48 %	
	Mean	SD	Range	Mean	SD	Range
Age (years)	47.9	9.92	(23–66)	49.2	11.47	(28–73)
Hb (g/dL)	11.4	1.6	(9.0–14.6)	10.9	1.1	(9.0–13.5)
Ht (%)	32.7	4.4	(25.0–43.0)	31.1	4.0	(24.0–40.0)
Serum ferritin (Ng/mL)	934.2	477.6	(11.4–5306.4)	643.0	611.4	(47.3–2298.3)
Transferrin saturation (%)	40.0	26.7	(10.0–99.0)	33.5	13.5	(9.1–74.3)
SGOT (μ/L)	39.1	28.0	(8.0–117.0)	32.6	27.8	(9.0–158.0)
SGPT (μ/L)	58.7	59.1	(7.0–227.0)	36.6	28.1	(6.0–135.0)
Anti HCV	N	%		N	%	
– Positive	0	0 %		0	0 %	
– Negative	35	100 %				

This table provides an overview of the demographics and characteristics of the subjects who were successfully randomized to continue the study

data were observed during the maintenance period. Week 33–36/37–40 is the treatment evaluation period. Hb mean data, weekly EPO dose, and Hematocrit (Ht) were compared with the baseline period as an efficacy evaluation parameter.

Statistical Analysis

The difference of change in Hb levels from baseline to the evaluation period between treatment groups was determined by ANCOVA (analysis of covariance) model with treatment as a factor, and baseline Hb level and the change in weekly dosage per kg body weight from baseline to the evaluation period of test or reference as covariates. To evaluate the change in weekly dosage per kg body weight from baseline to the evaluation period, the difference between treatment groups was analyzed by ANCOVA model with treatment as a factor, and baseline Hb level and baseline weekly dosage per kg body weight value as covariates. The percentage of subjects with Hb instability during the maintenance and evaluation period was compared between groups, and descriptive statistics were provided in the treatment groups for Hb and Ht levels at the maintenance and evaluation period.

▶ **Table 2** Mean Change in Hemoglobin Level Between Groups.

	Test (N = 35)		Reference (N = 33)		p	
	Mean	SD	Mean	SD		
Hb on baseline period (g/dL)	11.83	0.85	11.63	0.97		
Hb on evaluation period (g/dL)	11.68	1.69	10.95	1.71		
Changes of Hb (g/dL)	−0.14	1.81	−0.75	1.71	0.082	NS

Mean Changes in Haemoglobin Level at Baseline (Week 5–8/9–12) and Evaluation Period (Week 33–36/37–40) Between Test Product group and Reference Product group.; NS : not statistically significant ($p = 0.05$); S : statistically significant ($p < 0.05$); The negative value indicated the decrease in mean change of Hb

Results

A total of 84 patients were given informed consent across 3 study sites and assessed by the investigator to know whether they were eligible or not to participate in the study. 83 subjects were eligible according to the inclusion and exclusion criteria on screening and 82 of 83 continued to the titration period, but 1 of 83 died and could not continue to the titration period.

Only 72 of 82 subjects who underwent titration period entered baseline evaluation because 6 subjects were not eligible due to the Hb was not within 10–12 g/dL as required and 4 subjects dropped out.

After the evaluation of the Hb in the baseline period, 4 of 72 subjects could not achieve 10–12 g/dL, therefore those subjects were excluded and only 68 subjects underwent the randomization that consisted of 35 subjects who received the test product and 33 subjects received the reference product in the maintenance period. There were 31 subjects in the test group and 28 subjects in the reference group who completed the evaluation period. 4 subjects in the test group were dropped out due to death (2 subjects), recurrent Gravis anemia (1 subject), and screening failure (1 subject). 5 subjects in the reference group were dropped out due to death. Subject disposition was summarized in ▶ **Fig. 1**. Demographics and characteristics of study subjects were referred to ▶ **Table 1**.

▶ **Table 3** Mean Change in Weekly Dosage per kg Body Weight of Between Groups.

	Test (N = 35)			Reference (N = 33)			P	
	Mean	SD	Range	Mean	SD	Range		
Baseline (IU)	4042.86	2198.90	(2000–10000)	5826.96	3771.69	(2000–18000)		
Evaluation (IU)	5397.85	3628.17	(1000–14000)	6464.29	3646.23	(2000–12000)		
Change of dosage (IU)	1091.40	4000.00	(−6000–11000)	570.15	4787.30	(−12000–9500)	0.087	NS

Mean Changes in Weekly Dosage Level at Baseline (Week 5–8/9–12) and Evaluation Period (Week 33–36/37–40) Between Test Product group and Reference Product group; NS: not statistically significant (p = 0.05); S: statistically significant (p < 0.05); The negative value indicated the dose reducing

The primary endpoint was to demonstrate that the test product treatment was equivalent to the reference product by evaluating the changes in Hb level between baseline (Week 5–8/9–12) and evaluation period (Week 33–36/37–40) as referred to ▶ **Table 2**.

There was no statistical difference in the change of Hb between the test and the reference product (p > 0.05). In the test group, the Hb change was decreased by 0.14 g/dL, while the Hb change was decreased by 0.75 g/dL in the reference group.

The mean change of weekly dosage in the test and reference group were 1091.40 IU and 570.15 IU, and it was not statistically significantly different which referred to ▶ **Table 3**.

The number of subjects with Hb level < 8 g/dL or Hb level > 13 g/dL during maintenance and evaluation period were counted, and instability rate of Hb level during maintenance and evaluation period as defined when Hb level dropped 8 g/dL or increased by more than 13 g/dL as referred to ▶ **Table 4**.

There was no statistically significant difference in Hb instability rate in the maintenance and evaluation period of both test and reference group, with p-value 0.459 and 0.544 respectively.

Hb and Ht levels during the maintenance and evaluation period of both test and reference groups were descriptively presented in ▶ **Fig. 2,3**.

During the treatment period, 21 and 25 adverse events occurred in the test and reference group respectively as referred to ▶ **Table 5**.

▶ **Table 4** Instability Rate of Haemoglobin of Between Groups.

	Test (N = 35)		Reference (N = 33)		p	
	N	%	N	%		
Maintenance period						
Hb < 8 g/dL	2	6%	3	9%		
Hb > 13 g/dL	21	60%	15	45%		
Instability rate of Hb	22	63%	16	48%	0.459	NS
Evaluation period						
Hb < 8 g/dL	1	3%	1	3%		
Hb > 13 g/dL	8	23%	4	12%		
Instability rate of Hb	9	26%	5	15%	0.544	NS

The Instability Rate of Haemoglobin level during Maintenance and Evaluation (Week 33–36/37–40) period Between Test Product group and Reference Product group; NS: not statistically significant (p = 0.05); S: statistically significant (p < 0.05)

Discussion

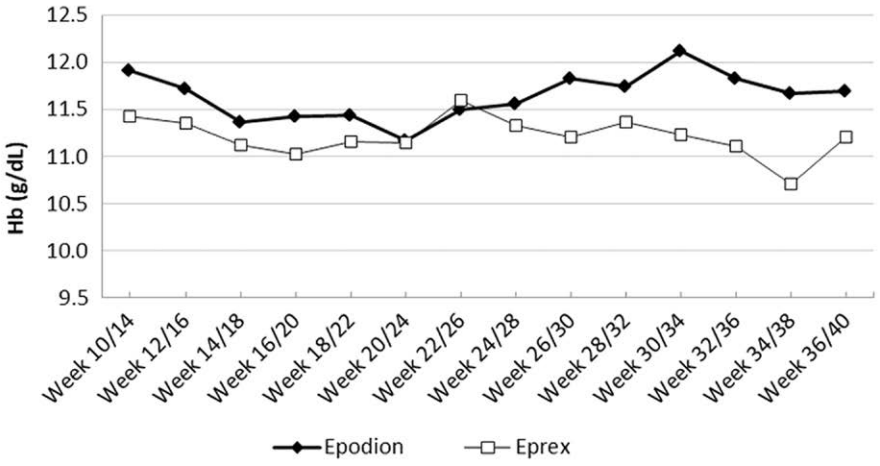
The test product is a biological product that is considered biosimilar to the original reference product hence the evaluation of the efficacy and safety comparison is important. The other studies, Comparative effectiveness of erythropoietin alpha and beta in hemodialysis patients: a single-center prospective observational study is to compare therapeutic efficacy of both erythropoietin alpha and erythropoietin beta in treating anemia associated with chronic kidney disease in our study population with the desired hemoglobin levels of ≥ 11 g/l [13].

Moreover from Comparison of the Therapeutic Efficacy of Epoetin Beta and Epoetin Alfa in Maintenance Phase Hemodialysis Patients, this study also measures the dose of Eprex and compares that to the dose of the beta preparation needed to maintain Hb levels [14].

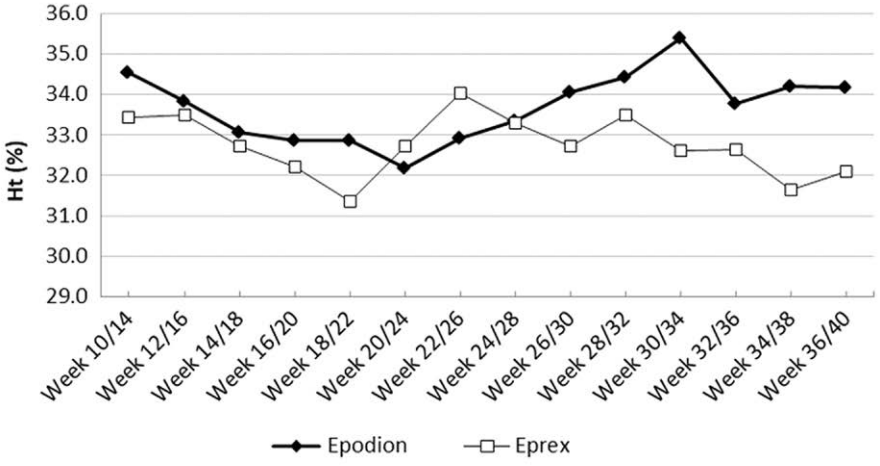
In this study, the primary endpoint is Hb level change between baseline (Week 5–8/9–12) and evaluation period (Week 33–36/37–40), and there was no statistically difference in the change mean of Hb between Epodion as the test group and the reference (p > 0.05). In the test group, the mean Hb change was decreased by 0.14 g/dL, while the reference group decreased by 0.75 g/dL, so there was no clinically significant difference as well. In another multicenter study conducted by Soo Kun Lim et.al in 2013–2017 which used the same reference product, the mean Hb change after 28 weeks of the reference product use was reported to decrease by 0.118 g/dL [15].

This study also evaluated the mean change in weekly dosage per kg of body weight between the baseline and the evaluation period. The mean of dosage change in the test group was 1,091.40 IU, while in the reference group the average was 570.15 IU, and since the p value = 0.087 (p > 0.05) it indicated no statistically significant difference. The change of dosage could be a dosage decreasing or increasing toward its baseline. The maximum decrease of dosage in the test group was 6,000 IU and the maximum increase was 11,000 IU. In the reference group, the maximum decrease was 12,000 IU and the maximum increase was 9,500 IU, it seemed smaller than the test group because the baseline value of the reference drug was higher than the test group.

The instability rate of Hb level that defined when Hb level dropped 8 g/dL or increased by more than 13 g/dL during maintenance and evaluation period between groups was not statistically significant difference with p-value was 0.459 and 0.544 respectively.



▶ **Fig. 2** Mean of Haemoglobin Level during Maintenance and Evaluation Period.



▶ **Fig. 3** Mean of Haematocrit Level during Maintenance and Evaluation Period.

In the maintenance period of the test group the instability rate of Hb was 63 % (22/35), the rate was higher than the reference group that found 48 % (16/33), but it was not statistically significant.

The evaluation period showed that the instability rate of Hb was 26 % (9/35) in the test group and it was higher compared to the rate in the reference group which found 15 % (5/33), nevertheless the difference was not statistically significant.

The other study stated the mean of Hb level could be maintained at > 10 g/dL every 2 weeks for 8 weeks of treatment with EPO [16]. "The efficacy and safety of biosimilar rhEPO on treating CKD-associated anemia were also shown in another study with pre-dialysis patients [17].

21 and 25 adverse events occurred in the test and reference group respectively. In the test group, 81 % of those events were serious adverse events while 76 % of total adverse events in reference were serious. Most of the adverse events were moderate (52 % in both groups), and 19 and 20 % were severe in the test and reference group respectively. No question maintaining hemoglobin levels in anemic CKD patients is extremely beneficial for physical and mental health and overall well-being [18].

Conclusion

This study proves that the efficacy and safety of Epodion and the reference product on chronic kidney disease was similar

Acknowledgments

The authors would like to thank the team of Gatot Soebroto Army Hospital, Dr. Esnawan Antariksa Airforce Hospital, and Cempaka Putih Jakarta Islamic Hospital for their valuable contribution to the

▶ **Table 5** Summary of Adverse Events According to the Number of Events in Each Group.

Adverse Event	Test (S 21)		Reference (S 25)		Not Randomized (S 24)		Total (S 70)	
	N	%	N	%	N	%	N	%
Severity								
1. Mild	6	29%	7	28%	7	29%	20	29%
2. Moderate	11	52%	13	52%	13	54%	37	53%
3. Severe	4	19%	5	20%	4	17%	13	19%
Causality								
1. Definitely Related	0	0%	0	0%	0	0%	0	11%
2. Related	0	0%	0	0%	0	0%	0	4%
3. Possibly Related	0	0%	2	8%	2	8%	4	23%
4. Not Related	17	81%	19	76%	21	88%	57	54%
5. Definitely Not Related	4	19%	1	4%	1	4%	6	7%
6. Unknown	0	0%	3	12%	0	0%	3	21%
Action taken								
1. Drug Treatment	6	29%	8	32%	7	29%	21	30%
2. Non-Drug Treatment	4	19%	3	12%	2	8%	9	13%
3. Drug/non-drug treatment	11	52%	14	56%	15	63%	40	57%
4. No Drug/non-drug treatment	0	0%	0	0%	0	0%	0	0%
AE Result								
1. Resolve	18	86%	15	60%	15	63%	48	69%
2. Continuous	1	5%	1	4%	2	8%	4	6%
3. Revolve, but the effect								
is remained	0	0%	3	12%	1	4%	4	6%
4. Death	2	10%	6	24%	6	25%	14	20%
Expectation								
1. Yes	9	43%	10	40%	17	71%	36	51%
2. No	12	57%	15	60%	7	29%	34	49%
Seriousness								
1. Yes	17	81%	19	76%	24	100%	60	86%
2. No	4	19%	6	24%	0	0%	10	14%

Summary of Adverse Events According to the Number of Events in Test and Reference Product group during Maintenance Period; Abbreviations: ALT, alanine transaminase; ANCOVA, analysis of covariance; AST, aspartate aminotransferase; CABG, coronary artery bypass grafting; CKD, Chronic Kidney Disease; EPO, erythropoietin; ESRD, End-Stage Renal Failure; GCP, Good Clinical Practice; GFR, Glomerular Filtration Rate; Hb, Hemoglobine; HIV, Human Immunodeficiency Virus; Ht, Hematocrit; IV, intravenously; PCI, percutaneous coronary intervention; rhEPO, Recombinant Human Erythropoietin; SC, subcutaneously; WHO, World Health Organization

study implementation, and thank Daewoong Pharmaceutical Co., Ltd as the contribution for investigational product providing and study operational funding.

Conflicts of Interest

The author reports no conflicts of interest in this work.

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