Cohort Prospective Study to Evaluate Immunogenicity of Epodion® (Biosimilar Epoetin-α) in Anemia Associated with Chronic Kidney Disease (CKD) Patients

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ABSTRACT

Background: *Anemia due to chronic kidney disease (CKD) is often associated with decreased erythropoietin (EPO) levels in the blood. Treatments available are improving blood iron levels and administration of exogenous EPO (rhEPO). This study aims to assess the safety and immunogenicity of Epodion, a biosimilar rhEPO product, in haemodialysis patients with CKD-associated anaemia in three Indonesian hospitals.* ***Methods:*** *This prospective, open label, single arm, and multicenter study enrolled patients with anemia associated with CKD under hemodialysis treatment. Patient eligibility was assessed within the 4-week screening period. Blood samples for determination of erythropoietin antibody (Anti-Drug Antibody) were taken at week-0, 24, and 52 using a validated and highly sensitive bridging ELISA method. Evaluation of Neutralizing Antibody (NAb) was carried out to confirm the impact of the antibody to pharmacological activity (e.g., antibody-mediated PRCA) when the ADA detection of patients was positive after screening and confirmatory assay.* ***Results****: Results from all tested patients show that Epodion could maintain hemoglobin and hematocrit levels. ADA detection using ELISA assay yielded negative results for all plasma samples of week-24 and week-52, so the evaluation of NAb was not carried out. No adverse events were considered relevant to tested product.* ***Conclusion:*** *This study proves no immunogenic effect of Epodion on stimulating immune system's antibodies in Indonesian patients with CKD-associated anemia.*

Keywords*: Anemia, anti-drug antibody, anti-rhEPO, chronic kidney disease, erythropoietin, Indonesia.*

INTRODUCTION

Chronic Kidney Disease (CKD) is clinically defined as kidney damage and/or decreased Glomerular Filtration Rate (GFR) for a minimum of three 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 positive, and malaria.[2] Globally, 1.2 million deaths recorded in 2015 are directly correlated with a decrease in glomerular filtration ability.[3] In Indonesia, 0.2% of the adult population were diagnosed with CKD in 2013, making it the second-largest disease in respect to the fund allocated by the national social insurance scheme.[4] A complication of CKD is anemia, which is often associated with decreased levels of erythropoietin (EPO), an endogenous hormone

responsible for inducing Red Blood Cells (RBCs) production in the bone marrow. This condition resulted from the damage of the kidney's cell mass responsible for EPO production. The standard treatment of anemia caused by CKD is the administration of exogenous EPO and improved blood iron levels.

Exogenous EPO has been developed on an industrial scale using recombinant technology (recombinant human EPO-rhEPO) to meet the market demand. Several rhEPO products that have been globally successful include Epoetin alpha manufactured by Amgen Inc., Procrit by Amgen Inc., and Eprex by Janssen Pharmaceuticals.[5] In Indonesia, several rhEPO products are developed by Indonesian and international pharmaceutical companies with marketing licenses, i.e., Epodion, Epoglobin, Epotrex, Hemapo, Rinofer, and Recormon. These products are categorized as biosimilar products, i.e., products with the same efficacy profiles, safety, and quality as those biological products approved by the Indonesian drug safety regulatory authority (BPOM) through their regulation number 17 year 2015.

As biological products with high levels of variation, the consistency between batches of production is a challenge in the manufacturing process. Insignificant differences or very small changes in production, transportation, or storage can change biological products' safety and efficacy profile. In addition, biosimilar products synthesized to resemble hormones can be recognized as foreign material by the human body and trigger immune response or immunogenicity.[6]

Indonesian government adopts WHO regulations[7] on evaluating biosimilar products. To obtain a marketing permit, pharmaceutical companies need to conduct a standard immunogenicity assessment[6,8] to ensure that the biosimilar product has similar efficacy and safety as the originator. Therefore, this study aims to assess the safety (i.e., side effects, adverse events, and serious adverse events) and immunogenicity of Epodion in hemodialysis patients with anemia associated with chronic kidney disease (CKD) within 52 weeks of the treatment period. Up to our knowledge, there have been no similar studies on CKD patients conducted in one year in Indonesia so far. The results of this study will give novel and valuable information on the safety aspect of Epodion as a biosimilar product derived from the hormone that can be used for anemia management in CKD patients.

METHODS

This study was an observational study that did not change the treatment regimen and routine received by the subject. The patients' dosage of Epodion was adjusted to the standard administration used as a routine procedure in each hospital using subcutaneous injection.

Patient eligibility was assessed within a 4-week screening period. Blood samples for determination of erythropoietin antibody (Anti-Drug Antibody) were taken at week-0, 24, and 52. Anti-Drug Antibody (ADA) was detected using a validated and highly sensitive bridging ELISA method carried out in Biotechnology Research Center Laboratory of University of Indonesia, Depok (UI Biotechnology Laboratory). Evaluation of NAb (Neutralizing Antibody) using the cell-based assay method was done to confirm the impact of the antibody on pharmacological activity (e.g., antibody-mediated PRCA) when the ADA detection of patients was positive after screening and confirmatory assay.

The Research Ethics Committee of the Faculty of Medicine, Universitas Indonesia, has reviewed the study protocol and issued the ethical clearance number: KET-1055/UN2. F1/ETIK/PPM.00.02/2019 on September 30, 2019. This ethical clearance was extended until September 29, 2021. The study was conducted according to the ethical principles set forth in the Declaration of Helsinki and carried out in accordance with the Good Clinical Practice (GCP) ICH E6 (R2) standards.

Product Information

Epodion is an alpha rhEPO product produced locally in Indonesia by PT. Daewoong Infion. This product is used in conjunction with other clinical treatments for anemic patients due to chronic kidney failure or chemotherapy. Yellowish transparent Epodion injection solution can be

injected intravenously (IV) or subcutaneously (SC). There are four Epodion products with different EPO content, i.e., 2000 IU, 3000 IU, 4000 IU, and 10000 IU.

Selection of Trial Subjects

The study was done at three Indonesian hospitals in Jakarta (Indonesia's capital) and Tangerang city, i.e., RSPAD Gatot Soebroto Jakarta, RS Pelni Jakarta, and RS Medika Tangerang from September 2019 to November 2020. Based on the prior feasibility study and calculation of precision analysis[9], 200 samples are considered a sufficient amount to represent the general population. Using this number of samples, 6.9% precision (margin of error) at 95% CI could be achieved and considered acceptable.

There are several patients' inclusion criteria, i.e., patients with anemia associated with CKD under hemodialysis treatment; male or female patients aged ≥18 years; patients with mean screening Hb concentration of ≤10 g/dL; patients on stable, adequate dialysis for at least three months (defined as no clinically relevant changes of hemodialysis regimen and/or 23/42 ©EMEA 2007 dialyzer); have used Epodion treatment at least in the past month; hemodialysis patients who are likely to remain on Epodion treatment for 52 weeks; and signed a written consent form.

Patient eligibility was assessed before the study began following the inclusion criteria. Only subjects that passed those criteria were included in the study. A consent form with detailed information about the nature, risks, and scope of the clinical trial and the expected desirable and adverse effects of the drug has been obtained before the screening began. Subjects were given enough time to freely consider their participation in this study before signing the form. Only after signing and fulfilling the inclusion and exclusion criteria, the subject could participate in the study.

Administration of Epodion

At the initial administration, patients were given Epodion dose of 50 units/kg body weight three times/week which can be done intravenously or subcutaneously. If needed, the dose can be increased to 75 units/ kg at four-week intervals from the initial administration. If the hemoglobin level increased by more than 2 g/dL after the initial dose, the administration of Epodion must be reduced to twice a week. Repair doses can be continued until the patient's hemoglobin level becomes 10 g/dL. Managed anemia condition can be maintained by administering doses between 25 to 50 units/ kg, two or three times/week. The expected hemoglobin range for treatment is 10-12 g/dL. The initial hemoglobin level and the patient's age determine the treatment dose. The maximum administration of Epodion should not exceed 200 units/kg and not more than three times/ week. During treatment, the patient's iron level was also controlled. In chronic kidney failure patients who did not undergo hemodialysis, a dose of 70-150 units/kg per week was proven to maintain 36-38% hematocrit levels for more than six months.

Endpoints

The primary endpoints were the incidence of Anti-Erythropoietin Antibodies (ADA) formation at week 52nd and the detection of Neutralizing Antibodies (NAb). The patient's plasma was used to evaluate the immune response by detecting ADA (Anti-Drug Antibody) using a validated and highly sensitive bridging ELISA method in UI Biotechnology Laboratory. The plasma was prepared based on the regular hospital procedure, i.e., blood samples were centrifuged, plasma samples were labelled and stored as aliquots at -20°C. These plasma samples were then subjected to evaluation analysis of NAb using the cell-based assay method. The Nab was carried out when the ADA detection of patients was positive after screening and confirmatory assay.

The secondary endpoints for this study were any adverse event, the incidence of ADA formation at week-24, and a comparison of the incidence of ADA formation at week-24 and week-52. Adverse Event (AE) defined in this study is any untoward event occurring in the patient after any dose of Epodion was administered. Two types of AE were used, i.e., Serious AE (SAE) and non-serious AE. SAE is defined as AE which result in death, is life-threatening, requires inpatient or prolonged hospitalization, and results in persistent or

significant disability/incapacity. Any occurring AE was assessed for its type, start date, end date, the severity of the symptoms, relevance to the test drug, measures related to the test drug, treatment, results, and significance and recorded in case report form (CRF). Any SAE that occurred was reported no later than 24 hours to the sponsor, three calendar days to the Ethics Committee, and seven calendar days to the head of the national agency of drug and food control (BPOM).

Statistical Analysis

The incidence of ADA, NAb, and AE was analyzed with descriptive statistics and displayed in frequency and percentage. A comparative analysis to compare the incidence of ADA and Nab at week 24 and week 52 were done using paired T-test with an alternative Wilcoxon Test at 95% CI and significance of $P < 0.05$.

RESULTS

Demographic Data

In this observational study, all data collected from three different sites were included (**Table 1**). Of the 200 subjects, 110 males and 90 females participated in this study with age ranging between 21 and 79 years old (average age 53 years old). Their average body weight when screening was 60.3 kg. Hematological tests, which consist of hemoglobin and hematocrit concentration, were also determined before blood sampling was performed. The average Hb and Hct concentrations were 8.5 g/dL and 27.2%, respectively. Vital sign measurement was also included at the screening period as baseline demographic data. Mean blood pressure and pulse rate were 147/77 mmHg and 79.2 bpm, respectively.

During the study period, several subjects dropped out for several reasons. By the week-24, 155 subjects (77.5%) remained, and 45 subjects (22.5%) dropped out (11 from RSPAD Gatot Soebroto, 9 from RS Pelni, 25 from RS Medika BSD). After 52 weeks of study, there were only 130 subjects (65%) remaining, and 25 subjects (12.5%) dropped out (9 from RSPAD Gatot Soebroto, 9 from RS Pelni, 7 from RS Medika BSD). Most subjects (31.5%) who did not complete the observation were due to passing away since those enrolled subjects' condition was already vulnerable. Other subjects could not complete the observation due to safety reasons (1.5%), i.e., two subjects were infected by COVID-19, and a subject had kidney improvement. Besides that, patient withdrawal (1.5%) was due to moving to another hospital. However, based on the observation of the principal investigator in this study, there is no SAE and AE related to the test product in all cases.

Table 1. Baseline demographic and characteristic of study subjects.

Baseline Demographic Data	RSPAD Gatot Soebroto (n= 50)		RS PELNI (n=58)		RS Medika BSD (n=92)		Total (n=200)	
	N		n		N		n	
Gender (%)								
- Male	27		32		51		110	
- Female	23		26		41		90	
	Mean	range	Mean	range	Mean	range	Mean	range
Age (years)	52	21-74	53	21-79	53	22-78	53	21-79
Body weight (kg)	64.3	37.0-113.3	62.7	41.0-89.0	57	29.8-96.2	60.3	29.8-113.3
Body height (cm)	161.5	142-184	160.4	140-173	-	-	160.9	140-184
Hematological Test								
- Hb (g/dL)	8.9	7.0-10.4	8.1	5.6-10.0	8.6	6.7-11.5	8.5	5.6-11.5
- Hct (%)	26.9	21-33	24.3	21.0-29.0	27.6	20.2-36.8	27.2	20.2-36.8
Vital Sign								
- Systole (mmHg)	156	100-201	148.7	99-199	140.8	81-193	147	81-201
- Diastole (mmHg)	83	43-120	75.1	55-102	75.1	36-102	77	36-120
- Pulse rate (bpm)	82	63-120	80.1	56-102	77.3	45-131	79.2	45-131

Mean of Hb, Hct, systolic and diastolic blood pressure, also pulse rate were similar and there were no clinically significant changes from week-0 to week-52 (**Figure 1, Table 2**). There was also no significant difference between value of week-0 and week-24. These shows that Epodion could maintain the hemoglobin and hematocrit levels of patients tested.

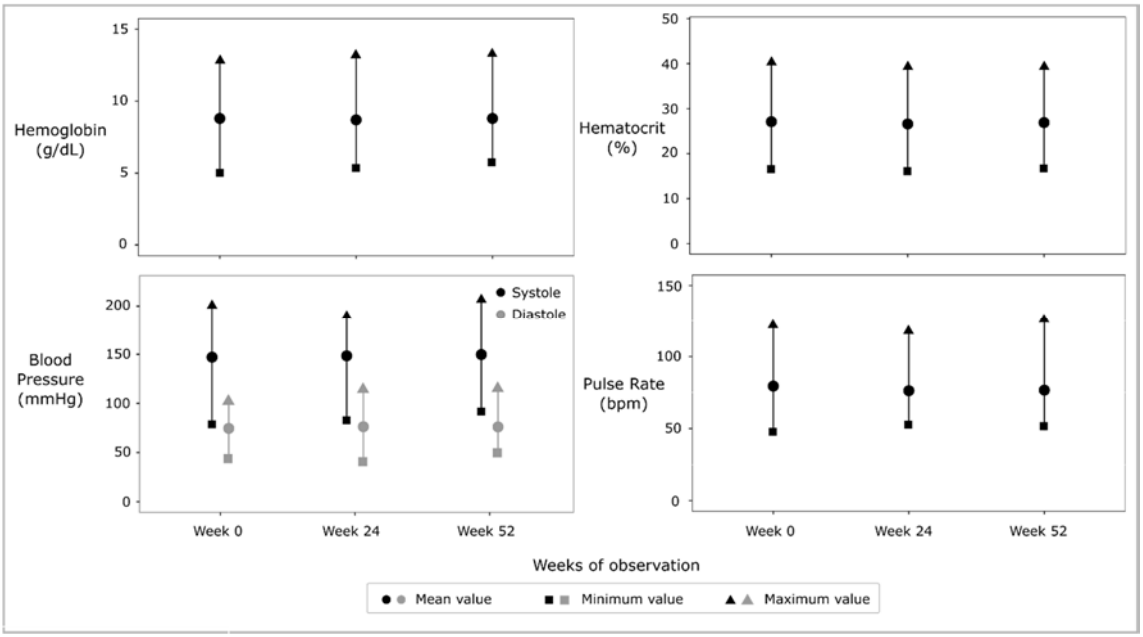

Figure 1. Measured hematological and vital signs during the treatment period.

Table 2. Paired T-test results between weeks of measurement on measured hematological and vital signs during the treatment period.

Parameters measured	Paired T-test results			
	Week 0-24		Week 0-52	
	p-value	Sig.	p-value	Sig.
Hematological Test				
- Mean Hb (g/dL)	0.256	NS	0.991	NS
- Mean Hct (%)	0.056	NS	0.828	NS
Vital Sign				
- Systole (mmHg)	0.435	NS	0.25	NS
- Diastole (mmHg)	0.076	NS	0.192	NS
- Pulse rate (bpm)	0.052	NS	0.103	NS

Primary Endpoints

After 52 weeks of treatment, there were no cases of positive Anti-Erythropoietin Antibodies (ADA) reported (Table 3). Nevertheless, the incidence rate of false positive results of ADA-screening from plasma samples of week-52 was 3.1% (**Table** 3). However, after confirmatory assay, all results become negative. Since there was no ADA detected in the plasma samples, further investigation to evaluate the neutralizing effect of the detected ADA using cell-based assay method to confirm the impact of the antibody to pharmacological activity (such as antibody mediated PRCA) was not required.

Secondary Endpoints

During the treatment period, one or more AEs were experienced by 51% (102/200) of subjects (T**able 4**). Serious AEs were experienced by 41.5% (83/200), with 63 subjects died during the treatment period. However, the observation by

Table 3. Summary results of immunoassay data.

	Week-24 N	%	Week-52 N	%
Total sample	158		130	
Negative ADA	155		126	
Positive ADA	0		0	
Likely false positive ADA	3	1.9	4	3.1
- re-analysis	3		4	
- final result negative	3		4	
- final result positive	0		0	
Total : Negative ADA	158		130	
Positive ADA	0		0	
NAb done	0		0	

the principal investigators in this study concludes that no deaths were considered relevant with the administered Epodion (Appendix 1). Of the 102 subjects who experienced AEs (Table 4), 189 adverse events occurred during a year treatment period (Table 5, Appendix 1). From 189 adverse events reported, the most frequent of adverse events was transfusion (28% of AE) occurred in 18 subjects, followed by hospitalization with unknown specific reason (19% of AE), and COVID-19 (4.8% of AE).

SAE cases that occurred during the study have been reported to the Ethic Committee. Subjects who suffered from SAE and required hospital admission were largely due to sepsis, pneumonia, COVID-19, and anemia. Similar to the incidence of ADA formation at week-52, all the results of week-24 were negative, with an incidence rate of false positive result was 1.9%. Thus, there was no data to compare between week-24 and week-52.

Table 4. Subject with adverse events.

Subjects with Adverse Events (AE)	RSPAD Gatot Soebroto (N = 50)		RS PELNI (N = 58)		RS Medika BSD (N = 92)		Total (N = 200, safety population)	
	N	%	n	%	N	%	n	%
Serious AE	23	46	21	36.2	39	42.4	83	41.5
Non-serious AE	9	18	20	34.5	1	1.1	30	15
All	**26**	**52**	**37**	**63.8**	**39**	**42.4**	**102**	51

Note: All data indicates the number of all patients experiencing Serious and/or Non-serious adverse events; one patient can experience both events

Table 5. Adverse events.

Adverse Events (AE) occured	RSPAD Gatot Soebroto (N = 50)		RS PELNI (N = 58)		RS Medika BSD (N = 92)		Total (N = 200, safety population)	
	N	%	n	%	n	%	n	%
Serious AE	31	36	31	16.7	52	49.1	114	30.2
Non-serious AE	12	14	62	33.3	1	0.9	75	19.8
All	43	50	93	50	53	50	189	50
Total	86	100	186	100	106	100	378	100

Note: All data indicates the number of all patients experiencing Serious and/or Non-serious Adverse Events; one patient can experience both events

Data Analysis

Antibody detection using ELISA assay showed negative results for all plasma samples of week-24 and week-52, even though some were detected as likely false positives before the confirmatory assay was performed. Therefore, the significance of data between week-24 and week-52 was not analyzed further.

DISCUSSION

Epodion is a biological product that is considered biosimilar to the original reference product (Eprex®); hence, evaluating its immunogenicity is crucial. Most biological products can induce unwanted immune reactions due to the formation of antibodies, which then contribute to potential adverse effects.[10] This immunogenic effect can impact the loss of efficacy of the therapeutic product.[11] Up to the moment this study was done, Epodion has been proven to successfully and safely treat anemia in patients with CKD. Patients receiving Epodion treatment showed a stable and maintained hemoglobin level.

The high AE observed is possibly related to the initial patient condition. Most of the patients recruited were elderly (mean age 53 years; see **Table 1**) with a considerably vulnerable condition of low Hb levels and underlying conditions, such as hypertension. Most AE incidence reported were blood transfusion to raise the patients' Hb level. Epodion treatment was meant to maintain their Hb level, which proved to be successful after weeks of observation. However, in most patients, their Hb was still considered low. A meta-analysis study[12] mentioned that a higher Hb target to patients with anemia caused by CKD using rhEPO might increase the risk of death. Therefore, in this study, treatments used were a combination between transfusion and a controlled dose of rhEPO Epodion.

The studied subjects did not develop antibodies on anti-epoetin, a result similar to other studies in European hospitals.[13,14] Another Indonesian study using biosimilar rhEPO products Renogen and biosimilar rhEPO origin Eprex[15] also showed similar findings. The efficacy and safety of biosimilar rhEPO on treating CKD-associated anemia were also shown in another study with pre-dialysis patients.[16]

The patient who develops an antibody to rhEPO can become severely anemic and requires frequent RBCs transfusions. These antibodies recognized the core protein of endogenous erythropoietin after complete deglycosylation of the molecule. The high-affinity binding sites also bound denatured erythropoietin, suggesting that these antibodies are directed against a linear epitope of the erythropoietin molecule. The level of immunoprecipitation antibodies was able to neutralize very high amounts of erythropoietin receptors. Thus, these antibodies can neutralize all erythropoietin molecules produced by the patients, fully inhibiting erythropoiesis.[17]

Based on the EMA guidelines, several factors may influence the immunogenicity of therapeutic proteins, e.g., patient-related factors, disease, or product itself. Immunogenicity data are highly dependent on the types of assays used. From different types of assays used to detect anti-Erythropoietin antibodies, the most reliable results is provided by ELISA assay. The bridging ELISA assay in this study is preferred for its sensitivity, specificity, and convenience for managing large numbers of serum samples.[18]

The analysis of plasma samples of 200 patients with CKD-associated anemia collected from three different hospitals showed the presence of anti-Erythropoietin antibodies from those samples. A screening assay should be capable of detecting antibodies (ADA) induced against the Epodion. Nevertheless, the detection of some false-positive results is inevitable since an absolute screening-assay specificity is normally unattainable (EMEA, 2007). These false-positive results were necessary to be confirmed through confirmatory assay. All of them were considered eliminated and showed negative results after the confirmatory assay was performed. There were no patients developing non-neutralizing or neutralizing anti-epoetin antibodies or pure red cells aplasia (PRCA). Therefore, determination of the neutralizing activity was not necessary. The data reflect that all patients using Epodion in a year were considered negative for antibody to Epodion in an ELISA assay and continuation of Epodion therapy will be possible.

This study has limitations. The data gathered

only covers a particular area of Indonesia, which did not fully represent the ethnic diversity of Indonesian people. Patients' characteristics such as ethnicity, nutritional status, and age can largely affect the prognosis and timing of AE happened in CKD patients.[19] These characteristics can act as confounding factors that may affect the parameters measured. Even though we did include quite extensive inclusion and exclusion criteria, it is quite difficult to obtain a wide array of subjects. Most subjects in this study were already in an initial vulnerable condition. Some of them did not follow the international treatment standard of three times per week hemodialysis. Nevertheless, the investigators in this study follow the standardized protocols of patient evaluation to obtain valid data.

CONCLUSION

This study proves that Epodion is considered safe and did not induce immunogenetic reaction in considered doses in patients from three Indonesian hospitals during one year of observation. These results also indicate that the administration of Epodion did not show any symptoms related to PRCA. However, this study also implies that the initial condition of patients plays a vital role in determining the potential adverse effect that might happen. Therefore, prospective future studies should include a wide array of patients in a less vulnerable condition. Datasets should cover patients from other Indonesian provinces since differences in patients' ethnicity, and nutritional diets may be confounding variables. Other recommended future studies may also involve EPO-naive patients, administration of EPO dose per body weight, and standardization of patients' hemodialysis frequency three times/ week according to international standards.

CONFLICT OF INTEREST

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