STUDY PROTOCOL

The Clinical Study for Evaluating The Safety And Efficacy Of Epodion® During Maintenance Period Until Evaluation Period On CKD (Chronic Kidney Disease) Patients: An Open Label, Randomized, Active Drug-Comparative, Parallel-Designed, Multi-Center Clinical Study

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DAEWOONG PHARMACEUTICAL CO., LTD.
2019

FORM OF AUTHORIZATION

1. Study Title	:	The Clinical Study for Evaluating The Safety And Efficacy Of Epodion® During Maintenance Period Until Evaluation Period On CKD (Chronic Kidney Disease) Patients: An Open Label, Randomized, Active Drug-Comparative, Parallel-Designed, Multi-Center Clinical Study
2. Principal Investigator		
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b. Institution	:	Gatot Soebroto Army Hospital
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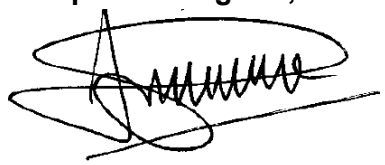
a. Name	:	dr. Kuspuji Dwitanto, Sp. PD-KGH
b. Institution	:	Cempaka Putih Jakarta Islamic Hospital
5. Study Location	:	3 hospitals at Jakarta (Gatot Soebroto Army Hospital, dr. Esnawan Antariksa Airforce Hospital, Cempaka Putih Jakarta Islamic Hospital)
6. Study Duration	:	October 2019 – July 2021

Jakarta, 2 April 2020

Principal Investigator,



dr. Jonny, Sp.PD-KGH, M.Kes, MM
Colonel CKM

STATEMENT SHEET

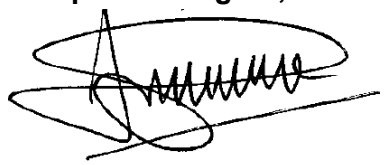
I, the undersigned below:

Principal Investigator	:	dr. Jonny, Sp.PD-KGH, M.Kes, MM
Study Title	:	The Clinical Study for Evaluating The Safety And Efficacy Of Epodion® During Maintenance Periode Until Treatment Evaluation Period On CKD (Chronic Kidney Disease) Patients: An Open Label, Randomized, Active Drug-Comparative, Parallel-Designed, Multi-Center Clinical Study
Institution	:	Gatot Soebroto Army Hospital

I hereby declare that in this research protocol/proposal no work has ever been submitted for approval in other institutions and to the best of my knowledge no work or opinion has ever been published or published by another person, except those published are referred to in this manuscript and mentioned. in the bibliography.

Jakarta, 2nd April 2020

Principal Investigaor,



dr. Jonny, Sp.PD-KGH, M.Kes, MM
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GLOSSARY OF TERM

ADR	Adverse Drug Reaction
AE	Adverse Event
CBC	Complete Blood Count
CKD	Chronic Kidney Disease
CI	Confidence Interval
CRO	Contract Research Organization
CSR	Clinical Study Report
CRF	Case Report Form
EMA	European Medicines Agency
EPO	Erythropoietin
GCP	Good Clinical Practice
IC	Informed Consent
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
ITT	Intent-To-Treat
IWRS	Interactive Web Response System
NAb	Neutralizing Antibody
PP	Per-protocol
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBP	Similar Biotherapeutic Product
SOC	System Organ Class
WHO	World Health Organization

PROTOCOL SYNOPSIS

Study title	The Clinical Study for Evaluating the Safety and Efficacy Of Epodion® During Maintenance Period Until Evaluation Period On CKD (Chronic Kidney Disease) Patients: An Open Label, Randomized, Active Drug-Comparative, Parallel-Designed, Multi- Center Clinical Study
Sponsor	Daewoong Pharmaceutical Co., Ltd.
CRO	PT. Equilab International
Institution and Principal Investigator	Gatot Soebroto Army Hospital Internal Medicine Department, **dr. Jonny, Sp. PD-KGH, M.Kes, MM**
Study Period	**Total 36 - 40 weeks** • Screening period (-4) weeks • Titration period 4~8 weeks • Baseline evaluation period 4 weeks • Maintenance period 24 weeks • Evaluation Period 4 weeks
Study Population	Anemia Associated with Chronic Kidney Disease aged ≥ 18 yearsand undergoing hemodialysis in hospital site
Objectives	To evaluate the safety and efficacy of Epodion® on Chronic KidneyDisease (CKD) patients
Study Phase and Design	An Open Label, Randomized, Active Drug-Comparative, Parallel-Designed, Multi-Center Clinical Study, Phase IV Study
Method	This clinical study was designed as an open label, randomized, active-drug comparator, parallel designed, and multicenter study in hemodialysis patients with anemia. Once subjects voluntarily consented to participate in the clinical study, medical examinations and tests required in the protocol will be conducted, eligibility of each subject will be checked, and only subjects who meet all of the screening criteria will be proceeded forfirst phase of study which is titration period. In Titration period (4 ~ 8 weeks), all eligible subjects will be administered with Eprex® at individualized dose. Routine hematological (Complete Blood Count, CBC) test will be performed every two weeks to monitor Hb level as consideration for dose adjustment. Eprex® doses should be

<table>
<tr><td></td><td>closely titrated to achieve target Hb range 10-12 g/dL. Subject who meets the target range at week 4 will be allowed to skip the remaining 4 weeks of titration period and continue to Baseline Evaluation Period.

During the 4 weeks of Baseline Evaluation Period, laboratory tests required in the protocol are performed every two weeks and recorded as baseline data.

Subjects who meet the inclusion criteria, none of the exclusion, and achieve baseline evaluation target criteria will be randomized into either test group (Epodion® treatment) or control group (Eprex® treatment).

In Maintenance period, the administration dose of Eprex® and Epodion® is equal to the previous dose in titration period. Dose is allowed to be increased or decreased during maintenance period at an appropriate level to maintain Hb level 10-12 g/dL according to condition of subjects. During maintenance period, blood samples will be collected every two weeks for routine hematological test to monitor the efficacy and as consideration for dose adjustment.

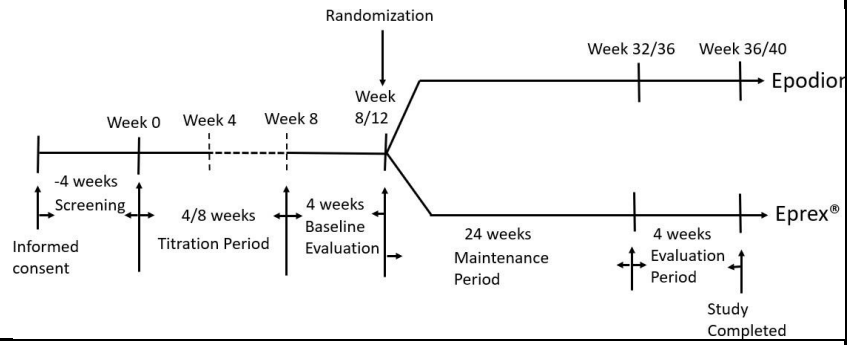
In the Evaluation period, blood samples will be collected every two weeks. The mean of Hb change, weekly dosage, and hematocrit between baseline and evaluation period will be evaluated as efficacy assessment.</td></tr>
<tr><td>Investigational Product</td><td>Treatment: Recombinant Human Erythropoietin Alfa, Epodion® (Daewoong Infion)

Reference: Recombinant Human Erythropoietin Alpha, Eprex® (Janssen)</td></tr>
<tr><td>Dosage & Administration, and Route of Administration</td><td>Initial Epoetin dose administered according to previous dose. In Maintenance period, Epoetin dose may be increased or decreased at an appropriate level according to the condition of the subjects.</td></tr>
<tr><td>Number of subjects</td><td><table>
<tr><th></th><th>Study Group (Epodion®)</th><th>Control Group (Eprex®)</th><th>Total Sample Size</th></tr>
<tr><td>Evaluated Case</td><td>50</td><td>50</td><td>100</td></tr>
</table></td></tr>
<tr><td></td><td>Inclusion Criteria:

a. Male or female patients who are at least 18 years old and youngerthan 75 years of age at the time of screening visit.</td></tr>
</table>

Screening Criteria:	b. Patients with End-Stage Renal Failure (ESRD) who are chronically receiving hemodialysis and have anemia. c. Patients with a mean baseline Hb concentration within Hb level ≥9 g/dL during the screening period. d. Haemodialysis patients with anemia associated with Chronic Kidney Disease (CKD) currently receiving stable maintenancetherapy with Epoetin alfa at least once per week. e. Adequate iron substitution status (serum ferritin ≥ 100 μg / L (100ng / mL) or saturated transferrin levels ≥ 20%). f. Patients who understand the information provided to them or their representatives and may provide written consent. **Exclusion Criteria:** a. Contraindication with Epoetin therapy. b. Documented active bleeding in the last 12 weeks prior to screening period. c. Any blood transfusion within the last 2 weeks prior Screening period. d. History of malignancy of any organ system within the last 5 years. e. 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). f. Patients hyporesponsive epoetin treatment or had medical history of experiencing pure red blood cell forming failure after being administered with Epoetin products. g. Known bone marrow fibrosis (osteitis fibrosa cystica). h. Patient with serious cardiovascular disorders: myocardial infarction, patients with congestive heart failure (NYHA class Ⅲ or higher), ischemic vascular disease. i. Patient received percutaneous coronary intervention (PCI),

	or coronary artery bypass grafting (CABG) during the last 6 monthsprior to screening. j. Patients with ALT or AST exceeding the upper limits of the normallevel by more than 5-folds. k. Patients whose kidney transplant is expected or already plannedfor survival. l. Secondary anemia to other causes different to the CKD (aplastic anemia, hemolytic anemia, sickle cell anemia, multiple myeloma,leukemia, myelodysplastic syndrome). m. 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. n. Pregnancy or lactation period in female patients, or women of childbearing potential without an effective method of birth control. o. Patients who were considered unfit for study by the principal investigators or by the co-investigator.
Baseline Evaluation Period Criteria	Subject who voluntarily consented to participate in the clinical study, meet eligible criteria, stable with Eprex®, will be evaluated again to assess the subject eligibility prior randomization and maintenance period. Only subjects who meet eligible baseline criteria will continue to randomization and maintenance period. Inclusion criteria: a. Subject achieved Hb target 10-12 g/dl. b. Adequate iron substitution status (serum ferritin ≥ 100 μg / L (100 ng / mL) or saturated transferrin levels ≥ 20%). c. Patients who have gone through the baseline evaluation at the time of the screening visit or before randomization. d. Patients with dry weight less than 5% during the baseline evaluation period. e. Subject are reliable and will willingly cooperate during the maintenance period and observe the restrictions.

	Exclusion Criteria: a. Any blood transfusion within the last 2 weeks prior to screeningperiod. b. In case the EPO administration dose during the baseline evaluation period (week 9-12 / 13-16) is increased or decreasedby 20% or more. c. Currently contraindicated with Epoetin therapy. d. Subject administered with prohibited drug (cyclosporine,androgen, and chemotherapy agents). e. Occurrence medical condition which can affect efficacy data during maintenance period judged by principal investigator orsub-investigator.
Outcome Measures:	**Primary endpoint** a. Mean change in Hb (hemoglobin) level between the baselineperiod and the evaluation period **Secondary endpoint:** b. Mean change in weekly dosage per kg body weight between thebaseline period and the evaluation period. Instability rate of Hb (hemoglobin) level during maintenance and evaluation period as defined when Hb (hemoglobin) level droppedbelow 8 g/dL or increase more than 13 g/dL. c. Evaluation Hb (hemoglobin) and hematocrit level during maintenance and evaluation period.
	Safety Evaluation: Incidence adverse events.
Study flow	
Study timeline	

Procedure and Assessment		Screening	Titration Period			Baseline Period				Maintenance Period													Evalu Peri
Week		-4	0	2	4	6	8	10	12	10/14	12/16	14/18	16/20	18/22	20/24	22/26	24/28	26/30	28/32	30/34	32/36	34/38	
Informed consent form		■																					
Patient demography		■																					
Medical history		■																					
Prior Medication		■																					
Inclusion/exclusion criteria		■																					
Baseline Target Evaluation [1]						■	■	■	■														
Randomization [3]							■		■														
Concomitant Medication										Every time													
Eprex® administration [2]			Administer at an appropriate level for each subject																				
Epodion® administration [2]										Administer according to the existing baseline dosage													
Lab Test	CBC (Hb)	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	
	CBC (Hct)	■								■	■	■	■	■	■	■	■	■	■	■	■	■	
	Iron status	■					■																
	HIV	■																					
	Blood Chemistry (ALT&AST)	■																					
Pregnancy Test		■																					
Safety Assessment [4]										Every time													

1. Subject must achieve baseline target Hb level 10-12 g/dL prior enter maintenance period. If during 4-week titration period subject did not achieve baseline Hb level 10-12 g/dL, titration period will be extended maximum until week 8.

2. Doses must be individualized to ensure that hemoglobin is maintained at an appropriate level for each subject. In the screening period, initial dose is 50 IU/Kg body weight three times per week. During titration, dose id titrated closely to achieve baseline Hb level 10-12g/dL. In maintenance period administer Eprex® and Epodion® equal previous stable dose in titration period. Dose is allowed to be increased or decreased during maintenance period at an appropriate level according to the condition of the subjects.

3. Only the subjects within the inclusion/exclusion criteria and achieved baselinetarget evaluation criteria should be processed to randomization and maintenance period. When the subject achieves baseline target Hb level 10-12 g/dL in 4 weeks titration period randomization will be done in week 8, if subject fail achieves Hb 10-12 g/dL in 4 weeks titration period, titration period will be extended until week 8. Subject will be screened failure and cannot enter maintenance period if during maximum 8 week titration cannot achievetarget baseline Hb level 10-12 g/dL.

4. Safety assessment will be evaluated based on comparison incidence of adverse event between Epodion® and Eprex®. Incidence of adverse eventswill be recorded during maintenance and evaluation period.

CHAPTER I. INTRODUCTION

1.1 Background of Clinical Study

World Kidney Day (WKD) is celebrated every Thursday on the second week in March. In 2017, the theme raised was "Kidney disease and obesity, a healthy lifestyle for healthy kidneys", which Chronic Kidney Disease (CKD) is a global public health problem with increased prevalence and incidence of kidney failure, poor prognosis, and high cost. Clinically, 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 (KDIGO, 2012).

CKD is also a comorbidity of diabetes and hypertension, and can also be caused by chronich glomerulonephritis, chronic interstitial nephritis, polycystic kidney disease, urinary tract infections, and obesity. CKD also has an indirect impact on increasing deaths from cardiovascular disease, diabetes, hypertension, infections in people with HIV, and malaria (Indonesia Ministry of Health, 2017).

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 (Luyckx et al., 2018).

In Indonesia, treatment of CKD patients is second rank after heart disease in the largest funding of BPJS health. Based on the results of the 2013 Basic Health Research (Riskesdas), 0.2% of the adult population were diagnosed with CKD. This number is lower than the prevalence of CKD in other countries based on Indonesia Renal Registry (Pernefri) 2006, which is 12.5%. The difference in prevalence rates caused by the diagnosis of CKD patients in Indonesia can only be done in the later and final stages (Indonesia Ministry of Health, 2013).

The prevalence of CKD increases as the increasing number of elderly people and the incidence of diabetes mellitus and hypertension. CKD is also more common in women because women generally have lower muscle mass, so the serum creatinine concentration is also different. Calculation of prevalence of CKD generally involves correction factors for women with CKD (Hill et al., 2016).

Anemia, which is a complication of chronic kidney disease, is often associated with decreased levels of erythropoietin (EPO) in the blood. This results from damage of the cell mass in the kidneys responsible for EPO production. Treatment of anemia caused by chronic kidney disease which has become the standard is the administration of exogenous EPO together with improvement in blood iron levels.

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. 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). The first recombinant human EPO was developed by Epoetin alpha by Amgen Inc. with the name Epogen market. Some other rhEPO products that have been widely used throughout the world include Procrit® from Amgen Inc. and Eprex® from Janssen Pharmaceutica (Zadeh, 2017).

In Indonesia, several RhEPO products that have obtained marketing licenses include Epodion®, Epoglobin®, Epotrex®, Hemapo®, Rinofer®, and Recormon® (MIMS, 2019; BPOM, 2019). These products are developed by both Indonesian and international pharmaceutical companies. The rhEPO products are categorized as biosimilar products. RhEPO products in Indonesia were developed referring to the RhEPO originator so that they have the same efficacy and safety as the rhEPO originator.

Similar biotherapeutic product (SBP) or can be called similar biological products are biological products with efficacy profiles, safety, and quality that are similar to biological products approved by the drug safety regulatory authority (BPOM, 2015). Development of biological products that are not as simple as synthetic chemical drugs can cause several aspects of similar product development to be different. The development of generic drugs from synthetic chemical drugs can go through the same stages and produce types of drugs with the same characteristics as the originator. However, this does not apply to the development of biological products.

Biological products are complex molecules that are produced using living cells and have very high levels of variation depending on the means, tools and materials used in the production process. The consistency between batches of production is a challenge in manufacturing biological products. Insignificant differences or very small changes in production, transportation or storage can result in changes in the safety and efficacy profile of biological products. Two similar biological products cannot always be proven to be identical products.

Biosimilar products can be produced by the pharmaceutical industry after the originator's product patent period has expired. At present, various biosimilar products are under development or have received marketing licenses in many countries. Development of science as well as the growth of pharmaceutical industry in Indonesia has an impact on improving domestic biosimilar products. Various biosimilar products that have been developed in Indonesia include erythropoietin, monoclonal antibodies, and several growth factor products.

Epodion® research has been carried out in several countries including Korea and Thailand with good results. Phase III studies in Korea evaluated the safety and efficacy of Eposis® in 198 CKD patients (Eposis®: 101, reference product: 97) using dose: ≤ 2000 IU / kg, 3 times/week. The efficacy of Eposis® is the same and or better than the reference product. Eposis also shows lower frequency of Adverse Events compared to reference products. Whereas in the Post Marketing Surveillance study in Korea with the number of subjects 640 CKD patients for 4 years. In the results of the safety assessment, 55 and 13 cases of adverse event occurred in the general PMS study and the long-term PMS study, respectively (An incidence of adverse events was 9.02% and 18.57%, respectively; in the exact 95% confidence level). All the reported adverse events were considered that there was no causal relationship with product and therefore there were no adverse drug reactions.

Phase IV study begins after drug approval. Therapeutic use studies go beyond the prior demonstration of the drug’s safety, efficacy and dose definition. Studies in Phase IV are all studies (other than routine surveillance) performed after drug approval and related to the approved indication. They are studies that were not considered necessary for approval but are often important for optimizing the drug's use. They may be of any type but should have valid scientific objectives.

1.2 Rationale for Clinical Study

1.2.1 Non-clinical Study

Nonclinical study was conducted based on “Guideline on non-clinical and clinical development of similar biological medicinal products containing recombinant erythropoietin” released by European Medicines Agency (EMEAjansse/CHMP/BMWP/301636/2008). In pharmacology studies, biosimilarity and bioequivalence of test product and reference product was confirmed in the regular animal model, acute blood loss induction model, and renal failure model. Both articles’s effects were determined to be equivalent. In pharmacokinetic studies, all parameters, blood concentration curve area (AUClast), maximum blood concentration (C_{max}), and half-life (T½), met the criteria for biosimilarity evaluation.

Biosimilarity and bioequivalence of reference and test product on the absorption was confirmed in intravenous and subcutaneous administration in rats. In the case of toxicology study, no abnormality was observed in the single dose toxicity studies in rats and beagle dogs. To investigate the toxicity caused by the 4-week repeated intravenous administration of test product, it was repeatedly administered intravenously to Sprague-Dawley rats for 4 weeks.

As a result of the test, there was no death rate or any abnormality in the ophthalmologic test, urinalysis, autopsy, and clinical signs caused by the administration of test product. When compared to reference product, test product showed that equivalent or non-inferior toxicological profile. For analysis of antigenicity, active systemic anaphylaxis test (ASA) and passive cutaneous anaphylaxis (PCA) were conducted in guinea pigs. Both articles had similar pattern in anaphylaxis reaction.

From the pharmacodynamics, pharmacokinetic and toxicology study results of test product and comparison with reference product, test product was proven that has similar pharmacokinetics, pharmacodynamic effect and toxicological profile with reference. In conclusion, no harmful effect is expected to be observed when test product is administered into human.

1.2.2 Clinical Safety Study

Post-marketing data was collected from December 4, 2007 to December 3, 2011 in Korea. A target number of subjects were more than 600 and the total number of collected CRFs was 640. Detailed report was attached in 5.3.6 Report of post-marketing experiences. In the results of safety assessment, 55 and 13 cases of adverse event occurred in the general PMS study and the long-term PMS study, respectively (An incidence of adverse events was 9.02% and 18.57%, respectively; in the exact 95% confidence level). All the reported adverse events were considered that there was no causal relationship with product and therefore there were no adverse drug reactions.

1.2.2 Efficacy Study

Therapeutic confirmatory study for evaluating the safety and efficacy of EPO PRODUCT on CRF (Chronic Renal Failure) patients: a double-blinded, randomized, active drug-comparative, parallel-designed, multi-center clinical study has been conducted on 192 patients in Korea. To verify the effects of treating anemia patients suffering from chronic renal failure, the indications of the test product and the reference product and trends in changes in RBC (Red Blood Cell), Hemoglobin, Hematocrit, and Reticulocyte, were examined during the period of clinical study.

During the process of the clinical study, the test group posted somewhat higher values compared with the reference group in 3 items, i.e., RBC, Hemoglobin, and Hematocrit.

1.3 Objective and Hypothesis

The objective of this study is to evaluate the safety and efficacy of Epodion® on Chronic Kidney Disease (CKD) patients.

1.3.1 Study Objectives

1.3.1.1 Efficacy Outcome

A. Primary Objectives
To demonstrate that the Epodion® treatment is equivalence to Eprex® by evaluating Hb level change between baseline and evaluation period.

B. Secondary Objectives
1. Obtain data mean change in weekly dosage per kg body weight between the baseline period and the evaluation period.

2. Calculating instability rate of Hb (hemoglobin) level during maintenance and evaluation period as defined when Hb (hemoglobin) level dropped below 8 g/dL or increase more than 13 g/dL.

3. Evaluating Hb (hemoglobin) and Hematocrit level during maintenance and evaluation period.

1.3.1.1 Safety Outcome

Obtain safety data (side effects, adverse events, and serious adverse events) hemodialysis patients during the use of Epodion®.

1.3.2 Hypothesis

Efficacy and safety of Epodion® was therapeutically equivalence to the reference product (Eprex®) in dialysis patients with renal anemia.

1.4 Research Benefit

This study will provide treatment in the form of hemodialysis three times a week during the study period to consenting and committed patients marked by signing on the explanation sheet after approval. In addition, subjects will receive routine Epoetin treatment during the study period.

CHAPTER 2. LITERATURE REVIEW

2.1 Chronic Kidney Disease (CKD)

Chronic Kidney Disease (CKD) is kidney damage due to structural or kidney function abnormalities that occurs for more than 3 months. The kidneys have various functions including excretion, endocrine and other metabolic functions. Glomerular filtration rate (GFR) is one component of excretion that is generally used as an index of renal function because in general kidney function will decline after damage to the spread structure and decrease in other kidney function decreases with glomerular filtration rate in CKD (KDIGO, 2013). The criteria for Chronic Kidney Disease (CKD) can be seen in the following table:

Table 1. CKD criteria (KDIGO, 2013)

Parameters of kidney damage (one or more)	• Albuminuria (AER> 30 mg / 24 hours; ACR> 30 mg / g [> 3mg / mmol]) • Urinary sediment abnormalities • Electrolyte abnormalities and others due to tubular damage • Abnormalities detected by histology • Structural damage detected by imaging • History of kidney transplants
Decreasing Glomerular Filtration Rate (LFG)	< 60 mL/minute/1.73 m^2

Based on the National Kidney Foundation Kidney Disease Improving Global Outcomes (NKF-KDIGO) in 2012, the classification of Chronic Kidney Disease (CKD) was divided based on glomerular filtration rate and albuminuria (Figure 1).

Prognosis of CKD by GFR and Albuminuria Categories: KDIGO 2012

GFR categories (ml/min/ 1.73 m²) Description and range				Persistent albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30-300 mg/g 3-30 mg/mmol	>300 mg/g >30 mg/mmol
	G1	Normal or high	≥90			
	G2	Mildly decreased	60-89			
	G3a	Mildly to moderately decreased	45-59			
	G3b	Moderately to severely decreased	30-44			
	G4	Severely decreased	15-29			
	G5	Kidney failure	<15			

Green: low risk (if no other markers of kidney disease, no CKD); Yellow: moderately increased risk; Orange: high risk; Red, very high risk.

Figure 1. Classification of Chronic Kidney Disease based on Glomerular Filtration Rate and albuminuria (KDIGO, 2012)

In patients with CKD, a decrease in the glomerular filtration rate causes a buildup of chemicals such as potassium and urea. Hemodialysis therapy, which is a blood cleansing process using a kidney replacement in the form of a dialyzer machine, is given to patients with CK level 5 or the final level or GFR <15 mL / minute / 1.73 m^2. This process involves the use of a dialysate containing sodium bicarbonate, sodium chloride, acid concentrate, and water distilled as an osmosis medium. The physiological working principle of hemodialysis is filtration, diffusion, osmosis, and ultrafiltration which are influenced by temperature, viscosity, and size of the molecule itself (Vadakedath & Kandi, 2017).

People with CKD often also suffer from anemia complications caused by a decrease in kidney function. Anemia diagnosis is given to adult PGK patients if the Hb concentration is <13 g / dl in men or <12 g / dl in women. 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 Epoetin therapy to increase levels of red blood cells or erythrocytes in the blood (Pollock et al. 2008).

Giving Epoetin in patients with CKD who undergo hemodialysis begins after symptoms of uremia, excess fluid, and stable hypertension. In addition, administration of Epoetin can only be done after all causes of anemia except erythropoietin deficiency are overcome, especially iron deficiency, folic acid, vitamin B12, and the presence of bleeding (Pollock et al. 2008).

2.2 Biosimilar

Biological products contain active compounds derived from living cells or organisms and are very necessary for the treatment of various serious and chronic conditions. Most biological products used clinically are groups of proteins with varying sizes and complexity. The production process of biological products is more complicated than medicinal products produced through a synthesis process with chemical reactions, because it often involves the engineering process of DNA recombination.

In the production process, the biological products produced can vary between batches which can affect the safety and efficacy of the product as a whole. Determination of standard variations is needed to ensure that active compounds can work in accordance with the objectives and at the intended level. Strict control of the quality of biological products is applied to each batch of production, both from physicochemical properties, biological activities, activity, purity, degree of sterilization, and stabilization.

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 have an effect on product safety and efficacy. Based on the level of similarity with the originator, biosimilar products are divided into 4 levels (Figure 2) (EMA, 2017).

Highly similar to the reference medicine	The biosimilar has physical, chemical and biological properties highly similar to the reference medicine's. There may be minor differences from the reference medicine which are not clinically meaningful in terms of safety or efficacy.
No clinically meaningful differences compared with the reference medicine	No differences are expected in clinical performance. Clinical studies that support the approval of a biosimilar confirm that any differences will not have an effect on safety and efficacy.
Variability of biosimilar kept within strict limits	Minor variability is only allowed when scientific evidence shows that it does not affect the safety and efficacy of the biosimilar. The range of variability allowed for a biosimilar is the same as that allowed between batches of the reference medicine. This is achieved with a robust manufacturing process to ensure that all batches of the medicine are of proven quality.
Same strict standards of quality, safety and efficacy	Biosimilars are approved according to the same strict standards of quality, safety and efficacy that apply to any other medicine.

Figure 2. Similarity level of biosimilar product toward the originator (EMA, 2017)

Biosimilar products are different from generic products because the production of generic products is carried out through a chemical synthesis process and does not involve variability so that the end product can have a similarity level of up to 100% (Table 2).

Table 2. Comparison of generic products with biosimilar products (EMA, 2017)

	Generic product	**Biosimilar product**
Production process	Chemically synthesized	Biological process
Final result	The exact same molecule	Molecules with high similarity levels
Molecule size	Small, can be easily characterized	Large, complex structures require technology for characterization
Development process	Emphasizes the bio-equivalence (speed of release of active compounds)	Emphasizing biosimilarity (structure, biological functions, efficacy, safety, and immunogenicity)

The biosimilar regulation was first compiled by the European Union in 2006 with the approval of the first biosimilar product, the somatotropin hormone. Approval of biosimilar products is given based on a balance between positive benefits and risks based on biosimilarity with the originator.

This is obtained through comparative studies to find out clinical data between biosimilar products and their originators.

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. Some requirements include characteristic structure, physicochemical properties, purity, biological activity, product composition, formulation, manufacturing process, and stability of active ingredients and products during storage (EMA, 2017).

Clinical trials for biosimilar products do not need to be done for all important stages (phase 1, 2, and 3 clinical trials) to find out analytical and functional data because these two aspects have been carried out by the originator. The comparability, security, and efficacy between biosimilar products and the originator are preferred (EMA, 2017).

2.3 Erythropoietin

Erythropoietin (EPO), otherwise known as epoetin is a glycopeptide hormone (figure 3) produced by renal erythropoietin producing cells in the kidneys. This hormone is functioning as a stimulator to produce red blood cells in the human red marrow. Increased hormone production is happening when low-oxygen level detected in kidney. EPO in humans was first isolated from anemic patients in 1977. The gene that encodes EPO in humans was first isolated in 1983. After one year later, the EPO gene was successfully cloned for the first time shown in the Chinese Hamster Ovary (CHO) cell. This cloning technology then became a stepping stone in the development of recombinant human EPO (rhEPO) as an anemia drug in patients with chronic kidney disease.

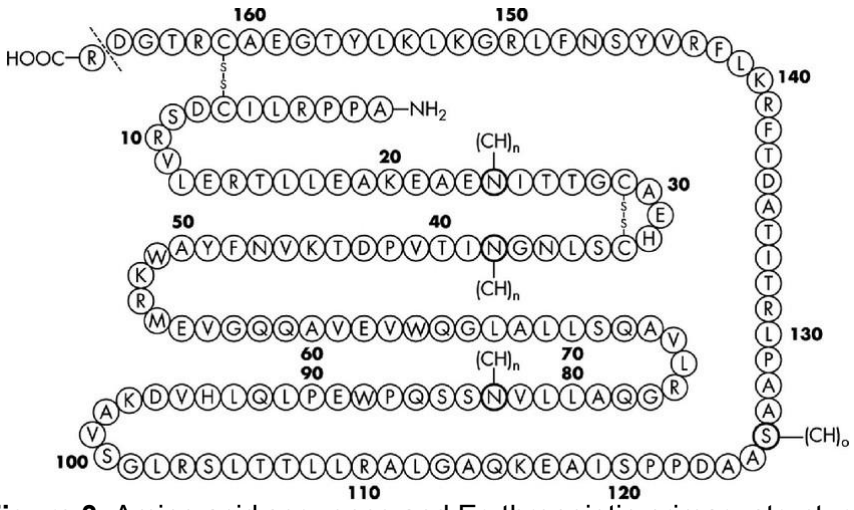


Figure 3. Amino acid sequence and Erythropoietin primary structure

Erythropoietin is known to cause physiological effects if it binds to EPO receptors (EpoR). EPO binds to its receptors on the surface of stem cells which will differentiate into red blood cells. EPO is known to have a mechanism of action on cells by activating the JAK2 signal cascade. The initiation of the JAK2 pathway will also activate the signal cascade on the STAT5, PIK3, and MAPK lines. The signaling causes erythroid cell differentiation and division. In addition, the SOCS1, SOCS3 and CIS paths are also activated and play an antagonistic role as a negative regulator of EPO. EPO receptors (EpoR) are found most frequently in stem cells in the red marrow. Even so, EpoR is also found in other tissues, such as the heart, muscles, kidneys, peripheral nerve networks and central nervous networks.

The level of EPO in blood in normal humans is around 10 mU/mL. Meanwhile, in conditions of hypoxia or lack of oxygen, EPO production has increased up to 1000 times to reach 10,000 mU/mL in blood. In adults, EPO is produced mainly in cells in the kidney, but a small fraction of the fraction of EPO in the blood is also produced by the liver and pericyte cells in the brain.

Regulation of EPO production is governed by a reciprocal mechanism of oxygen and iron levels in the blood.

2.4 Epodion®

Epodion® is an alpha rhEPO product produced by PT. Daewoong Pharmaceutical Company Indonesia. This product is used in conjunction with other clinical treatments for anemic patients due to chronic kidney disease or due to chemotherapy. Yellowish transparent Epodion® injection solution which can be injected intravenously or subcutaneously. Epodion® has four products with different EPO content, including 2000 IU, 3000 IU, 4000 IU, and 10000 IU.

At the beginning of Epodion® use, patients are given a dose of 50 units/kg of body weight three times a week which can be done intravenously or subcutaneously. If needed, the dose can be increased to 75 units/kg at 4-week intervals from the initial administration. If the increase in hemoglobin level increases by more than 2 gr/dL at the initial dose, the administration of Epodion® must be reduced to 2 times a week. Repair doses can be continued until the patient's hemoglobin level becomes 10 gr/dL. Anemia that has been overcome can be continued with a maintenance

dose of between 25 to 50 units/kg, 2 or 3 times a week. The expected hemoglobin range for treatment is 10-12 gr/dL. The initial hemoglobin level determines the treatment dose. In addition, the patient's age is also important in determining the dose. The dosage for the use of Epodion® should not exceed 200 units/kg and the frequency of administration is not more than 3 times a week. During treatment, the patient's iron levels need to be controlled. Chronic kidney failure patients who do not undergo hemodialysis, a dose of 70-150 units/kg per week is proven to maintain hematocrit levels 36-38% for more than 6 months.

Research on the effects of Epodion® on human bone marrow cell culture shows that Epodion® stimulates the formation of red blood cells and does not affect the formation of white blood cells. Animal studies using Epodion® showed in vivo efficacy in test animals. In addition, no cytotoxic effects were detected, changes in behavior, locomotor activity, circulation or breathing in test animals.

The time needed to reach maximum concentration in uremia patients averages 12-28 hours with subcutaneous administration. The bioavailability of Epodion® by subcutaneous administration is 23-42% compared with intravenous administration. Half-life of Epodion® given intravenously to healthy volunteers and kidney failure patients ranges from 4-12 hours with a distribution volume reaching 1 to 2 times the plasma volume. This is similar to the results found in studies in mice with uremia and normal mice. The half-life of the terminal Epodion® by subcutaneous administration in uremia patients averages 13-28 hours, longer than intravenous administration.

The most common side effect is hypertension or worsening hypertension. This increase in blood pressure can be treated with antihypertensive agents. If the hypertension that occurs cannot be overcome with anti-hypertensive drugs, it is recommended to temporarily stop giving Epodion®. Therefore, it is recommended to monitor the possibility of a hypertensive crisis with symptoms resembling encephalopathy (eg, headache, confusion, sensorimotor disorders, tonic clonic (seizures), including in patients with normal or low blood pressure.

In addition, leukocytosis, eosinophilia can sometimes occur. Granulocytopenia can sometimes occur in premature infants. Increases in serum potassium, BUN, creatinine and gout have been reported to occur occasionally. Although rare, thrombocytosis can occur. Reported red cell hypoplasia after administration of Epodion® product in patients with chronic kidney failure from several months to several years is rare. In addition, there may be an increase in platelet counts during Epodion® therapy, especially if given IV. This increase in platelet counts associated with the dose of Epodion® given is usually within normal limits and will improve if Epodion® therapy is given. The incidence of thrombocytosis is very rare. However, it is recommended to monitor platelet levels during the first 8 weeks of Epodion® therapy.

Often, a higher dose of heparin is needed during hemodialysis due to an increase in hematocrit levels. In addition, a dialysis system blockage may occur if heparinization is not optimal. Shunt thrombosis can occur in patients who tend to be hypotensive or patients with complications of the arteriovenous fistula (eg, aneurysm, stenosis). In these patients it is recommended to give thrombosis prophylaxis to administration of acetalisalate. In some patients, there is a decrease in serum ferritin levels together with an increase in hematocrit. For this reason, it is recommended to provide 200 mg / day of oral iron (Fe2 +) substitution in patients with serum ferritin levels <100 ug / L or transferrin saturation <20%. Then, there is a temporary increase in serum serum potassium and phosphate levels. Therefore, it is recommended to monitor these parameters regularly.

CHAPTER 3. STUDY DESIGN OVERVIEW

3.1 Study Design

This study is an open label, randomized, active drug-comparative, parallel-designed, multi-center study in hemodialysis patients with anemia.

3.2 Number of Research Subjects and Estimated Number of Samples

3.2.1. Number of Subjects

The total number of subjects in this study is 100 subjects. Only subject who achieve baseline target Hb level 10-12 g/dL will continue to maintenance period. Subject will be randomized into 2 study arms. For the randomized allocation code between reference product (Eprex®) and test product (Epodion®) will be maintained ratio 1:1.

Study Group	Epodion®	Eprex®
Evaluated	50 Subjects	50 Subjects

3.2. Rationale Number of Subject

A sample size of 90 subjects will be 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. Assumption of difference and standard deviation for sample size estimation in this study was derived from PDA10 ITT set. Difference between treatment groups in PDA10 ITT set was -0.009, but this study assumed to be 0. Standard deviation 0.8 was an approximate estimation derived from two-sided 90% confidence interval [-0.189, 0.171]. After an assumption of 10% drop-out rate for this trial, about 100 subjects will be enrolled to the trial. The sample size calculated using the POWER procedure (Proc Power procedure) of SAS ver. 9.4 (SAS Institute, Cary, NC, USA).

```
*************************************************************************
*    PROGRAM NAME.      : SAS Proc Power_EPO.sas
*    OUTPUT             : EPO_Biosimilar_Sample Size_20191014.pdf
*    SAS VERSION        : SAS 9.4
*    FIRST DATE         : 14 Oct 2019
*    WRITTEN BY         : DW Randoimzation Statistician
*    COMMENTS           : Sample Size Calculation & Power for EPO_Biosimilar
*                         Reference: PDA10 Study
*************************************************************************;

proc power;
   twosamplemeans test=equiv_add
      lower = -0.5
      upper = 0.5
      meandiff = 0
      stddev = 0.8
      groupweights = (1 1)
      ntotal = .
      power = 0.9;
run;
```

Figure 4. SAS code used in determining study subject number

SAS 시스템

The POWER Procedure
Equivalence Test for Mean Difference

Fixed Scenario Elements	
Distribution	Normal
Method	Exact
Lower Equivalence Bound	-0.5
Upper Equivalence Bound	0.5
Mean Difference	0
Standard Deviation	0.8
Group 1 Weight	1
Group 2 Weight	1
Nominal Power	0.9
Alpha	0.05

Computed N Total	
Actual Power	N Total
0.905	90

Figure 5. SAS output

3.3 Institutions Participating in the Clinical Study

1. Gatot Soebroto Army Hospital
2. dr. Esnawan Antariksa Airforce Hospital
3. Cempaka Putih Jakarta Islamic Hospital

3.4 Allocation of Treatment Group

To guarantee scientific appropriateness of the clinical study, investigator's subjective opinion shall not intervene in assignment of subjects into each treatment group, and randomization procedure will be used, based on the concrete probabilistic theory.

Randomization is done using envelopes. The envelope contains information about the product that the subject will receive. Once randomization envelope is opened, it cannot be re-issued to another subject. Randomized allocation code between reference product (Eprex®) and test product (Epodion®) will be maintained ratio 1:1.

CHAPTER 4. ASSESSMENT AND PROCEDURE OF STUDY

4.1 Efficacy Evaluation

4.1.1 Primary Endpoint

To demonstrate that the Epodion® treatment is equivalence to Eprex® by evaluating Hb level change between baseline (Week 5-8/9-12) and evaluation period (Week 33-36/37-40).

4.1.2 Secondary Endpoint

1. Obtain data mean change in weekly dosage per kg body weight between the baseline period and the evaluation period.

2. Calculating instability rate of Hb (hemoglobin) level during maintenance and evaluation period as defined when Hb (hemoglobin) level dropped below 8 g/dL or increase more than 13 g/dL.

3. Evaluating Hb (hemoglobin) and hematocrit level during maintenance and evaluation period.

4.2 Safety Evaluation

Safety was evaluated based on incidence of adverse event.

Reported any symptoms from subject or other health care practitioner defined adverse event if appear after subject administered with investigational product (both Eprex® or Epodion®), and divided into local reactions and general reactions, and the details are as mentioned below:

a. Local reaction: Pain, Tenderness, Erythema/Redness, Induration/Swelling
b. Systemic reaction: Fever, Nausea/vomiting, Diarrhea, Headache, Fatigue, Myalgia.

Vital sign abnormalities are defined as adverse event if there are any clinical significance increase or decrease value including blood pressure, body temperature, heart rate, and respiratory rate after subject administered with investigational product (both Eprex® or Epodion®.
Laboratory test findings defined as adverse event if there are any clinical significance increase or decrease laboratory results including hematology test, blood chemistry test, and urinalysis after subject administered with investigational product (both Eprex® or Epodion®). If any findings after subject administered with investigational product disease temporary, finding abnormalities of electrocardiogram, X-ray, MRI also recorded as adverse event.

4.3 Others

4.3.1 Demographic Investigation

Prior to participation in the clinical study, objective and content of this clinical study shall be explained to the subjects and LAR in detail, informed consent shall be obtained from them, screening number shall be given according to the sequence of receiving informed consent, and then demographic information shall be recorded. Records include written consent, date of consent, gender, date of birth, and age.

4.1.3 Investigation of medical and medication history

Medical history and medication history of the subject shall be investigated and recorded in detail by medical interview. Content that must be included in the medical history and medication history is as mentioned below.

For medical history, past history and current illness including surgical history, and hypersensitivity during 6 months before screening period shall be investigated. Time of onset (year or date of onset), investigator's opinion, etc. shall be written.

For medication history, medication history and current status of erythropoietin administration (dosage, dose, period, etc.) during the 4 weeks prior to screening period shall be investigated. Also, history of medication with cyclosporin and androgen during 3 months prior to screening period, shall be recorded.

If there is any change of concomitant medication compared to the medication investigated at screening, the information shall be documented in the CRF in detail.

4.4 Study Procedure

This research consists of a screening period (4 weeks), titration period (4~8 weeks) baseline evaluation period (4 weeks), maintenance period (24 weeks) and 4 weeks for evaluation period. For each subject, the end of the study was the last day of evaluation. In the case of a subject that has left the study (withdrawn), the exit date will be the end of the study.

Procedure and Assessment		Screening	Titration Period			Baseline Period				Maintenance Period												Evaluation Period	
Week		-4	0	2	4	6	8	10	12	10/14	12/16	14/18	16/20	18/22	20/24	22/26	24/28	26/30	28/32	30/34	32/36	34/38	36/40
Informed consent form		■																					
Patient demography		■																					
Medical history		■																					
Prior Medication		■																					
Inclusion/exclusion criteria		■																					
Baseline Target Evaluation [1]						■	■	■	■														
Randomization [3]							■		■														
Concomitant Medication										Every time													
Eprex® administration [2]			Administer at an appropriate level for each subject																				
Epodion® administration [2]										Administer according to the existing baseline dosage													
Lab Test	CBC (Hb)	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■
	CBC (Hct)	■								■	■	■	■	■	■	■	■	■	■	■	■	■	■
	Iron status	■					■																
	HIV	■																					
	Blood Chemistry (ALT&AST)	■																					
Pregnancy Test		■																					
Safety Assessment [4]										Every time													

Figure 6. Study method

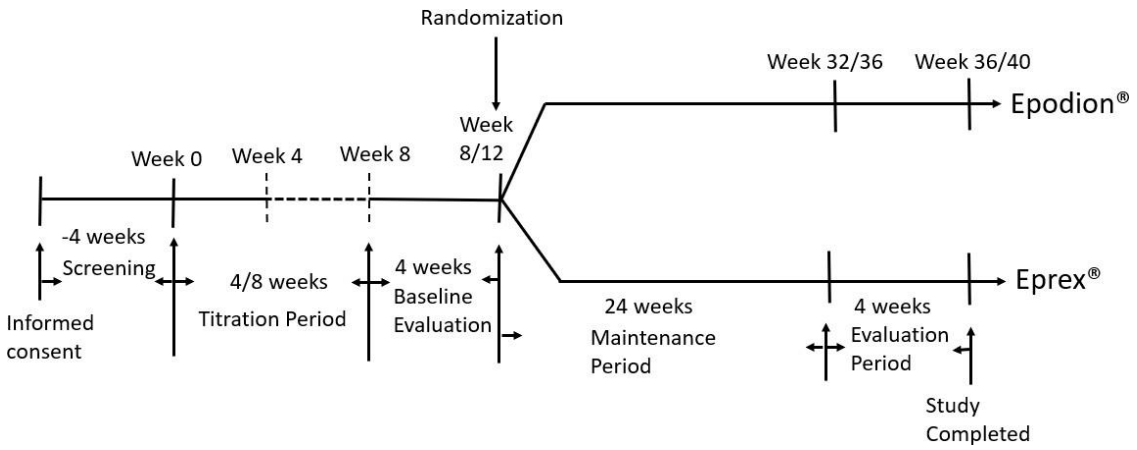


Figure 7. Study flow

4.4.1 Subject screening (-4 weeks)

Patient eligibility was assessed before study begins based on screening criteria and before entering maintenance period based on inclusion and exclusion criteria of study as stated in the protocol. Once subjects voluntarily consented to participate in the clinical study, medical examinations and tests required in the protocol will be conducted, eligibility of each subject will be checked, and only subjects who meet all of the screening criteria will be proceeded for first phase of study which is titration period.

4.4.2 Titration Period (Week 0-4/0-8)

In the Titration period (4 ~ 8 weeks), all eligible subjects will be given Eprex® at individualized dose for 3 times a week through intravenous injection. In this period, the Hb level of the subject was controlled to reach the target range of 10-12 g / dL. Patient demographics, patient medical history, and routine hematological test will be obtained in this period.

4.4.3 Baseline Evaluation Period (Week 5-8/9-12)

Week 5-8/9-12 is the baseline evaluation period. Hemoglobin mean data and mean weekly Epoetin dose will be used as efficacy assessment parameter.

Before entering the maintenance period, subject inclusion and exclusion criteria are examined before subjects received a randomization number and were allocated into a test or control group.

4.4.4 Maintenance Period (Week 9-32/13-36)

During the maintenance period (Week 9-32/13-36), subjects who met the criteria were given Epoetin treatment according to the randomization allocation. Administration of Eprex® or Epodion® will be done with same doses regimen during titration period through intravenous injection. Epoetin 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 is carried out once every two weeks for the purposes of routine hematological test. Adverse event concomitant medication, and instability rate of Hb data is observed during the maintenance period. Concomitant medication during the study were recorded in the Case Report Form (CRF).

4.4.5 Treatment Evaluation Period (Week 33-36/37-40)

The week 33-36/37-40 is the treatment evaluation period. Hemoglobin mean data, weekly Epoetin dose, and hematocrit will be compared with the baseline period as an efficacy evaluation parameter. Adverse events, concomitant medication, and instability rate of Hb data is observed during the maintenance period.

4.4.6 Dose Information

Doses must be individualized to ensure that hemoglobin is maintained at an appropriate level for each subject. Screening period initials dose 50 IU/Kg body weight three times per week. During titration, titrated dose closely to achieve baseline Hb level 10-12g/dL. In maintenance period administer Eprex® and Epodion® equal previous stable dose in titration period. Dose is allowed to be increased or decreased during maintenance period at an appropriate level according to the condition of the subject.

CHAPTER 5. SELECTION OF SUBJECTS AND DROPOUT CRITERIA

5.1 Screening Period Criteria

Inclusion:

a. Male or female patients who are at least 18 years old and younger than 75 years of age at the time of screening visit

b. Patients with End-Stage Renal Failure (ESRD) who are chronically receiving hemodialysis and have anemia

c. Patients with a mean baseline Hb concentration within Hb level ≥9 g/dL during the screeningperiod

d. Haemodialysis patients with anemia associated with Chronic Kidney Disease (CKD) currently receiving stable maintenance therapy with Epoetin at least once per week

e. Adequate iron substitution status (serum ferritin ≥ 100 μg / L (100 ng / mL) or saturated transferrin levels ≥ 20%)

f. Patients who understand the information provided to them or their representatives and may provide written consent.

Exclusion:

a. Contraindication with Epoetin therapy

b. Documented active bleeding in the last 12 weeks prior to screening period

c. Any blood transfusion within the last 2 weeks prior Screening period

d. History of malignancy of any organ system within the last 5 years

e. 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).

f. Patients hyporesponsive epoetin treatment or had medical history of experiencing pure red blood cell forming failure after being administered with Epoetin products

g. Known bone marrow fibrosis (osteitis fibrosa cystica)

h. Patient with serious cardiovascular disorders: myocardial infarction, patients with congestive heart failure (NYHA class Ⅲ or higher), ischemic vascular disease

i. Patient received percutaneous coronary intervention (PCI), or coronary artery bypass grafting (CABG) during the last 6 months prior to screening

j. Patients with ALT or AST exceeding the upper limits of the normal level by more than 5-folds

k. Patients whose kidney transplant is expected or already planned for survival

l. Secondary anemia to other causes different to the CKD (aplastic anemia, hemolytic anemia, sickle cell anemia, multiple myeloma, leukemia, myelodysplastic syndrome)

m. 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

n. Pregnancy or lactation period in female patients, or women of childbearing potential without an effective method of birth control

o. Patients who were considered unfit for study by the principal investigators or by the co-investigator

5.2 Baseline Evaluation Period Criteria

Subject who voluntarily consented to participate in the clinical study, meet eligible criteria, stable with Eprex®, will be evaluated again to assess the subject eligibility prior randomization and maintenance period. Only subjects who meet eligible baseline criteria will continue to randomization and maintenance period.

Inclusion criteria

a. Subject achieved Hb target 10-12 g/dl

b. Adequate iron substitution status (serum ferritin ≥ 100 μg / L (100 ng / mL) or saturated transferrin levels ≥ 20%.

c. Patients who have gone through the Baseline period at the time of the screening visit or before randomization

d. Patients with dry weight less than 5% during the baseline evaluation period

e. Subject are reliable and will willingly cooperate during the maintenance period and observe the restrictions

Exclusion

a. Any blood transfusion within the last 2 weeks prior to screening period

b. In case the EPO administration dose during the baseline evaluation period is increased or decreased by 20% or more

c. Currently contraindicated with Epoetin therapy

d. Subject administered with prohibited drug (androgen, cyclosporin, and chemotherapy agents)

e. Occurrence medical condition which can affect efficacy data during maintenance period judged by principal investigator or sub-investigator

5.3 Discontinuation and Dropout Criteria

The subject may discontinue participation in this clinical study at any time by his/her request, or by the investigator or sponsor's discretion for a safety, action or administrative reason. The investigator shall ask the subject dropout reason, ask them to perform the final visit. If applicable, the investigator shall make utmost efforts to follow up the subject's unresolved adverse events.

Patients who dropped out of this study were patients in one of the following cases:

1. Withdrawn of the consent.
2. Subject receives kidney transplantation during the study period.
3. Subjects that are unable to continue the study because of side effects.
4. Subject do not receive investigational product 4 week consecutively.
5. Not able to participate or continue the study or for any reason based on the assessment of the principal investigator.

5.4 Temporary Discontinuation

If the following situation occurs, the investigator shall delay investigational product administration until the situation will be settled. Then, investigational product administration shall be delayed to the extent of investigational product administration schedule indicated.

The following condition when investigational product should be delayed are detailed below:

- Increase blood pressure systole ≥ 180 mmHg and/or diastole ≥ 120 mmHg.
- Hb level exceed 13 g/dL, investigational product should be reinitiated at approximately 25% lower than the previous dose after haemoglobin levels fall to 12 g/dl (7.45 mmol/l) or below.
- Any reason based on the assessment of the principal investigator.

5.5 Management of Compliance and Deviations from Protocol

The Principal Investigator and sub investigator of this clinical study shall become fully aware of the protocol and perform the study so that the protocol is not violated. To follow the administration and test schedule of the investigational product in this study, the sub investigator shall take proper measures so that the subject makes an outpatient visit on the relevant date (for example, written notice of the next visit time or phone monitoring).

In case of major protocol violation, the subject shall be dropped out from analysis (Excluded from PP analysis) in principle and the following apply to this.

1. In case of no acquiring the informed consent
2. In case of violation of the inclusion/exclusion criteria
3. If the subject takes contraindicated drugs during study period
4. In case of an error in randomization

For minor protocol violations which are not deemed to influence the analysis of study results, the degree of violation or delay shall be exactly mentioned, and when a final report is written, whether or not the study has been influenced by the investigator, sponsor, monitor, and statistician shall be comprehensively evaluated in PP analysis.

CHAPTER 6. INVESTIGATIONAL PRODUCT

6.1 Overview of the Investigational Product

6.1.1 Study drug

1. Brand name : Epodion® 2000 IU
2. Manufacturer : PT. Daewoong Infion
3. Appearance : Colorless yellowish pre-filled syringe
4. Storage : 2-8 °C

6.1.2 Control drug

Control drug that is used as a comparator is Eprex® (Janssen).

6.2 Dosage, Administration, and Administration Period

The drug dose should be individualized, during titration period Eprex® doses should be closely titrated to achieve target Hb range 10-12 g/dl. During maintenance period, the administration dose of Eprex® and Epodion® is equal to the previous dose in titration period. Dose is allowed to be increased or decreased during maintenance period at an appropriate level to maintain Hb level 10-12 g/dl according to condition of subjects. Route of administration for this study is Intravenous injection (IV). Investigational product will be administered when subject enrolled until the end of the study.

6.3 Management of Investigational Products

6.3.1 Shipment and storage conditions of study drug

The study drug shall be kept in a safe place with limited access. The study drug shall be refrigerated at 2°C - 8°C. Temperature shall be closely observed throughout the clinical study and recorded in the specified form. If the drug is frozen, or if refrigeration has stopped, the drug shall not be given. In such case, the investigator or sub-investigator shall make inquiries to the monitor to take actions.

The clinical trial pharmacist shall store and manage study drugs to ensure guaranteed drug quality until given to patients.

6.3.2 Inventory of study drug

The clinical trial pharmacist responsible for drug procurement and control shall record must record the amount of drug used for research and reporting to sponsors for reimbursement purposes. If shortage of drugs is expected during the study period, clinical trial pharmacist shall be immediately reported to the clinical study monitor to avoid delays in drug supply. The sponsor's monitor shall make sure that there is consistency between the drug control record of the institution and record of the case report form.

6.4 Concomitant Medication and Treatment

6.4.1 Concomitant medication

The following drugs may be concomitantly administered during the study period.

a. Any drug the subject has been on medication prior to participating in the clinical trial, the drug which is considered not to affect the study result analysis shall be permitted during the study period by the clinician's judgement.
b. Any drug to be used temporarily for the purpose of treating other diseases or adverse events incurred during the study period shall be concomitantly administered through discussion with the investigator or physician.

All the information (commercial name, indication, daily dose, administration period etc.) of concomitant medications (including medication to treat other diseases or adverse events) shall be recorded in the CRF in detail.

6.4.2 Contraindications

Epodion is contraindicated in patients with the following conditions:

a. Hypersensitivity to other drugs or Erythropoietin products
b. Patients who develop pure red cell aplasia (PRCA) following treatment with any erythropoietin
c. Uncontrolled hypertension
d. Hypersensitivity to derivative products from mammalian cells or albumin
e. Patients experience events that result in severe damage to coronary, peripheral, carotid or cerebral vessels.
f. Patients scheduled to follow any surgery who for any reason cannot receive adequate antithrombotic prophylaxis or treatment

CHAPTER 7. STATISTICAL ANALYSIS PLAN

7.1 Definition of analysis group

7.1.1 Safety Set

The Safety Set will consist of all enrolled subjects who received at least 1 dose of the investigational product. In the case of dosing administration error, analyses on the Safety Set will be conducted according to actual treatment received.

7.1.2 Full Analysis Set (FAS)

The Full Analysis Set will be consisting of all randomized subjects who treated for at least 4 weeks of the investigational product, and for whom at least 1 Hb level for the evaluation period will be available. In the case of dosing administration error, analyses on the FAS will be conducted according to randomized treatment.

7.1.3 Per-Protocol Set (PPS)

The Per-Protocol Set will be defined as all subjects who completed the study without any major protocol deviations. The subjects who committed a major protocol deviation will be finally determined in the blind meeting before database lock.

In the study, the efficacy assessment will have the PPS as the primary analysis set, and the FAS will be additionally analyzed and the results of the two analysis sets will be compared.

7.2 General principle of statistics

The summary statistics will be presented with descriptive statistics including number of subjects, mean, standard deviation, median, minimum and maximum values for continuous variables. For categorical variables, number and percentage of subjects with event will be presented. For the test of significance between the two treatment groups, the two-sided test will be conducted at 5% significance level.

7.3 Analysis of demographic data and baseline characteristics

Demographic data and baseline characteristics will be summarized by treatment groups and overall. For continuous variables, the summary will be presented by number of subjects, mean, standard deviation, median, minimum and maximum value. For categorical variables, the summary will be presented by number and percentage of subjects in each category.

7.4 Efficacy Analysis

Efficacy analysis will be performed using the Full Analysis Set and Per-Protocol Set.

7.4.1 Primary Endpoint

Change in Hb levels from baseline to the evaluation period

Descriptive statistics will be provided by treatment group. The difference between treatment groups will be determined by ANCOVA (analysis of covariance) model with treatment as factor, and baseline Hb level and the change in weekly dosage per kg body weight from baseline to the evaluation period of Epodion® or Eprex® as covariates.

Therapeutic equivalence of Epodion® to the comparator Eprex® will be demonstrated if the two-sided 90% confidence interval of the difference of mean changes in Hb levels between treatment groups lay within the interval of ± 0.5 g/dL.

7.4.2 Secondary Endpoint

(1) Change in weekly dosage per kg body weight from baseline to the evaluation period.

Descriptive statistics will be provided treatment group. The difference between treatment groups will be analyzed by ANCOVA model with treatment as factor, and baseline Hb level and baseline weekly dosage per kg body weight value as covariates.

(2) Instablity rate of Hb level during maintenance and evaluation period

The number of subjects with Hb level <8 g/dl or Hb level >13 g/dl during maintenance and evaluation period will be provided by treatment groups along with rates and the two-sided 95% confidence intervals. Also, the difference in the rates between the treatment groups and two-sided 95% confidence interval will be provided.

(3) Hb and Hematocrit level during maintenance and evaluation period

Descriptive statistics will be provided treatment groups for Hb and Hematocrit levels at baseline and at each bi-week during maintenance and evaluation period. The time course figure of Hb levels will be presented using mean and standard deviation throughout maintenance and evaluation period.

7.5 Safety Analysis

Safety analysis will be performed using the Safety Set.

(1) Adverse events (AEs)

The incidence of the following events will be summarized by treatment group for all observed adverse events, local reactions and systemic reactions.

- Treatment-emergent adverse events (TEAEs)
- Adverse Drug Reactions (ADRs)
- Serious TEAEs/ADRs
- TEAEs/ADRs leading to investigational product discontinuation
- TEAEs/ADRs leading to death

(2) Vital sign, Laboratory test

Summary statistics for change from baseline in vital signs and the laboratory test evaluation will be provided. Clinically significant abnormal results in laboratory test will

also be summarized. If needed, laboratory re-tests may be carried out outside the schedule to monitor the patient's condition.

7.6 Handling of dropout or missing values

Analysis for efficacy variables will be performed for subjects who have at least 1 Hb level for the evaluation period. For by visit analysis (ANCOVA, Hb and Hematocrit level), missing data will be imputed by LOCF (last observation carried forward) method. For calculating the instability rate,only observed data will be used. For safety analysis, no imputation will be made for missing data.

CHAPTER 8. ADVERSE EVENTS

8.1 Definition of Adverse Event

a. Adverse event (AE)

Any untoward medical occurrence in a patient or subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product (see the ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).

b. Adverse Drug Reaction (ADR)

In the pre-approval clinical experience with a new medicinal product or its new usages, particularly as the therapeutic dose(s) may not be established: all noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions. The phrase responses to a medicinal product means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, i.e., the relationship cannot be ruled out.

Regarding marketed medicinal products: a response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of diseases or for modification of physiological function (see the ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).

c. Serious Adverse Event (SAE) or Serious Adverse Drug Reaction (SADR)

Any untoward medical occurrence that at any dose:

1. Results in death
2. Is life-threatening
3. Requires inpatient hospitalization or prolongation of existing hospitalization
4. Results in persistent or significant disability/incapacity, or
5. Is a congenital anomaly/birth defect

d. Unexpected Adverse Drug Reaction

It means that there is a difference in the aspect or risk of adverse drug reaction in view of available medication information such as from IB, insert paper or label.

8.2 Collection and Documentation of Adverse Events

If an adverse event is present, investigator should assess the type, start date, end date, severity of the symptoms, relevance to the test drug, measures related to the test drug, treatment, results and significance and record in Case report form (CRF).

8.3 Evaluation of Adverse Events

8.3.1 Severity

1. Mild: causes minimal discomfort without interfering with the normal daily life (function) of the subject, and can be easily tolerated by the subject
2. Moderate: It causes discomfort that significantly disturb the normal daily life (function) of the subject
3. Severe: If the person's daily life (function) becomes impossible

8.3.2 Causal relation with study drug

Investigator will examine the relationship between the adverse reaction and the study drug in terms of the patient's past history, health status, administration time, dosage status, etc.

a. Relevant: Relevant or potentially relevant

1) Definitely Related

1. If there is evidence that the test drug has been administered
2. If the time order of test drug administration and adverse events is reasonable
3. The adverse event is most likely explained by the administration of the test drug for any other reason
4. Adverse events disappear with discontinuation
5. If re-administration is possible, if the outcome is positive
6. If the adverse event is consistent with the information already known about the test drug or the same series of test drug.

2) Related

1. If there is evidence that the drug has been administered for study
2. If the timing of the administration of the drug and the adverse reaction is reasonable
3. Adverse events are more likely to be explained by the administration of the drug than for other reasons
4. Adverse events disappear with discontinuation

3) Possibly Related

1. If there is evidence that this drug has been administered
2. If the adverse event is judged to be due to the administration of the test drug at the same level as other potential causes
3. Adverse events disappear with discontinuation

4) Not Related

1. If there are other causes of the Adverse Event
2. If the discontinuation result is negative or ambiguous
3. If the re-administration of the test drug is negative or ambiguous

5) Definitely Not Related

1. If the subject does not receive investigational drug
2. If the time sequence between drug administration and side effects is not possible
3. If there are other obvious causes (such as the use of other drugs, latent diseases,

other factors, etc.) and there is a reasonable explanation for the adverse reaction

4) Unknown

If some information about the adverse reaction received but can not assess its relevance.

8.3.3 Treatment for Adverse Reaction

a. No treatment for adverse event
b. Medication for adverse event
c. Non-medication for adverse event

8.3.4 Results of Adverse Reaction

a. Resolve
b. Continuous
c. Revolve, but the effect is remain
d. Death

8.4 Reporting of Serious Adverse Events

The investigator should report any serious adverse events (SAEs) in the study immediately to sponsor and Ethics Comitee. The definition of a serious adverse event is a medical event which at any dose takes the form of:

a. Results in death
b. Is life-threatening
c. Requires inpatient hospitalization or prolongation of existing hospitalization
d. Results in persistent or significant disability/incapacity
e. A congenital anomaly/birth defect.

All SAEs above are reported to the sponsor no later than 24 hours since they are known and reporting to the ethics committee a maximum of 3 calendar days since they are known. Sponsors must report to the regulatory authority no later than 7 calendar days from the time it is first known (for the occurrence of death), 15 days for other serious adverse events. In this study the investigator immediately contacts the safety report and provides further and detailed reporting through.

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CHAPTER 9. ETHICAL CONSIDERATIONS AND ADMINISTRATIVE PROCEDURES

9.1 Protocol Compliance

The investigator shall conduct a clinical study in compliance with the protocol. The clinical study shall not be carried out contrary to the protocol with the exception that a risk factor incurred in the subject is required to be removed immediately, and upon a violation, the fact and the reason shall be stated. Even if the investigator thinks that violation of the protocol can improve the performance of the clinical study, this shall not be executed before consent by the Sponsor to the change and approval of the Institutional Review Board (including the National Agency of Drug and Food Control, if needed) will be obtained.

9.2 Approval and Amendment of Protocol

If the clinical study which is being approved will be modified, the protocol or protocol amendment shall be approved by the Institutional Review Board (IRB) per phase of the clinical study, and if necessary, approved by the National Agency of Drug and Food Control. Prior to approval, any subject is not allowed to participate in the clinical study.

9.3 Procedure of Consent by Subject

The subject information and the informed consent form are available only after they are approved by the IRB. The investigator shall obtain consent from each subject in accordance with the ethical principles under the Declaration of Helsinki and the Good Clinical Practice. Prior to execution of all of the study related procedures, the investigator shall fully explain the clinical study to each subject (or his/her representative) and obtain written consent from the subject. The investigator shall keep the signed original of the informed consent form in the investigator's file and offer copies of the signed informed consent form and subject information to the subject (or his/her representative). The patient consent procedure shall be stated in the supporting document. If it is impossible for the subject to consent, consent shall be obtained from the subject's representative. If both the subject and his/her representative are not able to read words, a witness shall participate in all consent processes. As the subject and his/her representative verbally consent to participate in the clinical study and sign their own autograph in the informed consent form if possible, and then the witness signs the informed consent form, this demonstrates that information in the informed consent form is exactly explained and understood.

If the subject information and informed consent form are changed, this shall be approved by the Institutional Review Board (IRB), as well as the ongoing subject (or his/her representative). Then, the investigator shall record the subject, date, and content of notification in the supporting document. The subject information and informed consent form of this clinical study can be viewed in separate document.

9.4 Measures for the Protection of Subject's Safety

The investigator shall carry out the clinical study in consideration of the subject's rights and welfare/well-being on the basis of the Declaration of Helsinki, and the investigators who participate in the clinical study shall be familiar with the Good Clinical Practice, Protocol, etc. before conducting the clinical study. The investigator shall take enough time for each subject and thoroughly assess eligibility of each subject and onset of adverse event through discussion and examination.

The Principal Investigator shall report AEs, study progress, and results to the Sponsor on a periodic basis, and the Sponsor shall routinely control the study progress.

9.5 Post-study Treatment of Subject and Treatment Criteria

The investigator shall make sure that a person who dropped out of the study or did not show response can receive proper treatment based on needs.

9.6 Subject Indemnification

The Sponsor, upon an adverse event incurred from the study drug or damage incurred during corrective treatment of an adverse event, or damage directly caused by the study drug, will indemnify the subject for such damages as subject indemnification detailed outside of the Protocol.

9.7 Keeping of Study Related Documents and Records

9.7.1 CRF and supporting document

Data of this clinical study will be collected in CRF. Data of CRF based on supporting document shall coincide with the supporting document, and the investigator shall make sure that all data entered in CRF are exact, complete, easy to read, and timely.

Whenever modifying or correcting contents of CRF, the original content shall be identifiable.

The monitor shall compare CRF with supporting document, notify the investigator of inconsistency, if any, and ask the investigator to make proper corrections. Only the investigator or a designated person can enter and correct CRF and supporting document.

9.7.2 Peruse of supporting data

The sponsor, monitor, and auditor involved in this study can peruse subject's records for the purposes of monitoring, audit, and progress management of this study. The investigator shall be aware of the fact that as the clinical study contract is concluded, the sponsor or monitor or auditor may review or copy relevant documents to verify the subject's chart and CRF record. Such information shall be kept confidential. The investigator shall ensure necessary support for the CRO and sponsor.

9.7.3 Keeping of clinical study data

The investigator shall keep data and records related to execution of the clinical study in a safe place, maintain their security, and keep them for 3 years from the date when the clinical study is completed or discontinued. After a clinical study report is completed, study related documents shall be transferred to the data keeping manager, and if the investigator is to discard study related records or to move them to another place, the investigator shall notify the sponsor in advance.

9.7.4 Audit and inspection

To ensure that the GCP and all related regulations are observed, the sponsor or a person authorized by the sponsor can perform quality assurance audit for this study, and the National Agency of Drug and Food Control can conduct inspection. After a relevant notice is given to the investigator, the investigator shall respond to such audit or inspection, allow the auditor or inspector to have personal access to all clinical study related documents, and consent to take the time to discuss all observations and related issues.

9.8 Confidentiality of Clinical Study Documents and Subject Records

All clinical study results and documents shall be kept confidential. The investigator, CRO, and the staff of the sponsor shall not expose any study related information without Sponsor's written approval.

Records that are capable of finding out subject's identity will be kept confidential, and all study related documents such as CRF etc. will be recorded with not the subject's name but the subject's identification code for differentiation. Even if the results of the clinical study are published, subject's identity will be kept confidential, too.

9.9 Monitoring of Institution

To protect subject's rights and well-being, confirm the accuracy, integrity, and verifiability of data through comparison between reported study related data and supporting document, and check if the clinical study is performed in compliance with the approved protocol, monitoring of the institution shall be conducted.

The monitor shall monitor the clinical study by routine site visits and phone, evaluate the study progress, and check whether the investigator's duty was fulfilled as per the protocol and regulations. When visiting the institution, the monitor shall check whether the originals of subject's records, CRFs, drug control records, and study-related data are being kept, and upon inconsistency or problem in the clinical study records, will discuss with the investigator.

9.10 Withdrawal of Study

If the institution or investigator, or a person authorized by the sponsor fails to observe the GCP, protocol, and terms and conditions of the contract, the sponsor will immediately correct this and takes measures. If continues violation of the said matter is found or the enrollment target is not achieved, or efficacy and safety information occurs which is likely to have a critical effect on continuation of the clinical study, the sponsor may direct the institution to withdraw the study.

9.11 Clinical Study Report and Publication

Once all the data of the institution are completely analysed, the sponsor shall prepare a clinical study report and notify the investigator of the results of the clinical study.

All the data and result arising out of this clinical study shall be owned by Daewoong Pharmaceuticals, Co. Ltd, and the sponsor has the right to publish the results of this study at any time. The investigator or any personnel from the institution shall not publish, announce, or disclose information related with the result of this study without Sponsor's prior written consent. In order to use only exact and verified data, the investigator shall necessarily submit all publication drafts or manuscripts to the sponsor prior to publication or announcement for discussion and withhold publication until approval in writing is obtained.

For a multicenter study, the investigator shall consent not to publish the study results before the other investigator publishes the results gathered from all institutions, with the exception that it is officially recognized by the principal investigator and sponsor.

CHAPTER 10. REFERENCES

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