CLINICAL STUDY PROTOCOL

A Prospective, Randomized, Double Blind, Parallel Group Study to evaluate a 1:1 Dose Conversion from EPREX to EPIAO in term of Clinical Efficacy and Safety in Subjects with End-Stage Renal Disease on Haemodialysis

Investigational Product	**EPIAO**
Sponsor	Shenyang Sunshine Pharmaceutical Co., Limited No.3 A I. Road 10, Economy & Technology Development Zone, Shenyang 11 0027, Peoples Republic of China
Protocol Number	EACL-CT-14-003
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01	03 Apr 2015
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PROTOCOL SYNOPSIS

EudraCT/IND Number:	Not applicable
Protocol Number:	EACL-CT-14-003
Investigational Product:	EPIAO
Active Ingredient(s)/INN:	Recombinant Human Erythropoietin
Study Title:	A Prospective, Randomized, Double Blind, Parallel Group Study to evaluate a 1:1 Dose Conversion from EPREX to EPIAO in term of Clinical Efficacy and Safety in Subjects with End-Stage Renal Disease on Haemodialysis
Study Phase:	Therapeutic equivalence
Indication Under Investigation:	End stage renal disease (Stage 5) receiving haemodialysis
Study Objectives:	Primary Objective • To evaluate a 1:1 dose conversion from EPREX to EPIAO in term of clinical efficacy and safety in subjects with end-stage renal disease (CKD stage 5) receiving hemodialysis after intravenous (IV) administration. Secondary Objectives • To observe the frequency of adverse events (AEs) following EPIAO with and EPREX with respect to their administration. • To monitor the occurrence of anti-epoetin antibodies among subjects following at least 12 months of therapy
Study Design:	This is a prospective, randomized, double blind, parallel group two arm study to evaluate a 1:1 dose conversion from EPREX to EPIAO in term of clinical efficacy and safety in subjects with end-stage renal disease (CKD stage 5) receiving hemodialysis. Subjects should be on a clinically stable haemodialysis for at least 3 months before screening. The eligible subjects will be treated with EPREX for a period of at least 3 months after screening (titration period). The subjects with haemoglobin levels within the target range of 10 to 12.5 g/dl with stable EPREX dosage and intra-individual change in Hb of ≤1.2 g/dl over 4 weeks during the titration period will be randomly assigned in a 1:1 ratio to switch

	to treatment with EPIAO or continue treatment with EPREX. In substantiated cases a prolongation of the titration period is allowed up to maximum of 4 to 5 months on a case to case basis which will be considered as extended titration period. The assessment will be similar to the visit 7 (week 12/Day 84) if there is prolongation of the titration period.
Inclusion/Exclusion Criteria:	<u>Inclusion Criteria at Screening</u> 1. Male and female subjects between the age of 18 to 75 years 2. Subjects with end stage renal disease (CKD stage 5*) on epoetin treatment for at least 3 months prior to screening 3. Subjects with haemoglobin between 10 g/dl to 12 g/dl 4. Subjects who are on clinically stable haemodialysis (defined as no clinically relevant changes of dialysis regimen and/or dialyzer) for at least 3 months prior to screening 5. Subject who had an adequacy of dialysis treatment measured by Kt/V a. Kt/V must be ≥ 1.2 for subjects with 3 times of HD/week b. Kt/V must be ≥ 1.8 for subjects with 2 times of HD/week 6. Subjects willing to provide a written informed consent 7. Subjects with serum ferritin ≥ 200 µg/L and/or transferrin saturation ≥ 20% 8. Subjects with a life expectancy of more than at least study period in clinical judgment of the investigator *CKD staging will be based on the five-stage system for classification of CKD based on KDIGO guidelines (page no: 32). GFR will be calculated based on the EPI equation as below **$GFR = 141 \times \min(S_{cr}/\kappa, 1)^{\alpha} \times \max(S_{cr}/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018$ [if female] $\times$ 1.159 [if black]** where: S_{cr} is serum creatinine in mg/dL, κ is 0.7 for females and 0.9 for males, α is -0.329 for females and -0.411 for males,

	min indicates the minimum of S_{cr} /κ or 1, and max indicates the maximum of S_{cr} /κ or 1. Eligibility Criteria at Baseline 1. Subjects with stable haemoglobin levels between 10 g/dl to 12.5 g/dl with stable EPREX dosage and intra-individual change in Hb of ≤1.2 g/dl over 4 weeks before randomization 2. Subjects with serum ferritin ≥ 200 µg/L and/or transferrin saturation ≥ 20% Patients who don't meet the eligibility criteria at baseline will be considered as screen failures. Exclusion Criteria at Screening 1. Subjects with anaemia due to other reasons (that is not renal anaemia) 2. Subjects who have undergone blood transfusion within the last 3 months 3. Subjects requiring epoetin dose of > 300 IU/kg/week 4. Subjects with major complication such as severe/chronic infections or bleeding or aluminum toxicity 5. Subjects with suspected or known pure red cell aplasia (PRCA) 6. Subjects with a history of aplastic anaemia 7. Subjects with uncontrolled diabetes (fasting blood glucose > 240 mg/dl) or uncontrolled hypertension (systolic blood pressure > 180 mm Hg, diastolic blood pressure > 110 mm Hg) 8. Subjects with HbA1C >6.5% 9. Subjects with known hypersensitivity to any of the ingredients of the investigational products, the mammalian cell-derived product or human albumin products 10. Subjects with history of seizure disorder 11. Subjects with hematological disorder (thrombocytopenia: platelet count below $100x10^9$/L, neutropenia: neutrophil count below $1.0x10^9$/L or hemolysis)

	12. Subjects with hyperparathyroidism (intact parathyroid hormone > 1000 pg/ml) 13. Subjects with alanine aminotransferase (ALT), aspartate aminotransferase (AST) and alkaline phosphatase levels 3 × upper limit of normal (ULN) at screening 14. Subjects with decompensated congestive heart failure (NYHA class III and IV) within 6 months prior to screening 15. Subjects with angina (functional class III and IV) within 6 months prior to screening 16. Subjects with myocardial infarction or stroke in the preceding 6 months of screening 17. Subjects with active malignancy in the previous 5 years 18. Subjects with gastrointestinal bleeding in the past 6 months 19. Subjects with immunosuppressive therapy in the previous 3 months 20. Subjects with active hepatitis B virus (positive for HBsAg and IgM anti-HBc in Thailand and positive for HBsAg in Russia) 21. Subjects with hepatitis C virus (HCV) (positive for Anti-HCV antibody) 22. Female subjects who are pregnant, breast-feeding, planning to be pregnant during the study, or women of child-bearing potential (any woman who is not surgically sterile i.e. bilateral tubal ligation, total hysterectomy or < 2 years post menopause) not using a reliable method of double contraception (e.g. condom plus diaphragm, condom or diaphragm plus spermicidal gel/foam, tubal ligation, or stable dose of hormonal contraception) throughout the study period 23. Subjects participating in trials involving long acting erythropoietin in the past 6 months before screening and short acting erythropoietin in the past 3 months before screening 24. Subjects currently participating or participation in an investigational study within 30 days prior screening
Study Duration:	The duration of the subject participation will be for a maximum of 68 weeks(77weeks in case of extension of titration period)including 4 weeks of screening period, titration period of

	at least 3 months (maximum duration for 5 months)treatment duration of 26 weeks for efficacy and safety evaluation (weeks 13 through weeks 39) and treatment duration of 26 weeks for immunogenicity evaluation (weeks 40 through weeks 64). In substantiated cases a prolongation of the titration period is allowed up to maximum of 4 to 5 months on a case to case basis which will be considered asextended titration period. The assessment will be similar to the visit 7 (week 12/Day 84) if there is prolongation of the titration period.
Planned Sample Size:	A sample size of 112 subjects per group is calculated to achieve a power of more than 80% for proof of equivalence for both co-primary endpoints. Considering 2 stratification factors i.e. body weight (Kg): ≤58, 59-74 & ≥75, Hb level (g/dl): 10 – 11 & > 11 – 12 and to balance between the two treatment groups in Thailand and Russia, the total number of subjects to be randomized is estimated to be 264 (n=132 subjects in each group) since a drop-out rate of approximately 18% was expected. The subjects will be randomized into two groups (n=132 subjects in each group) in a 1:1 ratio.
Dosage Form, Dose and Route of Administration of IP:	EPIAO injection will be administrated intravenously one to three times a week at the end of dialysis session for a period of 52 weeks. The maximum allowable dose is 300 IU/kg/week.
Dosage Form, Dose and Route of Administration of comparator:	EPIAO injection will be administrated intravenously one to three times a week at the end of dialysis session for a period of 52 weeks. The maximum allowable dose is 300 IU/kg/week.
Study Endpoints:	**Primary endpoint** • Mean absolute change in haemoglobin level from baseline to 6 months after treatment with EPIAO/EPREX in parallel groups (g/dl). • Mean absolute change in weekly epoetin dosage per kg body weight from baseline to 6 months after treatment with EPIAO/EPREX in parallel groups (IU/kg/week) **Secondary Endpoints:** • Proportion of subjects hemoglobin values are within 10 - 12 g/dl for the last 4 weeks of the period for assessment of treatment of efficacy and safety (weeks 32-36)

	• Proportion of subjects with any haemoglobin measurement outside the target range during the double-blind treatment period • Mean hemoglobin and hematocrit levels every 4 weeks within treatment period (52 weeks) • Mean doses of the study products (IU/kg/week) every 4 weeks throughout the study period (52 weeks) • Incidence of blood transfusions **Safety endpoints:** • Incidence and nature of adverse events • Incidence of drug related adverse events • Clinically significant changes in the vital signs, physical and laboratory examination • Number of subjects who prematurely withdrew from the study due to AE and SAE • Number of subjects with presence of anti-erythropoietin antibodies (anti-EPO Ab)
Statistical Analyses:	The SAS® package (SAS® Institute Inc., USA, and Version 9.2 or higher) will be used for statistical evaluation. Descriptive statistics, such as mean, standard deviation, median, minimum and maximum values will be provided for the continuous variables and the number of observations and percentage will be provided for the categorical variables. **Primary Endpoints** • Mean absolute change in haemoglobin level from baseline to 6 months after treatment with EPIAO/EPREX in parallel groups (g/dl). • Mean absolute change in weekly epoetin dosage per kg body weight from baseline to 6 months after treatment with EPIAO/EPREX in parallel groups (IU/kg/week) The ANCOVA will be performed based on the normality of data for mean change between baseline to 6 months of EPIAO and EPREX with center, Hb level and weight as covariates. The 95% confidence intervals will be calculated for the treatment differences and is compared with pre-defined acceptance ranges: ±0.5 g/dl for hemoglobin.

The ANCOVA will be performed based on the normality of data for mean change in weekly epoetin dosage per kg body weight baseline to 6 months treatment with EPIAO and EPREX with center, Hb level and weight as covariates. The 95% confidence intervals will be calculated for the treatment differences and is compared with pre-defined acceptance ranges: ±45 IU/kg/week for dosage.

Secondary Endpoints

- Proportion of subject's hemoglobin values are within 10 - 12 g/dl for the last 4 weeks of the period for assessment of treatment efficacy and safety (weeks 32-36)
- Proportion of subjects with any haemoglobin measurement outside the target range during the double-blind treatment period
- Mean hemoglobin and hematocrit levels every 4 weeks within treatment period (52 weeks)
- Mean doses of the study products (IU/kg/week) every 4 weeks throughout the study period (52 weeks)
- Incidence of blood transfusions

The appropriate descriptive statistics or frequency and percentages will be presented for the secondary end point. Other analysis will be carried out as deemed appropriate.

Safety Endpoints

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

Safety will be assessed by physical examination, vital sign, laboratory test, immunogenicity and adverse event recording. Summary statistics will be provided for the lab, ECG, physical examination, immunogenicity and vital signs data. Frequency and percentage of the incidence of adverse event, nature of adverse event and incidence of drug related adverse event will be

	presented in the treatment group. Summary statistics will be presented for the occurrence of PRCA. Proportion of subject who used concomitant medication during the study period will be computed by treatment group, classified by World Health Organization Drug Dictionary enhanced (WHO - DDE) Preferred Names. Concomitant medication will be coded using the WHO - DD enhanced version, classified by preferred names, and the categories tabulated and summarized. An interim analysis will be conducted to evaluate the therapeutic equivalence of EPIAO with the standard treatment EPREX after a treatment period of 24 weeks.

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LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION
ACE	Angiotensin Converting Enzyme
AE	Adverse Event
ALP	Aspartate Aminotransferase
ALT	Alanine Aminotransferase
Anti-EPO Ab	Anti-Erythropoietin Antibodies
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CKD	Chronic Kidney Disease
CRA	Clinical Research Associate
CRF	Case Report Form
CRO	Contract Research Organization
CS	Clinically Significant
DMP	Data Management Plan
EAL	Ecron Acunova Limited
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
ED_{50}	Effective Dose 50
EMA	European Medicines Agency
EPO	Erythropoietin
ESAs	Erythropoiesis-Stimulating Agents
GCP	Good Clinical Practice
GFR	Glomerular Filtration Rate
Hb	Haemoglobin
HbsAg	Hepatitis B surface Antigen
hCG	Human Chorionic Gonadotropin
Hct	Haematocrit
HCV	Hepatitis C Virus
HSA	Human Serum Albumin
ICF	Informed Consent Form
ICH	International Council for Harmonization
IEC	Independent Ethics Committee
IP	Investigational Product
IRB	Institutional Review Board
IV	Intravenous
KDIGO	Kidney Disease Improving Global Outcome
LD50	Lethal Dose 50
MCH	Mean Corpuscular Haemoglobin
MCHC	Mean Corpuscular Haemoglobin Concentration
MCV	Mean Corpuscular Volume

MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intention-to-Treat
NCS	Not Clinically Significant
NLS	Navitas Life Sciences
OTC	Over the Counter
PI	Principal Investigator
PP	Per Protocol
PRCA	Pure Red Cell Aplasia
PV	Pharmacovigilance
RBC	Red Blood Cell
RDC	Remote Data Capture
r-HuEPO	Recombinant Human Erythropoietin
RIA	Radio Immuno Assay
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	Subcutaneous
SIC	Subject Identity Code
SMC	Safety Monitoring Committee
SOPs	Standard Operating Procedures
SUSAR	Suspected Unexpected Serious Adverse Reaction
TIBC	Total Iron Binding Capacity
TSAT	Serum transferrin saturation
WBC	White Blood Cell
WHO – DDE	World Health Organization Drug Dictionary Enhanced
Wt	Weight

1 INTRODUCTION AND BACKGROUND INFORMATION

Chronic kidney disease (CKD) is a general term for heterogeneous disorders affecting the structure and function of the kidney. The variation in disease expression is related partly to cause and pathology, severity, and rate of progression. The definition of CKD is based on the presence of kidney damage (ie, albuminuria) or decreased kidney function (ie, glomerular filtration rate [GFR] <60 mL/min per 1·73 m²) for 3 months or more, irrespective of clinical diagnosis *(1)*.

Clinical guidelines define a five-stage system for classification of CKD (Kidney Disease Improving Global Outcome [KDIGO] Guidelines).

CKD STAGE	DESCRIPTION	GFR (ml/min per 1.73 m^2)
1	Kidney damage with normal or increased GFR	≥90
2	Kidney damage with mild decreased GFR	60-89
3	Moderate decreased GFR	30-59
4	Severe decreased GFR	15-29
5	Kidney failure	< 15 (or dialysis)

Secondary to the functional abnormality due to CKD, there is a decreased production of the erythropoietin, a glycoprotein hormone produced primarily by the kidney in response to hypoxia and which is the key regulator of red blood cell (RBC) production. Erythropoietin is involved in all phases of erythroid development, and has its principal effect at the level of erythroid precursors. Thus anaemia is a common complication of CKD. Although anaemia in subjects with CKD may develop in response to a wide variety of causes, the primary cause of anaemia associated with CKD is deficiency of erythropoietin. Other factors in the genesis of renal anaemia include functional or absolute iron deficiency, blood loss and presence of uraemic inhibitors (for example, parathyroid hormone, inflammatory cytokines) and deficiencies of folate or Vitamin B12 (*2*).

The primary therapeutic options for the anaemia of CKD include iron supplementation, erythropoiesis-stimulating agents (ESAs) and RBC transfusions. In subjects with CKD but stable kidney function, the appearance or progression of anaemia may herald a new problem that is causing blood loss or is interfering with red cell production. Thus anaemia should be evaluated independently of CKD stage in order to identify any reversible process contributing to the anaemia. *(3)* Early treatment of anaemia may reduce cardiovascular morbidity and improve quality of life.

The introduction of recombinant human erythropoietin (r-HuEPO) into clinical practice in the 1980 s was a major breakthrough in the treatment of the anaemia of subjects with CKD. The development of r-HuEPO was aimed at replacing the insufficient endogenous erythropoietin (EPO) production related to CKD progression. r-HuEPO administration was regarded by the nephrology community as a beneficial therapy for long-term dialysis subjects whose haemoglobin values fell to extremely low levels, making them transfusion-dependent *(3)*. r-HuEPO stimulates erythropoiesis in anaemic subjects with chronic renal failure in whom the endogenous production of erythropoietin is impaired. Because of the length of time required for erythropoiesis – several

days for erythroid progenitors to mature and be released into the circulation – a clinically significant increase in haemoglobin is usually not observed in less than two weeks and may require up to ten weeks in some subjects. *(4)*.

Erythropoietin interacts directly with the EPO receptor on the RBC surface, triggering activation of several signal transduction pathways, resulting in the proliferation and terminal differentiation of erythroid precursor cells and providing protection from RBC precursor apoptosis. The magnitude of increase in RBC concentration in response to administration of r-HuEPO is primarily controlled by the length of time EPO concentrations are maintained, not by the EPO concentration level. Subcutaneous (SC) EPO administration results in slower absorption than IV administration, leading to lower peak plasma levels and an apparent extended terminal half-life. However, SC administration is associated with an increased risk of immunogenicity compared with IV administration *(5)*.

EPIAO was approved for marketing in China in 1998. Currently, it is also approved for marketing in another 16 countries including Pakistan, Sri Lanka, Brazil, Egypt, Dominica, Trinidad & Tobago, Thailand, Philippines, Columbia, Mongolia, Guatemala, Salvador, Palestine, Azerbaijan, Myanmar, and Cambodia. So far, China and Thailand are the biggest EPIAO markets in worldwide. Since the marketing approval, it is estimated that about 587,897 domestic and foreign subjects have used EPIAO for the treatment of anaemia. (*6*)

1.1 Name of Investigational Product

Nonproprietary Name: Recombinant Human Erythropoietin Injection

Trade Name: EPIAO

1.1.1 Description

EPIAO falls under the pharmacological class of haematopoietic / anti anaemic agents. This r-HuEPO drug product, EPIAO has been developed for the treatment of anaemia in subjects with chronic kidney disease.

Erythropoietin, also known as EPO, is a glycoprotein hormone that controls erythropoiesis, or RBC production. It is a cytokine (protein signalling molecule) for erythrocyte precursors in the bone marrow. Human EPO has a molecular weight of 34,000.

The formulation of EPIAO contains r-HuEPO as active ingredient at strength of 2000 IU/ml, 3000 IU/ml, 4000 IU/ml and 10000 IU/ml, 0.25% of human serum albumin (HSA) as stabilizing agent, 20 mM of sodium citrate/citric acid monohydrate as buffer system, and 100 mM of sodium chloride as tonicity agent. The formulation of EPIAO is consistent during the clinical development and marketing. EPIAO is a solution for injection in either pre-filled syringe or vial, pH 6.9±0.5 and can be administrated by either IV or SC routes.

Pharmacokinetics: After subcutaneous administration, absorption of erythropoietin is slow from the injection site. Increase of serum concentration of r-HuEPO can be observed 2 hours after administration and the peak concentration is achieved 18 hours post dosing. Bone marrow is the specific absorption organ of r-HuEPO, and it is also absorbed in liver and kidneys. r-HuEPO is mainly metabolized in the liver. Results from animal (rat) studies also indicate that the kidneys, bone marrow and spleen can also metabolize a small portion of r-HuEPO. Kidney is not the

primary organ of excretion for r-HuEPO. In anaemia subjects treated with r-HuEPO, less than 10% of non-degraded r-HuEPO is excreted from the kidney.

EPIAO is indicated for the treatment of:

1. Anaemia due to chronic renal failure, including subjects on haemodialysis or not on dialysis.
2. Peri-operative subjects in order to reduce the need for allogeneic RBC transfusions.
3. Anaemia associated with chemotherapy in cancer subjects with non-myeloid malignancies. EPIAO is not indicated for the treatment of anaemia caused by other factors such as iron or folate deficiencies, hemolysis or gastrointestinal bleeding.

Dosage for treating anaemia in CKD subjects

EPIAO should be administered under direct medical supervision. It can be administered intravenously or subcutaneously, dividing into 2-3 times weekly or once a week. The dose should be adjusted according to subject's haemoglobin concentration, age and other related factors. The following dose schedule is recommended:

Maintenance period:

Weekly dividing dosing: When the content of Haematocrit (HCT) reaches 30-33 vol% or haemoglobin (Hb) reaches 10-11 g/dL, the dose should be adjusted to two-thirds of the initial dose. HCT should be monitored every 2-4 weeks to prevent excessive erythropoiesis and keep HCT and Hb at an adequate level.

Once a week dosing: When the content of HCT and Hb reach the above target, the dose frequency can be reduced (e.g., once every two weeks). The dose can be further adjusted according to the level of HCT and Hb.

EPIAO is contraindicated in subjects with uncontrolled hypertension, allergy to the product and other mammalian cell derivatives, allergy to human serum albumin and uncontrolled combined infection. Therapy with overdose of EPIAO can result in polycythemia and fatal cardiovascular complications. (7)

1.1.2 Intended Use under Investigation

The intended use of EPIAO is for treating subjects with anaemia associated with CKD.

1.1.3 Nonclinical Studies

The primary pharmacodynamics studies were performed in UT-7 cells and BalBc mice with comparison with EPREX (Janssen), as well as in SD rats with comparison with EPOGEN (Amgen) to evaluate the efficacy of EPIAO.

In a study conducted to compare the in vitro proliferation activity of EPIAO and EPREX in UT-7 cells demonstrated that EPIAO has similar proliferation effect to that of EPREX® by comparing the 50% effective dose (ED_{50}) of the proliferation effect to the effector cell. In another study, BalBc mice were administered with received 10, 20 or 40 IU of EIAO or EPREX injection (SC) to compare the in vivo biological activity of EPIAO with comparison with EPREX. The biological activity of EPIAO was virtually identical to the reference product EPREX in this animal study.

A study was conducted to compare the effects on the parameters of erythrocytes with one originator's product and demonstrate the therapeutic effects of EPIAO in anemic SD rats. The anemic rats model were derived from healthy male SD by continuous feeding with fodder comprising 0.75% adenine until they are induced to have anaemia associated chronic renal failure. These anemic rats were then treated with EPIAO once a day for 14 days by subcutaneous injection with doses of 500 IU/kg, 250 IU/kg, and 50 IU/kg respectively. As a positive control, r-HuEPO, supplied by Amgen, Inc., USA was used in parallel experiments where 250 IU/kg daily dosage was selected. Results showed that EPIAO treatment of the rats with anaemia associated with chronic renal failure has demonstrated significant therapeutic effects as measured by a variety of erythrocyte related indicators. The therapeutic effects of EPIAO are identical to that of Amgen's.

Hence the results of the pharmacodynamic study revealed the EPIAO had the pharmacologic functions in vivo. Dose dependent therapeutic effects were observed. The increase of erythrocytes represented by all parameters had confirmed that EPIAO was an effective product for the treatment of anaemia associated to chronic renal failure and had the same efficacy with the originator's product. No nonclinical pharmacokinetic data is available from EPIAO.

Single-dose toxicology studies conducted in mice at a dose of $1x10^6$ IU per kilogram by IV injection showed no abnormal reaction; however, the lethal dose 50 (LD_{50}) of EPIAO in mice by IV injection was more than $1x10^6$ IU/kg.

The acute toxicity studies were conducted in Kun Ming mice, and the results demonstrated that the dose used ($1x10^6$ IU/kg) caused no abnormal reactions. This dose is 6700 times superior to the initial clinical dose and 3330 times superior to the maximum clinical dose.

Chronic toxicity studies were conducted in Mongrel Dogs (IV) and Wistar Rats (SC). In these studies, 3 and 4 dose groups respectively were formed. In first study mongrel dogs were administered at doses of 150IU/kg and 1000 IU/kg per day by IV administration for 4 weeks followed by a recovery period of 2 weeks. No dogs died and no abnormal behaviors were observed, however conjunctival congestion and redness in mucous membrane of mouth were observed which disappeared by the end of study.

In another study conducted on Wistar rats, 40 IU/kg, 200 IU/kg and 1000 IU/kg per day subcutaneous injections were administered for 5 weeks. Redness was observed in limbs and earlaps of the rats in the high dose group were observed during the conduct of study which later disappeared after the study.

The study conducted in guinea pigs revealed a strong allergic reaction to the presence of human serum albumin in solvent and finished product, but not to bulk solution of EPIAO.

Clinical observation, hematological, biochemical and histopathological evaluations were conducted. The results of both studies show the safety of EPIAO finished product.

Local tolerance studies were conducted in guinea pigs. Two studies were conducted: an immunogenic study to determine the reaction of the immune system after subcutaneous administration of EPIAO finished product, bulk and solvent solution followed by IV administration; and a skin irritation experiment to determine any allergic reactions to EPIAO finished product and solvent solution by transdermic administration. The immunogenic study revealed a strong allergic reaction to the presence of human serum albumin in solvent and finished

product. The skin irritation experiment did not reveal any reaction to EPIAO finished product or solvent solution.

No study to evaluate carcinogenicity or genotoxicity was conducted because r-HuEPO is identical to EPO. Although EPO is a growth stimulating factor, it is an endogenous product, and therefore it's carcinogenic and genotoxic potential are extremely low. No reproductive and developmental toxicology was conducted due to the fact that it is not supposed to be administrated during pregnancy or nursing period.

The nonclinical development programs of EPIAO containing single-dose, repeated-dose toxicology and local tolerance studies were adequate to support the clinical safety of EPIAO.

EPIAO was well tolerated at all dosages used in toxicology studies and no overt clinical reactions were observed as well.

1.1.4 Clinical Experience

Two studies were carried out to determine the safety and efficacy of EPIAO. In these studies subjects who were on hemodialysis received 100-150 IU/kg/wt. intravenously and subjects on continuous ambulatory peritoneal dialysis received the same dose subcutaneously. Subjects who were not on dialysis received a dose of 80-150 IU/kg/wt. by subcutaneous administration.

In a multicenter, randomized, reference drug comparison Phase II study conducted in anemic subjects with chronic renal failure, to compare EPIAO with reference products ESPO (Kirin) or RECORMON (Boehringer) following SC or IV administration.

One hundred and forty-four subjects completed clinical study, and were divided into two groups (A, B). In group A, 72 subjects were given EPIAO (Sunshine) as therapy group. In group B, 72 subjects were given ESPO (Kirin) or RECORMON (Boehringer) as control group. The age, gender, route and dose of administration in therapy group (A) matched those of control group (B). And there was no significant difference between group A and B in Hb, Hct, RBC, liver and renal function and biochemical indexes prior to r-HuEPO therapy.

In EPIAO group, the rate of complete response, partial response and poor response were 61.1%, 30.6% and 8.3% respectively, and the overall response rate was 91.7%. In control group (ESPO and RECORMON), the rate of complete response, partial response and poor response were 63.9%, 29.2% and 6.9% respectively, and the overall response rate was 93.0%. There is no statistic difference between the two treatment groups.

Results of the clinical study indicated that the efficacy of EPIAO (Sunshine) was equivalent to that of marketed reference r-HuEPO products from Kirin and Boehringer. The incidence of adverse events between therapy group and control group showed no significant difference. No organic toxicity or other severe irreversible lesion was observed.

The clinical trial demonstrated that EPIAO (Sunshine) was safe and effective in the treatment of renal anaemia.

A phase III clinical trial with EPIAO was conducted to evaluate efficacy and adverse events in subjects with renal anaemia. A total of 162 subjects were enrolled in the trial, 80 of them completed EPIAO therapy for 8-12 weeks. The results of the clinical trial demonstrated that the curative effect

of EPIAO on subjects with renal anaemia was reliable, and similar to the results of the previous phase II study. Remarkable increments of Hb, HCT, and RBC were observed 2 weeks after EPIAO therapy. At 4, 8 and 12 weeks after therapy, the Hb level was 75.96±13.40 g/L, 85.56±14.44 g/L and 93.04±17.20 g/L respectively, which represented the increment from baseline at 19.28%, 32.50% and 43.30%, respectively. HCT contents were 23.62±4.19%, 26.30±4.85%, 29.51±4.80% respectively, which corresponded to the increment from baseline at 17.70%, 33.16% and 46.18% respectively. The increment of reticulocyte occurred a week after therapy, reached peak value after 4 weeks, and continuously maintained at normal level. Eighty subjects received EPIAO therapy for not less than 12 weeks. Among these subjects, complete response rate was 66.25% (53 subjects), partial response rate was 27.50% (22 subjects), poor response rate was 6.25% (5 subjects). In summary, the total efficacy of EPIAO was 93.75%. In conclusion, this clinical trial demonstrated that EPIAO therapy was safe and effective in renal anaemic subjects.

The most common adverse effects that were experienced in subjects enrolled into the two trials were fever, headache, local pain injection and skin rash. These symptoms were temporary and did not require specific treatment. Headache was more frequent in subjects with CKD, but it might be associated with hypertension, which is another frequent adverse effect, particularly in subjects with CKD. A few rare adverse events (AEs) that were reported were arthralgia, abdominalgia, local swelling and dizziness/hypodynamia.

No deaths occurred in these trials. Other adverse effects for r-HuEPO reported from published literature, such as seizures, thrombotic events and pure-red cell aplasia did not occur in these trials. Moreover, serious adverse events such as seizures, hypertension and increased blood clotting, might be related to the rapid increment in haemoglobin and hematocrit. These are more frequent in subjects with chronic renal failure. Careful and attention to the extent and rate of haemoglobin, correction control of blood, and care with technical aspects of dialysis could reduce these to a minimum. The administration of anticlotting therapy might help reducing the frequency of thrombotic events during surgical procedures.

Depletion of iron is a predicted adverse event which occurs during treatment with r-HuEPO. Iron supplementation was administrated to subjects in the two studies with EPIAO.

Safety data results indicate that the Adverse Drug Reaction (ADR) after administration with EPIAO is predictable and manageable. There was no major unexpected ADR(s) identified from multiple years of post-marketing surveillance. EPIAO possesses similar efficacy and safety profile as other innovative r-HuEPO products.

A total of 210 serum samples from 205 subjects were collected and analyzed. None of them was positive on the neutralized antibody against EPIAO. Epoetin-associated PRCA was first reported in 1998, and causation was attributed to formulations without human serum albumin, and antibody formation. There is no case of EPIAO associated PRCA reported in China. In addition, EPIAO has been marketed in Thailand since 2005. As reported by their regulatory authority Thai FDA, during the report period of January 2012 to March 2013, a total of nine cases of PRCA were reported. None of them were associated with EPIAO.

In summary, EPIAO possesses similar efficacy and safety profile as other innovative r-HuEPO products. The possible ADR after administration of EPIAO is predictable and manageable.

In a study by Praditpornsilpa *et al.* conducted in 2011, 30 patients developed sudden loss of efficacy after treated by subcutaneous injection with biosimilar r-HuEpo. It was not known whether various r-HuEpo products can be safely interchanged. Sera from 23 of 30 patients were positive for r-HuEpo-neutralizing antibodies, and their bone marrow biopsies indicated pure red-cell aplasia, indicating the loss of erythroblasts. The cause for r-HuEpo hyporesponsiveness was occult gastrointestinal bleeding. Thus, subcutaneous injection of biosimilar r-HuEpo can cause adverse immunological effects (8).

The results from this pilot study showed that there was an immunogenicity risk in using biosimilar r-HuEpo. Even at 1:10,000 dilutions of the sera, anti r-HuEpo were detected in patients using biosimilar agents.

Because of the nature of the pilot study and its aim to investigate whether biosimilar agents currently used in Thailand were capable of producing anti-r-HuEpo, the results could not provide sufficient information to determine exactly which specific biosimilar products are directly responsible for causing anti r-HuEpo-associated PRCA. However, the study clearly stated that repeated subcutaneous injections of biosimilar agents could result in the development of anti r-HuEpo-associated PRCA. Hence, long-term, pharmacovigilance study is necessary to monitor and ensure patient safety for these agents. (8).

Five studies that examined chronic renal failure and oncology population were reviewed by Abraham and MacDonald. In the renal setting, these studies include a randomized controlled trial on hemoglobin maintenance in patients receiving long-term hemodialysis, a randomized safety trial in patients with chronic kidney disease not yet requiring renal replacement therapy and a post-approval safety commitment study. Studies in the cancer setting include a clinical validation study in patients with solid tumors receiving antineoplastic chemotherapy and a retrospective clinical audit of Binocrit in routine clinical practice. Based on available therapeutic equivalence and safety data, the clinical and safety outcomes of treatment with HX575 (biosimilar Epoetin Alpha) were likely to be similar to those of the originator product Eprex/Erypo. Both products were considered interchangeable in the management of anemia in the approved indications and patients transferred from the reference product to the biosimilar product were expected to show the same efficacy and safety outcomes. There was no evidence of the interchangeability of HX575 with other biosimilar or originator erythropoietins other than Eprex/Erypo (9).

In a study where SB309 (Epotein Alpha) and Erypo were compared, the applicant provided the evidence that SB309 and the reference product Erypo are similarly effective in correcting and maintaining haemoglobin concentrations and in this respect qualify as biosimilar products.

The overall safety profile of SB309 and the reference product Erypo appear to be similar. Data from clinical studies with SB309 are in line with the safety profile of other authorized epoetin-containing medicinal products and did not reveal unanticipated or unusual safety findings (10).

Mikhail A in his review “Epoetin Biosimilars in Europe: Five Years On” (2012), says that switching between an original reference ESA and a biosimilar (and possibly also switching between biosimilar versions of the same product) should be regarded as a change in clinical management. Clinicians need to be fully involved in such decisions (11). If clinicians wish to ensure that a given patient receives a specific biologic or biosimilar, they should prescribe by brand

name to prevent unintentional substitution by pharmacists and allow for effective pharmacovigilance.

Switching from epoetin alfa to SB309 increased the dose required by approximately 10–15% and transiently decreased the hemoglobin level by approximately 5%. Switching from SB309 to epoetin alfa reduced the dose required by around 10% and increased hemoglobin levels by approximately 10%. As in the correction phase study, a correction factor was introduced to correct for differences in protein content of the two ESAs being compared. In the maintenance phase study, this led to a widening of the revised 95% CI for dosage of 3.086–13.917 IU/kg/week. Again, the 95% Cis were within the modified acceptance range of ±45 IU/kg/week. A further post-hoc analysis of the two 24-week, randomized, double-blind correction and maintenance studies and the 56-week, open label, follow-on study reported above evaluated the impact of switching hemodialysis patients with CKD between epoetin alfa and SB309 on hemoglobin concentration, epoetin dose and safety. In the maintenance study, 118 patients switched from epoetin alfa to SB309 and 121 switched from SB309 to epoetin alfa; 104 of the 121 patients switched back to SB309. Only 101 patients completed 12 weeks of follow-up treatment without apparent major protocol deviations. In the correction study, 249 of 268 patients switched from epoetin alfa to SB309. A total of 242 patients completed 12 weeks of follow-on treatment without any apparent major protocol deviations. Therapies were considered equivalent if the 95% CI of the mean intra-individual difference in hemoglobin concentration before and after the switch remained within the pre-specified equivalence limits (±1.0 g/dL).

Hemoglobin levels were considered to be maintained if the mean level remained within the target range (10.5–12.5 g/dL) 8–12 weeks after the switch. Mean differences in hemoglobin and 95% CIs following the switch remained within pre- specified equivalence ±1.0 g/dL limits (10.94±0.84 g/dL for SB309 vs. 11.02±0.94 g/dL for epoetin alfa at 12 weeks); however, this range was wider than the 0.50–0.75 g/dL ranges used in other epoetin comparative studies. The 95% CIs of the mean difference in weekly epoetin dose stayed within modified equivalence margins. The incidence and nature of treatment-emergent and serious adverse events was similar among all groups and was unaffected by the ESA switch. It was reported that no patient developed anti-epoetin antibodies or PRCA during the study.

During the reporting period of 1998-2013, there was no efficacy or safety-related information leading to a change in the benefit-risk evaluation of EPIAO. (12).

During the reporting period of 01Dec2013 to 30Nov2014, there was no efficacy or safety-related information leading to a change in the benefit-risk evaluation of EPIAO. (13)

During the reporting period (01Dec2014-30Nov2015), no confirmable serious adverse reactions related to EPIAO was found (*14*).

1.2 Study Rationale

This therapeutic equivalence study is conducted to evaluate a 1:1 dose conversion from EPREX to EPIAO in term of clinical efficacy and safety in subjects with end-stage renal disease on haemodialysis.

A randomized, investigator and subject blind, active-control, parallel group two arm study design is chosen as an appropriate study design as per the recommendation provided by European

Medicines Agency (EMA) *(15)* and Thailand guidelines *(16)* on non-clinical and clinical development of similar biological medicinal products containing recombinant erythropoietins.

As per EMEA guidelines (Guideline on non-clinical and clinical development of similar biological medicinal products containing recombinant erythropoietins (Revision), similar clinical efficacy between the similar and the reference product should be demonstrated in adequately powered, randomised, parallel group clinical trials. Since pharmacokinetics and dose requirements usually differ for IV and SC use, similar efficacy between the test and the reference product should be ensured for both routes of administration. This could be achieved by performing separate clinical trials for both routes or by performing one clinical trial for one route and providing adequate bridging data for the other route (see below). Confirmatory studies should preferably be double-blind to avoid bias. If this is not possible, at minimum the person(s) involved in decision-making (e.g. dose adjustment) should be effectively masked to treatment allocation.

As per EMEA maintenance phase study, may be more sensitive to detect differences in biological activity between the similar and the reference product, although experience suggests that correction phase studies are also likely to be sufficiently discriminatory. The study design for a maintenance phase study should minimise baseline heterogeneity and carry over effects of previous treatments. Patients included in a maintenance phase study should be optimally titrated on the reference product (stable haemoglobin in the target range on stable epoetin dose and regimen without transfusions) for a suitable duration of time (usually at least 3 months). Thereafter, study subjects should be randomised to the similar or the reference product, maintaining their pre-randomisation epoetin dosage, dosing regimen and route of administration.

The guidelines recommends to perform a ‘maintenance phase’ study using IV epoetin (e.g. in a haemodialysis population) for demonstration of similar efficacy of administration between the bio-similar product and the reference bio-similar product. The recommended choice of the reference product for erythropoietin bio-similar products, epoetin alfa is EPREX.

The maintenance phase study is designed to minimise baseline heterogeneity and carry over effects of previous treatments. Subjects included in a maintenance phase study will be optimally titrated on the reference product (EPREX) (stable haemoglobin in the target range on stable epoetin dose and regimen without transfusions) for duration of at least 3 months. In substantiated cases a prolongation of the titration period is allowed up to maximum of 4 to 5 months on a case to case basis which will be considered as extended titration period. The assessment will be similar to the visit 7 (week 12) if there is prolongation of the titration period. Thereafter, study subjects should be randomised to the EPIAO or continued on EPREX, maintaining their pre-randomisation epoetin dosage, dosing regimen and route of administration (IV).

1.3 Risks and Benefits for Study Subjects

Recombinant erythropoietins (epoetin) have a relatively wide therapeutic window and are usually well tolerated provided that the stimulation of bone marrow is controlled by limiting the amount and rate of haemoglobin increase. The rate of haemoglobin increase may vary considerably between subjects and is dependent not only on the dose and dosing regimen of epoetin but also other factors, such as iron stores, baseline haemoglobin and endogenous erythropoietin levels, and the presence of concurrent medical conditions such as inflammation. In subjects with CKD, treatment of anaemia with r-HuEPO has improved cardiovascular function and the quality of life

to a greater extent. However, treatment with r-HuEPO to target haemoglobin concentrations of 13 g/dL or more (achieved mean concentrations >11 g/dL or 12 g/dL) has been consistently associated with high rates of cardiovascular disease, especially in subjects who are ESA-hypo responsive. Exaggerated pharmacodynamic response may result in hypertension and thrombotic complications. Moreover, PRCA due to neutralising anti-erythropoietin antibodies has been observed, predominantly in renal anaemia subjects treated with subcutaneously administered epoetin. Antibody-induced PRCA is a very rare event and usually takes months to years of epoetin treatment to develop. Clinical decision making should balance risks and benefits and usually favours r-HuEPO administration in subjects undergoing dialysis in whom haemoglobin concentrations are lower, quality of life is poorer, and transfusion is needed more often than for subjects with earlier stages of chronic kidney disease. *(17)*

1.4 Route, Dosage, Dosage Regimen, Treatment Period

In this study EPIAO / EPREX will be administrated for a treatment period of 52 weeks, one to three times a week through IV route at the end of dialysis session. The dose will be adjusted individually to maintain haemoglobin at a level not exceeding 12 g/dl. The required dose will be calculated based on the haemoglobin.

Dosage adjustment: Refer section 5.1.7.

1.5 Compliance Statement, Ethics and Regulatory Compliance

This study will be conducted in compliance with the protocol, the ethical principles that have their origin in the Declaration of Helsinki, the International Council for Harmonization (ICH) consolidated Guideline E6 for Good Clinical Practice (GCP) (CPMP/ICH/135/95) and applicable regulatory requirement(s)

1.5.1 Subject Confidentiality

The Investigators and the Sponsor will preserve the confidentiality of all subjects taking part in the study, in accordance with GCP and local regulations.

The Investigator must ensure that the subject's anonymity is maintained. On the case report forms or other documents shared with Sponsor / Ecron Acunova (EA), subjects should be identified by a unique subject identifier as designated by EA. Documents that are not for submission to Sponsor / EA [e.g., signed Informed Consent Forms (ICF)] should be kept in strict confidence by the Investigator.

In compliance with ICH GCP guidelines, it is required that the Investigator and institution permit authorized representatives of the company, of the regulatory agency(s), and the Independent Ethics Committee (IEC) or Institutional Review Board (IRB) direct access to review the subject's original medical records for verification of study-related procedures and data. The Investigator is obligated to inform the subject that his/her study-related records will be reviewed by the above named representatives without violating the confidentiality of the subject.

1.5.2 Informed Consent Procedure

Before a subject's participation in the study, it is the investigator's responsibility to obtain freely given consent, in writing, from the subject or legally acceptable representative after adequate

explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol-specific screening procedures or any study drugs are administered. The written ICF will be prepared in the local language(s) of the potential subject population.

In obtaining and documenting informed consent, the Investigator should comply with the applicable regulatory requirements, and should adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki. The consent form and any revision(s) should be approved by the IEC or IRB prior to being provided to potential subjects.

The subject's written informed consent should be obtained prior to his/her participation in the study, and should be documented in the subject's medical records. The ICF should be signed and personally dated by the subject or a legally acceptable representative, and by the person who conducted the informed consent discussion (not necessarily the Investigator). The original signed ICF should be retained in accordance with institutional policy, and a copy of the signed consent form should be provided to the subject or legal representative. The date and time that informed consent was given should be recorded on the Case Report Form (CRF).

If the subject or legally acceptable representative cannot read, then according to ICH GCP Guideline, Section 4.8.9, an impartial witness should be present during the entire informed consent discussion. This witness should sign the ICF after the subject or the legally acceptable representative has orally consented to the subject's participation and, if possible, signed the ICF. By signing the ICF, the witness attests that the information in the ICF and any other written information was adequately explained to and apparently understood by the subject or the legally acceptable representative and that informed consent was freely given by the subject or the legally acceptable representative.

1.5.3 Regulatory Compliance

The study protocol, subject information and consent form, the investigator brochure or written instructions to be given to the subject, available safety information, subject recruitment procedures (eg, advertisements), information about payments and compensation available to the subjects and documentation evidencing the investigator's qualifications should be submitted to the IEC or IRB for ethical review and approval according to local regulations, prior to the study start. The written approval should identify all documents reviewed by name and version.

Changes in the conduct of the study or planned analysis will be documented in a protocol amendment and/or the Statistical Analysis Plan (SAP).

The investigator must submit and, where necessary, obtain approval from the IEC or IRB and/ or Sponsor for all subsequent protocol amendments and changes to the informed consent document or changes of the investigational site, facilities or personnel. The investigator should notify the IEC or IRB of deviations from the protocol and serious adverse events occurring at the site in accordance with local procedures.

2 STUDY OBJECTIVES AND HYPOTHESES

2.1 Study Objectives

2.1.1 Primary Objective

- To evaluate a 1:1 dose conversion from EPREX to EPIAO in term of clinical efficacy and safety in subjects with end-stage renal disease (CKD stage 5) receiving hemodialysis after IV administration.

2.1.2 Secondary Objectives

- To observe the frequency of adverse events following EPIAO and EPREX administration.
- To monitor the occurrence of anti-epoetin antibodies among subjects following at least 12 months of therapy

3 STUDY DESIGN

3.1 Overall Study Design

3.1.1 Study Type

This is a prospective, randomized, double blind, parallel group two arm study to evaluate a 1:1 dose conversion from EPREX to EPIAO in term of clinical efficacy and safety in subjects with end-stage renal disease (CKD stage 5) receiving hemodialysis.

Approximately 5 centers in Thailand and more than 8 centers in Russia will participate in the study.

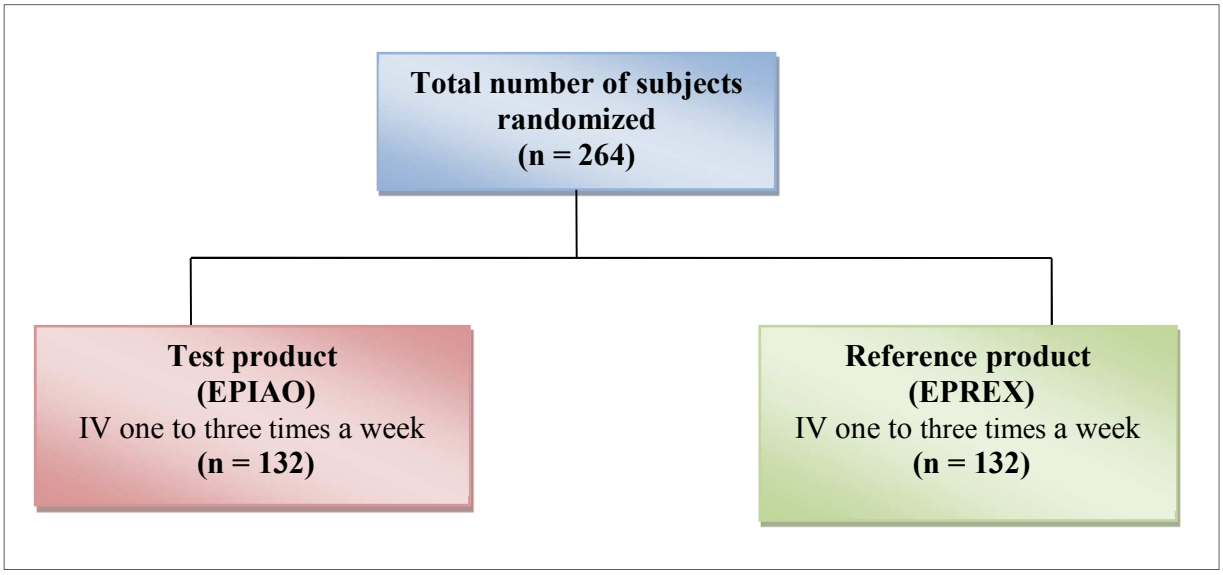
3.1.2 Treatment Groups

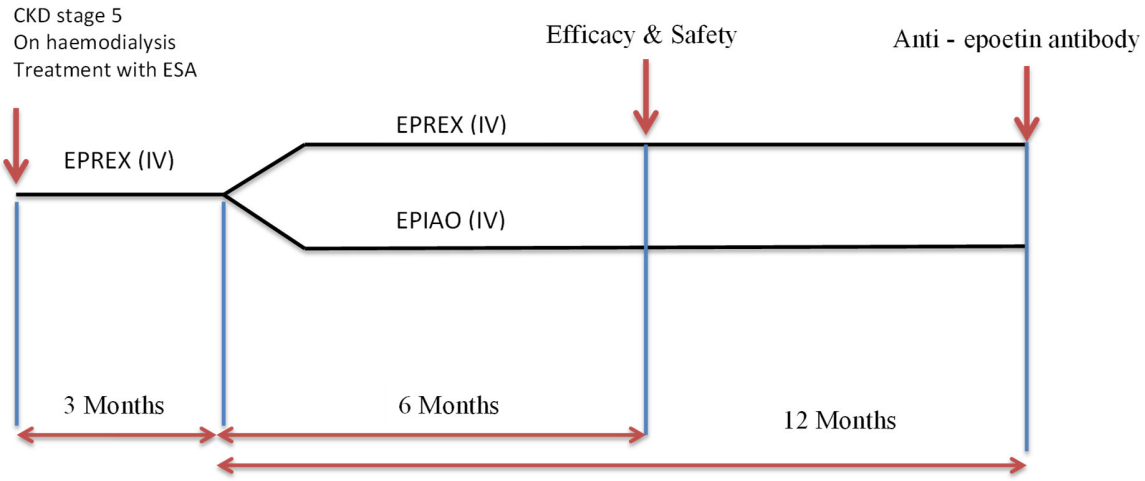
The study population will consist of end stage renal disease (CKD stage 5) receiving haemodialysis. Subjects should be on a clinically stable haemodialysis for at least 3 months before screening. Approximately 5 centres in Thailand and more than 8 centers in Russia will participate in the trial. The eligible subjects will be treated with EPREX for a period of at least 3 months after screening (titration period) so as to randomize 264 subjects into the treatment period. The subjects with haemoglobin levels within the target range of 10 to 12.5 g/dl during the titration period will be randomly assigned in a 1:1 ratio to switch to treatment with EPIAO or continue treatment with EPREX. In substantiated cases a prolongation of the titration period is allowed up to maximum of 4 to 5 months on a case to case basis which will be considered as extended titration period. The assessment will be similar to the visit 7 (week 12/Day 84) if there is prolongation of the titration period. Thus, there will be a total of 2 treatment arms in the study.

1. Treatment arm A having 132 subjects will switch to an equivalent dose (to maintain the haemoglobin level) of EPIAO, one to three times a week, intravenously for period of 52 weeks at the end of dialysis session
2. Treatment arm B having 132 subjects will continue with the same dose of EPREX, one to three times a week, intravenously for period of 52 weeks at the end of dialysis session

Competitiveness of patient enrolment will be used. The recruitment will be stopped when the total enrolment of 264 subjects is achieved.

Figure 1: Schematic diagram of study design





3.1.3 Study Endpoints

Primary endpoint

- Mean absolute change in haemoglobin level from baseline to 6 months after treatment with EPIAO/EPREX in parallel groups (g/dl).

- Mean absolute change in weekly epoetin dosage per kg body weight from baseline to 6 months after treatment with EPIAO/EPREX in parallel groups (IU/kg/week).

Secondary endpoint:

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

Safety endpoints:

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

3.1.4 Duration of the Study

The duration of the subject participation will be for a maximum of 77 weeks.

3.1.5 Duration of Subject Participation

The duration of the subject participation will be of a maximum of 68 weeks, (77weeks in case of extension of titration period) including 4 weeks of screening period, titration period of at least 3 months (maximum duration for 5 months), treatment duration of 26 weeks for efficacy and safety evaluation (weeks 13 through weeks 39) and treatment duration of 26 weeks for immunogenicity evaluation (weeks 40 through weeks 64). In substantiated cases a prolongation of the titration period is allowed up to maximum of 4 to 5 months on a case to case basis which will be considered as extended titration period. The assessment will be similar to the visit 7 (week 12/Day 84) if there is prolongation of the titration period.

3.1.6 Discontinuation Criteria

1. Subjects are free to drop out from the study at any time without stating any reason and they can choose not to receive the drug or equivalent after signing the consent. If the subject chooses not to receive the study drug after signing the consent, the subject must notify the Investigator before dispensing of the study drug. However, the subjects will continue to receive all the standard medical care, to which they are entitled.
2. Investigators may also, at their discretion, withdraw the subject from participating in the study at any time, with prior notification to the sponsor with the reason for the same.

However, subjects must be withdrawn from therapy, if any of the following events occur after giving the consent:

a. Subject suffers from significant intercurrent illness or undergoes surgery during the course of the study where continued participation in the study presents a significant safety concern.

b. Subject develops anti-epoetin antibodies or PRCA or severe allergic reaction

c. Subjects requires epoetin dose more than 300 IU/kg/week

d. Subject experiences adverse event or laboratory abnormality, when withdrawal would be in the best interest of the subject, as assessed by the investigator

e. The subject fails to comply with the requirements of the protocol (e.g., visit window deviation) the subject may be withdrawn at the discretion of investigator and/or after discussion with medical monitor.

f. It is necessary to further protect the health of the subject or the integrity of the study.

g. Pregnancy.

3. The study is terminated by Sponsor, Regulatory Authorities or IEC/ IRB.

4 STUDY POPULATION

4.1 Enrollment

Subjects are eligible for enrolment into the study if they meet all of the inclusion criteria and eligibility criteria and do not meet any of the exclusion criteria.

4.1.1 Inclusion Criteria at Screening

Subjects must satisfy all of the following criteria to be included in the study:

1. Male and female subjects between the age of 18 to 75 years
2. Subjects with end stage renal disease (CKD stage 5*) on epoetin treatment for at least 3 months prior to screening
3. Subjects with haemoglobin between 10 g/dl to 12 g/dl
4. Subjects who are on clinically stable haemodialysis (defined as no clinically relevant changes of dialysis regimen and/or dialyzer) for at least 3 months prior to screening
5. Subject who had an adequacy of dialysis treatment measured by Kt/V
    a. Kt/V must be ≥ 1.2 for subjects with 3 times of HD/week
    b. Kt/V must be ≥ 1.8 for subjects with 2 times of HD/week
6. Subjects willing to provide a written informed consent
7. Subjects with serum ferritin ≥ 200 μg/L and/or transferrin saturation ≥ 20%
8. Subjects with a life expectancy more than at least study period in clinical judgment of the investigator

*CKD staging will be based on the five-stage system for classification of CKD based on KDIGO guidelines (page no: 32).

GFR will be calculated based on the EPI equation as below *(18)*

$GFR = 141 \times \min(S_{cr}/\kappa, 1)^{\alpha} \times \max(S_{cr}/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018$ [if female] $\times$ 1.159 [if black]

where:
S_{cr} is serum creatinine in mg/dL,
κ is 0.7 for females and 0.9 for males,
α is -0.329 for females and -0.411 for males,
min indicates the minimum of S_{cr}/κ or 1, and
max indicates the maximum of S_{cr}/κ or 1.

4.1.2 Eligibility criteria at Baseline

Subjects must satisfy all of the following criteria to be included in the study:

1. Subjects with stable haemoglobin levels between 10 g/dl to 12.5 g/dl with stable EPREX dosage and intra-individual change in Hb of **≤1.2 g/dl** over 4 weeks before randomization
2. Subjects with serum ferritin ≥ 200 µg/L and/or transferrin saturation ≥ 20%

Patients who don't meet the eligibility criteria at baseline will be considered as screen failures.

4.1.3 Exclusion Criteria at Screening

Subjects who meet any of the following criteria will be disqualified from entering the study:

1. Subjects with anaemia due to other reasons (that is not renal anaemia)
2. Subjects receiving blood transfusion within the last 3 months
3. Subjects requiring epoetin dose of > 300 IU/kg/week
4. Subjects with major complication such as severe/chronic infections or bleeding, or aluminum toxicity
5. Subjects with suspected or known PRCA
6. Subjects with a history of aplastic anaemia
7. Subjects with uncontrolled diabetes (fasting blood glucose > 240 mg/dl) or uncontrolled hypertension (systolic blood pressure > 180 mm Hg, diastolic blood pressure > 110 mm Hg)
8. Subjects with HbA1C >6.5%
9. Subjects with known hypersensitivity to any of the ingredients of the investigational products, the mammalian cell-derived product or human albumin products
10. Subjects with history of seizure disorder

11. Subjects with hematological disorder (thrombocytopenia: platelet count below $100x10^9$/L, neutropenia: neutrophil count below $1.0x10^9$/L, or hemolysis)
12. Subjects with hyperparathyroidism (intact parathyroid hormone > 1000 pg/ml)
13. Subjects with alanine aminotransferase (ALT), aspartate aminotransferase (AST) and alkaline phosphatase levels 3 × upper limit of normal (ULN) at screening
14. Subjects with **decompensated** congestive heart failure (NYHA class III and IV) **within 6 months prior to screening**
15. Subjects with angina (functional class III and IV) within 6 months prior to screening
16. Subjects with myocardial infarction or stroke in the preceding 6 months
17. Subjects with active malignancy in the previous 5 years
18. Subjects with gastrointestinal bleeding in the past 6 months
19. Subjects with immunosuppressive therapy in the previous 3 months
20. Subjects with active hepatitis B virus (positive for HBsAg and IgM anti-HBc **in Thailand and positive for HBsAg in Russia**)
21. Subjects with hepatitis C virus (HCV) (positive for Anti-HCV antibody)
22. Female subjects who are pregnant, breast-feeding, planning to be pregnant during the study, or women of child-bearing potential (any woman who is not surgically sterile i.e. bilateral tubal ligation, total hysterectomy or < 2 years post menopause) not using a reliable method of double contraception (e.g. condom plus diaphragm, condom or diaphragm plus spermicidal gel/foam, tubal ligation, or stable dose of hormonal contraception) throughout the study period
23. Subjects participating in trials involving long acting erythropoietin in the past 6 months before screening and short acting erythropoietin in the past 3 months before screening"
24. Subjects currently participating or participation in an investigational study within 30 days prior screening

4.2 Removal of Subjects from Therapy

4.2.1 Reasons for Withdrawal/Early Discontinuation

Any subject, who discontinues from the study treatment for any reason, will have his/her study treatment discontinuation recorded.

Subjects withdrawn prior to randomization but after signing informed consent:

- Screen Failure
- Withdrawal by Subject
- Investigator Decision

Subjects withdrawn after randomization but before completing the study as per protocol:

- Adverse Event as per PI discretion

- If subjects develop anti-epoetin antibodies or PRCA or severe allergic reaction
- If the subject requires epoetin dose more than 300 IU/kg/week
- Death
- Lost to Follow-up
- Pregnancy
- Progressive Disease
- Study Terminated by Sponsor
- Withdrawal by Subject

If a subject withdraws from the study, the investigator will complete and report the observations as thoroughly as possible up to the date of withdrawal including the date of last treatment and the reason for withdrawal.

If the subject is withdrawn due to an adverse event, the investigator will follow the subject until the adverse event has resolved or stabilized.

All subjects who are withdrawn from the study, effort should be made to complete protocol specified withdrawal procedures (Section 4.2.2).

4.2.2 Withdrawal Procedures

Subjects who discontinue will be asked about the reason(s) for their discontinuation and about the presence of any adverse events. If a subject withdraws or is discontinued from the study before completion, every effort should be made to complete the last scheduled assessments. The PI must provide a written report on the appropriate CRF page describing the reason for discontinuation. The primary reason for the withdrawal must also be recorded in subject's medical record along with CRF. Adverse events should be followed up and all investigational products should be returned by the subject. All study procedures, including collection of efficacy and safety variables, should be conducted and recorded on the appropriate CRF. The final report will include reasons for withdrawal.

4.2.3 Subject Replacement

The subjects who do not complete the study will be considered dropouts and will not be replaced.

4.2.4 Subject Re-screening Procedures

Patients who are diagnosed with end stage renal disease (Stage 5) receiving hemodialysis and epoetin treatment but excluded for other reasons are allowed to be re-screened once in this study based on the clinical judgment of the investigator.

5 TREATMENTS ADMINISTERED

5.1 Investigational Product(s)

The Investigator must ensure that the investigational product (IP) will be used only in accordance with the protocol. The drug will be manufactured complying with all required regulations. Sufficient quantities of the drug will be supplied to the clinical study facility by the sponsor. Batch

numbers and expiration dates will be filed in the study documents when available. See the table below for ingredient list of each product.

Table 1: Investigational Product Details

	Treatment	Comparator
Active Ingredient	Recombinant human erythropoietin	Recombinant human erythropoietin
Brand name	EPIAO	EPREX
Dosage form	Pre-filled syringe	Pre-filled syringe
Strength	2000 IU, 4000 IU	2000 IU, 4000 IU
Frequency	1-3 times per week	1-3 times per week
Route of administration	Intravenous	Intravenous
Manufactured by	Shenyang Sunshine Pharmaceutical Co., Limited	Janssen Pharmaceuticals, Inc.

For the purpose of this trial, study medication / study drug / study treatment / investigational product / IP refer to EPIAO of Shenyang Sunshine Pharmaceutical Co., Limited and EPREX of Janssen Pharmaceuticals, Inc.

5.1.1 Method of Assigning Subjects to Treatments and Blinding

Subjects selected for participation will be randomly assigned to one of the two treatment arms, 264 subjects will be assigned to either treatment arm A (receiving EPIAO) or B (receiving EPREX) in a ratio of 1:1.

The randomization schedule will be generated by EA statistical team, using PROC PLAN in SAS, version 9.2 or higher, according to EA standard operating procedures (SOPs), listing subject randomization code number and treatment. The randomization allocation will be done by Interactive Voice Response System/ Interactive Web Response System (IVRS/IWRS) for dispensing the test drugs.

The investigator and sponsor's Medical and Safety Expert will have to contact the IVRS/IWRS for information regarding the identity of treatment sequence for each subject.

All subjects, who sign an IRB/IEC approved informed consent form and authorization for the use and disclosure of protected health information, will be assigned a unique subject identity code (SIC) consisting of two digit center code and three digit subject specific code. The randomization code will be captured separately as an additional identity.

5.1.2 Method of Assessing Treatment Compliance

Subjects will be asked about their compliance at each visit. This information will be appropriately recorded at scheduled visit in the CRF. Subjects judged to be non-compliant will be counselled on the importance of one to three times weekly administration of study medication, as prescribed. Subjects who are repeatedly or severely non-compliant may be discontinued, at investigator's discretion after discussion with the medical monitor.

5.1.3 Labeling and Packaging

It will be the sponsor's responsibility to provide the trial products. Packaging and labelling will be done as per local regulatory regulations and trial requirements.

The following general information will be provided on the clinical trial supply label:

- Product name – Study Number
- Subject #, subject initials
- Brief Instructions for use
- Storage Instructions
- Cautionary Statement – "For clinical trial purpose only"
- Batch or Lot #
- Date dispensed
- Expiry date
- Supplier of drug

5.1.3.1 Preparation

The dose of erythropoietin will be calculated based on the haemoglobin level. The study medication will be supplied in the form of pre-filled syringes for administration.

5.1.4 Storage

The study treatment supplies should be stored in a secure location and maintained at a temperature of 2°C to 8°C (refrigerated temperature). The pre-filled syringes should be protected from light.

5.1.5 Drug Accountability

When a drug shipment is received, unblinded pharmacist will check the amount and condition of the drug, temperature log during the transit, check for appropriate local language in the label, drug expiration date, and sign the Receipt of Shipment Form provided. The original will be retained at the site. In addition, the unblinded pharmacist shall contact Sponsor or Sponsor representative (local depot) as soon as possible if there is a problem with the shipment. The unblinded pharmacist will be responsible for blinding of IMP after receipt of the drug shipment.

The investigator designated person who is un-blinded, preferably a pharmacist, will be responsible for drug accountability, reconciliation, and record maintenance. In accordance with all applicable regulatory requirements, the designated site staff (study pharmacist) will maintain accurate IP accountability records throughout the course of the study. A drug accountability log for recording the receipt, dispensing and return of drug will be maintained to document the amount of drug received and the amount of drug used in the study. Study medication requests, receipts and dispensing records as well as study medication inventory forms will be examined and reconciled during and at the end of the study by EA personnel.

All unused or partially used study drug must be returned to sponsor or its representatives at the end of the study for destruction. Reconciliation between the amounts of drug supplied, used and

returned to EA must be performed and any discrepancies should be accounted for. This reconciliation will be logged on the drug reconciliation form, signed and dated. The study drug destroyed on site will be documented in the study files.

A Drug Accountability Record will be provided for the drugs. The record must be kept current and should contain, the date and quantities of drug received, subject's identification number and/or initials or supply number as applicable, for whom the IP was dispensed, the date and quantity of IP dispensed and the remaining IP.

5.1.6 Blinding and Unblinding

This will be a double blinded and randomized study. All investigators, subjects, site personnel (except the study nurse performing the drug administration and pharmacist) and Contract Research Organization (CRO) study team [except persons involved in preparation of the codes, clinical operations team in Russia and project manager who is responsible for convening the Safety Monitoring Committee (SMC) meeting] will be blinded to the medication codes.

A treating physician may request unblinding of study medication on an individual subject, if it is essential for the clinical management of the subject's health, to ensure safety. If a treating physician requires unblinding of study medication for a subject, e.g. for management of a SAE, investigators will be able to access this information via IVRS/IWRS. The sponsor / EA medical monitor should be contacted immediately (preferably before unblinding takes place) and the date and reason for unblinding has to be documented in the source document (medical record) and CRF, accordingly. The EA medical monitor or designee is required to contact and inform the sponsor regarding unblinding of the subject's treatment.

Blinding process in Thailand:

Co-sponsor will be responsible for IP relabeling/redressing. In this step, randomization number & kit number of each patient will be generated by IWRS, and then same will be informed to the un-blinded co-sponsor. The un-blinded person will know which of the IP, either EPIAO or EPREX needs to be administrated to each patient according to IWRS. Consequently, un-blinded co-sponsor will prepare double-blind re-labelled IP accordingly and then all pre-labelled IP will be shipped to each site. The blinded nurses/or blinded study coordinator will take the IP to un-blinded nurse to make injections to blinded patients.

Blinding process in Russia:

At each site, an un-blinded person (pharmacist) will be responsible for IP relabeling/redressing. In this step, randomization number & IP name of each patient will be generated by IWRS, and then same will be informed to the un-blinded person (study nurse/pharmacist). The un-blinded person will know which of the IP, either EPIAO or EPREX needs to be administrated to each patient according to IWRS. Consequently, un-blinded person (study nurse/pharmacist) will prepare double-blind re-labelled IP. The un-blinded nurse will take IP from un-blinded person (study nurse/pharmacist) to make injections to blinded patients. Investigator who will perform routine assessment of the patient will be blinded.

5.1.7 Dosing Schedule, Selection and Timing of dosing

Study drugs have to be administered in strict accordance with approved protocol.

Treatment arm A

EPIAO group (test product) having 132 subjects will receive EPIAO, one to three times a week, intravenously for period of 52 weeks at the end of dialysis session

Treatment arm B

EPREX group (reference product) having 132 subjects will receive EPREX, one to three times a week, intravenously for period of 52 weeks at the end of dialysis session

The blood pressure will be monitored after the haemodialysis procedure and if the blood pressure is within the normal range then the study medication will be administrated by the study nurse or designee. If systolic pressure >160 mm of Hg, the blood pressure will be monitored after half an hour. If the BP does not decrease then the subject will be asked to come the next day for drug administration.

The dose will be adjusted individually to maintain haemoglobin at a level not exceeding 12 g/dl. The required dose will be calculated based on the haemoglobin.

Dosage adjustment:

Titration period:

During titration period, EPREX will be administered one to three times weekly as per last dose which subject received previously before screening, for subject who are already on treatment. EPREX will be administered one to three times weekly as per Hb value at screening and as per PI discretion. The dose received by the subject at screening will be taken as the "basic initial dose" for all subjects. An increase or decrease of 2000 IU per week will be allowed for dose adjustment to maintain subject's Hb value within target range (10 – 12.5 g/dl). At this point, the "stable dose" of EPREX for each patient will be determined. The stable dose of EPREX / EPIAO will be calculated as IU/kg/week before the start of the treatment period and captured in the eCRF. In substantiated cases, a prolongation of the titration period is allowed up to maximum of 4 to 5 months on a case to case basis which will be considered as extended titration period.

During treatment period, subjects randomized to EPREX arm will continue on an equivalent dose of EPREX as during the titration period. Subjects randomized to EPIAO arm will receive EPIAO treatment 1:1 dose conversed from that of EPREX during the titration period. If subject's Hb value is out of target range, an increase or decrease of 2000 IU per week is allowed for dose adjustment. The maximum allowable dose is 300 IU/kg/week.

Treatment period:

The dose should be adjusted for each patient to achieve and maintain hemoglobin levels between 10-12 g/dl. The maximum dose of study drug is 300 IU/kg.

The investigator can adjust the dose by their own decision based on the best interest and safety of the subject and in any time

Two key factors will be considered for dose adjustment during the study period

1. Hemoglobin level at current visit
2. Changes in hemoglobin over past 4 weeks

- If haemoglobin decreases more than 1 g/dl over the past 4 weeks and current haemoglobin level is < 10.5 g/dl, the dosage may be raised by 25% of the last dose received by the subject (A).
- If haemoglobin decreases more than 1 g/dl over the past 4 weeks and current haemoglobin level is between 10.5 g/dl to 12.0 g/dl, the last dose received by the subject should be continued (B).
- If haemoglobin decreases more than 1 g/dl over the past 4 weeks but current haemoglobin is between 12.1 to 13.0 g/dl, the dose should be reduced by 25% of the last dose received by the subject (C).
- If haemoglobin decreases or an increase between 1.0 g/dl and current haemoglobin value is less than 10.5 g/dl, the dosage may be raised by 25% of the last dose received by the subject (D).
- If haemoglobin decreases or an increase between 1.0 g/dl and the current hemoglobin value is between 10.5 to 12.0 g/dl, the last dose received by the subject should be continued (E).
- If haemoglobin decreases or increase between 1.0 g/dl but the current haemoglobin is between 12.1 to 13.0 g/dl, the dose should be reduced by 25% of the last dose received by the subject (F).
- If haemoglobin increases more than 1 g/dl over the past 4 weeks and current haemoglobin is < 10.5 g/dl, the last dose received by the subject should be continued (G).
- If haemoglobin increases more than 1 g/dl over the past 4 weeks and haemoglobin level is between 10.5 to12.0 g/dl, the last dose received by the subject should be continued (H).
- If haemoglobin increases more than 1 g/dl over the past 4 weeks but current haemoglobin is between 12.1 to 13.0 g/dl, the dose should be reduced by 25% of the last dose received by the subject (I).
- If current haemoglobin level is greater than 13.0 g/dl, not depending on the change of haemoglobin in the past 4 weeks, dose should be temporarily withheld until the haemoglobin begins to decrease between 10.5 and 12.0 g/dl, at which point therapy should be reinitiated at 25% reduced from the previous dose (J).

	Current Haemoglobin			
Changes in Hb over past 4 weeks	Hb < 10.5 g/dl)	Hb 10.5 to 12.0 g/dl	Hb 12.1 to 13.0 g/dl	Hb > 13.0 g/dl

< 1.0	↑ A	No change B	C ↓	Hold until Hb is reduced within range of 10.5 to 12.0 g/dl and reinitiate the dose 25% reduced from the previous dose J
-1.0 to 1.0	↑ D	No change E	F ↓	
> 1.0	No change G	No change H	I ↓	

Note:

- *The iron status should be assessed and need to supplement, if required.*
- *The dose of the study medication will be rounded off to the highest value. E.g. if subject requires dose of 9000 IU, the dose will be rounded off to 10000 IU because of availability of study medication PFS in multiples of 2000 IU.*
- *The criteria mentioned about dose adjustment above are recommendation only, Investigator must act for the best interest of the patient whenever necessary*

5.1.8 Instructions for Subjects

1. The subject should be instructed to visit the study facility one to three times weekly for haemodialysis
2. During therapy, subjects should be advised of the importance of compliance with antihypertensive therapy
3. Instructions should be given as to when the subject needs to visit the study facility for further visits
4. The subjects will be instructed not to take any of the disallowed medications (section 5.1.9)

5.1.9 Concomitant Medications

Concomitant therapy will be permitted based on the investigator's discretion. Detailed history of concomitant medications at the baseline will be recorded in the CRF. All concomitant therapy taken by the subject during the study period will be recorded in the CRF in the concomitant medication section in detail.

Subjects will be instructed to report to the investigator any medication used over the course of the study. The investigator will address the significance of the reported medication use on study integrity. At the discretion of the investigator, these subjects may continue study participation if the medication is not anticipated to alter study integrity.

The medications that permitted are

- Iron supplements
- Folic acid
- Alkalizing agents
- Phosphate binder (i.e. Calcium carbonate)

Subjects will receive oral iron supplements if TSAT is < 20% and will continue on iron supplements to maintain the TSAT ≥ 20%.

Allopurinol and Angiotensin Converting Enzyme (ACE) inhibitors if required are permitted at doses not affecting the efficacy of study drug at the discretion of the investigators.

Androgens are not recommended as an adjuvant to epoetin therapy *(3)*.

6 STUDY PROCEDURES

A study visit schedule in tabular format is provided in Table 2

6.1 Screening / Visit 0 (Day -31 to Day 0)

Subjects considered likely to be eligible based on a pre-screening assessment will attend a screening assessment. Subjects will be screened to ensure enrolment of appropriate number of subjects into the study. The duration of screening period will be from Day -31 to Day 0. The Principal Investigator (PI) or his designee will explain the nature of the study, give full details and obtain a written informed consent from the subject prior to their participation in any study related procedures.

All inclusion/exclusion criteria will be assessed, demographic characteristics and vital signs will be recorded. A full physical examination will be performed. A detailed medical history will be elicited regarding symptoms, prior use of medications and prior medical/surgical therapies. Concomitant medications which are still on-going will be recorded at this visit. Laboratory investigations including haematology, serum chemistry and urinalysis (Appendix I) will be performed. Urinalysis test will be considered as optional for CKD patients as CKD patients may not be able to provide sufficient urine volume for urinalysis test due to low urine output. Serology and iron study will also be performed at screening visit. Menstrual and reproductive history will be recorded for all female subjects at this visit, including marital status, type of contraceptive used and details of menstrual cycle. Serum pregnancy test for women of childbearing potential will be done at the screening visit.

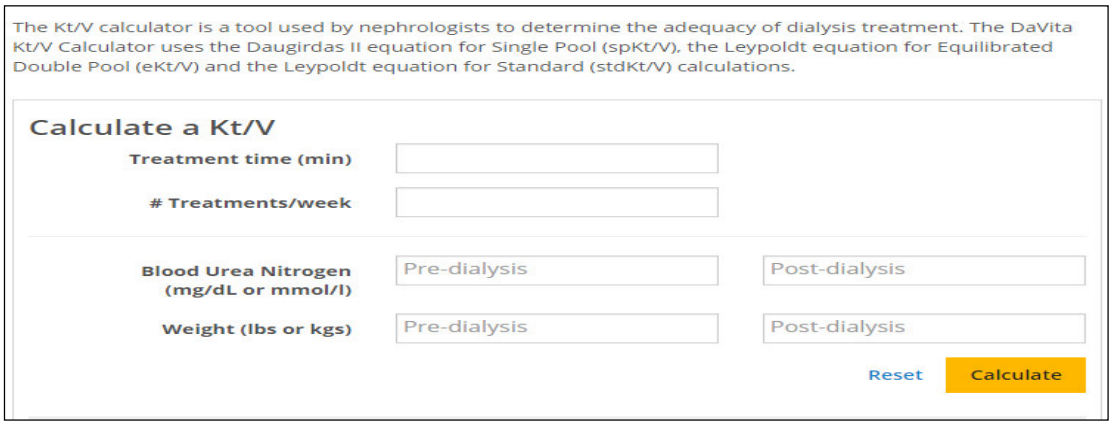
The Investigator will maintain a log of all the subjects screened for study participation and will record the reason(s) for excluding potential subjects. The subjects who successfully pass the screening tests and meet the inclusion exclusion criteria will be enrolled for the study.

Subjects 18 years of age or older must provide a signed, IRB approved written informed consent. No study related procedures or activities will be performed until each subject is fully informed and the consent form is signed and dated. All subjects will be given a copy of the signed and dated consent form.

The following assessments will be performed;

- Written informed consent
- Demographic data [i.e., date of birth, gender, race, weight (pre and post hemodialysis) and height]
- Detailed medical history with prior concomitant medication
- Menstrual and reproductive history (only for female subjects)
- Review and document inclusion and exclusion criteria
- Perform a standard general physical examination
- Vital signs including blood pressure, heart rate, respiratory rate, temperature
- Laboratory investigations (haematology, serum chemistry, urinalysis*, serology, fecal occult blood test (as per PI discretion), intact parathyroid hormone and iron study, reticulocyte count) (refer Table in Appendix I)
- BUN (pre and post hemodialysis)
- Immunogenicity testing for anti-EPO antibody
- Chest X ray$, ECG
- Adequacy of dialysis measurement by Kt/V formula

(K= dialyzer clearance; t= time; V= volume of body water)



- Serum Pregnancy Test (only for female subjects with child bearing potential)

*= Urinalysis test will be considered as optional for CKD patients as CKD patients may not be able to provide sufficient urine volume for urinalysis test due to low urine output. $= Chest X ray performed within one year prior to screening of the subject is acceptable.

6.2 Titration period / Visit 1 – 7 (Week 1/Day 1 Week 2/Day 14, week 4/Day 28, week 6/Day 42, week 8/Day 56, week 10/Day 70 and week 12/Day 84) with window period of ± 2 days

All the eligible subjects will enter the titration period (starting from week 1). The subjects will undergo haemodialysis one to three times a week. .

EPREX will be administered one to three times weekly as per last dose which subject received previously before screening in order to maintain the haemoglobin within the target range of 10 to 12.5 g/dl with intra individual change in the Hb of ≤1.2 g/dl over 4-week period before randomization i.e. during Week 8/Day 56 (V5), Week 10/Day 70 (V6) and Week 12/Day 84 (V7). The subject with target range Hb and intra individual change of ≤1.2 g/dl during V5, V6 and V7 will be considered as stable on Hb and will be scheduled in next week for randomization to appropriate arm after performing V8 procedure. The titration period of three months is considered based on the EMA guidelines [Guideline on non-clinical and clinical development of similar biological medicinal products containing recombinant erythropoietins (Revision)] which states that "Patients included in a maintenance phase study should be optimally titrated on the reference product (stable haemoglobin in the target range on stable epoetin dose and regimen without transfusions) for a suitable duration of time (usually at least 3 months)".

If subject fails to achieve target range Hb and intra individual change of ≤1.2 g/dl at week 12 (V7), such subject will enter into extended titration period. The extension of titration period will be performed every two weeks [Extended Week 14/Extended Day 98 (EV8), Extended Week 16/Extended Day 112 (EV9), Extended Week 18/Extended Day 126 (EV10) and Extended Week 20/Extended Day 140 (EV11)] for a maximum of 8 weeks after Week 12/Day 84 (V7). The assessment which will be performed in the extended titration period every two weeks will be similar to visit 7 assessments (Week 12/Day 84).

If subject fails to achieve target range Hb and intra individual change of ≤1.2 g/dl at week 12 (V7), the next evaluation of the subject will be done at Extended Week 14/Extended Day 98 (EV8) followed by Extended Week 16/Extended Day 112 (EV9). The target Hb range and intra individual change in Hb will be compared over Week 12/Day 84 (V7), Extended Week 14/Extended Day 98 (EV8) and Extended Week 16/ Extended Day 112 (EV9). If the subject with target range Hb and intra individual change of ≤1.2 g/dl is achieved during Extended Week 16/ Extended Day 112 (EV9), subject will be scheduled in next week for randomization and will perform V8 procedure.

If subject fails to achieve target range Hb and intra individual change of ≤1.2 g/dl at Extended Week 16/Extended Day 112 (EV9), such subject will continue the extension of titration period [Extended Week 18 (EV10/Extended Day 126) and Extended Week 20 (EV11/Extended Day 140)]. The extended titration period will be performed every two weeks. The assessment which will be performed in the extended titration period every two weeks will be similar to visit 7 assessments (Week 12/ Day 84). The target Hb range and intra individual change in Hb will be compared over Extended Week 16/Extended Day 112 (EV9), Extended Week 18/ Extended Day 126 (EV10) and Extended Week 20/ Extended Day 140 (EV11). If the subject with target range Hb and intra individual change of ≤1.2 g/dl is achieved during Extended Week 20/Extended Day 140 (EV11), subject will be scheduled in next week for randomization and will perform V8 procedure.

If the subject fails to achieve target range Hb and intra individual change of ≤1.2 g/dl at Extended Week 20/Extended Day 140 (EV11), such subject will be considered as screen failure.

The following assessments will be performed at week 2/Day 14, week 6/Day 42 and week 10/Day 70 at defined visit window;

- Demographic data (body weight: pre and post hemodialysis)

- Physical examination
- Vital signs
- Complete Blood Count (CBC)
- Adverse events
- Concomitant medication
- Dose adjustment if required as per section 5.1.7

The following assessments will be performed at the end of week 4/Day 28, week 8/ Day 56 and week 12/ Day 84;

- Demographic data (body weight: pre and post hemodialysis)
- Physical examination
- Vital signs
- Adverse events
- Concomitant medication
- Dose adjustment if required as per section 5.1.7
- Immunogenicity testing for anti-EPO antibody*
- Hematology
  - ✓ Haemoglobin
  - ✓ Haematocrit
  - ✓ Total WBC count
  - ✓ Differential WBC count
  - ✓ Platelet count
  - ✓ Red Blood Cell count
  - ✓ Reticulocyte count&
  - ✓ MCV
  - ✓ MCH
  - ✓ MCHC
  - ✓ Peripheral smear
  - ✓ Iron study#

* Only during week 8

Only during week 10

& Only during week 12/Day 84

The following assessments will be performed at the end of Extended Week 14/Extended Day 98 (EV8), Extended Week 16/ Extended Day 112 (EV9), Extended Week 18/Extended Day 126 (EV10) and Extended Week 20/Extended Day 140 (EV11) (as applicable for extended titration period) with window period of ± 2 days

- Demographic data (body weight: pre and post hemodialysis)
- Physical examination
- Vital signs
- Adverse events
- Concomitant medication
- Dose adjustment if required as per section 5.1.7
- Hematology
  - ✓ Haemoglobin
  - ✓ Haematocrit
  - ✓ Total WBC count
  - ✓ Differential WBC count
  - ✓ Platelet count
  - ✓ Red Blood Cell count
  - ✓ Reticulocyte count
  - ✓ MCV
  - ✓ MCH
  - ✓ MCHC
  - ✓ Peripheral smear

6.3 Randomization / Visit 8 (Day 91+3 / Week 13)

After the titration period of at least 3 months (or extended titration period of 2 months) with window period of ± 2 days,subjects who successfully fulfill the eligibility criteria at any of baseline visits will qualify for randomization and will be randomized to appropriate arm as per the study design. A negative serum pregnancy test is a must for females of child-bearing potential prior to randomization. If the subjects do not meet the eligibility criteria at the baseline visit, they will be considered as screen failures and will be discontinued from the study.

At this visit, vital signs will be recorded and physical examination will be done. AEs and concomitant medication will be recorded. The blood pressure will be monitored after the haemodialysis procedure and if the blood pressure is within the normal range then the study medication will be administrated by the study nurse or designee. If systolic pressure >160 mmHg, the blood pressure will be monitored after half an hour. If the BP does not decrease then the subject

will be asked to come the next day for drug administration. Assessments will be completed as per the study visit plan.

The following assessments will be performed;

- Demographic data (body weight: pre and post hemodialysis)
- Review and document eligibility criteria (Hb should be within the target range of 10 to 12.5 g/dl at visit 8 and intra individual change in Hb of ≤1.2 g/dl over previous 4 weeks i.e. over V5/V6/V7 or V7/EV8/EV9 or EV9/EV10/EV11).
- Serum pregnancy test
- Vital signs
- Adverse events
- Concomitant medication
- Physical examination
- Randomization of subjects
- CBC
- BUN (pre and post hemodialysis)
- Iron study
- Immunogenicity testing for anti-EPO antibody
- Adequacy of dialysis measurement by Kt/V formula

6.4 Treatment Period (Week 14/Day 98 to Week 64/Day 448)

The study treatment period will be for 52 weeks. The subject will receive either EPIAO or EPREX one to three times a week at the end of dialysis session. During the treatment period, the subject will be instructed to visit the study facility one to three times a week on week 14/Day 98, week 15/Day 105, week 16/Day 112, week 20/Day 140, week 24/Day 168, week 28/ Day 196, week 32/Day 224, week 36/Day 252, week 40/Day 280, week 44/Day 308, week 48/Day 336, week 52/Day 364, week 60/Day 420 and week 64/Day 448 following randomization for study assessment.

The following assessments will be performed;

Visit 9: Week 14/Day 98 ± 2 days

- Demographic data (body weight: post hemodialysis)
- Vital signs
- Physical examination
- Adverse events
- Concomitant medication
- CBC

- Dose adjustment if required as per section 5.1.7

Visit 10: Week 15/Day 105 ± 2 days

- Demographic data (body weight: post hemodialysis)
- Vital signs
- Physical examination
- Adverse events
- Concomitant medication
- CBC
- Reticulocyte countDose adjustment if required as per section 5.1.7

Visit 11: Week 16/Day 112 ± 2 days

- Demographic data (body weight: post hemodialysis)
- Vital signs
- Physical examination
- Adverse events
- Concomitant medication
- CBC
- Iron study
- Immunogenicity testing for anti-EPO antibody
- Dose adjustment if required as per section 5.1.7

Visit 12: Week 20/Day 140 ± 2 days

- Demographic data (body weight: post hemodialysis)
- Vital signs
- Physical examination
- Adverse events
- Concomitant medication
- CBC
- Dose adjustment if required as per section 5.1.7

Visit 13: Week 24 /Day 168± 2 days

- Demographic data (body weight: pre and post hemodialysis)
- Vital signs
- Physical examination

- Adverse events
- Concomitant medication
- CBC
- Iron study
- BUN (pre and post hemodialysis)
- Immunogenicity testing for anti-EPO antibody
- Adequacy of dialysis measurement by Kt/V formula
- Dose adjustment if required as per section 5.1.7

Visit 14: Week 28/Day 196 ± 2 days

- Demographic data (body weight: post hemodialysis)
- Vital signs
- Physical examination
- Adverse events
- Concomitant medication
- CBC
- Dose adjustment if required as per section 5.1.7

Visit 15: Week 32/Day 224 ± 2 days

- Demographic data (body weight: post hemodialysis)
- Vital signs
- Physical examination
- Adverse events
- Concomitant medication
- CBC
- Dose adjustment if required as per section 5.1.7

Visit 16: Week 36/Day 252 ± 2 days

- Demographic data (body weight: pre and post hemodialysis)
- Vital signs
- Physical examination
- Adverse events
- Concomitant medication

- Laboratory investigations [CBC, reticulocyte count, peripheral smear, renal function – Blood Urea Nitrogen (BUN: pre and post hemodialysis), serum creatinine, iron study, C-reactive protein (CRP), liver function test - Alanine Aminotransferase (ALT) Aspartate Aminotransferase (AST), alkaline phosphatase, peripheral smear, Immunogenicity testing for anti-EPO antibody]
- Chest X Ray
- Adequacy of dialysis measurement by Kt/V formula
- Dose adjustment if required as per section 5.1.7

Note: Window period for chest X Ray is ± 3days

Visit 17: Week 40/Day 280 ± 2 days

- Demographic data (body weight: post hemodialysis)
- Vital signs
- Physical examination
- Adverse events
- Concomitant medication
- CBC
- Dose adjustment if required as per section 5.1.7

Visit 18: Week 44/Day 308 ± 2 days

- Demographic data (body weight: post hemodialysis)
- Vital signs
- Physical examination
- Adverse events
- Concomitant medication
- CBC
- Dose adjustment if required as per section 5.1.7

Visit 19: Week 48/Day 336 ± 2 days

- Demographic data (body weight: pre and post hemodialysis)
- Vital signs
- Physical examination
- Adverse events
- Concomitant medication
- CBC

- Iron study
- BUN (pre and post hemodialysis)
- Adequacy of dialysis measurement by Kt/V formula
- Dose adjustment if required as per section 5.1.7

Visit 20: Week 52/Day 364 ± 2 days

- Demographic data (body weight: post hemodialysis)
- Vital signs
- Physical examination
- Adverse events
- Concomitant medication
- CBC
- Dose adjustment if required as per section 5.1.7

Visit 21: Week 56/Day 392 ± 2 days

- Demographic data (body weight: post hemodialysis)
- Vital signs
- Physical examination
- Adverse events
- Concomitant medication
- CBC
- Dose adjustment if required as per section 5.1.7

Visit 22: Week 60/Day 420 ± 2 days

- Demographic data (body weight: pre and post hemodialysis)
- Vital signs
- Physical examination
- Adverse events
- Concomitant medication
- CBC
- BUN (pre and post hemodialysis)
- Adequacy of dialysis measurement by Kt/V formula
- Dose adjustment if required as per section 5.1.7

6.5 End of Treatment / Study

Visit 23: End of study visit Week 64/ Day 448

- Demographic data (body weight: pre and post hemodialysis)
- Vital signs
- Physical examination
- Adverse events
- Concomitant medication
- Laboratory investigations (haematology, serum chemistry, urinalysis* and iron study and reticulocyte count) (refer Table in Appendix I)
- Chest X ray, ECG
- Serum Pregnancy Test (for all females of childbearing potential)
- Immunogenicity testing for anti-EPO antibody
- BUN (pre-and post Dialysis)
- Adequacy of dialysis measurement by Kt/V formula

*= Urinalysis test will be considered as optional for CKD patients as CKD patients may not be able to provide sufficient urine volume for urinalysis test due to low urine output.

Table 2: Study Visit Plan

		Screening	Titration period							Extended Titration period	Baseline*	Treatment Period														End of Study
S No.	*Procedures*	*V 0 (Day -31 to Day 0)*	*V1 (Wk 1/ Day 1)*	*V 2* (Wk 2/Day 14)	*V 3* (Wk 4/Day 28)	*V 4* (Wk 6/Day42)	*V 5* (Wk 8/Day 56)	*V 6* (Wk 10/Day 70)	*V 7* (Wk 12/Day 84)	*EV8/EV9/EV10/EV11*	*V 8 (Day 91/ Week 13)*	*V 9 (Wk 14/ Day 98)*	*V 10 (Wk 15/ Day 105)*	*V 11 (Wk 16/ Day 112)*	*V 12 (Wk 20/ Day 140)*	*V 13 (Wk 24/ Day 168)*	*V 14 (Wk 28/ Day 196)*	*V 15 (Wk 32/ Day 224)*	*V 16 (Wk 36/ Day 252)*	*V 17 (Wk 40/ Day 280)*	*V 18 (Wk 44/ Day 308)*	*V 19 (Wk 48/ Day 336)*	*V 20 (Wk 52/ Day 364)*	*V 21 (Wk 56/Day 392)*	*V 22 (Wk 60/ Day 420)*	*V 23 (Wk 64/Day 448)*
1	Informed Consent	X																								
2	Demographic Data[1]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
3	Medical History	X																								
4	*Menstrual and Reproductive History*	X																								
5	Physical/Clinical Examination[2]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
6	Vital signs[3]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
7	Inclusion & Exclusion Criteria	X																								
8	Eligibility Criteria										X															
9	Concomitant Medication[4]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
10	Peripheral smear	X			X		X		X	X									X							X
11	Complete Blood Count	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12	Reticulocyte Count	X							X	X			X						X							X
13	*Renal Function (BUN)*	X									X					X			X			X			X	X
14	*Iron study*	X						X			X			X		X			X			X				X
15	*CRP*																		X							
16	*Liver Function Test[5]*																		X							
17	*Serum Chemistry*	X																	X							X
18	*HbA1C*	X																								
19	*Urinalysis[#]*	X																								X
20	*Serology*	X																								X

21	***Fecal occult blood test[10] & intact parathyroid hormone***	*X*																							
22	***Immunogenicity testing***	*X*					*X*				*X*			*X*		*X*			*X*							*X*
23	***ECG***	*X*																							*X*
24	***Chest X Ray[9]***	*X*																	*X*						*X*
25	***Serum Pregnancy Test[6]***	*X*									*X*														*X*
26	***Randomization & Start of dosing[7]***										*X*														
27	***Adverse Events***		*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*
28	***IMP administration***		*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*
29	***Dose adjustment[8]***			*X*	*X*	*X*	*X*	*X*	*X*	*X*		*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	
30	***Kt/V assessment***	*X*									*X*					*X*			*X*			*X*			*X*	*X*

X = Activities applicable at the visit

*= Activities should be done prior to dosing

#= Urinalysis test will be considered as optional for CKD patients as CKD patients may not be able to provide sufficient urine volume for urinalysis test due to low urine output

1. Demographic data: includes date of birth, gender, race, pre and post hemodialysis body weight and height. Body weight of the subject should be captured at all the visits following screening.
2. Physical examination will include general appearance, skin, head, neck, ENT, heart, lungs, abdomen, extremities, neurological, musculoskeletal, and lymph nodes.
3. Vital signs: body temperature, heart rate, respiratory rate and systolic/diastolic blood pressure will be measured in a sitting position after a 5-minute rest.
4. Only those medications which are on-going at screening should be captured as concomitant medication at screening.
5. Liver Function Test includes ALT, AST and alkaline phosphatase
6. Serum pregnancy test only for female subjects with child bearing potential
7. Study medication should be administrated one to three times a week at the end of dialysis session

8. Dose adjustment if required as per section 5.1.7
9. Chest X ray performed within one year prior to screening of the subject is acceptable
10. Fecal occult blood test will be performed as per PI discretion.

Note: In substantiated cases, a prolongation of the titration period is allowed up to maximum of 4 to 5 months on a case to case basis which will be considered as extended titration period. The assessment will be similar to the visit 7 (week 12/Day 84) if there is prolongation of the titration period. Extended Week 14/Extended Day 98 is EV8, Extended Week 16/Extended Day 112 is EV9, Week Extended 18/Extended Day 126 is EV10 and Extended Week 20/Extended Day 140 is EV11

6.6 Protocol Deviations / Protocol Violations

After a subject is enrolled into the trial and is noticed to be noncompliant with inclusion and exclusion criteria, the same will be documented as a protocol violation(s). During the conduct of the trial process if deviation(s) are noticed from the norm mentioned in the protocol, the same will be documented as protocol deviation(s).

The investigator should conduct the study in compliance with the protocol agreed to by sponsor and, if required, by the regulatory authority (ies), and which was given approval/favorable opinion by the IRB/IEC. Any deviations from the protocol must be authorized in writing by sponsor prior to implementing the deviation except that a deviation to eliminate an apparent immediate hazard to a subject(s) may be implemented immediately. Sponsor must be notified of all intended or unintended deviations to the protocol (eg, inclusion/exclusion criteria, dosing, missed study visits) on an expedited basis.

The investigator, or person designated by the investigator, should document and explain any deviation from the approved protocol. The Investigator should notify the IEC or IRB of deviations from the protocol in accordance with local procedures.

Criteria for protocol deviation/ violation	
After a patient is enrolled into the trial and is noticed to be noncompliant with inclusion and exclusion criteria	Protocol violation
During the conduct of the trial process if deviation(s) are noticed from the norm mentioned in the protocol	Protocol deviation
Violation/deviation is not altering the integrity of the study plan or its safety and efficacy outcome	Minor
Violation/deviation is altering the integrity of the study plan or its safety and efficacy outcome	Major

7 EFFICACY ASSESSMENTS

The efficacy variables which will be assessed in this study are as follows:

- Mean absolute change in haemoglobin level (g/dl) in subjects before and after 6-months of treatment with EPIAO/EPREX
- Mean absolute change in weekly epoetin dosage per kg body weight (IU/kg/week) before and after 6-month treatment with EPIAO/EPREX.
- Proportion of subjects with any haemoglobin measurement outside the target range during the double-blind treatment period
- Incidence of blood transfusions

The haemoglobin assessment will be performed at all the scheduled visits and the epoetin dosage required for each subject will be calculated by the investigator and the same will be documented in the Electronic Case Report Form (eCRF).

8 SAFETY ASSESSMENTS

8.1 Adverse Events

All clinical adverse events occurring after the subject signs the ICF and up to 4 weeks after the last dose of study medication, whether observed by the investigator or reported by the subject, will be recorded on the Adverse Event CRF page. All serious adverse events (SAEs) are to be reported according to the procedures in Section 8.3 SAE Reporting-Procedure for Investigators. In addition, any untoward event that may occur subsequent to the reporting period that the Investigator assesses as related (definitely, possibly or probably) to study drug should also be reported and managed as an AE. Pre-planned procedure or hospitalization for pre-existing conditions which do not worsen in severity should not be reported as SAEs (see Section 8.1.1 for Definitions).

At each visit, the investigator will determine whether any adverse events have occurred by evaluating the subject. Adverse events may be directly observed, reported spontaneously by the subject or by questioning the subject at each study visit. Subjects should be questioned in a general way, without asking about the occurrence of any specific symptoms. All laboratory values must be appraised by the Investigator as to clinical significance. All post-baseline abnormal laboratory values considered clinically significant by the Investigator must be recorded in the adverse event page of the CRF.

Investigator should follow subjects with adverse events until the event has resolved or the condition has stabilized. In case of unresolved adverse events including significant abnormal laboratory values at the end of study assessment, these events will be followed up until resolution or until they become clinically not relevant.

8.1.1 Definitions

8.1.1.1 Adverse Event

Any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

An AE is therefore any unfavorable and unintended sign (an abnormal ophthalmic finding, for example), symptom (including physical, psychological or behavioral effect), or disease temporally associated with the use of a medicinal (investigational or marketed) product, experienced by a patient or subject during their participation in an investigational study, in conjunction with the use of the drug or biologic, whether or not considered product-related.

This includes any untoward signs, symptoms, illness or clinically significant laboratory test abnormality that has appeared or worsened during the course of the clinical trial, experienced by the subject from the time of signing the informed consent until completion of the study. Throughout the subject's participation in the study, any new clinically significant

findings/abnormalities that meet the definition of an adverse event must be recorded and documented as an adverse event.

8.1.1.2 Serious Adverse Event

During clinical investigations, AEs may occur which, if suspected to be drug-related (adverse drug reactions), might be significant enough to lead to important changes in the way the medicinal product is used or developed (e.g., change in dose, population, needed monitoring, consent forms). This is particularly true for reactions that, in their most severe forms, threaten life or function.

Any untoward medical occurrence that at any dose:

- Results in death,
- Is life-threatening,
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Results in persistent or significant disability/incapacity,
- Is a congenital anomaly/birth defect, or
- Is an important medical event.

Note: The term "life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situation, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. Examples include allergic bronchospasm, convulsions, and blood dyscrasias or development of drug dependency or drug abuse.

Note:

- A procedure is not an AE or SAE, but the reason for the procedure may be an AE.
- Pre-planned surgeries or hospitalizations for pre-existing conditions which do not worsen in severity are not SAEs.

Adverse Event Reporting Period

The study period during which adverse events must be reported is defined as the period from the initiation of any study procedures (after signing of ICF) up to 4 weeks after the last dose of study medication.

Medical History Condition

A medical history condition is any clinically significant medical/surgical condition already present at the time of screening *after informed consent.*

Pre-treatment *Adverse Events*

After informed consent during screening any clinically significant abnormality which meets the definition of AE should be recorded as a pre-treatment AE prior to the use of the product (Day 1) and should be recorded accordingly. Any new clinically significant event or worsening of existing medical history condition, which meets the definition of AE prior to the application of IP will also be considered as pre-treatment adverse event.

Post-treatment Adverse Events

All AEs recorded after the first dose of IP (Day 91) till the end of treatment will be considered as post-treatment AEs. Disease signs, symptoms and/or laboratory abnormalities already existing prior to the use of the product will not be considered as adverse experiences after treatment (post-treatment AEs) unless they reoccur after the subject/patient has recovered from the pre-treatment condition or they represent an exacerbation in intensity or frequency or the character of the condition worsens during the study period.

General Physical Examination Findings

At screening, any clinically significant abnormality should be recorded as a pre-existing condition. At the end of the study, any new clinically significant findings/abnormalities that meet the definition of an adverse event must also be recorded and documented as an adverse event.

Post-study Adverse Event

At the last scheduled visit, the investigator should instruct each subject to report any subsequent event(s) that occur within 14 days after discontinuation of treatment. The investigator should notify the sponsor of any death or adverse event occurring at any time after a subject has discontinued or terminated study participation that may reasonably be related to this study.

Abnormal Laboratory Values

A clinically significant laboratory abnormality should be documented as an adverse event if any one of the following conditions is met:

- The laboratory abnormality is not otherwise refuted by a repeat test to confirm the abnormality
- The abnormality suggests a disease and/or organ toxicity, then the underlying condition should be captured as an AE.
- The abnormality is of a degree that requires active management; e.g. change of dose, discontinuation of the drug, more frequent follow-up assessments, further diagnostic investigation, etc.

Lab abnormalities found during the screening tests will not be considered as adverse event.

Hospitalization, Prolonged Hospitalization or Surgery

Any adverse event that results in hospitalization or prolonged hospitalization should be documented and reported as a serious adverse event. Any condition responsible for surgery should be documented as an adverse event if the condition meets the criteria for an adverse event.

Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as an adverse event in the following circumstances:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for a pre-existing condition. Surgery should not be reported as an outcome of an adverse event if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study.
- Hospitalization or prolonged hospitalization for therapy of the target disease of the study, unless it is a worsening or increase in frequency of hospital admissions as judged by the clinical Investigator.

8.1.1.3 AE Severity

The following definitions should be used to assess intensity of adverse events:

- Mild: Symptom(s) barely noticeable to subject or does not make subject uncomfortable; does not influence performance or functioning; prescription drug not ordinarily needed for relief or symptom(s) but may be given because of personality of subject.
- Moderate: Symptom(s) of a sufficient severity to make subject uncomfortable; performance of daily activity is influenced; subject is able to continue in study; treatment for symptom(s) may be needed.
- Severe: Symptom(s) cause severe discomfort; symptoms cause incapacitation or significant impact on subject's daily life; severity may cause cessation of treatment with study treatment; treatment for symptom(s) may be given and/or subject hospitalization.

8.1.1.4 Causality Assessment

The relationship between an adverse event and the study product will be determined by the investigator on the basis or his/her clinical judgment and the following definitions:

- Definite: Causal relationship is certain. E.g. reasonable temporal relationship between drug exposure and AE, clinically compatible response to dechallenge, other causes eliminated, rechallenge response present definitive pharmacologically
- Probable: High degree of certainty for causal relationship. E.g. high degree of temporal relation between drug exposure & AE onset/course, clinically compatible response to dechallenge, other causes eliminated

- Possible: Causal relationship is uncertain /does not appear probable. Has a temporal relationship to the drug exposure but not a known or reported response to the drug, may be attributed to other causes also
- Unlikely: not reasonably related, however causal relationship can't be ruled out
- Not Related: No possible relationship, Causal relationship to study drug impossible

8.1.1.5 Action Taken Regarding the Study Product

1 = None

No change in study drug dosage was made.

2 = Discontinued Permanently

The study product was permanently stopped.

3 = Reduced

The dosage of study product was reduced.

4 = Interrupted

The study product was temporarily stopped.

5 = Increased

8.1.1.6 Adverse Event Outcome

1 = Recovered/Resolved

The subject fully recovered from the adverse event with no residual effect observed.

2 = Recovered/Resolved with Sequelae

The residual effects of the adverse event are still present and observable.

Identify sequelae/residual effects.

3 = Not Recovered/Not Resolved

The adverse event itself is still present and observable.

4 = Fatal

5 = Unknown

8.1.1.7 Other Action Taken for Event

1 = None.

2 = Medication required.

Prescription and/or Over the Counter (OTC) medication was required to treat the adverse event.

3 = Hospitalization or prolongation of hospitalization required.

Hospitalization was required or prolonged due to the adverse event, whether or not medication was required.

4 = Other.

8.2 Expected Adverse Events

The expected adverse events with the study drug are the following;

- Local pain
- Hypertension
- Headache
- Fever
- Skin rash
- Dizziness / hypodynia
- Local swelling
- Internal fistula obstruction
- Arthralgia
- Abdominalgia
- Nausea/vomiting
- Muscle pain
- High blood viscosity
- Epilepsy
- Stuffy nose
- Thrombosis
- Cerebral hemorrhage
- Diarrhoea
- Hyperkalemia
- PRCA

Preventive action for subject developing PRCA:

- Perform Anti- epoetin Antibody test at screening visit
- All high-risk patients will be excluded as per the inclusion and exclusion criteria.

- Performing regular test of immunogenicity at visit 5, 8, 11, 13, 16 and 23 to detect development of Anti- epoetin Antibody

Corrective action for patients developing PRCA:

- If immunogenicity test is positive, the epoetin treatment will be stopped and appropriate treatment will be provided to subject including kidney transplant. Cost of treatment will be supported by sponsor.

8.3 Serious Adverse Event Reporting Procedure for Investigators

8.3.1 Initial Reports

An event that is serious must be recorded on the SAE page of the CRF and requires expeditious handling and reporting to EA and the sponsor to comply with regulatory requirements.

A SAE, regardless of its relation to the study drug, must be reported to the study medical monitor EA by telephone or email within 24 hrs of the knowledge of event and the SAE form should be completed and faxed/mailed to the study medical monitor EA and Pharmacovigilance (PV) Cell within 24 hrs. Report serious adverse events by phone and facsimile to: **Medical Monitor**

Dr. Shivashankar P, MBBS, MD

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During this time a completed written report (SAE report form) must be completed and submitted (faxed or mailed) by the Investigator. For all SAEs, a SAE Report Form will include a detailed written description, copies of relevant subject/patient records, autopsy reports when available, and other documents which will be sent to EA medical monitor and PV cell within 24 hours. The causality assessment to the study medication should always be included. The investigator must complete, sign and date the SAE form, verify the accuracy of the information recorded on the SAE pages with the corresponding source documents, and send a copy (by fax/email) to EA monitor and PV Cell. The SAE information will be forwarded to the sponsor, within 24 hrs of knowledge of the event by EA / PV cell.

The PI will keep a copy of the SAE form in file at the study site. The subject identity should not be disclosed by the investigator while reporting SAE, unless specifically asked by the regulatory body or ethics committee. In case of emergency or occurrence of SAE, which requires unblinding of study medication for a subject, investigators will be able to access this information via IVRS/IWRS (see section 5.1.6).

All SAE communications and pregnancy notifications will be forwarded to the sponsor by EA /PV Cell within 24 hours of the knowledge of the event, by confirmed facsimile transmission or mailing of the completed SAE page. A facsimile transmission does not preclude mailing of the SAE page. At the time of the initial report, the following information should be provided:

• Subject Initials • Subject number • A description of SAE – Date of onset – Current status – De-challenge and re-challenge information (if applicable) – Setting – Outcome • Investigator assessment of the association between the event and drug	• Suspected drug details: – Generic name – Indications – Dosage of the drug administered to the subject – Route of administration – Start and stop date and time. • Other treatments • Details of the Investigator

8.3.2 Follow-up Reports

Significant new/follow-up information on ongoing SAE (hospital discharge summaries, operative reports etc.) should be sought after and a follow-up SAE form should be completed and submitted promptly to the Medical Monitor and PV Cell within same 24 hours deadline from the time of receipt of the information. A designation of causality from the study medication should always be included with a follow up report. All follow-up SAE reports will also be forwarded to the Sponsor within 24 hrs of PV cell receiving the information.

8.3.3 Notifying Investigators or Ethics Committee/Institutional Review Board

Sponsor and/or EA will undertake to inform Investigators of any serious, unexpected (not listed in the Investigator's Brochure) and related AEs occurring in other study centers or other studies of the investigational product, as appropriate.

Reports of all SAE (and follow-up information) must be submitted to the IEC of the site where the SAE occurred within 7 working days of occurrence of event. It is the responsibility of the PI to notify the IEC. Copies of each report and documentation of IEC notification and acknowledgement receipt will be kept in the investigator site file and the same will be sent to EA medical monitor and PV Cell EA by fax or email.

8.3.4 Regulatory Notification by Ecron Acunova Ltd

All SAEs including the suspected unexpected serious adverse reactions (SUSAR) (as defined in GCP Guidelines) occurring during the clinical trial will be communicated to applicable regulatory agency within 7 calendar days for AEs which are result in death/be life-threatening and within 15 days for AEs that are not life-threatening and to the other Investigator (s) participating in the study within the applicable timelines by the EA as per EA's SOPs.

If a previous AE(s) that was not initially deemed reportable is later found to fit the criteria for reporting, EA will submit the adverse event in a written report to the applicable regulatory agency as soon as possible, but no later than 15 calendar days from the time the determination is made.

8.4 Exposure in Utero during Clinical Studies

If a subject becomes pregnant any time after receiving a study treatment, she must not receive additional study treatment and must be discontinued from the study. The subject must be followed until the outcome of the pregnancy is known (i.e., delivery, elective termination, or spontaneous abortion). If the pregnancy results in the birth of a child, additional follow-up information may be requested.

The Investigator must notify EA within 24 hours of first learning of the occurrence of pregnancy using the Pregnancy Notification Form and faxing it to EA providing as much information as possible. The Investigator must notify EA about reported complications within 24 hours using the same procedure. Outcome of pregnancy once known by the Investigator must also be reported to EA within 24 hours using the Pregnancy Outcome Form and faxing it to EA. Pregnancy communications will be directed to:

Ecron Acunova
Fax: +91 (0) 80 6691 5719

Please note that pregnancy in and of itself is not an AE or SAE. Pregnancy should not be entered into the CRF as an AE unless the Investigator suspects an interaction between the study treatment and contraceptive method. Pregnancy will be documented as the reason for study discontinuation.

EA will direct the pregnancy communication to sponsor as soon as they are received.

8.5 Clinical Laboratory Evaluations

All laboratory values outside the normal range will be evaluated for clinical significance by the investigator and annotated as Clinically Significant (CS) or Not Clinically Significant (NCS). Subjects with values outside of the normal range (at the screening visit) may continue in the study at the Investigator's discretion or be withdrawn for further investigation.

All the laboratory investigations will be conducted in the respective site lab while the immunogenicity test will be conducted in Laboratory at HIV Netherlands Australia Thailand Research Collaboration (HIV-NAT) (Chula CRL). The valid list of reference ranges including the

methods for all parameters of central laboratory, and quality certificates will be provided to the sponsor prior to the start of the study.

Following laboratory tests will be performed during screening, titration period [week 12/Day 84 (visit 7)], extended titration period (in substantiated cases) and end of the study.

Haematology:

- Haemoglobin
- Haematocrit
- Total White Blood Cell (WBC) count
- Differential WBC count
- Platelet count
- RBC count
- Reticulocyte count
- Mean Corpuscular Volume (MCV)
- Mean Corpuscular Haemoglobin (MCH)
- Mean Corpuscular Haemoglobin Concentration (MCHC)
- Peripheral smear

Additionally, CBC (haemoglobin, haematocrit, total WBC count, differential WBC count, platelet count and RBC count) will be performed at all the visits, reticulocyte count will be performed at visit 7 (week 12/Day 84) only during titration period and visit 16 (week 36/Day 252). Peripheral smear will be performed at visit 16 (week 36/Day 252).

Serum chemistry:

- Fasting blood glucose
- Sodium
- Potassium
- Chloride
- BUN
- Serum creatinine
- Total bilirubin
- Total protein
- ALT

- AST
- Total cholesterol
- C-Reactive Protein
- Alkaline Phosphatase
- HbA1C*

These tests will be performed during screening and end of the study visit 23 (week 64/ Day 448). Additionally, BUN (pre and post haemodialysis) will be done on visit 8 (Day 91/week 13), visit 13 (week 24/Day 168), visit 16 (week 36/Day 252), visit 19 (week 48/ Day 336) and visit 22 (week 60/ Day 420), serum creatinine, CRP, liver function test – ALT, AST and alkaline phosphatase will be performed at visit 16 (week 36/ Day 252).

*HbA1C will be done at screening visit.

Serology

- HBV (HBsAg and IgM anti-HBc) & HCV (Anti-HCV antibody)
- IgM anti-HBC is optional for Russian sites.

These tests will be performed during screening visit.

Urinalysis:

- Colour
- Transparency
- pH
- Specific gravity
- Protein
- Glucose
- Ketone bodies
- Bilirubin
- Blood
- Nitrite
- Urobilinogen
- Microscopic examination

These tests will be performed during screening and end of the study visit 23 (week 64/ Day 448).

Serum Beta HCG at screening, baseline visit (visit 8/Week 13/Day 91) and end of study visit 23 (week 64/Day 448)

Immunogenicity assessments

- Anti- epoetin Antibody by Radio Immunoprecipitation (RIP) Assay

For determination of anti-epoetin antibodies in human serum samples a RIP-assay will be employed. Serum samples for immunogenicity assessments will be collected at screening, baseline visit (visit 8/Week 13/Day 91), visit 5 (week 8/Day 56), visit 11 (week 16/Day 112), visit 13 (week 24/Day 168), visit 16 (week 36/ Day 252) and visit 23 (week 64/ Day 448).

The samples will be frozen at -80º C (for long term storage) or -20º C (for storage of 3 – 4 months) and kept until analysis in a central laboratory. In all patients, the last available blood sample will be analysed first. The last available sample for the interim analysis will be visit 16 (week 36) and for the end of the study analysis will be visit 23 (week 64/Day 448). Only if anti-epoetin antibodies are detected, all previous blood samples for the respective patient will be analysed in order to detect the time point of first occurrence.

The blood samples from the Russian centers will be shipped to the Laboratory at Chulalongkorn hospital. Blood samples of subjects who test positive for anti-epoetin antibody will be retained for lifelong years while the negative samples will be retained for one year from testing.

Apart from the above-mentioned visits, if the any of the following develop suggestive of possible antibody-mediated PRCA, the investigator can test for anti-epoetin antibody. A positive antibody test will be confirmed by bone marrow biopsy to rule of the incidence of PRCA.

- Sudden rapid decrease in haemoglobin concentration at the rate of 0.5 to 1.0 g/dl OR requirement of transfusions at the rate of approximately 1 to 2 per week, AND
- Normal platelet and white cell counts, AND
- Absolute reticulocyte counts less than 10,000/µL. This test will be performed with every visit when the CBC was done
- The investigational product must be temporarily withheld until the result of immunogenicity assessments is shown negative, IP can be re-started upon confirmation of negative test for immunogenicity..

Fecal occult blood test

This test will be performed during screening visit as per PI discretion

Iron study

- Serum ferritin level
- Transferrin saturation (TSAT)
- Serum iron

- Total Iron Binding Capacity (TIBC) (optional)

These tests will be performed during screening, baseline visit (visit 8/Week 13/Day 91), visit 11 (week 16/Day 112), visit 13 (week 24/ Day 168), visit 16 (week 36/Day 252), visit 19 (week 48/Day 336) and visit 23 (week 64/ Day 448).

Intact parathyroid hormone level

This test will be performed during screening visit

8.6 Vital Signs

The vital signs - pulse, temperature, respiration rate, and BP (with the subject in sitting position for at least 5 minutes), data will be collected and documented at every visit. Changes to vitals from screening to end of trial will be recorded as AEs if the Investigator judges these as being clinically significant.

8.7 Electrocardiograms & Chest X-Ray

ECG and chest X ray will be performed at screening (Chest X ray performed within one year prior to screening of the subject is acceptable and need not be performed at the time of screening) and the end of the study visit [visit 23 (week 64/Day 448)]. Chest X ray will be performed at visit 16 (week 36/Day 252) also.

8.8 Physical Findings

The physical examination, data will be collected and documented at every visit. Changes to physical examination from screening to end of trial will be recorded as AEs if the Investigator judges these as being clinically significant.

8.9 Other Safety Assessments

The most frequent adverse drug reaction during treatment with epoetin is a dose-dependent increase in blood pressure or aggravation of existing hypertension. Special care should be taken to closely monitor and control blood pressure in subjects treated with epoetin. If blood pressure is difficult to control after initiation of appropriate measures, the dose of epoetin should be reduced or temporarily withheld until haemoglobin begins to decrease. An increased incidence of thrombotic vascular events has been observed in patients receiving epoetin. These include venous and arterial thrombosis and embolism (including some with fatal outcomes), such as deep venous thrombosis, pulmonary emboli, retinal thrombosis and myocardial infarction.

Hence adverse events of specific interest include hypertension/aggravation of hypertension and thromboembolic events.

9 STATISTICAL METHODS

9.1 Analysis Sets

Three cohorts will be considered for the analysis: The modified intention-to-treat (mITT) cohort, per protocol (PP) and safety cohort. Per-Protocol cohort population will be considered as primary population for analysis of efficacy.

Modified Intention-to-treat Cohort:

All randomized subjects who receive study medication, have a baseline and at least one post-treatment measurement will be included in the MITT Cohort.

Per-protocol Cohort:

All randomized subjects who complete both the baseline visit and end of treatment visit and who have no major protocol violations will be included in the PP population. Subjects with major protocol violations will be excluded from this cohort.

Detailed description of what constitutes a protocol violation will be defined in the SAP.

Safety Cohort:

All subjects who are randomized at baseline visit will be included in the safety analyses for safety endpoints.

9.2 General Statistical Considerations

Analysis for all efficacy endpoints using the PP population will be the primary approach for analysis. Secondary analysis will be performed using the mITT population. For safety endpoints using the safety cohort will be the primary approach for analysis.

The SAS® package (SAS® Institute Inc., USA, and Version 9.2 or higher) will be used for statistical evaluation.

Descriptive statistics, such as mean, standard deviation, median, minimum and maximum values will be provided for the continuous variables and the number of observations and percentage will be provided for the categorical variables.

9.2.1 Missing data

Efficacy

No imputation will be done on missing efficacy data.

Safety

No imputation will be done on missing safety data, unless otherwise stated below

Dates

Dates of remote events (e.g. AEs or concomitant medication) may be partially incomplete, as the day and/or month may be unknown. AEs with incomplete start dates will be considered as

treatment emergent, only if they are definitely known to have started after randomization. For treatment, emergent AEs with incomplete start dates (unknown date and known month), the start date will be taken as the first of the corresponding month or date of randomization, whichever is later. Incomplete dates for concomitant medications will not be imputed.

9.3 Study Population Data

The following demographic and baseline characteristics will be summarized by treatment group as follows: age, weight, gender, race and vital signs.

For continuous measurements such as age, the mean, median, standard deviation and range will be tabulated.

For categorical measurements such as gender, the frequencies will be computed.

9.4 Efficacy Analyses

9.4.1 Primary Efficacy Analyses

- Mean absolute change in haemoglobin level from baseline to 6 months after treatment with EPIAO/EPREX in parallel groups (g/dl).
- Mean absolute change in weekly epoetin dosage per kg body weight from baseline to 6 months after treatment with EPIAO/EPREX in parallel groups (IU/kg/week).

The ANCOVA will be performed based on the normality of data for mean change between baseline to 6 months of EPIAO and EPREX with center, Hb level and weight as covariates. The 95% confidence intervals will be calculated for the treatment differences and is compared with pre-defined acceptance ranges: ±0.5 g/dl for haemoglobin.

The ANCOVA will be performed based on the normality of data for mean change in weekly epoetin dosage per kg body weight baseline to 6-month treatment with EPIAO and EPREX with center, Hb level and weight as covariates. The 95% confidence intervals will be calculated for the treatment differences and is compared with pre-defined acceptance ranges: ±45 IU/kg/week for dosage.

9.4.2 Secondary Efficacy Analyses

- Proportion of subject's hemoglobin values are within 10 - 12 g/dl for the last 4 weeks of the period for assessment of treatment efficacy and safety (Weeks 32-36)
- Proportion of subjects with any haemoglobin measurement outside the target range during the double-blind treatment period
- Mean hemoglobin and hematocrit levels every 4 weeks within treatment period (52 weeks)
- Mean doses of the study products (IU/kg/week) every 4 weeks throughout the study period (52 weeks)
- Incidence of blood transfusions

The appropriate descriptive statistics or frequency and percentages will be presented for the secondary end point. Other analysis will be carried out as deemed appropriate.

9.5 Safety Analyses

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

Safety will be assessed by physical examination, vital sign, laboratory test, immunogenicity and adverse event recording. Summary statistics will be provided for the laboratory, ECG, physical examination, immunogenicity and vital signs data. Frequency and percentage of the incidence of adverse event, nature of adverse event and incidence of drug related adverse event will be presented in the treatment group. Summary statistics will be presented for the occurrence of PRCA.

9.5.1 Adverse Event Analyses

All adverse events will be summarized in terms of severity, relation to study treatment, duration, action taken and subjects outcome. The number and the proportion of subjects who experienced AEs will be computed by treatment group, classified by Medical Dictionary for Regulatory Activities (MedDRA) Primary System Organ Class and Preferred Terms.

9.5.2 Clinical Laboratory Evaluation Analyses

Descriptive statistics, such as mean, standard deviation, median, minimum and maximum values will be provided for the continuous variables and the number of observations and percentage will be provided for the categorical variables.

9.5.3 Vital Sign Analyses

Descriptive statistics such as mean, standard deviation, median, minimum and maximum values will be presented.

9.5.4 Physical Finding Analyses

Descriptive statistics such as number of observation and percentage will be presented.

9.5.5 Concomitant Medications:

Proportion of subject who used concomitant medication during the study period will be computed by treatment group, classified by World Health Organization Drug Dictionary enhanced (WHO - DDE) Preferred Names. Concomitant medication will be coded using the WHO - DD enhanced version, classified by preferred names, and the categories tabulated and summarized.

9.6 Interim Analysis

An interim analysis will be conducted to evaluate the therapeutic equivalence of EPIAO with the standard treatment EPREX after a treatment period of 24 weeks. The analysis will be performed by an independent statistician, who is not involved in the trial conduct other than this interim analysis. The independent statistician will be unblinded and will conduct the analysis using actual treatment assignments. This interim analysis will be conducted after all the randomized patients complete the Visit 16 (Week 36/Day 252). The results of the interim analysis will be communicated to Independent sponsor representative. All other personnel involved in the study will remain blinded. The analysis will be performed in terms of efficacy, safety and immunogenicity between the treatment arms as per the final analysis stated in section 9.

The sponsor of the study wishes to use the data from the interim analysis to plan for registration of EPIAO in other countries where it is yet to be marketed. An interim report will be used to meet the requirement for local registration. A complete analysis will be conducted at the end of the treatment period.

9.7 Safety Monitoring Committee (SMC)

The SMC will consist of 3 doctors independently from the study centers. The SMC will meet at least every 6 months to review the safety data from the study. The SMC can also meet on an ad-hoc basis in case of an occurrence of an SAE.

9.8 Sample Size Determination

A sample size of 112 subjects per group is calculated to achieve a power of more than 80% for proof of equivalence for both co-primary endpoints. Considering 2 stratification factors i.e. body weight (Kg): ≤58, 59-74 & ≥75, Hb level (g/dl): 10 – 11 & > 11 – 12 and to balance between the two treatment groups in Thailand and Russia, the total number of subjects to be randomized is estimated to be 264 (n=132 subjects in each group) since a drop-out rate of approximately 18% was expected.

10 DATA INTEGRITY AND QUALITY ASSURANCE

The Investigator/investigational site will permit study-related monitoring, audits, IRB/IEC review and regulatory inspections by providing direct access to source data/documents. Direct access includes permission to examine, analyze, verify, and reproduce any records and reports that are important to the evaluation of a clinical study.

10.1 Study Monitoring Plan

Before the first subject is recruited into the study, the monitor(s) of EAL will visit the selected clinical study facilities to:

- Determine the adequacy of the clinical study facility
- Discuss with the Investigator(s) (and other personnel involved with the study) their responsibilities with regard to protocol adherence and other responsibilities

During the progress of the study, the monitor(s) from EA will have regular contacts with the clinical study facility, including visits at regular intervals to:

- Provide information and support to Investigator(s)
- Confirm the continued adequacy of the clinical study facility
- Confirm that the investigational team is adhering to the protocol, GCP and applicable regulatory requirements
- Perform source data verification (a comparison of the data in the eCRFs with the subject's medical records, and other records relevant to the study).
- Check that the data are being accurately and completely recorded in the eCRFs, and that drug accountability checks are being performed
- Verify the protection of the rights and well-being of the subjects

During these visits, CRFs and supporting documentation related to the study will be reviewed and any discrepancies or omissions or any other issues will be resolved. The monitor or another EA representative will be available between visits if the investigator(s) or other staffs need information or advice.

After each monitoring visit, the monitor will prepare a monitoring report. A follow up letter will be prepared and sent to the investigator for activities done and the resolution plan, if any. These all activities will be as per the current version of EA SOP's.

The Principal Investigator will also ensure that the monitor or other compliance or quality assurance reviewer is given access to all the above noted study-related documents and study related facilities (e.g. pharmacy, etc.), and has adequate space to conduct the monitoring visit.

The Investigator agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits are addressed and documented.

10.2 Data Collection

The study CRF is the primary data collection instrument for the study. Data will be collected using electronic case report forms (eCRFs) that are specifically designed for this study. The eCRFs are used to record study data and are an integral part of the study and subsequent reports. Therefore, the eCRFs must be completed for each subject screened or enrolled according to the subject's source data. All the eCRF entries should be made according to the instructions given in the investigator's Remote Data Capture (RDC) manual.

If applicable, subjects are to be identified by initials, birth date and subject number. All data requested will be first recorded on the source document and then on the CRF. Data will be entered at the site by the appropriately designated and trained site personnel.

Each entered eCRF must be approved by the site investigator, verified against the subject's source documents by the Clinical Research Associate (CRA)/monitor and reviewed by Data Management prior to locking the database. Once all the eCRFs for a subject have been completed, approved, verified, reviewed and cleaned, the subject's eCRFs will be locked.

10.3 Data Management

Data management will be handled by EA. EA shall ensure that clinical study data collected throughout the trial are complete, accurate and of the highest quality and shall be performed in accordance with applicable ICH guidelines and regulations. All the source documents will be maintained at the study site for audit and monitoring purposes.

Data Management Plan (DMP) shall include all general and study-specific data management processes and will identify the applicable processes, the people responsible for performing it, all relevant SOPs to be used and what is expected as output/ documentation.

CRFs shall be made available to the data management site in electronic format. Clinical data discrepancies will be identified and data queries shall be resolved depending on the type of query as described in the DMP. Types of data to be coded will include, but may not be limited to, adverse events and medications. Adverse events will be coded using the MedDRA (latest version) adverse experience coding dictionary. Medications will be coded using the WHO – DDE (latest version).

Periodic reviews of the safety database and the clinical database will occur to ensure consistency between the databases. The protocol and/or CRFs may be amended after the database and DMP have been approved. If changes to the database structure, database contents, or DMP are needed, appropriate documentation, re-validation and approval will occur as necessary.

All data management documentation collected and stored by EAL during the course of study will be sent to Sponsor at study closeout as determined by the study team. This documentation will include, but is not limited to, subject folders, database specifications, the DMP with any amendments, etc.

Source documentation supporting the CRF data (lab reports for pregnancy test etc.) should indicate the subject's participation in the study and should document the dates and details of study procedures, AEs, and subject status. For subjects who discontinue or terminate from the study, the CRFs will be completed as much as possible, and the reason for the discontinuation or termination clearly and concisely specified on the Study exit Form. All CRFs must be kept current so that they always reflect the latest observations on the subjects participating in the study.

10.4 Study Documentation and Storage

The Investigator will maintain a Signature List of appropriately qualified persons to whom he/she has delegated study duties. All persons authorized to make entries and/or corrections on case report forms will be included on the Signature List.

Source documents are original documents, data, and records from which the subject's case report form data are obtained. These include but are not limited to hospital records, clinical and office charts, laboratory and pharmacy records, diaries, microfiches, X-rays, and correspondence.

The Investigator and study staff are responsible for maintaining a comprehensive and centralized filing system (Trial Master File) of all study-related (essential) documentation, suitable for inspection at any time by representatives from sponsor and/or applicable regulatory authorities.

Essential documents include:

- Subject files containing demographic information, evidence supporting the diagnosis/condition for which the subject is being studied, general information supporting the subject's participation in the study, general history and physical findings, hospitalization or emergency Room records (if applicable), each study visit by date, including any relevant findings/notes by the investigator(s), occurrence (or lack) of AEs, and changes in medication usage, including the date the study drug commenced and completed, any additional visits during the study, any relevant telephone conversations with the subject regarding the study or possible adverse events
- An original, signed informed consent form for study participation and supporting copies of source documentation (if kept).
- Study files containing the protocol with all amendments, Investigator's Brochure, copies of relevant essential documents required prior to commencing a clinical study, and all correspondence to and from the IRB and sponsor.
- Records related to the IP(s) including acknowledgment of receipt at site, accountability records and final reconciliation and applicable correspondence.
- The investigator must also retain all subject specific printouts/reports of tests/procedures performed as a requirement of the study. During monitoring visits the monitor will need to validate data in the eCRFs against these sources of data.

In addition, all original source documents supporting entries in the case report forms must be maintained and be readily available.

During this study, an Investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation on each individual treated with the investigational product or entered as a control in the investigation. Data reported on the eCRF, that are derived from source documents, must be consistent with the source documents or the discrepancies must be explained. In accordance with the applicable regulatory requirement(s), the confidentiality of records that could identify subjects must be protected, respecting the privacy and confidentiality rules.

Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical

development of investigational product. These documents should be retained for a longer period however if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

10.5 Record Keeping

Records of subjects, source documents, monitoring visit logs, inventory of study product, regulatory documents (eg, protocol and amendments, IRB/EC correspondence and approvals, approved and signed informed consent forms, Investigator's Agreement, clinical supplies receipts, distribution and return records), and other sponsor correspondence pertaining to the study must be kept in appropriate study files at the site.

Source documents include all recordings and observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical study. These records will be retained in a secure file for the period required by the institution or site policy. Prior to transfer or destruction of these records sponsor must be notified in writing and be given the opportunity to further store such records.

In the event of PI withdraws from the study (*e.g.,* relocation, retirement), the records shall be transferred to a mutually agreed upon designee (*e.g.,* another Investigator, IRB). Notice of such transfer will be given in writing to Sponsor.

10.6 Audits and Inspections

Authorized representatives of sponsor, EACL, a regulatory authority, an IEC or an IRB may visit the center to perform audits or inspections, including source data verification. During this visit, they will be allowed access to eCRFs, source documents and other study files. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, GCP, guidelines of ICH and any applicable regulatory requirements. The investigator should contact EA immediately if contacted by a regulatory agency about an inspection at his or her center.

10.7 Training of Staff

The PI will maintain a record of all individuals involved in the study (medical, nursing and other staff). He or she will ensure that appropriate training relevant to the study is given to all of these staff members, and that any new information of relevance to the performance of this study is forwarded to the staff involved. There will be training and information on all study related processes at an Investigators start up meeting and at local initiation and monitoring meetings.

10.8 Changes to the Protocol

The study shall be conducted as described in this approved protocol. Any significant deviation must be documented in the eCRF. All revisions of the protocol will be discussed with sponsor or sponsor's representatives. The study procedures will not be changed without the mutual agreement

of EA and the sponsor. Administrative changes also require the mutual agreement of EA and sponsor.

In the event a deviation or change to a protocol is implemented to eliminate an immediate hazard(s) prior to obtaining IRB/IEC approval/favorable opinion, as soon as possible the deviation or change will be submitted to:

- IRB/IEC for review and approval/favorable opinion
- Sponsor
- Regulatory Authority(ies), if required by local regulations

Documentation of approval signed by the chairperson or designee of the IRB(s)/IEC(s) must be sent to the sponsor. If it is necessary for the study protocol to be amended, the amendment or a new version of the study protocol (AMENDED Protocol) must be provided to or approved by IEC, and if applicable, also the regulatory authority, before implementation. In the event an amendment substantially alters the study design or increases the potential risk to the subject:

1. The consent form must be revised and submitted to the IRB(s)/IEC(s) for review and approval/favorable opinion;
2. The revised form must be used to obtain consent from subjects currently enrolled in the study if they are affected by the amendment; and
3. The new form must be used to obtain consent from new subjects prior to enrollment.

EA will distribute amendments and new versions of the protocol to the principal investigator or designee, who in turn is responsible for the distribution of these documents to IEC / IRB. The distribution of these documents to the regulatory authority will be handled by EA.

10.9 Protocol Deviations and Violations: Condition where the Study will be terminated

After a subject is enrolled into the trial and is noticed to be noncompliant with inclusion and exclusion criteria, the same will be documented as a protocol violation(s). During the conduct of the trial process if deviation(s) are noticed from the norm mentioned in the protocol, the same will be documented as protocol deviation(s).

The severity of the protocol violation and protocol deviation will be graded as minor if the violation/deviation is not altering the integrity of the study plan or its safety and efficacy outcome, as major if the violation/deviation is altering the integrity of the study plan or its safety and efficacy outcome.

Sponsor reserves the right to terminate the study at any time and bears the responsibility for informing applicable regulatory authorities. Whereas the principal investigator reserves the right to discontinue the study for safety reasons at any time and bears the responsibility to inform the IEC. The reason for this termination will be provided to the subjects.

11 FINANCING AND INSURANCE

11.1 Finances

Prior to starting the study, the Principal Investigator and/or institution will sign a clinical study agreement with EA. This agreement will include the financial information agreed upon by the parties.

11.2 Reimbursement, Indemnity, and Insurance

Reimbursement, indemnity and insurance shall be addressed in a separate agreement on terms agreed upon by the concerned parties.

12 ETHICAL CONSIDERATIONS

This study will be consistent with GCP and applicable regulatory requirements and will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

The study will be conducted in compliance with the protocol. The protocol and any amendments and the subject informed consent must receive IRB/IEC approval/favorable opinion prior to initiation of the study. Freely given written informed consent must be obtained from every subject prior to clinical trial participation. The rights, safety and well-being of the trial subjects are the most important considerations and should prevail over interests of science and society. Study personnel involved in conducting this trial should be qualified by education, training, and experience to perform their respective task(s). This trial will not use the services of study personnel where sanctions have been invoked or where there has been scientific misconduct or fraud (*e.g.,* loss of medical licensure, debarment).

Systems with procedures will be implemented to assure the quality of every aspect of the study.

12.1 IEC Review and Communications

This protocol and any amendments will be submitted to IEC / IRB in agreement with local regulations, for formal approval of the study to be conducted. The opinion of the IEC/ IRB concerning the conduct of the study will be made in writing to the Investigator and a copy of this decision will be provided to the Sponsor before commencement of this study. The Investigator will provide a list of IEC / IRB members and their affiliate to the Sponsor.

12.2 Informed Consent Process

The subject's written informed consent should be obtained prior to his/her participation in the study, and should be documented in the subject's medical records. The principal investigator(s) at each center will ensure that the subject is given full and adequate oral and written information about the nature, purpose, possible risk and benefits of the study. The procedures to be carried out and the possible potential hazards will be described to the subjects in a language which the subject comprehends. The subject will be required to read and sign the consent form summarizing the discussion prior to enrolment in the study. A copy of the written informed consent form will be given to the subject, which describes the study procedures including the clinical/laboratory tests

and the possible potential hazards in non-technical terms in conformity with regulatory requirements. If the subject is unable to read, an impartial witness should be present during the entire informed consent discussion. After the written informed consent form and any other written information to be provided to subject is read and explained to the subject in a language understood by him / her and if the subject has orally consented to his participation in the screening/study, the witness should sign and personally date the consent form. By signing the consent form, the witness attests that the information in the consent form and any other written information was accurately explained to and apparently understood by the subject and that the informed consent was freely given by the subject. The ICF will be signed and dated by the subject and the PI or designee.

The consent form will include a statement that the sponsor or designated sponsor's representatives), ethics committee and regulatory authorities will have direct access to subject records. The Investigator must have the IRB/IEC's written approval/favorable opinion of the written informed consent form and any other information to be provided to the subjects prior to the beginning of the study.

The ICF provided to subjects or the subject's legally acceptable representative, should be revised whenever important new information becomes available that is relevant to the subject's consent, and they should receive IRB/IEC approval/favourable opinion prior to use. Any updates to the consent form and any updates to the written information will be provided to the subject during a subject's participation in the trial.

12.3 Statement of Subject Confidentiality Including Ownership of Data

The records of the subject's medical history, physical examination, laboratory results and any other information or data generated during the study will be made available to sponsor or its designees (auditors, monitors), ethics committee and will be made available to drug regulatory bodies in Thailand and Russia and possibly other countries, formulary committees of hospitals, at the opinion of the sponsor. A pre-condition for entry into this study will be subject's agreement to release all of the above-mentioned documentation and data for any lawful purpose. In such cases, the subjects name will be removed from all documentation to ensure anonymity.

12.4 Termination of Study

The Sponsor and the IEC/ IRB reserve the right to terminate the study at any time. The reason for this termination will be provided to the subjects. The PI reserves the right to discontinue the study for safety reasons at any time.

13 PUBLICATION POLICY

The data generated from the study is exclusive property of the sponsor. Prior permission of the sponsor is required to publish/present this data by any study investigators/CRO.

By signing this protocol the Investigator reaffirms to the Sponsor that he / she will maintain in confidence all information furnished to him / her, or resulting from this study. He / She will only divulge such information as may be necessary to the IEC/IRB and the members of the staff and the subjects who are involved in this study.

The results of the study including all obtained data will be the property of the sponsor. However, the investigator may seek permission to publish results of the study from the sponsor. Unpublished data cannot be disclosed to any third party by the investigators without the written approval of sponsor.

14 SPECIAL CONSIDERATIONS

14.1 Procedures in Case of Medical Emergency

In a medical emergency requiring immediate attention, study staff will apply appropriate medical intervention, according to current standards of care. Regulatory authorities and IEC/ IRB will be notified of the event(s) when applicable.

14.2 Investigator's Responsibilities

The Investigators responsibilities involves the following-

1. Monitor and record all AE(s), which includes SAE(s), regardless of the severity or relationship to IP.
2. Determine the seriousness, relationship, and severity of each event.
3. Determine the onset and resolution dates of each event.
4. Complete an SAE form for each SAE and fax it to the medical monitor within 24 hours of the study site staff becoming aware of the event.
5. Pursue SAE follow-up information actively and persistently. Follow-up information must be reported to the medical monitor within 24 hours of the study site staff becoming aware of the information and to IEC within 7 working days.
6. Ensure all AE and SAE reports are supported by documentation in the subject's medical records.
7. Notification of the Ethics Committee must be sent to the Sponsor or designee in a timely manner.
8. During and following the subject's participation in the trial, the investigator should ensure that adequate medical care is provided to the participant for any adverse events.

14.3 In case of pregnancy

- To ensure subject safety, each pregnancy in a subject on study drug must be reported to EA within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.
- If a female subject becomes pregnant, study treatment must be discontinued immediately.

- The Investigator must report pregnancies (female subjects and male subject's partners), by faxing the appropriate form or by other communication means, to the EA Medical Monitor within 24 hours of the study site staff becoming aware of the pregnancy. The investigator or study site staff must report the outcome of pregnancy to the safety Medical Monitor and follow-up on the status of the infant.