STATISTICAL ANALYSIS PLAN

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

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

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1. Definition of analysis group

1.1. Safety Set

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

1.2. Full Analysis Set (FAS)

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

1.3. Per-Protocol Set (PPS)

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

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

2. General principle of statistics

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

Analysis of demographic data and baseline characteristics

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

3. Efficacy Analysis

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

3.1. Primary Endpoint

Change in Hb levels from baseline to the evaluation period

Descriptive statistics will be provided by treatment group. The difference between treatment groups will be determined by ANCOVA (analysis of covariance) model with treatment as factor, and baseline Hb level and the change in weekly dosage per kg body weight from baseline to the evaluation period of Epodion® or Eprex® as covariates. Therapeutic equivalence of Epodion® to the comparator Eprex® will be demonstrated if the two-sided 90% confidence interval of the difference of mean changes in Hb levels between treatment groups lay within the interval of ± 0.5 g/dL.

3.2. Secondary Endpoint

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

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

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

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

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

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

3.3. Safety Analysis

Safety analysis will be performed using the Safety Set.

3.3.1. Adverse events (AEs)

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

3.3.1.1. Treatment-emergent adverse events (TEAEs)

3.3.1.2. Adverse Drug Reactions (ADRs)

3.3.1.3. Serious TEAEs/ADRs

3.3.1.4. TEAEs/ADRs leading to investigational product discontinuation

3.3.1.5. TEAEs/ADRs leading to death

3.3.2. Vital sign, Laboratory test

Summary statistics for change from baseline in vital signs and the laboratory test evaluation will be provided. Clinically significant abnormal results in laboratory test will also be summarized. If needed, laboratory re-tests may be carried out outside the schedule to monitor the patient's condition.

3.4. Handling of dropout or missing values

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