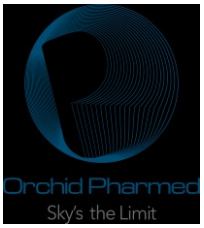

STATISTICAL ANALYSIS PLAN

A Phase III, randomized, two armed, multicenter, parallel, double blind (patient and assessor blinded), active controlled non inferiority clinical trial to determine the non-inferior therapeutic efficacy and safety between CinnaPoietin® (Beta erythropoietin) and Eprex® (epoetin alpha) on treatment of anemia in ESRD hemodialysis patients.

Date: 19 April 2017

NCT number: NCT03408639

1. Section 1: Administrative information

1.1. Title and Trial registration

1.1.1. Descriptive title that matches the protocol, with 'Statistical analysis plan' either as a fore runner or sub title, and trial acronym

Statistical analysis plan for the Phase III, randomized, two armed, multicenter, parallel, double blind (patient and assessor blinded), active controlled non inferiority clinical trial to determine the non-inferior therapeutic efficacy and safety between CinnaPoietin® (Beta erythropoietin) and Eprex® (epoetin alpha) on treatment of anemia in ESRD hemodialysis patients.

1.1.2. Trial registration number

IRCT201601156135N6

1.2. Objectives (Description of specific objectives or hypotheses)

Assessment of non-inferiority effect of CinnaPoietin® (Beta erythropoietin) compared with Eprex® (epoetin alpha) in correction of hemoglobin levels of anemic ESRD hemodialysis patients.

Primary objective(s):

Determination of non-inferior efficacy of Beta erythropoietin (CinnaPoietin®) compared with Eprex® (epoetin alpha) in correction of hemoglobin levels of anemic patients with chronic kidney disease (CKD) under hemodialysis

Secondary objective(s):

The secondary outcomes of interest include assessment of efficacy, safety and immunogenicity of Beta erythropoietin (CinnaPoietin®).

2. Section 2: Trial Methods

2.1. Trial design – description of trial design (Brief description of trial design including type of trial, allocation ratio and brief description of interventions)

The study is designed as phase III, randomized, two armed, multicenter, parallel, double blind (patient and assessor blinded), active controlled non inferiority clinical trial with primary outcome of hemoglobin level change in anemic patients with CKD under hemodialysis.

2.2. Randomization (Randomization details)

Cluster Randomization Method will be used to randomize patients in the study. After randomization procedure, a code will be allocated to each patients that will be used as patients' identifier throughout the study.

2.3. Sample size (Full details of the sample size calculation or alternatively reference to sample size calculation in protocol (instead of replication in SAP)

156 patients will be equally (1:1) divided into intervention arms (78 in each considering drop out) for achieving 80% power in order to determine non-inferiority using a one-sided, independent sample t-test. The margin of non-inferiority is -1.The true difference between the means is assumed to be -0.5. The significance level (alpha) of the test is 0.05. The data are drawn from populations with standard deviations of 1.2 and 1.2.

3. Section 3: Statistical Principles

3.1. Confidence intervals and p-values (Level of statistical significance)

The primary endpoints will be performed using a one-sided test with 5% significance level. All other applicable statistical tests will be 2-sided and will be performed using a 5% significance level.

3.2. Analysis populations (Definition of Analysis populations e.g. intention-to-treat (ITT), per-protocol, complete case, safety.)

The primary analysis population for efficacy analyses will be the Per-Protocol (PP) population as defined below. The secondary variables will be analyzed using the ITT population. All safety analysis will be based on the safety population.

1- Per-protocol population. All patients who were randomized treated with study medication and did not have a major protocol deviation (to be defined before the unblinding of the database).

2- Modified intention-to-treat population. All patients who were randomized and received at least one dose of study medication. Patients will be analyzed according to the treatment to which they were randomized.

3- Safety population. All patients who were randomized and received at least one dose of study medication. Patients will be analyzed according to the treatment which they received.

3.3. Baseline patient characteristics

3.3.1. List of baseline characteristics to be summarized

Patients will be described with respect to age, gender, weight, height, BMI, history of high blood pressure, and history of diabetes type 1 & 2 at baseline separately for the two randomized groups. In fact, descriptive statistics will be presented to assess the distribution of the baseline variables across treatment groups.

3.3.2. Details of how baseline characteristics will be descriptively summarized

Categorical data will be summarized by numbers and percentages. Continuous data will be summarized by mean, SD.

4. Section 4: Analysis

4.1. Outcome definitions

4.1.1. Specification of outcomes and timings

Primary outcomes:

The primary efficacy endpoints will be analyzed using per-protocol (PP) analysis.

The mean Hb change level during the last four weeks of treatment is considered as the primary endpoint of the study.

The mean weekly epoetin dosage per kg body weight during the last four weeks of treatment necessary to maintain the Hb level within 10-12 g/dl during the last four weeks of treatment is considered as the second primary endpoint.

Secondary outcomes:

- The secondary variables will be analyzed using the ITT population.
- The proportion of patients with any permanent or transient dose change during main study phase is considered as the first secondary endpoint.
- The proportion of patients with any Hb measurement outside the target range is considered as the second secondary endpoint.
- The incidence of blood transfusions is considered as the third secondary endpoint.
- The proportion of patients with treatment success (Hb concentration≥11.0 g/dl and two consecutive weeks without any blood transfusion within the preceding three months) is considered as the fourth secondary endpoint.
- The proportion of patients with maintenance success (maintenance of mean Hb concentration of 11.0 ± 1.0 g/dl for at least four consecutive weeks) is considered as the fifth secondary endpoint.
- Percentage of Hb measurements>10.0 g/dl is considered as the sixth secondary endpoint.
- Percentage of hematocrit measurements>30% is considered as the seventh secondary endpoint.

Safety outcomes:

The incidence of Hb levels above 13 g/dl is considered as the first safety endpoint. Patients with at least one Hb measurement above 13 g/dL from week 2nd to week 26th will be taken into account to calculate this proportion.

The proportion of patients with an increase in Hb concentration of > 1.0 g/dl for four weeks is considered as the second safety endpoint.

Adverse events will be reported as incidence rate.

4.2. Analysis methods

4.2.1. What analysis method will be used, and how the treatment effects will be presented

For the primary efficacy variable, the following null hypothesis will be tested:

H_0: CinnaPoietin® is not non-inferior to Eprex®

Versus

H_1: CinnaPoietin® is non-inferior to Eprex®

CinnaPoietin® (produced by CinnaGen Company) efficacy will be judged non-inferior to Eprex® (the reference drug, produced by Janssen-Cilag) if the lower limit (UL) of the one-sided 95% confidence interval (95% CI) of the mean Hb change, calculated by Two Sample T-test, was more than accepted non inferiority margin.

Chi-Square test or Fisher exact test (if the expected frequencies are less than 5) will be performed for analyzing the secondary and safety outcomes.

All safety data will be analyzed descriptively by treatment group.

4.2.2. List and describe each primary and secondary outcome including details of: methods used for assumptions to be checked for statistical methods

For analyzing the primary efficacy outcomes using independent t-tests, following assumptions should be considered:

- The dependent variable should be measured on a continuous scale
- The independent variable should consist of two categorical, independent groups.
- Observations should be independent, which means that there is no relationship between the observations in each group or between the groups themselves.
- There should be no significant outliers.
- The dependent variable should be approximately normally distributed for each group of the independent variable.
- There needs to be homogeneity of variances.

For analyzing the secondary efficacy and safety outcomes using Chi-square tests, following assumptions should be considered:

- The data in the cells should be frequencies, or counts of cases rather than percentages or some other transformation of the data.
- The levels (or categories) of the variables are mutually exclusive. That is, a particular subject fits into one and only one level of each of the variables.
- Each subject may contribute data to one and only one cell in the χ^2.
- The study groups must be independent.
- There are 2 variables, and both are measured as categories, usually at the nominal level.
- The value of the cell expected should be 5 or more in at least 80% of the cells, and no cell should have an expected of less than one.

4.3. Statistical Software (Details of statistical packages to be used to carry out analyses)

The analysis will be carried out using Stata version 14. Some graph will be plotted by R statistical software.