Cinnapoietin® Clinical Trial Protocol

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: 23 August 2015

NCT number: NCT03408639

Cinnapoietin® clinical trial synopsis

Title	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 the treatment of anemia in ESRD hemodialysis patients
Aim of Study (Primary objective)	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 objectives	The secondary outcomes of interest include assessment of efficacy and safety of Beta erythropoietin (CinnaPoietin®).
Study Design	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.
Registration	This study is planned to be registered in Iranian Registry of Clinical Trial (IRCT)
Sponsor	CinnaGen Co
Contract Research Organization (CRO)	CRO Trial, Tehran University of Medical Sciences, Tehran, Iran.
Principal Investigator	Investigator name: Dr. Mohammad Reza Abbasi Affiliation: Nephrology Research Center, Tehran University of Medical Sciences, Tehran, Iran Recruitment centers: Ghiasi Hospital

Co-investigators and recruitment centers	**1. Dr. Jalal Azmandian** Affiliation: Department of Nephrology, Kerman University of Medical Sciences, Kerman, Iran. Recruitment centers: 1. SHAFA Hospital 2. Javad Ol Aemeh Hospital **2. Dr Vahid Pourfarziani** Affiliation: Nephrology and Urology Research Center, Baqyiatallah University of Medical Sciences, Tehran, Iran Recruitment centers: 1. Milad Hospital **3. Dr Shahrzad Ossareh** Affiliation: Hasheminejad Kidney Center, Iran University of Medical Sciences, Tehran, Iran Recruitment centers: 1.Hashemi Nezhad Hospital **4. Dr Hooshang Sanadgol** Affiliation: Hasheminejad Kidney Center, Iran University of Medical Sciences, Tehran, Iran Recruitment centers: 1. Hashemi Nezhad Hospital **5. Dr. Amirahmad Nasiri** Affiliation: Imam Hossein Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran Recruitment centers: 1. Imam Hossein Hospital 2. Madar Hospital **6. Dr Shahrokh Ezzat zadegan jahromi** Affiliation: Nephro-Urology Research Center, Shiraz University of Medical Sciences, Shiraz, Iran Recruitment centers: 1. Haj Ebrahimi dialysis center
Investigational Drug	Erythropietin beta biosimilar (CinnaGen co, Iran)
Comparator	Eprex® (erythropoietin alfa) (the reference drug, produced by Janssen-Cilag)
Sample size	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.
Eligibility criteria	**Inclusion Criteria:** • Aged between 18 and 70 • ESRD patients who are on hemodialysis for ≥3 months. • Hb level 8- 11.5 g/dl • Patients are on adequate hemodialysis: the minimally adequate dose of hemodialysis given 3 times per week should be a spKt/V (single-pool delivered Kt/V; clearance of urea x dialysis time/volume of distribution) of 1.2 per dialysis. For treatment periods of less than 5 hours, an alternative minimum dose is a urea reduction rate (URR) of 65%. All types of hemodialysis systems and hemodiafiltration, including high-flux membranes are allowed as long as there is no plan to change the patient's regimen during the study. • Sufficient iron stores, defined as serum ferritin ≥ 200 ng/ml and transferrin saturation ≥20%. (Patients not meeting these criteria may receive iron supplementation therapy during the Screening and stabilization period to appropriately correct their iron store deficiency to meet the criterion required for randomization); • Ability to comply with study medication use, study visits, and study procedures as judged by the investigator; • Females of childbearing potential agree to use an acceptable method of birth control (e.g., abstinence, hormonal or barrier methods, partner sterilization, or IUD) for the duration of the study. • Qualified and willing to sign the informed consent form with the commitment of complying with all the scheduled visits, and study procedures as judged by the investigator; • In any circumstances that potential participants are not able to give consent, it may be given by responsible parents or guardian. **Exclusion criteria** • Uncontrolled hypertension (defined as pre-dialysis diastolic blood pressure ≥ 100 mmHg or systolic blood pressure ≥180 mmHg); • Anemia secondary to other causes different to the CKD (e.g. multiple myeloma, aplastic anemia, leukemia….)

	• Decompensated liver failure; • Clinical evidence of concurrent uncontrolled hyperparathyroidism (defined as serum parathyroid hormone (iPTH) > 800 pg/ml); • Heart failure [New York Heart Association (NYHA) class III and IV]; • Unstable angina pectoris, active cardiac disease, stroke and/or cardiac infarction within the last six months; • History of or active blood coagulation disorders including DVT, PTE, native access Thrombosis during last six months. • Thrombocytosis (platelet count > 500,000/µl); • Thrombocytopenia (platelet count < 100,000/µl); • White blood cell count < 3,000/µl); • White blood cell count >15,000/µl) • Recent Bleeding (acute or chronic bleeding within three months prior to screening); • Suspicion of or confirmed occult bleeding (increased reticulocyte count); • Clinical evidence of concurrent systemic infection, or inflammatory disease (e.g; diabetic foot, bed sore, access infection, CRP> 30 mg/l) • Currently receiving treatment for epilepsy; • Major surgery within 3 months prior to randomization and during the conduct of the trial (except vascular access surgery); • Concomitant immunosuppressive therapy; patients on a short course of steroids (up to 7 days), topical or intranasal steroids are allowed in the study; • History of any malignant disease within the last 5 years (except excised non-melanoma skin cancer); • Women who are pregnant or breastfeeding; • Known history of severe drug-related allergies; • Known history of drug related allergy to Erythropoietin or one of the ingredients of the test or the reference products or hypersensitivity to mammalian-derived products; • Transplant received within one year prior to the start of the study;

	• Simultaneous participation in another clinical study or having received an Investigational Medicinal Product within three months before randomization in this study. • Psychiatric, addictive (drugs or alcohol) or any other disorder that compromises the ability to give an informed consent; • Any red blood cell transfusion during the last 3 months (measured at the time of eligibility verification); • Primary hematological disorder (e.g. myelodysplastic syndrome, myeloma, sickle cell anemia, hematological malignancy, multiple myeloma hemolytic anemia); • known resistance to the rHuEPO defined by a requirement > 450 IU/kg/week by IV or 300 IU/kg/week by SC, equivalent to approximately 20.000 IU/week SC and in absence of iron deficiency; • who have suffered an event of active bleeding in the 30 days prior to the beginning of the study; • Morbid obesity, defined by a Body Mass Index (BMI) > 37 kg/m2 in women and > 40 kg/m2 in men.
Pre Intervention	Pre-intervention treatment with iron will be of interest to reach a transferrin saturation percentage (TSAT) ≥ 20% and a ferritin ≥ 200 ng/ml. According to the KDIGO guidelines [41], if the TSAT is <20% and the serum ferritin <200 ng/ml (<200 µg/l) and an increase in Hb concentration without starting ESA treatment is desired, it is suggested to administer a trial of IV iron. IV iron may be provided as a single large dose or as repeated smaller doses depending on the specific IV iron preparation used (with the highest single dose varying by specific formulation). It is common practice to provide an initial course of IV iron amounting to approximately1000 mg; this may be repeated if an initial dose fails to increase Hb level and allow a decrease in ESA dose and if the TSAT remains <20% and serum ferritin remains <200 ng/ml (<200 mg/l)
Randomization	Cluster Randomization Method will be used to randomize patients in the study. The randomization monitor will create unblinding envelopes and packaged the drug with blinded labels. After the randomization, each patient will be given an identification code in order to be recognized

	during the study and the treatment will be started based on allocated group of intervention.
Blinding	To prevent the influence of knowing intervention group on study conclusion, the Subjects and those who assess the study outcomes will be unaware of the state of the patient with regard to receiving the active drugs or standard remedy. For this purpose, Subjects and administrator of drug will be blinded by using a similar masked prefilled syringes. All drugs packages will be identified by unique numbers.
Intervention	The treatment proposed in this study was elaborated according to the KDIGO guidelines. Before the beginning of the protocol, for the patient to be able to enter the treatment, it shall be controlled that the iron (Fe) stores are adequate. In addition to main intervention, Nephrovit tablet /daily and B12 100 mcg (Amp)/monthly will be prescribed.
Outcomes	**Efficacy outcomes** *Primary outcomes:* • The mean Hb change level during the last 4 weeks of treatment • The mean weekly epoetin dosage per kg body weight during the last 4 weeks of treatment necessary to maintain the Hb level within 10-12 g/dl during the last 4 weeks of treatment will be considered as a second primary endpoint *Secondary outcomes:* • The proportion of patients with any permanent or transient dose change during main study phase, • The proportion of patients with any Hb measurement outside the target range, • Incidence of blood transfusions. • Proportion of patients with treatment success (Hb concentration≥11.0 g/dl AND two consecutive weeks without any blood transfusion within the preceding 3 months), • Proportion of patients with maintenance success (maintenance of mean Hb concentration of 11.0 ± 1.0 g/dL for at least 4 consecutive weeks), • Percentage of Hb measurements>10.0 g/dL,

	• Percentage of hematocrit measurements>30% *Safety outcomes:* • The incidence of Hb levels above 13 g/dL, • Proportion of patients with an increase in Hb concentration of > 1.0 g/dL for 4 consecutive weeks, • Incidence rate of adverse events

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Participants timeline

	Study Period										
	Screening/ Intervention Allocation	**Post Allocation**									**Close-out**
Time point	Visit0	Visit 1	Visit 2	Visit3	Visit4	Visit5	Visit6	Visit7	Visit8-1	Visit8-2	Visit9
Day	-28 to 0	1	14 ± 2	28 ± 2	42 ± 2	56 ± 2	84 ± 2	140 ± 2	156 ± 2	168 ± 2	182 ± 2
Week	-4 - 0	0	2	4	6	8	12	20	22	24	26
Screening	×										
Informed consent	×										
Allocation	×										
Clinical evaluation.	×	×	×	×	×	×	×	×	×	×	×
Concomitant medication	×	×	×	×	×	×	×	×	×	×	×
Intervention		×	×	×	×	×	×	×	×	×	
Adverse Event		×	×	×	×	×	×	×	×	×	×
Drug accountability		×	×	×	×	×	×	×	×	×	×