ANTIREMODELING EFFECT OF ALDOSTERONE RECEPTORS BLOCKADE WITH CANRENONE IN MILD CHRONIC HEART FAILURE:

AREA IN - CHF

AMENDMENT 1

STUDY SPONSOR: HEART CARE FOUNDATION

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MODIFICATION OF EXCLUSION CRITERIA AND STUDY POPULATION

Exclusion criteria

Age limits
One of the major criticisms in the evaluation of the results of clinical trials in heart failure is that the included population do not represent what actually happens in clinical practice. A typical example is age. Since in clinical practice, patients with heart failure are generally older than in trials, the Steering Committee of the study, in order to make the study population more representative of the real world, established to extend the age limit from 75 to 80 years.

ORIGINAL VERSION

4.3 Exclusion criteria
Patients with any of the following conditions must be excluded

- Age <18 and >75
- Serum creatinine level > 2.5 mg per deciliter
- Serum potassium level > 5.0 mmol per liter
- Valvular heart disease amenable to surgical treatment
- Congenital heart disease
- Unstable angina and/or acute myocardial infarction and/or coronary revascularization procedure within three months before enrolment
- Intravenous therapy with inotrope drugs within three months before enrolment
- History of resuscitated ventricular fibrillation or tachycardia, unless these occurred within 24 hours of an acute myocardial infarction or the subject has an implanted an automatic cardioverter defibrillator
- Chronic active hepatitis or cirrhosis
- Malignant neoplasm or any life threatening non cardiac disease
- History of hypersensitivity to study drug
- Pregnancy or lactating or childbearing age women who are not protected by an accepted method of contraception
- History of drug or alcohol abuse
- Legal incapacity and/or other circumstances rending the patient unable to understand the nature, scope and possible consequences of the study.
- Evidence of uncooperative attitude
- Any condition other than heart failure that does not permit an optimal participation to the trial
- Participation to other RCTs during the last 3 months
- Treatment with: Lithium salts, Potassium sparing diuretics, αTNF antagonists, or any investigational drug

AMENDED VERSION

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Patients with any of the following conditions must be excluded

- Age <18 and >80
- Serum creatinine level > 2.5 mg per deciliter
• Serum potassium level > 5.0 mmol per liter
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SAMPLE SIZE CONSIDERATIONS

➢ **Reduction of the number of patients to be randomized from 800 to 500.**

In the absence of reliable data from the literature on LV size of patients with heart failure in NYHA class II, treated at the best of the today recommended treatments, the Steering Committee of the study, in designing the protocol, decided to use the information collected by the large network of the IN-CHF Registry, despite the fact that

- patients enrolled in the registry have different baseline characteristics than those foreseen to enter the trial;
- echocardiographic examinations were analyzed peripherally at the recruiting centers, without any centralized evaluation.

In order to have more definite and reliable data with respect to the baseline LV volume of the enrolled population, the Steering Committee decided:

- to analyze centrally the echocardiograms of the first 100 patients included in the study;
- recalculate the sample size of the study maintaining the same assumptions of the original protocol.

The recalculated sample size is 250 patients per treatment arm. The adoption of this policy will allow:
- to have more reliable assumptions, based on information derived from a patient population with the eligibility criteria of the study;
- to demonstrate the same hypothesis with an identical power and alpha value;
- to do it exposing a lower number of patients to the experimental design.

**ORIGINAL VERSION**

4 Study population
4.1 Number of patients

800 patients, aged 18 to 75 years, with congestive heart failure in NYHA Class II.

9. Statistical analysis and data management
9.1 Rationale for sample size

The study is designed to show that treatment of patients with mild heart failure with an aldosterone receptor blocker determines an antiremodeling effect or restores a physiological LV geometry.

A sample size of 400 patients in each treatment group will be estimated to provide > 90% power at the 0.05 level of statistical significance to detect a relative change in left ventricular end-diastolic diameter volume of 10%, assuming a mean left ventricular end-diastolic volume of 200±79 ml. This assumption is based on the analysis of the IN CHF database including 4000 patients with NYHA class II heart failure.

**AMENDED VERSION**

4 Study population
4.1 Number of patients

500 patients, aged 18 to 80 years, with congestive heart failure in NYHA Class II.

9. Statistical analysis and data management
9.1 Rationale for sample size

The study is designed to show that treatment of patients with mild heart failure with an aldosterone receptor blocker determines an antiremodeling effect or restores a physiological LV geometry.

A sample size of 250 patients in each treatment group will be estimated to provide > 90% power at the 0.05 level of statistical significance to detect a relative change in left ventricular end-diastolic diameter volume of 10%, assuming a mean left ventricular end-diastolic volume of 246±82 ml. This assumption is based on the centralized analysis of 100 echocardiographic examinations performed in patients with the eligibility criteria of the study.

**SUMMARY MODIFICATIONS**

As a consequence of the aforementioned decisions of the Steering Committee, the Summary has been modified as follows:

**ORIGINAL VERSION**

The RALES study has shown that spironolactone reduces the risk of morbidity and mortality both from progressive heart failure and sudden death, in patients with NYHA III or IV heart failure. This favourable effect was clearly independent from a diuretic effect. Antialdosterone drugs may be effective because they oppose the effects of aldosterone on sodium retention, loss of magnesium...
and potassium, sympathetic activation, baroreceptor function and vascular compliance. Antialdosterone treatment may also antagonize the effect of aldosterone in promoting cardiac fibrosis. In a RALES substudy baseline serum PIIINP, a marker of cardiac fibrosis synthesis showed an independent negative correlation with survival and CHF hospitalizations in the placebo group. Therefore it seems interesting to evaluate the effect of an Aldosterone receptor blocker on progression of left ventricular dysfunction in patients with mild heart failure assuming standard therapy.

AIM OF THE STUDY

Primary: Changes in echocardiographic left ventricular diastolic volume.
Secondary: Changes in left ventricular systolic volume, ejection fraction, NYHA class, cardiac mortality, hospitalization for cardiac causes and the combination of cardiac mortality hospitalizations for cardiac causes.

STUDY DESIGN

Multicentre, randomized, double blind, parallel group comparison of an aldosterone receptor blocker, canrenone 25 mg od, versus placebo. Follow up visits and laboratory examinations are performed monthly for the first three months, than every three months up to the end of the study (12 months). Serum aldosterone determination is performed at baseline evaluation, while PIIINP and BNP at baseline and at six month from randomization. Echocardiographic evaluation is performed 3 times: randomization, six month and 12 month.

STUDY POPULATION

Inclusion criteria:
- Established diagnosis of congestive heart failure in NYHA class II
- Left ventricular ejection fraction ≤ 45% measured within 6 months from enrolment
- Stable standard heart failure therapy (if patients are on beta blocker drugs, treatment must have been started at least three months before enrolment)
- Informed consent (obtained prior of any study procedures)

Exclusion criteria:
- Age < 18 and > 75
- Serum creatinine level > 2.5 mg per deciliter
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