CASE STUDY
Renin Angiotensin System Combination Antagonists for Life (RASCAL)

Multinational, multicenter, double-blind, randomized, active controlled, parallel group phase III study comparing the efficacy and safety of long-term treatment with a NEW versus STANDARD renin angiotensin aldosterone system antagonist, and versus their combination in high risk patients after myocardial infarction.

This is a prospective multinational (26 countries), multicenter, double-blind, randomized, active controlled study with 3 parallel treatment groups. The protocol is intended to have minimal interference with usual clinical practice as recommended by professional society guidelines.

Planned enrollment
12,300 participants will be recruited in 26 countries (Asia, Canada, USA, EU, Latin America).

Treatment allocation
Eligible and consenting participants will be randomly allocated in a 1:1:1 ratio to:
1. NEW monotherapy (investigational drug). Target dose XX mg twice daily.
2. STANDARD monotherapy (active control drug). Target dose YY mg three times daily.
3. The combination of NEW and STANDARD (investigational regimen). Target doses XX mg twice daily and YY mg three times daily, respectively.

The dose of study medication is to be adjusted with four titration steps, based on blood pressure, renal function and serum electrolytes. Each patient should receive the maximum tolerated dose of study medication up to the target dose. The titrations are as clinically tolerated with a target of step 3 by hospital discharge and step 4 during the outpatient phase. Subsequent backtitrations and uptitrations are at the discretion of the investigators according to the patient's clinical status.

Primary objectives
1. To demonstrate that long-term administration of NEW given as monotherapy is more effective than STANDARD given as monotherapy in the reduction of total mortality after an acute myocardial infarction.

2. To demonstrate that long-term administration of the combination of NEW with STANDARD is more effective than STANDARD given as monotherapy in the reduction of total mortality after an acute myocardial infarction.

3. If NEW as monotherapy cannot be shown to be superior to STANDARD as in objective 1, to demonstrate that long-term administration of NEW given as monotherapy is at least as effective as STANDARD given as monotherapy in the reduction of total mortality after an acute myocardial infarction.

Secondary objective

To demonstrate that long-term administration of the combination of NEW with STANDARD is more effective than NEW given as monotherapy in the reduction of total mortality after an acute myocardial infarction.

Eligibility

Inclusion criteria

To be eligible for randomization, potential participants must fulfill both of the following criteria:
1. Men and women, age 18 years or older
2. Acute myocardial infarction more than 12 hours and no later than 10 days after the onset of symptoms; and
3. Evidence of heart failure and/or left ventricular systolic dysfunction:
   o Either radiologic evidence of pulmonary venous congestion with interstitial or alveolar edema or clinical evidence (pulmonary edema, bilateral posttussive rales in at least the lower third lung fields or an S3 gallop with persistent tachycardia) OR An echocardiographic left ventricular ejection fraction ≤35% or a wall motion index of ≤1.2 OR A radionuclide or contrast angiography left ventricular ejection fraction ≤40% or 35%, respectively, would satisfy entry criteria for left ventricular systolic dysfunction.

Exclusion criteria

Individuals with any of the following are not eligible for randomization:
- Cardiogenic shock (within the 24 hours prior to randomization)
- Systolic blood pressure < 100 mm Hg
- Serum creatinine > 221 μmol/L (2.5 mg/dl)
- Known or suspected bilateral renal artery stenosis
- Stroke or transient ischemic attack within the previous one month
- Refractory potentially lethal ventricular arrhythmia
- Refractory angina
- Cardiac surgery planned to occur within the 15 days after randomization
- Known intolerance of, or contra-indication to, study drug
- Clinically significant right ventricular qualifying myocardial infarction
- Obstructive cardiomyopathy
- Pregnant or nursing women
- Previous major organ (e.g., lung, liver, heart, kidney) transplantation or on waiting list
- Other conditions/circumstances likely to lead to poor treatment adherence (eg, history of poor compliance, alcohol or drug dependency, psychiatric illness)

Study schedule

The study consists of two phases, 1) a study medication initiation and titration phase and 2) a maintenance phase. The duration of these two phases depends upon the patient's status and response to study medication.

Randomization visit (Day 0)

A patient can be randomized and study medication started on the day of myocardial infarction (must be at least 12 hours after the onset of symptoms) or on any day up to and including the tenth day after the onset of symptoms. For most patients, this visit will occur in hospital.

Assessments at Randomization Visit:
- Informed consent
- Inclusion/Exclusion criteria
- Chest X-ray
- Cardiac panel (troponin, NT-proBNP, creatinine, electrolytes, full blood count)
- Medical history
- 12-lead ECG
- NYHA class
- Evaluation of heart failure
- Vital signs
- Adverse events
- End point criteria evaluated
- Medication dispensed
- Quality of life assessment
- Pharmacoeconomic assessment

Follow-up Visits

Follow-up 1   Day 15 or at hospital discharge (if still in hospital)
Follow-up 2-13   Monthly. (Visit may take place within 15 days of the target date.)
Follow-up 14-20   6 monthly. (Visit may take place within 30 days of the target date.)

Assessments at each follow-up visit:

- Vital signs and NYHA class
- Adverse events
- End point criteria evaluated
- Compliance assessed (pill count)
- Dose titration
- Medication returned and dispensed
- Serum creatinine, electrolytes
- Quality of life assessment
- Pharmacoeconomic assessment

Study duration:
The study duration is planned to continue until there have been 2,225 primary efficacy endpoints.
For planning purposes, the expected study duration is approximately 4.5 years including an enrollment period of 24 months. The actual study duration will depend upon the accrual rate and the observed death rate.

Withdrawal:
Subjects may withdraw from the trial at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety or other appropriate reasons. If a subject does not return for a scheduled visit, at least three documented efforts should be made to contact them.

Data Monitoring Committee
An Independent Data Monitoring Committee (IDMC) will be formed to assure subject safety in this clinical trial. The IDMC will also evaluate efficacy data at the time of the pre-specified interim analysis and make a recommendation about early termination.

Statistical methods:
Data will be summarized with respect to demographic and baseline characteristics, efficacy observations and measurements, and safety observations and measurements. The primary objectives will be investigated by comparing the treatment groups with respect to time to death (all-cause mortality), using Cox regression models containing treatment group, age, and history of prior MI. For the superiority hypotheses, two-sided significance levels of 0.0253 will be used in order to maintain a global significance level ≤ 0.05 for the trial; for the non-inferiority of NEW relative to STANDARD, a one-sided significance level of 0.0253 and an equivalence margin of 0.13 will be used. Secondary efficacy parameters will be tested using Cox regression analyses or Cochran-Mantel-Haenszel tests. Two formal interim analyses of the primary efficacy variable will be performed when one-third and two-thirds of the total planned number of 2,225 primary endpoints have occurred; O'Brien-Fleming-type boundaries based on a Lan-DeMets alpha spending function will be used to define criteria for determining whether treatment groups differ significantly at the interim analyses.