PARADISE-MI

NCT02924727

Principal Investigator: Dr. Rao Gudipati, MD (Covenant)

Condition: Acute Myocardial Infarction

Drug: LCZ696 (sacubitril/valsartan) and placebo of ramipril vs. ramipril and placebo of LCZ696; valsartan vs. placebo of valsartan

Official Title: A Multi-center, Randomized, Double-blind, Active-controlled, Parallel-group Phase 3 Study to Evaluate the Efficacy and Safety of LCZ696 Compared to Ramipril on Morbidity and Mortality in High Risk Patients Following an AMI

Sponsor: Novartis Pharmaceuticals

Purpose: The purpose of this study is to evaluate the efficacy and safety of LCZ696 titrated to a target dose of 200 mg twice daily, compared to ramipril titrated to a target dose of 5 mg twice daily, in addition to conventional post-AMI treatment, in reducing the occurrence of composite endpoint of CV death, HF hospitalization and outpatient HF (time-to-first event analysis) in post-AMI patients with evidence of LV systolic dysfunction and/or pulmonary congestion, with no known prior history of chronic HF.

Inclusion Criteria:

1. Male or female patients ≥ 18 years of age.
2. Diagnosis of spontaneous AMI based on the universal MI definition* with randomization to occur between 12 hours and 7 days after index event presentation. (*patients with spontaneous MI event determined to be secondary to another medical condition such as anemia, hypotension, or arrhythmia OR thought to be caused by coronary vasospasm with document normal coronary arteries are not eligible; patients with clinical presentation thought to be related to Takotsubo cardiomyopathy are also not eligible)
3. Evidence of LV systolic dysfunction and/or pulmonary congestion requiring intravenous treatment associated with the index MI event defined as:
   - LVEF ≤40% after index MI presentation and prior to randomization and/or
   - Pulmonary congestion requiring intravenous treatment with diuretics, vasodilators, vasopressors and/or inotropes, during the index hospitalization
4. At least one of the following 8 risk factors:
   - Age ≥ 70 years
   - eGFR <60 mL/min/1.73 m^2 based on MDRD formula at screening visit
   - Type I or II diabetes mellitus
   - Documented history of prior MI
   - Atrial fibrillation as noted by ECG, associated with index MI
   - LVEF <30% associated with index MI
   - Worst Killip class III or IV associated with index MI requiring intravenous treatment
   - STEMI without reperfusion therapy within the first 24 hours after presentation
5. Hemodynamically stable defined as:
   - SBP ≥ 100 mmHg at randomization for patients who received ACEi/ARB during the last 24 hours prior to randomization
   - SBP ≥ 110 mmHg at randomization for patients who did not receive ACEi/ARB during the last 24 hours prior to randomization
   - No IV treatment with diuretics, vasodilators, vasopressors and/or inotropes during the 24 hours prior to randomization

Exclusion Criteria:

1. Known history of chronic HF prior to randomization
2. Cardiogenic shock within the last 24 hours prior to randomization

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Exclusion Criteria (Continued):

3. Persistent clinical HF at the time of randomization
4. Coronary artery bypass graft (CABG) performed or planned for index MI
5. Clinically significant right ventricular MI as index MI
6. Symptomatic hypotension at screening or randomization
7. Patients with a known history of angioedema
8. Stroke or transient ischemic attack within one month prior to randomization
9. Known or suspected bilateral renal artery stenosis
10. Clinically significant obstructive cardiomyopathy
11. Open-heart surgery performed within one month prior to randomization or planned cardiac surgery w/in the 3 months prior to randomization
12. eGFR < 30 ml/min/1.73 m^2 as measured by MDRD at screening
13. Serum potassium > 5.2 mmol /L (or equivalent plasma potassium value) at randomization
14. Known hepatic impairment (as evidenced by total bilirubin > 3.0 mg/dL or increased ammonia levels, if performed), or history of cirrhosis with evidence of portal hypertension such as esophageal varices
15. Previous use of LCZ696
16. History of malignancy of any organ system (other than localized basal cell carcinoma of the skin) within the past 3 years with a life expectancy of less than 1year.
17. History of hypersensitivity to the study drugs or drugs of similar chemical classes or known intolerance or contraindications to study drugs or drugs of similar chemical classes including ACE inhibitors, ARB or NEP inhibitors
18. Pregnant or nursing women or women of child-bearing potential unless they are using highly effective methods of contraception

Source: https://clinicaltrials.gov/ct2/show/NCT02924727
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