PARADIGM HF

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Sponsor:
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Study Purpose:
A multicenter, randomized, double-blind, parallel group, active-controlled study to evaluate the efficacy and safety of LCZ696 compared to enalapril on morbidity and mortality in patients with chronic heart failure and reduced ejection fraction
Protocol No.: CLCZ696B2314

Objective:
The primary objective of this study is to test if LCZ696 is superior to enalapril in delaying time to first occurrence of the composite endpoint, which is defined as either CV death or HF hospitalization, in patients with CHF (NYHA class II – IV) and reduced ejection fraction (LVEF ≤ 40%).

Inclusion Criteria:
1. Patients must give written informed consent before any assessment is performed.
2. Outpatients ≥ 18 years of age, male or female.
3. Patients with a diagnosis of CHF NYHA class II-IV and reduced ejection fraction:
    - o LVEF ≤ 40% at Visit 1 (any local measurement, made within the past 6 months usingechocardiography, MUGA, CT scanning, MRI or ventricular angiography is acceptable, provided no subsequent measurement above 40%)
    - o BNP ≥ 150 pg/ml (NT-proBNP ≥ 600 pg/ml) at Visit 1 **OR** BNP ≥ 100 pg/mL (NTproBNP ≥ 400 pg/ml) and a hospitalization for HF within the last 12 months
4. Patients must be on an ACEI or an ARB at a stable dose of at least enalapril 10 mg/d or equivalent for at least 4 weeks before Visit 1
    - o For this protocol doses of other ACEIs considered to be equivalent to enalapril 10 mg/d include captopril 100 mg/d, cilazapril 2.5 mg/d, fosinopril 20 mg/d, lisinopril 10 mg/d, moexipril 7.5 mg/d, perindopril 4 mg/d, quinapril 20 mg/d, ramipril 5 mg/d, trandolapril 2 mg/d, and zofenopril 30 mg/d.

o For this protocol doses of ARBs considered to be equivalent to enalapril 10 mg/d include candesartan 16 mg/d, eprosartan 400 mg/d, irbesartan 150 mg/d, losartan 50 mg/d, olmesartan 10 mg/d, telmisartan 40 mg/d, and valsartan 160 mg/d.

5. Patients must be treated with a β-blocker, unless contraindicated or not tolerated, at a stable dose for at least 4 weeks prior to Visit 1 (reason should be documented for patients not on CHF target doses per local guidelines, or in absence of that medication).

Exclusion Criteria:

1. Use of other investigational drugs at the time of enrollment, or within 30 days or 5 halflives of enrollment, whichever is longer
2. History of hypersensitivity or allergy to any of the study drugs, drugs of similar chemical classes, ACEIs, ARBs, or NEP inhibitors as well as known or suspected contraindications to the study drugs
3. Previous history of intolerance to recommended target doses of ACEIs or ARBs
4. Known history of angioedema
5. Requirement of treatment with both ACEIs and ARBs
6. Current acute decompensated HF (exacerbation of chronic HF manifested by signs and symptoms that may require intravenous therapy)
7. Symptomatic hypotension and/or a SBP < 100 mmHg at Visit 1 (screening) or < 95 mmHg at Visit 3 or at Visit 5 (randomization)
8. Estimated GFR < 30 mL/min/1.73m2 as measured by the simplified MDRD formula at Visit 1 (screening), Visit 3 (end of enalapril run-in), or Visit 5 (end of LCZ696 run-in and randomization) or > 25% decline in eGFR between Visit 1 and Visit 3 or between Visit 1 and Visit 5
9. Serum potassium > 5.2 mmol/L at Visit 1 (screening) or > 5.4 mmol/L at Visit 3 or Visit 5 (randomization)
10. Acute coronary syndrome, stroke, transient ischemic attack, cardiac, carotid or other major CV surgery, percutaneous coronary intervention (PCI) or carotid angioplasty within the 3 months prior to Visit 1
11. Coronary or carotid artery disease likely to require surgical or percutaneous intervention within the 6 months after Visit 1
12. Implantation of a cardiac resynchronization therapy device (CRTD) within 3 months prior Visit 1 or intent to implant a CRTD
13. History of heart transplant or on a transplant list or with left ventricular assistance device (LVAD)
14. History of severe pulmonary disease
15. Diagnosis of peripartum or chemotherapy induced cardiomyopathy within the 12 months prior to Visit 1
16. Documented untreated ventricular arrhythmia with syncopal episodes within the 3 months prior to Visit 1
17. Symptomatic bradycardia or second or third degree heart block without a pacemaker
18. Presence of hemodynamically significant mitral and/or aortic valve disease, except mitral regurgitation secondary to left ventricular dilatation

19. Presence of other hemodynamically significant obstructive lesions of left ventricular outflow tract, including aortic and sub-aortic stenosis
20. Any surgical or medical condition which might significantly alter the absorption, distribution, metabolism, or excretion of study drugs, including but not limited to any of the following:
    - o History of active inflammatory bowel disease during the 12 months before Visit 1.
    - o Current duodenal or gastric ulcers during the 3 months prior to Visit 1
    - o Evidence of hepatic disease as determined by any one of the following: AST or ALT values exceeding 2 x ULN at Visit 1, history of hepatic encephalopathy, history of esophageal varices, or history of portacaval shunt
    - o Active treatment with cholestyramine or colestipol resins
21. Presence of any other disease with a life expectancy of < 5 years
22. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test (> 5 mIU/mL)
23. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, including women whose career, lifestyle, or sexual orientation precludes intercourse with a male partner and women whose partners have been sterilized by vasectomy or other means, UNLESS they are using two birth control methods. The two methods can be a double barrier method (if accepted by the local regulatory authority and ethics committee) or a barrier method plus a hormonal method
    - o Adequate barrier methods of contraception include: diaphragm, condom (by the partner), intrauterine device (copper or hormonal), sponge or spermicide. Hormonal contraceptives include any marketed contraceptive agent that includes an estrogen and/or a progesterone agent.
    - o Reliable contraception should be maintained throughout the study and for 7 days after study drug discontinuation.
    - o Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or six m onths of spontaneous amenorrhea with serum FSH levels > 40 mIU/mL [***for US only:*** and estradiol < 20 pg/mL] or have had surgical bilateral oophorectomy (with or without hysterectomy) at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment.

Status:
Active enrollment

If you have any questions, please feel free to contact the coordinators, and they will be happy to answer any questions you have regarding this study.