Appendix - Supplementary Material

Inclusion Criteria

1. Male or female patients 18 years and older.
2. Patients within 7-42 days of an acute myocardial infarction associated with left ventricular systolic dysfunction prior to Visit 1 (see below). A qualifying myocardial infarction will require **each** of the following:
   - Typical clinical presentation consistent with myocardial infarction (i.e., chest pain, shortness of breath)
   - Elevation of cardiac markers (*any of the following will fulfill the requirement for an increase in cardiac markers*):
     - Both total CK and CK-MB are above the upper limit of normal (ULN) and either total CK or CK-MB are at least twice the upper limit of normal (2xULN)
     - CK-MB is elevated to at least twice the upper limit of normal (2xULN) when total CK is not available, and is confirmed by an accompanying Troponin T or I level at least three times the upper limit of normal (3xULN)
     - Total CK is elevated to at least twice the upper limit of normal (2xULN) when CK-MB is not available, or to above the ULN if confirmed by an accompanying Troponin T or I level at least three times the upper limit of normal (3xULN)
     - Troponin T or I level is at least five times the upper limit of normal (5xULN).

   - Typical ECG changes, including evolving ST-segment or T-wave changes in two or more contiguous ECG leads, the development of new pathological Q/QS waves in two or more contiguous ECG leads, or the development of new left bundle branch block.

3. Documented left ventricular systolic dysfunction associated with the qualifying acute myocardial infarction obtained as a clinical evaluation (study) post-MI but prior to Visit 1. Systolic dysfunction will be defined by at least one of the following criteria:
   - Echocardiography: LVEF $\leq$ 45%
   - Radionuclide ventriculography: LVEF $\leq$ 45%
   - Ventricular contrast angiography: LVEF $\leq$ 40%
   - Left Ventricular Wall Motion Index (LVWMI) $\geq$ 1.5
4. Patients should be on stable doses of the following standard of care post-MI concomitant medications for at least 2 weeks prior to Visit 1 unless contraindicated due to intolerance:

- A Beta-blocker
- An Anti-platelet agent
- A Statin

5. Patients must be on a stable evidence-based dose (see Appendix 3) of an Angiotensin Converting Enzyme Inhibitor (ACEI) or Angiotensin Receptor Blocker (ARB) but not both, for at least 2 weeks prior to Visit 1, unless contraindicated due to intolerance. For patients not on an evidence–based dose of an ACEI or an ARB, the reason (e.g., patient intolerant of these medications) must be documented.
6. Patients who are eligible, able to participate in the study, and who consent to do so after the purpose and nature of the investigation has been clearly explained to them (written informed consent).
7. Qualifying Echocardiogram:
   - Patients who fulfill the screening inclusion and exclusion criteria will have a qualifying echocardiogram performed and transmitted to the Echo Core Laboratory. To be eligible for randomization, patients must fulfill the following criteria by the core laboratory:
     - Acceptable image quality
     - Confirmed LVEF ≤ 45%
     - Qualifying Myocardial Infarct Percentage ≥ 20% (akinetic or dyskinetic segment length as percent of total cavity perimeter).

Exclusion Criteria

1. Patients requiring **both** ACEI **and** ARB combination therapy at V1 or any time during the study.
2. Hypertrophic cardiomyopathies due to etiologies other than hypertension (i.e., idiopathic or valvular).
3. Severe refractory hypertension defined as MSSBP ≥ 180 mmHg and/or MSDBP ≥ 110 mmHg) at Visit 2.
4. Hemodynamically significant stenotic or obstructive valvular, subvalvular or supravalvular lesions.
5. Secondary forms of cardiomyopathy such as restrictive cardiomyopathy or infective cardiomyopathy (e.g., Chagas' disease).
6. Cardiogenic shock or systolic BP < 100 mmHg or diastolic BP < 60 mmHg within the 24 hours prior to Visit 1 or Visit 2.
7. Estimated Glomerular Filtration Rate (eGFR) < 30 ml/min/1.73m^2 using the MDRD formula at Visit 1.
8. Stroke or transient ischemic event (TIA) within 6 months of Study Visit 1.
9. Serum potassium ≥ 5.1 mEq/L, or dehydration at Study Visit 1.
10. Significant valvular cardiovascular disease expected to lead to cardiac surgery during the course of the study.
11. Unstable angina requiring intervention between Visit 1 and Visit 2.

12. Any coronary artery revascularization procedure within 7 days prior to Visit 1.
13. Planned or anticipated elective CABG, PCI, CRT, LVAD or cardiac transplant after the patient is enrolled into the study.
14. Current abuse or recent history of alcohol or other drug substance abuse (past 12 months).
15. Significant non-cardiovascular illness or condition likely to result in death prior to trial completion, e.g., major organ transplant (life expectancy < 1 year).
16. 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:
    - History of major gastrointestinal tract surgery such as gastrectomy, gastroenterostomy, or bowel resection.
    - Currently active or previously active inflammatory bowel disease during the 12 months prior to Study Visit 1.
    - Currently active gastritis, duodenal or gastric ulcers, or gastrointestinal/rectal bleeding during the 3 months prior to Study Visit 1.
    - Current pancreatitis or evidence of impaired pancreatic function/injury as indicated by abnormal lipase or amylase.
    - Evidence of hepatic disease as determined by any one of the following: AST or ALT values exceeding 3 x ULN at Study Visit 1, a history of hepatic encephalopathy, a history of esophageal varices, or a history of portocaval shunt.
    - Current treatment with cholestyramine and colestipol resins.
17. Any surgical or medical condition that in the opinion of the investigator may place the patient at higher risk from his/her participation in the study or is likely to prevent the patient from complying with the requirements of the study or completing the study.
18. History of noncompliance to medical regimens or unwillingness to comply with the study protocol.
19. Any condition that in the opinion of the investigator or the Novartis medical monitor would jeopardize the evaluation of efficacy or safety.
20. Persons directly involved in the execution of this protocol.
21. Use of other investigational drugs within 30 days or 5 half-lives prior to Visit 1, whichever is longer.
22. Known or suspected contraindications to or history of hypersensitivity to any of the study drugs or to drugs belonging to the same therapeutic class (e.g., renin inhibitors) as the study drug.
23. History of malignancy of any organ system, treated or untreated, within the past 5 years whether or not there is evidence of local recurrence or metastases, with the exception of localized basal cell carcinoma of the skin.
24. 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).
25. Women of child-bearing potential (WOCBP), 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 meet the following definition of post-menopausal: 12 months of natural (spontaneous) amenorrhea or 6 months of spontaneous amenorrhea with serum FSH levels > 40 mIU/m or 6 weeks post surgical bilateral oophorectomy with or without hysterectomy OR are using one or more of the following acceptable methods of contraception: surgical sterilization (e.g., bilateral or tubal ligation), hormonal contraception (implantable, patch, oral), and double-barrier methods (any double combination of: IUD, male or female condom with spermicidal gel, diaphragm, sponge, cervical cap) if accepted by local ethics committees. Reliable contraception should be maintained throughout the study and for at least 7 days after study drug discontinuation.

26. Known or suspected bilateral renal artery stenosis.
27. Clinically symptomatic heart failure NYHA class IV.
28. For those patients participating in the cardiac-MRI sub-study, the following exclusion criteria also apply:
    - Use of pacemakers, ICD, defibrillators or any device which interferes with an MRI.
    - Patients with non-sinus rhythm.
    - Patients who cannot lie supine for at least 30 minutes.
    - Patients who cannot hold their breath for 15 seconds.
    - Presence of cranial aneurysm clips or ocular metallic shards.
    - Patients whose body structure (e.g., weight, height, body circumference, etc.) exceeds the restrictions of the local site MRI instrument.
    - Significant claustrophobia (not responsive to light and/or intravenous anxiolytics).