PARENT Trial Pilot

Pulmonary **A**rtery Pressure **R**eduction with **ENT**resto (sacubitril/valsartan)

Detailed Protocol

Version 4.2

This pilot study will compare the hemodynamic impact of approved drugs for heart failure (HF) on the elevated pulmonary artery pressures measured by an implanted monitoring device that is also approved for such patients. Both the medications and the monitoring device will be used according to approved indications. The only aspects of the study that are not standard care will be the increased frequency of pressure measurement and clinical assessment schedule.

I. BACKGROUND AND STUDY RATIONALE

a. Background

Almost 25 years ago, the CONSENSUS and SOLVD trails demonstrated a decrease in the mortality rate of patients with heart failure with reduced ejection fraction (HFrEF) on angiotensin-converting enzyme inhibitors (ACEi).[1, 2] Since then, ACEi have been a cornerstone HFrEF treatment. They are included in every major set of guidelines for HFrEF management.[3, 4] Angiotensin receptor blockers (ARB's, such as valsartan) have similarly been shown to decrease the mortality rate of patients with HFrEF for patients who could not tolerate ACEi therapy. [5, 6]

The Medication: The newest neurohormonal therapy approved for heart failure (August 2015) is sacubitril/valsartan (trade name Entresto). This medication is the first of a new family of agents (ARNI = angiotensin receptor antagonist with neprolysin inhibitor), combining the approved angiotensin receptor blocker valsartan with sacubitril, an inhibitor of neprilysin, which is a neutral endopeptidase that degrades endogenous vasoactive peptides.[7 ,8,9,10] Sacubitril increases circulating natriuretic peptides, which have been shown to facilitate natriuresis and vasodilation. Entresto reduces fluid retention and vasoconstriction that contribute to heart failure symptoms, and is also thought to decrease apoptosis and remodeling that lead to disease progression.[11]

The Monitoring Device: Progress in HF management outside the hospital has included validation of a strategy of ongoing monitoring of pulmonary artery pressures every day from home via a monitor implanted in a distal pulmonary arteriole, the CardioMEMS device. The information is transmitted to a website where it is reviewed by the HF team, who can intervene to adjust diuretics and other medications by phone to avert decompensation and re-hospitalization. The device received FDA approval in mid 2014, and is now being implanted in many cardiac catheterization laboratories, including at Brigham and Women's Hospital. The pressure information is reviewed regularly by the HF management team who are in regular contact with the patient to aid in management decisions.

b. Previous Pre-Clinical or Clinical Studies

The Medication: Entresto (sacubitril/valsartan) was first tested in hypertensive patients in 2010, compared to valsartan (an ARB) alone.[12] In a study of over 1300 patients, Entresto reduced blood pressure more than the valsartan alone..[12] In the PARADIGM-HF trial of 8442 patients, Entresto was shown to be superior to the ACEi enalapril, reducing the risk of death and hospitalization among patients with heart failure with reduced ejection fraction (HFrEF).[13] The study was stopped early for overwhelming benefit after a median follow-up of 27 months, at which time the hazard ratio for the primary outcome of death/HF hospitalization was 0.80 (95% CI 0.73-0.87) for patients randomized to Entresto, as compared to enalapril. The hazard ratio for reducing all cause mortality was 0.84. These impressive results lead the FDA to grant priority review and full approval in August 2015. Entresto is now being used increasingly in the care of patients with HFrEF.

The Monitoring Device: The CardioMEMS HF System, a wireless hemodynamic monitoring system has been shown to measure pulmonary artery pressures reliably over years. The device was implanted in all patients in the randomized single-blind CHAMPION trial, which compared the management strategy using these pressures together with clinical information to guide therapy, compared to management based only on weight and symptoms in patients whose care team were not able to see the pressure information. The device was associated with a 37% reduction in HF hospitalizations and a reduction in total hospitalizations, and the freedom from device-related complications was 98.6%. As of May 2014 it was approved by the FDA for the management of HF in patients who had at least one hospitalization during the previous year for heart failure.[14] Subsequent information published this year in Lancet demonstrated a 48% reduction in hospitalization rate in the real-world setting when the control patients crossed over to pressure management strategy.[15]

c. Study Rationale

The clinical benefits of Entresto are widely accepted, but there are many pathways through which these benefits may be derived. The increase in circulating natriuretic peptides are considered to decrease myocardial apoptosis and ventricular remodeling and to oppose other systemic effects of adverse activation of the renin-angiotensin and sympathetic nervous systems. The natriuretic peptides also have direct hemodynamic effects on sodium and water excretion and on vascular tone. These effects could lead to reduction in elevated pulmonary artery pressures, which are associated with many of the symptoms of HF and with the development of pulmonary hypertension which impairs right heart function and contributes to development of secondary right heart failure.

This pilot study takes advantage of the availability of the home monitoring device for HF management, and will include only patients in whom this device has already been implanted for management according to clinical indications. It will test the primary hypothesis that the

replacing ACEI/ARB therapy with Entresto will lower pulmonary artery pressure at 6 weeks compared to continuation of ACE inhibitor/ARB therapy and that that improvement will be sustained over the course of 20 additional weeks of therapy. In addition, the immediate first-dose response will be assessed on the first day of administration, with the hypothesis that the first dose will lead to immediate reduction in pulmonary artery pressures. The durability of the effect will be assessed over the next 20 weeks during the longitudinal phase, with the hypothesis that early reductions in pulmonary artery pressure will be sustained.

II. OBJECTIVES AND ENDPOINTS

a. Specific Objectives and Hypotheses to Test in the Research Project

Co-Primary Objectives:

Intensive Phase:

- Determine the difference between mean change in PAPm after 6 weeks on Entresto compared to 6 weeks on continued ACEi/ARB

Acute First-Day Response

- Determine the change in PAPm between baseline and first 3 hours after the first dose of Entresto

Secondary Objectives:

- Determine the mean change in PAPm in both groups on Entresto from week 12 to week 32 in longitudinal study
- Determine the difference between mean change in PAPm from baseline on ACEI/ARB to 6 weeks on Entresto (Groups A and B)
- *Determine the change in distance walked during and the change in exercise recovery PAPm after a standard 6 minute walk test
- *Determine the impact of therapy over time on double Master's Step test[16], assessing changes in PAPm during recovery after test.
- *Determine the impact of therapy over time on Handgrip Test[17], assessing changes in PAPm, blood pressure and heart rate during isometric exercise and recovery after test.
- *Determine the impact of therapy over time on Stroop Color Test[18], assessing changes in PAPm, blood pressure and heart rate during mental stress challenge and recovery after test.
- *Determine the change in NT-proBNP and the BNP/NT-proBNP ratio

Tertiary Objectives (Exploratory):

- Examine the relationship of change in PAPm to change in the questions in the Kansas City Cardiomyopathy Questionnaire (KCCQ) 3, 7,8,9 which describe the severity of symptoms of congestion
- Determine the mean change in total daily diuretic dose while on Entresto

**Will be 3 comparisons:*

1) 6 weeks of Entresto vs 6 weeks of continued ACEI/ARB (Group A compared to B at 6 weeks)

2) Baseline on ACEI/ARB compared to 6 weeks on Entresto (Groups A and B combined)

3) 12 weeks on Entresto compared to 32 weeks on Entresto in longitudinal study (all pts)

II. STUDY DESIGN

The study is a randomized, active comparator study of the hemodynamic effects of Entresto vs. ACEi/ARB as measured by an implantable hemodynamic monitor. Formal blinding is not possible due to the lack of placebos available to match all potential ACE inhibitors and ARBs, but every effort will be made to mask the specific drug assignment from the patients to limit bias. For safety reasons, physicians will not be blinded to study drug assignment.

III. PATIENT POPULATION

a. Inclusion/Exclusion Criteria

Inclusion Criteria

Key inclusion criteria: The disease to be studied is HF with reduced ejection fraction (HFrEF).

1. Patients able to provide written informed consent
2. Patients ≥18 years of age, male or female, in NYHA Class II- III HF, previously hospitalized for HFrEF with LVEF < 35% (measured within the past year), and who have no subsequent LVEF>35%.
3. Systolic BP ≥ 95 mm Hg at most recent clinical assessment.
4. Stable, ambulatory patients without the need for change in diuretics and other HF drugs (RAS blockers, beta blockers or mineralocorticoid receptor blockers) during the past 5 days
5. Currently treated with an ACEi or ARB
6. CardioMEMS HF System implanted for NYHA Class III HF. Patient transmitting information regularly and system functioning appropriately.
7. NT-proBNP > 500 pg/ml within 90 days of CardioMEMS implantation.
8. Average PAPm >20mm Hg during the 7 days prior to enrollment, including at least 4 daily measurements.

   Women of childbearing age must be practicing a highly effective method of contraception Acceptable methods of "high effective contraception" include abstinence, prior sterilization, contraceptive implants, intrauterine device, injectable contraception, contraception pills, contraception patches, and contraceptive rings.

Exclusion Criteria

1. Treatment with vasodilators (other than nitrates, hydralazine) and/or IV inotropic drugs.
2. Entresto taken within the past 30 days.
3. History of hypersensitivity, intolerance or angioedema to previous renin-angiotensin system (RAS) blocker, ACE inhibitor, ARB, or Entresto.
4. eGFR < 30 ml/min/1.73 m2 as measured by the simplified MDRD formula.
5. Serum potassium > 5.5 mmol/L.
6. Acute coronary syndrome, stroke, transient ischemic attack, cardiovascular surgery, PCI, or carotid angioplasty within the preceding 3 months.
7. Coronary or carotid artery disease likely to require surgical or percutaneous intervention within 3 months after trial entry.
8. Non-cardiac condition(s) as the primary cause of dyspnea.
9. Implantation of a cardiac resynchronization therapy device (CRT/D) within the preceding 3 months or intent to implant a CRT/D, which may alter the pressures during the course of the study.
10. History of heart transplantation, placement of an LVAD, listing for Status IA for cardiac transplantation or planned placement of an LVAD within 3 months following randomization.
11. Documented untreated ventricular arrhythmia with syncopal episodes within the prior 3 months.
12. Symptomatic bradycardia or second or third degree heart block without a pacemaker.
13. Hepatic dysfunction, as evidenced by total bilirubin > 3 mg/dl.
14. Pregnancy
15. Women who are breastfeeding
16. Chronic lithium use
17. Participation in another study with investigational drug/device within the past 30 days

b. Source of Subjects

Research staff will identify potential patients by reviewing the panel of patients at Brigham and Women's Hospital (BWH) and Massachusetts General Hospital (MGH) with CardioMEMS devices. Patients must carry a diagnosis of HFrEF and have a documented ejection fraction ≤35% within the past year so that they have an indication for Entresto Patients must also have a previously placed CardioMEMS device to allow measurement of pulmonary pressures during the study. This study is open to individuals of both genders and all racial/ethnic backgrounds who are over the age of 18. Only adult patients will be considered for enrollment because Entresto has only been studied and FDA approved for adults.

IV. SUBJECT ENROLLMENT

a. Identification of Patients and Consent

The investigators and study staff will screen the outpatient cardiology clinic rosters to identify eligible subjects. If a subject is eligible, the investigator and/or study staff member will follow Partners Human Research Committee (PHRC) guidelines on recruitment. Permission to approach a potential subject will be obtained from the attending physician who will gain permission from the potential subject before a study staff member proceeds to introduce the study.

A licensed physician investigator will obtain written informed consent from subjects after all aspects of the study have been discussed and the potential subject has agreed to participate in the study. Sufficient time will be allowed for the potential subject to review the consent form. All questions will be answered by the investigator before the consent form is signed. Contact information will be given to the potential subject so that he or she may contact the study physician or staff with any questions or concerns.

When a potential subject is the investigator's own patient, every effort will be made to have an investigator other than the patient's physician obtain informed consent. It will be made clear to the potential subject that participation in the study is entirely voluntary and that their decision will not affect their care now or in the future.

b. Treatment Assignment and Randomization

Randomized codes designating treatment group assignment will be generated for each patient. After informed consent is obtained, study personnel will obtain assigned to treatment group A or B based on the relevant randomization code.

Three study drugs will be utilized during the study:

Study Drug A = Masked Placebo, dosed twice daily

Study Drug B = Masked Active Entresto

Study Drug C = Masked Active Entresto

Group A will receive Study Drug A + Study Drug B for weeks 1-6 , Study drug A + Study Drug C for weeks 6-12, and then open-label Entresto only for weeks 13-32.

Group B will receive Study drug A + their previous ACEi/ARB for weeks 1-6, and then, after a 2 day (minimum 36 hours as per FDA labelling) washout period, switch to Study Drug A + Study Drug C for weeks 7-12. This group will then receive open-label Entresto only for weeks 13-32 (as with Group A).

V. STUDY PROCEDURES

a. Visit Schedule and Assessments

Over the course of the study, patients will come in for a total of 10 clinic visits (baseline visit, 6 during the intensive phase and 3 during the longitudinal phase) during which the following parameters will be measured:

		Intensive Phase						**Longitudinal Phase**		
Visit	Enroll/ Baseline Assmnt.	Week 2 Visit	Week 4 Visit	Week 6 Clinic Visit	Week 8 Visit	Week 10 Visit	Week 12 Clinic Visit	Week 18 Clinic Visit	Week 24 Clinic Visit	Week 32 Clinic Visit
Inclusion/ Exclusion	**X**									
Informed Consent	**X**									
Physical Exam	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Symptom and Side Effect Assessment		**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
PAP Recording CardioMEMS	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
6 Minute Walk Test	**X**			**X**			**X**			**X**
NT-ProBNP & BNP/NT-ProBNP	**X**			**X**			**X**			**X**
*Safety Labs		**X (Group A)**			**X (Group B)**					
Urine Pregnancy Test for Women of Childbearing Age	**X**									
Quality of Life (KCCQ)	**X**			**X**			**X**			**X**
Double Master's step test	**X**			**X**			**X**			**X**
Handrip test	**X**			**X**			**X**			**X**
Stroop color test	**X**			**X**			**X**			**X**

**Safety labs (potassium and creatinine) will also be drawn within 2 weeks any dose change of either Entresto or ACEi/ARB*

b. Drug Administration and Drug Dosing Guidelines

Entresto dosing

Entresto (valsartan/sacubitril) will be given to patients during the study. This FDA approved drug is currently available in three doses: 24/26 mg, 49/51 mg, and 97/103 mg (equivalent to 50 mg, 100 mg, and 200 mg of LCZ696). Entresto is dosed twice a day. Patients will initially be transitioned to a dose of Entresto that is based on their previous ACEi/ARB dose using the dosing conversion algorithm[19] provided by the manufacter (see table below):

Patients on ACEi	
Prior ACEi Dose	***Initial Starting Dose of Entresto***
Patients receiving a total daily dose of >10 mg of enalapril or therapeutically equivalent doses of another ACEi *Examples:* • Lisinopril >10mg • Ramipril >5mg	Start Entresto 49/51mg BID (100 mg LCZ696 BID)
Patients receiving a total daily dose of ≤10 mg of enalapril or therapeutically equivalent doses of another ACEi *Examples:* • Lisinopril ≤10 mg • Ramipril ≤5 mg	Start Entresto 24/26mg BID (50 mg LCZ696 BID)
Patients on ARB	
Prior ARB Dose	***Initial Starting Dose of Entresto***
Patients receiving a total daily dose of >160 mg of valsartan or therapeutically equivalent doses of another ARB *Examples:* • Losartan >50 mg • Olmesartan >10 mg	Start Entresto at 49/51 mg BID (100 mg LCZ696 BID)
Patients receiving a total daily dose of ≤160 mg of valsartan or therapeutically equivalent doses of another ARB *Examples:* • Losartan ≤50 mg • Olmesartan ≤10 mg	Start Entresto at a dose of 24/26 mg BID (50mg of LCZ696 BID)

Dosage of Entresto will be titrated at the 2 and 4 week visits towards the maximum dose of 97/103 mg bid as tolerated.

ACEi/ARB Dosing

Following randomization atients assigned to group B will restart their previously prescribed ACEi/ARB at the previously prescribed dose. This dose will be further titrated towards the target dose as directed by guidelines at the 2 and 4 week visits as tolerated.

Placebo Dosing

	Group A	**Group B**
Weeks 1-6	Placebo 1 pill BID	Placebo 1 pill BID
Weeks 7-12	Placebo 1 pill BID	Placebo 1 pill BID
Weeks 13-32	No placebo	No placebo

Method

Entresto is only available orally.

Schedule of Administration

Entresto is administered twice a day. On day 5 and day 47, patients will be instructed to hold their other morning medications and take only their first dose of Entresto and placebo or ACEi/ARB and placebo. They will then be asked to measure their PA pressures using their home CardioMEMS device 1, 2, and 3 hours after their first dose of Entresto or ACEi/ARB.

Both groups will do this on day 5 and day 47. On day 5, Group A will be measuring the first dose effect of Entresto and Group B will be measuring the first dose effect of ACEi/ARB after the washout period. On day 47, Group A will be measuring the acute effects of Entresto after 6 weeks of therapy and Group B will be measuring the first dose effects of Entresto.

Patients will also be asked to complete this “acute PA pressure measurement” schedule, i.e. holding morning medications, measuring PA pressure before and at hours 1, 2, 3 after their morning dose of Entresto or ACEi/ARB, after any dosing change.

On all other days, patients will take their morning dose of Entresto or ACEi/ARNB and placebo with their other morning medications. The evening dose of Entresto or ACEi/ARB and placebo can be taken with other evening medications as well.

Dose Modifications

At each clinic visit, if clinically indicated, the dose of Entresto and/or ACEi/ARB will be uptitrated if possible, per standard clinical protocol depending on blood pressure and tolerability. The goal dose of Entresto for all patients will be 97/103 mg BID (dose studied in the trials). ACE-inhibitors and ARBs will be titrated to the effective target doses prescribed by clinical guidelines. fter each medication dose change (of either Entresto or ACEi/ARB) the patients will

be asked to measure "acute PA pressures" at home (see above regimen) and have safety labs will be checked within 2 weeks of the dosing change. Patients will be called by a study nurse 2-3 days after any dosing changes to assess for any side effects.

Toxicities

In this study, we will be supplying patients Entresto, a chronic heart failure medication which has been proven efficacious in large, randomized clinical research trials. After any dosing changes, of either Entresto or ACEi/ARB, for the first administration of the new dose, patients will hold their other medications, measure their PA pressures before medication administration and then every hour for 3 hours after the new dose. Patients will be called by a study nurse 2-3 days after any dosing changes to assess for any side effects.

During the ACEi/ARB "washout periods," all patients will have 24/7 access to study staff and/or study physicians to report any new symptoms or ask questions.

Similar to ACEi therapy, Entresto has a small risk of angioedema (0.2% in the Entresto group compared to 0.1% in the ACEi group in the PARADIGM trial, with no incidence of upper airway obstruction). To eliminate any increased risk of angioedema from prior ACEi or ARB exposure in this study, all patients will undergo a mandatory 2 day (minimum 36 hours as per FDA labelling) washout period between any administration of these medications and Entresto administration. This is consistent with prior clinical trials and the standard of care as would be practiced for any patient switching from ACEi to Entresto, regardless of whether or not they were enrolled in this study.

c. Devices to be Used

Only HF patients with previously implanted CardioMEMS devices will be eligible for enrollment. The CardioMEMS device has been studied extensively in previously clinical trials and shown to be both effective and safe, decreasing HF hospitalization by 37%, with freedom from device-related or system-related complication rate of 98.6%.[14] The FDA approved the CardioMEMS device on May 28, 2014 for patients with NYHA III heart failure who have been hospitalized for heart failure within the previous year. Once the device is implanted, patients are set up with a home monitoring system and instructed to transmit their PA pressures daily. They record and transmit their pulmonary artery pressures non-invasively by laying on a special pillow connected to a home recording and transmission consol. Each recording requires that the patient lay still for approximately 18 seconds. The PA pressure measurement is automatically and electronically transmitted to a trained HF nurse who checks the recording for accuracy and reliability. If the recording is not acceptable, the monitoring nurse will call the patient and ask that the recording be repeated. The recording and transmission process is quick and completely painless. The PA pressure measurement and waveforms are visible to the monitoring nurse and the clinical team, but not to the patients.

Each CardioMEMS recording provides a PA systolic (PAPs), diastolic (PAPd) and mean (PAPm) pressure as well as the tracings. These measurements and their trend over time are reviewed by the patient's heart failure team. Medications and other therapies are adjusted based on these trends. Patients are called every few days to review their trends and discuss medication changes. If a patient has an acute change in their measurements, they are called as part of standard clinical care the next business day to assess their clinical status and potential changes in therapy.

Patients will continue their regular, daily monitoring schedule just as before the trial. The only change will be additional PA pressure measurements will be "acute PAP measurements" before and at hours 1,2,3 after Entresto/ACEi/ARB on day 5 and 47. Patients will also be asked to measure their PA pressure on day 5 and 47 in the evening, before they take their evening dose of Entresto/ACEi/ARB.

"Acute PA pressure measurements" will also be obtained on the first day of any new dosing regimen (after any dosing changes) for safety.

PA pressure measurements before and at 5 minute intervals for 30 minutes after the 6 minute walk test will be performed by the study staff in the clinic setting.

PA pressure measurements before and at 5 minute intervals for 30 minutes after the double Master's Step test will be performed by the study staff in the clinic setting.

PA pressure and blood pressure measurements before, during the Handgrip test (with 30 seconds intervals during the 2-minute test) and at 5 minutes intervals for 15 minutes of recovery will be performed by the study staff in the clinic setting. Heart rate is going to be recorded throughout test and recovery.

PA pressure and blood pressure measurements before, during the Stroop Color test (with 30 seconds intervals during the 3-minute test) and at 5 minutes intervals for 15 minutes of recovery will be performed by the study staff in the clinic setting. Heart rate is going to be recorded throughout test and recovery.

d. Procedures/Surgical Interventions

There will be no procedures or surgical interventions undertaken during this study.

e. Data to be Collected

Baseline Clinic Visit, Variables to be Collected:

- **Demographics and HF History (first visit only)**
  - Age
  - Sex (male/female)
  - Race (white, black, other)

- Ethnicity (Hispanic, non-Hispanic)
- Type of Insurance (Medicare, Medicaid, commercial, other)
- Etiology of heart failure (ischemic, nonischemic)
- NYHA (I-IV) in clinic
- Number of previous hospitalizations for heart failure in the past year
- Time since diagnosis of heart failure (years)
- Time since placement of CardioMEMS (months
- Time of most recent echo (< 1 month, 1-5 months, 6-12 months, > 1 year
    - LVEF
    - LVDD mm
    - MR (0,trace,mild/mod/mod-sev/severe)
    - TR (0,trace,mild/mod/mod-sev/severe)

- **Medication Data**
    - Beta blocker total daily dose (metoprolol equivalents, mg/d), has there been a dose change
    - ACEi no/yes (if yes, total daily dose in captopril equivalents, mg/d), has there been a dose change
    - ARB no/yes (if yes, total daily dose in valsartan equivalents, mg/d), has there been a dose change
    - Nitrate no/yes (if yes total daily dose mg), has there been a dose change
    - Hydralazine no/yes (if yes total daily dose mg), has there been a dose change
    - Diuretic total daily dose (furosemide equivalents, mg/d), has there been a dose change
    - Use of thiazide diuretic in past 14 days (no/yes) if yes, # days, has there been a dose change
- **Clinical Assessment**
    - History:
        - Orthopnea or paroxysmal nocturnal dyspnea within last 14 days (no/yes) If yes, # days
        - Bendopnea within last 14 days (no/yes) If yes, # days
        - Dizziness or lightheadedness on standing (no/yes)
            - If yes, rare / 1-2 x weekly / only if stand quickly / often
        - Symptoms limiting bathing and dressing (no/yes) If yes, #days
    - Examination
        - HR sitting
        - Rhythm (from EKG) regular (SR/paced/
        - SBP/ DBP mmHg sitting and standing
        - Jugular venous pressure (estimated cmH20)
        - S3 yes/ no

        - Systolic murmur (0,1,2,3,4)
        - Rales (absent/bases/one-quarter/one third up)
        - Hepatomegaly no/yes if yes, 1-3, 4-6, > 6 cm)
        - Peripheral edema (none/trace/1+/2+/3+/4+)
- **PA pressure measurements baseline in clinic (recorded by staff)**
    - PA systolic/ diastolic/ mean pressures at rest (in clinic, mmHg)
- **Planned Medication Changes after this Visit**
    - Do you plan to uptitrate Entresto or ACEi/ARB?
    - If not, why not? (postural hypotension, resting hypotension, renal dysfunction, fatigue)
    - Did you consider decreasing diuretics instead?
    - If not, why not? (PAP not low, signs of fluid retention _____, symptoms of fluid retention _____)

- **6 Minute Walk Test**
    - Distance walked (meters) # stops if any
    - PA systolic/diastolic, and mean pressure immediately before 6 minute walk

      Then repeat X 7: Immediately after walk, 5, 10, 15, 20, 25, 30 minutes
- **Double Master's step test**
    - PA systolic/diastolic, and mean pressure immediately before double Master's step test .

      Then repeat X 7: Immediately after walk, 5, 10, 15, 20, 25, 30 minutes

- **Handgrip test**
    - Maximal handgrip effort
    - PA systolic/diastolic, and mean pressure
        - Immediately before
        - Each 30 seconds during the test (total= 4 measurements)
        - Then repeat X 3: 5, 10, 15 minutes after test

    - Blood pressure
        - Immediately before
        - Each 30 seconds during the test (total= 4 measurements)
        - Then repeat X 3: 5, 10, 15 minutes after test
    - Heart rate
        - Continuously recorded during the test and recovery

- **Stroop Color test**
    - PA systolic/diastolic, and mean pressure
        - Immediately before

        - Each 30 seconds during the test (total= 6 measurements)
        - Then repeat X 3: 5, 10, 15 minutes after test

    - Blood pressure
        - Immediately before
        - Each 30 seconds during the test (total= 6 measurements)
        - Then repeat X 3: 5, 10, 15 minutes after test
    - Heart rate
        - Continuously recorded during the test and recovery
    - Level of difficulty of the test
- **Quality of Life KCCQ Questionnaire**
    - Total score and specifically questions 3,7,8,9 which relate to symptoms of congestion
- **Laboratory Data**
    - Serum sodium (in clinic, mEq/L)
    - Serum potassium (in clinic, mEq/L)
    - Blood urea nitrogen (in clinic, mEq/L)
    - Serum creatinine (in clinic, mEq/L)
    - NT-proBNP (in clinic, ng/L)
    - Urine pregnancy test for women of childbearing age

PA pressure measurements done by the patient at home

"Acute PAP Measurement" (Done on Days 5 and 47 and done on the first day of any dosing change)

- Baseline Time 1 (time before taking medication) – 1st PA pressure measurement
- Time of measurement 1 (1 hour post dose) – 2nd PA pressure measurement
- Time of measurement 2 (2 hours post dose) – 3rd PA pressure measurement
- Time of measurement 3 (3 hours post dose) – 4th PA pressure measurement
- Heart rate
- PA pressures
- Any instructions required to optimize tracing (e.g. breath-hold, turn on pillow, reposition wand)
- Any comments on PA tracing morphology

Routine Daily Pulmonary Pressure Data

Transmitted routinely in the morning before meds, emphasis on Mon and Thurs

- Time of measurement
- Morning medications taken? No/if yes, how long previously
- Heart rate
- PA pressures (measured at end-expiration if variable)
- Any comments on PA tracing morphology

ALL CLINIC VISITS AFTER RANDOMIZATION:

- **Hospitalization or ED visit since last visit? No / Yes, if yes, When**
- **If so, cause:**
  - HF/Syncope or Heart rhythm/ Other cardiac / Renal / Pulmonary
  - Other non-cardiac
- **Medication Data**
  - Beta blocker total daily dose (metoprolol equivalents, mg/d), any change since the last visit?
  - ACEi no/yes (if yes, total daily dose in captopril equivalents, mg/d) , any change since the last visit?
  - ARB no/yes (if yes, total daily dose in valsartan equivalents, mg/d), any change since the last visit?
  - Nitrate no/yes (if yes, total daily dose mg), any change since the last visit?
  - Hydralazine no/yes (if yes, total daily dose mg), any change since the last visit?
  - Diuretic total daily dose (furosemide equivalents, mg/d) , any change since the last visit?
  - Use of thiazide diuretic in past 14 days (no/yes) if yes, # days, any change since the last visit?
  - Study drug # tablets / day
- **Side Effect Assessment**
  - Swelling/respiratory distress/angioedema/anaphylaxis (yes/no)
  - Decreased urinary output (yes/no)
  - Palpitations (yes/no)
  - New/changed difficulty breathing (yes/no)
  - New/changed orthopnea, paroxysmal nocturnal dyspnea, peripheral edema (yes/no)
- **Clinical Assessment**
  - History:
    - Orthopnea within last 14 days (no/yes) If yes, # days
    - Bendopnea within last 14 days (no/yes) If yes, # days
    - Dizziness or lightheadedness on standing (no/yes)
      - If yes, rare / 1-2 x weekly / only if stand quickly / often
    - Symptoms limiting bathing and dressing (no/yes) If yes, #days
  - Examination
    - HR sitting
    - Rhythm (from EKG) regular (SR/paced/
    - SBP/ DBP mmHg sitting /// SBP/DBP mmHg standing
    - Jugular venous pressure (estimated cmH20)
    - S3 yes/ no
    - Systolic murmur (0,1,2,3,4)

        - Rales (absent/bases/one-quarter/one third up)
        - Hepatomegaly no/yes if yes, 1-3, 4-6, > 6 cm)
        - Peripheral edema (none/trace/1+/2+/3+/4+)
    - Laboratory Data
        - Urine pregnancy test for women of childbearing age
    - PA systolic/ diastolic/ mean pressures at rest (in clinic, mmHg)

Additional Data Obtained At Endpoints As Below:

+ Week 6, Week 12, (Week 24) Week 32, for study endpoints :

- 6 Minute Walk Test
    - Distance walked (meters) # stops if any
    - PA pressures after 6 minute walk
        - PA systolic/diastolic/mean
        - Repeat X 7: Immediately after peak exercise 5, 10, 15, 20, 25, 30 minutes
- Double Master's step test
    - PA pressures after step test
        - PA systolic/diastolic/mean
        - Repeat X 7: Immediately after peak exercise 5, 10, 15, 20, 25, 30 minutes
- **Handgrip test**
    - Maximal handgrip effort
    - PA systolic/ diastolic/ mean
        - Immediately before
        - Each 30 seconds during the test (total= 4 measurements)
        - Then repeat X 3: 5, 10, 15 minutes after test
    - Blood pressure
        - Immediately before
        - Each 30 seconds during the test (total= 4 measurements)
        - Then repeat X 3: 5, 10, 15 minutes after test
    - Heart rate
        - Continuously recorded during the test and recovery
- **Stroop Color test**
    - PA systolic/diastolic/ mean
        - Immediately before
        - Each 30 seconds during the test (total= 6 measurements)
        - Then repeat X 3: 5, 10, 15 minutes after test
    - Blood pressure

        - Immediately before
        - Each 30 seconds during the test (total= 6 measurements)
        - Then repeat X 3: 5, 10, 15 minutes after test
    - Heart rate
        - Continuously recorded during the test and recovery
    - Level of difficulty of the test

- Quality of Life KCCQ questionnaire, total score and specifically questions 3,7,8,9
- Natriuretic peptides
    - NT proBNP
    - BNP

+ Week 2, Week 6, Week 8, Week 12, Week 24, Week 32 and after any adjustment of study medication or if otherwise clinically indicated for standard care

- Serum sodium (in clinic, mEq/L)
- Serum potassium (in clinic, mEq/L)
- Blood urea nitrogen (in clinic, mEq/L)
- Serum creatinine (in clinic, mEq/L)

Pulmonary pressure monitoring transmitted from home:

Patients will transmit pressures every morning before taking medications. Specific case report data entry in addition to the clinic measurements and first dose time points at home will include PA pressures every Monday and Thursday and daily for 5 days following any change in study drug or in other heart failure medications. All transmitted pressure information remains available on the CardioMEMS website so can be retrieved at any time if other questions arise about trends from pressure transmitted on other days.

VI. STATISTICAL METHODS AND DATA ANALYSIS

f. Specific Data Variables being Collected for the Study (e.g. Data Collection Sheet)

Baseline Visit Data Collection Sheet

Demographic Data	
Age	_____ (years)
Sex	____Male ____Female
Race	____ White ____Black ____Other
Ethnicity	____ Non-Hispanic ____Hispanic
Type of Insurance	____ Medicare ____Medicaid ____Commercial ____ Other
Etiology of Heart Failure	____Male ____Non-Ischemic
Ejection Fraction	_____ (%)
NYHA	____ I ____ II ____ III ____IV
Number of Previous HF Hospitalizations within the Past Year	_____ (hospitalizations)
Time since diagnosis of heart failure	_____ (years)
Time Since Placement of CardioMEMS	_____ (months)
Time Since Most Recent Echo	_____< 1 month _____ 1-5 months _____ 6-12 months _____ > 1 year
Most Recent Echo Results	LVEF _____%

	LVDD _____ mm MR ___ none ___ trace ___ mild ___mod ___ mod/severe ___ severe TR ___ none ___ trace ___ mild ___mod ___ mod/severe ___ severe
Medication Data	
Beta Blocker Total Daily Dose	_____ (metoprolol equivalents, mg/d) _____ Not on a beta blocker Any dose change since most recent clinic visit? _____ Yes _____No If there has been a recent dose change, describe: _____ Increased Dose _____ Decrease Dose Dose change: From _____mg/d to _____ mg/d.
ACEi Total Daily Dose	_____ (captopril equivalents, mg/d) _____ Not on an ACEi Any dose change since most recent clinic visit? _____ Yes _____No If there has been a recent dose change, describe: _____ Increased Dose _____ Decrease Dose Dose change: From _____mg/d to _____ mg/d.

ARB Total Daily Dose	_____ (valsartan equivalents, mg/d) _____ Not on an ARB Any dose change since most recent clinic visit? _____ Yes _____No If there has been a recent dose change, describe: _____ Increased Dose _____ Decrease Dose Dose change: From _____mg/d to _____ mg/d.
Nitrates	_____ (total daily dose equivalents, mg/d) _____ Not on nitrates Any dose change since most recent clinic visit? _____ Yes _____No If there has been a recent dose change, describe: _____ Increased Dose _____ Decrease Dose Dose change: From _____mg/d to _____ mg/d.
Hydralazine	_____ (total daily dose equivalents, mg/d) _____ Not on hydralazine Any dose change since most recent clinic visit? _____ Yes _____No If there has been a recent dose change, describe: _____ Increased Dose _____ Decrease Dose Dose change: From _____mg/d to _____ mg/d.

Diuretic Total Daily Dose	_____ (furosemide equivalents, mg/d) _____ Not on diuretics Any dose change since most recent clinic visit? _____ Yes _____No If there has been a recent dose change, describe: _____ Increased Dose _____ Decrease Dose Dose change: From _____mg/d to _____ mg/d.
Use of thiazide diuretic in past 14 days	_____ Yes If yes, how many days ago?_____ days _____ No Any dose change since most recent clinic visit? _____ Yes _____No If there has been a recent dose change, describe: _____ Increased Dose _____ Decrease Dose Dose change: From _____mg/d to _____ mg/d.
Clinical Assessment	
Orthopnea or paroxysmal nocturnal dyspnea within last 14 days	_____ Yes If yes, how many days_____ _____ No
Bendopnea within last 14 days	_____ Yes _____ No If yes, how many days? _____ days
Dizziness or lightheadedness on standing	_____ Yes _____ No dizziness or lightheadedness standing If yes, how often?

	_____ Rare _____ 1-2x/week _____ Only if Stand Quickly _____ Often
Symptoms limiting bathing and dressing	_____ Yes _____ No If yes, how many days has this happened?_____ days
Examination	
Heart Rate (sitting)	_____ (bpm)
Rhythm (from EKG)	_____ NSR _____ Irregular _____ Paced
Systolic Blood Pressure	_____ (mmHg)
Diastolic Blood Pressure	_____ (mmHg)
Systolic Blood Pressure (sitting)	_____ (mmHg)
Diastolic Blood Pressure (sitting)	_____ (mmHg)
Systolic Blood Pressure (standing)	_____ (mmHg)
Diastolic Blood Pressure (standing)	_____ (mmHg)
Jugular Venous Pressure	_____ (cmH20)
S3 present	____Yes ____No
Systolic Murmur	____Yes ____No If yes, how severe? _____1/6, _____2/6, _____ 3/6, _____4/6, _____5/6, _____6/6

Rales	____Yes ____No If yes, how severe? _____ bases, _____1/4, _____ 1/3, _____>1/2 or more of the way up
Hepatomegaly	____Yes ____No If yes, how severe? _____1-3cm below costal margin, _____4-6cm below costal margin, ___ >6cm below costal margin
Peripheral Edema	____None ____ Trace ____1+ _____2+
CardioMEMS Measurements (recorded by staff)	
PA Systolic Pressure (at rest)	_____ (mmHg)
PA Diastolic Pressure (at rest)	_____ (mmHg)
PA Mean Pressure (at rest)	_____ (mmHg)
Planned Medications Changes after this Visit	
Do you plan to uptitrate Entresto or ACEi/ARB?	_____ Yes _____ No
If not, why not?	_____ Postural hypotension _____ Resting hypotension _____ Renal dysfunction _____ Fatigue _____ Other (if "other," describe: _____)
If not, did you consider decreasing diuretics instead?	_____ Yes _____ No If no, why not? _____ PAP not low _____ Signs of fluid retention If so, what: _____

	_____ Symptoms of fluid retention If so, what: _____
6 Minute Walk Test	
Distance Walked	_____ (meters) _____ # of stops (if any)
Stopped Early (before six minutes)	_____ Yes _____ No *IF "YES" ONLY: (indicating that the patient stopped walking before 6 minutes had elapsed)* _____ Time Walked (minutes) _____ Distance Walked (meters) REASON FOR STOPPING EARLY (check only 1 as the "primary reason") _____ Orthopedic/Joint Pain _____ Chest Pain _____ Shortness of Breath _____ Fatigue _____ Leg Pain/Fatigue (not joint related) _____ Dizziness _____ Other
PA pressures immediately after walk	PA systolic _____ (mmHg) PA diastolic_____ (mmHg) PA mean _____ (mmHg)
PA pressures 5 minutes after stopping exercise	PA systolic _____ (mmHg) PA diastolic_____ (mmHg) PA mean _____ (mmHg)

PA pressures 10 minutes after stopping exercise	PA systolic _____ (mmHg) PA diastolic_____ (mmHg) PA mean _____ (mmHg)
PA pressures 15 minutes after stopping exercise	PA systolic _____ (mmHg) PA diastolic_____ (mmHg) PA mean _____ (mmHg)
PA pressures 20 minutes after stopping exercise	PA systolic _____ (mmHg) PA diastolic_____ (mmHg) PA mean _____ (mmHg)
PA pressures 25 minutes after stopping exercise	PA systolic _____ (mmHg) PA diastolic_____ (mmHg) PA mean _____ (mmHg)
PA pressures 30 minutes after stopping exercise	PA systolic _____ (mmHg) PA diastolic_____ (mmHg) PA mean _____ (mmHg)
Quality of Life	
KCCQ Score (total)	_____ (points
Score on Questions 3,7,8,9 which relate to symptoms of congestion	_____ (points)
Double Master's Step test	

Stopped Early (before three minutes)	_____ Yes _____ No *IF "YES" ONLY: (indicating that the patient stopped climbing before three minutes had elapsed)* _____ Time stepping (minutes) _____ Number of trips REASON FOR STOPPING EARLY (check only 1 as the "primary reason") _____ Orthopedic/Joint Pain _____ Chest Pain _____ Shortness of Breath _____ Fatigue _____ Leg Pain/Fatigue (not joint related) _____ Dizziness _____ Other
PA pressures immediately after test	PA systolic _____ (mmHg) PA diastolic_____ (mmHg) PA mean _____ (mmHg)

PA pressures 5 minutes after stopping test	PA systolic _____ (mmHg) PA diastolic_____ (mmHg) PA mean _____ (mmHg)
PA pressures 10 minutes after stopping test	PA systolic _____ (mmHg) PA diastolic_____ (mmHg) PA mean _____ (mmHg)
PA pressures 15 minutes after stopping test	PA systolic _____ (mmHg) PA diastolic_____ (mmHg) PA mean _____ (mmHg)
PA pressures 20 minutes after stopping test	PA systolic _____ (mmHg) PA diastolic_____ (mmHg) PA mean _____ (mmHg)

PA pressures 25 minutes after stopping test	PA systolic _____ (mmHg) PA diastolic_____ (mmHg) PA mean _____ (mmHg)
PA pressures 30 minutes after stopping test	PA systolic _____ (mmHg) PA diastolic_____ (mmHg) PA mean _____ (mmHg)
Handgrip test	
Maximal handrip effort	Max handgrip_____(Pounds Force)
PA pressures immediately before test	PA systolic _____ (mmHg) PA diastolic_____ (mmHg) PA mean _____ (mmHg)
Blood pressure immediately before test	BP systolic _____ (mmHg) BP diastolic_____ (mmHg)
Heart rate immediately before test	HR _____(bmp)

PA pressures at 30s of Handrip	PA systolic _____ (mmHg) PA diastolic_____ (mmHg) PA mean _____ (mmHg)
Blood pressure at 30s of Handrip	BP systolic _____ (mmHg) BP diastolic_____ (mmHg)
Heart rate at 30s of Handrip	HR _____(bmp)
PA pressures at 60s of Handrip	PA systolic _____ (mmHg) PA diastolic_____ (mmHg) PA mean _____ (mmHg)
Blood pressure at 60s of Handrip	BP systolic _____ (mmHg) BP diastolic_____ (mmHg)
Heart rate at 60s of Handrip	HR _____(bmp)
PA pressures at 90s of Handrip	PA systolic _____ (mmHg) PA diastolic_____ (mmHg) PA mean _____ (mmHg)
Blood pressure at 90s of Handrip	BP systolic _____ (mmHg)

	BP diastolic_____ (mmHg)
Heart rate at 90s of Handrip	HR _____(bmp)
PA pressures at 120s of Handrip	PA systolic _____ (mmHg) PA diastolic_____ (mmHg) PA mean _____ (mmHg)
Blood pressure at 120s of Handrip	BP systolic _____ (mmHg) BP diastolic_____ (mmHg)
Heart rate at 120s of Handrip	HR _____(bmp)
PA pressures 5 minutes after stopping the test	PA systolic _____ (mmHg) PA diastolic_____ (mmHg) PA mean _____ (mmHg)
Blood pressure 5 minutes after stopping the test	BP systolic _____ (mmHg) BP diastolic_____ (mmHg)
Heart rate 5 minutes after stopping the test	HR _____(bmp)
PA pressures 10 minutes after stopping the test	PA systolic _____ (mmHg) PA diastolic_____ (mmHg)

	PA mean _____ (mmHg)
Blood pressure 10 minutes after stopping the test	BP systolic _____ (mmHg) BP diastolic_____ (mmHg)
Heart rate 10 minutes after stopping the test	HR _____(bmp)
PA pressures 15 minutes after stopping the test	PA systolic _____ (mmHg) PA diastolic_____ (mmHg) PA mean _____ (mmHg)
Blood pressure 15 minutes after stopping the test	BP systolic _____ (mmHg) BP diastolic_____ (mmHg)
Heart rate 15 minutes after stopping the test	HR _____(bmp)
Stroop Color test	
PA pressures immediately before test	PA systolic _____ (mmHg) PA diastolic_____ (mmHg) PA mean _____ (mmHg)
Blood pressure immediately before test	BP systolic _____ (mmHg)

	BP diastolic_____ (mmHg)
Heart rate immediately before test	HR _____(bmp)
PA pressures at 30s of Stroop Color test	PA systolic _____ (mmHg) PA diastolic_____ (mmHg) PA mean _____ (mmHg)
Blood pressure at 30s of Stroop Color test	BP systolic _____ (mmHg) BP diastolic_____ (mmHg)
Heart rate at 30s of Stroop Color test	HR _____(bmp)
PA pressures at 60s of Stroop Color test	PA systolic _____ (mmHg) PA diastolic_____ (mmHg) PA mean _____ (mmHg)
Blood pressure at 60s of Stroop Color test	BP systolic _____ (mmHg) BP diastolic_____ (mmHg)
Heart rate at 60s of Stroop Color test	HR _____(bmp)
PA pressures at 90s of Stroop Color test	PA systolic _____ (mmHg)

	PA diastolic_____ (mmHg) PA mean _____ (mmHg)
Blood pressure at 90s of Stroop Color test	BP systolic _____ (mmHg) BP diastolic_____ (mmHg)
Heart rate at 90s of Stroop Color test	HR _____(bmp)
PA pressures at 120s of Stroop Color test	PA systolic _____ (mmHg) PA diastolic_____ (mmHg) PA mean _____ (mmHg)
Blood pressure at 120s of Stroop Color test	BP systolic _____ (mmHg) BP diastolic_____ (mmHg)
Heart rate at 120s of Stroop Color test	HR _____(bmp)
PA pressures at 150s of Stroop Color test	PA systolic _____ (mmHg) PA diastolic_____ (mmHg) PA mean _____ (mmHg)
Blood pressure at 150s of Stroop Color test	BP systolic _____ (mmHg)

	BP diastolic_____ (mmHg)
Heart rate at 150s of Stroop Color test	HR _____(bmp)
PA pressures at 180s of Stroop Color test	PA systolic _____ (mmHg) PA diastolic_____ (mmHg) PA mean _____ (mmHg)
Blood pressure at 180s of Stroop Color test	BP systolic _____ (mmHg) BP diastolic_____ (mmHg)
Heart rate at 180s of Stroop Color test	HR _____(bmp)
Level of difficulty	( ) non-stressful ( ) slightly stressful ( ) moderately stressful ( ) very stressful ( ) extremely stressful.
PA pressures 5 minutes after stopping the test	PA systolic _____ (mmHg) PA diastolic_____ (mmHg) PA mean _____ (mmHg)
Blood pressure 5 minutes after stopping the test	BP systolic _____ (mmHg) BP diastolic_____ (mmHg)
Heart rate 5 minutes after stopping the test	HR _____(bmp)

PA pressures 10 minutes after stopping the test	PA systolic _____ (mmHg) PA diastolic_____ (mmHg) PA mean _____ (mmHg)
Blood pressure 10 minutes after stopping the test	BP systolic _____ (mmHg) BP diastolic_____ (mmHg)
Heart rate 10 minutes after stopping the test	HR _____(bmp)
PA pressures 15 minutes after stopping the test	PA systolic _____ (mmHg) PA diastolic_____ (mmHg) PA mean _____ (mmHg)
Blood pressure 15 minutes after stopping the test	BP systolic _____ (mmHg) BP diastolic_____ (mmHg)
Heart rate 15 minutes after stopping the test	HR _____(bmp)
Laboratory Data	
Serum Sodium	_____ (in clinic, mEq/L)
Serum Potassium	_____ (in clinic, mEq/L)
Blood Urea Nitrogen	_____ (in clinic, mEq/L)
Serum Creatinine	_____ (in clinic, mEq/L)

NT-proBNP	_____ (ng/L)
Urine Pregnancy Test (for women of childbearing age)	_____ (Not Pregnant) _____ (Pregnant) * If pregnant, must discontinue Entresto or ACEi/ARB immediately

PA Pressure Measurements Done By Patient At Home Collection Sheet

Acute PAP Measurement (Days 5 and 47 and after any dose change)

Times recorded by patient **PAP measurements added by study staff**	
Baseline Time (time before medications taken)	_____:_____ AM/PM (record time) PA systolic _____ (mmHg) PA diastolic_____ (mmHg) PA mean _____ (mmHg)
Time medication taken	_____:_____ AM/PM (record time)
Measurement #1 (1 hours after dose)	_____:_____ AM/PM (record time) PA systolic _____ (mmHg) PA diastolic_____ (mmHg) PA mean _____ (mmHg)
Measurement #2 (2 hours after dose)	_____:_____ AM/PM (record time) PA systolic _____ (mmHg) PA diastolic_____ (mmHg)

	PA mean _____ (mmHg)
Measurement #3 (3 hours after dose)	_____:_____ AM/PM (record time) PA systolic _____ (mmHg) PA diastolic_____ (mmHg) PA mean _____ (mmHg)
Heart Rate	_____ beats/minutes
To be completed by study staff	
Any instructions required to optimize tracing	_____ Yes If so, what? _____ _____ No
Any comments on PA tracing morphology	

Routine Daily PA Pressure Data

Times recorded by patient **PAP measurements added by study staff**	
Time of PAP Measurement	_____:_____ AM/PM (record time)
Morning Medications Taken?	_____ Yes If yes, when? _____:_____ AM/PM (record time) _____ No
Heart Rate	_____ beats/minute
Measurement (study staff)	PA systolic _____ (mmHg) PA diastolic_____ (mmHg) PA mean _____ (mmHg)

Data Collection Form for ALL Clinic Visits After Randomization

Hospitalization or Emergency Room Visits	
Any hospitalizations or ER visits since your last study visit?	_____ Yes _____ No If yes, for what? _____ Heart Failure _____ Syncope _____ Heart Rhythm _____ Other cardiac _____ Kidney/Renal issue _____ Pulmonary/Lung issue _____ Other, non-cardiac reason
Medication Data	
Beta Blocker Total Daily Dose	_____ (metoprolol equivalents, mg/d) _____ Not on a beta blocker Any dose change since most recent clinic visit? _____ Yes _____No If there has been a recent dose change, describe: _____ Increased Dose _____ Decrease Dose Dose change: From _____mg/d to _____ mg/d.
ACEi Total Daily Dose	_____ (captopril equivalents, mg/d) _____ Not on an ACEi Any dose change since most recent clinic visit? _____ Yes _____No If there has been a recent dose change, describe:

	_____ Increased Dose _____ Decrease Dose Dose change: From _____mg/d to _____ mg/d. Any dose change since most recent clinic visit? _____ Yes _____No If there has been a recent dose change, describe: _____ Increased Dose _____ Decrease Dose Dose change: From _____mg/d to _____ mg/d.
ARB Total Daily Dose	_____ (valsartan equivalents, mg/d) _____ Not on an ARB Any dose change since most recent clinic visit? _____ Yes _____No If there has been a recent dose change, describe: _____ Increased Dose _____ Decrease Dose Dose change: From _____mg/d to _____ mg/d.
Nitrates	_____ (total daily dose equivalents, mg/d) _____ Not on nitrates Any dose change since most recent clinic visit? _____ Yes _____No If there has been a recent dose change, describe: _____ Increased Dose _____ Decrease Dose Dose change: From _____mg/d to _____ mg/d.

Hydralazine	_____ (total daily dose equivalents, mg/d) _____ Not on hydralazine Any dose change since most recent clinic visit? _____ Yes _____No If there has been a recent dose change, describe: _____ Increased Dose _____ Decrease Dose Dose change: From _____mg/d to _____ mg/d.
Diuretic Total Daily Dose	_____ (furosemide equivalents, mg/d) _____ Not on diuretics Any dose change since most recent clinic visit? _____ Yes _____No If there has been a recent dose change, describe: _____ Increased Dose _____ Decrease Dose Dose change: From _____mg/d to _____ mg/d.
Use of thiazide diuretic in past 14 days	_____ Yes If yes, how many days ago?_____ days _____ No Any dose change since most recent clinic visit? _____ Yes _____No If there has been a recent dose change, describe: _____ Increased Dose _____ Decrease Dose

	Dose change: From _____mg/d to _____ mg/d.
Study Drug # tablets/day	_____ Tablets/day
Was your Study Drug dose changed since your last clinic visit?	_____ Yes _____No If there has been a recent dose change, describe: _____ Increased Dose _____ Decrease Dose Dose change: From _____mg/d to _____ mg/d.
Side Effect Assessment **(within the last 14 days, does the patient report any of the following symptoms that are new or different/worsened)**	
Swelling/respiratory distress/angioedema/anaphylaxis	_____ Yes _____ No If yes, quantify severity (*check most severe symptom)* _____ Swelling (least severe) _____ Respiratory Distress _____ Angioedema _____ Anaphylaxis (most severe)
Palpitations	_____ Yes _____ No
Difficulty Breathing/Shortness of Breath	_____ Yes _____ No
Orthopnea	_____ Yes _____ No
Paroxysmal Nocturnal Dyspnea	_____ Yes _____ No
Peripheral Edema	_____ Yes _____ No
Clinical Assessment	

Orthopnea or paroxysmal nocturnal dyspnea within last 14 days	_____ Yes If yes, how many days? _____days _____ No
Bendopnea within last 14 days	_____ Yes If yes, how many days? _____ days _____ No
Dizziness or lightheadedness on standing	_____ Yes _____ No dizziness or lightheadedness standing If yes, how often? _____ Rare _____ 1-2x/week _____ Only if Stand Quickly _____ Often
Symptoms limiting bathing and dressing	_____ Yes If yes, how many days?_____ days _____ No
Examination	
Heart Rate (sitting)	_____ (bpm)
Rhythm (from EKG)	_____ NSR _____ Irregular _____ Paced
Systolic Blood Pressure (sitting)	_____ (mmHg)
Diastolic Blood Pressure (sitting)	_____ (mmHg)

Systolic Blood Pressure (standing)	_____ (mmHg)
Diastolic Blood Pressure (standing)	_____ (mmHg)
Jugular Venous Pressure	_____ (cmH20)
S3 present	____Yes ____No
Systolic Murmur	____Yes ____No If yes, how severe? _____1/6, _____2/6, _____ 3/6, _____4/6, _____5/6, _____6/6
Rales	____Yes ____No If yes, how severe? _____ bases, _____1/4, _____ 1/3, _____>1/2 or more of the way up
Hepatomegaly	____Yes ____No If yes, how severe? _____1-3cm below costal margin, _____4-6cm below costal margin, ___ >6cm below costal margin
Peripheral Edema	____None ____ Trace ____1+ _____2+
Laboratory Data	
Urine Pregnancy Test (for women of childbearing age)	_____ (Not Pregnant) _____ (Pregnant) * If pregnant, must discontinue Entresto or ACEi/ARB immediately
CardioMEMS Measurements (recorded by staff in clinic)	
PA Systolic Pressure (at rest)	_____ (mmHg)
PA Diastolic Pressure (at rest)	_____ (mmHg)
PA Mean Pressure (at rest)	_____ (mmHg)

Additional Data Obtained at Endpoint Visits

(In addition to the data collection sheet above for ALL visits, this additional data collection sheet will be used on weeks 6, 12, 24, 32 only)

6 Minute Walk Test	
Distance Walked	_____ (meters) _____ # of stops (if any)
Stopped Early (before six minutes)	_____ Yes _____ No *IF "YES" ONLY: (indicating that the patient stopped walking before 6 minutes had elapsed)* _____ Time Walked (minutes) _____ Distance Walked (meters) REASON FOR STOPPING EARLY (check only 1 as the "primary reason") _____ Orthopedic/Joint Pain _____ Chest Pain _____ Shortness of Breath _____ Fatigue _____ Leg Pain/Fatigue (not joint related) _____ Dizziness _____ Other
PA pressures immediately after stopping walk	PA systolic _____ (mmHg) PA diastolic_____ (mmHg) PA mean _____ (mmHg)
PA pressures 5 minutes after stopping exercise	PA systolic _____ (mmHg) PA diastolic_____ (mmHg) PA mean _____ (mmHg)

PA pressures 10 minutes after stopping exercise	PA systolic _____ (mmHg) PA diastolic_____ (mmHg) PA mean _____ (mmHg)
PA pressures 15 minutes after stopping exercise	PA systolic _____ (mmHg) PA diastolic_____ (mmHg) PA mean _____ (mmHg)
PA pressures 20 minutes after stopping exercise	PA systolic _____ (mmHg) PA diastolic_____ (mmHg) PA mean _____ (mmHg)
PA pressures 25 minutes after stopping exercise	PA systolic _____ (mmHg) PA diastolic_____ (mmHg) PA mean _____ (mmHg)
PA pressures 30 minutes after stopping exercise	PA systolic _____ (mmHg) PA diastolic_____ (mmHg) PA mean _____ (mmHg)
Quality of Life	
KCCQ Score (total)	_____ (points
Score on Questions 3,7,8,9 which relate to symptoms of congestion	_____ (points)
Double Master's Step test	

Stopped Early (before three minutes)	_____ Yes _____ No *IF "YES" ONLY: (indicating that the patient stopped climbing before three minutes had elapsed)* _____ Time stepping (minutes) _____ Number of trips REASON FOR STOPPING EARLY (check only 1 as the "primary reason") _____ Orthopedic/Joint Pain _____ Chest Pain _____ Shortness of Breath _____ Fatigue _____ Leg Pain/Fatigue (not joint related) _____ Dizziness _____ Other
PA pressures immediately after test	PA systolic _____ (mmHg) PA diastolic_____ (mmHg) PA mean _____ (mmHg)
PA pressures 5 minutes after stopping test	PA systolic _____ (mmHg) PA diastolic_____ (mmHg) PA mean _____ (mmHg)
PA pressures 10 minutes after stopping test	PA systolic _____ (mmHg) PA diastolic_____ (mmHg) PA mean _____ (mmHg)
PA pressures 15 minutes after stopping test	PA systolic _____ (mmHg) PA diastolic_____ (mmHg)

	PA mean _____ (mmHg)
PA pressures 20 minutes after stopping test	PA systolic _____ (mmHg) PA diastolic_____ (mmHg) PA mean _____ (mmHg)
PA pressures 25 minutes after stopping test	PA systolic _____ (mmHg) PA diastolic_____ (mmHg) PA mean _____ (mmHg)
PA pressures 30 minutes after stopping test	PA systolic _____ (mmHg) PA diastolic_____ (mmHg) PA mean _____ (mmHg)
Handgrip test	
Maximal handrip effort	Max handgrip_____(Pounds Force)
PA pressures immediately before test	PA systolic _____ (mmHg) PA diastolic_____ (mmHg) PA mean _____ (mmHg)
Blood pressure immediately before test	BP systolic _____ (mmHg) BP diastolic_____ (mmHg)

Heart rate immediately before test	HR _____(bmp)
PA pressures at 30s of Handrip	PA systolic _____ (mmHg) PA diastolic_____ (mmHg) PA mean _____ (mmHg)
Blood pressure at 30s of Handrip	BP systolic _____ (mmHg) BP diastolic_____ (mmHg)
Heart rate at 30s of Handrip	HR _____(bmp)
PA pressures at 60s of Handrip	PA systolic _____ (mmHg) PA diastolic_____ (mmHg) PA mean _____ (mmHg)
Blood pressure at 60s of Handrip	BP systolic _____ (mmHg) BP diastolic_____ (mmHg)
Heart rate at 60s of Handrip	HR _____(bmp)
PA pressures at 90s of Handrip	PA systolic _____ (mmHg) PA diastolic_____ (mmHg) PA mean _____ (mmHg)

Blood pressure at 90s of Handrip	BP systolic _____ (mmHg) BP diastolic_____ (mmHg)
Heart rate at 90s of Handrip	HR _____(bmp)
PA pressures at 120s of Handrip	PA systolic _____ (mmHg) PA diastolic_____ (mmHg) PA mean _____ (mmHg)
Blood pressure at 120s of Handrip	BP systolic _____ (mmHg) BP diastolic_____ (mmHg)
Heart rate at 120s of Handrip	HR _____(bmp)
PA pressures 5 minutes after stopping the test	PA systolic _____ (mmHg) PA diastolic_____ (mmHg) PA mean _____ (mmHg)
Blood pressure 5 minutes after stopping the test	BP systolic _____ (mmHg) BP diastolic_____ (mmHg)
Heart rate 5 minutes after stopping the test	HR _____(bmp)
PA pressures 10 minutes after stopping the test	PA systolic _____ (mmHg)

	PA diastolic_____ (mmHg) PA mean _____ (mmHg)
Blood pressure 10 minutes after stopping the test	BP systolic _____ (mmHg) BP diastolic_____ (mmHg)
Heart rate 10 minutes after stopping the test	HR _____(bmp)
PA pressures 15 minutes after stopping the test	PA systolic _____ (mmHg) PA diastolic_____ (mmHg) PA mean _____ (mmHg)
Blood pressure 15 minutes after stopping the test	BP systolic _____ (mmHg) BP diastolic_____ (mmHg)
Heart rate 15 minutes after stopping the test	HR _____(bmp)
Stroop Color test	
PA pressures immediately before test	PA systolic _____ (mmHg) PA diastolic_____ (mmHg) PA mean _____ (mmHg)

Blood pressure immediately before test	BP systolic _____ (mmHg) BP diastolic_____ (mmHg)
Heart rate immediately before test	HR _____(bmp)
PA pressures at 30s of Stroop Color test	PA systolic _____ (mmHg) PA diastolic_____ (mmHg) PA mean _____ (mmHg)
Blood pressure at 30s of Stroop Color test	BP systolic _____ (mmHg) BP diastolic_____ (mmHg)
Heart rate at 30s of Stroop Color test	HR _____(bmp)
PA pressures at 60s of Stroop Color test	PA systolic _____ (mmHg) PA diastolic_____ (mmHg) PA mean _____ (mmHg)
Blood pressure at 60s of Stroop Color test	BP systolic _____ (mmHg) BP diastolic_____ (mmHg)
Heart rate at 60s of Stroop Color test	HR _____(bmp)

PA pressures at 90s of Stroop Color test	PA systolic _____ (mmHg) PA diastolic_____ (mmHg) PA mean _____ (mmHg)
Blood pressure at 90s of Stroop Color test	BP systolic _____ (mmHg) BP diastolic_____ (mmHg)
Heart rate at 90s of Stroop Color test	HR _____(bmp)
PA pressures at 120s of Stroop Color test	PA systolic _____ (mmHg) PA diastolic_____ (mmHg) PA mean _____ (mmHg)
Blood pressure at 120s of Stroop Color test	BP systolic _____ (mmHg) BP diastolic_____ (mmHg)
Heart rate at 120s of Stroop Color test	HR _____(bmp)
PA pressures at 150s of Stroop Color test	PA systolic _____ (mmHg) PA diastolic_____ (mmHg) PA mean _____ (mmHg)

Blood pressure at 150s of Stroop Color test	BP systolic _____ (mmHg) BP diastolic_____ (mmHg)
Heart rate at 150s of Stroop Color test	HR _____(bmp)
PA pressures at 180s of Stroop Color test	PA systolic _____ (mmHg) PA diastolic_____ (mmHg) PA mean _____ (mmHg)
Blood pressure at 180s of Stroop Color test	BP systolic _____ (mmHg) BP diastolic_____ (mmHg)
Heart rate at 180s of Stroop Color test	HR _____(bmp)
Level of difficulty	( ) non-stressful ( ) slightly stressful ( ) moderately stressful ( ) very stressful ( ) extremely stressful.
PA pressures 5 minutes after stopping the test	PA systolic _____ (mmHg) PA diastolic_____ (mmHg) PA mean _____ (mmHg)
Blood pressure 5 minutes after stopping the test	BP systolic _____ (mmHg) BP diastolic_____ (mmHg)

Heart rate 5 minutes after stopping the test	HR _____(bmp)
PA pressures 10 minutes after stopping the test	PA systolic _____ (mmHg) PA diastolic_____ (mmHg) PA mean _____ (mmHg)
Blood pressure 10 minutes after stopping the test	BP systolic _____ (mmHg) BP diastolic_____ (mmHg)
Heart rate 10 minutes after stopping the test	HR _____(bmp)
PA pressures 15 minutes after stopping the test	PA systolic _____ (mmHg) PA diastolic_____ (mmHg) PA mean _____ (mmHg)
Blood pressure 15 minutes after stopping the test	BP systolic _____ (mmHg) BP diastolic_____ (mmHg)
Heart rate 15 minutes after stopping the test	HR _____(bmp)
Laboratory Data (natriuretic peptides)	
NT-proBNP	_____ (ng/L)

Additional Lab Data

(Collected on Weeks 2, 6, 8, 12, 24, 32 or after ANY adjustment of study medication or if otherwise indicated for standard care)

Laboratory Data	
Serum Sodium	_____ (in clinic, mEq/L)
Serum Potassium	_____ (in clinic, mEq/L)
Blood Urea Nitrogen	_____ (in clinic, mEq/L)
Serum Creatinine	_____ (in clinic, mEq/L)

Study Endpoints

Co-Primary Endpoints:

Intensive Phase:

- Difference between mean change in PAPm after 6 weeks on Entresto compared to 6 weeks on continued ACEI/ARB

Acute First-Day Response

- Change in PAPm between baseline and first 3 hours after the first dose of Entresto

Secondary Endpoints:

- The mean change in PAPm in both groups on Entresto from week 12 to week 32 in longitudinal study
- Difference between mean change in PAPm from baseline on ACEI/ARB to 6 weeks on Entresto (groups A and B)
- *Change in exercise recovery PAPm
- *Change PAPm, blood pressure and heart rate during isometric exercise and recovery after isometric exercise.
- Change PAPm, blood pressure and heart rate during isometric exercise and recovery after mental stress chalenge.
- *Change in NT-proBNP and the BNP/NT-proBNP ratio

Tertiary Endpoints (Exploratory):

- Relationship of change in PAPm to change in the questions in the Kansas City Cardiomyopathy Questionnaire (KCCQ) 3, 7,8,9 which describe the severity of symptoms of congestion
- Mean change in total daily diuretic dose while on Entresto

Other Endpoints:

- *Death*
- *All-cause re-hospitalization*
- *Need to progress to advanced therapies (i.e. start home inotropes, place a ventricular assist device or list for cardiac transplantation)*
- *Unscheduled visits for IV loop diuretics*
- *Other interventions (i.e. nutrition referrals)*

**Will be 3 comparisons:*

1) 6 weeks of Entresto vs 6 weeks of continued ACEI/ARB (Group A compared to B at 6 weeks)
2) Baseline on ACEI/ARB compared to 6 weeks on Entresto (Groups A and B combined)
3) 12 weeks on Entresto compared to 32 weeks on Entresto in longitudinal study (all pts)

Statistical Analysis

Co-Primary Endpoints:

Intensive Phase:

- *Determine the difference between mean change in mean pulmonary artery pressure (PAPm) after 6 weeks on Entresto compared to 6 weeks on continued ACEi/ARB*
    - Statistical Plan: These changes from baseline to 6 weeks constitute continuous data. Therefore, the distribution of average changes in PAPm from baseline to 6 weeks will be assessed in Group A and Group B. If both distributions are normal, t-testing will be performed to compare the mean changes between groups. If the distributions are not normal, Wilcoxon testing will be used. $P < 0.05$ will be significant.

Acute First-Day Response

- *Determine the change in PAPm between baseline and first 3 hours after the first dose of Entresto*
    - Statistical Plan: These changes in PAPm from baseline to 2 hours after Entresto constitute a distribution of continuous data. The distribution of change in PAPm from the morning baseline visit (before Entresto) to 2 hours after the first dose of Entresto will be assessed in both groups. The distribution of changes will be assessed for normality. If the distributions are normal, the results will be presented as means with standard errors. If the distributions are not normal, the results will be presented as medians with interquartile ranges.

Secondary Endpoints:

- *Determine the mean change in PAPm in both groups on Entresto from week 12 to week 32 in longitudinal study*
    - Statistical Plan: The changes in PAPm from week 12 to week 32 constitute continuous data. The distribution of average change in PAPm from week 8 to week 32 will be assessed in both group A and B. The distribution of changes in

PAPm will be assessed for normality. If the distributions are normal, the results will be presented as means with standard errors. If the distributions are not normal, the results will be presented as medians with interquartile ranges.

- *Determine the difference between mean change in PAPm from baseline on ACEI/ARB to 6 weeks on Entresto (Groups A and B)*
    - Statistical Plan: The distribution of the average change in PAPm from baseline to 6 weeks will be assessed in Group A and combined with the distribution of change in PAPm from week 6 to week 12 in Group B. The combined distributions will be assessed for normality. If the combined distribution of changes in PAPm is normal, the results will be presented as means with standard errors. If the distributions are not normal, the results will be presented as medians with interquartile ranges.

- *Determine the impact of therapy over time on standard 6 minute walk test, assessing distance walked and changes in PAPm during recovery after the walk.*
    - Statistical Plan: These changes in distance walked from baseline to 6 weeks constitute continuous data. Therefore, the distribution of average changes in PAPm from baseline to 6 weeks will be assessed in Group A and Group B. If both distributions are normal, t-testing will be performed to compare the mean changes between groups. If the distributions are not normal, Wilcoxon testing will be used. $P < 0.05$ will be significant.
    - Statistical Plan (*Intensive Phase, patients in both groups as their own control after 6 weeks of Entresto- Group A: week 6 minus baseline; Group B: week 12 minus week 6):* The change in PAPm from pre to peak exercise at baseline and at 5 minute intervals for 30 minutes of recovery will be compared to the change in PAPm from pre to peak exercise and at 5 minute intervals for 30 minutes of recovery at 6 weeks in Group A. If the distributions are normal, the results will be presented as means with standard errors. If the distributions are not normal, the results will be presented as medians with interquartile ranges. The change in PAPm from pre to peak exercise at 6 weeks and at 5 minute intervals for 30 minutes of recovery will be compared to the change in PAPm from pre to peak exercise and at 5 minute intervals for 30 minutes of recovery at week 12 in Group B. If the distributions are normal, the results will be presented as means with standard errors. If the distributions are not normal, the results will be presented as medians with interquartile ranges.

- Statistical Plan (*Intensive Phase, patients on the Entresto Group A: week 6 minus baseline) compared to patients on continued ACEi/ARB therapy; Group B: week 6 minus baseline):* The change in PAPm from pre to peak exercise and at 5 minute intervals for 30 minutes of recovery at 6 weeks in Group A will be compared to the change in PAPm from pre to peak exercise and at 5 minute intervals for 30 minutes of recovery at 6 weeks in Group B. If both distributions are normal, t-testing will be performed to compare the mean changes between groups. If the distributions are not normal, Wilcoxon testing will be used. $P < 0.05$ will be significant.
- Statistical Plan *(Longitudinal Phase, Patients in both groups - week 32 minus week 12):* The change in PAPm from pre to peak exercise and at 5 minute intervals for 30 minutes of recovery at 32 weeks will be compared to the change in PAPm from pre to peak exercise and at 5 minute intervals for 30 minutes of recovery at 12 weeks in both groups. If the distributions are normal, the results will be presented as means with standard errors. If the distributions are not normal, the results will be presented as medians with interquartile ranges.

- *Determine the impact of therapy over time on standard double Master's step test, assessing changes in PAPm during recovery after the test.*

  - Statistical Plan (*Intensive Phase, patients in both groups as their own control after 6 weeks of Entresto- Group A: week 6 minus baseline; Group B: week 12 minus week 6):* The change in PAPm from pre to peak exercise at baseline and at 5 minute intervals for 30 minutes of recovery will be compared to the change in PAPm from pre to peak exercise and at 5 minute intervals for 30 minutes of recovery at 6 weeks in Group A. If the distributions are normal, the results will be presented as means with standard errors. If the distributions are not normal, the results will be presented as medians with interquartile ranges. The change in PAPm from pre to peak exercise at 6 weeks and at 5 minute intervals for 30 minutes of recovery will be compared to the change in PAPm from pre to peak exercise and at 5 minute intervals for 30 minutes of recovery at week 12 in Group B. If the distributions are normal, the results will be presented as means with standard errors. If the distributions are not normal, the results will be presented as medians with interquartile ranges.

  - Statistical Plan (*Intensive Phase, patients on the Entresto Group A: week 6 minus baseline) compared to patients on continued ACEi/ARB therapy; Group B: week 6 minus baseline):* The change in PAPm from pre to peak exercise and at 5 minute intervals for 30 minutes of recovery at 6 weeks in Group A will be compared to the change in PAPm from pre to peak exercise and at 5 minute intervals for 30 minutes of recovery at 6 weeks in Group B. If both distributions are normal, t-testing will be performed to compare the mean changes between

groups. If the distributions are not normal, Wilcoxon testing will be used. P <0.05 will be significant.

- Statistical Plan *(Longitudinal Phase, Patients in both groups - week 32 minus week 12):* The change in PAPm from pre to peak exercise and at 5 minute intervals for 30 minutes of recovery at 32 weeks will be compared to the change in PAPm from pre to peak exercise and at 5 minute intervals for 30 minutes of recovery at 12 weeks in both groups. If the distributions are normal, the results will be presented as means with standard errors. If the distributions are not normal, the results will be presented as medians with interquartile ranges.

- *Determine the impact of therapy over time on standard Handgrip test, assessing changes in PAPm, blood pressure and heart rate during test and recovery.*

    - Statistical Plan (*Intensive Phase, patients in both groups as their own control after 6 weeks of Entresto- Group A: week 6 minus baseline; Group B: week 12 minus week 6):* The change in PAPm, blood pressure and heart rate from pre to peak isometric exercise at baseline and at 5 minute intervals for 15 minutes of recovery will be compared to the changes in PAPm, blood pressure and heart rate from pre to peak isometric exercise and at 5 minute intervals for 15 minutes of recovery at 6 weeks in Group A. If the distributions are normal, the results will be presented as means with standard errors. If the distributions are not normal, the results will be presented as medians with interquartile ranges. The change in PAPm, blood pressure and heart rate from pre to peak isometric exercise at 6 weeks and at 5 minute intervals for 15 minutes of recovery will be compared to the change in PAPm, blood pressure and heart rate from pre to peak isometric exercise and at 5 minute intervals for 15 minutes of recovery at week 12 in Group B. If the distributions are normal, the results will be presented as means with standard errors. If the distributions are not normal, the results will be presented as medians with interquartile ranges.

    - Statistical Plan (*Intensive Phase, patients on the Entresto Group A: week 6 minus baseline) compared to patients on continued ACEi/ARB therapy; Group B: week 6 minus baseline):* The change in PAPm, blood pressure and heart rate from pre to peak isometric exercise and at 5 minute intervals for 15 minutes of recovery at 6 weeks in Group A will be compared to the change in PAPm, blood pressure and heart rate from pre to peak isometric exercise and at 5 minute intervals for 15 minutes of recovery at 6 weeks in Group B. If both distributions are normal, t-testing will be performed to compare the mean changes between groups. If the distributions are not normal, Wilcoxon testing will be used. P <0.05 will be significant.
    - Statistical Plan *(Longitudinal Phase, Patients in both groups - week 32 minus week 12):* The change in PAPm, blood pressure and heart rate from pre to peak

isometric exercise and at 5 minute intervals for 15 minutes of recovery at 32 weeks will be compared to the change in PAPm, blood pressure and heart rate from pre to peak isometric exercise and at 5 minute intervals for 15 minutes of recovery at 12 weeks in both groups. If the distributions are normal, the results will be presented as means with standard errors. If the distributions are not normal, the results will be presented as medians with interquartile ranges.

- *Determine the impact of therapy over time on standard Stroop Color test, assessing changes in PAPm, blood pressure and heart rate during test and recovery.*

    - Statistical Plan (*Intensive Phase, patients in both groups as their own control after 6 weeks of Entresto- Group A: week 6 minus baseline; Group B: week 12 minus week 6):* The change in PAPm, blood pressure and heart rate during Stroop Color test at baseline and at 5 minute intervals for 15 minutes of recovery will be compared to the changes in PAPm, blood pressure and heart rate during Stroop Color test and at 5 minute intervals for 15 minutes of recovery at 6 weeks in Group A. If the distributions are normal, the results will be presented as means with standard errors. If the distributions are not normal, the results will be presented as medians with interquartile ranges. The change in PAPm, blood pressure and heart rate during Stroop Color test at 6 weeks and at 5 minute intervals for 15 minutes of recovery will be compared to the change in PAPm, blood pressure and heart rate during Stroop Color test and at 5 minute intervals for 15 minutes of recovery at week 12 in Group B. If the distributions are normal, the results will be presented as means with standard errors. If the distributions are not normal, the results will be presented as medians with interquartile ranges.

    - Statistical Plan (*Intensive Phase, patients on the Entresto Group A: week 6 minus baseline) compared to patients on continued ACEi/ARB therapy; Group B: week 6 minus baseline):* The change in PAPm, blood pressure and heart rate during Stroop Color test and at 5 minute intervals for 15 minutes of recovery at 6 weeks in Group A will be compared to the change in PAPm, blood pressure and heart rate during Stroop Color test and at 5 minute intervals for 15 minutes of recovery at 6 weeks in Group B. If both distributions are normal, t-testing will be performed to compare the mean changes between groups. If the distributions are not normal, Wilcoxon testing will be used. $P < 0.05$ will be significant.
    - Statistical Plan *(Longitudinal Phase, Patients in both groups - week 32 minus week 12):* The change in PAPm, blood pressure and heart rate during Stroop Color test and at 5 minute intervals for 15 minutes of recovery at 32 weeks will be compared to the change in PAPm, blood pressure and heart rate during Stroop Color test and at 5 minute intervals for 15 minutes of recovery at 12 weeks in both groups. If the distributions are normal, the results will be presented as means with

standard errors. If the distributions are not normal, the results will be presented as medians with interquartile ranges.

- *Determine the change in NT-proBNP and the BNP/NT-proBNP ratio*
    - Statistical Plan (*Intensive Phase, patients in both groups as their own control - Group A: week 4 minus baseline; Group B: week 8 minus week 4)* The change in NT-proBNP from baseline to week 6 will be assessed in Group A and combined with the change in NT-proBNP levels from week 6 to week 12 in Group B. These distributions will be continuous distributions. If the distributions are normal, the results will be presented as means with standard errors. If the distributions are not normal, the results will be presented as medians with interquartile ranges.
    - Statistical (*Intensive Phase, patients on the Entresto Group A: week 6 minus baseline) compared to patients on continued ACEi/ARB therapy; Group B: week 6 minus baseline):* The change in NT-proBNP levels will be assessed from baseline to week 6 in Group A and Group B. If both distributions are normal, t-testing will be performed to compare the mean changes between groups. If the distributions are not normal, Wilcoxon testing will be used. $P < 0.05$ will be significant.
    - Statistical Plan *(Longitudinal Phase, Patients in both groups - week 32 minus week 8):* The change in NT-proBNP levels from week 12 to week 32 will be assessed in both groups. If the distributions are normal, the results will be presented as means with standard errors. If the distributions are not normal, the results will be presented as medians with interquartile ranges.

<u>*Tertiary Endpoints (Exploratory):*</u>

- Relationship of change in PAPm to change in the questions in the Kansas City Cardiomypathy Questionnaire (KCCQ) 3, 7,8,9 which describe the severity of symptoms of congestion
    - Statistical Plan (*Intensive Phase, patients in both groups as their own control - Group A: week 6 minus baseline; Group B: week 12 minus week 6)*: The change in KCCQ questions #3, 7, 8 & 9 will be assessed from baseline to week 6 in Group A and from week 6 to week 12 in Group B. The change in "score" for these four questions will be a continuous distribution when the groups are combined. If the combined distribution is normal, the results will be presented as means with standard errors. If the distributions are not normal, the results will be presented as medians with interquartile ranges.

- Statistical Plan (*Intensive Phase, patients on the Entresto Group A: week 6 minus baseline) compared to patients on continued ACEi/ARB therapy; Group B: week 6 minus baseline):* The change in KCCQ questions #3, 7, 8 & 9 from baseline to week 4 will be assessed in Group A and Group B. The change in "score" for these four questions will be a continuous distribution for both groups. If both distributions are normal, t-testing will be performed to compare the mean changes between groups. If the distributions are not normal, Wilcoxon testing will be used. P <0.05 will be significant.
- Statistical Plan *(Longitudinal Phase, Patients in both groups - week 32 minus week 12):* The change in KCCQ questions #3, 7, 8 & 9 from week 12 to week 32 will be assessed in both groups. The change in "score" for these four questions will be a continuous distribution when the groups are combined. If the distribution is normal, the results will be presented as means with standard errors. If the distributions are not normal, the results will be presented as medians with interquartile ranges.

- Mean change in total daily diuretic dose while on Entresto
  - Statistical Plan (*Intensive Phase, patients in both groups as their own control - Group A: week 6 minus baseline; Group B: week 12 minus week 6)*: The change in total daily diuretic dose from baseline to week 6 in Group A and from week 6 to week 12 in Group B will be assessed. If the distributions are normal, the results will be presented as means with standard errors. If the distributions are not normal, the results will be presented as medians with interquartile ranges.
  - Statistical Plan (*Intensive Phase, patients on the Entresto Group A: week 6 minus baseline) compared to patients on continued ACEi/ARB therapy; Group B: week 6 minus baseline):* The change in total daily diuretic dose score from baseline to week 6 in Group A and Group B will be assessed. If both distributions are normal, t-testing will be performed to compare the mean changes between groups. If the distributions are not normal, Wilcoxon testing will be used. P <0.05 will be significant.
  - Statistical Plan Plan *(Longitudinal Phase, Patients in both groups - week 32 minus week 12):* The change in total daily diuretic dose from week 12 to week 32 will be assessed in both groups. If the distributions are normal, the results will be presented as means with standard errors. If the distributions are not normal, the results will be presented as medians with interquartile ranges.

Power Analysis

There will be 20 patients total, 10 in each group.

Between group comparison: This sample size will provide 90% power with 2-sided alpha of 0.05 to detect a 20% difference between the 2 groups (Entresto and ACEI/ARB) in the PAPm change at 6 weeks, based on an assumed baseline PAPm of 25 mm, using a t-test with a standard deviation in the mean change of as high as 3.4. We do not yet have data on which to estimate the standard deviation of this change, but we have found a standard deviation of 3-4 mm Hg of PAPm pressures during 5 day periods in stable patients followed on Cardiomems devices at Brigham and Women's Hospital (unpublished data).

All patients after 6 weeks of Entresto compared to chronic ACEI/ARB at baseline: There is additional power for this highest secondary endpoint. Assuming the PAPm baseline on ACEI/ARB mean of 25mm, a sample size of 20 patients will provide 90% power with two-sided alpha of 0.05 paired t-test to detect a 20% decrease (to PAPm of 20 mm) after 6 weeks of Entresto, with a standard deviation for the change as high as 6.8.

VII. RISKS AND DISCOMFORTS

Complications from Surgical and Non-Surgical Procedures : Not applicable to this study. There are no surgical and non-surgical procedures.

a. Although all patients are eligible for open-label Entresto at randomization, those randomized to group B will be initiated 6 weeks later than those in group A. This may delay access to the potential incremental benefits of Entresto; however, there is currently a wide variation of practice in initiation of Entresto. This is partly relatd to cost and partly to concern for how best to titrate this agent in the setting of diuretics and beta blocking agents that the patient will continue to take.

b. Drug Side Effects and Toxicities

Subjects are not exposed to any risks other than those occurring during standard approved care for HFrEF, which includes both the medication Entresto and the CardioMEMS monitoring device. The only way in which their enrollment in the study differs from standard of care is that they will undergo more frequent monitoring, which increases the safety of drug titration to avoid lowering of filling pressures to levels that might be associated with postural hypotension when Entresto is added to their previous HF regimen.

It is unlikely that there will be any adverse effects of holding ACEI/ARB for 2 days (minimum 36 hours as per FDA labelling) at the beginning of the study. For the A group, this would occur anyway for safety, as a washout period of at least 2 days (minimum 36 hours as per FDA labelling) is required before initiation of Entresto. For the B group who will resume ACEI/ARB after 2 days (minimum 36 hours as per FDA labelling), such pauses in one component of therapy

are common around the time of surgery and are not anticipated to lead to any symptoms, as the other medications will be continued as usual.

Common: Based on Novartis' published prescribing guidelines for Entresto and previous clinical trials, the major side effects are similar to ACEi/ARB therapy: hypotension, hyperkalemia and renal dysfunction. All of these potential side effects will all be monitored for by study staff with frequent lab work, as is standard of care. In addition, due to their enrollment in this trial, hemodynamic assessment (including blood pressure) will be checked at each visit and PA pressures will be monitored daily by patient and reviewed by the study staff. This will increase the patient's level of safety as compared to standard clinical practice. Any dose changes will be followed by "acute PAP measurements" the next day and safety lab work as clinically indicated.

Uncommon: Similar to ACEi therapy, Entresto has a small risk of angioedema (0.2% in the Entresto group compared to 0.1% in the Enalapril group in the PARADIGM trial). These events have to date not been known to cause airway compromise.

To eliminate any increased risk of angioedema from prior ACEi exposure in this study, all patients will undergo a mandatory 2 day (minimum 36 hours as per FDA labelling) washout period between any ACEi administration and any Entresto administration. This is consistent with prior clinical trials as well as the standard of care and for any patient switching from ACEi to Entresto, regardless of whether or not they were enrolled in this study.

If a patient has an adverse reaction to any drug in the study (ACEi, ARB or Entresto) that cannot be ameliorated with dose reduction or adjustment, the medication will be stopped. No patients will be "removed" from the study. Even if a patient experiences symptoms that require cessation of the medication, we will continue to monitor them for the duration of the study.

c. Device Complications/Malfunctions

Subjects are not exposed to any risks from their monitoring device other than those consistent with the standard of care for HFrEF. All of the patients enrolled in this study already have CardioMEMS devices in place for clinical indications. Therefore, they incur no additional risk from the CardioMEMS device by enrolling in this study. There is essentially no risk from making pressure measurements and transmitting them to a central server.

d. Psychological (Non-Medical) Risks

Common: There are no expected, common psychological risks to the patients in this study. Patients undergoing pulmonary pressure monitoring at home generally feel reassured by regular transmission of data to a health care team. Monitoring in this study will be even more frequent and intensive than normal care, which may be even more reassuring to the patient. *Uncommon:* There are no expected, uncommon psychological risks to the patient from participation in this

study. If a patient experiences any new psychological symptoms during the course of this study, he/she will be referred, as per standard care, to the appropriate psychological and/or psychiatric resources.

e. Radiation Risks

This is not applicable to this study since patients are not exposed to radiation during this study. No statement from the Radiation Safety Committee is necessary.

VIII. POTENTIAL BENEFITS

a. Potential Benefits to Participating Individuals

The subjects enrolled in this study will receive Entresto at no cost. This medication decreases both HFrEF mortality and hospital readmission rates.. Patients enrolled in this study will be provided with Entresto for the duration of the study (Group A 32 weeks, Group B 26 weeks). At the conclusion of the trial, subjects can discuss receiving Entresto as part of their heart failure medical therapy with their physician. It is likely that the information gained from monitoring PAP will allow earlier identification of a need for adjustment in a concomitant medication. This could lead to lower incidence of reversible side effects such as hypotension and renal dysfunction. As compensation for patient time and effort, the study will provide $25/visit for each of the 8 required clinic visits during this study. This will cover both the cost of parking ($10 for up to 4 hours in the BWH patient parking lot) and the cost of a meal at the hospital.

b. Potential Benefits to Society

It is hoped that this study will help the medical community to better understand what effect, if any, Entresto has on pulmonary pressures. It is hoped that this information will allow physicians to better select the right doses and to adjust other medications with Entresto for greater benefit and safety. If, as anticipated, Entresto is shown to cause a sustained decrease in PA pressures, a further trial can be designed to determine if and how it could delay or prevent the development of secondary right-sided heart failure, which often heralds irreversible decompensation for patients with reduced left ventricular ejection fraction.

IX. SAFETY MONITORING AND REPORTING

a. **Independent Monitoring of Source Data**

Trained research assistants will be responsible for inputting the data into the locked study database. The study's project coordinator will then be responsible for verifying key baseline data within one week of enrollment for each patient enrolled. The project coordinator will also review the study data on a monthly basis thereafter for accuracy. The study database will be checked monthly using random audits of ~10% of subjects for data for missing, out-of-range, or inconsistent values.

b. Safety Monitoring

Due to the fact that we are using an FDA approved drug for its FDA approved indication and a previously-placed FDA approved device for its FDA approved indication, we will not have a formal Data Safety Monitoring Board. Nevertheless, we will take all necessary steps to ensure the safety of our patients and the validity of the results.

All of the study data will be stored on a Partners desktop computer housed in a locked office in the Advanced Heart Failure section of Building A at BWH. A dedicated and trained data entry research assistant will enter all initial demographic data within 2 days of a patient's enrollment in the study into a secure, password protected database. A study coordinator will verify the accuracy of the information on a regular basis to check for accuracy.

Subsequent clinical information obtained during the course of the study, will be entered into the password-protected database by a trained research assistant per standard protocol and a study coordinator will review the accuracy of this information as well. The investigators will review all safety and data management policies and procedures with new staff and annually with current staff.

This study will have an independent reviewer (licensed cardiologist who practices outside of the Partners System and has no involvement with or relation to the study) to review, in a de-identified fashion, any/all potential adverse events and determining if they are appropriate to report to Novartis and the Partners IRB.

c. Outcome Monitoring

This study will have an independent reviewer (licensed cardiologist who practices outside of the Partners System and has no involvement with or relation to the study) to review both results of the study. The independent reviewer for this study will be:

Robb D. Kociol, MD
Beth Israel Deaconess Medical Center.
Director of the Ventricular Assist Device Program
Associate Director of Advanced Heart Failure

Dr. Kociol is a heart failure specialist outside the Partners system who is experienced in both the clinical care of heart failure patients and in clinical investigation, having participated in clinical

events adjudication, patient recruitment, and Data Safety Monitoring Committee roles for a number of cardiovascular device and pharmaceutical trials. He is an active clinical member of the Cardiovascular Division and the Associate Director of the Advanced Heart Failure Program at Beth Israel Deaconess Medical Center. In addition, he is currently a member of the Clinical Events Committee for the Harvard Clinical Research Institute in Boston, MA as well as a member of the Data Safety Monitoring Committee for a clinical trial of esmolol in severe sepsis.

Specifically, Dr. Kociol will review all endpoint data including PA pressures (daily trends, acute/first dose/dose change PA pressures, exercise recovery PA pressures) hemodynamic and side effect information obtained in clinic, 6-minute walk test, double Master's step test, Handgrip test, Stroop Color test, laboratory work, KCCQ scores and medication dose changes. He will be blinded to the study group assignment and will review this data in a de-identified fashion. He will also be responsible for reviewing any/all potential adverse events and determining if they are appropriate to report to Novartis and the Partners IRB. He will review all clinical and safety data after every 5 patients have been enrolled. Potential adverse events will be reviewed as soon as possible if/when they occur. The study will have a pre-specified stopping guideline of $p<0.01$ for harm on any safety outcomes.

d. Adverse Event Reporting Guidelines

All of the following events will be collected for review by the independent reviewer and reported to Novartis Pharmaceuticals (along with the relevant randomization codes): All serious adverse events (SAE), all reports of drug exposure during pregnancy, all non-serious adverse events, all reports of misuse and abuse of the study drug, other medication errors, and uses outside what is foreseen in the protocol (irrespective of whether a clinical event has occurred). Any member of the study team can report a potential adverse event. Since Entresto is an FDA approved drug and it will be using it for its FDA approved indication, any adverse events thought to be related to Entresto will be reported FDA's MedWatch program, in keeping with standard practice. Given the mechanism of action of the drug, angioedema is an event of special interest, and all angioedema-like events will be submitted for independent review. Any adverse events that are deemed "significant" by the independent reviewer will also be reported to the Partners IRB.

An SAE is defined as any adverse event (appearance of or worsening of any pre-existing) undesirable sign(s), symptom(s) or medical conditions(s) which meets any one of the following criteria:

- is fatal or life-threatening
- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:

- routine treatment or monitoring of the studied indication, not associated with any deterioration in condition (specify what this includes)
- elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
- treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
- social reasons and respite care in the absence of any deterioration in the patient's general condition
- is medically significant, i.e. defined as an event that jeopardizes the patient or may require medical or surgical intervention.

All malignant neoplasms will be assessed as serious under "medically significant" if other seriousness criteria are not met.

Life-threatening in the context of a SAE refers to a reaction in which the patient was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if more severe.

X. REFERENCES

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