Demonstration of Reverse Remodeling Effects of Entresto™ (valsartan/sacubitril) Using Echocardiography Endocardial Surface Analysis

Product: Entresto™ (valsartan/sacubitril)

Indication: Chronic systolic heart failure with reduced ejection fraction

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Study Rationale:

The PARADIGM-HF trial found that valsartan/sacubitril, an angiotensin receptor-neprilysin inhibitor, significantly reduced the rates of death from any cause and from cardiovascular causes as well as the rates of hospitalizations for worsening heart failure as compared to a target-dose enalapril-based regimen for patients with heart failure reduced ejection fraction (HFrEF) (1). Inhibition of the renin-angiotensin-aldosterone system (RAAS) has been shown to decrease vasoconstriction and myocardial fibrosis with improved survival and functional status (2-4). Valsartan/sacubitril targets both RAAS inhibition and inhibition of the breakdown of natriuretic peptides. Natriuretic peptides are secreted by the heart, kidney, vasculature, and central nervous system in a response to increased cardiac wall-stress. These natriuretic peptides lead to natriuresis, vasodilation, RAAS inhibition, and decreased sympathetic drive. Neprilysin is an endopeptidase that degrades natriuretic peptides; so neprilysin inhibition leads to an increase in natriuretic peptides. The clinical benefit on survival and rates of hospitalizations has been demonstrated by PARADIGM-HF. The pathophysiology underlying the benefit of valsartan/sacubitril and its effects on remodeling remain unknown. The proposed study seeks to further elucidate the benefits of dual RAAS/neprilysin inhibition with valsartan/sacubitril on ventricular remodeling, exercise capacity, functional status, quality of life, and biomarker activity.

Objectives:

This study intends to measure the effects of valsartan/sacubitril compared to baseline standard medical heart failure therapy on reverse remodeling using echocardiographic endocardial surface analysis techniques to assess changes in ventricular volume, function, and shape. Furthermore, Metaiodobenzylguanidine (MIBG) scintigraphy and the heart to mediastinum (H/M) ratio will be used to assess LV volume regression and risk reduction. We also intend to measure the effects of valsartan/sacubitril on exercise capacity as assessed by the 6 minute walk test and peak V02 on cardiopulmonary exercise testing. Additionally, we will examine the impact of valsartan/sacubitril on functional status and quality of life using the KCCQ and Qualia Health (a novel iPhone application that incorporates Fitbit technology to provide a “real time” daily 6 minute step count and assesses quality of life using a series of short targeted questions. We will also measure BNP, NT-proBNP, and Rho-kinase (a biomarker associated with heart failure) levels at multiple time-points throughout the study period.

Primary objective:

The primary objective is to examine the effect of valsartan/sacubitril therapy on reverse remodeling using novel echocardiographic post-processing surface analysis to assess ventricular volume, function, and shape.

Secondary objectives:

Secondary objectives include examining the effect of valsartan/sacubitril therapy on MIBG scintigraphy and the heart to mediastinum (H/M) ratio, exercise capacity, functional status, quality of life, and biomarker activity (BNP, NT-proBNP, and Rho-kinase).

Primary endpoint:

The primary endpoint will be the degree of reverse remodeling as measured by echocardiography endocardial surface analysis of ventricular volumes, ejection fraction, and LV shape indexes (LV conicity and LV sphericity). This LV shape analysis allows for quantitative assessment of geometric changes in LV morphology due to LV remodeling.

Secondary endpoints:

1. 6 minute walk test (16)
2. Peak V02 on cardiopulmonary exercise testing (17)
3. Qualia Health Assessment (18)
    a. Daily measurement of functional status with a “real time” daily 6 minute step count (the program records the fastest real life 6 minute step count for the day)
    b. Brief quality of life questionnaire collected
4. Kansas City Cardiomyopathy Questionnaire (KCCQ)
5. Rho-kinase levels (19-24)
6. BNP levels
7. NT-proBNP levels
8. (MIBG) scintigraphy and the heart to mediastinum (H/M) ratio (25-30).

Methodology Background:

Echocardiography Endocardial Surface Analysis

Prior studies have demonstrated that LV function and LV shape are intertwined. A decline in LV function leads to a change in LV shape in attempts to restore normal function (5-7). Normal LV shape is ellipsoid and in a response to volume overload, the left ventricle dilates to a more spherical shape (8,9). This LV dilation and increase in sphericity is associated with a decrease in ejection fraction (10). LV shape has been correlated with exercise capacity and prognosis in patients with cardiomyopathy (11-13).

Real-time echocardiography allows for the measurement of LV size, function, mass, and shape. Shape analysis is a new technique that has recently been developed to quantify LV morphology through volumetric shape analysis from LV endocardial surfaces extracted from images. LV endocardial surfaces are obtained semiautomatically from real-time echocardiography using commercial software. After manual tracing of the endocardial borders on end-diastolic (ED) and end-systolic (ES) frames, the software automatically generates the LV surfaces throughout the cardiac cycle. From these LV surfaces, one can obtain LV volume-versus-time curves throughout the cardiac cycle, and thus measure ED volume, ES volume, and calculate the ejection fraction (EF). Custom software is then implemented directly from the endocardial surface for shape analysis. Important LV shape parameters are spherecity and conicity, measured both at ED and ES. These indices were chosen given the normal LV shape is ellipsoid and that the pathophysiological response to dilation is

to become more spherical. The conicity index was chosen because the shape of the normal LV cavity at end-systole is conical. The spherecity index and LV conicity index correlate with LV volumes and EF (14, 15).

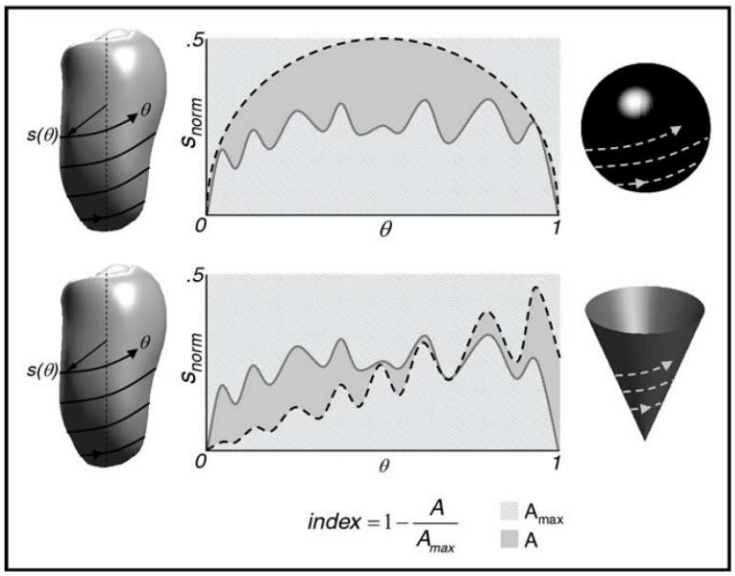

Figure 1. Schematic description of the computation of LV shape indexes. First, the LV endocardial surface is sampled from apex to base along a helical curve wrapped around the left ventricle and aligned with the long axis. The relevant 1-dimensional signal *(solid line)* is obtained by normalizing for long-axis length. The shape index is defined as the point-by-point similarity between the LV signal and that obtained from the reference shape *(dashed line)*, a sphere *(top)* or a cone *(bottom)*. See text for details.

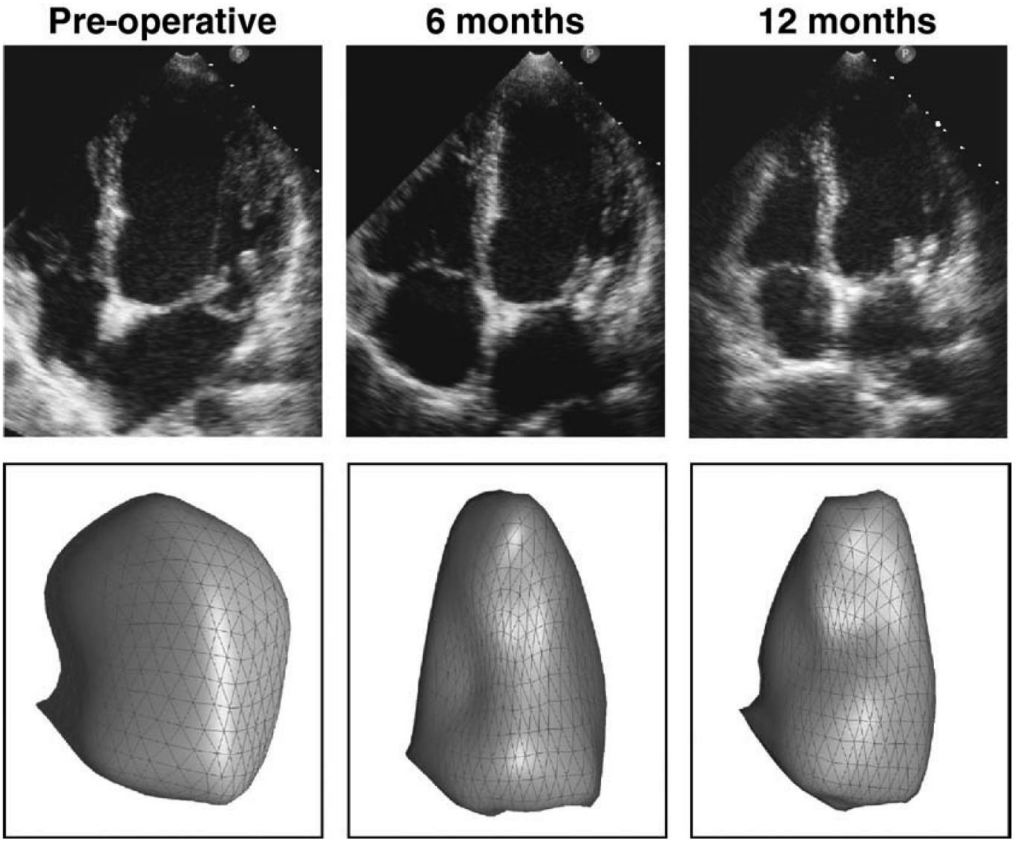

Figure 2: Example of ED 4-chamber views (top) and the corresponding LV endocardial surfaces (bottom) extracted from transthoracic echocardiographic data sets in a patient who underwent MV repair, before (left) and 6 months (center) and 12 months (right) after MV repair, showing decreased LV volume associated with changes in LV shape during follow-up.

*Figures 1 and 2 from reference 15.

Rho-kinase:

Rho-kinase is an effector of the small GTP-binding protein Rho, and enhances myocardial stiffness, ventricular fibrosis, and cardiac hypertrophy. Rho-kinase is a strong predictor of first major cardiovascular event and is activated in heart failure patients. Rho-kinase activity has been shown to be elevated in patients admitted to the hospital with heart failure and an elevation of Rho-kinase activity when added to NT-proBNP levels was an independent predictor of mortality. (19-24)

Qualia:

Qualia is a novel iPhone application that assesses functional status and quality of life. It includes a brief quality of life questionnaire assessment (QOL), as well as the ability to measure number of steps for a 6 minute walk test. It incorporates Fitbit technology to provide a “real time” daily 6 minute step count (the program records the fastest real life 6 minute step count for the day). Each one of the parameters will be assessed longitudinally while the overall trend will be evaluated.

An Apple product (iPhone or iPod) and a FitBit are needed to use the Qualia Ap. For patients who do not already have one or both, the study team can lend out either of these items from existing supplies in Heart Failure research group.

MIBG) scintigraphy and the heart to mediastinum (H/M) ratio (25-30).

Metaiodobenzylguanidine (MIBG) scintigraphy is a noninvasive method of measuring sympathetic nervous system activity. MIBG imaging has been extensively studied in heart failure, and the heart to mediastinum (H/M) ratio of counts has been shown to have prognostic significance. Lower H/M ratios have been associated with progression of heart failure, cardiovascular mortality and the incidence of

sudden cardiac death. The relationship between MIBG imaging and left ventricular (LV) remodeling has been previously explored in a randomized trial (25-30).

Methodology (Study Design):

This is a single-center, non-randomized trial, where each patient serves as a control to themselves. As such, it is a one arm open-label trial. This is a 24 month study with multiple analysis points. The 2nd half of the study which includes Visits 9 and 10 is optional to subjects.

Entresto™ (valsartan/sacubitril) has been recently FDA approved for the treatment of chronic systolic heart failure with reduced ejection fraction, and is being used in the FDA approved manner throughout this study. The medication washout and dose escalation described below are part of standard of care practice, and are described in the approved drug prescribing information. .

Visit 0 – Initial visit:

- Initial screening with assessment for optimized heart failure medications and physical exam/vitals.

Visit #1 (2 weeks): +/- 2 days

- Assessment with a physical exam/vitals, echocardiographic endocardial surface analysis, MIBG scintigraphy, CPX test, 6 minute walk test, Kansas City Cardiomyopathy Questionnaire (KCCQ), and measurement of BMP, BNP, NT-proBNP, Rho-kinase.
- Urine pregnancy test for females of child bearing potential
- 36 hour wash-out period during which their ACEI or ARB will be stopped.
- Start valsartan/sacubitril at 49mg/51mg mg BID
- Adverse event collection
- Qualia Ap initiation, and FitBit and iPod distribution if necessary.

Visit #2 (3 weeks): +/- 2 days

- Assess tolerance of valsartan/sacubitril at 49mg/51mg mg BID, physical exam, and BP check
- If tolerated, increase valsartan/sacubitril 97mg/103mg mg BID
- Adverse event collection

Visit #3 (4 weeks): +/- 1 week

- Assess tolerance of valsartan/sacubitril at 97mg/103mg mg BID, physical exam, and BP check
- Adverse event collection

Visit #4 (8 weeks): +/- 1 week

- Physical Exam/Vitals, KCCQ
- BMP
- Adverse event collection

Visit #5 (12 weeks): +/- 1 week

- Physical Exam/Vitals.
- BMP
- Adverse event collection

Visit # 6 (16 weeks): +/- 1 week

- Assessment with a physical exam/vitals, echocardiographic endocardial surface analysis, MIBG scintigraphy, CPX test, 6 minute walk test, KCCQ, and measurement of BMP, BNP, NT-proBNP, Rho-kinase.
- Adverse event collection

Visit #7 (28 weeks): +/- 1 week

- Assessment with a physical exam/vitals, echocardiographic endocardial surface analysis, CPX test, 6 minute walk test, KCCQ, and measurement of BMP, BNP, NT-proBNP, Rho-kinase.

- Adverse event collection
- Analysis of Data collected thus far

Visit #8 (52 weeks): +/- 1 week
- Assessment with a physical exam/vitals, echocardiographic endocardial surface analysis, CPX test, 6 minute walk test, KCCQ, and measurement of BMP, BNP, NT-proBNP, Rho-kinase.
- Adverse event collection
- Final analysis point.
- FitBit and iPod collection where applicable.

Visit #9 (18 Months): +/- 3 months
- Assessment with a physical exam/vitals, echocardiographic endocardial surface analysis, CPX test, KCCQ, and measurement of BMP and NT-proBNP.
- Adverse event collection
- Final analysis point.

Visit #10 (24 Months): +/- 3 months
- Assessment with a physical exam/vitals, echocardiographic endocardial surface analysis, CPX test, 6 minute walk test, KCCQ, and measurement of BMP and NT-proBNP.
- Adverse event collection
- Final analysis point.

Daily Qualia Assessments:
Throughout the study period subjects will undergo daily QUALIA assessments of (1) quality of life measures and (2) daily real-time 6 minute step count. To measure step count, Qualia will measure number of steps per day from the subject's FitBit and will automatically calculate the greatest number of steps in a 6 minute period, and will save this as the study data point for that day.

Sample size justification:

Primary endpoints

Sphericity index: ES (0.69 +/- 0.07) ED (0.72 +/- 0.07)

We are planning a study of a continuous response variable from heart failure subjects before and after medication initiation. If the true difference in the mean response is 0.04, we will need to study 26 subjects to be able to reject the null hypothesis that this response difference is zero with probability (power) 0.8. The Type I error probability associated with this test of this null hypothesis is 0.05. We assume 30% drop off or failure to acquired images. With 40 patients we will have 28 subjects after the drop off.

Conicity index: ES (0.77 +/- 0.03) ED (0.75 +/- 0.03) (Reference 14)

We are planning a study of a continuous response variable from heart failure subjects before and after medication initiation. If the true difference in the mean response is 0.04, we will need to study 7 subjects to be able to reject the null hypothesis that this response difference is zero with probability (power) 0.8. The Type I error probability associated with this test of this null hypothesis is 0.05. Since the number of subjects required for the sphericity index is higher, we will plan to enroll 40 patients.

Secondary endpoints:

6 min walk (374 +/- 117) (Reference 24)

We are planning a study of a continuous response variable from subjects before and after medication initiation. Prior data indicate that the difference in the response is normally distributed with standard deviation 117. If the true difference in the mean response of matched pairs is 60 meters, we will need

to study 32 subjects to be able to reject the null hypothesis that this response difference is zero with probability (power) 0.8. The Type I error probability associated with this test of this null hypothesis is 0.05. We assume 20% drop off and no problem in getting 6 min walk data. With 40 patients we will have 32 subjects after the drop off.

MIBG H/M ratio:
A previous study has demonstrated improvements in the H/M ratio of approximately 0.18 following the addition of spironolactone to standard medical therapy in heart failure patients. If we conservatively estimate a standard deviation of 0.35, 32 patients will provide 80% power to detect a mean difference of 0.18 with a Type I error of 0.05. To account for loss to follow-up, we will enroll 40 patients in this study.

Population:

Key inclusion criteria

1) Males and females aged ≥18 years
2) CHF NYHA class II-IV with 25%≤ LVEF ≤40% (ECHO within last 6 months)
3) Stable on an ACEI or ARB dose equivalent to enalapril ≥10 mg/d for at least 4 weeks
4) Treatment with a stable dose of a β-blocker for at least 4 weeks, unless otherwise contraindicated or not tolerated
5) Optimized dosing of background HF medications and use of aldosterone antagonists, where indicated

Key exclusion criteria

1) History of angioedema related to previous ACE Inhibitor or ARB therapy
2) eGFR < 30 ml/min/1.73 m2 at screening
3) Serum potassium > 5.2 mmol/L at screening
4) Symptomatic hypotension as defined by PI, SBP < 100 mmHg at screening
5) Current acute decompensated heart failure
6) History of severe pulmonary disease
7) Active malignancy
8) Requirement for treatment with both ACEI and ARB

Total number of patients: 40 patients total with LVEF 25-40%

Evaluation (visit) schedule:

Study Title: Demonstrating Reverse Remodeling Effects of LCZ696 Using Three Dimensional Echocardiography Endocardial Surface Analysis									
PI: Nir Uriel, MD									
Schedule of Tests and Procedures									
Visit #	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Time of Visit	**Day 1**	**Week 2**	**Week 3**	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 28**	**Week 52**
Informed Consent	X								
Inclusion/Exclusion Criteria	X								
Physical Exam	X	X	X	X	X	X	X	X	X
Vital signs	X	X	X	X	X	X	X	X	X
Medications	X	X	X	X	X	X	X	X	X
Echo		X					X	X	X
CPX		X					X	X	X
NT-pro-BNP		X					X	X	X
BNP		X					X	X	X
BMP****		X	X	X	X	X	X	X	X
6 minute walk**		X					X	X	X
MIBG Nuclear Testing		X					X		
Blood work: Rho-kinase		X					X	X	X
KCCQ questionnaire		X		X		X		X	X
Study Drug Administration		X	X*						
Pregnancy****	X								
Qualia:		X	X	X	X	X	X	X***	X***
Adverse Events	X	X	X	X	X	X	X	X	X
*Up titrate study drug									
** 6 MW performed by research staff									
*** Qualia Analysis									
****BMP and pregnancy testing will be performed as needed per SOC determined by the treating physician									

Please note: BMP includes K and BUN/Cr minimum.
Windows for Patient Completion:
Visit 1 & 2: +/- 2 days
Visit 3-8: +/- 1 week
Qualia measures are automatically recorded daily: 6 minute walk readings, and daily brief QOL questions.

Visit #	**9**	**10**
Time of Visit	**18 Months (+/- 3 months)**	**24 Months (+/- 3 months)**
Informed Consent		
Inclusion/Exclusion Criteria		
Physical Exam	X	X
Vital Signs	X	X
Medications	X	X
Echo	X	X
CPX	X	X
NT-pro-BNP	X	X
BNP		
BMP	X	X
6 minute walk**	X	X
MIBG Nuclear Testing		
Blood work: Pho-kinase		
KCCQ questionnaire	X	X
Study Drug Administration		
Pregnancy		
Qualia		
Adverse Events	X	X
** 6 MW performed by research staff		

Safety Monitoring and Reporting

Pharmacovigilance requirements:
Throughout the study period, the patient will be closely monitored for AE/SAE (as described below) at each visit and will receive contact information to report any AE/SAE if they occur. Patients will be evaluated on an individual basis for decreasing or discontinuing the study drug per PI clinical judgment. Additional interventions will be considered based on the patient's individual clinical needs as decided by PI.

Definition of an AE: Any untoward medical occurrence in a subject administered a pharmaceutical product that does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the investigational medicinal product.

Medical conditions/diseases present before starting the drug of interest are only considered adverse events if they worsen after starting the drug of interest.

Adverse event information will be collected at each visit during the study. Adverse events may also be detected when they are volunteered by the patient during or between visits or through physical examination, laboratory test, or other assessments. All adverse events will be recorded in the study database including the following information:

1. the severity grade (mild, moderate, severe)
2. its relationship to sacubitril/valsartan (suspected/not suspected)
3. its duration (start and end dates or if continuing at final exam)
4. whether it constitutes a serious adverse event (SAE)

A SAE is any untoward medical occurrence that at any dose:

- results in death,
- is life-threatening,
- requires inpatient hospitalization or prolongation of existing hospitalization,
- results in persistent or significant disability/incapacity,
- is a congenital anomaly/birth defect,
- is otherwise a significant medical event.

This includes any SAEs likely to arise from chronic systolic heart failure or progression of underlying/concomitant illness

Reporting of Adverse Events:

The Institution (University of Chicago) shall be responsible for ensuring that all Adverse Events are recorded and appropriately reported to the relevant health authorities according to applicable laws and regulations.

Although the Institution is responsible for Adverse Events (AE) reporting for the trial, Novartis may also submit these AEs in any country as required by local legislation under Novartis licenses for the product.

Any SAE, irrespective of causality, occurring after the subject has provided informed consent and until four weeks after the subject has stopped study participation must be reported to Novartis within 24 hours of PI knowledge. The Institution will provide to Novartis details of all serious adverse events ("SAEs") as permitted by applicable data protection laws, irrespective of causality within fifteen (15) calendar days of first notification of the SAE or subsequent follow-up information to the Institution. SAEs will be followed until resolution or until it is judged to be permanent, and an assessment will be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the drug of interest, the interventions required to treat it, and the outcome. The

Institution shall support Novartis in the following-up of all SAEs so that complete information is available to maintain patient safety and also as part of any commitments by Novartis to any Health authority OR specific Health authority follow-up requests regarding sacubitril/valsartan..

The Institution shall ensure that Novartis is provided with all SAEs, both initial and follow-up information, that have been collected from the initiation of the trial for the duration agreed upon in the contract.

The Institution shall prepare and issue expedited safety reports for suspected unexpected SAEs ("SUSARs") in the Study in accordance with the applicable laws and regulations, this includes preparing and issuing Investigator Notifications (INs) or biannual SUSAR listings, where applicable. The Institution shall provide a copy of any Institution -generated INs to Novartis within fifteen (15) calendar days of first notification of the suspected unexpected SAE or subsequent follow-up information to the Institution.

The Institution shall prepare and submit their own Development Safety Update Report (DSUR) to the applicable Regulatory Authorities. A copy of the DSUR shall also be provided to Novartis within one (1) month of such submission.

Reporting to the University of Chicago IRB:
Per the University of Chicago IRB, any AE that is unexpected will be reported to the IRB within 10 days of PI knowledge. SAE's that are unexpected are to be reported directly to the IRB Chairman upon PI knowledge and formally to the IRB within 48 hours.

Any AE's and SAE's that are not considered to be related to the study will be reported to the IRB at the time of annual study review (per IRBs policy).

Pregnancies: Any occurrences of a pregnancy in a patient (or a patients partner) during study participation will be collected. All pregnancies will be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Recruitment:
Dr. Nir Uriel, the Principal Investigator, manages heart failure patients. Dr. Sara Kalantari Tannenbaum, a Co-Investigator, is a cardiology fellow in the heart failure clinic.
Dr. Uriel, Dr. Kalantari Tannenbaum, and other members of the study team will approach all heart failure patients that meet inclusion criteria and do not meet exclusion criteria in ambulatory clinics, and they will provide an explanation of the study. Patients that are willing to participate in the study will sign the informed consent, and they will subsequently be entered into the study.

Informed Consent Process:
Informed consent will be obtained by members of the study team.

Confidentiality of Study Data:
All efforts will be made to keep patient information confidential as only the principal investigator and key study personnel will have access to the password protected, de-identified electronic database and all original CRF forms will be stored in a locked cabinet file. The data will be stored electronically in a password-protected database and on a networked computer. The CRF forms will be stored in a locked cabinet, which only the principal investigator and select key study personnel have the key to.

Potential Risks: Drug, blood draw, MIBG, CPX, 6 minute walk, echo,

Risks of taking study drug
Potential side-effects of valsartan-sacubitril include hypotension, hyperkalemia, renal dysfunction, dizziness, lightheadedness, and cough.

Risk associated with blood draws

Patients may experience mild discomfort associated with the blood draw. There is a small risk of dizziness, fainting, minor bruising and infection associated with blood draws.

Risk associated with MIBG testing
Reported adverse reactions associated with ^{123}I-*m*IBG have been very uncommon (<1%). If administered too quickly, palpitations, dyspnea, heat sensations, transient hypertension, and abdominal cramps may occur during or immediately post administration. Within 1 hour these symptoms disappear. In rare cases, the following undesirable effects have occurred: blushes, urticaria, nausea, cold chills and other symptoms of anaphylactic reactions. [31, 32]
There is a small risk secondary to radiation exposure associated with MIGB scintigraphy. The dose of radioactive contrast medium is relatively small, approximately twice the normal annual background radiation from the environment.

Risk associated with 6 minute walk and CPX testing:
These are standard clinical tests commonly used for patients with heart failure. There are very minimal risks associated with these tests. There is a small risk of tripping or falling during the 6 minute walk and CPX testing. There is a small risk for arrhythmias, and patients may experience shortness of breath, chest pain, or fatigue during the testing. Patients are closely monitored and supervised during testing in attempts to minimize risk.

Risk associated with echocardiography
There is no radiation risk associated with echocardiography. The only small risk is a potential skin allergic reaction to the ultrasound gel and mild pressure from the echocardiogram probe.

Mitigation:
Mitigations and treatment for all adverse events will be performed per the current practice standards/standards of care as determined by the investigator. This includes regular physical exams, in addition to monitoring potassium levels and kidney function prior to drug administration, and post administration as needed (determined by standard of care practice and treating physician).
Potential subjects will be evaluated by a heart team prior to enrollment. Study staff will undergo training regarding sacubitril/valsartan as well as the overall study prior to initiating study activities. All subjects will be closely monitored throughout the trial to assess their clinical status.

Data and Safety Monitoring:
Throughout the study period, the patient will be closely monitored for AE/SAE (as described below) at each visit and will receive contact information to report any AE/SAE if they occur. Patients will be evaluated on an individual basis for decreasing or discontinuing the study drug per PI clinical judgment. Additional interventions will be considered based on the patient's individual clinical needs as decided by PI.

Potential Benefits:
Results of the recent PARADIGM-HF trial revealed that potential benefits include decreased rates of death from any cause and from cardiovascular causes as well as the rates of hospitalizations for worsening heart failure.

Alternatives:
The subject may decline participation in this study, and continue with current therapies for managing chronic systolic heart failure.

References:

1. McMurray J, Milton Packer MD, Desai A, et al. Angiotensin-Neprilysin Inhibition versus Enalapril in Heart Failure. N Engl J Med 2014; 371: 993-1004.
2. The CONSENSUS Trial Study Group. Effects of enalapril on mortality in severe congestive heart failure: results of the Cooperative North Sandinavian Enalapril Survival Study (CONSENSUS). N Engl J Med 1987; 316: 1429-1435.
3. The SOLVD Investigators. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. N Engl J Med 1991; 325: 293-302.

4. Von Lueder TG, Sangaralingham SJ, Wang BH, et al. Renin-angiotensin blockade combined with natriuretic peptide system augmentation: novel therapeutic concepts to combat heart failure. Circ Heart Fail 2013;6:594-605
5. Harjai KJ, Edupuganti R, Nunez E, Turgut T, Scott L, Pandian NG. Does left ventricular shape influence clinical outcome in heart failure? Clin Cardiol 2000;23:813-819.
6. Pfeffer MA, Braunwald E. Ventricular remodeling after myocardial infarction. Experimental observations and clinical implications. Circulation 1990; 81 (1161): 72.
7. Opie LH, Commerford PJ, Gersh BJ, Pfeffer MA. Controversies in ventricular remodeling. Lancet 2006; 367: 356-367.
8. Douglas PS, Morrow R, Ioli A, Reichek N. Left ventricular shape, afterload and survival in idiopathic dilated cardiomyopathy. J Am Coll Cardiol 1989; 13: 311-315.
9. Devereux RB. Left ventricular geometry, pathophysiology and prognosis. J Am Coll Crdiol 1995; 25: 885-887.
10. Lewis RP, Sandler H. Relationship between changes in left ventricular dimensions and the ejection fraction in man. Circulation 1971;44:548-557.
11. Douglas PS, Morrow R, Ioli A, Reicheck N. Left ventricular shape, afterload and survival in idiopathic dilated cardiomyopathy. J Am Coll Cardiol 1989; 13: 311-315.
12. Kass DA, Traill TA, Keating M, Altierei PI, Maughan WL. Abnormalities of dynamic ventricular shape change in patients with aortic and mitral valvular regurgitation: assessment by Fourier shpape analysis and global geometric indexes. Circ Res 1988; 62: 127-138.
13. Tischler MD, Niggel J, Borowski DT, LeWinter MM. Relation between left ventricular shape and exercise capacityin patients with left ventricular dysfunction. J Am Coll Cardiol 1993:22;751-757.
14. Maffessanti F, Lang R, Corsi C, et al. Feasibility of Left Ventricular Shape analysis from Transthoracic Real-Time 3-D Echocardiographic Images. Ultrasound Med Biol; 2009: 35: 1953-1962
15. Maffessanti F, Caiani E, Tamborini G, et al. Serial Changes in Left Ventricular Shape Following Early Mitral Valve Repair. Am J Cardiol; 2010: 106: 836-842.
16. Bittner V, Weiner D, Yusuf S et al. Prediction of Mortality and Morbidity With a 6-Minute Walk Test in Patients With Left Ventricular Dysfunction. JAMA 1993: 270 (14): 1702-1707.
17. Stelken A, Younis L, Jennison S, et al. Prognostic Value of Cardiopulmonary Exercise Testing Using Percent Achieved of Predicted Peak Oxygen Uptake for Patients with Ischemic and Dilated Cardiomyopathy. JACC 1996; 27(2): 345-352.
18. http://qualiahealth.com
19. Kajikawa M, Noma K, Maruhashi T, et al. Rho-associated kinase activity is a predictor of cardiovascular outcomes. Hypertension 2014; 63(4): 856-864.
20. Do Z, Fukumoto Y, Sugimura K, et al. Rho-kinase activation in patients with heart failure. Circ 2013; 77(10): 2542-2550.
21. Fukui S, Fukumoto Y, Suzuki J, et al. Long-term inhibition of Rho-kinase ameliorates diastolic heart failure n hypertensive rats. J Cardiovasc Pahrmacol 2008; 51: 317-326.
22. Dong M, Jiang X, Liao JK, et al. Elevated rho-kinase activity as a marker indicating atherosclerosis and inflammation burden in polyvascular disease patients with concomitant coronary and peripheral arterial disease. Clin Cardiol 2013; 36(6): 347-351.
23. Dong M, Liao JK, Fang F, et al. Increased Rho kinase activity in congestive heart failure. Eur J Heart Fail 2012; 14(9): 965-973.
24. Dong M, Liao JK, Yan B, et al. R. Li, M. Zhang and C. M. Yu (2013). A combination of increased Rho kinase activity and N-terminal pro-B-type natriuretic peptide predicts worse cardiovascular outcome in patients with acute coronary syndrome. Int J Cardiol 2013: 167(6): 2813-2819.
25. Merlet P, Valette H, Dubois-Rande JL et al. Prognostic value of cardiac metiodobenzylguanidine imaging in patient with heart failure. J Nucl Med 1992;33:471-7

26. Jacobson AF, Senior R, Cerqueira MD et al. Myocardial iodine-123 meta-iodobenzylguanidine imaging and cardiac events in heart failure: results of the prospective ADMIRE-HF (AdreView Myocardial Imaging for Risk Evaluation in Heart Failure) study. J Am Coll Cardiol 2010;55:2212-21.

27. Nakata T, Nakajima K, Yamashina S et al. A pooled analysis of multicenter cohort studies of (123)I-mIBG imaging of sympathetic innervation for assessment of long-term prognosis in heart failure. JACC Cardiovasc Imaging 2013;6(7):772-84.

28. Jain KK, Hauptman PJ, Spertus JA et al. Incremental utility of iodine-123 meta-iodobenzylguanidine imaging beyond established heart failure risk models. J Card Fail 2014;20(8):577-83.

29. Kasama S, Toyama T, Sumino H et al. Additive effects of spironolactone and candesartan on cardiac sympathetic nerve activity and left ventricular remodeling in patients with congestive heart failure. J Nucl Med 2007;48(12):1993-2000.

30. Drakos SG, Athanasoulis T, Malliaras KG et al. Myocardial sympathetic innervation and long-term left ventricular mechanical unloading. JACC Cardiovasc Imaging 2010;3(1):64-70

31. Ebina T, Takahashi N, Mitani I, Sumita S, Ishigami T, Ashino K, et al. Clinical implications of cardiac (123)I-meta-iodobenzylguanidine scintigraphy and cardiac natriuretic peptides in patients with heart disease. Nucl Med Commun 2002;23:795-801.

32. Merlet P, Benvenuti C, Moyse D, Pouillart F, Dubois-Rande JL, Duval AM, et al. Prognostic value of MIBG imaging in idiopathic dilated cardiomyopathy. J Nucl Med 1999;40:917-923.