Protecting with **AR**NI **A**gainst Cardiac Consequences of **Cor**onavirus Disease 2019
(PARACOR-19)

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1 LIST OF ABBREVIATIONS

Abbreviation	Definition
ACEI	Angiotensin-Converting Enzyme Inhibitor
AE	Adverse Event
ARB	Angiotensin Receptor Blocker
ARNI	Angiotensin Receptor Neprilysin Inhibitor
CRF	Case Report Form
DSMB	Data Safety Monitoring Board
EF	Ejection Fraction
eGFR	Estimated Glomerular Filtration Rate
GFR	Glomerular Filtration Rate
HF	Heart Failure
HFpEF	Heart Failure with Preserved Ejection Fraction
HFrEF	Heart Failure with Reduced Ejection Fraction
ITT	Intention To Treat
IRB	Institutional Review Board
LV	Left Ventricular
LVAD	Left Ventricular Assist Device
LVEF	Left Ventricular Ejection Fraction
mmHG	Millimeters of mercury
mmol/L	Millimole per liter
MDRD	Modification of Diet in Renal Disease
NT-proBNP	N-terminal pro-B-type natriuretic peptide
PO	“Per os,” or by mouth
PPI	Patient Package Insert
SAE	Serious Adverse Event
SBP	Systolic Blood Pressure
sST2	Soluble ST2

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3 EXECUTIVE SUMMARY

Title	**P**rotecting with **AR**NI **A**gainst Cardiac Consequences of **Cor**onavirus Disease 2019 **(PARACOR-19)**
Indication	To decrease risk of cardiac injury and abnormalities in cardiac structure and function following COVID-19 infection
Location	Duke University Hospital
Brief Rationale	Although many patients presenting with Coronavirus Disease 2019 (COVID-19) face high-risk of death, the vast majority of patients recover from the acute infection, either in the hospital or at home. Nonetheless, despite clinical improvement or resolution of symptoms, accumulating evidence supports significant potential for longer-term and insidious cardiac involvement. Moreover, within the heart, the virus appears to localize to interstitial cells and the extracellular matrix, with relative sparing of the myocytes themselves. These data, combined with others noting high levels of inflammation with COVID-19, suggest that the virus may increase propensity for downstream cardiac fibrosis and dysfunction. These collective data raise significant concerns that cardiomyopathy, heart failure, or other cardiovascular complications will evolve as the natural history of COVID-19 for many patients who recover from acute infection. Pre-clinical and clinical data across multiple cardiometabolic conditions suggest that sacubitril/valsartan may be particularly well-suited to prevent adverse cardiac remodeling and new-onset HF following COVID-19 infection. Renin-angiotensin-aldosterone system (RAAS) inhibition has been postulated to have a cardio-protective role in COVID-19, but there is biologic plausibility that a dual compound with a neprilysin inhibitor would better prevent cardiac injury and dysfunction. In this context, the goal of the PARACOR-19 trial is to generate further evidence regarding the effects of sacubitril/valsartan on markers of cardiac injury, structure, and function among patients who have recovered from acute COVID-19 infection. **Hypothesis:** Among patients with cardiovascular risk factors and 4-16 weeks from prior COVID-19 infection, sacubitril/valsartan will reduce levels of high-sensitivity troponin T and/or soluble ST2 (sST2), compared with placebo.
Study Design	The PARACOR-19 trial will be an investigator-initiated, single center, double-blind trial of patients who have recovered from acute COVID-19

	infection. There will be 1:1 randomization to sacubitril/valsartan or placebo. Approximately 50 participants will be randomized into the study. A subset of approximately 30 patients will be enrolled in the cardiac magnetic resonance (CMR) sub-study.
Treatment	Sacubitril/valsartan versus placebo
Primary Objective and Endpoint	1. Change from baseline in high-sensitivity troponin T 2. Change from baseline in sST2
Exploratory Objectives and Endpoints	1. Change from baseline in high-sensitivity C-reactive peptide 2. Change form baseline in PINP 3. Change from baseline in Galectin-3 4. Change from baseline in NT-proBNP 5. Change from baseline in GDF-15 6. Change from baseline in IL-6 7. Change from baseline in CITP 8. Change from baseline in CMR measures (LVEF, LVEDVi, LVESVi, Native T1, Native T2) 9. Change from baseline in focal fibrosis by delayed-enhancement 10. Change from baseline in focal fibrosis as percentage of LV myocardial mass 11. Change from baseline in health related quality of life, as measured by EQ-5D utility score and EQ-5D visual analog scale

4 OBJECTIVES

4.1 Primary Objectives

To determine the effect of sacubitril/valsartan versus placebo over 12 weeks on biomarkers of cardiac injury and fibrosis, as reflected in changes in high-sensitivity troponin T and sST2.

Hypothesis: Among patients with cardiovascular risk factors and 4-16 weeks from prior COVID-19 infection, sacubtril/valsartan will reduce levels of high-sensitivity troponin T and/or soluble ST2 (sST2), compared with placebo.

4.2 Exploratory Objectives

To determine the effect of sacubitril/valsartan versus placebo over 12 weeks on cardiac biomarkers and measures of cardiac dysfunction and fibrosis on cardiac magnetic resonance imaging, as reflected by the following exploratory endpoints:.

1. Change from baseline in high-sensitivity C-reactive peptide
2. Change form baseline in PINP
3. Change from baseline in Galectin-3
4. Change from baseline in NT-proBNP
5. Change from baseline in GDF-15
6. Change from baseline in IL-6
7. Change from baseline in CITP
8. Change from baseline in cardiac MRI (CMR) measures (LVEF, LVEDVi, LVESVi, Native T1, Native T2)
9. Change from baseline in focal fibrosis by delayed-enhancement
10. Change from baseline in focal fibrosis as percentage of LV myocardial mass
11. Change from baseline in health related quality of life, as measured by EQ-5D utility score and EQ-5D visual analog scale

5 BACKGROUND AND STUDY RATIONALE

Although many patients presenting with Coronavirus Disease 2019 (COVID-19) face high-risk of death, the vast majority of patients recover from the acute infection, either in the hospital or at home. Nonetheless, despite clinical improvement or resolution of symptoms, accumulating evidence supports significant potential for longer-term and insidious cardiac involvement. For example, in a recent study of patients seen a mean 71 days after COVID-19 diagnosis, 76% had detectable high-sensitivity troponin, 78% had demonstrable cardiac involvement on cardiac magnetic resonance (CMR) imaging, and 60% had evidence of cardiac inflammation by abnormal T1 and T2 imaging.[1] Two-thirds of these patients recovered at home and there were no meaningful differences in troponin or CMR measures between patients who did and did not require hospitalization, suggesting that ongoing cardiac involvement may be common even

among those with a mild acute presentation.[1] Likewise, in an autopsy study of patients with COVID-19 pneumonia as the clinical cause of death, 62% of patients had virus present in the heart, despite not meeting clinical or histologic criteria for acute myocarditis.[2] Viral load was high and evidence of active viral replication was seen in most cases.[2] Notably, the virus appeared to localize to interstitial cells and the extracellular matrix of the heart, with relative sparing of the myocytes themselves.[3] These data, combined with others noting high levels of inflammation with COVID-19, suggest that the virus may increase propensity for downstream cardiac fibrosis and dysfunction. These collective data raise significant concerns that cardiomyopathy and heart failure will evolve as the natural history of COVID-19 for many patients who recover from acute infection.[4]

Pre-clinical and clinical data across multiple cardiometabolic conditions suggest that sacubitril/valsartan may be particularly well-suited to prevent adverse cardiac remodeling and new-onset HF following COVID-19 infection. Renin-angiotensin-aldosterone system (RAAS) inhibition has been postulated to have a cardio-protective role in COVID-19, but there is strong biologic plausibility that a dual compound with a neprilysin inhibitor would better prevent cardiac injury and dysfunction.[5] Across cardio-renal disease states, compared with ACEI/ARB therapy, sacubitril/valsartan offers superior cardio-protection for reducing clinical events and biomarkers of cardiac injury/ wall stress (e.g., troponin, natriuretic peptides), and these incremental benefits emerge quickly within a few weeks.[6-11] Likewise, compared with ACEI/ARB, sacubitril/valsartan lowers levels of pro-inflammatory cytokines and other inflammatory biomarkers.[12-14] Most recently, among patients with preserved ejection fraction, sacubitril/valsartan was shown to favorably alter biomarkers of cardiac extracellular matrix and collagen regulation compared with valsartan, adding further support for an anti-fibrotic mechanism well-suited to combat the propensity of COVID-19 for the cardiac interstitium.[15]

In this context, the goal of the PARACOR-19 trial is to generate further evidence regarding the effects of sacubitril/valsartan on markers of cardiac injury, structure, and function among patients who have recovered from acute COVID-19 infection.

6 STUDY DESIGN

6.1 Screening and Randomization (Study Visit 1)

Willing participants deemed likely to meet eligibility criteria will be consented. Participants will have an initial screening evaluation, including laboratory tests, at which time preliminary subject eligibility will be confirmed. Patients will also complete EuroQOL-5D (EQ-5D) surveys in order to be eligible. Participants consenting for and meeting entry criteria for the CMR substudy will undergo a CMR examination.

Patients confirmed to meet study eligibility criteria will be randomized 1:1 in double-blind fashion to sacubitril/valsartan twice daily versus matching placebo twice daily. The starting dose of study drug will be dictated by systolic blood pressure. If systolic blood pressure is 100-120 mmHg at randomization, participants will receive sacubitril/valsartan 24/26 mg twice daily or

matching placebo. If systolic blood pressure >120 mmHg at randomization, participants will receive sacubitril/valsartan 49/51 mg twice daily or matching placebo. At time of randomization, patients will also have serum biomarkers collected for central and local laboratory analysis.

6.2 Dose Titration and Safety Visit

Patients will return between 7 and 21 days post-randomization for **Study Visit 2**. At this visit, tolerability and adherence to study medication will be assessed, renal function and potassium levels will be checked via local labs, and patients will have the dose of medication titrated based on systolic blood pressure and clinician assessment regarding presence of symptomatic hypotension.

If systolic blood pressure >100 mmHg and no symptomatic hypotension or deemed medication-related adverse effects, dose of study medication will be increased to the next highest dose of sacubitril/valsartan or matching placebo (i.e., patients originally receiving sacubitril/valsartan 24/26 mg twice daily will be increased to sacubitril/valsartan 49/51 mg twice daily; patients originally receiving sacubitril/valsartan 49/51 mg twice daily will be increased to sacubitril/valsartan 97/103 mg twice daily). Patients not meeting criteria for dose uptitration will remain on their original dose of study therapy, as tolerated. For patients who are reporting symptomatic hypotension or other possible medication related adverse effects from study drug, the investigator may use their discretion in decreasing the dose of study drug to the next lowest dosing level.

6.3 Final Study Visit

Participants will return for a final study visit between 77 and 91 days (11-13 weeks) for the 12-week visit **(Study Visit 3)**. Tolerability and adherence to study medication will be assessed, and renal function and potassium levels will be checked via local labs. Participants will also have serum biomarkers collected for central and local laboratory analysis. Participants who consented for the CMR sub-study will undergo a CMR examination.

7 PATIENT POPULATION

7.1 Study Population

It is anticipated that approximately 50 participants meeting eligibility criteria listed below will be randomized into the study. It is anticipated that 30 of these patients will be included within the CMR substudy. Individuals suitable for this protocol are patients with cardiovascular risk factors and 4-16 weeks from prior COVID-19 infection.

7.2 Inclusion Criteria

1. Patient with a history of laboratory proven-diagnosis of COVID-19 who is 4-16 weeks

from their last positive COVID-19 test

2. Systolic blood pressure ≥100 mmHg at screening
3. ≥18 years of age
4. Successful collection of baseline serum biomarkers
5. Successful completion of baseline EQ-5D questionnaire
6. Successful completion of baseline CMR study (CMR sub-study only)
7. High-sensitivity troponin at or above the level of detection on screening labs
8. Presence of ≥1 of the following:
    a. Age ≥60
    b. History of atherosclerotic cardiovascular disease (ASCVD), including myocardial infarction, coronary artery disease, ischemic stroke/transient ischemic attack, or peripheral artery disease
    c. Diabetes mellitus (Type 1 or Type 2)
    d. Body mass index ≥35 kg/m^2
    e. eGFR 30-60 ml/min/1.73m^2
    f. History of atrial fibrillation/flutter

7.3 Exclusion Criteria

1. Fever within the past 96 hours of >100.3 degrees Fahrenheit
2. Actively receiving therapy with an angiotensin-converting enzyme inhibitor (ACEI), angiotensin II receptor blocker (ARB), aliskiren, or sacubitril/valsartan
3. Last known left ventricular ejection fraction of ≤40%
4. eGFR <30 ml/min/1.73m^2 on screening labs, including patients on dialysis therapy
5. Serum potassium >5.0 mEq/L on screening labs
6. Prior intolerance, allergy or angioedema to ACEI, ARB, or sacubitril/valsartan
7. Pregnant or breast-feeding
8. In women of childbearing age, unwillingness to use birth control for the duration of the study
9. History of heart transplant or durable left ventricular assist device
10. Currently implanted permanent pacemaker, defibrillator, or other device or condition that would preclude CMR testing (CMR sub-study only)
11. Currently participating in another trial of an investigational medication or device for COVID-19.
12. Any other condition that in the judgment of the investigator would jeopardize the patient's compliance with the study protocol

8 TREATMENT

8.1 Intervention

This will be a 2-arm randomized, double-blind, controlled trial. The therapeutic intervention will be treatment with either sacubitril/valsartan or placebo. Study drug will be given for 12 weeks

(+/- 1 week).

8.2 Drug Dispensing

Sacubitril/valsartan and matching placebo will be provided to Duke University Hospital by Novartis Pharmaceuticals. Participants will receive a sufficient supply of study drug at each study visit to last until the next study visit by a blinded member of the study team. Drug storage, inventory, accountability, and dispensing will be managed at Duke University Hospital. Participants will be instructed to take the medication as required by the protocol and compliance will be assessed at each visit.

8.3 Drug Administration

Subjects will take sacubitril/valsartan or placebo twice daily by mouth, with dosing determined as outlined in Section 6 above.

8.4 Drug Storage Requirements

Study mediation must be received by designated personnel at Duke University Hospital, handled and stored safely and properly, and kept in a secured location to which only the investigator and designated site personnel have access. Upon receipt, doses of sacubitril/valsartan and matching placebos should be stored according to the instructions specified on the drug labels.

8.5 Drug accountability

Participants are instructed to return all used, partly used and unused trial product at each study visit. Returned trial product(s) (used, partly used or unused including empty packaging material) must be stored separately from the non-allocated trial product(s) until drug accountability has been reconciled. The investigators will keep track of all received, used, partly used and unused trial products.

8.6 Destruction

Used and unused study drug may be destroyed at the site according to accepted pharmacy practice, local and national guidelines, using the site's destruction procedure.

8.7 Randomization, Stratification and Blinding

Patients will be consented and enrolled at the first study visit. Eligible patients will be randomized in a 1:1 allocation ratio to one of two treatment groups. Since this is a single center pilot study, randomization will not involve a permuted block design or any stratification.

Blinding of the study, with respect to treatment groups, will be preserved by the use of matching placebo. The investigator may be asked at the end of the trial if they had obtained any

information which may have led to the unblinding of treatment.

8.8 Unblinding

The investigator will be given access to the treatment code for their participants for emergency unblinding only. Any suspected study drug-related events should be treated as though the subject received sacubitril/valsartan. Randomization data are kept strictly confidential, accessible only to authorized persons, until the time of unblinding. Randomization codes will be provided to Novartis Pharmaceuticals at the time of study initiation. Upon completion of the double blind period, Novartis Pharmaceuticals will unblind data in the Argus safety database once database lock is completed and confirmed by Duke University Medical Center. This time frame is in accordance with Novartis standard operating procedures and unblinding will take place in coordination with the Duke study.

8.9 Concomitant Medication

Participants should be treated per standard care with their regular clinicians. However, the following medications should not be taken during the treatment period of this study: ACEI, ARB, aliskiren, or sacubitril/valsartan (other than blinded study drug), bile acid sequestering agents (e.g., cholestyramine), and nesiritide or intravenous nitrates (interrupt or discontinue study drug, as concomitant administration of sacubitril/valsartan with nesiritide or intravenous nitrates has not been studied).

The following medications should be used with caution during the study period: agents that raise potassium (e.g., potassium sparking diuretics, potassium supplements, mineralocorticoid receptor antagonists), and phosphodiesterase-5 inhibitors (may increase risk of hypotension).

9 RECRUITMENT AND SCREENING PROCEDURES

9.1 Common Recruitment Procedures

Individual meeting eligibility criteria will be approached regarding participation in this study.

9.2 Estimated Enrollment Period

This study will randomize approximately 50 subjects in the Duke University Health System in the U.S. The anticipated enrollment period is approximately 12 months.

9.3 Informed Consent

Study personnel will explain to eligible individuals the purpose of the study, study interventions and evaluations, and the potential risks and benefits of participation, and will answer any questions. If a subject agrees to participate in the study, they will review and sign the Duke University institutional review board (IRB) approved informed consent form (ICF).

9.4 Confidentiality and HIPAA Requirements

All information collected on study subjects will be stored in a confidential manner using the procedures in place at Duke University Hospital. Only approved study personnel will have access to data collected as part of the study. Consented study subjects will be identified by a subject ID number on all study documents.

9.5 Protections of Human Subjects

Protections for human subjects of research are required under Department of Health and Human Services (HHS) regulations at 21 CFR parts 50, 56, and 312.

9.6 Summary of the Risks and Benefits

Blood draws: The risks of drawing blood include bleeding at the puncture site, bruising and pain. These occur in a very small portion of the population.

Cardiac Magnetic Resonance Imaging (sub-study patients only): Serious reactions to the contrast agent used during some MRI tests are very rare. However, side effects are possible and include headache, nausea, dizziness, changes in taste, and allergic reactions. Rarely, the contrast agent can harm people who have severe kidney or liver disease. The substance may cause nephrogenic systemic fibrosis.

Sacubitril/valsartan: Sacubitril/valsartan is indicated to reduce the risk of cardiovascular death and hospitalization for heart failure in adult patients with chronic heart failure.[7, 8, 16] Moreover, sacubitril/valsartan has been shown to reduce mortality in patients with heart failure and reduced ejection fraction (HFrEF).[7] This agent is recommended in all patients with HFrEF (Class I, Level of Evidence B-R), unless contraindicated.[17]

Sacubitril/valsartan is teratogenic and contraindicated in pregnancy. Use of drugs that act on the renin-angiotensin system (of which sacubitril/valsartan is included) during the second and third trimesters of pregnancy reduces fetal renal function and increases fetal and neonatal morbidity and death. When pregnancy is detected, discontinue study drug as soon as possible. These adverse outcomes are usually associated with use of these drugs in the second and third trimesters of pregnancy. There is no information regarding the presence of sacubitril/valsartan in human milk, the effects on the breastfed infant, or the effects on milk production. Sexually active subjects must agree to use appropriate contraception as long as they are taking study drug. Medically acceptable contraceptives include:

- surgical sterilization (such as a tubal ligation or hysterectomy)
- approved hormonal contraceptives (such as birth control pills, patches, implants or injections)
- barrier methods (such as a condom or diaphragm) used with a spermicide, or
- Intrauterine device (IUD)

Sacubitril/valsartan should be used with caution in the setting of concomitant non-steroidal anti-inflammatory drugs, lithium, other potassium-sparing diuretics. Sacubitril/valsartan is contraindicated with use an ACEI, ARB, and should not be used with aliskiren in patients with diabetes.

In the PARADIGM-HF trial of patients with chronic heart failure with reduced ejection fraction, sacubitril/valsartan reduced the risk of cardiovascular mortality or heart failure hospitalization by 20%, as compared with guideline-indicated ACEI therapy (i.e., enalapril). In the PARADIGM-HF trial, use of sacubitril/valsartan was associated with a greater incidence of angioedema than the comparator drug enalapril (0.5% vs. 0.2%).[7] The risk of angioedema with sacubitril/valsartan compared with enalapril was relatively greater among Black patients (2.4% vs. 0.5%). Patients with a history of angioedema are contraindicated from taking this drug. Trial data indicate adverse reactions occurring ≥5% are hypotension, hyperkalemia, cough, dizziness, and renal failure. Symptomatic hypotension in PARADIGM-HF was more common among patients taking sacubitril/valsartan than enalapril (18% vs. 12%).[7] In the PARAGON-HF trial, which tested the efficacy and safety of sacubitril/valsartan versus valsartan among patients with heart failure with preserved ejection fraction, no new adverse reactions were identified.[8]

10 VISIT SCHEDULE AND ASSESSMENTS

10.1 Baseline Evaluation, Enrollment and Randomization Visit

A schedule of assessments throughout the study is also provided in Appendix A.

Study Visit 1 (Enrollment and Randomization)
This visit will include the screening and informed consent process followed by a baseline assessment including:

- Demographics and medical history
- Review of medications patient is actively taking, and the doses
- Vital signs, including systolic and diastolic blood pressure, heart rate, height, weight
- EQ-5D quality of life questionnaire
- Residual COVID-19 symptoms
- Local laboratory testing, including the following:
  - Basic metabolic/renal function panel, including sodium, potassium, chloride, CO2/bicarbonate, blood Urea Nitrogen (BUN), creatinine
  - High-sensitivity troponin

- Central laboratory testing, including the following
  - High-sensitivity troponin T
  - sST2
  - hs-CRP
  - PINP
  - Galectin-3
  - NT-proBNP
  - GDF-15
  - IL-6
  - CITP
- CMR examination, with intravenous gadolinium contrast (CMR sub-study patients only)
- Urine pregnancy test on women of childbearing potential

Patients will be initiated on blinded study medication, as dictated by systolic blood pressure. If systolic blood pressure is 100-120 mmHg at randomization, participants will receive sacubitril/valsartan 24/26 mg twice daily or matching placebo. If systolic blood pressure >120 mmHg at randomization, participants will receive sacubitril/valsartan 49/51 mg twice daily or matching placebo.

10.2 Follow-up Evaluations

Study Visit 2 (Titration Visit)
Visit 2 should take place within 7-21 days after the randomization visit.
Assessments at this visit include:

- Review of medications patient is actively taking, and the doses
- Vital signs, including systolic and diastolic blood pressure, and heart rate
- Local laboratory testing, including the following:
  - Basic metabolic/renal function panel, including sodium, potassium, chloride, CO2/bicarbonate, BUN, creatinine
- Urine pregnancy test on women of childbearing potential
- Adverse event monitoring, including hospitalizations
- Study medication adherence

If systolic blood pressure >100 mmHg and no symptomatic hypotension or deemed medication-related adverse effects, dose of study medication will be increased to the next highest dose of sacubitril/valsartan or matching placebo (i.e., patients originally receiving sacubitril/valsartan 24/26 mg twice daily will be increased to sacubitril/valsartan 49/51 mg twice daily; patients originally receiving sacubitril/valsartan 49/51 mg twice daily will be increased to sacubitril/valsartan 97/103 mg twice daily). Patients not meeting criteria for dose uptitration will remain on their original dose of study therapy, as tolerated. For patients who are reporting

symptomatic hypotension or other possible medication related adverse effects from study drug, the investigator may use their discretion in decreasing the dose of study drug to the next lowest dosing level.

Study Visit 3 (Final Study Visit)

Participants will return for a final study visit between 77 and 91 days (11-13 weeks) for the 12-week visit.

Assessments at this visit include:

- Review of medications patient is actively taking, and the doses
- Vital signs, including systolic and diastolic blood pressure, heart rate, weight
- EQ-5D quality of life questionnaire
- Residual COVID-19 symptoms
- Local laboratory testing, including the following:
  - Basic metabolic/renal function panel, including sodium, potassium, chloride, CO2/bicarbonate, BUN, creatinine
- Central laboratory testing, including the following
  - High-sensitivity troponin T
  - sST2
  - hs-CRP
  - PINP
  - Galectin-3
  - NT-proBNP
  - GDF-15
  - IL-6
  - CITP
- CMR examination, with intravenous gadolinium contrast (CMR sub-study patients only)
- Urine pregnancy test on women of childbearing potential
- Adverse event monitoring, including hospitalizations
- Study medication adherence

Study Drug Interruption:

If a subject should stop taking study medication for any reason before completing the 12 weeks of study drug dosing, an attempt should be made to restart the study drug at the last tolerated dose when the subject is stable, per physician discretion. If the treating physician decides to stop study medication and start the patient on an ACEI, then a 36 hour wash-out period is required after the last dose of study drug before starting the ACEI. All subjects will complete all study assessments through study visit 3, regardless of whether they continue to receive the study drug for the full 12 weeks.

Unscheduled Visits:

If the Investigator determines that a participant should be brought to the clinic to be evaluated

for a potential change in study drug dose between scheduled study visits, an “unscheduled visit” should be done. Study drug dose changes will be recorded in the eCRF.
Assessments at this visit include:

- Interim history
- Review of medications patient is actively taking, and the doses
- Vital signs, including systolic and diastolic blood pressure, and heart rate
- Local laboratory testing, including the following:
  - Basic metabolic/renal function panel, including sodium, potassium, chloride, CO2/bicarbonate, BUN, creatinine
- Adverse event monitoring
- Study medication adherence

11 OUTCOME DETERMINATIONS

11.1 Primary Endpoints

1. Relative change from baseline in high-sensitivity troponin T levels from randomization to 12 weeks.
2. Relative change from baseline in sST2 from randomization to 12 weeks.

11.2 Exploratory Endpoints

1. Change from baseline in high-sensitivity C-reactive peptide
2. Change form baseline in PINP
3. Change from baseline in Galectin-3
4. Change from baseline in NT-proBNP
5. Change from baseline in GDF-15
6. Change from baseline in IL-6
7. Change from baseline in CITP
8. Change from baseline in CMR measures (LVEF, LVEDVi, LVESVi, Native T1, Native T2)
9. Change from baseline in focal fibrosis by delayed-enhancement
10. Change from baseline in focal fibrosis as percentage of LV myocardial mass
11. Change from baseline in health related quality of life, as measured by EQ-5D utility score and EQ-5D visual analog scale

12 PARTICIPANT SAFETY MONITORING AND REPORTING

12.1 Institutional Review Boards

The study protocol, consent form, and other study documents will be submitted to Duke University IRB for approval. Any amendments to the protocol, other than minor administrative changes, must be approved by each Duke University IRB before they are implemented.

12.2 Adverse Event Definition

An adverse event (AE) is any untoward medical occurrence associated with the use of a drug in a participant, whether or not considered drug or biologic related. An AE can therefore be any undesirable sign, symptom or medical condition occurring after starting study drug, even if the event is not considered to be related to the pharmaceutical product.

12.3 Suspected Adverse Reaction Definition

A suspected adverse reaction (SAR) is any adverse event for which there is a reasonable possibility that the drug caused the event. “Reasonable possibility” suggests there is a causal relationship between the drug and the adverse event. “Suspected adverse reaction” implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

12.4 Serious Adverse Events (SAE)

An adverse event or suspected adverse reaction is considered serious if the investigator or sponsor believes any of the following outcomes occurred:

- Death
- Life-threatening AE: Places the subject at immediate risk of death at the time of the event as it occurred. It does not include an AE that, had it occurred in a more severe form, might have caused death.
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- Inpatient hospitalization or prolongation of hospitalization.
- Congenital anomaly or birth defect.
- Important medical events that may not result in death, be life threatening, or require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition above. This determination is based on the opinion of the investigator.

12.5 Laboratory Test Abnormalities

For laboratory test abnormalities that meet the definition of an SAE, that required the participant to have the investigational product discontinued or interrupted or require the participant to receive specific corrective therapy, the clinical diagnosis rather than the laboratory term will be used by the reporting investigator (e.g., anemia versus low hemoglobin value).

12.6 Assessment of Causal Relationship

A medically-qualified investigator must assess the relationship of any AE to the use of study drug, based on available information, using the following guidelines:

- **Not related:** There is not a reasonable causal relationship to the investigational product and the adverse event.
- **Unlikely related:** No temporal association or the cause of the event has been identified, or the drug or biologic cannot be implicated.
- **Possibly related:** There is reasonable evidence to suggest a causal relationship between the drug and adverse event.
- **Related:** There is evidence to suggest a causal relationship, and the influence of other factors is unlikely.

12.7 Assessment of Adverse Event Severity

The determination of adverse event severity rests on medical judgment of a medically-qualified investigator. The severity of AEs will be graded using the following definitions:

- **Mild:** Awareness of sign, symptom, or event, but easily tolerated;
- **Moderate:** Discomfort enough to cause interference with usual activity and may warrant intervention;
- **Severe:** Incapacitating with inability to do usual activities or significantly affects clinical status, and warrants intervention.

12.8 Recording and Reporting of Adverse Events

The site Investigator is responsible for monitoring the safety of subjects enrolled into the study.

All AEs occurring from signed informed consent through study visit 3 will be captured on the AE eCRF. For patients who die during the course of the study, the cause of death will be reported by the investigator in the eCRF. The Duke Heart Center Clinical Research Unit will share all SAEs with Novartis Pharmaceuticals within 24 hours after the investigators are made aware. AE reports will be shared with Novartis Pharmaceuticals, as requested.

Any misuse or abuse of the study drug, other medication errors and uses outside of what is foreseen in the protocol (irrespective of whether a clinical event has occurred) will also be documented in the eCRF.

12.9 Follow-up of Adverse Events

When additional relevant information becomes available, the investigator will record follow-up information according to the same process used for reporting the initial event as described above. The Investigator will follow all reportable events until resolution, stabilization or the event is otherwise explained.

Investigators are also responsible for promptly reporting AEs to Duke University IRB in accordance with local requirements. The Data Safety Monitoring Board (DSMB) will review detailed safety data approximately every 6 months throughout the study.

12.10 Expectedness

The expectedness of an AE or Suspected Adverse Reaction (SAR) shall be determined according to the most current patient package insert (PPI). Any AE that is not identified in nature, severity, or specificity in the current PPI is considered unexpected. Events that are mentioned in the PPI as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but not specifically mentioned as occurring with the particular drug under investigation are considered unexpected.

12.11 Suspected Unexpected Serious Adverse Reaction

AEs that meet the criteria of serious, related to study drug, and unexpected per PPI, qualify for expedited reporting to the regulatory authorities. The site Investigator will assess all SAE's occurring at his/her site and evaluate for "unexpectedness" and relationship to study drug. The site Investigator is required to complete and submit a voluntary MedWatch Report for events viewed as serious, study drug related and unexpected at: https://www.accessdata.fda.gov/scripts/medwatch/.

12.12 Pregnancy

Pregnancy occurring during a clinical investigation, although not considered a serious adverse event, will be recorded in the eCRF. Study drug will be discontinued among patients confirmed to be become pregnant during the study. The pregnancy will be followed until final outcome. Any associated AEs or SAEs that occur to the mother or fetus will be recorded in the AE/SAE eCRF,. The pregnancy outcome of a female partner to a male study participant will not be followed.

13 STATISTICAL METHODS AND DATA ANALYSIS

13.1 General Design Issues

Planned analyses will be prospectively defined for this study prior to unblinding of data.

Primary analysis of the PARACOR-19 trial will be based on the intention to treat (ITT) principle. That is, subjects will be analyzed (and endpoints attributed) according to the treatment strategy to which subjects are randomized, regardless of subsequent additional post-randomization treatment and medical care. The ITT population will correspond to all randomized subjects. Secondary analysis will include per-protocol analysis, which will include randomized patients who remain on assigned study drug and complete the entirety of the study protocol.

Statistical comparisons will be performed using two-sided significance tests. Baseline demographic and clinical variables will be summarized for each randomized arm of the study. Descriptive summaries of the distribution of continuous variables will be presented in terms of percentiles (e.g., median, 25th and 75th percentiles) along with means and standard deviations.

Categorical variables will be summarized in terms of frequencies and percentages.

In addition, exploratory analyses will be performed to help explain and understand findings observed from the planned analyses. Statistical tests with a 2-sided p-value <0.05 will be considered statistically significant, unless otherwise stated. Analyses will be performed using SAS software (SAS Institute, Inc, Cary, NC).

13.2 Sample Size Justification and Randomization

Subjects will be randomized in a 1:1 allocation ratio. We plan to randomize approximately 50 participants with planned follow-up of 12 weeks. Given the exploratory nature of this early phase study, the co-primary endpoints (relative change in hs-troponin T, relative change in sST2) will be assessed separately using a type 1 error of 0.05.

We assume a 25% relative reduction in hs-troponin T compared with placebo at 12 weeks, and a 25% relative reduction in sST2 compared with placebo at 12 weeks. A two-sided, two-sample t-test with group sample sizes of 25 and 25 achieves at least 80% power to detect a ratio of 0.75 when the ratio under the null hypothesis is 1.00. The coefficient of variation (CV) on the original scale is assumed to be ≤ 0.36 which is reasonable based on historical data.[18] The significance level (alpha) is 0.05. As the CV decreases, the statistical power increases; however, it the CV increases we would need to find a larger ratio to have at least 80% power. For example, if the CV were actually 0.57, then we would have 80.3% power to find a significant ratio of 35%. For all primary and exploratory biomarker endpoints, values below the lower limit of the assay will be imputed with values just below the level of detection, consistent with approaches in prior cardiovascular biomarker trials.[18]

13.3 Interim Analyses and Safety Reviews

It is anticipated that the DSMB will review the accumulating data and schedule ad hoc meetings if SAEs accrue. During such meetings, the DSMB may be provided the following information: subject enrollment reports, rates of adherence with the assigned treatment, and description of SAEs. The DSMB will review data masked by study group (such as X vs. Y). Due to the size of the trial, no formal interim analysis of efficacy is planned. There will be no futility analysis.

13.4 Analysis of the Co-Primary Endpoints

For each serum biomarker, we will calculate the ratio of geometric means at baseline and 12 weeks for the sacubitril/valsartan treatment arm compared with the placebo arm, with 95% confidence intervals. A two-sample t-test will be used to test for a significant difference using a p-value <0.05 for each co-primary endpoint. A sensitivity analysis will be done using generalized linear regression to assess the ratio after adjusting for possible baseline differences.

13.5 Analysis of Exploratory Endpoints

Serum biomarker exploratory endpoints will be assessed in an identical manner to the co-primary endpoints.

CMR exploratory endpoints will be analyzed as change from baseline using linear regression (with treatment, randomization group assignment, and the baseline value as covariates) to determine estimated mean, the differences compared with placebo, and 95% confidence intervals (CI). Sensitivity analyses will be considered adjusting for possible baseline differences.

14 DATA MANAGEMENT PROCEDURES

14.1 Overview of Data Management

The Duke Heart Center Clinical Research Unit will have primary responsibility for data management, including the development of data collection systems, data monitoring processes, and data storage and back-up.

14.2 Data Security

Access to databases will be controlled centrally by Duke Heart Center Clinical Research Unit through user passwords linked to appropriate privileges. This protects the data from unauthorized changes and inadvertent loss or damage. Database and web servers will be secured by Duke University firewall and through controlled physical access. All disk drives that provide network services, and all user computers, will be protected using virus-scanning software.

14.3 Publication Policy

Dissemination of preliminary information can adversely affect the objectivity of study data. For this reason, investigators will not be allowed to perform subset analyses at any point before the conclusion of the study, and any data, other than safety data, cannot be used for publication or reporting outside of this study until the study is completed or discontinued by the DSMB.

15 STUDY ADMINISTRATION

15.1 Data and Safety Monitoring Board

An independent DSMB will be for this trial. This committee will consist of a group of highly experienced individuals with extensive pertinent expertise in HF and clinical trials. The DSMB will advise the investigators regarding the continuing safety of current subjects and those yet to be recruited, as well as the continuing validity and scientific merit of the trial. Safety data, summarized at the treatment level, will be assessed approximately every 6 months by the

DSMB. The safety analyses will be based on the entire ITT population. Safety will be evaluated by comparing the occurrence of AEs and changes in laboratory values of the active treatment arm compared to the active control arm.

15.2 Biomarker Core Laboratory

Plasma specimens collected for central laboratory analysis will be sent to the core laboratory for measurement of serum biomarkers. These specimens will be collected at Study Visits 1 and 3, processed at the Duke Heart Center Clinical Research Unit according to the appropriate procedures, and shipped to the core laboratory on ice.

16 REGULATORY ISSUES

16.1 Ethics and Good Clinical Practice

This study must be carried out in compliance with the protocol. These procedures are designed to ensure adherence to Good Clinical Practice, as described in the following documents:

1. ICH Harmonized Tripartite Guidelines for Good Clinical Practice 1996.
2. US 21 Code of Federal Regulations dealing with clinical studies (including parts 50 and 56 concerning informed consent and IRB regulations).

The investigators agree to adhere to the instructions and procedures described in the protocol and thereby to adhere to the principles of Good Clinical Practice that it conforms to.

16.2 Institutional Review Board/Independent Ethics Committee

Before implementing this study, the protocol, the proposed informed consent form and other information to subjects must be reviewed by the Duke University IRB. Documentation that the protocol and informed consent have been approved by the IRB must be in place before study initiation. Any amendments to the protocol, other than administrative ones, must be approved by the IRB.

16.3 Informed Consent

The investigator or designee must explain to each subject (or legally authorized representative) the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved and any discomfort it may entail. Each subject must be informed that participation in the study is voluntary and that he/she may withdraw from the study at any time and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician. The informed consent form(s) must be submitted by the investigator for IRB approval.

17 APPENDICES

17.1 Appendix A - Schedule of Assessments

Visit number Time of Visit	**1** **Enrollment/ Randomization**	**2** **Titration Visit (Week 1-2)**	**3** **12 weeks**
Inclusion/Exclusion criteria	X		
Informed consent	X		
Dispense study medication	X	X	
Demographics, past medical history	X		
Vital signs	X	X	X
Concurrent medications and doses	X	X	X
EQ-5D questionnaire	X		X
Residual COVID Symptoms	X		X
Urine pregnancy test[1]	X	X	X
Local laboratories	X[2]	X[3]	X[3]
Serum biomarkers	X[4]		X[4]
Cardiac MRI (30 patients, sub-study patients only)	X		X
Vital status			X
Adverse events, including hospitalizations		X	X
Study medication adherence		X	X

[1] For women of childbearing potential

[2] hs-TnT, basic metabolic panel (including serum creatinine and serum potassium)

[3] Basic metabolic panel (including renal function and serum potassium)

[4] hs-TnT, sST2, hs-CRP, PINP, Galectin-3, NT-proBNP, GDF-15, IL-6, CITP

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