Interleukin-1 Blockade in Recently Decompensated Heart Failure

A Randomized Placebo-controlled Double-blinded Study

The REDHART2 study

STUDY PROTOCOL

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Virginia Commonwealth University

CHANGES TO PRIOR VERSION

Prior version dated 10-25-2018 → new version 11-13-2018

- Personnel updated in the DSMB Charter per NHLBI Liaison request (see also section 8.6, and DSMB charter);
- Modified BNP criteria to include also NT-proBNP criteria – according to the European Society of Cardiology 2016 Heart Failure Guidelines (Ponikowski P et al. Eur Heart J 2016;37:2129-2200.

Prior version dated 11-13-2018 → new version 01-23-2019

- **Section 5.2:** Addition of the IPAQ questionnaire to the quality of life assessments. It will be administered at baseline, 6, 12 and 24 weeks to assess patient perception of changes
- **Section 6.3:** Changed exclusion criteria from "prior or current malignancy" to just "current malignancy receiving targeted therapy".
- **Section 7.1**: We clarify that the patient may need to come for additional visits between the pre-specified clinic visits for assessment and/or drug dispensing.
- **Section 7.7:** Addition of the IPAQ questionnaire to the list of study activities and clarification on when a physician will be alerted to review a participant's chart based on questionnaire responses.
- **Section 11.3.2**: Clarification on when cases with missing CPX data will result in omission from efficacy analysis.

DSMB Charter 3.f.: Clarification of the Biostatistician as Voting Member of the DSMB.

Prior version dated 01-23-2018 → new version 03-14-2019

- **Section 5.2:** Updated echocardiography description to include 6 and 12 week ECHO timepoints
- **Sections 7.5 and 7.9:** Updated echocardiography paragraph and procedure table to include ECHOs at weeks 6 and 12
- **Section 7.8:** Removed "troponin I" from text as biomarker being tested

Prior version dated 03-14-2019 → 08-27-2019

- Section 6.3: Clarified exclusion criterion related to CRT and valve surgery ('Cardiac resynchronization therapy (CRT) during index hospitalization, or planned CRT or valve surgeries within the following 6 months').
- Section 7.9: Corrected the time window for Visit 4 to 168±14 days (24±2 weeks).
- Section 8.3.1: We have updated the AE section to list the most common risks related to anakinra or completion of the study procedures.
- Section 10.1: We clarified that arthritis is a manifestation of hypersensitivity reaction that can demand discontinuation of the drug.

Prior version dated 08-27-2019 -> 10-07-2019

- Section 10.1: Specified the rules for restarting study drug after it has been suspended
- Section 10.2: Distinction between withdrawing treatment and withdrawing from the study and clarification of how long each patient will be followed for safety reasons and how the data will be used after each type of withdrawal
- Section 11.3.2: Clarification of primary method for handling missing data (LOCF)

Temporary Amendment in response to COVID19 Pandemic Emergency 03/27/2020

- Enrollment has been halted on 03/17/2020.
- All patients were instructed to interrupt treatment on that date.
- Follow up provided to assess for any research-related adverse events up to 6 months.
- Adjudication for events after 03/17/2020 will not be completed in consideration of the dynamic changes in the clinical care, challenges in diagnosis ascertainment, and possibility of COVID19 contributing to excess cardiovascular events.

Resuming clinical research operations during COVID19 pandemic change in Protocol version dated 10-07-2019 → 04-24-2020

- Resume screening and enrollment when Governor of Virginia and VCU / VCU Health authorize resumption of elective clinical procedures.
- Change in exclusion criteria, adding a criterion related to COVID19:
    - Evidence of COVID19 within the last 60 days or recent (21 days) exposure to close personal contact. (Section 6.3, bullet 9).

Changes to Key Personnel and DSMB Charter

- Amy Ladd, PhD, has taken on a new position as Associate Director of the Pauley Heart Center and will no longer serve as Regulatory Coordinator for the REDHART2 study; Dr. Ladd will however serve as DSMB Liaison to the study instead of Dr. Christine DeWilde, who has left VCU as June 10, 2020.

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Appendix: DSMB Charter

1) KEY PERSONNEL

Please refer to the IRB Roster and Delegation Log for a complete personnel list

Name	Role	Institution/ Division
Antonio Abbate, MD/PhD	Medical Responsible PI	VCU, Cardiology
Benjamin Van Tassell, PharmD	Study Operation PI	VCU, School of Pharmacy
Salvatore Carbone, PhD	Clinical Trial Operations	VCU, Cardiology
Ross Arena, PhD	CPX Core Lab	University of Illinois, Chicago
Robin Sculthorpe, PharmD	Investigational Pharmacy	VCU, School of Pharmacy
Juan Lu, PhD	Biostatistician	VCU, Biostatistics
Dominick Angiolillo, MD	DSMB Chair	University of Florida, Cardiology
Gonzalo Bearman, MD	DMSB member	VCU, Infectious disease
Ramesh Kundur	DSMB member	Virginia Cardiovascular Specialists
Brant Ward, MD	DSMB member	VCU, Immunology
Robert Perera, PhD	DSMB member	VCU, Biostatistics, CCTR
Amy Ladd, PhD	DSMB liaison	VCU, Pauley Heart Center

Abbreviations: DSMB=Data Safety Monitoring Board

2) PROTOCOL SUMMARY

Title: Interleukin-1 Blockade in Recently Decompensated Heart Failure

Population: 102 patients (age >21 years) with a clinical diagnosis of systolic heart failure, and recent (within 2 weeks of discharge) hospitalization for heart failure

Site(s): Virginia Commonwealth University, Richmond, VA

Study Duration: 40 months

Description: Phase II clinical trial of Anakinra (or Placebo) (2:1 allocation) for the treatment of patients with recently decompensated systolic (LVEF≤40%) heart failure and increased systemic inflammation (CRP>2 mg/L)

Objectives: To determine the effects of Anakinra (or Placebo) on peak of aerobic exercise capacity (peak VO_2) measured with a cardiopulmonary test after 24 weeks

Study Design: Single-center, randomized, double-blinded, placebo-controlled clinical trial with allocation to Anakinra 100 mg daily or placebo in 2:1 ratio for 24 weeks

Estimated Time to Complete Enrollment: 36 months

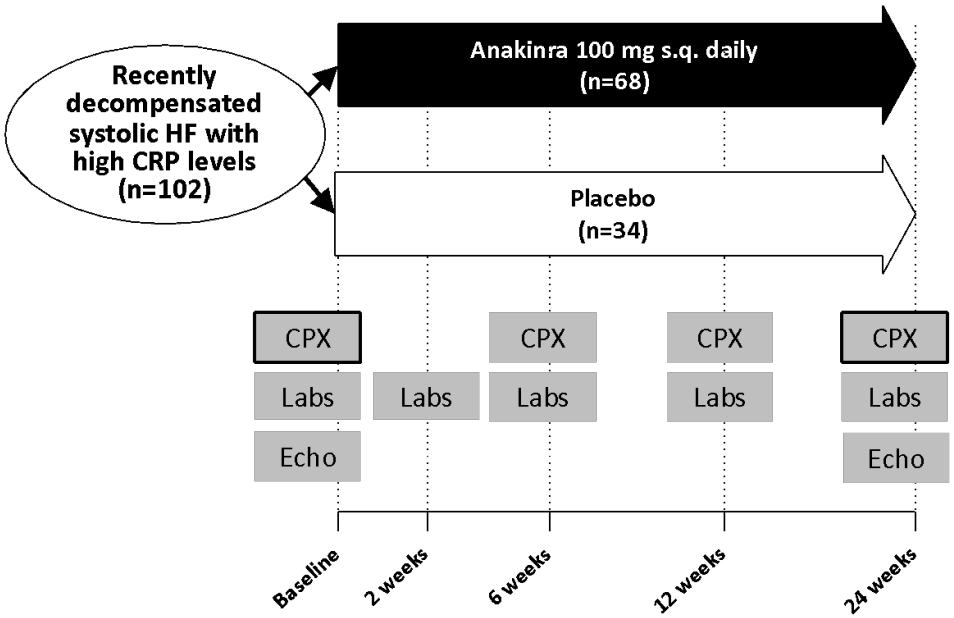
Estimated Time to:

First patient in: 6-12 months from funding

Last patient in: 34 months from first patient enrolled

Last patient out: 40 months from first patient enrolled

3) SCHEMATIC OF STUDY DESIGN



4) DESCRIPTION

The ***REDHART2*** (*REcently Decompensated Heart failure Anakinra Response Trial 2*) study is a phase II clinical trial of anakinra or placebo to improve aerobic exercise capacity in patients with recently decompensated systolic heart failure (HF).

The recently completed pilot REDHART study, supported by a R34 NHLBI pilot clinical trial grant randomly assigned 60 patients with recently decompensated systolic heart failure to one of 3 strategies: 1) short-term treatment with anakinra for 14 days; 2) longer-term treatment with anakinra for 12 weeks; 3) placebo for 12 weeks. An additional group of eligible patients who declined participation in the study was enrolled in an observational study to evaluate the rate of HF hospitalizations. Anakinra treatment for 12 weeks led to a significant improvement in peak aerobic exercise capacity (peak VO_2), whereas anakinra treatment for 2 weeks did not. No significant changes were seen in placebo. The hospital readmission rate at 6 months was 5% in anakinra 12-week treatment group, 30% in the placebo group, 32% in the anakinra 2-week group, and 35% in the observational group of eligible patients who were not randomized to treatment.

The REDHART2 study is designed to expand and confirm the beneficial effect of sustained anakinra treatment (24 weeks) on peak VO_2, and to explore the potential effect size on hospital readmissions for HF.

The rationale of Interleukin-1 (IL-1) blockade with anakinra in heart failure stems from the evidence of *a)* reduced adverse cardiac remodeling and heart failure in animal models of

acute myocardial infarction (AMI); *b)* reduced incidence of heart failure in patients with ST-segment elevation AMI; *c)* enhanced IL-1 activity in patients with heart failure, *d)* quenching of the acute inflammatory response in patients with acute decompensated heart failure, *e)* direct cardiodepressant effects of IL-1 in animal models, *f)* improved exercise capacity in pilot studies including patients with stable systolic heart failure, stable diastolic heart failure, and, recently decompensated systolic heart failure in the pilot REDHART study.

5) OBJECTIVES

The Objective of REDHART2 is to study the effects of IL-1 blockade with anakinra on parameters of aerobic exercise capacity (peak VO_2) at cardiopulmonary exercise test (CPX) after 24 weeks of active treatment, as well as the effects of anakinra on inflammatory biomarkers, structural and functional echocardiographic data, and non-invasive hemodynamics.

5.1 Primary Endpoint(s)

Placebo-corrected changes in peak VO_2 at CPX after 24 weeks of treatment will be considered the primary endpoint. This will compare patients treated with anakinra (N=68) vs placebo (N=34), and provide a randomized, double-blinded assessment of the effects of IL-1 blockade on aerobic exercise performance. The data will be collected and electronically transferred to the core laboratory at the University of Illinois, Chicago, IL (Ross Arena, PhD).

5.2 Secondary Exploratory Endpoints

Secondary exploratory endpoints will include parameters measured at CPX, echocardiography, non-invasive hemodynamics, as well as biomarkers, and clinical outcomes.

Additional CPX parameters: secondary endpoints include changes in peak VO_2 at earlier endpoints (6 and 12 weeks), and changes in other CPX variables such as ventilatory efficiency (ventilation-carbon dioxide elimination slope [VE/VCO_2 slope] and oxygen utilization efficiency slope [OUES]), anaerobic threshold, and peak oxygen pulse at 6, 12, and 24 weeks.

Echocardiography: secondary endpoints include measuring left ventricular end-diastolic and end-systolic volumes, ejection fraction, stroke volume estimated by left ventricular outflow tract velocity-time integral, measures of myocardial relaxation at tissue Doppler E', and estimate of left ventricular filling pressure using E/E' ratio at baseline, 6, 12 and at 24 weeks.

Non-invasive hemodynamics: secondary endpoints include estimates of arterial elastance (E_a), a measure of afterload, end-systolic elastance (E_{es}), a measure of load-independent contractility also defined as end-systolic pressure-volume relationship,

ventriculo-arterial coupling is defined as the ratio of E_a to E_{es}, at 6, 12 and 24 weeks. The hemodynamic assessment will be conducted with echocardiography and non-invasive blood pressure measuring.

Quality of life assessment: the Duke Activity Status Index (DASI), the Kansas City Cardiomyopathy Questionnaire (KCCQ), the International Physical Activity questionnaire (IPAQ-SF) and the Patient Health Questionnaire-9 (PHQ-9) will be administered at baseline, 6, 12 and 24 weeks to assess patient perception of changes.

Biomarkers: Blood will be collected at each visit (baseline, 6, 12, and 24 weeks) and analyzed for a panel of complete blood cell count with differential, basic metabolic panel, high sensitivity C- reactive protein (CRP), and NT-proBNP. In addition, 5 – 10mL of blood will stored frozen for later batch analysis and phenotyping of the inflammatory response .

Clinical outcomes: the incidence of death (cardiac and non-cardiac), hospitalizations (for HF, for other cardiac causes not related to HF, for non-cardiac reasons), medications use (number of HF medications, doses) will be recorded at each visit in every patient. Adjudication of events for research purposes will be performed by an *ad hoc* committee blinded to treatment allocation, based on all the data available in the chart including notes, pre-formatted sheets, laboratory and imaging modalities.

6) ENROLLMENT IN THE STUDY

6.1 Screening

Patients will be screened through one of the following routes:

- Patients admitted to the main VCUHealth hospital in Richmond, VA
  Our hospital receives >1000 hospitalizations per year for acute decompensated systolic heart failure, of which, we anticipate approximately 30 per month (~36%) will be preliminary eligible for REDHART2 participation. These subjects may be identified by multiple means: direct patient contact by the co-PIs or one of the co-investigators during their regular clinical practice, referral to the research team by coworkers or by the HF Navigator Nurse (a program set to establish post-discharge follow up care for patients), manual screening of the new daily admission list on the electronic medical record by research team, and an automatic alert system generated by the electronic medical record that identifies all new cases that meet pre-specified criteria (i.e., receiving intravenous diuretics, BNP>200 ng/mL, edema on chest radiography). We have been using these strategies for clinical enrollment over the past 3 years. While the system may not be specific (many false positive alerts – screen failures) it is very sensitive with virtually no HF-patient being lost to evaluation.

- Patients admitted to neighboring hospitals in Virginia
  Being the only academic medical center in Central Virginia we receive a large number of referrals for inpatient transfers or for outpatient evaluations, i.e., after acute decompensation, especially in underserved population such as the uninsured. In the

recent years, VCUHealth has partnered with the Community Memorial Hospital in South Hill, VA (a 200-bed hospital in the southern corridor of I-85) and with the Virginia Medical Group in Colonial Heights, VA (including a specialized cardiac center with 7 specialists).

- Post-hospital discharge clinics
  We have implemented a dedicated clinic for heart failure patients to be seen in clinic within 1 week of hospital discharge as part of the HF Navigator program. This clinic is staffed by a nurse practitioner and a nurse, and supervised by a HF specialist. The research team has access to the daily scheduling list and thus has access to those patients that may have been missed during hospitalization or that may be following up after hospitalization at a different hospital.

6.2 Inclusion Criteria

All 6 criteria need to be met for enrollment of the patient in the study

1. Primary diagnosis for hospitalization is decompensated heart failure established as the finding at admission of both conditions listed below:
   - dyspnea or respiratory distress or tachypnea at rest or with minimal exertion;
   - evidence of elevated cardiac filling pressure or pulmonary congestion (at least one of the conditions must be met):
     - pulmonary congestion/edema at physical exam OR chest X-Ray;
     - plasma BNP levels ≥200 pg/mL or proBNP ≥600 pg/ml;
     - invasive measurement of left ventricular end-diastolic pressure >18 mmHg or of pulmonary artery occluding pressure (wedge) >16 mmHg.
2. The patient has a prior documentation of impaired left ventricular systolic function (ejection fraction ≤40%) at most recent assessment by any imaging modality (within 12 months).
3. The patient is now clinically stable, euvolemic, and meets standard criteria for hospital discharge as documented by all the 3 conditions listed below:
   - absence of dyspnea or pulmonary congestion/distress at rest;
   - absence of pitting edema in the lower extremities, or in any other region;
   - stable hemodynamic parameters (blood pressure, heart rate).
4. The patient is of age ≥21 years old, and is willing and able to provide written informed consent.
5. The patient is willing and able to comply with the protocol (i.e., self-administration, or exercise test).
6. The patient has screening high sensitivity plasma C-reactive protein levels (hsCRP) >2 mg/L.

6.3 Exclusion Criteria

Subjects will not be eligible if they meet any one of the following 15 exclusion criteria.

1. The primary diagnosis for admission is NOT decompensated heart failure, including

diagnosis of acute coronary syndromes, hypertensive urgency/emergency, tachy- or brady-arrhythmias.
2. Concomitant clinically significant comorbidities that would interfere with the execution or interpretation of the study including but not limited to acute coronary syndromes, uncontrolled hypertension or orthostatic hypotension, tachy- or brady-arrhythmias, acute or chronic pulmonary disease or neuromuscular disorders affecting respiration.
3. Cardiac resynchronization therapy (CRT) during index hospitalization, or planned CRT or valve surgeries within the following 6 months.
4. Previous or planned implantation of left ventricular assist devices or heart transplant.
5. Chronic use of intravenous inotropes.
6. Recent (<14 days) use of immunosuppressive or anti-inflammatory drugs (including oral corticosteroids at a dose of prednisone equivalent of 0.5 mg/kg/day but not including inhaled or low dose oral corticosteroids or non-steroidal anti-inflammatory drugs).
7. Chronic inflammatory disorder (including but not limited to rheumatoid arthritis, systemic lupus erythematosus).
8. Active infection (of any type), including chronic/recurrent infectious disease (i.e. HBV, HCV, and HIV/AIDS) – but excluding HCV+ with undetectable plasma RNA.
9. Evidence of COVID19 within the last 60 days or recent (21 days) exposure to close personal contact.
10. Current malignancy (excluding carcinoma in situ [any location] or localized non-melanoma skin cancer) receiving targeted therapy
11. Any comorbidity limiting survival or ability to complete the study.
12. Stage V kidney disease or on renal-replacement therapy.
13. Neutropenia (<1,500/mm^3 or <1,000/mm^3 in African-American patients).
14. Pregnancy.
15. Angina, hypertension, arrhythmias, electrocardiograph (ECG) changes, or other non-cardiac limitations (i.e., peak respiratory exchange ratio VCO2/VO2 [RER]<1.0, reflecting sub-maximal test) that limit maximum exertion during CPX obtained during the baseline testing.
16. Hypersensitivity to Kineret or to E. coli derived products.

6.4 Alternate Consent Group

The subjects who are eligible to enroll in the study but decline to participate will be asked to sign an alternate consent that allows the research team to access the electronic health record for 6 months after the enrollment and make one follow up telephone call at the end of the 6 months period if needed to ascertain vital status and incidence of new event. This alternate consent group will provide an estimate of the event rate in a group free of other research interventions.

7) STUDY DESIGN

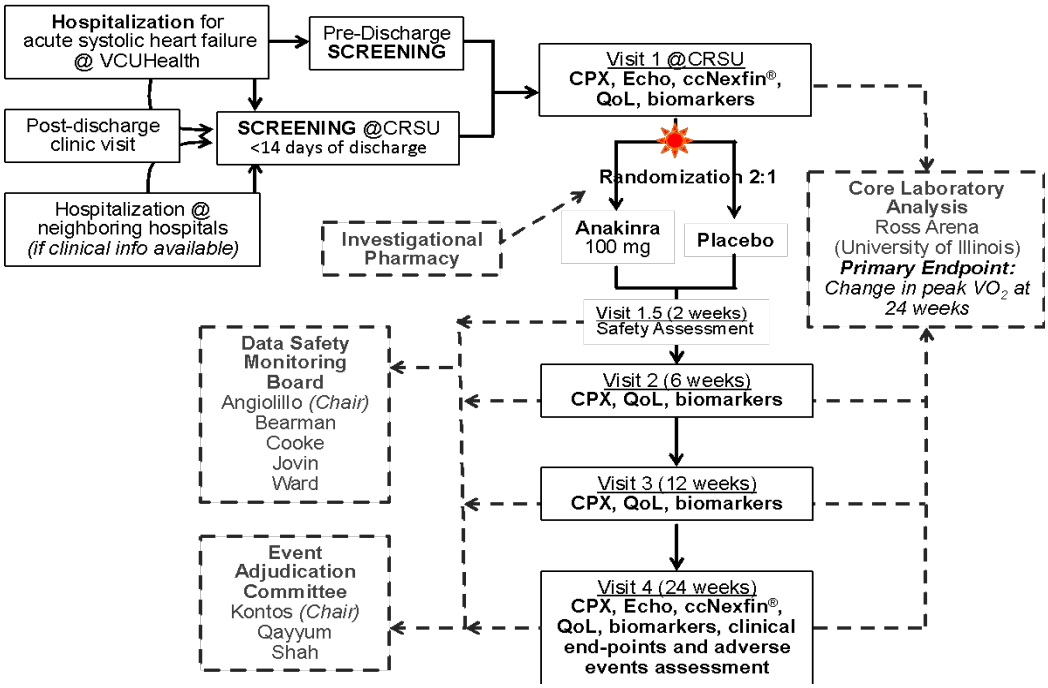
We designed a single center, placebo-controlled, double-blinded randomized study of Anakinra in patients with recently decompensated systolic heart failure. Patients will undergo baseline clinical assessment, CPX, echocardiogram, non-invasive hemodynamics, and blood tests for biomarkers. The CPX, the echocardiogram, non-invasive hemodynamics and blood tests will be repeated at each visit (6, 12 and 24 weeks). See Schematic of Study Design.

7.1 Clinical Assessment

A physician on the research team will conduct a thorough clinical assessment and review of the chart at time of enrollment to evaluate for all inclusion and exclusion criteria. Some of the information needed to determine eligibility may be missing, in which case additional testing would not be performed prior to consenting, and it would be completed only after the patient provided informed consent and it would be charged to the study charge account.

A clinical evaluation will also be completed at Visit 1.5 (14±3 days) to determine tolerability of the treatment and side effects, medication reconciliation and completion of a complete blood cell count with differential and basic metabolic panel.

Visits 2 (6±1 weeks), 3 (12±1 weeks) and 4 (24±2 weeks) will include a clinical safety evaluation as well as assessment of the endpoints. Additional visits may be scheduled as needed.



7.2 Randomization and Allocation Concealment

Randomization will be handled by the investigational pharmacy using a dedicated randomization algorithm. Access to randomization log will be restricted and allowed only on an emergency basis, or as requested by the Data Safety and Monitoring Board (DSMB), or at the end of the study after event adjudication and the database has been locked.

In case of an emergency, a physician treating any patient enrolled in the study may request un-blinding of that individual patient if the physician determines that un-blinding is necessary to make a treatment decision. The PI will contact the VCU Investigational Pharmacy to provide the treatment allocation to the PI, who will then relay the information to the treating physician. If requested by the DSMB, the PI will contact the VCU Investigational Pharmacy to provide the randomization log directly to the DSMB.

Upon completion of the study (including completion of all data collection and event adjudication), the PI will request the complete randomization log from the VCU Investigational Pharmacy. The investigators will also be kept blinded on all inflammatory biomarkers by limiting access to results if obtained during the study (i.e., CRP) and by analyzing all other markers (i.e., cytokines) in a single-batch at the end of the study.

7.3 Investigational treatment

Anakinra or placebo (vehicle) dispensed in small syringes (0.67 mL) will be provided to the patient for daily subcutaneous injection. The syringes for anakinra or placebo will be undistinguishable. This will be achieved by assuring that the syringes provided by the supplier (Swedish Orphan Biovitrum, Stockholm, Sweden) are labeled only by a number or other code. If the supplier is unable to provide placebo syringes that are indistinguishable, then the pharmacist will transfer the content of each syringe into an unlabeled syringe which will then be marked in a way that neither the patient nor the physician will be able to distinguish between anakinra or placebo.

After completion of all baseline testing, patients will be given a 14-day supply of anakinra or placebo. Additional syringes from the initial batch may be given to assure that the patient has a sufficient number to last until the 14-day follow up visit, which will be scheduled within 14±3 days after baseline visit. Patients will also receive instruction from the investigators regarding self-injection technique. The next set of syringes (for another 4±1 weeks of treatment) will be given to the patient at the time of 14-day follow-up visit. If needed, the first 2 sets of syringes (6±1 weeks) may be dispensed at the same time. A third set of syringes (for another 6±1 weeks of treatment) will be given at time of the 6 weeks visit. A final set of syringes (for another 12±2 weeks) will be given at the 12-week visit.

Adherence to the investigational treatment will be addressed by count of syringes and completion of all study visits. All concomitant medications will also be recorded at each clinic visit. Patients in the study will receive guidelines-based medical treatments as indicated. Such treatments may include diuretics, β-adrenergic receptor blockers, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, neprilysin inhibitors, aldosterone blockers, isosorbide dinitrate, hydralazine, digoxin, ivabradine, aspirin, and statins. For such medications, we will record the start date and the daily dose, and any change in dose or suspension.

Administration of anakinra with medications that affect the immune system (i.e., immunosuppressant) or increase the risk of infection (i.e., cancer chemotherapy) is NOT permitted. If a patient requires treatment with such treatments, he/she will not be eligible for inclusion in the study. If a patient already enrolled in the study requires such treatments, the investigational treatment (anakinra or placebo) will need to be discontinued (see reason for discontinuation).

7.4 Cardiopulmonary Test

Upon completion of screening/enrollment, all subjects will be scheduled for the CPX. A physician-supervised maximal exercise test will be administered using a metabolic cart (UltimaCardioO2, MGC Diagnostics, Saint Paul, MN) that is interfaced with a treadmill. A conservative ramping treadmill protocol will be used with workload increases of 0.3 metabolic equivalents every 30-seconds. Prior to each test, the oxygen and carbon dioxide sensors will be calibrated using gases of known oxygen, nitrogen, and carbon dioxide concentrations and the flow sensor will also be calibrated using a 3-liter syringe. Subjects will then be briefed regarding the protocol and will be requested to exercise to volitional fatigue. Twelve-lead ECG monitoring will be conducted at baseline, throughout the test and into recovery. Blood pressure will be measured every two minutes using an automated exercise-compatible device (Tango M2, SunTech Medical, Morrisville, NC). In this technique, expired gases are sampled using a mouthpiece-mounted sensor, and analyzed to continuously measure oxygen (O_2) uptake; the highest 10-second average value for O_2 uptake during the final 30 seconds defines peak oxygen consumption (VO_2 peak in $mL \cdot kg^{-1} \cdot min^{-1}$). The ventilatory equivalents method will be used to determine VO_2 at the ventilatory anaerobic threshold. Ten second averaged VE and VCO_2 data, from the initiation of exercise to peak, will be input into spreadsheet software (Microsoft Excel, Microsoft Corp., Bellevue, WA) to calculate the VE/VCO_2 slope via least squares linear regression ($y = mx + b$, m=slope). Peak Respiratory Exchange Ratio (VCO_2/VO_2) will be used for determining maximal to near maximal effort. A peak RER≥1.10 is well accepted as a criterion for maximal effort and a peak RER≥1.0 is considered a minimal acceptable threshold. Subjects with RER<1.0, reflecting deconditioning as a non-cardiac cause of interruption of exercise, will be excluded. American Heart Association guidelines for exercise testing contraindications and termination criteria will be followed.

Upon completion of exercise testing, the results of the CPX will be reviewed and discussed with the patients. Patients with angina, abnormal blood pressure or heart rate response, or ECG changes suggestive of coronary ischemia will be excluded from the study.

Subjects will return to the cardiopulmonary exercise suite for the additional visits upon completion of 6 weeks (Visit 3, 42±7 days) and 12 weeks (Visit 4, 84±7 days) and 24 weeks (Visit 5, 168±14 days) of treatment with Anakinra or placebo. At each visit, subjects will undergo a brief physical exam and repeat exercise testing. Raw data from the cardiopulmonary test will be electronically transferred, free of patient identifiers, to the Core Lab at the University of Illinois, Chicago, IL.

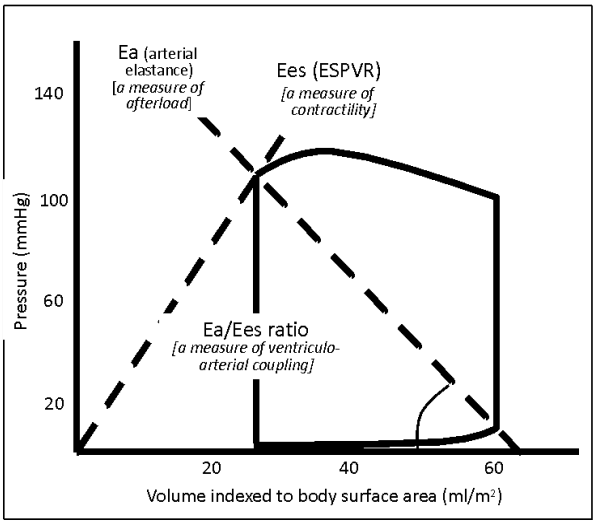
7.5 Doppler Echocardiogram

Prior to initiation of treatment, all subjects will undergo a transthoracic Doppler echocardiogram to measure left ventricular diastolic and systolic volumes, transmitral flow Doppler spectra, mitral and tricuspidal valve annulus tissue Doppler spectra, and tricuspidal annulus plane systolic excursion, and global longitudinal strain analysis, according to the recommendations of the American Society of Echocardiography. The echocardiogram will be repeated at visits 2-4. All images and loops will be acquired in an electronic format and measurements will be performed at the end of the study by 2 operators blinded to treatment allocations. The average of the two measurements will be used for measures differing ≤10%, whereas those with >10% were re-reviewed and discussed by the 2 operators resulting in a consensus.

7.6 Non-invasive hemodynamics and Bio-Impedance

The non-invasive hemodynamic assessment will be performed using an automated blood pressure cuff measurement in the arm (V100 Dinamap, GE, Boston, MA, United States) and concomitant measurements from the echocardiography. Patients will be asked to seat, with both feet flat on the floor, knees bent at 90-degree angles and hands resting on the homolateral knee for 5 minutes. Arterial elastance (E_a) is a measure of LV afterload, including both pulsatile and non-pulsatile components. E_a is defined as the negative slope of left ventricular end-systolic pressure/end-diastolic volume relationship and was calculated as left ventricular end-systolic pressure/stroke volume. LV end-systolic pressure is estimated as 0.9 x brachial artery systolic blood pressure measured with an arm cuff. End-systolic elastance (E_{es}) is a measure of load-independent LV contractility and is defined as the LV end-systolic pressure-volume relationship. E_{es} is calculated as LV end-systolic pressure / LV end-systolic volume. Ventriculo-arterial coupling is defined as the ratio of E_a to E_{es}.

Non-invasive Left ventricular pressure-volume loop analysis. The loops will be constructed with data obtained non-invasively from concomitant echocardiography volume assessment and using an automated blood pressure cuff measurement in the arm (V100 Dynamap, GE, Boston, MA, United States). End-systolic pressure (ESP) is estimated as 90% of systolic pressure measured non-invasively at brachial artery. The Doppler derived E/E' value is used as a surrogate for end-diastolic pressure (EDP). The negative slope of the line connecting EDP and ESP characterize arterial elastance (Ea), a measure of afterload. The positive slope of the line connecting the pressure 0 to ESP characterizes the end-systolic elastance (Ees), a measure of contractility. Systolic heart failure is characterized by abnormal Ea/Ees coupling with increased Ea and reduced Ees and increased Ea/Ees. Measurement of changes in Ees, Ea and Ea/Ees before and after treatment, will allow to detect load-independent changes in cardiac contractility and ventriculo-arterial coupling. The pressure-volume loops allow to measure the work performed with each heart beat, as the area under the curve: the area included in the loop is the stroke work, the amount of energy used for the actual systole, whereas the area below the end-diastolic volume-pressure relationship (diastolic) and the triangular area below the Ees left of the ESP reflects the amount of energy used by the heart but not resulted in a systole and thus not effective. Stroke work efficiency (SWE) measures the ratio of stroke work divided by the total work and reflects a measure of efficiency of the heart.



Bioelectrical Impedance Analysis or Bio-Impendance is a non-invasive, quick and safe technique that allows estimating body composition. Impedance is briefly defined as the property of the electrical ionic conduction of soft tissue where fat and bone are considered poor conductors, however the microampere range developed during the test does not represent any hazard for the patient. The patient will be asked to stay still on the bed, with superior limbs abducted at 30° and the inferior ones at 45°. Four cutaneous electrodes (two on the foot and two on the homolateral hand) are applied. Between two electrodes, at least 5 cm distance is required. A small electricity current is applied to the electrodes. We will measure how the electricity is conducted through the body using a Quantum IV Body Composition Analyzer RJL Systems) and then, using a dedicated software, we will determine the body composition (water, lean mass and fat). The estimated duration of the study is less than 10 min.

7.7 Questionnaires

Prior to each CPX, subjects will complete the Kansas City Cardiomyopathy Questionnaire (KCCQ), the Duke Activity Status Index (DASI) questionnaires, and the Patient Health Questionnaire-9 (PHQ-9). The KCCQ is a 20-question graded questionnaire that has been extensively validated to measure impairment in quality of life in patients with HF. The questions are designed to measure a wide range of physical, emotional, social, and mental domains that contribute to overall quality of life. (Link to KCCQ through FDA website and direct access to PDF; https://www.fda.gov/downloads/MedicalDevices/ScienceandResearch/MedicalDeviceDevelopmentToolsMDDT/UCM581761.pdf / http://columbiaheartvalve.org/sites/default/files/PDF-Kansas-City-Questionaire.pdf). The DASI is a twelve-item “yes/no” questionnaire that allows for the calculation of perceived functional capacity. Each question describes a different physical activity and asks the subjects if they feel they can perform the task. The questions are weighted according to their degree of physical exertion. The weighted values from the “yes” responses are summed to produce a score in metabolic equivalents (https://www.mdcalc.com/duke-activity-status-index-dasi). The IPAQ-short form (IPAQ-SF) is a 7-question questionnaire that allows the estimation of daily physical activity by asking the subjects about duration and intensity of their daily physical activity. Lastly, subjects will also be asked to complete the Patient Health Questionnaire-9 (PHQ-9) (https://www.phqscreeners.com/sites/g/files/g10049256/f/201412/PHQ-9_English.pdf), a nine question standardized test which has been validated in patients with heart failure. Patients who score question 9 on the PHQ-9 as one or higher or have a total score ≥ 20 will prompt the team to alert a study team physician for patient evaluation.

7.8 Biomarkers assessment

Blood samples will be taken from a peripheral vein at time of screening, baseline visit, 2, 6, 12 and 24 weeks, and used for analysis of complete cell count with differential, comprehensive metabolic profile [including inflammatory markers] and cardiac specific biomarkers [NT-proBNP]. Testing will be performed at VCUHealth, with the exception of research-only inflammatory markers, for which the samples will be processed and stored

for single batch analysis at the end of the study. Research-only biomarkers will not be used for clinical care and will not be shared with the patient nor with the referring providers.

7.9 Study Schedule

	Screening (≤14 days from discharge)	Visit 1 (Baseline)	Visit 1.5 (14±3 days)	Visit 2 (42±7 days)	Visit 3 (84±7 days)	Visit 4 (128±14 days)
Visit location	**Hospital or CRSU**	**CRSU**	**CRSU*** **	**CRSU**	**CRSU**	**CRSU**
Screening *	**X**					
Consent	**X**					
Clinical assessment **	**X**	**X**	**X**	**X**	**X**	**X**
Medication reconciliation	**X**	**X**		**X**	**X**	**X**
Investigational therapy dispensing		**X**		**X**	**X**	
CPX		**X**		**X**	**X**	**X**
Echocardiogram		**X**		**X**	**X**	**X**
Non-invasive hemodynamics/ Bio-Impedance		**X**		**X**	**X**	**X**
Safety labs (CBC, renal function)		**X**	**X**	**X**	**X**	**X**
Biomarkers (hsCRP, NTproBNP)		**X**		**X**	**X**	**X**

*Includes hsCRP - Pregnancy test will be performed, if indicated
**Clinical assessment includes history and physical, medication reconciliation, and assessment of adverse events
***Visit 1.5 may happen in the CRSU or in other clinics with the patient's own provider.

7.10 Cost coverage analysis

A cost coverage analysis has been conducted by the team: all tests listed in the Schedule of Events will be considered 'research' and paid for with the study funds. Any additional tests (not listed above) that is necessary for patient care will be considered standard of care and will be billed to the patient or the insurer.

8) ASSESSMENT OF SAFETY

8.1 Specification of Safety Parameters

Safety parameters will include data deriving from history and physical examination performed at each visit, laboratory data and results of functional and imaging tests. To enhance detection of adverse events between visits, all patients will be encouraged to

contact the research team at any time with concerns or any perceived changes in their healthcare status.

Disease-related data (HF-related) will be assessed including changes in symptoms (or new symptoms), functional capacity, vital signs (including weight), renal function, or any significant changes in medications.

Data specific to the treatment will also be assessed. The patient will be asked about symptoms and examined for signs of infection. Considering that Anakinra may mask signs of infection such as fever, a low threshold for further investigation will be advocated. A complete cell count will be measured at each visit to exclude the unusual cases of Anakinra-related neutropenia (ANC<1000), for which suspension of active treatment will be considered until return to a value of ANC>1,800/mm^3 (or >1,000/mm^3 if patient is African-American). Cessation of Anakinra will not be mandatory. Changes to treatment for side-effects or unanticipated problems will be performed without breaking the randomization code, unless deemed necessary for the treatment of the individual patient by the physician, in which case the physician will be made aware while the remainder of the team, especially the investigators performing and interpreting the tests, will be maintained blinded. The risks of the tests performed have been described above. In order to reduce risk, the procedures will be performed by skilled practitioners in the standard clinical fashion. Abnormal or incidental findings will be handled on a case by case basis as clinically indicated.

8.2 Data collection

The principal investigator at the site will be provided with a data collection sheets or case report forms on which data about the individual subject will be collected. The subjects will be identified as a consecutive number (i.e., 01, 02, …08). The data collected on these forms will not contain any personal identifiable information. A database of de-identified data will be created.

8.3 Methods of Timing for Assessing, Recording, and Analyzing Safety Parameters

8.3.1 Adverse Events

All Adverse Effects (AEs) will be recorded on an AE form regardless of causality.

An AE is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product considered to be causally related to the study treatment or research conduct. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of medicinal (investigational) product. The occurrence of an AE may come to the attention of study personnel during study visits and interviews of a study recipient for medical care, or upon review by an investigator or study coordinator. An event that is considered by the investigator(s) to be expected and related

to the natural history of the disease is NOT considered an AE.

All events considered AEs including local and systemic reactions not meeting the criteria for “serious AE” should be captured on the appropriate AE form. Information to be collected includes event description, time of onset, clinician’s assessment of severity, relationship to study intervention (assessed only by those with the training and authority to make a diagnosis, which would include a physician) and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the patient is screened should be considered as baseline and not reported as an AE. However, if it deteriorates at any time during the study, it should be recorded as an AE.

Most common AEs expected with Anakinra are:

Anakinra, recombinant human IL-1 receptor antagonist, has been FDA-approved for the treatment of inflammatory disorders such as rheumatoid arthritis for many years. It has been used in more than 150,000 patients with rheumatoid arthritis with a favorable risk profile.

Anakinra is given as a subcutaneous injection of 100 mg (0.67 mL) daily or every other day in patients with severe impairment in renal function. There is no loading dose and no dose-adjustments needed with age, weight, or liver failure. Drug-to-drug interactions have not been reported. There are no known toxic effects of anakinra in pregnancy (category B), however pregnant women will be excluded from this research study.

In a study following patients with rheumatoid arthritis for up to 3 years, anakinra was generally well-tolerated with few side effects.

The most likely side effects associated with the use of anakinra include:
- Injection site reaction (>10%, up to 50%, but infrequently leading to interruption of treatment <5%)
- Serious Infection (1.8% in anakinra vs 0.6% in placebo in clinical trial of rheumatoid arthritis);
- Headache, generally mild and self-limiting (1-10%);
- Diarrhea, generally mild and self-limiting (1-10%);
- Nausea, generally mild and self-limiting (1-10%)
- Neutropenia (rare, <1%, reversible).
- Hypersensitivity reaction (rash, anaphylaxis, arthritis)(rare, 1-2%).

The injection site reactions are by far the most common adverse reaction. The reactions present as painful irritation/redness at the site of injection usually occurring 1-2 weeks after start of treatment. They are responsive to topical steroids and/or antihistamine therapy. The reactions are common (up to 50%) but are rarely cause of discontinuation of therapy (<5%).

Despite the increase in risk of serious infection with anakinra, such events are rather rare (<2% during chronic treatment). Anakinra is indeed not associated with an increase in infection-related mortality, nor associated with opportunistic infection. Anakinra may, however, mask some of the signs of infection such as fever and leukocytosis, and therefore education on the need to be aware of risk of infection is warranted. Nevertheless when given to patients with sepsis in the setting of a clinical trial anakinra had no negative effect on survival. While anakinra is postulated to prevent inflammatory-based hypercoagulability, anakinra has not been associated with any appreciable bleeding risk in pre-clinical, clinical, or post-marketing surveillance (including animal studies at >100X the clinically relevant dose).

There is a social/psychological risk in this study of breaching confidentiality and having a patient's diagnosis discovered. The likelihood of this occurring, however, is very low, and not different from the patient receiving clinical care at the same time. The number of study visits could impact some aspects of the patients' social lives. Loss of confidentiality is a potential risk. However, except when required by law patients will not be identified by name, social security number, address, telephone number or any other personal identifier. Study related tests may be reported to the NHLBI but patients will not be identified.

The following risks pertain to the different tests that are being used for monitoring the treatment responses:

• ECG: no greater than minimal risk.
• Blood draw: minor bleeding (rare) and infection (extremely rare) at puncture site
• Cardio pulmonary exercise test (CPX): very low risk of rhythm disturbance of the heart and syncope. With adequate medical supervision extremely low risk of serious complication. A physician will be present during the CPX.
• Bioimpedance analysis: no greater than minimal risk
• Echocardiogram: no greater than minimal risk.
• Questionnaires: the PHQ-9 is a depression screening tool that includes questions that may be upsetting to some patients

All AEs must be graded for severity and relationship to study product.
Severity of Event: All AEs will be assessed by the study investigator using the following guidelines:

- Mild: events that require minimal or no treatment and do not interfere with the patient's daily activities.
- Moderate: events that result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning and may require systemic drug therapy or other treatment.
- Severe: events interrupt a patient's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually incapacitating.
- Life threatening: any adverse drug experience that places the patient or subject, in the view of the investigator, at immediate risk of death from the reaction as it occurred

(i.e. does not include a reaction that might have caused death had it occurred in a more severe form).

A dedicated AE form will be used to capture of pertinent information about the event. Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of intensity to be performed. Adverse events characterized as intermittent require documentation of onset and duration of each episode.

Relationship to the intervention: All suspected AEs must have their relationship to study intervention assessed using the terms: associated or not associated. In a clinical trial, the study intervention must always be a suspect. To help assess, the following guidelines are used to assess causality:

- Definitely related: The event is temporally related to the administration of the study intervention and, in the opinion of the investigator, no other etiology explains the event.
- Probably related: The event is temporally related to the administration of the study intervention and represents, in the opinion of the investigator, the most plausible explanation of the event.
- Possibly related: The event is temporally related to the administration of the study intervention but, in the opinion of the investigator, it does not represent the most likely explanation of the event.
- Definitely Unrelated: The event is temporally independent of study intervention and/or the event appears, in the opinion of the investigator, to be explained by another etiology.

8.3.2 Serious Adverse Events

A serious adverse event (SAE) is any adverse event/experience occurring between baseline assessments and the patients final study visit that results in any of the following outcomes and is considered by the investigator(s) to be unexpected or not consistent with the natural history of the disease:

- Death
- Life threatening (subject at immediate risk of death)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in a persistent or significant disability or incapacity
- Important medical events that may not result in death, be life threatening, or require hospitalization may be considered SAEs when, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

All the unexpected SAE will be promptly (within 24 hours) reported to the local IRB and DSMB (see reporting procedures). The DSMB report to the investigators will be forwarded to the NHLBI Program Officer, including the discussion of the concerns, and the basis for any recommendations that the DSMB has made in response to the concerns (within 7 calendar days if fatal or life-threatening unexpected, suspected serious adverse reactions; or within 14 days for unanticipated problem that is not an SAE or within 15

calendar days for all non-fatal, non-life threatening unexpected, suspected serious adverse reactions, or within 30 days of receipt of the DSMB or IRB report for all other unanticipated problems or scheduled meetings).

8.4 Reporting Procedures

8.4.1 Serious Adverse Events

All unexpected AEs that result in death or are otherwise reportable SAEs or AEs will be reported promptly to the Data Safety Monitoring Board (DSMB) and the IRB within 1 business day of investigators becoming aware of the event. AEs (serious or non-serious) that transpire secondary to an overdose must also be reported to the DSMB within 1 business day of knowledge of the event, using an AE form. The SAE form will always be completed as thoroughly as possible with all available details of the event, signed by the investigator (or designee), and, if a reportable adverse event as defined herein, forwarded to the DSMB within the designated time frames. If the investigator does not have all information regarding an SAE, he/she will not wait to receive additional information before notifying the DSMB of the event and completing the SAE form. The form will be updated when additional information is received. The investigator will always provide an assessment of causality at the time of the initial report.

8.5 AE/SAE Data Collection

When an AE/SAE is suspected, it is the responsibility of the investigator(s) to review all documentation (e.g., hospital progress notes, laboratory and diagnostic reports) relative to the event. The investigator will then record all relevant information regarding a suspected AE/SAE on the AE form. The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis should be documented as the AE/SAE and not the individual signs/symptoms.

8.6 The Data and Safety Monitoring Board (DSMB)

For this study, the DSMB is composed of a coordinator, 5 voting members (see DSMB Chapter in the Appendix), chaired by a cardiologist from University of Florida in Jacksonville, Florida, who has extensive clinical trial experience, and including an infectious disease specialist. an immunologist, a heart failure specialist, and a biostatistician. The composition of the DSMB will have been reviewed and approved by the VCU IRB. The DSMB will meet every 6 months or sooner in case of unanticipated serious adverse events. The DSMB coordinator will provide the board members with data regarding screening, enrollment, adverse events and withdrawals, and he/she will not participate in the voting. The board members may request unblinding at any time. Upon request of the DSMB (following positive vote by 3 or more members), the coordinator will retrieve the randomization code for one or more individual patients (as needed). If necessary the DSMB will inform the investigators of the unblinding of the randomization code, if not necessary the investigators (and the patients) will be kept blinded. The DSMB

may request an expert opinion by one or more non-members, however only the DSMB members will vote on any individual issue. The DSMB (following positive vote by 3 or more members) may request temporary or permanent halting of the study (see halting rules), or interruption of treatment of one or more patients. The minutes from each meeting will be distributed to the board members, NHLBI Program Officer, and to the IRB, and not to the investigators unless specifically requested by the DSMB. A brief conclusive statement addressing whether the study should continue as planned or not will be provided to the investigators and the IRB every 6 months. The investigators will provide the NHLBI staff with reports from the DSMB and the IRB in a timely fashion (within 7 calendar days if fatal or life-threatening unexpected, suspected serious adverse reactions; or within 15 calendar days for all non-fatal, non-life threatening unexpected, suspected serious adverse reactions, or within 30 days of receipt of the DSMB or IRB report for all other unanticipated problems or scheduled meetings). See Appendix – DSMB Chapter.

8.7 Regulatory Reporting

This study is conducted in accordance to the NIH Good Clinical Practice guidelines. An Investigational New Drug use waiver from the Division of Cardiovascular & Renal Products, Center for Drug Evaluation & Research, Food & Drug Administration was given to Dr. Abbate. The study protocol, consent, and Data and Safety Monitoring Plan will have been approved by the VCU IRB prior to study initiation. The investigators will provide the NHLBI staff with reports from the DSMB and the IRB in a timely fashion (within 7 calendar days if fatal or life-threatening unexpected, suspected serious adverse reactions; or within 15 calendar days for all non-fatal, non-life threatening unexpected, suspected serious adverse reactions, or within 30 days of receipt of the DSMB or IRB report for all other unanticipated problems).

8.8 Type and Duration of Follow-up of Subjects after Adverse Events

All AEs and SAEs will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, whichever occurs first. All AEs and SAEs documented at a previous visit/contact and designated as ongoing, will be reviewed at subsequent visits/contacts, where the designation may remain ongoing. The investigator will ensure that the follow-up includes any supplemental investigations as may be indicated to elucidate the nature and/or causality of the SAE. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals. SAEs that are ongoing at the time of the subjects' final study visit/contact will be documented as ongoing.

8.9 Halting Rules

The DSMB will monitor the progress of the present trial. No interim efficacy analyses are planned; however, an interim analysis could be performed at any time to assess efficacy and futility, if requested by the 3 or more members of the DSMB. The DSMB will meet regularly to review safety data every 6 months (or sooner in case of unanticipated serious

adverse events). All meetings and actions taken by the committee will be recorded along with the reasons for the actions. These documents will include any data summaries or analyses provided to the DSMB and will remain confidential until the study is concluded. The DSMB may choose to stop enrollment on the basis of safety data observed. If safety concerns are found, further enrollment will not be allowed until issues are resolved. If no safety concerns are found, enrollment will continue until the target sample size is reached.

9) ADJUDICATION OF CLINICAL EVENTS

9.1 Event-adjudication committee

The event-adjudicating committee will be composed of professionals from different backgrounds including general cardiologists, cardiologists with training in heart failure, general internal medicine specialists, emergency medicine specialists, and infectious disease specialists. Each event will be reviewed by at least 3 members. Agreement will be necessary for all 3 members, disagreement will be resolved with discussion of the case, followed by voting of at least 5 members if disagreement remains. The committee will meet at the end of the study and review all adjudicated events. The committee will be blinded to treatment allocation. In order to favor allocation concealment, the committee will also be blinded to C-reactive protein levels, which may be affected by treatment.

9.2 Definition of the events

The events adjudicated will include:
- Death;
- Cardiac death (in which a direct cause attributable to cardiac disease is present);
- Sudden cardiac death (in which cardiac death occurred out of the hospital and suddenly; or in the hospital due to ventricular arrhythmias unrelated to other concomitant cardiac conditions);
- Non-cardiac death (in which the event of death is considered not to be a direct consequence of cardiac disease);
- Hospitalization for any cause;
- Hospitalization for heart failure (in which the primary diagnosis for hospitalization is decompensated heart failure established as the finding at admission of all 2 conditions listed: *a.* dyspnea or respiratory distress or tachypnea at rest or with minimal exertion; *b.* evidence of elevated cardiac filling pressure or pulmonary congestion (at least one of the conditions must be met: pulmonary congestion/edema at physical exam OR chest X-ray; plasma BNP levels ≥200 pg/ml; or invasive measurement of left ventricular end-diastolic pressure >18 mmHg or of pulmonary artery occluding pressure (wedge) >16 mmHg);
- Outpatient worsening of heart failure (defined as the need for intravenous diuretic treatment or need for increase in oral diuretic dose, or new prescription for first or add-on diuretic);
- Acute myocardial infarction, as defined by the WHO consensus statement 4th edition;
- Unstable angina, or need for coronary revascularization;

- Cardiac tachy-or brady-arrhythmias leading to a new hospitalization or to prolongation of hospital stay;
- Acute renal failure (defined as in increase in plasma creatinine levels of 50% or 0.5 mg/L);
- Acute respiratory failure (not due to heart failure);
- Sepsis or other serious infection requiring antibiotic therapy;
- Acute stroke.

The analysis will consider time to first event and time to each event. It will also consider event rates at 1, 3 and 6 months, in order to favor comparisons with other studies. The number of days free of hospitalization during the first 1, 3 and 6 months will also be measured and compared between groups.

9.3 Implications of the findings of the event-adjudicating committee

The events will be adjudicated only after the completion of the study, and therefore the findings by the committee will have no implications on the conduct of the study.

10) DISCONTINUATION OF TREATMENT AND WITHDRAWAL

10.1 Reasons for Discontinuation of Treatment or Withdrawal from the Study

Patients may withdraw from the study at any time. The investigators may temporarily suspend treatment at any time in patients experiencing an adverse event considered possibly, probably, or definitely to related to the study drug. The study drug may then be restarted upon resolution of the adverse event unless the adverse event is considered likely to reoccur or the patient is unwilling to restart treatment. The investigators can withdraw any patient at any time from the study if medically necessary. It will be extremely important to obtain complete follow-up data on each patient, except on those who withdraw consent to release such information. It will be documented whether or not each patient completed the study. If for any reason the study treatment or observations were discontinued, the reasons will be recorded and the IRB will be informed.

Reasons for discontinuation of Anakinra (or placebo):
1) Systemic infection (sepsis)*;
2) Surgery*;
3) New diagnosis of cancer that requires local or systemic treatment;
4) Hypersensitivity reaction (rash, anaphylaxis, arthritis);
5) Severe injection site reactions*;
6) Need for immunosuppressant therapy;
7) Acute myocardial infarction or stroke*;
8) Severe neutropenia (<1,000/mm3) if there is a perception of increased infectious risk by the provider*.

* treatment may be restarted by investigators after the condition is resolved

10.2 Handling of Withdrawals

Patients who permanently stop study injection (whether due to adverse event, investigator decision, or patient decision) will be considered withdrawn from treatment. Patients that have withdrawn from treatment will still be offered to complete all the functional assessments to analyze data in an intention-to-treat strategy. Patients who have withdrawn from treatment will also be followed for the complete duration of 6 months follow-up to monitor for safety. Loss to follow-up can occur due to patients' withdrawal or unreported death. If patients are lost to follow up and their clinical condition cannot be established (alive vs dead, hospitalized vs not), they will be excluded from the initial analysis, and then reintroduced for sensitivity analysis considering all potential outcomes.

Patients will be considered withdrawn from study if they express a desire to stop active participation. However, the investigators will continue to record adverse events, hospitalizations, and survival in these patients from the electronic medical record in an observational manner unless these patients withdraw consent. Upon withdrawal of consent, no further information will be collected from those patients.

10.3 Termination of Study

The decision regarding continuation or termination of the study will be solely based on safety data, and will be made by the DSMB. Interim analyses will be performed by the DSMB upon request by the co-PIs. The co-PIs will meet every month (or sooner in case of unanticipated SAE) to discuss enrollment, withdrawals, and adverse events. If protocol modifications are warranted, close consultation with the DSMB and IRB will be required, and their approval will be needed.

11) STATISTICAL CONSIDERATIONS

11.1 Study Hypothesis

We hypothesize that IL-1 blockade with Anakinra will improve aerobic exercise performance and reduce hospital admission rates in patients with recently decompensated systolic HF. As the first step in testing this hypothesis, we propose a randomized, double-blinded, pilot study to determine the effect of anakinra on aerobic exercise performance over the course of 6 months. Although this pilot study will not be powered to detect differences in the 6-month hospital admission rates, we believe this study will provide an estimate of the potential effect. An improvement in aerobic exercise performance alone would represent a valuable achievement in this HF population, and would provide the rationale—especially if paired with a signal showing reduced readmission rates—for a subsequent Phase III clinical study to evaluate IL-1 blockade on the key outcomes of HF morbidity and mortality.

11.2 Sample Size Considerations

The sample size for this pilot study is calculated according to the primary endpoint of

difference in interval change in peak VO_2 at 24 weeks between anakinra and placebo. Given an expected average peak VO_2 of 15 mL/kg/min for HF patients, 68 subjects randomized to anakinra and 34 subjects randomized to placebo (2:1 randomization) would provide approximately >95% power to detect a difference of 1.6 $mL \cdot kg^{-1} \cdot min^{-1}$ (standard deviation of 1.7-2.0 $mL \cdot kg^{-1} \cdot min^{-1}$) in peak VO_2 on top of placebo. A conservative estimate of 20% loss to follow-up or withdrawal would retain >90% power.

		Effect size of treatment on top of placebo				
	$mL \bullet kg^{-1} \bullet min^{-1}$	+1.2	+1.4	+1.6	+2.4	**+3.2**
Standard Deviation	2.3	0.70	0.83	0.91	>0.99	>0.99
	2.0	0.82	0.92	**0.97†**	>0.99	>0.99
	1.7	0.92	0.98	**0.99**	>0.99	>0.99
	1.4	0.98	0.99	>0.99	>0.99	**>0.99***

11.3 Statistical Analysis

11.3.1 Demographics and Baseline Characteristics

Descriptive summaries of continuous measurements will be reported as median and interquartile ranges due to potential deviation from Gaussian distribution. Descriptive summaries of categorical measurements consist of frequencies, proportions and 95% confidence intervals, when applicable. All analyses will be conducted after database locking once all data has been gathered and electronically captured. All analyses will be based on the intention-to-treat principle (i.e., analyzing groups as randomized and including all patients with outcome data available). The difference in interval changes in peak VO_2 at 24 weeks between the anakinra vs. placebo groups will be compared using random-effect analysis of variance for repeated measures to analyze the effects of treatment within each group and the effect of time_x_group allocation. Unadjusted p-values will be reported throughout, with statistical significance for the primary endpoint set at the 2-tailed 0.050 level. To evaluate the group differences in the secondary endpoints, data will be compared across all groups using the random-effect analysis of variance for repeated measures as indicated above for paired analyses, or Kaplan-Meier curves with Log-rank testing for event rates.

11.3.2 Handling of Missing Data

Cases with missing data for all follow-up CPX at 6, 12 and 24 weeks will be omitted from the efficacy analysis due to inability to calculate the primary endpoint (change in peak VO_2). Considering that the main variable of interest (peak VO_2) is expected not to improve over time with placebo in patients with systolic HF and exclusion of patient with missing

data would inevitably lead to a survivorship bias, we will use the last observation carried forward (LOCF) method to impute the missing data at 12 and 24 weeks for the primary analysis. We will also perform the Little's Missing Completely At Random (MCAR) test to determine whether the appropriateness of imputing missing values and perform a Multivariate Imputation by Chained Equation (MICE) to validate the finding of peak VO_2 using a different method for data inference.

11.3.3 Analysis of the Primary Endpoint

The data will be collected and electronically transferred to the core laboratory at the University of Illinois, Chicago, IL, where Dr. Ross Arena, PhD, will analyze data at the end of the study. After locking the database, he will be provided a group allocation according to treatment A or B (blinded to real treatment). The data will be analyzed according to blinded group allocation and the description of the group allocation will be disclosed only after completion of the analysis. The differences in interval changes between the treatments will be compared using random-effect analysis of variance for repeated measures to analyze the effects of time and group allocation. Unadjusted p values will be reported throughout, with statistical significance set at the 2-tailed 0.05 level. All analyses will be based on a 'complete case' approach.

DSMB CHARTER
Charter, Data and Safety Monitoring Board for
NHLBI 1R34HL118348-01A1
Interleukin-1 blockade in heart failure with preserved ejection fraction:
REcently **D**ecompensate **H**eart failure **A**nakinra **R**esponse **T**rial -2
(REDHART2)
Updated on October 25, 2018
DSMB Liaison: Amy Ladd, PhD – amy.ladd@vcuhealth.org

1 Introduction

This Charter is for the Data and Safety Monitoring Board (DSMB) for the study: **Interleukin-1 blockade in recently decompensated heart failure: the REcently Decompensated Heart failure Anakinra Response Trial-2 (REDHART2),** hereafter referred to as "REDHART2".

The Charter is intended to be a living document. The DSMB may wish to review it at regular intervals to determine whether any changes in procedure are needed.

2 Responsibilities of the DSMB

The DSMB is responsible for safeguarding the interests of study participants, assessing the safety and efficacy of study procedures, and for monitoring the overall conduct of **REDHART2.**

The DSMB is an independent group advisory to the investigators, and is required to provide recommendations about starting, continuing, and stopping the study **REDHART2**. In addition, the DSMB is asked to make recommendations, as appropriate, to the investigators about:

- Participant safety
- Benefit/risk ratio of procedures and participant burden
- Selection, recruitment, and retention of participants
- Adherence to protocol requirements
- Completeness, quality, and analysis of measurements
- Amendments to the study protocol and consent forms
- Notification of and referral for abnormal findings
- Efficacy of the intervention at study termination (no interim analyses planned)

3 Organization and Interactions

Communication with DSMB members will be primarily through the DSMB executive liaison, Amy Ladd, PhD, NIH Officer and the investigators at Virginia Commonwealth University (VCU). It is expected that study REDHART2 investigators will not communicate with DSMB members about the study directly, except when making

presentations or responding to questions at DSMB meetings or during conference calls.

a. DSMB Members and NHLBI Program Staff
DSMB members and their expertise are listed in Appendix A. Consistent with NHLBI policy, the DSMB is assigned an Executive Secretary (ES) to provide an unbiased staff interface for the DSMB, especially during executive sessions. The ES is responsible for assuring the accuracy and timely transmission of the final recommendations and DSMB minutes.

b. Scheduling, Timing, and Organization of Meetings
DSMB meetings will be held at the Virginia Commonwealth University, Richmond, VA, unless otherwise specified. For DSMB members residing outside of Virginia, telephone participation will be allowed for all meetings. The purpose of the first meeting is to review and discuss this Charter, to provide an overview of study REDHART2 activities, to review and make recommendations about the protocol(s), and to determine the frequency of interim analyses and whether data will or will not be masked to identity of randomized groups. Enrollment in a study cannot begin until the DSMB's recommendation for approval of the protocol has been made and IRB approval for the protocol including the DSMP has been obtained.

Meetings are held every 6 months, with additional meetings or conference calls scheduled as needed. Once the DSMB has established its working routine, consideration can be given to replacing one or both meeting per year with a conference call, if the agenda permits. Meetings and conference calls will be scheduled, and the agenda will be developed by the ES in close consultation with the Chair and the NHLBI Program Officer.

- For this DSMB, meetings will be held twice per year.
- The DSMB will monitor the progress of the present trial.
- No interim efficacy analyses are planned; however, an interim analysis could be performed at any time to assess efficacy and futility, if requested by the 3 or more members of the DSMB.
- The DSMB may choose to stop enrollment on the basis of safety data observed. If safety concerns are found, further enrollment will not be allowed until issues are resolved. If no safety concerns are found, enrollment will continue until the target sample size is reached.

The agenda for DSMB meetings and calls will be drafted by the ES in consultation with the Chair, investigators and the NHLBI Program Officer. The ES will finalize the agenda after consultation with the DSMB Chair. The agenda and meeting materials should be distributed by the ES 4 weeks before each meeting or call to the DSMB members, investigators, and the NHLBI Program Officer. The ES will collect and document all potential conflicts of interest from each member of the DSMB related to the design, conduct, interpretation, and publication of the study. Before each meeting, when the agenda is sent out, the ES will ask all DSMB members to state whether they have developed any new conflicts of interest since last meeting. This review will

be conducted in addition to the review for conflicts of interest conducted by the VCU IRB at the time of initial IRB approval. If a new conflict is reported, the Chair and staff will determine if the conflict limits the ability of the DSMB member to participate in the discussion. The DSMB also will review adverse event data, other safety data, quality and completeness of study data, and enrollment data at each meeting to ensure proper trial conduct.

It is expected that all DSMB members will attend every meeting and call. However, it is recognized that this may not always be possible. Quorum for voting is considered to be half the number of standing members plus one. The Board may wish to decide if particular expertise is needed within the quorum for the meeting to be valid. All standing Monitoring Board members are voting members. The Board may also wish to decide in advance whether *ad hoc* members can vote.

A quorum of this DSMB is considered to be 3 members out of total 5. Alternate members will be added to fill in cases in which the quorum of 3 cannot be achieved. All alternate members will receive equal vetting from the local IRB and from the Sponsor, NHLBI.

c. Discussion of Confidential Material

DSMB meetings and calls will be organized into open, closed, and executive sessions.

● During the **open sessions**, information will be presented to the DSMB by the Study Investigators and the NHLBI Program Staff as appropriate, with time for discussion.

● During the **closed sessions**, the DSMB will discuss confidential data from the study REDHART2, including information on efficacy and safety by treatment arm, if available. The DSMB will decide whether to remain masked to the treatment assignments at each meeting. If the closed session occurs on a conference call, steps will be taken to ensure that only the appropriate participants are on the call, and to invite others to re-join the call only at the conclusion of the closed session. NHLBI Program Officer would join the session only at the discretion of the Chair.

The DSMB may elect to hold an **executive session** in which only the DSMB members, NHLBI Program Officer (at the discretion of the Chair) and the ES are present in order to discuss study issues independently. Voting on recommendations will follow Roberts' Rules of Order (**Robert's Rules of Order Newly Revised (10th Edition) RONR** by Henry M. Robert III, William J. Evans (Editor), Daniel H. Honemann (Editor), Thomas J. Balch (Editor), Sarah Corbin Robert, Henry M. Robert III, General Henry M. Robert)

If the executive session occurs on a conference call, steps will be taken to ensure that only the appropriate participants are on the call, and to invite others to re-join the call only at the conclusion of the executive session.

At the conclusion of the closed and executive sessions, the participants will be re-

convened so that the DSMB Chair can provide a summary of the DSMB's recommendations. This provides an opportunity for study investigators and NHLBI Program Officer to ask questions to clarify the recommendations, if necessary. The meeting is then adjourned.

d. Reports of DSMB Deliberations

● Formal minutes: The ES is responsible for the accuracy and transmission of the formal DSMB minutes, within 14 days of each meeting or call. These minutes prepared to summarize the key points of the discussion and debate, requests for additional information, response of the investigators to previous recommendations, and the recommendations from the current meeting. Prior to submission to the investigators and the NHLBI Program Officer, minutes will be reviewed by the DSMB Chair for final review and approval. The DSMB Chair may sign the minutes or indicate approval electronically via email. Then, the minutes are sent to the investigators and the NHLBI Program Officer.

● Reports to IRBs: The investigators will prepare a memo documenting DSMB's deliberations and recommendations and send the memo to VCU IRB and NHLBI Program Officer.

● The DSMB report to the investigators will be forwarded to the NHLBI Program Officer, including the discussion of the concerns, and the basis for any recommendations that the DSMB has made in response to the concerns (within 7 calendar days if fatal or life-threatening unexpected, suspected serious adverse reactions; or within 14 days for unanticipated problem that is not an SAE or within 15 calendar days for all non-fatal, non-life threatening unexpected, suspected serious adverse reactions, or within 30 days of receipt of the DSMB or IRB report for all other unanticipated problems or scheduled meetings).

e. Reports to the DSMB

For each meeting, the investigators will prepare summary reports and tables to facilitate the oversight role of the DSMB. The DSMB should discuss at the first or subsequent meetings what data they wish to review and how it should be presented. The regular reports to the DSMB will contain blinded data for all enrolled subjects. If necessary, the DSMB may request un-blinding of the data, in which case, the DSMB will request that the randomization log be sent to the study biostatistician (Juan Lu, PhD), who will then prepare an un-blinded report for the DSMB.

f. Statistical Monitoring Guidelines

A biostatistician will serve as a voting member of the DSMB. At the first meeting, review of the protocol will include review of the statistical analysis plan. The DSMB should discuss the adequacy of that plan. The final plan, whether part of a research protocol or separate document, will be maintained as an appendix to this charter. The DSMB should discuss the statistical monitoring procedures they propose to follow to guide their recommendations about termination or continuation of the trial (if applicable). These procedures could include guidelines for early termination for benefit, termination for futility, and termination for safety reasons (if applicable).

Appendix A:

DSMB voting members

Dominick Angiolillo, MD, PhD DSMB Chair
Dr. Angiolillo is a Professor of Medicine in Cardiology at the University of Florida in Jacksonsville. He is board certified in Cardiology and Interventional Cardiology, and serves as Medical Director for the Cardiovascular Research Program in the division of Cardiology.
http://www.hscj.ufl.edu/directory/bio.aspx?id=1318

Gonzalo Bearman, MD DSMB Member
Dr. Bearman is a Professor of Medicine and serves as Chief of the Division of Infectious Disease as well as Hospital Epidemiologist. Dr. Bearman is Board Certified in Internal Medicine, Infectious Diseases, and General Preventive Medicine and Public Health. https://intmed.vcu.edu/divisions/infectious/chair.html

Ramesh Kundur, MD DSMB Member
Dr. Kundur is a practicing cardiologist with Virginia Cardiovascular Specialist. He is board-certified in Internal Medicine, Cardiovascular Medicine, and Heart Failure and Transplantation. www.vacardio.com/vcs-physicians/dr-ramesh-n-kundur/

Brant Ward, MD DSMB member
Dr. Ward is an Assistant Professor in the Division of Allergy, Immunology and Rheumatology. He has extensive experience in chronic autoimmune and autoinflammatory diseases as well as with immunodeficiency states. Dr. Ward is board certified in Internal Medicine and in Allergy/ Immunology. https://www.vcuhealth.org/find-a-provider/find-a-provider/brant-ward

Robert Perera, PhD DSMB Biostatistician (voting member)
Dr. Perera is an Assistant Professor of Biostatistics, and a Biostatistician on staff for the *Wright* Center for Clinical and Translational Research at VCU. www.biostatistics.vcu.edu/robert-perera

DMSB Liaison

Amy Ladd, PhD DMSB Liaison
Dr. Ladd, PhD, is the Associate Director of the Pauley Heart Center.

NHLBI Liaison

Emily Tinsley, PhD NHLBI Program Officer

Alternate Members

Ion Jovin, MD, PhD Alternate DSMB member

Dr. Jovin is an Associate Professor of Medicine in Cardiology, and serves as Director of the Cardiac Catheterization Laboratories at the Hunter McGuire Veterans Administration Medical Center in Richmond, VA. Dr. Jovin is board certified in Cardiology and Interventional Cardiology.
https://health.usnews.com/doctors/ion-jovin-633298

Patricia Uber, PharmD Alternate DSMB Member

Dr. Uber is a pharmacist in the Division of Cardiology, Section of Heart Failure and Transplantation, at VCU. She is an expert in the field of pharmacology of heart failure and transplantation, including immunosuppressive therapies. She is also the Executive Editor of the Journal of Heart-Lung Transplantation. https://vcuphc-thebeat.org/2018/01/dr-patricia-uber-assists-heart-patients/