RESEARCH PARTICIPANT INFORMATION AND CONSENT FORM

TITLE: The Effects of Interleukin-1 Blockade On Exercise Capacity In Patients With Recently Decompensated Systolic Heart Failure (REDHART2)

VCU IRB PROTOCOL NUMBER: HM20014686

INVESTIGATORS: Benjamin Van Tassell, PharmD, Antonio Abbate, MD, PhD

SPONSOR: National Heart, Lung, and Blood Institute, National Institutes of Health

ABOUT THIS CONSENT FORM

You are being invited to participate in a research study. **It is important that you carefully think about whether being in this study is right for you and your situation.**

This consent form is meant to assist you in thinking about whether or not you want to be in this study. **Please ask the study doctor or the study staff to explain any information in this consent document that is not clear to you.** You may take home an unsigned copy of this consent form to think about or discuss with family or friends before making your decision.

Your participation is voluntary. You may decide not to participate in this study. If you do participate, you may withdraw from the study at any time. Your decision not to take part or to withdraw will involve no penalty or loss of benefits to which you are otherwise entitled.

KEY INFORMATION ABOUT THIS STUDY

Heart failure is a condition in which the heart struggles to pump blood effectively. Inflammation in the body may affect heart function and contribute to heart failure. This study will test the safety, tolerability, and effectiveness of an anti-inflammatory medicine (anakinra) in patients with heart failure. You are being asked to participate in this study because you have recently been hospitalized for heart failure and may meet the study entry requirements.

Anakinra (Kineret®) is a naturally occurring protein that blocks inflammatory signaling in the body. The Food and Drug Administration (FDA) has approved Anakinra for the treatment of rheumatoid arthritis, but Anakinra is not currently approved for the treatment of heart disease. Anakinra is generally well-tolerated, but can cause pain or redness at the injection site and may affect your risk of infections. The study team will work with you to help you avoid (or manage) any side effects throughout the study.

The study is designed to measure the effect of Anakinra on heart function. Your participation in this study will last approximately 24 weeks. During this time, you will give yourself daily injections with Anakinra or placebo (a liquid that looks like Anakinra but contains no active medicine) for 24 weeks. Your assignment to treatment with Anakinra or placebo will be determined by randomization (like the “flip of a coin”). Approximately 102 people will participate in this study over the course of 4 years.

Your participation in this study will consist of cardiac ultrasounds (to measure your heart function), exercise tests, and questionnaires about your heart failure symptoms. We will also draw blood for safety assessments and record any side effects or hospitalizations during study participation.

WHAT WILL HAPPEN IF I PARTICIPATE?

After you sign this consent form, the investigators will perform a screening evaluation to determine your eligibility for the study. This screening will consist of a brief interview about your medical history, followed by a brief physical assessment (including height, weight, pulse, blood pressure, and temperature), and blood draw to measure basic laboratory and inflammatory biomarkers (approximately 1 to 2 tablespoons of blood). This screening may include a pregnancy test (if indicated).

If you meet all the requirements to participate in this study, you will be asked to schedule five study visits at VCU Health over the next 24 weeks.

Visit 1

Upon arrival to the Clinical Research Services Unit (North Hospital, 8th floor), you will have your vital signs measured (height, weight, blood pressure, temperature, breathing rate) and undergo a blood draw (1 to 2 tablespoons of blood). The blood draw will measure inflammatory biomarkers and routine safety tests. You will then complete a bioimpedance analysis, transthoracic echocardiogram, patient surveys, and cardiopulmonary test.

A **bioimpedance analysis** measures the water, lean mass, fat content of your body. A technician will place small patches (electrodes) on your skin and deliver a very small amount of electricity while you lie down on a bed. You will not be able to feel the electricity running through the body. This procedure will last approximately 10 minutes.

A **transthoracic echocardiogram** is an ultrasound of your heart. To perform this procedure, you will lie down in a bed while a technician applies a small amount of gel to your chest and uses a probe to take pictures of your heart. This procedure will last approximately 10 minutes.

You will complete four **surveys** to evaluate your heart failure symptoms, physical activity, and symptoms of depression. The Duke Activity Status Index (DASI) questionnaire contains 12 questions to which you will answer “yes” or “no”. Each question asks you to describe your ability to perform different activities. The Kansas City Cardiomyopathy Questionnaire contains 15 questions that ask you to mark how often you experience various symptoms of heart failure (i.e. swelling in your legs, shortness of breath, etc). The Patient Health Questionnaire-9 (PHQ-9) contains 9 questions about your mood and potential symptoms of depression. The International Physical Activity Questionnaire (IPAQ) contains 7 questions about the kinds of physical activities that you do as part of your everyday life. Please talk to the study team if you are uncomfortable answering any of these questions.

The **cardiopulmonary test** will evaluate your aerobic exercise capacity as you walk on a treadmill. The test will begin at a slow walking speed. The speed (or incline) of the treadmill will then gradually increase every 30 seconds. Small electrodes will be placed on your chest (electrocardiogram [ECG]) to measure your heart rhythm at the beginning of testing, during the test, and at the end of the test. Blood pressure will be measured throughout the exercise test using a standard blood pressure cuff on your arm. American Heart Association (AHA) guidelines for exercise testing will be followed. A trained physician will supervise all exercise tests. If you experience significant chest pain or signs of poor blood flow to the heart ("ischemia") that limit your ability to complete the exercise test, you will not be permitted to continue the study. This procedure will take approximately 30-40 minutes.

After the exercise test, you will receive your first supply of study medication. The investigators will teach you how to self-administer subcutaneous (under the skin) injections of the study medication. You will administer the medication daily throughout the course of the 24-week study while you are at home. The syringes should be stored in the refrigerator.

The entire visit will take approximately 2 hours.

Visit 2

Approximately 2 weeks after Visit 1, you will return the Clinical Research Services Unit (North Hospital, 8th floor), to undergo a blood draw (1 to 2 tablespoons of blood) and brief physical assessment. This visit will take approximately 30 minutes. If needed, this visit may also be performed by your own cardiologist or clinical provider.

Visits 3, 4, and 5

You will return to the Clinical Research Services Unit (North Hospital, 8th floor) after 6 weeks, 12 weeks, and 24 weeks to repeat all of the procedures from Visit 1. These procedures include a brief physical assessment, blood draw, bioimpedance analysis, questionnaires, cardiac ultrasound, and exercise test. These visits will take approximately 2 hours each.

Upon completion of Visit 5, your active participation in the study will be over. However, investigators may contact you at the conclusion of the entire study (after all 102 patients have finished their participation) to verify whether you have been re-hospitalized since the beginning of the study.

Visit	**1**	**2**	**3**	**4**	**5**
Week	0	2	6	12	24
Physical assessment	X	X	X	X	X
Blood draw	X	X	X	X	X
Bioimpedance analysis	X		X	X	X
Echocardiogram	X		X	X	X
Questionnaires	X		X	X	X
Exercise test	X		X	X	X
Receive new study medicine	X	(X)	X	X	

Throughout the study, any test results that may affect your heart failure treatment will be provided and explained to you. All of your individual results from the study will be made available to you upon your request. No genetic testing or sequencing will be conducted as part of this research.

Additional study visits may be requested for things such as additional blood draws for safety reasons or to pick up additional medication.

You will not be able to participate if you have been recently affected by COVID-19 in the prior 60 days or you have been in close contact with a person affected by COVID-19 in the prior 21 days. At each visit, you may be asked to undergo screening questions and tests for COVID-19 as per standard protocol at VCU Health, which may include answering questions about your health, measuring your temperature, or having a nasopharyngeal test performed to detect the presence of SARS-CoV2 virus.

WHAT ALTERNATIVE TREATMENTS OR PROCEDURES ARE AVAILABLE?
If you decide not to enter this study, you can still receive the usual medical treatments for heart failure. You do not have to participate in this study to be treated for heart failure.

WHAT ARE THE BENEFITS OF BEING IN THE STUDY?
There is no guarantee that you will receive any medical benefits from being in this study. However, possible benefits include improved exercise capacity and reduced heart failure symptoms during your participation. You may also benefit from the information obtained through the physical exams, lab tests, and other study procedures. We hope that the information from this research study may lead to a better treatment in the future for people with heart failure.

WHAT RISKS AND DISCOMFORTS COULD I EXPERIENCE FROM BEING IN THE STUDY?
Your condition may not get better (or may become worse) while you are in this study.

Possible Risks Associated with Anakinra
Anakinra is generally well-tolerated, but some side effects are possible.

- Injection site reaction (>10%) such as pain, redness, or irritation at the site of injection.
- Serious infection (<5%)
- Headache (1 –10%)
- Nausea (1 – 10%)
- Diarrhea (1 – 10%)
- Low white blood cell count (rare, but not associated with increased risk of infection)
- Hypersensitivity reaction (rash, anaphylaxis, arthritis)(rare 1-2%)

Anakinra may block your body's ability to have a fever. This means that you may not have a fever if you become sick or ill. If you are feeling sick during the study, please contact your study doctor immediately. Allergic reaction to Anakinra is possible. Severe allergic reactions can be life threatening. Please contact your study doctor or seek immediate medical attention if you experience skin rash, swelling, or difficulty breathing as these may be signs of allergic reaction.

Other risks to participation in this study include the following:

- Pain or bruising during blood draws. In rare cases, blood draws may result in skin/tissue

infection.
- Shortness of breath, chest pain, fatigue, or an abnormal cardiovascular response during exercise testing (i.e. markedly elevated blood pressure or heart rate).
- Minor skin irritation (rare) from the adhesives or gels used in bioimpendance analysis, electrocardiograms, or cardiac ultrasound.
- Minor discomfort of your arm during blood pressure measurement.

Only the study participant can take the study drug. It must be kept out of the reach of children and persons who may not be able to read or understand the label.

Non-Physical Risks
Participation in research might involve some loss of privacy. There is a small risk that someone outside the research study could see and misuse information about you. The questions in the depression surveys may be upsetting to some patients.

Unknown or Unforeseeable Risks
During the course of the research, we will inform you of any significant new findings that may affect your willingness to continue participation.

As the study procedures might injure an unborn child, pregnant women may not participate. Women who might become pregnant should use a medically accepted form of birth control such as total abstinence, birth control pills, an IUD, diaphragm, progesterone injections or implants, or condoms plus a spermicide. Methods of birth control other than total abstinence are not 100% effective, and should a women become pregnant there is a risk of injury to an unborn child. For similar reasons, women who are nursing an infant may not participate.

For men, the study procedures might increase the risks for birth defects of any child conceived during treatment and several months after treatment is stopped. Men in this study who have the potential of fathering children should be aware of this possibility and consider using a medically accepted form of birth control. For men this would include total abstinence and condoms plus a spermicide, or for the female partner, birth control pills, an IUD, diaphragm, progesterone injections or implants. Methods of birth control other than total abstinence are not 100% effective, and should a woman become pregnant there is a risk of injury to an unborn child.

WHAT ARE THE COSTS?
Study drug will be provided at no cost to you. You will not be charged for the study visits or any study-related procedures.

WILL I BE PAID TO PARTICIPATE IN THE STUDY?
You will receive $100 compensation for each study visit to account for the time and expense of study participation. You will receive an additional $50 compensation if you are asked to return for an unscheduled visit.

Total payments within one calendar year that exceed $600 will require the University to report these payments annually to the IRS and you. This may require you to claim the compensation

you receive for participation in this study as taxable income. VCU is required by federal law to collect your social security number. Your social security number will be kept confidential and will only be used to process payment.

Please be aware that the investigative team and the University may receive money for the conduct of this study.

WHAT HAPPENS IF I AM INJURED OR BECOME SICK BECAUSE I TOOK PART IN THE STUDY?

If you are injured by, or become ill, from participating in this study, please contact your study doctor immediately. Medical treatment is available at the Virginia Commonwealth University Health System (VCU Health System). Your study doctor will arrange for short-term emergency care at the VCU Health System or for a referral if it is needed. Fees for such treatment may be billed to you or to appropriate third party insurance. Your health insurance company may or may not pay for treatment of injuries or illness as a result of your participation in this study. To help avoid research-related injury or illness it is very important to follow all study directions.

CAN I STOP BEING IN THIS STUDY?

You can stop being in this research study at any time. Leaving the study will not affect your medical care, employment status, or academic standing at VCU or VCU Health. Tell the study staff if you are thinking about stopping or decide to stop.

Your participation in this study may be stopped at any time by the study doctor or the sponsor without your consent. The reasons might include:

- the study doctor thinks it necessary for your health or safety;
- you have not followed study instructions;
- the sponsor has stopped the study; or
- administrative reasons require your withdrawal.

HOW WILL INFORMATION ABOUT ME BE PROTECTED?

VCU and the VCU Health System have established secure research databases and computer systems to store information and to help with monitoring and oversight of research. Your information may be kept in these databases but are only accessible to individuals working on this study or authorized individuals who have access for specific research related tasks.

Identifiable information in these databases are not released outside VCU unless stated in this consent or required by law. Although results of this research may be presented at meetings or in publications, identifiable personal information about participants will not be disclosed.

Personal information about you might be shared with or copied by authorized representatives from the following organizations for the purposes of managing, monitoring and overseeing this study:

- The study Sponsor, representatives of the sponsor and other collaborating organizations
- Representatives of VCU and the VCU Health System

- Officials of the Department of Health and Human Services or the Federal Food and Drug Administration

It will be noted in your protected electronic health record at VCU Health that you are in this study. Information about the study (including any medications you may receive) will be included in the record. This information is protected just as any of your other health records are protected.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Website will include a summary of the results. You can search this Web site at anytime.

There are no plans to share any money or profits with you if the use of your sample(s) results in inventions or discoveries that have commercial value. In the future, identifiers might be removed from the information and samples you provide in this study, and after that removal, the information/samples could be used for other research studies by this study team or another researcher without asking you for additional consent.

To help us protect your privacy, we have obtained a Certificate of Confidentiality from the National Institutes of Health. The researchers can use this Certificate to legally refuse to disclose information that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings, for example, if there is a court subpoena. The researchers will use the Certificate to resist any demands for information that would identify you, except as explained below.

The Certificate cannot be used to resist a demand for information from personnel of the United States Government that is used for auditing or evaluation of federally funded projects or for information that must be disclosed in order to meet the requirements of the federal Food and Drug Administration (FDA).

You should understand that a Certificate of Confidentiality does not prevent you or a member of your family from voluntarily releasing information about yourself or your involvement in this research. If an insurer, employer, or other person obtains your written consent to receive research information, then the researchers may not use the Certificate to withhold that information.

HOW WILL MY HEALTH INFORMATION BE USED AND SHARED DURING THIS STUDY?
As part of this research study, we will ask you to share identifiable health information with us and/or permit us to access existing information from your healthcare records. New health information may also be created from study-related tests, procedures, visits, and/or questionnaires. This type of information is considered "Protected Health Information" that is protected by federal law.

What type of health information will be used or shared with others during this research?
The following types of information may be used for the conduct of this research:

☒ Complete health record	☐ Diagnosis & treatment codes	☐ Discharge summary
☒ Complete billing record	☐ Consultation reports	☐ Progress notes

☐ History and physical exam ☐ X-ray reports ☐ X-ray films / images
☐ Photographs, videotapes ☐ Laboratory test results ☐ Itemized bill
☐ Information about drug or alcohol abuse ☐ Information about Hepatitis B or C tests
☐ Information about psychiatric care ☐ Information about sexually transmitted diseases

Who will use or share protected health information about me?
VCU and VCU Health are required by law to protect your identifiable health information. By consenting to this study, you authorize VCU/VCU Health to use and/or share your health information for this research. The health information listed above may be used by and/or shared with the following people and groups to conduct, monitor, and oversee the research:

- Principal Investigator and Research Staff
- Research Collaborators
- Data Safety Monitoring Boards
- Others as Required by Law
- Study Sponsor
- Institutional Review Boards
- Government/Health Agencies

When will this authorization (permission) to use my protected health information expire?
This authorization will expire when the research study is closed, or there is no need to review, analyze and consider the data generated by the research project, whichever is later.

Right to Revoke Authorization and Re-disclosure
You may change your mind and revoke (take back) the right to use your protected health information at any time. Even if you revoke this Authorization, the researchers may still use or disclose health information they have already collected about you for this study. If you revoke this Authorization you may no longer be allowed to participate in the research study. To revoke this Authorization, you must write to the Principal Investigator.

Statement of Privacy Rights
You may change your mind and revoke (take back) the right to use your protected health information at any time. However, even if you revoke this authorization, the researchers may still use or disclose health information they have already collected about you for this study. If you revoke this Authorization, you may no longer be allowed to participate in the research study. To revoke this Authorization, you must write to the Principal Investigator at Benjamin Van Tassell, 410 North 12th Street, Richmond VA, 23298-0533.

QUESTIONS
If you have any questions, complaints, or concerns about this research, contact:

Benjamin Van Tassell, PharmD
Virginia Commonwealth University
410 North 12th Street, Rm 660A
Richmond, VA 23298
(804) 828-4583

Roshanak Markley, MD
Virginia Commonwealth University
West Hospital, 5th Floor, Rm 528B
Richmond, VA 23298
(804) 628-3981 (pager 3440)

If you have general questions about your rights as a participant in this or any other research, or if you wish to discuss problems, concerns or questions, to obtain information, or to offer input about research, you may contact:

Virginia Commonwealth University Office of Research
800 East Leigh Street, Suite 3000, Box 980568, Richmond, VA 23298
(804) 827-2157; https://research.vcu.edu/human_research/volunteers.htm

Do not sign this consent form unless you have had a chance to ask questions and have received satisfactory answers to all of your questions.

CONSENT

I have been provided with an opportunity to read this consent form carefully. All of the questions that I wish to raise concerning this study have been answered. By signing this consent form, I have not waived any of the legal rights or benefits, to which I otherwise would be entitled. My signature indicates that I freely consent to participate in this research study. I will receive a copy of the consent form once I have agreed to participate.

_____
Participant Name (Printed)

_____ _____
Participant Signature Date

_____
Name of Person Conducting Informed Consent Discussion (Printed)

_____ _____
Signature of Person Conducting Informed Consent Discussion Date

_____ _____
Principal Investigator Signature (if different from above) Date