Cardiac Allograft Vasculopathy Inhibition With Alirocumab (CAVIAR)

Informed Consent Form

NCT03537742

January 23, 2024

Are you participating in any other research studies? _____ Yes _____No

PURPOSE OF RESEARCH

You are invited to participate in a research study on the use of a new cholesterol reducing medication and its effect on coronary artery disease after heart transplantation.

We hope to learn more about the role of a class of medications called PCSK9 inhibitors in the development of cardiac allograft vasculopathy (CAV), a condition in which there is thickening in the coronary arteries that supply blood to your heart. PCSK9 inhibitors like the medication alirocumab, used in this study, are medications that lower LDL cholesterol. The buildup of LDL cholesterol is thought to increase the risk of developing CAV. Although alirocumab is FDA approved to lower LDL cholesterol, it is not approved for the treatment of CAV in heart transplant recipients, and therefore considered investigational. The use of alirucomab in adult heart transplant patients does not significantly increase the risk of the use of this drug as it does not interact with immunosuppressants used in transplantation and has been shown to be safe in adults with cardiovascular disease. We hope to learn if it is useful for people who have had a heart transplant. We hope to learn whether PCSK9 inhibitors slow down the progression of coronary artery disease in the new heart after transplantation.

You were selected as a possible participant in this study because you have had a heart transplant.

If you decide to terminate your participation in this study, you should notify William Fearon MD at [redacted].

This research study is looking for 120 people at Stanford University who have had a heart transplant and are otherwise healthy.

VOLUNTARY PARTICIPATION

Your participation in this study is entirely voluntary. Your decision not to participate will not have any negative effect on you or your medical care. You can decide to participate now but withdraw your consent later and stop being in the study without any loss of benefits or medical care to which you are entitled.

DURATION OF STUDY INVOLVEMENT

This research study is expected to take approximately 12 months of active participation, and 4 ½ years to complete the whole trial.

PROCEDURES

If you choose to participate, you will have your routine first (baseline) coronary angiogram and intravascular ultrasound study (IVUS) which is usually done within the first 6 -12 weeks after your heart transplant, but due to the CoVID-19 virus may be done up to 6 months after your heart transplant. The baseline coronary angiogram and IVUS is routine or standard of care in an adult patient after heart transplantation. Delaying this routine baseline angiogram and IVUS will not cause any increase harm to you.

In addition to the angiogram and IVUS Dr. William Fearon and his associates routinely, use a special pressure wire to evaluate the blood flow in both the large and the small vessels of the heart. This wire will give us more information on physiological changes in the large and small vessels supplying your heart early after transplantation, which may better guide future therapy. The ability of the coronary arteries to relax or dilate will be determined by administering a short-acting medication called acetylcholine. This is a commonly performed method for assessing the health of the lining of the coronary arteries.

Dr. Fearon, or his associates and research study staff will explain the research study to you again after your heart transplant procedure, they will make sure that you are healthy in all other ways by reviewing your medial record, checking your lab work, and other routine studies. Only after your heart angiogram and IVUS will you be randomized to the study medication or a placebo.

Randomized means that the decision about whether you will take the placebo or the active agent alirocumab is made by random assignment, like flipping a coin. You have a 50% chance of getting on the active medication PCSK9 inhibitor (alirocumab) and a 50% chance of getting on the placebo arm of the study. A placebo is a substance that has no therapeutic effect, it is harmless and is used as a control in testing new drugs or new indications for drugs. The placebo is normal saline (sterile saltwater). During the study you will not know if you are receiving the study medication or placebo. You will continue to receive all your routine post-transplant medications as prescribed by your treating physician. Your clinic visits will be the same standard schedule.

The study medication, whether it is the active agent or the placebo will be given to you the day of or after your heart angiogram procedure. It is given as a small (1ml) single dose (150mg) pre-filled pen given as a sub cutaneous (Sub-Q, under the skin) injection once every two weeks for one year. One of the research nurses will teach you and/or your caregiver how to inject yourself with the prefilled, disposable syringe and you will also be given educational information regarding how to use the pen and inject yourself. At your one-year annual evaluation, when you are scheduled for your routine follow-up angiogram (i.e., up to 18 months after date of transplant and about 12 months after baseline angiogram), Dr Fearon and colleagues will again look at the health of your coronary arteries. You will then stop the study medication. The un-blinding, which is when the research team reveals if you were on the study medication or placebo, will occur when all of the study participants have completed the study at the end of the 4-year study period.

During the active study period, your study visits and lab work will be monitored in the usual and standard schedule including cholesterol levels. Research lab work, which are special cholesterol lab tests, will be done once every 3 months (4 times in one year) at the same time they are doing your routine lab work, or more often if needed to monitor your cholesterol level. These extra lab tests will be about one and a half teaspoons (7ml), and will be covered under the research study.

If you cannot tolerate or have side effects on the 150 mg dose, or if your LDL-cholesterol level goes below 20mg/dl ,we may consider decreasing your other cholesterol lowering medication , and/or if needed we may decrease your dose of study medication to 75 mg every other week.

Description of visits:

Your study visits will be at the same time as your routine post transplantation visits and lab work for the research study will be done at the same time as your visit lab work as described above.

We will ask you to return your used pens at each visit, and will dispose of them for you here at Stanford Health Care.

We will ask you how you are doing on the study medication and will give you a new supply of study medication at each visit.

The study medication pens will be given to you during your clinic visits for in quantities of 6-8 pens per study visit for a total of about 30 pens over the course

of the first year. We will provide you with a bag and ice packs to transport the study medication. As stated above, please return the used pens at each visit.

We will give you reading materials about the medication and review these with you at your first visit.

Women of Childbearing Potential

If you are a woman who is able to become pregnant, it is expected that you will use an effective method of birth control to prevent exposing a fetus to a potentially dangerous agent with unknown risk. If you are pregnant or currently breast feeding, you may not participate in this study. You understand that if you are pregnant, if you become pregnant, or if you are breast-feeding during this study, you or your child may be exposed to an unknown risk.

To confirm to the extent medically possible that you are not pregnant, you agree to have a pregnancy test done before beginning this research study.

You must agree to avoid sexual intercourse or use a birth control method judged to be effective by the investigator and which will not interfere with the proposed investigation. You must accept the risk that pregnancy could still result despite the responsible use of reliable method of birth control. You agree to notify the investigator as soon as possible of any failure of proper use of your birth control method, or if you become pregnant, either of which may result in your being withdrawn from the study.

PARTICIPANT RESPONSIBILITIES

As a participant, your responsibilities include:

- Follow the instructions of the Protocol Director and study staff.
- Take the study drug as instructed.
- Keep your study or clinic appointments. If it is necessary to miss an appointment, please contact the Protocol Director or research study staff to reschedule as soon as you know you will miss the appointment.
- Tell the Protocol Director or research study staff about any side effects, doctor visits, or hospitalizations that you may have.
- Tell the Protocol Director or research staff if you believe you might be pregnant.
- Store the study drug per instructions and away from children and for your use only.
- Ask questions as you think of them.
- Tell the Protocol Director or research staff if you change your mind about staying in the study.

WITHDRAWAL FROM STUDY

If you first agree to participate and then you change your mind, you are free to withdraw your consent and discontinue your participation at any time. Your decision will not affect your ability to receive medical care for your disease and you will not lose any benefits to which you would otherwise be entitled.

If you decide to withdraw your consent to participate in this study, you should notify William Fearon at ([redacted]) or Helen Luikart RN, Research Nurse at 650-724-2883.

If you withdraw from the study, or the study medication is stopped for any reason, please inform Dr. Fearon or Helen Luikart RN right away. (There are no anticipated problems from stopping the medication).

Stopping the medication may cause the study investigator to withdraw you from the study and should be discussed to ensure complete understanding of the process. You must return all study-related supplies, including the unused study drug.

The Protocol Director may also withdraw you from the study and the study medication may be stopped without your consent for one or more of the following reasons:

- Failure to follow the instructions of the Protocol Director and study staff.
- The Protocol Director decides that continuing your participation could be harmful to you.
- Pregnancy
- You need treatment not allowed in the study.
- The study is cancelled.
- Other administrative reasons.
- Unanticipated circumstances.

POSSIBLE RISKS, DISCOMFORTS, AND INCONVENIENCES

There are risks, discomforts, and inconveniences associated with any research study. These deserve careful thought. You should talk with the Protocol Director if you have any questions.

The most common risks associated with the active study medication are an allergic reaction to the study medication (less than 1%), if a serious allergic reaction occurs, the study medication would be stopped. The symptoms will be treated until they are resolved. Hypersensitivity reactions are serious allergic

reactions that can produce symptoms such as pruritus (itching), rash, hives (red raised itchy bumps), or swelling of the tongue or lips or trouble breathing.

The most commonly occurring adverse reactions (a little over 5% of patients treated with alirocumab and occurring more frequently than with placebo are nasopharyngitis(runny nose, sore throat), injection site reactions,(soreness, redness, itching, swelling, and pain/tenderness at site of injection) and flu like symptoms.

A rare adverse reaction is liver-related disorders (elevated liver lab tests) in about 2.5% of patients treated with alirocumab and 1.8% of patients treated with placebo. The high liver lab test went back to normal after the medication was stopped. Other less frequent adverse reactions are diarrhea, bronchitis, muscle pains, muscle spasms, cough. Extremely rare adverse events (Less than 0.2% of patients on drug had complaints of confusion or memory impairment.

The injection is from a pre-filled, single-dose disposable pen. It contains 150 mg of (alirocumab) in 1 mL(or 75 mg of alirocumab in 1 ml) or the placebo in one mL of normal saline (sterile salt water).

The pen contains the study medication or placebo prescribed by the study investigator MD. The study medicine is injected under your skin and can be given by yourself or someone else (caregiver). You can inject the study medication into your thighs, stomach (except for the 2 inch area around your navel) or upper arms.

If you are receiving the placebo this does NOT mean that your cholesterol will go uncontrolled. As standard post transplant therapy all heart transplant patients, regardless of total cholesterol level are prescribed a cholesterol or lipid lower medication commonly called a "statin" which are proven to reduce blood cholesterol. You will be on the standard of care "statin" medication either rosuvastatin or atorvastatin will be routinely used or another statin if necessary.

POTENTIAL BENEFITS

The potential benefit for the active arm participant may be reduced or prevention of the development of Coronary Artery Vasculopathy (CAV). Placebo participants will have no potential benefit. We believe this project will contribute significantly to the evidence base for an important health matter, namely the optimal medical treatment for cardiac transplant recipients. **We cannot and do not guarantee or promise that you will receive any benefits from this study.**

ALTERNATIVES

The alternative to this study is not to participate and you will get all the standard of care usually given to the heart transplant recipient, except for the study drug

PARTICIPANT'S RIGHTS

You should not feel obligated to agree to participate. Your questions should be answered clearly and to your satisfaction. If you decide not to participate, tell the Protocol Director.

You will be told of any important new information that is learned during the course of this research study, which might affect your condition or your willingness to continue participation in this study.

ClinicalTrials.gov

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 Web site will include a summary of the results. You can search this Web site at any time.

CONFIDENTIALITY

The results of this research study may be presented at scientific or medical meetings or published in scientific journals. Your identity and/or your personal health information will not be disclosed, except as authorized by you or as required by law**.** However, there is always some risk that even de-identified information might be re-identified.

Patient information may be provided to Federal and other regulatory agencies as required. The Food and Drug Administration (FDA), for example, may inspect research records and learn your identity if this study falls within its jurisdiction.

The purpose of this research study is to obtain data or information on the safety and effectiveness of alirocumab; the results will be provided to the sponsor, the Food and Drug Administration and other federal and regulatory agencies as required.

CERTIFICATE OF CONFIDENTIALITY

This research is covered by a Certificate of Confidentiality from the National Institutes of Health. The researchers with this Certificate may not disclose or use information, documents, or biospecimens that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other action, suit, or proceeding, or be used as evidence, for example, if there is a court subpoena, unless you have consented for this use. Information, documents, or biospecimens protected by this Certificate cannot be disclosed to anyone else who is not connected with the research except, if there is a federal, state, or local law that requires disclosure (such as to report child abuse or communicable diseases but not for federal, state, or local civil, criminal, administrative, legislative, or other proceedings, see below); if you have consented to the disclosure, including for your medical treatment; or if it is used for other scientific research, as allowed by federal regulations protecting research subjects

The Certificate cannot be used to refuse a request for information from personnel of the United States federal or state government agency sponsoring the project that is needed for auditing or program evaluation by NIH which is funding this project 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 from voluntarily releasing information about yourself or your involvement in this research. If you want your research information released to an insurer, medical care provider, or any other person not connected with the research, you must provide consent to allow the researchers to release it.

The Certificate of Confidentiality will not be used to prevent disclosure for any purpose you have consented to in this informed consent document such as including research data in the medical record.

Authorization To Use Your Health Information For Research Purposes

Because information about you and your health is personal and private, it generally cannot be used in this research study without your written authorization. If you sign this form, it will provide that authorization. The form is intended to inform you about how your health information will be used or disclosed in the study. Your information will only be used in accordance with this authorization form and the informed consent form and as required or allowed by law. Please read it carefully before signing it.

What is the purpose of this research study and how will my health information be utilized in the study?

The aim of this research study is to evaluate the effect of alirocumab, a medication within the class of PCSK9 inhibitors, on the progression of heart disease after heart transplantation. Your identity will be kept as confidential as possible as required by law. The results of this research study may be presented at scientific or medical meetings or published in scientific journals. However, your identity will not be disclosed. As this is a clinical trial, your information may be provided to Federal and other regulatory agencies as required.

Do I have to sign this authorization form?

You do not have to sign this authorization form. But, if you do not, you will not be able to participate in this research study, including receiving any research-related treatment. Signing the form is not a condition for receiving any medical care outside the study.

If I sign, can I revoke it or withdraw from the research later?

If you decide to participate, you are free to withdraw your authorization regarding the use and disclosure of your health information (and to discontinue any other participation in the study) at any time. After any revocation, your health information will no longer be used or disclosed in the study, except to the extent that the law allows us to continue using your information (e.g., necessary to maintain integrity of research). If you wish to revoke your

authorization for the research use or disclosure of your health information in this study, you must write to: Dr. William Fearon, 300 Pasteur Dr. H2103, Stanford CA 94305 or at [redacted]

What Personal Information Will Be Obtained, Used or Disclosed?

Your health information related to this study, may be used or disclosed in connection with this research study, including, but not limited to, the coronary angiogram or other imaging data, pressure and flow measurements of the coronary vasculature, clinical history, electrocardiogram, laboratory results, physical examination and vital signs, and informed consent.

Who May Use or Disclose the Information?

The following parties are authorized to use and/or disclose your health information in connection with this research study:

- The Protocol Director, Dr. William Fearon
- The Stanford University Administrative Panel on Human Subjects in Medical Research and any other unit of Stanford University as necessary
- Research Staff

Who May Receive or Use the Information?

The parties listed in the preceding paragraph may disclose your health information to the following persons and organizations for their use in connection with this research study:

- The Office for Human Research Protections in the U.S. Department of Health and Human Services
- National Institutes of Health
- The Food and Drug Administration
- Data Safety and Monitoring Board

Your information may be re-disclosed by the recipients described above, if they are not required by law to protect the privacy of the information.

When will my authorization expire?

Your authorization for the use and/or disclosure of your health information will end on December 31, 2050 or when the research project ends, whichever is earlier.

Will access to my medical record be limited during the study?
To maintain the integrity of this research study, you may not have access to any health information developed as part of this study until it is completed. At that point, you would have access to such health information if it was used to make a medical or billing decision about you (e.g., if included in your official medical record).

_____ _____
Signature of Adult Participant Date

_____
Print Name of Adult Participant

_____ _____
Signature of Legally Authorized Representative (LAR) Date
(e.g., parent, guardian or conservator)

_____
Print Name of LAR

_____
LAR's Authority to Act for Participant
(e.g., parent, guardian or conservator)

FINANCIAL CONSIDERATIONS

Payment/Reimbursement
You will not be paid to participate in this research study.

Costs
There is no cost to you for participating in this study, other than basic expenses like transportation and the personal time it will take to come to all of the study visits.

If you participate in this study, the study will pay for those services, supplies, procedures, and care associated with the study that are not a part of your routine medical care. However, there may be additional costs to you. These include basic expenses like transportation and the personal time it will take to come to the study visits. You and/or your health insurance must pay for services, supplies, procedures, and care that are required during this study for routine medical care. You will also be responsible for any co-payments and/or deductibles as required by your insurance. Participation in this study is not a substitute for health insurance."

Sponsor
The National Institutes of Health is providing financial support and/or material for this study. Regeneron is providing the study and placebo medication.

COMPENSATION for Research-Related Injury

All forms of medical diagnosis and treatment – whether routine or experimental – involve some risk of injury. In spite of all precautions, you might develop medical complications from participating in this study. If such complications arise, the Protocol Director and the research study staff will assist you in obtaining appropriate medical treatment. In the event that you have an injury or illness that is directly caused by your participation in this study, reimbursement for all related costs of care first will be sought from your insurer, managed care plan, or other benefits program. **You will be responsible for any associated co-payments or deductibles as required by your insurance.**

If costs of care related to such an injury are not covered by your insurer, managed care plan or other benefits program, you may be responsible for these costs. If you are unable to pay for such costs, the Protocol Director will assist you in applying for supplemental benefits and explain how to apply for patient financial assistance from the hospital.

You do not waive any liability rights for personal injury by signing this form.

CONTACT INFORMATION

Questions, Concerns, or Complaints:
If you have any questions, concerns or complaints about this research study, its procedures, risks and benefits, or alternative courses of treatment, you should ask the Protocol Director William Fearon MD, at [redacted] You should also contact him at any time if you feel you have been hurt by being a part of this study.

Independent Contact: If you are not satisfied with how this study is being conducted, or if you have any concerns, complaints, or general questions about the research or your rights as a participant, please contact the Stanford Institutional Review Board (IRB) to speak to someone independent of the research team at (650)-723-5244 or toll free at 1-866-680-2906. You can also write to the Stanford IRB, Stanford University, 1705 El Camino Real, Palo Alto, CA 94306.

Alternate Contact: If you cannot reach the Protocol Director, please contact Helen Luikart RN, MS Research Nurse Manager at 650-724-2883

EXPERIMENTAL SUBJECT'S BILL OF RIGHTS

As a research participant you have the following rights. These rights include but are not limited to the participant's right to:

- be informed of the nature and purpose of the experiment;
- be given an explanation of the procedures to be followed in the medical experiment, and any drug or device to be utilized;
- be given a description of any attendant discomforts and risks reasonably to be expected;
- be given an explanation of any benefits to the subject reasonably to be expected, if applicable;
- be given a disclosure of any appropriate alternatives, drugs or devices that might be advantageous to the subject, their relative risks and benefits;
- be informed of the avenues of medical treatment, if any available to the subject after the experiment if complications should arise;
- be given an opportunity to ask questions concerning the experiment or the procedures involved;

- be instructed that consent to participate in the medical experiment may be withdrawn at any time and the subject may discontinue participation without prejudice;
- be given a copy of the signed and dated consent form; and
- be given the opportunity to decide to consent or not to consent to a medical experiment without the intervention of any element of force, fraud, deceit, duress, coercion or undue influence on the subject's decision.

Signing your name means you agree to be in this study and that you will receive a copy of this signed and dated consent form.

_____ _____
Signature of Adult Participant Date

_____
Print Name of Adult Participant

_____ _____
Signature of Legally Authorized Representative (LAR) Date
(e.g., parent, guardian or conservator)

_____
Print Name of LAR

_____
LAR's Authority to Act for Participant
(e.g., parent, guardian or conservator)

_____ _____
Signature of Person Obtaining Consent Date

_____
Print Name of Person Obtaining Consent

The following witness line is to be signed only if the consent is provided as a summary form and accompanied by a short form foreign language consent.

_____ _____
Signature of Witness Date

_____
Print Name of Witness

(e.g., staff, translator/interpreter, family member)

• Translated short form must be signed and dated by both the participant (or their LAR) AND the witness.
• The English consent form (referred to as the "Summary Form" in the regulations):
-Must be signed by the witness AND the Person Obtaining Consent (POC).
-The non-English speaking participant/LAR does not sign the English consent.
-The non-English speaking participant/LAR should not sign the HIPAA participant line
-If the participant or the LAR is non-English speaking, the Person Obtaining Consent (POC) must ensure that 1) the LAR's Description of Authority is completed and 2) that any questions or options presented by the consent form are documented and initialed by the POC on the Summary Form, per the participant's wishes, as they are understood during the consent process.