ClinicalTrials.gov Cover Page

Title: Impact of Evolocumab (Repatha) in Cardiac Transplant Patients with Coronary Allograft Vasculopathy (CAV)

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Document: Copy of blank Informed Consent document

ADULT CONSENT - CLINICAL BIOMEDICAL
Adult Consent Form

Title of this Research Study

Invitation
You are invited to take part in this research study. You have a copy of the following, which is meant to help you decide whether or not to take part:

- Informed consent form
- "What Do I need to Know Before Being in a Research Study?"
- The Rights of Research Subjects

Why are you being asked to be in this research study?
You are being asked to voluntarily participate in this research study because you are between 19 and 80 years old and have received a heart transplant and have been diagnosed with mild to moderate coronary allograft vasculopathy (CAV). Participating in this study is different from receiving regular clinical care. You are encouraged to ask the investigator or members of the research team any questions you have regarding this research study. If you decide to participate, you will be asked to sign this consent form. Participating in research is voluntary, therefore it is your decision to participate or not. Your decision not to participate will not affect the care you receive, your relationship with your doctor, or any benefits to which you are entitled.

If you are pregnant, nursing an infant, or plan to become pregnant during this study, you may not be in this study.

What is the reason for doing this research study?
The purpose of this study is to evaluate if PCSK9 inhibitors improve outcomes for patients with CAV. CAV is similar to coronary artery disease for patients who have received a heart transplant. Nearly half of heart transplant patients will develop CAV after 10 years of receiving a heart transplant. PCSK9 inhibitors are a lipid lowering therapy currently approved by the United States Food and Drug Administration (FDA) for patients with coronary artery disease. However, the FDA has not approved the use of PSCK9 inhibitors for heart transplant patients with CAV. Evolocumab (Brand name: Repatha) is the PCSK9 inhibitor used in this study.

With this study, we hope to:

- Measure the impact of evolocumab on serum LDL in heart transplant patients
- Assess the effect of evolocumab on CAV progression

- Assess the effect of evolocumab on immunuosuppression regimens and graft rejection
- Measure the effect of evolocumab on serum lipids after 1 year of therapy

This study is only enrolling patients at Nebraska Medicine/University of Nebraska Medical Center. Forty subjects are expected to participate. This study is expected to last two years and individual participation is expected to last 1 year.

What will be done during this research study?

Week 0: If you decide to participate, the study investigator or a member from the research team will review your medical history with you. This review will include general health questions, transplant history, CAV history, and transplant rejection history. You will undergo a medical evaluation and a blood draw to test your immunosuppressant blood level and lipid panel. The study team will also test your blood for pregnancy if you are of childbearing potential, and the sponsor will pay for this test. The results of the pregnancy test will be shared with you as soon as the results are available. Some of the mentioned tests will be done as part of your standard care, meaning these tests are typically performed for heart transplant patients during their annual visit.

Throughout this study, it is important that you notify the investigator if you think you may be pregnant. If you report that you are pregnant or may be pregnant during your participation in this study, you will be given a pregnancy test per standard of care.

A study pharmacist will teach you how to self-administer the study drug subcutaneously using an autoinjector with a needle in your skin either on your upper arm, stomach, or thigh. The autoinjectors will be mailed to you on a monthly basis, and you will be directed to self-administer 140mg of the study drug every two weeks during your participation in this study. If you happen to miss a dose of the study drug during your participation in this study, please contact a member of the study team or the investigator for further instruction.
It is important to note that this therapy may be given as an addition to other to other therapies, such as a prescribed statin or other LDL lowering therapies.

Week 2 and 4: You will be assessed by research personnel for any side-effects or adverse events. This can be done either by phone survey or during a standard-of-care clinic visit.

Week 12: You will have follow up visits at week 12, 26, and 38. During these visits, you will be asked about adverse events, potential side effects, about your compliance with the study drug. At week 12, a blood samples will be collected to check your lipid

panel and immunosuppressant blood level. With the exception of the week 12 lipid panel test, you may be able to complete your blood samples locally if appropriate.

Week 52: The week 52 visit may be scheduled to take place during your routine annual visit. During your final visit, the investigator or study staff will review your CAV history, transplant rejection history, and you will undergo a medical evaluation. Blood samples will be collected to check your immunosuppressant levels and lipid panels as part of your standard of care.

What are the possible risks of being in this research study?

Risks associated with the study drug: Evolocumab is currently FDA-approved and commercially available for patient use in the United States. Allergic reactions and injection-site reactions have occurred in patients using PCSK9 inhibitors.

Other studies have noted risks associated with evolocumab, including muscle-related events, new-onset diabetes, nasopharyngitis, upper respiratory tract infection, influenza, back pain, cough, urinary tract infection, sinusitis, headache, myalgia, dizziness, musculoskeletal pain, hypertension, diarrhea, and gastroenteritis.

Risks associated with blood samples: collection of blood samples may cause bleeding or leave a bruise at the site of collection. There is a small risk of infection. Your blood samples will only be collected by trained staff members.

Low LDL Levels: There are potential harmful effects of very low LDL, including increased risk of neurocognitive disease, increased risk of new-onset diabetes, and increased risk of malignancy. Clinical trials have yet to demonstrate or validate these concerns.

Pregnancy: It is unknown if evolocumab is harmful to a fetus or not, and it is unknown if nursing mothers can pass the study drug through breastmilk. If you are pregnant or plan to become pregnant during the course of this study, you may not participate in this study. If you find out you are pregnant or become pregnant during the course of this study, you must inform the study investigator or research team member immediately.

It is possible that other rare side effects could occur which are not described in this consent form. It is also possible that you could have a side effect that has not occurred before.

What are the possible benefits to you?

Your condition may improve, it may stay the same, or it could get worse. You may not get any benefit from being in this research study.

What are the possible benefits to other people?
It is possible that we may learn something from this research study that may help improve medical treatment for heart transplant patients

What are the alternatives to being in this research study?
Instead of being in this research study, you can choose not to participate. Current therapies include statin therapy and aspirin therapy. Please ask the study investigator if you would like more information about alternative treatments.

What will being in this research study cost you?
The sponsor, Amgen, will pay for the study drug; there will be no cost to you for the study drug. Your insurance company will be billed for standard of care procedures; You will be responsible for any applicable insurance deductibles and co-payments. If you wish to speak with a financial counselor about your insurance coverage and benefits, let the investigator or other study personnel know. A contact for personal assistance will be made available for you.

Will you be paid for being in this research study?
You will not be paid to be in this research study.

Who is paying for this research?
This research is being paid for by grant funds from Amgen. UNMC/Nebraska Medicine receives money from Amgen to conduct this study. Dr. Douglas Stoller, the Principal Investigator of this study, received money for participating on an advisory board for Amgen, Inc., the sponsor of this study.

What should you do if you are injured or have a medical problem during this research study?
Your welfare is the main concern of every member of the research team. If you are injured or have a medical problem as a direct result of being in this study, you should immediately contact one of the people listed at the end of this consent form. Emergency medical treatment for this injury or problem will be available at the Nebraska Medical Center. If there is not sufficient time, you should seek care from a local health care provider.

The sponsor, Amgen, along with UNMC/Nebraska Medicine have no plans to pay for any required treatment or provide other compensation. If you have insurance, your

insurance company may or may not pay the costs of medical treatment. If you do not have insurance, or if your insurance company refuses to pay, you will be expected to pay for the medical treatment.

Agreeing to this does not mean you have given up any of your legal rights.

How will information about you be protected?
You have rights regarding the protection and privacy of your medical information collected before and during this research. This medical information is called "protected health information" (PHI). PHI used in this study may include your medical record number, address, birth date, medical history, the results of physical exams, blood tests, x-rays as well as the results of other diagnostic medical or research procedures. Only the minimum amount of PHI will be collected for this research. Your research and medical records will be maintained in a secure manner.

Who will have access to information about you?
By signing this consent form, you are allowing the research team to have access to your PHI. The research team includes the investigators listed on this consent form and other personnel involved in this specific study at UNMC/Nebraska Medicine.

Your PHI will be used only for the purpose(s) described in the section "What is the reason for doing this research study?"

You are also allowing the research team to share your PHI, as necessary, with other people or groups listed below:

- The UNMC Institutional Review Board (IRB)
- Institutional officials designated by the UNMC IRB
- Federal law requires that your information may be shared with these groups:
    - The HHS Office for Human Research Protections (OHRP)
    - The Food and Drug Administration (FDA)
- The HIPAA Privacy Rule requires the following groups to protect your PHI:
    - Your health insurance company

You are authorizing us to use and disclose your PHI for as long as the research study is being conducted. You may cancel your authorization for further collection of PHI for use in this research at any time by contacting the principal investigator in writing. However, the PHI which is included in the research data obtained to date may still be used. If you cancel this authorization, you will no longer be able to participate in this research.

How will results of the research be made available to you during and after the study is finished?
In most cases, the results of the research can be made available to you when the study is completed, and all the results are analyzed by the investigator or the sponsor of the research. The information from this study may be published in scientific journals or presented at scientific meetings, but your identity will be kept strictly confidential.

If you want the results of the study, contact the Principal Investigator at the phone number given at the end of this form or by writing to the Principal Investigator at the following address:

Douglas Stoller, MD, PhD
982265 Nebraska Medical Center
Omaha, Nebraska
68198-2265

A description of this clinical trial will be available on www.ClinicalTrials.gov, as required by U.S. law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

What will happen if you decide not to be in this research study?
You can decide not to be in this research study. Deciding not to be in this research will not affect your medical care or your relationship with the investigator or UNMC/Nebraska Medicine. Your doctor will still take care of you and you will not lose any benefits to which you are entitled.

What will happen if you decide to stop participating once you start?
You can stop participating in this research (withdraw) at any time by contacting the Principal Investigator or any of the research staff. Deciding to withdraw will otherwise not affect your care or your relationship with the investigator or UNMC/Nebraska Medicine. You will not lose any benefits to which you are entitled.

For your safety, please talk to the research team before you stop taking any study drugs or stop other related procedures. They will advise you how to withdraw safely. If you withdraw you may be asked to undergo some additional tests. You do NOT have to agree to do these tests. You may be taken off the study if you do not follow instructions of the investigator or the research team.

You may also be taken off the study if you find out you are pregnant or become pregnant during the course of this study, or the study investigator believes it is in your best interest. Serious adverse events considered related to treatment, death, and pregnancy will all result in immediate discontinuation of the study drug. Any research data obtained to date may still be used in the research. This study may also be terminated by the investigator or by the sponsor for various reasons including if the study is stopped by a Health Authority.

Will you be given any important information during the study?
You will be informed promptly if the research team gets any new information during this research study that may affect whether you would want to continue being in the study.

What should you do if you have any questions about the study?
You have been given a copy of "*What Do I Need to Know Before Being in a Research Study?*" If you have any questions at any time about this study, you should contact the Principal Investigator or any of the study personnel listed on this consent form or any other documents that you have been given.

What are your rights as a research participant?
You have rights as a research subject. These rights have been explained in this consent form and in The Rights of Research Subjects that you have been given. If you have any questions concerning your rights, or want to discuss problems, concerns, obtain information or offer input, or make a complaint about the research, you can contact any of the following:

- The investigator or other study personnel
- Institutional Review Board (IRB)
    - Telephone: (402) 559-6463
    - Email: IRBORA@unmc.edu
    - Mail: UNMC Institutional Review Board, 987830 Nebraska Medical Center, Omaha, NE 68198-7830
- Research Subject Advocate
    - Telephone: (402) 559-6941
    - Email: unmcrsa@unmc.edu

Documentation of informed consent
You are freely making a decision whether to be in this research study. Signing this form means that:

- You have read and understood this consent form.
- You have had the consent form explained to you.

- You have been given a copy of The Rights of Research Subjects
- You have had your questions answered.
- You have decided to be in the research study.
- If you have any questions during the study, you have been directed to talk to one of the investigators listed below on this consent form.
- You will be given a signed and dated copy of this consent form to keep.

Signature of Subject _____
Date _____

My signature certifies that all the elements of informed consent described on this consent form have been explained fully to the subject. In my judgment, the subject possesses the legal capacity to give informed consent to participate in this research and is voluntarily and knowingly giving informed consent to participate.

Signature of Person obtaining consent _____
Date _____

Authorized Study Personnel
Principal
* Stoller, Douglas
phone: 402-559-1350
alt #: 402-559-5151
degree: MD, PhD

Secondary
* Burdorf, Adam (Adam)
phone: 402-559-8049
alt #: 402-888-1058
degree: DO

* Hyden, Marshall
phone: 402-559-1485
alt #: 402-888-6508
degree: MD

* Lowes, Brian
phone: 402-559-5530
alt #: 402-559-5151
degree: MD, PhD

* Lundgren, Scott
phone: 402-559-5151
alt #: 402-888-1147
degree: DO

* Zolty, Ronald
phone: 402-559-5591
alt #: 402-559-4224

degree: MD