IRB APPROVED
AS MODIFIED
Oct 30, 2018

UF Institutional Review Board
UNIVERSITY of FLORIDA

University of Florida – Jacksonville

SUBJECT INFORMATION AND CONSENT FORM

TITLE: Impact of the PCSK9 Inhibitor Evolocumab on the Pharmacodynamic Effects of Clopidogrel in Patients with Atherosclerotic Cardiovascular Disease and High or Normal On-Treatment Platelet Reactivity

PROTOCOL NO.: None
WIRB® Protocol #20170222
IIS AMG001
NCT03096288

SPONSOR: University of Florida

INVESTIGATOR: Dominick J. Angiolillo, MD, PhD
655 West 8th Street
Jacksonville, Florida 32209
United States

STUDY-RELATED PHONE NUMBER(S): Dominick J. Angiolillo, MD, PhD
904-244-3933
904-244-0411 (24 hours)

Name of person seeking your consent: _____

Place of employment & position: _____

Name of Participant ("Study Subject") _____

This consent form may contain words that you do not understand. Please ask the study doctor or the study staff to explain any words or information that you do not clearly understand.

WHAT WILL BE DONE AS PART OF YOUR NORMAL CLINICAL CARE (EVEN IF YOU DID NOT PARTICIPATE IN THIS RESEARCH STUDY)?
If you choose not to participate in this study, you will be treated and followed by your primary care team per normal standard of care.

WHY IS THIS RESEARCH STUDY BEING DONE?
You are being asked to participate in this study because you have atherosclerotic cardiovascular disease (a prior heart attack, or a stroke, mini stroke, peripheral arterial disease or a stent placed in one of the arteries of your body) and you are taking blood thinning medications including clopidogrel (commercially known as Plavix®). You must be informed so you can decide whether you want to participate.

Platelets are parts of your blood that stick together to help form a clot. The stickier your platelets are, the greater your chances of having heart attacks, strokes, or clots in your stents. Platelets from patients with vascular disease tend to stick together more, increasing the risk of having further heart attacks or stroke. To prevent these, there are antiplatelet drugs (blood thinners) to keep your platelets from sticking together. Clopidogrel (Plavix®) is the most common antiplatelet drug used in the treatment of patients with vascular disease like yours. However, the effect of clopidogrel is extremely variable and it is not uncommon that patients who are on treatment with clopidogrel have insufficient effect. However, it has been shown that cholesterol lowering medications, such as statins, are able to improve clopidogrel effects. Different types of treatments are used to lower high LDL (bad cholesterol). Statins are the most commonly prescribed treatments. Recently, a new cholesterol lowering medication, called evolocumab (Repatha®), has been approved for use by the U.S. Food and Drug Administration (FDA). Repatha is an injectable medicine that is an antibody and helps the liver to clear LDL by limiting the actions of PCSK9, a protein involved on how much LDL is in your blood. Taken together, Repatha plus a statin is proven to dramatically lower LDL. However, the effects of adding Repatha on platelets of patients already taking a statin and clopidogrel is unknown.

The purpose of this study is to evaluate the effects of Repatha injection in addition to statin therapy on the ability of clopidogrel to prevent platelets from sticking together in subjects with atherosclerotic cardiovascular disease who have reduced response (known as “poor responders”) or normal response to clopidogrel. You will not be asked to be part of the study if you have a strong response to clopidogrel as your platelets are not sticky enough to be able to observe an effect of Repatha. Subjects participating in this study will be randomized (like a flip of a coin) to receive either a single injection of either Repatha or placebo (a water injection) in addition to their therapy with a statin and clopidogrel. Afterwards you will receive your standard-of-care therapy.

The dose in which Repatha is being used in this research has been approved by the FDA, and subjects taking part in this study have a clinical indication to be on Repatha.

HOW MANY PEOPLE ARE EXPECTED TO TAKE PART IN THIS RESEARCH STUDY?
Up to 90 people are expected to take part in this study and receive either Repatha or placebo. Up to 500 people are expected to be screened.

HOW LONG WILL YOU BE IN THIS RESEARCH STUDY?
If you are eligible and agree to participate, you will be expected to take part in the research for up to 32 days.

WHO CAN PARTICIPATE IN THIS STUDY?
Your study doctor will determine if you are able to participate in this research study. Please feel free to ask the study doctor about the study requirements for participation.

WHAT WILL BE DONE ONLY BECAUSE YOU ARE IN THIS RESEARCH STUDY?
Your study doctor will fully explain the study, other possible treatments, and any known or possible side effects of participating in this study. If you consent to participate in this study, your study doctor will collect data from your medical records. You will be evaluated to see if you meet criteria to enter into the research protocol. If you are a woman of childbearing potential, a pregnancy test will be done prior to taking any study medication. If you are found to be pregnant, you will not be randomized and your participation in this study will end. If you are breastfeeding you will not be randomized and your participation in this study will end.

At the screening visit, if results from blood tests performed in the last 90 days are not available, blood will be collected for determination of complete blood count and kidney function. In any case, at the screening visit blood will be collected to evaluate the effects of clopidogrel and the levels of PCSK9, and a buccal swab will be performed to evaluate your genetic profile of response to clopidogrel. After undergoing screening, if you are shown to be a "poor responder" or normal responder to clopidogrel, you will be considered eligible to participate in the rest of the study. You will come for a total of 3 visits and a total of 1 blood draw per visit. Approximately 30 cc (or two tablespoons) of blood will be collected at each visit from you by inserting a needle directly into your vein or from a catheter in your vein. Baseline platelet function tests (while you are taking clopidogrel and statin) will be done to see how sticky your platelets are. After this, you will be randomized (chosen, like the flip of a coin) to one receive a single dose (3 injections) of either Repatha 420 mg or placebo. You will be asked to come to our clinical site after 14±2 days in the morning, 24±4 hours after the last dose of clopidogrel, to re-assess how sticky your platelets are, your cholesterol levels, and your levels of PCSK9. After 30±2 days from the day of the injections you will be asked to return to our clinical site in the morning, 24±4 hours after the last dose of clopidogrel, to perform the last blood draw (to assess how sticky your platelets are, your cholesterol levels, and your levels of PCSK9). After this blood draw, the study will be over and you will resume your standard of care therapy as instructed by your treating physician.

WHAT ARE THE POSSIBLE DISCOMFORTS AND RISKS?
Your study doctor will be responsible for reviewing and monitoring your well-being.

The following are potential risks:

i. Blood drawing. There is the discomfort of blood drawing and you may experience bruising, and/or bleeding where the needle is inserted. Occasionally some people become dizzy or feel faint.
ii. The most common side effects of Repatha are: runny nose, sore throat, symptoms of the common cold, flu or flu-like symptoms, back pain, and redness, pain, or bruising at the injection site.
iii. Repatha may cause allergic reactions that may be life-threatening and require immediate health care treatment. An allergic reaction may include a severe rash, redness, severe itching, a swollen face or trouble breathing.
iv. Loss of confidentiality.

To protect you from above concerns:

i. The blood tests will be drawn by experienced personnel.
ii. Research personnel will evaluate you and the need for treatment
iii. The data will be stored as secured coded access.

This study may include risks that are unknown at this time.

Taking part in more than one research study or project may further increase the risks to you. If you are currently enrolled or have recently taken part in another research study, you must tell the person reviewing this consent form with you.

Throughout the study, the researchers will notify you of new information that may become available and might affect your decision to remain in the study.

If you wish to discuss the information above or any discomforts you may experience, you may ask questions now or call the Principal Investigator or contact person listed on the front page of this form.

WHAT ARE THE POSSIBLE BENEFITS TO YOU?
Participation in this study will not help to improve your condition. It is also possible that your condition may worsen. There is no guarantee that you will personally benefit by participating in this research study.

HOW COULD OTHERS POSSIBLY BENEFIT FROM THIS RESEARCH STUDY?
Your participation in this study may help the investigators to learn more about the effects of administering Repatha in addition to clopidogrel and a statin, and may help other people in the future.

HOW COULD THE RESEARCHERS BENEFIT FROM THIS RESEARCH STUDY?
The sponsor is paying the University of Florida for conducting this research study. In general, presenting research results helps the career of a scientist. Therefore, the study doctor may benefit if the results of this study are presented at scientific meetings or in scientific journals.

CONFLICT OF INTEREST
Dr. Angiolillo has received consulting fees from Amgen, the maker of Repatha, in the past 12 months. Please feel free to ask any further questions you might have about this matter.

IF YOU CHOOSE TO TAKE PART IN THIS STUDY, WILL IT COST YOU ANYTHING?
The study drug will be provided at no cost to you while you are participating in this study. The Sponsor will pay for the medical services that you receive as part of your participation in this study which are described in the section of the consent form headed by the question "What Will Be Done Only Because You Are in This Research Study". This may include some medical services that you would have received if you were not in this study. All other medical services will be billed to you or your insurance company. You will be responsible for paying any deductible, co-insurance, or co-payments for those services, and for any non-covered or out-of-network services. Some insurance companies may not cover costs associated with research studies. Please contact your insurance company for additional information.

WILL YOU BE PAID FOR TAKING PART IN THIS RESEARCH STUDY?
You will be paid $15.00 in Visa debit cards for each completed study visit to help cover time and travel. It may take up to 48 hours to process your debit card. If you do not complete all of your visits you will be paid for the visits that were completed.

If you are paid more than $75 for taking part in this study, your name and social security number will be reported to the appropriate University employees for purposes of making and recording the payment as required by law. You are responsible for paying income taxes on any payments provided by the study. If the payments total $600 or more or you are a nonresident alien, payment will be processed through the University of Florida Accounts Payable department and the University must report the amount you received to the Internal Revenue Service (IRS). The IRS is not provided with the study name or its purpose. If you have questions about the collection and use of your Social Security Number, please visit: http://privacy.ufl.edu/SSNPrivacy.html.

Your payment for participation in this research study is handled through the University of Florida's Human Subject Payment (HSP) Program. Your information which will include your name, address, date of birth, and SSN (depending on amount of money you are paid) is protected. Access to the (HSP) Program site is limited to certain staff with the assigned security role. You will be randomly assigned a specific identification (ID) number to protect your identity.

The study team will provide you with an informational form called the Prepaid Card Facts document. If you have any problems regarding your payment call the HSP Office at: (352) 392-9057.

WHAT IF YOU ARE INJURED BECAUSE OF THE RESEARCH STUDY?
If you are injured as a direct result of your participation in this study, only professional medical care that you receive at the University of Florida Health Science Center will be provided without charge. Hospital expenses will be billed to you or your insurance. You will be responsible for any deductible, co-insurance, or co-payments. Some insurance companies may not cover costs associated with research studies. Please contact your insurance company for additional information.

No additional compensation is routinely offered.

The Principal Investigator and others involved in this study may be University of Florida employees. As employees of the University, they are protected under state law, which limits financial recovery for negligence.

Please contact Dominick Angiolillo, MD, PhD at 904-244-0411 if you experience an injury or have questions about any discomforts that you experience while participating in this study.

WHAT OTHER CHOICES DO YOU HAVE IF YOU DO NOT WANT TO BE IN THIS RESEARCH STUDY?
If you choose not to participate in this study, you will still continue receiving your medical care just as you normally do.

DO YOU HAVE TO BE IN THIS STUDY?
Your participation in this study is voluntary. You may decide not to participate or you may leave the study at any time. Your decision will not result in any penalty or loss of benefits to which you are entitled.

If you leave this study for any reason, please contact Dominick J. Angiolillo, M.D., Ph.D. at 904-244-3933 or 904-244-0411 (24 hours). They will tell you how to stop your participation safely.

CAN YOU BE WITHDRAWN FROM THIS RESEARCH STUDY?
The FDA, your study doctor, your local institution, has the right to stop your participation in the study, or cancel the study, without your consent at any time. Your study doctor may take you off the study at any time for any of the following reasons:

- if he/she decides it is in your best interest.
- if you do not consent to continue in the study after being told of changes in the research that may affect you;
- or for any reason.

AUTHORIZATION TO USE AND DISCLOSE INFORMATION FOR RESEARCH PURPOSES
If you agree to participate in this study, the study doctor will create, collect, and use private information about you and your health. This information is called protected health information or PHI. In order to do this, the study doctor needs your authorization. The following section describes what PHI will be collected, used and shared, how it will be collected, used, and shared, who will collect, use or share it, who will have access to it, how it will be secured, and what your rights are to revoke this authorization.

Your protected health information may be collected, used, and shared with others to determine if you can participate in the study, and then as part of your participation in the study. This information can be gathered from you or your past, current or future health records, from procedures such as physical examinations, x-rays, blood or urine tests or from other procedures or tests. This information will be created by receiving study treatments or participating in study procedures, or from your study visits and telephone calls. More specifically, the following information may be collected, used, and shared with others:

- Complete past medical history to determine eligibility criteria
- Records of physical exams
- Laboratory, x-ray, MRI, and other test results
- Records about study medications or drugs

This information will be stored in locked filing cabinets or in computers with security passwords.

Some of the information collected could be included in a "limited data set" to be used for other research purposes. If so, the limited data set will include only information that does not directly identify you. For example, the limited data set cannot include your name, address, telephone number, social security number, or any other photographs, numbers, codes, or so forth that link you to the information in the limited data set. If limited data sets are created and used, agreements between the parties creating and receiving the limited data set are required in order to protect your identity and confidentiality and privacy.

Your PHI may be collected, used, and shared with others to make sure you can participate in the research, throughout your participation in the research, and to evaluate the results of the research study. More specifically, your PHI may be collected, used, and shared with others for the following study-related purpose(s):

- to determine the effectiveness of the study drug in treating patients with atherosclerotic cardiovascular disease
- to evaluate a possible new use for the study drug
- to determine the causes or effects of the study condition: atherosclerotic cardiovascular disease

Once this information is collected, it becomes part of the research record for this study.

Only certain people have the legal right to collect, use and share your research records, and they will protect the privacy and security of these records to the extent the law allows. These people include:

- the study doctor, and research staff associated with this project
- other professionals at the University of Florida or Shands Hospital that provide study-related treatment or procedures
- The University of Florida Institutional Review Board

Your PHI may be shared with:

- The study sponsor Dominick J. Angiolillo, MD, PhD and Amgen.
- United States and foreign governmental agencies who are responsible for overseeing research, such as the Food and Drug Administration, the Department of Health and Human Services, and the Office of Human Research Protections
- Government agencies who are responsible for overseeing public health concerns such as the Centers for Disease Control and federal, state and local health departments
- Western Institutional Review Board
- Your insurance company for purposes of obtaining payment

Every attempt will be made to protect your right to privacy within legal limits. However, records associated with your participation in the study, including medical histories (case histories) which may identify you, and this informed consent signed by you, will be made available for inspection by the Western Institutional Review Board® (WIRB®), Amgen or designee (including any persons or companies which are contracted by Amgen to have access to the research information during and after the study, such as the monitor(s) and auditor(s)), the US Food and Drug Administration (FDA), and state and other local authorities. Because of the need to release information to these parties, absolute confidentiality cannot be guaranteed. In addition, the results of treatment and laboratory data may be published for scientific purposes, but your identity will not be disclosed. By signing a written informed consent form, you are authorizing such access.

Otherwise, your research records will not be released without your permission unless required by law or a court order. It is possible that once this information is shared with authorized persons, it could be shared by the persons or agencies who receive it and it would no longer be protected by the federal medical privacy law.

Your PHI will be used and shared with others until the end of study.

This information will be destroyed 2 years after research is conducted or longer per University of Florida and/or FDA requirements.

You may not be allowed to see or copy certain information in your medical records collected in connection with your participation with this study while the research is in progress if the research includes treatment. When the research study is completed you will have access to inspect or copy your records with certain exceptions under applicable law.

You are not required to sign this consent and authorization or allow researchers to collect, use and share your PHI. Your refusal to sign will not affect your treatment, payment, enrollment, or eligibility for any benefits outside this research study. However, you cannot participate in this research unless you allow the collection, use and sharing of your protected health information by signing this consent and authorization.

You have the right to review and copy your protected health information. However, we can make this available only after the study is finished.

You can revoke your authorization at any time before, during, or after your participation in this study. If you revoke it, no new information will be collected about you. However, information that was already collected may still be used and shared with others if the researchers have relied on it to complete the research. You can revoke your authorization by giving a written request with your signature on it to the study doctor.

Your withdrawal must be made in writing and sent to Dominick J. Angiolillo, M.D. Ph.D., 655 West 8th Street, Jacksonville, Florida 32209.

NEW INFORMATION ON THE STUDY DRUG
You will be informed about any new information, such as adverse reactions (side effects) that could affect your decision to continue in this study. You may be asked to sign a new consent form if that should occur.

WHAT IF I BECOME PREGNANT DURING THE STUDY?
If you are pregnant or nursing before you enroll in the study, you may not participate in the study.

WHERE CAN I FIND INFORMATION ABOUT THE STUDY?
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.

WHO WOULD YOU CALL IF YOU HAVE ANY QUESTIONS?
If you have questions about the study, please ask us before signing this form. If you require further general information regarding the research study, if at any time you feel you have had a research-related injury or reaction to the study drug, or if you have questions, concerns or complaints about the research please contact:

Dominick J. Angiolillo, M.D., Ph.D. at 904-244-3933 or 904-244-0411 (24 hours).

If you have questions about your rights as a research subject or if you have questions, concerns or complaints about the research, you may contact:

Western Institutional Review Board® (WIRB®)
1019 39th Avenue SE Suite 120
Puyallup, Washington 98374-2115
Telephone: 1-800-562-4789 or 360-252-2500
E-mail: Help@wirb.com

Or

The University of Florida in Jacksonville at (904) 244-9478.

WIRB is a group of people who perform independent review of research.

WIRB will not be able to answer some study-specific questions, such as questions about appointment times. However, you may contact WIRB if the research staff cannot be reached or if you wish to talk to someone other than the research staff.

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CONSENT TO PARTICIPATE IN THIS RESEARCH STUDY.
I have been informed about this study's purpose, procedures, possible benefits and risks. I have also been told alternatives to being in the study and how my protected health information will be collected, used, and shared with others. I have been given the opportunity to ask questions. My questions have all been answered satisfactorily. I agree to be in this research study. I have received a copy of this form.

By signing this consent form, I have not given up any of my legal rights.

I authorize the release of my medical records for research or regulatory purposes to those agencies listed under the Authorization section of this consent form.

Name of Participant (Print) Date

Signature of Participant

As an investigator or the investigator's representative, I have explained to the participant the purpose, the procedures, the possible benefits, and the risks of this research study, the alternative to being in the study; and how the subject's protected health information will be collected, used, and shared with others:

Printed Name of Person Conducting Informed Consent Discussion Position

Signature of Person Conducting Informed Consent Discussion Date