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Official Title: Effects of Evolocumab on Platelet Reactivity in Patients With Diabetes Mellitus (ISS-DMII)

Brief Title: The HI-REACT-SIRIO study

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Health Insurance Portability and Accountability Act (HIPAA) Authorization to Use/ Disclose Protected Health Information for Research

This form will explain how health information about you will be used, protected, and disclosed (shared). In addition, you will receive a summary of Inova Health System's "Notice of Privacy Practices". If the study requires you to have follow-up visits in the investigators' private practice office, you should ask for a copy of his/her "Notice of Privacy Practices" at the time of your visit. If you agree to participate in the research, and allow the use and disclosure of your medical information for research purposes, please sign this form. If you choose not to allow the use and disclosure of your health information you may not participate in the research study.

What protected health information about me will be used or disclosed as part of this research?
You will be asked about your health information that is related to the study. In addition, your non-research medical records will be reviewed and researchers may need to discuss your health information with your treating doctor(s), if applicable. Researchers will also collect new information about you as a result of the research tests, procedures, visits and/or questionnaires/interviews. This collected information constitutes and is called your "Research Record".

The following health information will be obtained from my medical record:

- Your medical history including any medications you have been taking;
- Specific tests and/or procedures and treatments you have had;
- Personal information such as, your name, address, telephone number, and date of birth will be collected and placed in your research record.

The following new information will be obtained about me as a result of the research:

- Records about your lipid profile, platelet function, and biomarker testing;
- Records about the study drug you received
- Information on any side effects you may experience during your participation in the study and how these side effects have been treated;
- Follow-up information about your health status collected in this study.

Who will be allowed to use or share my protected health information?
If you agree to participate in the study, you allow the investigators and research study staff to use and share your protected health information contained in your Research Record. In addition, Inova offices that manage research oversight, billing or quality assurance will be able to use and release your protected health information.

To whom will the protected health information be shared?
Your protected health information will be shared with the following:

- The sponsor of the study Amgen, Inc. or others that are assisting the sponsor to collect data at Inova Heart and Vascular Institute.

Your information <u>may</u> be given to:

- Inova Institutional Review Board, the hospital committee that oversees the research.
- Federal and state agencies that have authority over the study, Inova Health System, or patients. Government agencies may include the U.S. Food and Drug Administration (FDA), and the U.S. Department of Health and Human Services (DHHS).

- To your health insurer or payer, if necessary, in order to secure their payment for any covered treatment not paid for through the research.

All reasonable efforts will be used to protect the privacy of your protected health information. Once your health information is shared with the sponsor, federal agencies and others as described above, they may share your information without your permission.

Why is it necessary to share my protected health information with others?
The reason is to conduct the research as described in the consent form for the research study.

How long does my authorization remain in effect?
This authorization expires when the study is complete, or if you take it back.

How can I take back my authorization?
You may take back your authorization at any time by sending a written request to Dr. Paul Gurbel at Inova Heart and Vascular Institute, 3300 Gallows Road, Falls church, VA, 22042. If you take back your authorization, your participation in the study will end and no further private health information will be collected. The research study staff may keep or share information obtained before you took back your authorization in order to preserve the scientific reliability of the study.

If you choose not to authorize the use and release of your information or withdraw from the study, you will continue to have access to medical care at Inova Heart and Vascular Institute.

Will I have access to the information in my Research Record?
While the study is in progress, your access to your Research Record will be temporarily limited to ensure proper evaluation of the research study results. You will continue to have access to your non-research medical record during the study. You will be able to see your Research Record when the research is completed. You have the right to see and copy the medical information that is collected from you during the study and kept by the Inova Health System. You will have that right for so long as that information is maintained by the research staff and the other entities that are subject to federal privacy regulations. This does not include information about the study itself, such as study documents which may otherwise be confidential, and do not relate to an individual subject.

I have been told that I will be given a signed copy of this authorization form.

_____ _____
Signature of Research Participant Date

_____ _____
Witness Signature Date

RESEARCH CONSENT
Date Approved: June 19, 2019
Inova IRB: Joanne Muratori, IRB Coordinator
IRB File # 17-2639

Informed Consent for a Research Study

Study Title: Effects of Evolocumab on Platelet Reactivity in Patients with Diabetes Mellitus after Elective Percutaneous Coronary Intervention: The HI-REACT-SIRIO study

Funding Source: Amgen, Inc.

Principal Investigator: Paul A. Gurbel, M.D.

Sub-Investigators: Alexander Truesdell, MD; Behnam Tehrani, MD; Hamid Taheri, MD; Kelly Epps, MD; Marjaneh Akbari, MD; Nadim Geloo, MD; Matthew Sherwood, MD; Shahram Yazdani, MD

Site of Investigation: Inova Fairfax Hospital, Falls Church, VA

Study Related Contact Information: (703) 776-3330 (During Office Hours)
(410) 202-0960 (After Office Hours, ask to have Dr. Gurbel or the doctor covering for Dr. Gurbel paged)

Introduction

You may be eligible to take part in a research study because you have diabetes, heart disease, and you will be undergoing a procedure, called percutaneous coronary intervention (PCI). This research consent form gives you important information about the study. It explains why this research study is being done, what is involved in participating in the research study, the possible risk and benefits of participation, choices for participation and your rights as a research participant.

Please take your time to review this information carefully. You may also wish to talk to others (for example, your family, friends, or other doctors) about your participation. The decision to participate is yours. You may leave the study at any time without losing any benefits you would have normally received. If you decide to take part in the study, you will be asked to sign and date at the end of this form. We will give you a copy of the form so that you can refer to it while you are involved in this research study. We encourage you to ask questions now and at any time in the future.

You should know that Inova Heart and Vascular Institute and Dr. Paul Gurbel as the principal investigator are being paid by Amgen Inc. to conduct this research study.

What if I am already participating in another study?

Are you already participating in any other research studies? Yes ☐ No ☐
If yes, please state which study (ies) _____

While participating in this study, you may not take part in any other research study without approval from the principal investigator.

Why is this study being done?
Over time, diabetes can lead to serious long-term health complications. When you have diabetes, your body does not produce enough insulin or cannot use it properly; therefore, cannot control its blood sugar level. High blood sugar can damage and speed up the hardening of the arteries (blood vessels), called atherosclerosis. Atherosclerosis is a disease, in which plaque builds up inside the arteries that carry oxygen-rich blood to the heart and other parts of the body. Atherosclerosis can lead to a heart attack, stroke or peripheral artery disease.

Plaque is made up of fat, cholesterol, and other substances in the blood. When plaque builds up, it narrows the coronary arteries and reduces blood flow to the heart, which may cause chest pain, shortness of breath, or other heart problems. If plaque breaks or ruptures, it causes injury to the inside wall of the affected artery. As a response to the injury, platelets (blood cell fragments that help blood clotting) become sticky and clump at the site to form a blood clot within the artery causing a blockage. A complete blockage can cause a heart attack.

In addition people with diabetes are more likely to have certain risk factors that increase the chances of having heart disease or stroke, such as high cholesterol. There are two types of cholesterol: LDL (low-density lipoprotein), known as the "bad' cholesterol and HDL (high-density lipoprotein), known as the "good" cholesterol. Having high levels of LDL stimulates plaque buildup in the arteries, causes platelets to become sticky, and thus increases the risk of heart attack and stroke. Cholesterol and triglycerides (another type of fat in the blood) are important to our life, however in excess they may do harm to our body.

Evolocumab (Repatha®) is an injectable medication developed by Amgen Inc., a for-profit biopharmaceutical company to help lower the LDL cholesterol in the blood. Evolocumab is approved by the U.S. Food and Drug Administration for use in addition to diet and optimal statin therapy in people with atherosclerotic disease. In clinical trials, evolocumab has shown to dramatically lower the levels of "bad" cholesterol and, in the same time, to reduce the occurrences of cardiovascular events such as, heart attack, stroke, hospitalization for worsening chest pain, coronary angioplasty, or bypass surgery. We have reason to believe that evolocumab will favorably affect platelet function (making platelets less sticky) in patient with diabetes and, therefore, lower the risks of cardiovascular events.

This research is being done to evaluate the effects of evolocumab on platelet function and biomarkers (substances in the blood that can indicate the presence of certain diseases) in patients with diabetes undergoing a PCI procedure.

How many people will take part in this study?
Approximately 150 people, 18 years of age or older will be enrolled at Inova Heart and Vascular Institute.

What other choices do I have if I do not take part in this study?
If you decide not to take part in this study, you have other choices. For example:

- You may choose to have the usual standard therapy for your condition as prescribed by your doctor.
- You may choose to take part in a different study, if one is available.

- You could decide not to be treated.

This study is designed for research purposes only and is not intended to treat a medical condition.

How long will I be in this study?
If you decide to participate, you will be in this study for about 30 days.

What will happen if I take part in this research study?
Most of the exams, tests and procedures you will have during your participation in the study are part of the usual approach for your coronary artery disease and may be done even if you do not join the study. However, there are some extra exams, tests or procedures that you will need to have if you take part in the study.

If you qualify to participate and agree to take part, you will be asked to sign this consent form before any study related tests and procedures are performed.

If you agree to take part in the study, you will be "randomized" to receive either evolocumab or placebo (a substance that has no therapeutic effect). Randomization means that you will be assigned to receive either evolocumab or placebo by chance, like flipping a coin. Neither you, nor your doctor will choose what you will receive. You will have an equal chance to receive the study drug or matching placebo.

This is a double-blinded study, which means that neither you nor the study doctor will know which study group you have been assigned to. However, in a medical emergency, the study doctor will be able to find out your group.

<u>The effect of evolocumab/placebo on platelet function and biomarkers will be measured at 3 time points during the study:</u>

- Before PCI procedure to determine your 'usual clotting level' prior to drug administration;
- At 16-24 hours after administration of evolocumab/placebo; and
- At 30 days (+/- 5 days) after administration of evolocumab/placebo.

For the purpose of this study, evolocumab and placebo are called "study drug".

<u>Visit 1 - Prior to PCI procedure:</u>

- Provide informed consent and demographic information (sex, date of birth, race, ethnicity);
- Provide your complete medical and surgical history (including any allergies, tobacco use, contraceptive method/s use);
- Provide your current medications (including vitamins, over-the-counter drugs and herbal supplements);
- Have a physical exam and your vital signs checked (blood pressure and heart rate)
- Have your height and weight measured;
- If you are a woman of childbearing potential, provide urine specimen for pregnancy test;

- Provide blood samples (approximately 5 teaspoons) for:
  - safety laboratory tests;
  - platelet function and biomarker testing;
  - lipid profile (cholesterol and triglycerides).

Visit 2 - During and After your PCI procedure

Your doctor will use the current standard of care guidelines, your medical condition, and the local practices at the Inova Heart and Vascular Institute to perform your PCI procedure. You have already received information about the procedure including the possible risks and benefits, and have provided consent separately with your study doctor as part of your routine medical care. As part of the study you will:

- Be randomized to receive either 420 mg of evolocumab or placebo;
- Receive either 420 mg of evolocumab or placebo subcutaneously. You will receive the study drug/placebo as three separate subcutaneous injections, given consecutively within 30 minutes.

After your PCI procedure, while you are still in the hospital, about 16-24 hours after the administration of the study drug, you will be required to:

- Report if you have any changes in you medical history and medications you are taking;
- Report if you have experienced any side (bad) effects since your last study visit;
- Have your vital signs checked (blood pressure and heart rate);
- Provide blood sample (about 4 teaspoons) platelet function, biomarkers, and lipid profile.

Visit 3/End of Study - 30 Days (+/-5days) after your study drug administration

You will be asked to come to the study center 30 days of the study drug administration. You will be required to:

- Report if you have any changes in you medical history and medications you are taking;
- Report if you have experienced any side (bad) effects since your last study visit;
- Have your vital signs checked (blood pressure and heart rate);
- Provide blood sample (about 5 teaspoons) for:
  - safety laboratory tests;
  - platelet function and biomarker testing;
  - lipid profile (cholesterol and triglycerides).

What side effects or risks can I expect from taking part in this study?

If you choose to take part in this study, there is a risk that you may:

- Lose time at work or home and spend more time in the hospital or doctor's office than usual
- Be asked sensitive or private questions which you normally do not discuss
- The most important non-medical risk is the disclosure of your protected health information (PHI). PHI is any health information that is collected about you, including your history and new information collected during this study. You will have an opportunity to review the ways in which your PHI may be used and disclosed in the HIPAA Authorization for Research form may also have access to these records.

There is also a risk that you could have side effects. Here are important points about side effects:

- The study doctors do not know who will or will not have side effects.
- Some side effects may go away soon, some may last a long time, or some may never go away.
- Some side effects may interfere with your ability to have children.
- Some side effects may be serious and may even result in death.

Here are important points about how you and the study doctor can make side effects less of a problem:

- Tell the study doctor if you notice or feel anything different so they can see if you are having a side effect.
- The study doctor may be able to treat some side effects.

The table below shows the most common and the most serious side effects that researchers know about. There might be other side effects that researchers do not yet know about. If important new side effects are found, the study doctor will discuss these with you.

Risks and side effects related to administering evolocumab include those which are:

COMMON, SOME MAY BE SERIOUS In 100 people receiving evolocumab, between 1 and 10 may have:
• Runny nose (nasopharyngitis) • Nose and throat infection (upper respiratory tract infection) • Back pain • Feeling sick to the stomach (nausea) • Flu (influenza) • Joint pain (arthralgia) • Injection site reactions (redness, pain, and bruising) • Rash

UNCOMMON, SOME MAY BE SERIOUS In 1000 people receiving evolocumab, between 1 and 10 may have:
• Hives (urticaria)

Other potential side effects with evolocumab:

- Low Levels of Cholesterol
  It is possible that evolocumab could decrease your cholesterol to very low levels in your blood. In clinical studies with evolocumab there was no difference in side effects in patients who achieved very low cholesterol compared with those patients who did not. The long-term effects of very low levels of cholesterol are unknown.
- Allergic Reactions
  Allergic reactions to evolocumab have been reported, including rash and hives. In addition, you may experience other symptoms of an allergic reaction including headache,

itching, flushing, swelling, shortness of breath, nausea and sometimes vomiting. Severe allergic reactions can cause dizziness, severe skin reactions, difficulty breathing or swallowing, a decrease in blood pressure, and could be life threatening.

- Antibodies
  After you start taking evolocumab, it is possible that your body may make antibodies (proteins that may stop evolocumab from working or cause side effects). In clinical studies with evolocumab to date, no patients have made antibodies that caused evolocumab not to work or that caused side effects.

Evolocumab may cause all, some, or none of the side effects listed above. These side effects can be mild but could also be serious and life-threatening.

You should talk to your study doctor about any side effects that you have while taking part in the study.

Are there reproductive risks while on this study?
You should not get pregnant, breastfeed, or father a baby while on this study because we cannot predict the effects on an unborn baby.

A pregnancy test will be performed on all women who may be pregnant before taking part in this study. This includes all women except those whose menstrual periods have not occurred for more than one year after menopause (change of life) or those who have had sterilization surgery (tubes tied) or a hysterectomy (removal of the uterus or womb). Pregnant women may not take part in this research study.

If you decide to take part in this study, you must agree to protect yourself or your partner from becoming pregnant. You must protect yourself or your partner before, during the study and for 15 weeks after the last dose of the study drug. If you or your partner becomes pregnant when either parent is taking the drug, birth defects may occur. If you are a female and think that you might be pregnant, you must immediately tell your study doctor. It may be harmful for a child to breastfeed from a woman taking a study drug. Because of this, female participants must not breastfeed during the study and for 15 weeks after the study ends.

If you become pregnant while taking study drug, you will agree to release your health records while pregnant. You will also agree to release your child's health records for the first year of his/her life.

Acceptable methods of contraception (birth control) while taking part in this study are:

1. Total Abstinence (no sexual intercourse), absence of menstrual periods in women for more than one year after menopause (change of life), sterilization surgery, including tubal ligation (tubes tied) or hysterectomy (removal of the uterus or womb) in women or a vasectomy in men.
2. Oral contraceptives (birth control pills), intrauterine device (IUD), implantable or injectable contraceptives (Norplant or Depo-Provera), contraceptive patch, vaginal ring or use of condom with spermicide. These methods must be used exactly as directed.

The following methods of contraception are <u>not</u> acceptable to prevent pregnancy during study participation: diaphragm, cervical cap, vaginal sponge, and "female condom".

Are there benefits to taking part in this study?
Taking part in this study may or may not make your health better. We hope the information learned from this study will benefit others in the future.

Can I stop being in the study?
Yes. You can choose not to be in the study. You can decide to stop at any time. It is important to tell the study doctor if you are thinking about stopping a study drug or leaving the study so any risks from the evolocumab can be evaluated by your doctor. You may want to discuss what follow-up care and testing could be most helpful for you.

Your participation can also be stopped without your approval by any of the following:
- the study doctor;
- the Institutional Review Board (IRB – hospital committee that reviews and approves research).

The study doctor may decide to take you off this study for any of the following reasons:
- If your health changes and the study is no longer in your best interest
- If new information becomes available
- If you do not follow the study rules
- If the study is stopped by the sponsor

What are the costs of taking part in this study?
You will not be responsible for the cost of the following procedures and tests that are a part of the study:
- Lipid profile, platelet and function and biomarkers testing;
- The study drug will be provided to you for free.

You and/or your health plan/ insurance company will need to pay for some or all of the costs of treating coronary artery disease in this study. Check with your health plan or insurance company to find out the total costs to you for treatment while on this study. You may be responsible for any co-payments and deductibles that are standard for your insurance charges

Will I be paid for taking part in this study?
You will be compensated for your time in the study. You may receive a total of $120 for your participation (Visit 1 - $40, Visit 2 - $40, and Visit 3 - $40). If you do not finish the study, you will be paid only for the visits you have completed.

What if I am injured because I took part in this study?
In the event that you believe you have been injured because of taking part in this study, it is important that you call your study doctor. You can call Dr. Paul Gurbel, the principal investigator, at (703) 776-3330 during business hours or (410) 202-0960 after business hours, and he will review the matter with you. Inova Health System and the study doctor do not provide funds or free medical treatment for injuries that result from taking part in this study. Medical treatment is available to you if you are injured as a result of taking part in this study.

You and/or your health plan will be billed for the cost of this care. If your insurance does not pay for your care, or pays only a portion of the cost of such care, you may be billed for any unpaid amounts.

You should not expect anyone to pay you for pain, worry, lost income, or non-medical care costs that occur from taking part in this research study. No funds have been set aside, by Inova Health System and Inova Heart and Vascular Institute to repay you in case of injury.

You are not waiving any legal claims or rights because of your participation in this study.

Will my medical information be kept private?
We will keep your records private to the amount allowed by law. Research records are stored and kept according to legal requirements. You will not be identified in any reports or publications about this study. However, certain people and groups will have access to your research and medical records. The sponsor of the study will look at your research and medical records. The Inova Health System Institutional Review Board (IRB) and federal and state agencies that have authority over the study may look at your research records. Members of the study staff will also have access to your research records. Additional groups, explained in the HIPAA Authorization for Research form may also have access to these records.

You will be assigned a unique study number by which you will be identified for the study.

What are my rights if I take part in this study?
Taking part in this study is your choice. No matter what decision you make, and even if your decision changes, there will be no penalty to you. You will not lose medical care or any legal rights. A member of your research team will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

If you would like more information about your rights as a participant in a research study, contact: Inova Health System Institutional Review Board (IRB) at (571) 472-3458. The Inova Health System IRB may contact you by mail or telephone to find out if you were satisfied with your study participation.

Who can answer my questions about the study?
You can talk to your study doctor about any questions or concerns you have about this study. Contact your study doctor, Dr. Paul Gurbel, at (703) 776-3330 during business hours or (410) 202-0960 after business hours.

Where can I get more information?
A description of this clinical trial will be available on 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.

SIGNATURE

I have read (or someone has read to me) this form and I am aware that I am being asked to participate in a research study. I have had the opportunity to ask questions and have had the questions answered to my satisfaction. I voluntarily agree to participate in this study.

I am not giving up any legal rights by signing this form. I will be given a copy of this form**.**

_____ _____
Signature of Subject Printed Name of Subject

_____
Date

Investigator/Research Staff

I have explained the purpose, the procedures, the benefits and risks that are involved in this research study before requesting the signature(s) above. Any questions that have been raised have been answered to the individual's satisfaction. A copy of this form has been given to the participant or his/her representative.

_____ _____
Signature of Person Obtaining Consent Printed Name of Person Obtaining Consent

_____
Date

The following witness lines may be left blank, unless an impartial witness is required.

An impartial witness, **who is a witness to the informed consent process that is not involved in the conduct of the research**, is required when utilizing a legally authorized representative or when an oral interpreter and short form is used.

_____ _____
Signature of Impartial Witness Printed Name of Impartial Witness

_____
Date