The Effects of Evolocumab on Endothelial and Inflammatory Biocellular Markers in Patients With Diabetes and Atherosclerotic Vascular Disease (METCHNIKOFF)
PI: Robert Rosenson, MD
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## TITLE OF RESEARCH STUDY:

**Title: THE EFFECTS OF EVOLOCUMAB ON ENDOTHELIAL AND INFLAMMATORY BIOCELLULAR MARKERS IN PATIENTS WITH MYOCARDIAL MICROVASCULAR DYSFUNCTION**

## PRINCIPAL INVESTIGATOR (HEAD RESEARCHER) NAME AND CONTACT INFORMATION:

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## WHAT IS A RESEARCH STUDY?

A research study is when scientists try to answer a question about something that we don't know enough about. Participating may not help you or others.

People volunteer to be in a research study. The decision about whether or not to take part is totally up to you. You can also agree to take part now and later change your mind. Whatever you decide is okay. It will not affect your ability to get medical care within the Mount Sinai Health System.

Someone will explain this research study to you. Feel free to ask all the questions you want before you decide. Any new information that develops during this research study that might make you change your mind about participating will be given to you promptly.

Basic information about this study will appear on the website http://www.ClinicalTrials.gov. There are a few reasons for this: the National Institutes of Health (NIH) encourages all researchers to post their research; some medical journals only accept articles if the research was posted on the website; and, for research studies the U.S. Food and Drug Administration (FDA) calls "applicable clinical trials" 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.

## PURPOSE OF THIS RESEARCH STUDY:

The purpose of this study is to better understand how blocking one specific protein (proprotein convertase subtilisin kinexin 9 or PCSK9) lowers the risk of heart attack and stroke. In three large trials of patients with cardiovascular disease, it has been shown that blocking the effect of PCSK9 lowered the “bad cholesterol” or LDL cholesterol, and lowered the risk of heart attack and stroke. Heart attacks and strokes occur when there is interruption of blood flow to the arteries that supply the heart or brain. Most often, the blood flow is interrupted when there is cholesterol buildup in an inflamed artery. Further research is needed to determine whether blocking PCSK9 has an effect on inflammation.

Inflammation in the arteries is caused when a certain type of white blood cell, the mononuclear cell, moves from the blood stream into the artery. The movement of white cells is controlled by messages sent from the white blood cells to the artery wall. One of the most established pathways that direct this movement are the Toll like receptors. In this study, we will examine how these Toll like receptor pathways are changed in people given a Food and Drug Administration approved inhibitor of PCSK9.

This study involves treatment of one group with evolocumab (Repatha) and one group with a matching placebo for 4 months. This study has been supported by Amgen, the manufacturer of Repatha, through a research grant to the Icahn School of Medicine at Mount Sinai.

## LENGTH OF TIME AND NUMBER OF PEOPLE EXPECTED TO PARTICIPATE

Your participation in this research study is expected to last about 16 weeks from the day you are enrolled in the study.

The number of people expected to take part in this research study at Icahn School of Medicine at Mount Sinai is 100.

During your participation, if the primary investigator (head researcher) decides to withdraw you from the research study because you experienced an event (such as major bleeding) and the event continues, the primary investigator and research study team will follow-up with you at least until the cause of the event is determined. The length of this planned follow-up will be determined based on the type of event and other factors as determined by the primary investigator. The primary investigator will discuss the details, appropriate length of follow-up, and answer any questions that you may have to ensure your safety and understanding.

## DESCRIPTION OF WHAT'S INVOLVED:

If you agree to participate in this research study, the following information describes what may be involved.

You need come to our site (the address mentioned above), sign this informed consent form.

After you sign the informed consent and pass the initial screening (first visit), the data such as your age, gender, medical history and medication use will be recorded. A physical exam, ECG, blood pressure measurement, and vital signs will be done. Additionally, blood samples will be collected for laboratory tests. Once we received the results of all the tests from the screening visit, we will decide your eligibility according to the inclusion and exclusion criteria and inform you by phone. The first visit will take about 2 hours, the remaining visits will take about one to one and half hour. Here is the detail information of the study visits:

**Visit 1: Screening**

- Written informed consent
- Demographics
- Medical history
- Vital signs, including heart rate, sitting and standing blood pressure using standardized techniques
- 12-lead ECG – the electrocardiogram will only be done at visit 1. The ECG is a test that checks for problems with the electrical activity of your heart

- Physical exam – will be a general examination of the major organ systems of your body

- Blood samples for the laboratory tests – about one tablespoon [20 ml] of blood will be drawn from your vein for testing complete blood count (CBC), TSH, chemistry, fasting lipid profile, and a comprehensive metabolic panel (the tests to make sure that you will be safe and eligible to participate in this clinical trial), urine sample will be collected for urinalysis and pregnancy test (if female of child bearing potential). Blood samples that are collected will be stored in tubes with a unique barcode that will not directly identify you. Some of the blood samples will be analyzed at Mount Sinai while other samples will be analyzed at an outside laboratory. Also, some of your blood samples will be stored in -70°C freezer for future analysis and genetic testing. The outside laboratory will not have access to any of your personal information, just the unique barcode on tube in which your blood was collected. All laboratories will deliver your results using a unique ID number to Dr. Robert S. Rosenson and his research study team in a secure and private manner.

- Review for adverse events (AEs)/serious adverse events (SAEs)

- Concomitant therapy (any therapy during the period you participating this trial)

- Dietary instruction; medication compliance reminder

- Body height, waist circumference

- Body weight

- Seattle Angina Questionnaire

- Screening placebo injection and 30 minute post-injections observation

**Visit 2 (Randomization) 7-28 days after Screening**

- Review for AEs/SAEs/cardiovascular (CV) events

- Vital signs

- Concomitant therapy



- Dietary instruction; medication compliance reminder

- Randomization

- Seattle Angina Questionnaire

- Laboratory assessments: about one tablespoon [20 ml] of blood will be drawn from your vein for testing of your blood in order to make sure again that you are safe to participate in this trial and to get the baseline of the test before you have the treatment of the study medication, including fibrinogen, whole blood viscosity analysis, lipoprotein subclass analysis, lipoprotein (a), biocellular marker analysis.

- DNA/mRNA test for lipoprotein and inflammatory polymorphisms that may influence the response to therapy.

- Investigational product (IP, study medication) administration subcutaneously (SC), every month (QM) (in-clinic) and 30 minute post-injections observation

**Visit 3 (Week 2) ±4 days**

- Review for AEs/SAEs/CV events

- Concomitant therapy

- Vital signs

- Dietary instruction; medication compliance reminder

- Seattle Angina Questionnaire

- Laboratory assessments: about one tablespoon [20 ml] of blood will be drawn from your vein for testing hematology, blood chemistry, Liver Function Tests (LFTs), fibrinogen, whole blood viscosity analysis, lipoprotein subclass analysis, lipoprotein (a), biocellular marker analysis.

**Visit 4 (Week 4) ±7 days**

- Review for AEs/SAEs/CV events



- Concomitant therapy
- Vital signs
- Dietary instruction; medication compliance reminder
- Seattle Angina Questionnaire
- SC IP administration, QM (in-clinic) and 30 minute post-injections observation

**Visit 5 (Week 8) ±7 days**

- Review for AEs/SAEs/CV events
- Concomitant therapy
- Vital signs
- Dietary instruction; medication compliance reminder
- Seattle Angina Questionnaire
- SC IP administration, QM (in-clinic) and 30 minute post-injections observation

**Visit 6 (Week 12) ±7 days**

- Body height, waist circumference
- Body weight
- Vital signs
- Review for AEs/SAEs/CV events
- Concomitant therapy
- Seattle Angina Questionnaire
- Laboratory assessments: about one tablespoon [20 ml] of blood will be drawn from your vein for testing hematology, blood chemistry, Liver Function Tests (LFTs), fibrinogen, whole blood viscosity analysis, lipoprotein subclass analysis, lipoprotein (a), biocellular marker analysis, urine sample will be collected for urinalysis.



## Fasting

You will be asked to fast for at least 9 hours before each of your visits to prepare for your blood tests. Fasting means that you have not eaten any food or had a drink (except water) before coming to the study site. If you have not been fasting, or if some of the procedures cannot be done during the visit for other reasons, you may be asked to return to the study site to complete these procedures. The research facility staff will provide you with a schedule for when you need to return to the research facility.

## Diet and Exercise

Your doctor will discuss with you how maintaining a “heart healthy” diet is beneficial for reducing cardiovascular risk.

## Evolocumab Administration

As we mentioned previously, Evolocumab (Repatha) was approved by FDA in 2015 for reducing cholesterol by blocking PCSK9 as the PCSK 9 inhibitor. Evolocumab will be given by subcutaneous (that is, under the skin) injection. Study drug injections every 4 weeks will be with a prefilled 1.0 mL autoinjector/pen (AI/Pen) that will contain the study drug and can be used to administer the drug yourself after being trained at the beginning of the trail when study team member giving you the injection. Each administration will be 3 injections, using 3 AI/Pens.

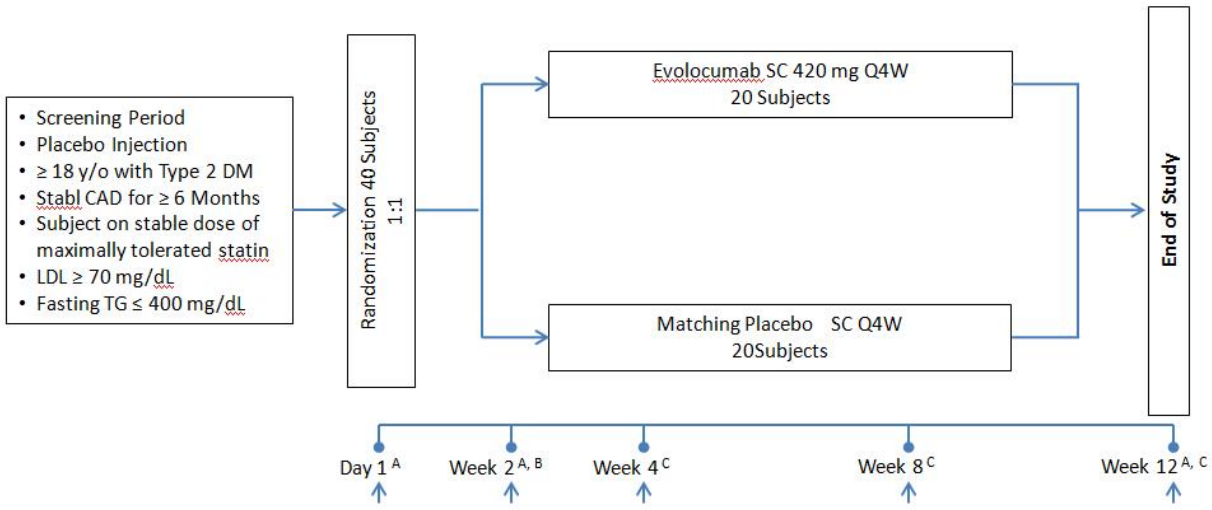
To help you to remember your study visit appointments and when to take your study drug injections, the study site staff may contact you.

**The table and schema below showed the information of this clinical trial.**

The study treatment you get will be chosen by chance, like flipping a coin. Neither you nor the study doctor will choose what study treatment you get. You will have an equal chance of being given a placebo medication or a real treatment, placebo is the fake medication which is not distinguishable from real medication. Neither you nor the study doctor will know which study treatment you are getting. This information could be obtained in an emergency, however, you will not be told which study treatment you are getting; only your study doctor will know.



**Study Flow Sheet**




[A] Laboratory Assessments: Hemotology, whole blood viscosity, NMR lipid profile, LFTs, creatinine/eGFR.
[B] Time Window is ± 4 days.
[C] Time Window is ± 7 days.

These study procedures will be performed at each study visit. These procedures involve measurement of your weight, blood pressure and pulse rate; collection of blood and urine specimens, and investigational product injection.

| No. | Description | Electrocardiogram | Lab samples | IP injection | Total Time |
|---|---|---|---|---|---|
| Visit 1 | Screening | Yes | Yes | Yes (Placebo) | 1.5-2 Hrs |
| Visit 2 | Randomization | No | Yes | Yes | 1-1.5 Hr |
| Visit 3 | Week 2 | No | Yes | No | 1-1.5 Hr |
| Visit 4 | Week 4 | No | No | Yes | 1-1.5 Hr |
| Visit 5 | Week 8 | No | No | Yes | 1-1.5 Hr |
| Visit 6 | Week 12 | No | Yes | No | 1-1.5 Hr |

## Other Medications

During your participation in this study, you are required to continue taking your cholesterol-lowering medication (such as a statin), unless a change is clinically necessary. Depending on the statin you are taking, there may be restrictions on certain other medicines that you may be taking. A Patient Information Leaflet (PIL) with this information will be provided to you by the doctor who is prescribing or providing you with your statin (the cholesterol lowering medication, such as a statin, will be provided as the routine care by your cardiologist). Since statins or other cholesterol lowering medications are not the study medication, you should follow your doctor's instruction of the cholesterol lowering medication (such as the restrictions on certain other medications). The only requirement for this study is that you should continue taking the cholesterol lowering medication since the study requires a stable treatment for cholesterol.

It is very important that you notify the study doctor what medication you are currently receiving or have received in the past. It is also very important that you notify the study doctor or the study staff before you take any new medication during the study, including changes to your current medications. The dose of any prescription or over-the-counter drugs or preparations to lower your cholesterol should not be changed during the entire time that you are on the study. However, if your primary care physician prescribes any adjustment in the medications that you are taking, you must inform your study doctor.

## Birth Control:

For Women:

Since you are participating in a study that involves drugs or investigational treatment with potential risks to a developing fetus, it is recommended, for your protection, that you not become pregnant for the duration of the study. Also, you should not participate if you are breastfeeding. Therefore, practicing effective contraception is important. No individual contraceptive is 100% effective.

Recommended methods of birth control are:

- The consistent use of an approved hormonal contraception (birth control pill/patches, rings),
- An intrauterine device (IUD),

- Contraceptive injection (Depo-Provera),
- Double barrier methods (Diaphragm with spermicidal gel or condoms with contraceptive foam),
- Sexual abstinence (no sexual intercourse) or
- Sterilization.

If you have any questions about birth control, your study coordinator or study doctor will be able to answer your questions and give you advice.

Should you become pregnant, regardless of the outcome, the sponsor may ask for information on your pregnancy, even if you are withdrawn from the study. Your written consent will be obtained separately in the case that this happens.

For Men:

Since you are participating in a study that involves drugs or treatment with potential risks to a developing fetus, it is recommended that you use a condom and not father a child or donate sperm while you are taking the study drug. Also, it is recommended that you use a condom and not father a child and/or donate sperm for 90 days after you stop taking the study drug. This is because levels of the study drug may be present in the sperm and/or seminal fluid even after you stop taking the study drug. Continuing to use a condom and not donating sperm during this 90-day period may allow time for any study drug that is still present in sperm and/or seminal fluid to be eliminated from your body before you attempt to father a child or donate sperm. You are encouraged to tell your female partner(s) and/or their doctor(s) that you are participating in a clinical trial.

**Future research:**

The researchers will not keep information collected about you during this study to use it in future research studies. However, the researchers would like to ask your permission to keep specimens (blood sample) collected from you during this study to use them in future research studies. They would also like to know your wishes about how they might use your specimens in future research studies. You should also know that it is possible that products may someday be developed with the help of your specimens, and there are no plans to share any profits from such products with you.



**(1)** Will you allow the researchers to store your specimens to use in future research studies?

Yes_____ No_____

If no, please stop here. If yes, please continue to the next question.

**(2)** The researchers can keep your specimens stored in one of two different ways: one way will store your specimens in a way that it is linked to your identity (through the use of a code that can indicate the information came from you personally) and the other way will store your specimens anonymously (no one will know who the information is from). It will not be stored both ways, so you must choose one of these two options. Please note that if you choose to have your specimens stored anonymously, you will not be able to change your mind to ask for your specimens to be destroyed at a future date.

How would you like your specimens stored? Please initial **ONE** choice:

I would like my specimens stored with a link to my identity_____

I would like my specimens stored anonymously _____

**(3)** Do you give the researchers permission to **contact you** in the future to collect additional information about you, discuss how your specimens might be used, or to discuss possible participation in another research project? Please initial your choice:

Yes_____ No_____

**(4)** Do you give the researchers permission to keep the specimens indefinitely and use them for future studies that are **directly related** to the purpose of the current study? Please initial your choice:

Yes_____ No_____

**(5)** Do you give the researchers permission to keep the specimens indefinitely and use them for future studies that are **not related** to the purpose of the current study (for example, a different area of research)? Please initial your choice:

Yes_____ No_____

**(a)** If the future research in a different area can be done without having to know that the specimens came from you personally, that will be done.

**(b)** If the future research in a different area requires that it is known specifically who the specimens came from, then one of the following will be done:

**(i)** If you allowed the researchers to contact you in the future, they will be able to contact you to explain why your specimen is needed and what will be done with it. Your permission will be asked to use your specimens in that research project.

**(ii)** If you do not give permission to be contacted in the future, or if it is found that contacting you is not practical, for example, because you have moved, your specimens may still be used. Either all links to your identity will be removed from the specimens, or an Institutional Review Board will be asked for permission to use the specimens linked to your identity. The Institutional Review Board (IRB) is a committee of doctors and scientists and non-scientists and people not associated with this hospital or medical school whose job it is to protect people who participate in research. The IRB can give permission for researchers to use and share health information connected to specimens that are linked to people's identities, but only if it determines that doing this will not be more than a minimal risk to people or their privacy.

**(6)** Your specimens will not be **given to other researchers** at Mount Sinai or other institutions for any use in research that is either related or not related to the purpose of this study.

## YOUR RESPONSIBILITIES IF YOU TAKE PART IN THIS RESEARCH:

If you decide to take part in this research study you will be responsible for the following things:

1. Attend the scheduled visits
2. Take study drugs
3. Take the study tests at Mount Sinai
4. Tell the study doctor and research study team about any other medicines that you are taking
5. Agree to complete research study surveys if you are asked
6. Agree to have the health diet and excise as the study team discussed with you.
7. Agree to participate in follow-up and data collection for the remainder of the study, including the study doctor collecting information regarding study related health



information from available sources such as medical records and outside hospitals and care providers

8. In the event, that you have a serious or emergency medical treatment, have concerns, and/or side-effects, you will tell the study doctor and/or research study team.
9. Agree to use birth control while participating in the study, and in the event that you learn that you or your partner is pregnant, you will stop using the study drug and contact the study doctor and/or research study team as soon as possible.

## COSTS OR PAYMENTS THAT MAY RESULT FROM PARTICIPATION:

You will not be paid for participating in this research study. Being in this research study will not lead to extra costs to you.

Taking part in this research study will not lead to added costs to you. You will receive study medications and the medical testing needed for this study at no cost. There are no costs to you or your insurance for study medications and study procedures. Lab tests and medications will all be provided at no cost to you. However, if your study doctor arranges for you to have additional medical tests which are not part of the study but are needed for your regular healthcare or usual care, you may have to pay for these if they are not covered by your government's health plan or your private insurance.

If you agree to take part in this research study, we will pay you $75 per visit to cover travel expenses and for your time and effort. Reimbursement will be paid by check and the payment process will take approximately 4 to 6 weeks. Checks require some time to be prepared and will be given to you as available. The total amount of the reimbursement will be $450 if you complete all the six study visits.

Tax law may require the Mount Sinai Finance Department to report the amount of payment you receive from Mount Sinai to the Internal Revenue Service (IRS) or other agencies, as applicable. Generally, this reporting would take place if you receive payments that equal $600 or more from Mount Sinai in a calendar year. You would be responsible for the payment of any tax that may be due.

## POSSIBLE BENEFITS:

No one knows if participation in this study will help you. Your condition may get better if you are signed in the treatment group since evolocumab was approved by FDA in 2015 as a lipid regulating medication. However, since you have the chance to be assigned to the placebo group, your condition could stay the same or even get worse. The information from this study might help in the development of additional treatments in the future for cardiovascular disease.

You may have possible benefit for LDL reduction if you are randomized into real treatment group.

## REASONABLY FORESEEABLE RISKS AND DISCOMFORTS:

**a. Are there any risks from taking part in this study?**

There may be risks to being in this study, from the study drug (evolocumab), from the device(s) used to deliver evolocumab (1.0 mL prefilled autoinjector/pen [AI/Pen]), or from some of the procedures or tests done in this study. Also, your condition may get better but it could stay the same or even get worse.

If you participate in this study, you or your family members should tell the study doctor or the study staff immediately if you have any unusual health problems, injuries, or side effects, even if you do not think these problems are caused by the study, or evolocumab, or the device(s).

If there is any new important safety information or other information that could affect your willingness to participate in this study, the study doctor will let you know.

**b. What are the likely risks with evolocumab?**

Evolocumab may cause all, some, or none of the side effects listed below. These side effects can be mild but could also be serious, life threatening, or even result in death. You may also experience an allergic reaction that has not been seen before.



As of July 2016, approximately 22,000 study participants have received evolocumab in research studies and, approximately 44,000 patients have been prescribed evolocumab by their doctors. Evolocumab (Repatha®) was approved for sale in July 2015.

Side effects that people have had in research studies that are thought to have been caused by evolocumab are:

Common side effects (which may affect between 1 and 10 people in every 100):

• 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 side effects (which may affect between 1 and 10 people in every 1000):

• Hives (urticaria)

**Potential side effects with evolocumab reported from research studies:**

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. There are people with a very rare inherited condition who lack the PCSK9 protein (the protein that evolocumab blocks) and have very low cholesterol levels in their blood. These people appear to be healthy.



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 or even result in death.

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.

Blood tests will be used to check for such anti-evolocumab antibodies during the study.

**c. What are the risks of using evolocumab in combination with other drugs?**

Tell the study doctor or the study staff about any drugs you are taking, have recently taken or are planning to take, including herbal remedies, supplements, experimental therapies, and drugs you take without a prescription. The side effects of using evolocumab in combination with other drugs are unknown at this time. Please discuss any concerns you may have with the study doctor.

**d. What are the risks of taking the other drugs required by this study?**

The following drugs are not being studied by Amgen, but you are required to take them as part of this study. These drugs are often used to treat your condition as standard of care. The study doctor will talk with you about the risks of taking these drugs.

Cholesterol-lowering medications

It is recommended that you continue taking the same cholesterol-lowering medication, such as a statin, for the duration of this study. Cholesterol-lowering medications, such as a statin, are not being studied by Amgen but are often used to treat your condition. The study doctor will talk with you about the risks of taking cholesterol-lowering medications (such as a statin).

**e. What are the risks associated with procedures done in this study?**

The known risks and side effects of study related tests or procedures (listed in Section 2) are noted here.

Fasting

You will need to be fasting (not eating or drinking anything except water) for at least 9 hours before each of your visits to prepare for your blood tests. Possible side effects of fasting are feeling weak, hungry, sweaty, nervous or restless.

Blood draws

You will have your blood drawn during the study. Possible side effects of having blood drawn are tenderness, pain, bruising, bleeding, and/or infection where the needle goes into the skin and blood vein. Having your blood drawn may also cause you to feel nauseated and/or lightheaded.

**f. What are the risks associated with the prefilled AI/Pen used to give evolocumab into the tissue below your skin?**

If you agree to participate in this study, a prefilled AI/Pen will be used to inject evolocumab into the soft tissue below your skin.

When using the prefilled AI/Pen, you may experience all, some, or none of the following every time after you having the IP administration:

• Pain or discomfort at the injection site during or after the injection

• Bleeding, bruising, redness, warmth, itching, swelling, or firmness of the skin near the injection site

• Infection at the injection site

When using the prefilled AI/pen, you may experience the following:



• An allergic reaction to the dry natural rubber in a specific part of the prefilled AI/pen. The needle cover contains dry natural rubber, (which is derived from latex). Tell your study doctor or the study staff if you are allergic to latex.

It is possible that the AI/pen will not work properly during the injection. If this occurs, it is possible that you could receive an incomplete dose or even no dose at all of evolocumab. Contact your study doctor immediately if you believe that your AI/pen used to administer evolocumab did not work properly during the injection.

**g. What if you become pregnant, breastfeed, or father a child during the sudy?**

Please notify the study doctor if you become pregnant, or breastfeed (nurse), or father a child while you are taking evolocumab because further information may be asked of you (the study doctor will discuss the details with you).

**h. Could evolocumab be harmful to an unborn or breastfed baby?**

It is not known if evolocumab is harmful to an unborn or breastfed baby.

If you become pregnant during this study and within 15 weeks after stopping evolocumab, potential risks could include complications such as a miscarriage (loss of the pregnancy) or birth defects.

**Female Participants**

Pregnant or breastfeeding (nursing) women, and women planning to become pregnant or breastfeed, should not participate in this study.

If you are unable to become pregnant for one of the following reasons, the use of birth control methods is not required during this study:

• Your healthcare provider has confirmed that you are postmenopausal

• You have had your uterus, or both ovaries, or both fallopian tubes removed

If you could become pregnant, you:



• Must agree to use an acceptable method of effective birth control during treatment and for an additional 15 weeks after the last dose of evolocumab

• Must discuss your pregnancy prevention method with the study doctor to ensure it is acceptable. You should be aware that true sexual abstinence is the only 100% effective method of birth control

Acceptable Methods of Effective Birth Control for Female Participants include:

o Hormonal methods of birth control (combined estrogen and progestogen or progestogen-only): pills, shots/injections, implants (placed under the skin by a healthcare provider), vaginal rings, or skin patches

• Intrauterine device (IUD)

• Intrauterine hormonal-releasing system (IUS)

• Surgery to tie both fallopian tubes (bilateral tubal ligation/occlusion)

• Your male partner has had a vasectomy and testing shows there is no sperm in the semen

• Sexual abstinence (not having sex)

o Double barrier method: the male uses a condom and the female may choose either a cervical cap, diaphragm, or contraceptive sponge with spermicide (a female condom is not an option due to the risk of tearing when both partners use a condom).

Unacceptable methods of contraception include:

Periodic abstinence (calendar), withdrawal, or spermicides only.

It is not known if evolocumab is transferred into breast milk. If you are breastfeeding (nursing) and wish to be in this study, you will be required to discontinue breastfeeding (nursing) during treatment with evolocumab and for an additional 15 weeks after the end of treatment with evolocumab.

**Male Participants**

Male participants are not required to use birth control during treatment with evolocumab. However, you should let your female partner know that you are in this study. Based on long-term monkey data, evolocumab does not damage sperm. Based on human data with a different monoclonal antibody, the concentration of evolocumab in semen is expected to be so low it will not harm your partner or unborn baby.

**Female and Male Participants**

The pregnancy, breastfeeding (nursing), and birth control information in this document is specific to evolocumab. There may be additional risks to an unborn child or breastfed baby from other drugs, such as statins, that you may receive during the study. This may require that you change the type and/or length of time that you must use birth control or length of time that you must avoid breastfeeding (nursing). Please discuss this with the study doctor.

i**. What if you become pregnant or breastfeed during the study?**

If you decide to participate in this study, you must agree to not become pregnant or breastfeed (nurse).

If you think you are pregnant, or accidentally become pregnant or breastfeed (nurse) during treatment with evolocumab and for an additional 15 weeks after stopping evolocumab, you must tell the study doctor or the study staff right away. Treatment with evolocumab may be stopped. The study doctor will notify Amgen of the pregnancy or that you are breastfeeding (nursing). You will be asked to provide information on the pregnancy or breastfeeding (nursing) outcome for you and the baby.

**j. What if your partner becomes pregnant during the study?**

If your partner becomes pregnant during treatment with evolocumab and for an additional 15 weeks after stopping evolocumab, you must tell the study doctor or the study staff as soon as possible.

The study doctor will notify Amgen of the pregnancy and ask to obtain information on the pregnancy outcome for both the mother and baby.

There is a Federal law called the Genetic Information Nondiscrimination Act (GINA). In general, this law makes it illegal for health insurance companies, group health plans, and most employers of over 15 people to discriminate against you based on your genetic information. However, it does not protect you against discrimination by companies that sell life insurance, disability insurance, or long-term care insurance.

## OTHER POSSIBLE OPTIONS TO CONSIDER:

You may decide not to take part in this research study without any penalty. The choice is totally up to you.

If you decide not to participate, this will not affect your ability to receive medical care at Mount Sinai or to receive any benefits to which you are otherwise entitled. You still will get the standard care for coronary heart disease and lipid reduction.

Your primary doctor or study doctor can explain other treatments that are available.

Optimal medical therapy for the prevention of cardiovascular events in CAD patients includes treatment with aspirin and/or other lipid regulating medication, such as Statins. It also includes the procedures of re-vascularization or treatment with Evolocumab (Repatha®), a FDA approved drug in 2015 which is available even if you decide not to participate in this study. This is the same medication used in this study for reducing cholesterol by blocking PCSK9 as the PCSK 9 inhibitor.

## IN CASE OF INJURY DURING THIS RESEARCH STUDY:

If you believe that you have suffered an injury related to this research as a participant in this study, you should contact the Principal Investigator.

If you are injured or made sick from taking part in this research study, medical care will be provided. The sponsor will reimburse your reasonable and necessary medical expenses for diagnosis and treatment of a research-related injury or illness.

This does not prevent you from seeking payment for injury related to malpractice or negligence. Contact the investigator for more information.



By agreeing to the above, you do not waive any of your legal rights which you otherwise would have as a research subject, nor do you release Amgen, study doctors, or the hospital from liability for negligence.

## ENDING PARTICIPATION IN THE RESEARCH STUDY:

You may stop taking part in this research study at any time without any penalty. This will not affect your ability to receive medical care at any of the Mount Sinai Health System hospitals or to receive any benefits to which you are otherwise entitled.

If you decide to stop being in the research study, please contact the Principal Investigator or the research staff. You should not stop taking the study medication without talking to the Principal Investigator first. If you decide to stop being in the research study, you should be aware that people who stop taking the study medication may have a higher risk of getting a blood clot or having a heart attack. The study doctor will instruct you as to what you should do.

If you decide to stop being in the research study, already collected information may not be removed from the research study database and will continue to be used to complete the research analysis. You may be asked whether the investigator can collect information from your routine medical care. If you agree, this data will be handled the same as research data. You may also withdraw your permission for the use and disclosure of any of your protected information for research, but you must do so in writing to the Principal Investigator at the address on the first page.

You may also withdraw your permission for the use and disclosure of any of your protected information for research, but you must do so in writing to the Principal Investigator at the address on the first page. Even if you withdraw your permission, the Principal Investigator for the research study may still use the information that was already collected if that information is necessary to complete the research study. Your health information may still be used or shared after you withdraw your authorization if you have an adverse event (a bad effect) from participating in the research study.

Withdrawal without your consent: The study doctor, the sponsor or the institution may stop your involvement in this research study at any time without your consent. This may be because the research study is being stopped, the instructions of the study team have not



been followed, the investigator believes it is in your best interest, or for any other reason. If specimens or data have been stored as part of the research study, they too can be destroyed without your consent. The study doctor will make the decision and let you know if it is not possible for you to continue in the study.

## CONTACT PERSON(S):

If you have any questions, concerns, or complaints at any time about this research, or you think the research has hurt you, please contact the office of the research team and/or the Principal Investigator at phone number Dr. Robert S. Rosenson at telephone number 212-241-9101. If you experience an emergency during your participation in this research, contact Dr. Robert S. Rosenson at telephone number 212-241-9101. You may also call 911 or go to the emergency room.

This research has been reviewed and approved by an Institutional Review Board. You may reach a representative of the Program for Protection of Human Subjects at the Icahn School of Medicine at Mount Sinai at telephone number (212) 824-8200 during standard work hours for any of the reasons listed below. This office will direct your call to the right person within the Mount Sinai Health System:

- Your questions, concerns, or complaints are not being answered by the research team.
- You cannot reach the research team.
- You are not comfortable talking to the research team.
- You have questions about your rights as a research subject.
- You want to get information or provide input about this research.

## DISCLOSURE OF FINANCIAL INTERESTS:

Sometimes, physicians/researchers receive payments for consulting or similar work performed for industry. Effective September 2014 Mount Sinai reviews only payments to an

individual totaling more than $5,000 a year per entity when determining potential conflicts of interest. If you have questions regarding industry relationships, we encourage you to talk your physician/researcher or visit our website at http://icahn.mssm.edu/ where Mount Sinai publicly discloses the industry relationships of our faculty.

The company sponsoring this research study manufactures the drug/device being tested and so has a financial interest that could be affected by the outcome of this research study.

**MAINTAINING CONFIDENTIALITY – HIPAA AUTHORIZATION:**

As you take part in this research project it will be necessary for the research team and others to use and share some of your private protected health information. Consistent with the federal Health Insurance Portability and Accountability Act (HIPAA), we are asking your permission to receive, use and share that information.

What protected health information is collected and used in this study, and might also be disclosed (shared) with others?

As part of this research project, the research team at the hospital(s) involved in the research will collect your Name, Address and Telephone number.

The researchers will also get information from your medical record from Mount Sinai Medical Center and your referring physicians.

During the study the researchers will gather information by:

- taking a medical history (includes current and past medications or therapies, illnesses, conditions or symptoms, family medical history, allergies, etc.)
- doing a physical examination that generally also includes blood pressure reading, heart rate, breathing rate and temperature
- completing the tests, procedures, questionnaires and interviews explained in the description section of this consent.

Why is your protected health information being used?

Your personal contact information is important to be able to contact you during the study. Your health information and the results of any tests and procedures being collected as part of this research study will be used for the purpose of this study as explained earlier in this consent form. The results of this study could be published or presented at scientific meetings, lectures, or other events, but would not include any information that would let others know who you are, unless you give separate permission to do so.

The Principal Investigator may also use and share the results of these tests and procedures to treat you in collaboration with others in the Mount Sinai Health System.

The research team and other authorized members of The Mount Sinai Health System ("Mount Sinai") workforce may use and share your information to ensure that the research meets legal, institutional or accreditation requirements. For example, the School's Program for the Protection of Human Subjects is responsible for overseeing research on human subjects, and may need to see your information. If you receive any payments for taking part in this study, the Mount Sinai Finance Department may need your name, address, social security number, payment amount, and related information for tax reporting purposes. If the research team uncovers abuse, neglect, or reportable diseases, this information may be disclosed to appropriate authorities.

Who, outside Mount Sinai, might receive your protected health information?

As part of the study, the Principal Investigator, study team and others in the Mount Sinai workforce may disclose your protected health information, including the results of the research study tests and procedures, to the following people or organizations: (It is possible that there may be changes to the list during this research study; you may request an up-to-date list at any time by contacting the Principal Investigator.)

- Outside laboratory who will be performing laboratory analysis for all the research centers involved in this project: LabCorp and Rheovector, LLC

- The commercial sponsor and/or their representative (who will use the results for submissions to the Food and Drug Administration): Amgen, and its Affiliates, which are located around the world A Data Safety Monitoring Board or other committee that will monitor the study on an ongoing basis for safety.

- The United States Food and Drug Administration

- The United States Department of Health and Human Services and the Office of Human Research Protection.

In all disclosures outside of Mount Sinai, you will not be identified by name, social security number, address, telephone number, or any other direct personal identifier unless disclosure of the direct identifier is required by law. Some records and information disclosed may be identified with a unique code number. The Principal Investigator will ensure that the key to the code will be kept in a locked file, or will be securely stored electronically. The code will not be used to link the information back to you without your permission, unless the law requires it, or rarely if the Institutional Review Board allows it after determining that there would be minimal risk to your privacy. It is possible that a sponsor or their representatives, a data coordinating office, a contract research organization, may come to inspect your records. Even if those records are identifiable when inspected, the information leaving the institution will be stripped of direct identifiers. Additionally, when applicable, the monitors, auditors, the IRB, the Office of Human Subjects Protection (OHRP) of the Department of Health and Human Services as well as the Food and Drug Administration (FDA) will be granted direct access to your medical records for verification of the research procedures and data. OHRP and FDA are authorized to remove information with identifiers if necessary to complete their task. By signing this document you are authorizing this access. We may publish the results of this research. However, we will keep your name and other identifying information confidential.

For how long will Mount Sinai be able to use or disclose your protected health information?

The sponsor may use and share your PHI for internal reference, for comparison with other data, to help design subsequent trials, and in papers submitted to United States and/or foreign regulatory agencies regarding later-developed products. Your authorization for use of your protected health information for this specific study does not expire.

Will you be able to access your records?

During your participation in this study, you will not be able to access your medical records. This will be done to prevent the knowledge of study results from affecting the reliability of the study. Your information will be available should an emergency arise that would require your treating physician to know this information to best treat you. You will have access to your medical record and any study information that is part of that record when the study is over or



earlier, if possible. The investigator is not required to release to you research information that is not part of your medical record.

Do you need to give us permission to obtain, use or share your health information?

NO! If you decide not to let us obtain, use or share your health information you should not sign this form, and you will not be allowed to volunteer in the research study. If you do not sign, it will not affect your treatment, payment or enrollment in any health plans or affect your eligibility for benefits.

Can you change your mind?

You may withdraw your permission for the use and disclosure of any of your protected information for research, but you must do so in writing to the Principal Investigator at the address on the first page. Even if you withdraw your permission, the Principal Investigator for the research study may still use your protected information that was already collected if that information is necessary to complete the study. Your health information may still be used or shared after you withdraw your authorization if you should have an adverse event (a bad effect) from being in the study. If you withdraw your permission to use your protected health information for research that means you will also be withdrawn from the research study, but standard medical care and any other benefits to which you are entitled will not be affected. You can also tell us you want to withdraw from the research study at any time without canceling the Authorization to use your data.

If you have not already received it, you will also be given The Hospital's Notice of Privacy Practices that contains more information about how The Hospital uses and discloses your protected health information.

It is important for you to understand that once information is disclosed to others outside Mount Sinai, the information may be re-disclosed and will no longer be covered by the federal privacy protection regulations. However, even if your information will no longer be protected by federal regulations, where possible, Mount Sinai has entered into agreements with those who will receive your information to continue to protect your confidentiality.

If as part of this research project your medical records are being reviewed, or a medical history is being taken, it is possible that HIV-related information may be revealed to the researchers. If that is the case, the following information concerns you. If this research does



not involve any review of medical records or questions about your medical history or conditions, then the following section may be ignored.

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**Notice Concerning HIV-Related Information**

If you are authorizing the release of HIV-related information, you should be aware that the recipient(s) is (are) prohibited from re-disclosing any HIV-related information without your authorization unless permitted to do so under federal or state law. You also have a right to request a list of people who may receive or use your HIV-related information without authorization. If you experience discrimination because of the release or disclosure of HIV-related information, you may contact the New York State Division of Human Rights at (888) 392-3644 or the New York City Commission on Human Rights at (212) 306-5070. These agencies are responsible for protecting your rights.

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## Signature Block for Capable Adult

Your signature below documents your permission to take part in this research and to the use and disclosure of your protected health information. A signed and dated copy will be given to you.

| | |
|---|---|
| Signature of subject | Date |
| Printed name of subject | Time [required if used for FDA documentation purposes] |

## Person Explaining Study and Obtaining Consent

| | |
|---|---|
| Signature of person obtaining consent | Date |
| Printed name of person obtaining consent | Time |

***Witness Section: For use when a witness is required to observe the consent process, document below (for example, subject is illiterate or visually impaired, or this accompanies a short form consent):***

*My signature below documents that the information in the consent document and any other written information was accurately explained to, and apparently understood by, the subject, and that consent was freely given by the subject.*

| | |
|---|---|
| *Signature of witness to consent process* | *Date* |
| *Printed name of person witnessing consent process* | Time |