The Effect of Vericiguat on Peripheral Vascular Function, Patient Health Status and Inflammation in Patients with Heart Failure with Reduced Ejection Fraction

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Consent and Authorization Document

BACKGROUND

You are being asked to take part in a research study. Before you decide, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with friends and relatives if you wish. Take time to decide whether or not to volunteer to take part in this research study and ask the study doctor or staff any questions you may have. You are being asked to participate because you have heart failure (HF), which is when the pumping power of the heart is weaker than normal.

Vericiguat has been approved by the Food and Drug Administration (FDA) for patients with heart failure. Vericiguat has been tested in previous clinical trials and this research study is to further evaluate the benefits of the drug for patients with heart failure. In particular, this study aims to see: 1. What effect Vericiguat has on the function of arteries in your body, 2. What effect Vericiguat has on quality of life and physical strength, and 3. What effect Vericiguat has on inflammation. The University of Utah Medical Center will be paid by the Sponsor, Merck Sharp & Dohme Corp., a subsidiary of Merck & Co. Inc., for conducting this study.

Should you decide to participate, you will be one of approximately 24 participants expected to be enrolled at the University of Utah Medical Center and *George E. Wahlen VA Medical Center*. The average time for participation in the study will be approximately 12 weeks. Your study doctor or staff can answer any questions you may have about study participation duration.

There may be reasons why you are not allowed to take part in this study. Some of these reasons include:

- You do not have the type of heart failure being evaluated in this research study.
- Medication changes have been done in previous 4 weeks.
- You are currently taking or plan to take a medication that is not allowed in the study.

The study doctor or staff will discuss these and any other reasons why you may not be allowed to enter the study.

STUDY PROCEDURES

This form is called an informed consent document or consent form. It contains a full explanation about the study in which you are being asked to participate. Your participation is voluntary. If you agree to participate after reading this document and asking questions about this study, you will be asked to sign your approval for consent. 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.

If you take part in the study, you will be asked to visit the study doctor about 4 times. You will be asked to take study medication. At each visit you will be asked to discuss your medications you are currently taking and asked to answer written questionnaires concerning your health and quality of life. If you choose to participate in this study, the study doctor will follow you until the end of the study. To monitor your health the study doctor will ask that you come to the study clinic to complete the study visits until the study ends. If you permanently stop taking study drug during the study, you will be asked to continue attending study visits in the clinic, just like those who remain on study drug. If you are not able to attend scheduled study visits, follow-up of your health status may continue by phone.

- This is a randomized research trial and involves comparing different treatments. In a randomized trial, one group will get one treatment and another group will get a different treatment. Participants are put in one group or the other by random chance, like flipping a coin. You will have a 50:50 chance of being placed in either group. A computer will decide by chance which group a person is in, not the doctors running the trial. In this trial, neither you nor your doctor will know which treatment group you are in (although, if your doctor needs to find out for important medical reasons, he/she can do so). If you participate you will be randomly assigned to either a treatment group (study medication) or a placebo group. A placebo is a dummy treatment such as a pill which looks like the study medication but is not. Placebos contain no drugs or active ingredients. This study is testing the effect of vericiguat compared with placebo (dummy treatment), added to best usual treatment for heart failure. This means that if you are randomly assigned to the placebo group, you will still be receiving best usual care for your heart failure. You should take your study drug once daily with food and your usual treatment for heart failure as instructed.

Enrollment-Visit

The Enrollment Visit will take about 1-2 hours. During this visit, tests will be completed to see if you qualify for this research study. The study staff will review the results of these tests with you. If you do not qualify, you will be told why.

At this visit the following will be done:

- Review of information including date of birth, gender, ethnicity and race
- Medical history (past and present illnesses/diseases, surgeries, smoking history and alcohol use)
- You will be asked about the medications you have taken and are currently taking
    - Some medications should not be taken with Vericiguat, and some medications are not allowed on the study. You may be asked to discontinue these medications to participate in the study. Your study doctor will tell you which medications may need to be stopped, as well as how and when to stop them.
- Records from tests that you have had done in the past will be reviewed

- Vital signs (sitting blood pressure, heart rate and breathing rate), weight and height will be collected
- Approximately 2 ½ Tablespoons (38 ml) of blood will be collected to measure heart function, kidney function, current blood count, as well as inflammation.

*If you are a female of childbearing potential, you will be given a urine pregnancy test to determine if you are pregnant.

If you qualify for the study after completing all of the above, you will be scheduled for Randomization

Randomization-Visit 1.
The Randomization Visit will take about 2 hours.

At this visit the following procedures will be done:

- You will be asked about any changes to your health and medications since your last visit, including questions about your HF.
- You will complete two short questionnaires about your overall health and quality of life.
- Six Minute Walk Test (6-MWT) will be done. The 6-MWT involves having you walk in a hallway for 6 minutes to see how far you can go.
- Flow Mediated Dilation (FMD) evaluation will be done. Blood flow response after a blood pressure cuff release will be measured using Doppler Ultrasound machine. After a blood flow recording, a blood pressure cuff will be wrapped around your forearm and inflated for up to five minutes to stop blood flow in the artery that will be examined for change in diameter upon cuff release. Since obstructing the blood flow for five minutes may be painful and/or uncomfortable for some, it should be noted that if you wish to stop this test at any point during the measurement the research staff will do so.
- You will be provided a blood pressure machine and cuff to take home for week 2 (phone call A) and week 8 (phone call B) follow-up visits performed by phone.

After all of these procedures are complete, you will be randomized, and you will receive study drug or placebo.

- You will begin on a lower dose of study drug or placebo, and your dose will be increased over several weeks.
- You should take your study drug once daily with food. It is important you take study drug every day as instructed by your study doctor.
- If you miss the daily dose of study drug, do not take two doses at the same time. It is important that you leave all of the unused medication in the bottle so your study doctor or staff can count the number of tablets that you took.

Dose Increases and Decreases

After the Randomization Visit, you will return to the clinic 2 times and will be contacted by phone 2 times over 12 weeks to evaluate your response to the study drug and have your study drug dose modified. Additional visits during the study may also occur to change your study dose if necessary.

- At these visits you will receive enough study drug medication to last until your next visit.
- You may be counseled on dosing instructions if you do not take the study drug as prescribed or have any questions.

Follow-Up Phone Call A

You will receive a follow up phone call approximately 14 days after your randomization visit in the study. At this phone call you will be asked about any changes to your health and medications since your last visit, including questions about your HF. You will be asked to perform at-home blood pressure measurement using blood pressure machine provided at previous visit. Moreover, study drug doses will be titrated accordingly.

Week 4 - Visit 2.

Visit 2 will take place approximately 4 weeks after randomization. This visit can occur as early as day 24 or as late as day 32 after you begin the study drug, depending on your medical condition. This visit will take approximately 2 hours.

At this visit the following procedures will be done:

- You will be asked about any changes to your health and medications since your last visit, including questions about your HF.
- Blood pressure, pulse and weight will be collected.
- You will return all study medication, including all unused tablets, and receive enough new study drug to last until your next visit. You may be counseled on dosing instructions if you do not take the study drug as instructed or if you have questions.
- Approximately 2 Tablespoons (30 ml) of blood will be collected to measure heart function, kidney function, and current blood count.

Follow-Up Phone Call B

You will receive a follow up phone call approximately 14 days after Visit 2 in the study. At this phone call you will be asked about any changes to your health and medications since your last visit, including questions about your HF. You will be asked to perform at-home blood pressure

measurement using blood pressure machine provided at previous visit. Moreover, study drug doses will be titrated accordingly.

End of Study- Visit 3

The Final visit will take about 2 hours.
At this visit the following procedures will be done:

- You will be asked about any changes to your health and medications since your last visit, including questions about your HF.
- A physical exam including your blood pressure, pulse and weight will be done
- You will complete two short questionnaires about your overall health and quality of life.
- Approximately 2 ½ Tablespoons (38 ml) of blood will be collected to measure heart function, general liver, kidney function, current blood count, as well as inflammatory markers.
- Six Minute Walk Test (6-MWT) will be done. The 6-MWT involves having you walk in a hallway for 6 minutes to see how far you can go.
- Flow Mediated Dilation (FMD) evaluation will be done (see description above).
- You will return all study medication, including all unused tablets

Follow-Up Phone Call C
You will receive a follow up phone call approximately 14 days after your last visit in the study. At this phone call you will be asked about any changes to your health and medications since your last visit, including questions about your HF.

What is known about this study drug?
Vericiguat has been tested in a number of studies. In the largest one 2,526 patients with heart failure received Vericiguat and 2,524 received placebo. Patients treated with Vericiguat had less hospital admissions for heart failure and death due to heart failure. Vericiguat is now approved for treatment of heart failure by the Food and Drug Administration.

RISKS
There are possible risks and/or discomforts with treatments and procedures in this study.

The following side effects have been seen in studies completed to date with Vericiguat:

- Inflammation of the airways (Bronchitis)
- Low red cell count (Anemia)
- Dizziness

- Common cold
- Low blood pressure
- Heartburn, indigestion
- Nausea
- Red eyes
- Headache
- Fainting

Other less common side effects have been reported with the use of the drugs in this study.

The study doctor or staff can discuss these with you.

There may be other side effects or risks that are not known at this time.

In addition to the possible side effects listed above you may also experience the following during the course of your medical exam.

Blood Draws

Possible side effects from drawing blood include faintness, inflammation of the vein, mild pain, bruising, irritation, redness, or bleeding at the site of the blood draw. In rare cases, you may get an infection.

Six Minute Walk Test

There are only minor risks associated with this test. They include, fatigue, shortness of breath, chest pain, dizziness, and falling.

Flow Mediated Dilation

You may experience minor discomfort during the measurement due to the 5 minutes of cuff inflation. The trained personnel will ensure that the blood pressure cuff is completely deflated as soon as the measurement is completed.

REPRODUCTIVE RISKS

It is not known if study drug may affect an unborn or nursing baby. Pregnant women must not take part in this study, nor should women who plan to become pregnant during the study. Women who are at risk of pregnancy will be asked to have a pregnancy test before taking part to exclude the possibility of pregnancy. If you could become pregnant you must use an effective contraceptive during the course of this study. Acceptable methods of birth control include*:*

Practice abstinence from heterosexual activity,
OR
Use of two (2) of the following in combination:

- Diaphragm with spermicide (cannot be used in conjunction with cervical cap/spermicide)

- Cervical cap with spermicide (for women who have not given birth)
- Contraceptive sponge (for women who have not given birth)
- Male condom or female condom (cannot be used together)
- Hormonal contraceptives (estrogen/progestin pill or progestin-only pill), contraceptive skin patch, vaginal contraceptive ring, or subcutaneous contraceptive injection

OR

One (1) of the following:

- Intrauterine Device (IUD)
- Vasectomy of a female subject's male partner
- Contraceptive rod implanted into the skin.

If you become pregnant while taking part in the study, you must immediately tell your research doctor. Options will be discussed with you at that time. Whether or not you remain on study treatment, we will follow the outcome of your pregnancy and we will continue to follow you according to the study plan.

UNFORESEEABLE RISKS

In addition, there may be uncommon or previously unknown problems that might occur with the use of the drugs in this study. The study doctor or staff can discuss these with you. You should report any problems you have to the study team.

BENEFITS

If you agree to take part in this study, there may or may not be direct medical benefit to you. The information that is learned from this study may benefit other people with the same condition as yours and may improve medical understanding of heart failure and heart failure treatment. You may benefit from being evaluated at regular intervals, as required by the study visit schedule.

ALTERNATIVE PROCEDURES

You do not have to participate in this study. You can get treatment or care for your medical conditions even if you are not in a research study. Your alternative choices are to continue your current treatment as is with no change. Treatments are available outside of the study and each has its own risks and benefits. You should think about all of your choices and talk with your doctor about them before you decide if you will take part in this study.

PERSON TO CONTACT

For questions about the study or a research-related injury, or if you have complaints, concerns or suggestions about the research, contact Dr. Josef Stehlik at (801) 585-7676 during regular business hours; or at (801) 581-2121 to reach the Hospital Operator after hours or on a weekend

or holiday. When calling this number, please ask to have Dr. Josef Stehlik or a covering physician to be paged.

Institutional Review Board: Contact the Institutional Review Board (IRB) if you have questions regarding your rights as a research participant. Also, contact the IRB if you have questions, complaints or concerns which you do not feel you can discuss with the investigator. The University of Utah IRB may be reached by phone at (801) 581-3655 or by e-mail at irb@hsc.utah.edu.

Research Participant Advocate: You may also contact the Research Participant Advocate (RPA) by phone at (801) 581-3803 or by email at participant.advocate@hsc.utah.edu.

RESEARCH-RELATED INJURY
The study sponsor will not provide any other form of compensation. You are not being asked to release or waive any of your legal rights against the institution, the investigator or the sponsor for liability for negligence.

If you are injured from being in this study, medical care is available to you at the University of Utah, as it is to all sick or injured people. The University of Utah has not set aside any money to pay the costs for such care. The University will work with you to address costs from injuries. Costs would be charged to you or your insurance company (if you have insurance), to the study sponsor or other third party (if applicable), to the extent those parties are responsible for paying for medical care you receive. Since this is a research study, some health insurance plans may not pay for the costs. By signing this consent form, you are not giving up your right to pursue legal action against any parties involved with this research.

The University of Utah is a part of the government. If you are injured in this study, and want to sue the University or the doctors, nurses, students, or other people who work for the University, special laws may apply. The Governmental Immunity Act of Utah is a law that controls when a person needs to bring a claim against the government, and limits the amount of money a person may recover. See sections 63G -7-101 to -904 of the Utah Code.

VOLUNTARY PARTICIPATION
Research studies include only people who choose to take part. You can tell us that you don't want to be in this study. You can start the study and then choose to stop the study later. We will still give you medical care and answer any questions you have. Your decision will not affect your relationship with your doctor or the study team in any way. If you choose not to participate, or to leave the study at any time, you will not be penalized or lose any benefits to which you are otherwise entitled. If you want to stop being in this study, please let the research doctor know.

That way you can find out what should be done about your normal medical care outside of the study.

RIGHT OF INVESTIGATOR TO WITHDRAW PARTICIPANTS
You can stop taking study medication or withdraw from this study at any time, without penalty. The investigators also have the right to stop your participation at any time. This could be because you have had an unexpected reaction, or have failed to follow instructions, or because the entire study has been stopped. If you withdraw your participation, no new information will be collected but we will use data that has already been collected.

You may have to leave the study without your consent if you need other treatment, do not follow the study plan, have a study-related injury, or for any other reason.

If you leave the study for any reason, the study doctor may ask you to have some end-of-study tests.

COSTS AND COMPENSATION TO PARTICIPANTS
Some of the tests or treatments used in this study may be part of standard care used to maintain your health even if you did not take part in this study. You or your insurance company may be responsible for the cost of this standard care. All trial medication and trial-related tests will be paid for by Merck Sharp & Dohme Corp., at no cost to you.

You and/or your insurance provider will be responsible for all costs related to your routine medical care, which is care you would have received whether or not you were part of this study.

COMPENSATION TO PARTICIPANTS
You will be reimbursed up to $1,000 if you complete the study. You will receive $150.00 per visit for your expenses related to your participation to cover your time and travel costs, and the remaining amount at the final visit. Because you will be paid for participating in this study, it is necessary for us to collect your Social Security Number. You will provide this information for a Federal W-9 Form that is filed with our Accounts Payable department. You can choose not to provide us with your Social Security Number for this form and still participate in this study; however, we will not be able to pay you as outlined in this consent form.

NEW INFORMATION
If important new findings come up that might change your decision to be in this study, you will be given information about those findings as soon as possible. If you choose to stay in the study, you may be asked to sign a new version of the consent form.

AUTHORIZATION FOR USE OF YOUR PROTECTED HEALTH INFORMATION

Signing this document means you allow us, the researchers in this study, and others working with us to use some information about your health for this research study, as described in this consent document. If you decide not to sign this document, you will not be able to participate in the study.

This is the information the study doctor and research team will use and include in our research records:

- Demographic and identifying information like: name, address, telephone number, and email address.
- Social Security Number for a Federal W-9 Form for compensation reimbursement. You may decline to provide your SSN and still participate in the study; however, you will not be able to be compensated.
- Related medical information like: family medical history, allergies, past and present medical records, current and past medications or therapies, information from physical examinations such as blood pressure, heart rate, temperature, etc.
- All tests and procedures that will be done in the study including phone calls made as part of this research, records about your study visits, physical exams, laboratory and other test results, records about procedures and implantable devices you have or receive.

Your information may also be given to:

- The US Food and Drug Administration (FDA), Department of Health and Human Services agencies, Health Canada and other governmental agencies
- The Review Board for this institution who reviewed and approved this study

How we will protect and share your information:

- We will do everything we can to keep your information private, but we cannot guarantee this. Study information will be kept in a secured manner and electronic records will be password protected. Study information may be stored with other information in your medical record. Other doctors, nurses, and third parties (like insurance companies) may be able to see this information as part of the regular treatment, payment, and health care operations of the hospital. We may also need to disclose information if required by law.

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

- If we share your identifying information with groups outside of University of Utah Health Sciences Center, they may not be required to follow the same federal privacy laws that we follow. They may also share your information again with others not described in this form.
- If the results of this study are made public, information that identifies you will not be used.
- A copy of this consent form will go into your medical record. This will allow the doctors caring for you to know what study medications or tests you may be receiving as a part of the study and know how to take care of you if you have other health problems or needs during the study.

- Research information collected about you might be put in your medical record. It is possible that you may not be able to see some of the research study information that has become part of your medical record until the entire research study is over.

- The permission you give us to access your medical record will last until the end of the study. You will be given a copy of this authorization.

- If you do not want us to use information about your health, you should not be part of this research. If you choose not to participate, you can still receive health care services at the University of Utah Health Sciences Center.

What if I decide to Not Participate after I sign the Consent and Authorization Form?

You can tell us anytime that you do not want to be in this study and do not want us to use your health information. You can also tell us in writing. If you change your mind, we will not be able to collect new information about you, and you will be withdrawn from the research study. However, we can continue to use information we have already started to use in our research, as needed to maintain the integrity of the research. This authorization does not have an expiration date. You have a right to information used to make decisions about your health care. However, your information from this study will not be available during the study; it will be available after the study is finished.

Statement of Consent

I confirm that I have read this consent and authorization document and have had the opportunity to ask questions and they have been answered. I will be given a signed copy of the consent and authorization form to keep. I give permission to use and share my health data as described in this form.

I agree to take part in this research study and authorize you to use and disclose health information about me for this study, as you have explained in this document.

_____
Participant's Name

_____ _____
Participant's Signature Date

_____
Name of Person Obtaining Authorization and Consent

_____ _____
Signature of Person Obtaining Authorization and Consent Date