The following document is: Informed Consent Document for Research

Approval date: 10/31/2024

NCT number: NCT05274243

Study Title: **2-HOBA Phase 2 Clinical Trial in Rheumatoid Arthritis**
Version Date: **07/03/2024**
PI: **Michelle J Ormseth, MD, MSCI**

Name of participant: _____ Age: _____

The following is given to you to tell you about this research study. Please read this form with care and ask any questions you may have about this study. Your questions will be answered. Also, you will be given a copy of this consent form.

Key Information:
The first section of this document contains some key points that the research team thought you would find important. The study is described in more detail after this section. If you do not understand something, please ask someone.

Key information about this study:
The purpose of this study is to test a new potential drug for Rheumatoid Arthritis (RA), called 2-hydroxybenzylamine acetate (2-HOBA). 2-HOBA blocks some of the down-stream products of oxidative stress (an imbalance in tissues that can lead to chronic health problems). We are testing how patients with RA tolerate the drug and its effects on disease activity and blood pressure.

After screening you will have two study visits, one at baseline and one about four weeks later. At the baseline study visit we will ask about your medical history and medication use and do a physical examination. We will draw your blood and ask you to collect urine. If you are of childbearing capacity, we will test your urine to see if you are pregnant. We will outfit you with a 24-hour blood pressure monitor to wear home for one day while doing your normal activities. We will give you either 2-HOBA or a placebo (an inactive substance) to take three times a day for about 4 weeks. You will have equal chance of being given 2-HOBA or placebo (i.e. like the flip of a coin). You can take the drug with or without food. We will contact you between study visits to ask about any side effects. At the 4-week visit we will ask about side effects, draw blood, and collect urine. We will have to measure blood pressure over 24-hours. Each study visit will take about 1 to 2 hours.

During the course of the study, we ask that you not change your current RA medications, not take non-steroid anti-inflammatory drugs (NSAIDs), and not take over the counter 2-HOBA supplements. We ask that you take the medication three times a day as directed. If you accidentally miss a dose, we ask that you record it for us.

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Institutional Review Board
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2-HOBA is not approved by the Food and Drug Administration (FDA) for any disease. 2-HOBA is currently available in the food chain as both a compound found naturally in buckwheat as well as used as a self-affirmed "GRAS" (generally regarded as safe) ingredient in food and dietary supplements.

Detailed Information:
The rest of this document includes detailed information about this study (in addition to the information listed above).

You are being asked to take part in this research study because you have RA. The purpose of this study is to examine the use of 2-HOBA as a possible therapy for RA as both a treatment to reduce RA disease activity and to reduce hypertension. Oxidative stress is increased in patients with RA. Some products of oxidative stress alter proteins and can make a person's immune system target the protein as foreign and cause excess inflammation. Treatments which focus on decreasing oxidative stress may not be safe in patients with RA because some immune cells need to have oxidative stress to work properly. Scavenging products of oxidative stress may be a better option. 2-HOBA is a compound that occurs naturally in buckwheat seeds that scavenges products of oxidative stress. 2-HOBA has been evaluated for safety in humans at Vanderbilt University Medical Center and found to be safe when given as a single dose of 825 mg or up to 750 mg every 8 hours for 2 weeks in healthy volunteers. About 32 patients with RA will take part in this study.

You do not have to be in this research study. You may choose not to be in this study and get other treatments without changing your healthcare, services, or other rights. You can stop being in this study at any time. If we learn something new that may affect the risks or benefits of this study, you will be told so that you can decide whether or not you still want to be in this study. Your medical record will contain a note saying you are in a research study and may contain some research information about you. Anyone you authorize to receive your medical record will also get this information.

Side effects and risks that you can expect if you take part in this study:
Taking blood using a needle in your vein may be painful and may cause pain, redness, soreness, bruising, or infection may occur at the needle stick site. Rarely some people may faint. Urine sample collection can be inconvenient. Wearing the 24-hour blood pressure monitor may be annoying and disturb sleep.
2-HOBA is a compound that naturally occurs in buckwheat grain and is available to purchase without a prescription. 2-HOBA has previously been given to humans in two clinical trials. In these studies, there were no serious side effects. Common side effects (>10%) reported included frequent urination. Uncommon side effects (<10%) reported include headache, GI distress (such as abdominal

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pain/cramping, bloating, heartburn, vomiting, or diarrhea), itchy throat, rash, sleepiness and abdominal bloating. Rare side effects (< 1%) reported included dry mouth, eye irritation and nasal congestion.

Risks that are not known:
Because this treatment is investigational, meaning non-FDA approved, there may be risks that we do not know about at this time. At this time the characterization of the genotoxic potential (the ability of the drug to cause DNA damage which could lead to cancer) of 2-HOBA is incomplete.

Other Risks:
One risk of giving samples for this research may be the release of your name that could link you to the stored samples and/or the results of the tests run on your samples. This may cause problems with insurance or getting a job.

To prevent this, these samples will be given a code. Only the study staff will know the code. The name that belongs to the code will be kept in a locked file or in a computer with a password. Only Dr Ormseth and her study personnel will have access to your name.

Health insurance companies and group health plans may not use your genetic information when making decisions regarding your eligibility or premiums. Employers with 15 or more employees may not use your genetic information that comes from this research when making a decision to hire, promote, or fire you or when setting the terms of your employment.

Your sample will be used to extract DNA that will be kept for an unknown length of time (maybe years) for future research. The sample will be destroyed when it is no longer needed.

Good effects that might result from this study:
The benefits to science and humankind that might result from this study: We may find a new drug for RA that may also decrease blood pressure and cardiovascular risk which is increased in RA. Because this drug is cheaply made compared to other RA drugs, it could reduce drug costs for patients with RA.

Procedures to be followed:

Screening
If you agree to be in this study, we will screen you for eligibility. We will review your chart and ask you about your RA history, other medical history, medication usage, and do a physical examination to see if you qualify for the study. Also, we will draw your blood (approximately 3

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Institutional Review Board
VANDERBILT

tablespoons) and ask for a urine sample to see if you are pregnant if you have childbearing capacity.

If you qualify for the study, you will return for a baseline study visit at the Vanderbilt Clinical Research Center. We ask that you not change your RA medications, which also includes prednisone, for at least 4 weeks prior to your baseline visit and throughout the study. We ask that you discontinue NSAID use 2 weeks prior to the baseline visit. Because there is no data about the effect of 2-HOBA on a developing fetus, if you are of childbearing potential, we ask that you use effective birth control (examples: condom, diaphragm, oral contraceptive pill, intrauterine device) throughout the study and for 4 weeks after completion of the study.

Baseline visit

At your baseline study visit we will ask additional questions about your medical history and give you a questionnaire about your health, confirm which medications you are taking, examine you, draw blood (approximately 6 tablespoons of blood), and ask you to collect urine. If you are of childbearing capacity, we will check to see if you are pregnant. You will be given either 2-HOBA or placebo capsules to begin taking after you have finished your 24-hour blood pressure monitoring.

We will provide you with a 24-hour blood pressure monitor which we will teach you how to use. This will measure your blood pressure every 15-30 minutes during the day and every 30 minutes at night for the next 24 hours. You will wear this for 24 hours. When the machine takes your blood pressure, the cuff will get tight around your arm. If it is so tight that it feels painful, you can push the button to stop the measurement. The cuff will go down and release the pressure on your arm. If the arm gets swollen, numb, or bruised you should stop the readings and take the cuff off. You will be asked to keep an activity diary while wearing the 24-hour blood pressure monitor.

We will ask you to bring the monitor to your week 4 study visit, drop it off, or send it back to us in a prepaid box. If you are not able to put the monitor on yourself or if it does not work properly we will put it on for you on at the end of your study visit. After it has run for 24-hours we will ask you to return the monitor and activity diary to us either by dropping them off or sending them in a prepaid box.

After you complete the 24-hour blood pressure monitoring, you should start the study drug. You will take three capsules three times a day until your week-4 visit. Between your baseline and week-4 study visit, we will contact you about how you are doing. We ask that you keep record of any missing doses.

This box is for IRB USE ONLY Do not edit or delete
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Institutional Review Board
VANDERBILT

Study Title: **2-HOBA Phase 2 Clinical Trial in Rheumatoid Arthritis**
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Week-4 visit

At your week-4 study visit we will ask about any side effects, give you a questionnaire about your health, confirm which medications you are taking, examine you, draw blood, and ask you to collect urine. We will collect remaining capsules. We may send you the 24-hour blood pressure machine to wear just prior to your week-4 study visit, or outfit you with the 24-hour blood pressure machine at the time of the week-4 visit.

In the future we may look at genes (DNA) and how they affect health and disease. Genes are the instruction manual for your body. The genes you get from your parents decide what you look like and how your body behaves. They can also tell us a person's risk for certain diseases and how they will respond to treatment.

Some of the blood collected may be used for genetic research. What we learn about you from this sample will not be put in your health record. Your test results will not be shared with you or your doctor. No one else (like a relative, boss, or insurance company) will be given your test results.

Payments for your time spent taking part in this study or expenses:
You will be offered $125 for each study visit for up to $250 for completion of the full study.

You are not allowed to accept any money for taking part in this study if you are not eligible to receive money from a U.S. person or company or the U.S. government because of U.S. national security and/or foreign policy laws. You can still take part in the study however, you will not be paid if you are a resident of a country restricted by the U.S. government's comprehensive territorial sanctions or if you are listed on the U.S. Treasury Department's Office of Foreign Assets Control's Specially Designated Nationals (SDN) list of prohibited individuals. You do not have to say why you choose not to be paid.

Costs to you if you take part in this study:

There is no cost to you for taking part in this study.

If you agree to take part in this research study, you and/or your insurance will not have to pay for the tests and treatments that are being done only for research. However, you are still responsible for paying for the usual care you would normally receive for the treatment of your illness. This includes treatments and tests you would need even if you were not in this study. These costs will be billed to you and/or your insurance.

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Institutional Review Board
VANDERBILT

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Version Date: **07/03/2024**
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You have the right to ask what it may cost you to take part in this study. If you would like assistance, financial counseling is available through the Vanderbilt Financial Assistance Program. The study staff can help you contact this program. You have the right to contact your insurance company to discuss the costs of your routine care (non-research) further before choosing to be in the study. You may choose not to be in this study if your insurance does not pay for your routine care (non-research) costs and your doctor will discuss other treatment plans with you.

Payment in case you are injured because of this research study:
If it is determined by Vanderbilt and the Investigator that an injury occurred as a direct result of the tests or treatments that are done for research, then you and/or your insurance will not have to pay for the cost of immediate medical care provided **at Vanderbilt** to treat the injury.

There are no plans for Vanderbilt to pay for any injury caused by the usual care you would normally receive for treating your illness or the costs of any additional care. There are no plans for Vanderbilt to give you money for the injury.

Who to call for any questions or in case you are injured:
If you should have any questions about this research study or if you feel you have been hurt by being a part of this study, please feel free to contact Dr Michelle Ormseth at 615-835-5771 or 615-480-2265.

For additional information about giving consent or your rights as a person in this study, to discuss problems, concerns, and questions, or to offer input, please feel free to call the VUMC Institutional Review Board Office at (615) 322-2918 or toll free at (866) 224-8273.

Reasons why the study doctor may take you out of this study:
If you have a side effect which may be due to the drug, your study doctor may ask you to discontinue to the study drug but complete the study visits and procedures. In such a case you would not be removed from the study, but you would simply stop the drug. Information even after you stop the drug is scientifically important. You may be removed from this study ("withdrawn") without your consent if:

- Staying in the study would be harmful to you
- You no longer meet the requirements of the study
- The study is stopped.

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Institutional Review Board
VANDERBILT

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What will happen if you decide to stop being in this study?
If you decide to stop being part of the study, you should tell your study doctor. You may be asked to conduct an exit visit prior to withdraw from the study. Deciding to not be part of the study will not change your regular medical care in any way.

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

Confidentiality:
Information we collect from you will be stored in a secure, password-protected database. Your samples will be labeled with a code instead of your name. Access to this information will be granted only to members of the study team.

Dr. Ormseth and/or Vanderbilt may share your information and/or samples, without identifiers, to others or use it for other research projects not listed in this form. Vanderbilt, Dr Ormseth and her staff will comply with any and all laws regarding the privacy of such information. There are no plans to pay you for the use or transfer of this de-identified information or samples.

This study may have some support from the National Institutes of Health (NIH). If so, your study information is protected by a Certificate of Confidentiality. This Certificate allows us, in some cases, to refuse to give out your information even if requested using legal means.

It does not protect information that we have to report by law, such as child abuse or some infectious diseases. The Certificate does not prevent us from disclosing your information if we learn of possible harm to yourself or others, or if you need medical help.

Disclosures that you consent to in this document are not protected. This includes putting research data in the medical record or sharing research data for this study or future research. Disclosures that you make yourself are also not protected.

Privacy:

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Institutional Review Board
VANDERBILT

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Any samples and information about you may be made available to others to use for research. To protect your privacy, we will not release your name. You will not receive any benefit as a result of the tests done on your samples. These tests may help us or other researchers learn more about the causes, risks, treatments, or how to prevent this and other health problems.

Your samples may be used to make new products or tests. These may have value and may be developed and owned by the study staff, Vanderbilt University, Vanderbilt University Medical Center, and/or others. If this happens, there are no plans to provide money to you. The research may include whole genome sequencing.

At any time, you may ask to have your sample destroyed and no longer used for research. You should contact Dr Ormseth at:

Dr. Michelle Ormseth
Vanderbilt Rheumatology
1161 21st Avenue So.
T-3113 MCN
Nashville, TN 37232
615-835-5771

We will not be able to destroy research data that has already been gathered using your sample. Also, if your identity was removed from the samples, we will not be able to locate and destroy them.

There will be no costs to you for any of the tests done on your samples. You will not be paid for the use of your samples.

Study Results:
The study results will be published and presented in clinicaltrials.gov.

Authorization to Use/Disclose Protected Health Information

What information is being collected, used, or shared?

To do this research, we will need to collect, use, and share your private health information. By signing this document, you agree that your health care providers (including both Vanderbilt University Medical Center and others) may release your private health information to us, and that we may use any and all of your information that the study team believes it needs to conduct the study. Your private information may include things learned from the procedures described in this consent form, as well as information from your medical record (which may include information such as HIV status, drug, alcohol or STD treatment, genetic test results, or mental health treatment).

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Who will see, use or share the information?
The people who may request, receive or use your private health information include the researchers and their staff. Additionally, we may share your information with other people at Vanderbilt, for example if needed for your clinical care or study oversight. By signing this form, you give permission to the research team to share your information with others outside of Vanderbilt University Medical Center. This may include the sponsor of the study and its agents or contractors, outside providers, study safety monitors, government agencies (such as NIAMS, the funding agency or its representatives), other sites in the study, data managers and other agents and contractors used by the study team. We try to make sure that everyone who sees your information keeps it confidential, but we cannot guarantee that your information will not be shared with others. If your information is disclosed by your health care providers or the research team to others, federal and state confidentiality laws may no longer protect it.

Do you have to sign this Authorization?
You do not have to sign this Authorization, but if you do not, you may not join the study.

How long will your information be used or shared?
Your Authorization for the collection, use, and sharing of your information does not expire. Additionally, you agree that your information may be used for similar or related future research studies.

What if you change your mind?
You may change your mind and cancel this Authorization at any time. If you cancel, you must contact the Principal Investigator in writing to let her know by using the contact information provided in this consent form. Your cancellation will not affect information already collected in the study, or information that has already been shared with others before you cancelled your authorization.

If you decide not to take part in this research study, it will not affect your treatment, payment or enrollment in any health plans or affect your ability to get benefits. You will get a copy of this form after it is signed.

Future studies:
You may be contacted in the future for other studies for which you may be eligible. Other studies are optional, and you may decline participation.

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STATEMENT BY PERSON AGREEING TO BE IN THIS STUDY

I have read this consent form and the research study has been explained to me verbally. All my questions have been answered, and I freely and voluntarily choose to take part in this study.

_____ _____
Date Signature of patient/volunteer

Consent obtained by:

_____ _____
Date Signature

_____
Printed Name and Title

Time: _____

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VANDERBILT

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Consent for Genetic Research

The purpose of part of this study may look at genes (DNA) and how they affect health and disease. Genes are the instruction manual for your body. The genes you get from your parents decide what you look like and how your body behaves. They can also tell us a person's risk for certain diseases and how they will respond to treatment.

You are being asked to give a blood sample for genetic research. What we learn about you from this sample will not be put in your health record. Your test results will not be shared with you or your doctor. No one else (like a relative, boss, or insurance company) will be given your test results. Health insurance companies and group health plans may not request your genetic information that comes from this research.

A blood sample will be taken at the same time we take the sample for your lab work, so you will not be stuck an extra time.

One risk of giving samples for this research may be the release of your name that could link you to the stored samples and/or the results of the tests run on your samples. This may cause problems with insurance or getting a job.

Health insurance companies and group health plans may not use your genetic information when making decisions regarding your eligibility or premiums. Employers with 15 or more employees may not use your genetic information that comes from this research when making a decision to hire, promote, or fire you or when setting the terms of your employment.

To prevent this, these samples will be given a code. Only the study staff will know the code. The name that belongs to the code will be kept in a locked file or in a computer with a password. Only Dr. Ormseth and members of her study team will have access to your name.

Your sample will be used to make DNA that will be kept for an unknown length of time (maybe years) for future research. The sample will be destroyed when it is no longer needed.

Your samples may be used to make new products, tests or findings. These may have value and may be developed and owned by the study staff, Vanderbilt University, Vanderbilt University Medical Center, and/or others. If this happens, there are no plans to provide money to you.

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Your samples and information about you may be shared with others to use for research. To protect your privacy, we will not release your name.

You will not receive any benefit as a result of the tests done on your samples. These tests may help us learn more about the causes, risks, treatments, or how to prevent this and other health problems.

Giving samples for research is your free choice and you may be in the study even if you do not want your samples used or stored for gene research.

At any time, you may ask to have your sample destroyed. You should contact Dr. Ormseth at

Dr. Michelle Ormseth
Vanderbilt Rheumatology
1161 21st Avenue So.
T-3113 MCN
Nashville, TN 37232
615-835-5771

to have your sample destroyed and no longer used for research. We will not be able to destroy research data that has already been gathered using your sample. Also, if your identity was removed from the samples, we will not be able to locate and destroy them.

There will be no costs to you for any of the tests done on your samples.

Please check Yes or No to the questions below:

My blood/tissue sample may be used for gene research in this study.

☐ Yes ☐ No

My blood/tissue sample may be stored/shared for future gene research in rheumatoid arthritis and heart disease.

☐ Yes ☐ No

My blood/tissue sample may be stored/shared for future gene research for other health problems (such as cancer, kidney disease, etc).

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☐ Yes ☐ No

Signature: _____ Date: _____

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