Informed Consent Form

A randomized placebo-controlled, double blind pilot crossover trial of levocarnitine for the treatment of keratoconjunctivitis sicca in Sjogren's syndrome

Date: 1/19/2022

NCT03953703

Study Title:	**A randomized placebo-controlled, double blind pilot crossover trial of levocarnitine for the treatment of keratoconjunctivitis sicca in Sjogren's syndrome**
Version Date:	08/27/2021
PI:	Christine Shieh, M.D.

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 about this study:
You are being asked to take part in this research study because you have Sjogren's syndrome (SjS) and have problems related to dry eye. The purpose of this study is to evaluate the safety and effectiveness of the drug levocarnitine in treating the symptoms of dry eye in SjS over the course of three and a half months. Levocarnitine is approved by the US Food & Drug Administration (FDA) for the treatment of primary and secondary carnitine deficiency, but levocarnitine is considered investigational for the purposes of this study. We are seeking to understand whether levocarnitine will improve your dry eye symptoms. After you finish the study, we will look at your medical records, review the results of our testing, and conduct additional laboratory studies on your blood and tear samples to determine if there are similarities among the patients who improved with levocarnitine treatment. This information will help to better identify patients who may benefit from levocarnitine treatment. Approximately 18 people with SjS will be evaluated at Vanderbilt University Medical Center to determine if they are eligible to 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:

Common
Transient nausea and vomiting; abdominal cramps; diarrhea

Rare
Seizures in patients without pre-existing seizure activity; increase in seizure frequency and/or severity in patients with pre-existing seizure activity

Study Title: **A randomized placebo-controlled, double blind pilot crossover trial of levocarnitine for the treatment of keratoconjunctivitis sicca in Sjogren's syndrome**
Version Date: 08/27/2021
PI: Christine Shieh, M.D.

Pregnancy
Levocarnitine is classified as an FDA pregnancy risk. There are no adequate and well-controlled studies in pregnant women. If you are a female who could get pregnant, we will do a urine pregnancy test to make sure you are not pregnant. If you are pregnant, you will not be able to be in the study.

Additional Risks
There are minor risks and discomforts associated with blood draws. We will insert a small needle into the vein to draw blood. This may cause a brief period of pain and possibly a small bruise at the site. Occasionally, a person feels faint when their blood is drawn. There is a small risk of bleeding after removal of the needle and possibly a bruise at the site, which can be prevented by tight compression on the site. Rarely, an infection develops which can be treated. We will use careful and sterile techniques to minimize these side effects. In patients taking levocarnitine, reports of INR increase with the use of warfarin have been observed. It is recommended that INR levels be monitored in patients on warfarin therapy after the initiation of treatment with levocarnitine or after dose adjustments.

Risks that are not known:
There may be risks that we do not know about at this time. If we should find out any new information, we will notify the participants.

Good effects that might result from this study:
a.) The benefits to science and humankind that might result from this study: We may learn about using levocarnitine as a new treatment for certain symptoms of SjS. However, there is no guarantee that you will benefit from being in this research. Additionally, if you are randomized to be in the group of participants taking the placebo pills then it is unlikely you will experience any benefits from taking those pills.

b.) The benefits you might get from being in this study: You may experience an improvement in certain symptoms of your SjS. You may also not benefit from participating in this study.

Procedures to be followed:
If you agree to be in this study, we will ask you to come to the Vanderbilt Clinical Research Center (CRC) three additional study visits over 14 weeks. At the screening visit, we will ask you about your medical history to be sure you are eligible to be in the study. We will draw some blood tests to be sure it will be safe for you to take levocarnitine. You will also undergo testing to be sure that you have measurable dry eye symptoms. If we cannot measure the problems you are having we will not be able to enroll you in the study. At each of the four study visits, tear and blood samples will be taken to measure laboratory

Study Title: **A randomized placebo-controlled, double blind pilot crossover trial of levocarnitine for the treatment of keratoconjunctivitis sicca in Sjogren's syndrome**
Version Date: 08/27/2021
PI: Christine Shieh, M.D.

values that are important for study outcomes and monitoring your safety. We will also ask you a series of questions about your SjS symptoms and you will complete questionnaires and tests to help us measure dry eye and overall SjS disease activity. If you are a woman who could become pregnant, we will ask you for a urine sample to test for pregnancy at the first study visit.

Over the course of the study, you will take pills by mouth twice a day each day. You will receive a medication diary and instructions how to document each time you take the pills. This is a randomized, double-blind, placebo-controlled crossover study which means that you will either receive pills containing the drug levocarnitine or pills that do not contain the drug (placebo) during the first treatment period and the opposite during the second treatment period. You will not know which type of pills you receive during each treatment period and no one on the study team will know which pills you are being given. No one is able to choose who receives which type of pill, and so it is entirely due to random chance which type of pill you will receive. If you begin having side effects that you cannot tolerate we will reduce your dose or take you out of the study.

If you have 1) recently changed medications that may affect dry eye symptoms, 2) regularly use certain medications including drugs of abuse, 3) are pregnant, 4) have any severe psychiatric diseases including schizophrenia, psychosis, or suicidal depression, 5) have a known defect in oxidative phosphorylation, 6) have undergone laser in situ keratomileusis (LASIK), photorefractive keratectomy (PRK), or radial keratectomy, 7) have severe liver or kidney disease, or 8) have a history of seizures you will not be allowed to be in this study. If you are a woman who could become pregnant, we will ask you for a urine sample to test for pregnancy. We will ask you about your medical history to be sure you are eligible to be in the study.

Participants will also be asked to discontinue the use of both contacts and immunomodulatory eye drops/serum tears for a month prior to the study as well as the entire duration of the study (a total of ~14 weeks).

We will also collect and store blood and tear specimens to be used for research. These samples will be stored by a unique number, not by your name.

Your samples may be made available to others to use for research. To protect your privacy, we will not release your name or any other information that might identify you. 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, or prevention of dry eyes or other manifestations of SjS.

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

Please check Yes or No to the questions below:

Study Title: **A randomized placebo-controlled, double blind pilot crossover trial of levocarnitine for the treatment of keratoconjunctivitis sicca in Sjogren's syndrome**
Version Date: 08/27/2021
PI: Christine Shieh, M.D.

My blood may be used for research.
☐ Yes ☐ No

My blood may be stored/shared for future research in SjS or other autoimmune diseases.

☐ Yes ☐ No

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

☐ Yes ☐ No

My tears may be used for research.

☐ Yes ☐ No

My tears may be stored/shared for future research in SjS or other autoimmune diseases.

☐ Yes ☐ No

My tears may be stored/shared for future research for other health problems (such as cancer, heart disease, etc.).

☐ Yes ☐ No

You may contact me for future studies of SjS or other autoimmune diseases.

☐ Yes ☐ No

In the future, your 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 in other studies.

Study Title: **A randomized placebo-controlled, double blind pilot crossover trial of levocarnitine for the treatment of keratoconjunctivitis sicca in Sjogren's syndrome**
Version Date: 08/27/2021
PI: Christine Shieh, M.D.

Visit 1: Screening and Treatment Period 1 Baseline
This visit will take approximately 2 hours. You will come into the CRC where we will ask you some questions about your medical history, conduct a physical exam, take your blood pressure and weigh you. We will collect tear, urine and blood samples and you will complete some tests that measure overall SjS disease activity. You will also undergo an eye examination. Tears will be collected (up to 10 uL per eye) using Schirmer filter paper and/or microcapillary tubes without mechanical stimulation of the conjunctiva. The blood and urine taken during this visit will be used to perform laboratory tests to help determine if you qualify to move on to the drug study. We will approximately take 1-2 tablespoons (up to 15.5mL) of blood from your arm.

Patients that meet final eligibility criteria for this study will move forward to the drug treatment study. If you are eligible for the study, a study coordinator will call you to schedule the second study visit, which will take place in 6 weeks. You will receive pills containing either levocarnitine or placebo, which you will begin taking every day for a total of 6 weeks. Between study visits 1 and 2, a study coordinator will contact you weekly by phone to ask if you are experiencing any side effects from the study drug.

Visit 2: Treatment Period 1 Endpoint
This visit will take approximately 2 hours. You will come into the CRC where we will ask you some questions about your medical history, conduct a physical exam, take your blood pressure and weigh you. We will collect tear and blood samples and you will complete some tests that measure overall SjS disease activity. You will also undergo an eye examination. Tears will be collected at all study visits (up to 10 uL per eye) using Schirmer filter paper and/or microcapillary tubes without mechanical stimulation of the conjunctiva. The blood taken during this visit will be used to perform laboratory tests to confirm your safety. You will schedule study visit 3 to take place after a 2 week washout period.

Visit 3: Treatment Period 2 Baseline
This visit will take approximately 2 hours. You will come into the CRC where we will ask you some questions about your medical history, conduct a physical exam, take your blood pressure, and weigh you. We will collect tear, urine and blood samples and you will complete some tests that measure overall SjS disease activity. You will also undergo an eye examination. Tears will be collected at all study visits (up to 10 uL per eye) using Schirmer filter paper and/or microcapillary tubes without mechanical stimulation of the conjunctiva. The blood and urine taken during this visit will be used to perform laboratory tests to confirm your safety. You will receive your second set of pills (either levocarnitine or placebo) at this study visit. You will take these pills twice a day for a total of 6 weeks. Between study visits 3 and 4, a study coordinator will contact you weekly by phone to ask if you are experiencing any side effects from the study drug.

Study Title:	**A randomized placebo-controlled, double blind pilot crossover trial of levocarnitine for the treatment of keratoconjunctivitis sicca in Sjogren's syndrome**
Version Date:	08/27/2021
PI:	Christine Shieh, M.D.

Visit 4: Treatment Period 4 Endpoint
This visit will take approximately 2 hours. You will come into the CRC where we will ask you some questions about your medical history, conduct a physical exam, take your blood pressure and weigh you. We will collect tear and blood samples and you will complete some tests that measure overall SjS disease activity. You will also undergo an eye examination. Tears will be collected at all study visits (up to 10 uL per eye) using Schirmer filter paper and/or microcapillary tubes without mechanical stimulation of the conjunctiva. The blood and urine taken during this visit will be used to perform laboratory tests to confirm your safety.

Payments for your time spent taking part in this study or expenses:
You will be paid for your time for being in this research study ($50 gift card each visit). You will be paid for each visit you complete including the screening visit even if you do not qualify for the treatment study. You will need to provide your social security number (SSN) in order for us to pay you. You may choose to participate without being paid if you do not wish to provide your SSN for this purpose. You will also need to provide your address so that a check can be mailed to you. Your SSN is obtained for payment purposes only and it will not be retained for research purposes. It may take up to 4-6 weeks to receive your check following completion or withdrawal from the study.

Costs to you if you take part in this study:
There is no cost to you for taking part in this study.

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 Jonathan Williams, PhD (Study Coordinator) at 615-875-9200 orChristine Shieh, MD (Principal Investigator) at 615-936-2020.

Study Title:	**A randomized placebo-controlled, double blind pilot crossover trial of levocarnitine for the treatment of keratoconjunctivitis sicca in Sjogren's syndrome**
Version Date:	08/27/2021
PI:	Christine Shieh, M.D.

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:
[The study doctor may take you out of the study if you are having side effects that you cannot tolerate.

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. 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:
All efforts, within reason, will be made to keep your personal information in your research record confidential but total confidentiality cannot be guaranteed. The study results will be kept in your research record for at least six years after the study is over for as long as we need the information for the study. All the information on paper will be kept locked in a secure location. Any information kept in a computer will be through REDCap or the Vanderbilt CRC data system, which has many safeguards. Only members of Dr.Shieh's research team will be able to see any of the information that would identify you. Any research data entered into your medical record will be kept as long as it is needed.

Vanderbilt may share your information, without identifiers, to others or use it for other research projects not listed in this form. Vanderbilt, Dr. Shieh 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.

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.

Study Title:	**A randomized placebo-controlled, double blind pilot crossover trial of levocarnitine for the treatment of keratoconjunctivitis sicca in Sjogren's syndrome**
Version Date:	08/27/2021
PI:	Christine Shieh, M.D.

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:

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.

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).

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, 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.

Study Title: **A randomized placebo-controlled, double blind pilot crossover trial of levocarnitine for the treatment of keratoconjunctivitis sicca in Sjogren's syndrome**
Version Date: 08/27/2021
PI: Christine Shieh, M.D.

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 them 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.

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

Study Title:	**A randomized placebo-controlled, double blind pilot crossover trial of levocarnitine for the treatment of keratoconjunctivitis sicca in Sjogren's syndrome**
Version Date:	08/27/2021
PI:	Christine Shieh, M.D.

Time: _____