Informed Consent Form

Antibiotic-mediated Improvements in Vigilance: Mechanisms of Action of Clarithromycin in Hypersomnia Syndromes

IRB Approval Date: September 18, 2024

NCT04026958

You Are Being Asked to Be in a Research Study

Concise presentation of key concepts

You are being asked to be in a research study. A research study is designed to answer a scientific question.

Why is this study being done?

This study is being done to answer the question: How does the medication clarithromycin reduce excessive daytime sleepiness? You are being asked to be in this research study because you have idiopathic hypersomnia, narcolepsy with cataplexy (narcolepsy type 1),or narcolepsy without cataplexy (narcolepsy type 2). If you agree to be in the study, you will be one of up to 150 people who are being studied at Emory.

Do you have to be in the study?

It is your decision to be part of this research study. You do not have to be in it. Your choice will not affect your access to medical care for your condition. Before you make your decision, you should take time to learn about the study.

What do I have to do if I choose to participate in this study?

If you are eligible and want to be part of the study, you will participate for up to four weeks (five study visits). The researchers will ask you to do the following: take a study medication (either the medication clarithromycin or a placebo) twice a day for two weeks, provide two blood samples, provide two spinal fluid samples, provide two stool samples, undergo two daytime nap tests, and have two brain MRIs. All of these procedures will be paid for by the study.

How is this study going to help you?

If you are in the study, you will be helping the researchers answer the study question. If you are assigned to take clarithromycin during this study, your sleepiness may improve, although it may not. It could even get worse.

How are the risks or discomforts I should know about before making a decision?

The study will take time. The drug that is being tested may not work any better than regular care and may even cause harm. All studies have some risks. Some risks are relatively small, like being bored or losing time. Some are more serious – for this study, these include: 1) the risks of clarithromycin, some of which are infection, liver or kidney disease, pancreatitis, abnormal heart rhythms, low blood cell counts, reversible hearing loss, seizures, psychosis or behavioral disturbances, hallucinations, allergic reaction, severe drug rashes, low blood sugar, worsening of myasthenia gravis, or muscle breakdown; 2) the risks of spinal tap, which include

nerve or brain damage, infection, and bleeding; 3) loss of privacy; and 4) breach of confidentiality. A full list of expected risks, their frequency and severity are in the "What are the possible risks and discomforts?" section of this document.

Alternatives to Joining This Study

Treatment with clarithromycin is available outside of this study. If you are interested in clarithromycin treatment without participating in this study, please contact the doctor who treats your idiopathic hypersomnia or narcolepsy.

Costs

You will not have to pay for the study procedures. There is more information in the cost section below.

What Should I Do Next?

Read this form, or have it read to you. Make sure the study doctor or study staff explains the study to you. Ask questions (e.g., about exact time commitment, about unfamiliar words, more details on specific procedures, etc.) Take time to consider this and talk about it with your family and friends.

Emory University
Consent to be a Research Subject / HIPAA Authorization

Title: Antibiotic-mediated improvements in vigilance: mechanisms of action of clarithromycin in hypersomnia syndromes

Principal Investigator: Lynn Marie Trotti, MD, MSc, Associate Professor of Neurology

Study-Supporter: The National Institutes of Health

Introduction
You are being asked to be in a medical research study. This form is designed to tell you everything you need to think about before you decide if you want to be a part of the study. **It is entirely your choice. If you decide to take part, you can change your mind later on and withdraw from the research study.** The decision to join or not join the research study will not cause you to lose any medical benefits. If you decide not to take part in this study, your doctor will continue to treat you.

Before making your decision:
- Please carefully read this form or have it read to you
- Please listen to the study doctor or study staff explain the study to you
- Please ask questions about anything that is not clear

You can take a copy of this consent form, to keep. Feel free to take your time thinking about whether you would like to participate. You may wish to discuss your decision with family or friends. Do not sign this consent form unless you have had a chance to ask questions and get answers that make sense to you. By signing this form you will not give up any legal rights.

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.

What is the purpose of this study?
The purpose of this study is to evaluate a medication called clarithromycin for treating sleepiness in three related conditions, narcolepsy with cataplexy, narcolepsy without cataplexy, and idiopathic hypersomnia. Studies have shown that clarithromycin can reduce sleepiness, but researchers do not know how clarithromycin does this. This study will look at brain activity (on MRI and brainwaves/EEG), inflammation, bacteria living in the gut, and cerebrospinal fluid, to better understand how clarithromycin can reduce sleepiness. If you agree to be in the study, you will be one of up to 150 people who are being studied at Emory. We intend to complete the study procedures on 92 people.

What will I be asked to do?

This study involves five different visits.
Visit 1: Enrollment: During this visit, you will discuss the study. You will provide some information about your medical history and complete some questionnaires. This visit is expected to take up to one hour. If you are taking certain medications (modafinil, armodafinil, stimulants, other medications to wake you up), you may be asked to wean off of this medication before and during the study.
- During the research slow-down created by the COVID19 pandemic, several modifications will be made to allow continued data collection while protecting the health of participants, study staff, and the population:

- Consent and questionnaires will be completed virtually, rather than in-person. The video platform that will be used to complete virtual consents and questionnaires is Zoom. This platform is currently approved by Emory.
- You can discuss the study with a member of the study team by phone or video.

Participants with treated moderate to severe OSA (obstructive sleep apnea), who also have a diagnosis of narcolepsy type 1, narcolepsy type 2, or idiopathic hypersomnia, will be considered for enrollment if the following are true:
Treated OSA-

- Documentation that OSA is being effectively treated
- Documentation that participant is using prescribed treatment
- Documentation of IH, NT1, or NT2 diagnosis either established prior to development of moderate to severe sleep apnea or by testing after sleep apnea is treated

Participants needing MSLT after treatment of OSA will be scheduled for an additional study visit. During this visit, participants will come to the Sleep Center at approximately 7 am and remain until approximately 5 pm to complete a "multiple sleep latency test" (MSLT), taking naps five times during the day. For the week leading up to the MSLT, the participant will keep a sleep log and wear actigraphy.

Visit 2: MRI: During this visit, you will have a special cap placed on your head to measure your brain waves. Once the cap is placed, you will have an MRI (magnetic resonance imaging) scan of your brain. You will be provided with a specimen container and instructions to provide a stool sample, to be returned to the researchers at or after Visit 3. The visit should last approximately 2 hours, with up to 1 hour spent in the MRI scanner.

Visit 3: Nap testing and sample collection: This visit will generally occur one day after Visit 2. During this visit, you will undergo a Maintenance of Wakefulness Test. This is a daytime sleep test that asks you to sit comfortably in a dark room and try to remain awake for 40 minutes at a time, done four times over the course of a day. In between nap opportunities, you will have free time. Following the fourth nap opportunity, you will undergo blood draw and spinal tap. A spinal tap is a routine medical procedure. The spinal tap will take approximately 15-20 ml of cerebrospinal fluid (CSF) and last about 20-30 minutes. During the spinal tap you will be asked to lie on your side curled up in a fetus-like position. Your lower back will be sterilized with liquid iodine or alcohol solutions, a local anesthetic will then be applied under the skin, and the CSF withdrawn using a needle that will be passed between a pair of lower back bones. Your spinal fluid will be examined for levels of substances that can help us understand sleep and wakefulness. About three-four tablespoons of your blood will be drawn from a vein in your arm. The blood will be used to look at substances that may affect sleepiness and, if you are a woman, to do a pregnancy test to make sure you are not pregnant. You will be given a study medication to take home. You should take this medication twice a day, once with breakfast and once with lunch, until your participation in the study has finished. You should start taking this medication the day after Visit 3. If you have not provided a stool sample by the end of Visit 3, wait until after you provide this sample to start the study medication. This visit should last approximately 8 hours.

Visit 4: On-treatment MRI: Two weeks after Visit 2, you will return for a second MRI, performed the same way as Visit 2. During this visit, you will be given a container for a second stool sample and a series of questionnaires to perform. This visit should last approximately 2 hours.

Visit 5: On-treatment nap testing and sample collection. Two weeks after Visit 3, you will return for a second Maintenance of Wakefulness Test and repeat sample collection. At the completion of this visit, your participation in the study is complete and you should discontinue the study medication.

However, we are also asking for your permission to use any leftover blood, cerebrospinal fluid (CSF), and stool samples in the future, so we can look at new questions about sleep disorders that may arise. This is important, because the types of tests we would like to do can change over time as science advances and providing your permission now will allow us to make the most use of your sample for the purposes of better understanding sleep disorders. This step would not require you to provide any additional blood or do any additional questionnaires. The use of data in future research is

a requirement of participation, but participants can later request that their samples and data no longer be used. Please refer to the section, *Who owns my study information and samples*, for instructions on how to proceed if you no longer want your samples and data to be used.

How will my medicine be provided?
The medicine that you will take will be dispensed by the pharmacy and delivered to the principal investigator or study team member. The principal investigator or health care providers on his/her research team will provide the medicine to you. If you have questions about the medicine, you should ask one of the study doctors (Drs. Trotti or Rye). You may also call the pharmacy at [redacted] if you have questions about the medicine. The number for the pharmacy is included on your medicine package.

Who owns my study information and samples?
If you join this study, you will be donating your samples and study information. You will not receive any compensation if your samples or information are used to make a new product. If you withdraw from the study, data and samples that were already collected may still be used for this study. If you would like your samples to be destroyed, you must notify Dr. Trotti in writing at [redacted]

What are the possible risks and discomforts?
There may be side effects from the study drug or procedures that are not known at this time.

The most common risks and discomforts expected in this study are:

Related to the study medication: upset stomach (21%) or any gastrointestinal distress (73%), bad taste (9-68%%), insomnia (11-27%%), headache (2-14%), a panicky feeling or anxiety (2-5%), vomiting (2%), or a feeling of weakness (2%). In a small clinical trial, none of these symptoms were more common with clarithromycin than with placebo, except for bad taste.

Related to weaning off of your medications for sleepiness: In preparation for the study, if you are taking medications to treat excessive sleepiness, reducing the dose and then stopping these medications is likely to result in a temporary return of sleepiness (i.e., until you resume medication).

Related to the MRI: claustrophobia (approximately 5%)

Related to the EEG: mild scalp discomfort (approximately 5%)

Related to the MWT and/or MSLT test: mild skin or scalp discomfort (less than 5%)

Related to the spinal tap: headache (between 5-30%), low back pain (approximately 10-20%). To minimize the chance of headache, smaller or rounded needles will be used when possible and you will be asked to ingest more fluids than usual and to restrict strenuous physical activity for at least 24-48 hours.

Related to the blood draw: discomfort or bruising (approximately 10-20%)

The less common risks and discomforts expected in this study are:

Related to the blood draw:
possible lightheadedness or fainting

Related to the spinal tap:

Headaches that persist more than a few days may require evaluation for performance of a what is called a "blood patch" procedure that is routinely performed by Neurologists and Anesthesiologists (estimated < 1.0% of cases).

Rare but possible risks include:

Related to the study medication (all less than 1% risk): infection, liver or kidney disease, pancreatitis, abnormal heart rhythms, low blood cell counts, reversible hearing loss, seizures, psychosis or behavioral disturbances, hallucinations, allergic reaction, severe drug rashes, low blood sugar, worsening of myasthenia gravis, or muscle breakdown.

Related to the spinal tap: Very rare complications include an accumulation of blood in the brain; inflammation of the brain or the membranes that cover the brain (meningitis or encephalitis); temporary inflammation of the back bones; temporary or exceptionally rare permanent deafness; collapse of your back bones or spinal tumor (induced inadvertently by a physician). A theoretically possible, but exceptionally rare risk, may involve serious neurological consequences or death in the event of an undiagnosed associated neurological condition, such as an increase in the amount of CSF within the brain that causes expansion of the ventricles and an enlargement of the skull (high pressure hydrocephalus).

If you are a woman: to protect against possible side effects of the study drug, women who are pregnant or nursing a child may not take part in this study. If you become pregnant, there may be risks to you, the embryo, or fetus. These risks are not yet fully known, but may include pregnancy loss, birth defects, heart defects, and poor growth. If you are a woman of childbearing ability, you and the study doctor must agree on a method of birth control to use throughout the study. If you think that you have gotten pregnant during the study, you must tell the study doctor immediately. Pregnant women will be taken out of the study.

If you will be taking the study drug home, keep it out of the reach of children or anyone else who may not be able to read or understand the label. Do not let anyone else take the study drug besides you.

It is possible that the researchers will learn something new during the study about the risks of being in it. If this happens, they will tell you about it. Then you can decide if you want to continue to be in this study or not. You may be asked to sign a new consent form that includes the new information if you decide to stay in the study.

Will I benefit directly from the study?

If you are provided with clarithromycin, this study may benefit you directly by reducing your sleepiness. However, while your sleepiness may improve while you are in this study, it may not, and it may even get worse. This study is designed to learn more about how clarithromycin changes the brain and body, and how these changes are related to improvements in sleepiness. The study results may be used to help others in the future.

Will I be compensated for my time and effort?

You will get $400 total, if you complete all study visits. If you do not finish the study, we will compensate you for the visits you have completed, as follows:

-Visit 1 (Enrollment visit): $10
-Visit 2 (MRI before treatment): $90
-Visit 3 (MWT before treatment): $100
-Visit 4 (MRI on treatment): $100
-Visit 5 (MWT on treatment): $100

You will be asked to fill out a tax form, including your Social Security or Taxpayer Identification Number, in order to be reimbursed, depending on the amount and method of payment. Some payment methods involve mail coming to your house, which may be seen by others in your household. You can decline payment if you are concerned about confidentiality, or you can talk to the study team to see if there are other payment options.

What are my other options?

If you decide not to enter this study, there is care available to you outside of this research study. This includes several medications for excessive daytime sleepiness, including modafinil/armodafinil and psychostimulants. There may be other research studies, including treatment studies, for which you are eligible. You do not have to be in this study to be treated for idiopathic hypersomnia or narcolepsy.

You may wish to research other study options at websites like clinicaltrials.gov and ResearchMatch.org.

How will you protect my private information that you collect in this study?

Whenever possible, a study number, rather than your name, will be used on study records. Your name and other identifying information will not appear when we present or publish the study results.

Certificate of Confidentiality

There is a Certificate of Confidentiality from the National Institutes of Health for this Study. The Certificate of Confidentiality helps us to keep others from learning that you participated in this study. Emory will rely on the Certificate of Confidentiality to refuse to give out study information that identifies you. For example, if Emory received a subpoena for study records, it would not give out information that identifies you.

The Certificate of Confidentiality does not stop you or someone else, like a member of your family, from giving out information about your participation in this study. For example, if you let your insurance company know that you are in this study, and you agree to give the insurance company research information, then the investigator cannot use the Certificate to withhold this information. This means you and your family also need to protect your own privacy.

The Certificate does not stop Emory from making the following disclosures about you:

- Giving state public health officials information about certain infectious diseases,
- Giving law officials information about abuse of a child, elderly person or disabled person.
- Giving out information to prevent harm to you or others.

Giving the study sponsor or funders information about the study, including information for an audit or evaluation.

Storing and Sharing your Information

De-identified data from this study (data that has been stripped of all information that can identify you) may be placed into public databases where, in addition to having no direct identifiers, researchers will need to sign data use agreements before accessing the data. We will remove or code any personal information that could identify you before your information is shared. This will ensure that, by current scientific standards and known methods, it is extremely unlikely that anyone would be able to identify you from the information we share. Despite these measures, we cannot guarantee anonymity of your personal data.

Your data [and specimens] from this study will be stored indefinitely and may be useful for future studies or other research being done by investigators at Emory or elsewhere. To help further science, we may provide your deidentified data and/or specimens to other researchers. If we do, we will not include any information that could identify you. If your data or specimens are labeled with your study ID, we will not allow the other investigators to link that ID to your identifiable information.

We will use your sample and data only for research. We will not sell them. However, the results of this research might someday lead to the development of products (such as a drug or other commercial product) that could be sold by a company. You will not receive money from the sale of any such product.

In general, we will not give you any individual results from the study of the samples you give us, with the exception of pregnancy test results and cerebrospinal fluid hypocretin results. If we find something of urgent medical importance to you, we will inform you, although we expect that this will be a very rare occurrence.

You will be getting an MRI scan for research purposes only. The research does not require health professionals to read the scan. The researchers are not qualified to interpret the images for healthcare purposes. Do not rely on the scan for clinical or diagnostic purposes. However, if the researchers have a question about something they see on the scan they will tell you and ask you if you want the scan sent to a qualified health professional for review and any further medical treatment. You or your insurance company may have to pay for the review and any such treatment.

Medical Record

If you have been an Emory Healthcare patient before, then you already have an Emory Healthcare medical record. If you have never been an Emory Healthcare patient, you do not have one. An Emory Healthcare medical record will be made for you if an Emory provider or facility gives you any services or procedures for this study.

Copies of the consent form/HIPAA authorization that you sign will be put in any Emory Healthcare medical record you have now or any time during the study.

The results of some study tests and procedures will be used only for research purposes and will *not* be placed in your medical record. For this study, those items include: blood, spinal fluid, and stool sample analyses, MRI results, MWT results, EEG results, questionnaires.

The researchers will be looking at the results of some tests that may be useful for your clinical care as well as for the research study and may be included in your medical record or disclosed to you. For this study, those items may include: hypocretin values (cerebrospinal fluid), pregnancy test results

Tests and procedures done at non-Emory places may not become part of your Emory medical record. Also, if you decide to be in this study, it is up to you to let your other health providers know.

In Case of Injury

If you believe you have become ill or injured from this research, you should contact Dr. Trotti at telephone number [redacted]. You should also let any health care provider who treats you know that you are in a research study.

If you get ill or injured from being in the study, Emory will help you to get medical treatment. Neither Emory nor the sponsor will pay for your medical treatment. Your insurer will be billed for your treatment costs. If you do not have insurance, or if your insurance does not pay, then you will have to pay these costs.

Emory and the sponsor have not, however, set aside any money to pay you if you are injured as a result of being in this study or to pay for this medical treatment. For Emory, the only exception is if it is proven that your injury or illness is directly caused by the negligence of an Emory employee. “Negligence” is the failure to follow a standard duty of care. You do not give up any legal rights you may have by being in this study, including any right to bring a claim for negligence.

Costs

There will be no costs to you for participating in this study, other than basic expenses like transportation. You will not be charged for any of the research activities. If the study procedures result in any medical complications that would not fall under "injury" as discussed above, the cost of treatment for those complications may be charged to you or your insurance.

Withdrawal from the Study

You have the right to leave a study at any time without penalty.

For your safety, however, you should consider the study doctor's advice about how to go off the study treatment.

The researchers also have the right to stop your participation in this study without your consent for any reason, especially if they believe it is in your best interest or if you were to object to any future changes that may be made in the study plan.

These are the expected reasons why the researchers may stop your participation:

- You cannot tolerate one of the study procedures
- You cannot remain awake during the MRI scan

Authorization to Use and Disclose Protected Health Information

The privacy of your health information is important to us. We call your health information that identifies you, your "protected health information" or "PHI." To protect your PHI, we will follow federal and state privacy laws, including the Health Insurance Portability and Accountability Act and regulations (HIPAA). We refer to all of these laws as the "Privacy Rules." Here we let you know how we will use and disclose your PHI for the study.

PHI that Will be Used/Disclosed:

The PHI that we will use or share for the main research study includes:

- Medical information about you including your medical history and present/past medications.
- Results of exams, procedures and tests you have before and during the study.
- Laboratory test results.

Purposes for Which Your PHI Will be Used/Disclosed:

We will use and share your PHI for the conduct and oversight of the research study. We will use and share your PHI to provide you with study related treatment and for payment for such treatment. We will also use and share your PHI to conduct normal business operations. We may share your PHI with other people and places that help us conduct or carry out the study, such as laboratories, data management centers, data monitors, contract research organizations, Institutional Review Boards (IRBs) and other study sites. If you leave the study, we may use your PHI to determine your health, vital status or contact information.

Use and Disclosure of Your Information That is Required by Law:

We will use and disclose your PHI when we are required to do so by law. This includes laws that require us to report child abuse or abuse of elderly or disabled adults.

Authorization to Use PHI is Required to Participate:

By signing this form, you give us permission to use and share your PHI as described in this document. You do not have to sign this form to authorize the use and disclosure of your PHI. If you do not sign this form, then you may not participate in the research study or receive research-related treatment. You may still receive non-research related treatment.

People Who will Use/Disclose Your PHI:
The following people and groups will use and disclose your PHI in connection with the research study:

- The Principal Investigator and the research staff will use and disclose your PHI to conduct the study and give you study related treatment.
- Emory may use and disclose your PHI to get payment for study related treatment and to run normal business operations.
- The Principal Investigator and research staff will share your PHI with other people and groups to help conduct the study or to provide oversight for the study.
- The National Institutes of Health is the Supporter of the study. The Supporter may use and disclose your PHI to make sure the research is done correctly and to collect and analyze the results of the research. The Supporter may disclose your PHI to other people and groups like study monitors to help conduct the study or to provide oversight for the study.
- The research team and the Supporter may use and disclose your PHI, including disclosure to insurance carriers to administer payment for subject injury.
- The following people and groups will use your PHI to make sure the research is done correctly and safely:
    - Emory offices that are part of the Human Research Participant Protection Program and those that are involved in study administration and billing. These include the Emory IRB, the Emory Research and Healthcare Compliance Offices, and the Emory Office for Clinical Research.
    - Government agencies that regulate the research including: Office for Human Research Protections, Food and Drug Administration
    - Public health agencies.
    - Research monitors and reviewer.
    - Accreditation agencies.
- Sometimes a Principal Investigator or other researcher moves to a different institution. If this happens, your PHI may be shared with that new institution and their oversight offices. PHI will be shared securely and under a legal agreement to ensure it continues to be used under the terms of this consent and HIPAA authorization.

Expiration of Your Authorization
Your PHI will be used until this research study ends.

Revoking Your Authorization
If you sign this form, at any time later you may revoke (take back) your permission to use your information. If you want to do this, you must contact the study team at:

Dr. Lynn Marie Trotti
Emory Sleep Center
[redacted]

At that point, the researchers would not collect any more of your PHI. But they may use or disclose the information you already gave them so they can follow the law, protect your safety, or make sure that the study was done properly and the data is correct. If you revoke your authorization you will not be able to stay in the study.

Other Items You Should Know about Your Privacy
Not all people and entities are covered by the Privacy Rules. HIPAA only applies to health care providers, health care payers, and health care clearinghouses. If we disclose your information to people who are not covered by the Privacy

Rules, including HIPAA, then your information won't be protected by the Privacy Rules. People who do not have to follow the Privacy rules can use or disclose your information with others without your permission if they are allowed to do so by the laws that cover them. The Supporter, and people and companies working with the Supporter on this study are not covered by the Privacy Rules. They will only use and disclose your information as described in this Consent and Authorization.

To maintain the integrity of this research study, you generally will not have access to your PHI related to this research until the study is complete. When the study ends, and at your request, you generally will have access to your PHI that we maintain in a designated record set. A designated record set is data that includes medical information or billing records that your health care providers use to make decisions about you. If it is necessary for your health care, your health information will be provided to your doctor.

We may remove identifying information from your PHI. Once we do this, the remaining information will not be subject to the Privacy Rules. Information without identifiers may be used or disclosed with other people or organizations for purposes besides this study.

Contact Information

Contact Dr. Trotti at [redacted]:

- if you have any questions about this study or your part in it,
- if you feel you have had a research-related injury or a bad reaction to the study drug, or
- if you have questions, concerns or complaints about the research

Contact the Emory Institutional Review Board at 404-712-0720 or 877-503-9797 or irb@emory.edu:

- if you have questions about your rights as a research participant.
- if you have questions, concerns or complaints about the research.
- You may also let the IRB know about your experience as a research participant through our Research Participant Survey at http://www.surveymonkey.com/s/6ZDMW75.

Other information

Study team members Dr. Rye and Dr. Jenkins have ownership interests in Balance Therapeutics, a company that has licensed the novel use of certain products evaluated in the research. The terms of this arrangement have been reviewed and approved by Emory University in accordance with its conflict of interest policies.

Consent and Authorization

TO BE FILLED OUT BY SUBJECT ONLY

Please **print** your name, **sign**, and **date** below if you agree to be in this research study. By signing this consent and authorization form, you will not give up any of your legal rights.

_____

Name of Subject

_____ _____

Signature of Subject (18 or older and able to consent) **Date** **Time**

TO BE FILLED OUT BY STUDY TEAM ONLY

_____

Name of Person Conducting Informed Consent Discussion

_____ _____

Signature of Person Conducting Informed Consent Discussion **Date** **Time**