Effects of Intravenous (IV) Omadacycline on Gut Microbiome

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Wake Forest®
School of Medicine

Department of Internal Medicine / Section of Infectious Diseases

EFFECTS OF IV OMADACYCLINE ON GUT MICROBIOME

Informed Consent Form to Participate in Research
John Williamson, PharmD, Principal Investigator

SUMMARY

You are invited to participate in a research study. The purpose of this research is to better understand the effect that certain antibiotics have on the human microbiota. The bacteria that live in and on our body are known as our microbiome. This microbiome provides health benefits. Antibiotics are life-saving in that they kill bacteria that are causing us to be ill. However, many antibiotics also kill the healthy bacteria microbiome. Killing of our healthy microbiota is known as dysbiosis. How antibiotics cause dysbiosis and steps to prevent this dysbiosis are poorly understood. You are invited to be in this study because you are a healthy volunteer who has not recently taken antibiotics. Your participation in this research involves taking a 10-day course of an antibiotic called omadacycline. We will collect stool and saliva samples from you prior to starting the antibiotic, daily while on the antibiotic, at three days after stopping the antibiotic, and at 21 days after stopping the antibiotic. For the first five days of participation, visits will last about an hour each day. On days 6-10, 13, and 31, "visits" will only consist of you delivering your samples to the research clinic.

Participation in this study will involve taking an antibiotic via intravenous (administered through your veins) and oral (by mouth) routes. All research studies involve some risks. A risk of this study that you should be aware of is side effects from the antibiotic. You will not benefit from participation in this study, but the knowledge gained from this study may help doctors use antibiotics in the safest possible way in the future.

Your participation in this study is voluntary. You do not have to participate in this study if you do not want to. The alternative is to not participate in this research. You will not lose any services, benefits, or rights you would normally have if you choose not to participate.

The remainder of this form contains a more complete description of this study. Please read this description carefully. You can ask any questions if you need help deciding whether to join the study. The person in charge of this study is John Williamson, PharmD. If you have questions, suggestions, or concerns regarding this study or you want to withdraw from the study, his contact information is: [redacted].

If you have any questions, suggestions or concerns about your rights as a volunteer in this research, contact the Institutional Review Board at [redacted] or the Research Subject Advocate at Wake Forest at [redacted].

INTRODUCTION

You are invited to be in a research study. Research studies are designed to gain scientific knowledge that may help other people in the future. You are being asked to take part in this study because you are considered a healthy volunteer who has not recently taken antibiotics or probiotics. Your participation is voluntary. Please take your time in making your decision as to whether or not you wish to participate. Ask your study doctor or the study staff to explain any words or information contained in this informed consent document that you do not understand. You may also discuss the study with your friends and family.

WHY IS THIS STUDY BEING DONE?

The purpose of this research study is to better understand the effect that an antibiotic called omadacycline has on the human microbiome. As part of this study, we will collect stool and saliva samples and evaluate the types of bacteria that live in your microbiome. As part of this research, we extract DNA (genetic information) from these bacterial samples. However, this genetic information is from the bacteria that live in your gut and NOT your human DNA.

Omadacycline has been approved by the US Food and Drug Administration (FDA) for treatment of certain soft tissue (e.g. skin) infections and a type of pneumonia called community-acquired bacterial pneumonia. However, in this study, we are investigating the impact that taking omadacycline has on your microbiome, rather than using it to treat an infection.

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY?

Eight people at will take part in this study. This study is only being done at Wake Forest University Health Sciences.

WHAT IS INVOLVED IN THE STUDY?

If you decide to participate, you will be asked a series of questions about your medical history and all medications that you have recently taken. If you are a female who is of child-bearing potential, your urine will be checked to make sure that you are not pregnant. This test will be provided by the study team. If you are eligible to continue after these questions (and a negative pregnancy test if you are a female of childbearing potential), you will come to the study clinic and be given omadacycline by IV for five days. Then, you will take omadacycline by mouth at home for five days.

You will also be asked to collect a stool and saliva sample that you will bring in to the study investigators on a daily basis while taking the antibiotic, and two more times after you are finished taking the antibiotic. You will be given kits (with instructions) that allow you to collect these samples. The samples should be immediately refrigerated and then transported to the research lab in a refrigerated transport container that will be provided to you. You will be asked to bring in a stool and saliva sample daily while you are on the antibiotics (your first 10 days of participation), once at 3-4 days after stopping your antibiotic, and then once at a follow-up visit about 21 days after you have stopped your antibiotic.

STORAGE OF BIOLOGICAL SPECIMENS

If you agree to participate in this study, we will obtain stool and saliva samples. You will deliver your samples to the Infectious Diseases Clinical Trials Unit staff at Wake Forest University Baptist Medical Center in Winston-Salem, NC. Your samples will be stored temporarily in Winston-Salem, NC, but will eventually be shipped to the Garey Lab at University of [redacted] for microbiome analysis. Your samples will be given only to researchers approved by the Garey Lab administrators. An Institutional Review Board (IRB) must approve any future research study using your stool and saliva samples.

The research that may be performed with your stool and saliva samples is not designed to help you specifically. There is no personal benefit to you from taking part in this research study. The knowledge gained from this study might help doctors choose antibiotics more appropriately in the future for people who have infections. For instance, a condition called Clostridiodes difficile colitis (inflammation of the colon) occurs because of dysbiosis resulting from certain antibiotics. Knowledge from this study may help doctors choose antibiotics that are less likely to cause dysbiosis and reduce the risk of C. difficile colitis. The results of the research performed with your stool and saliva samples will not be given to you or your doctor. The results will not be put in your medical record. The research using your stool and saliva samples will not affect your care.

Your stool and saliva samples will be used only for research and will not be sold. The findings from this research may result in the future development of products that are of commercial value. There are no plans to share any of the profits with you which may occur as a result of the research.

Your stool and saliva samples will be stored with a unique identifier and will not include any identifiable information about you such as your name, address, telephone number, social security number, medical record number or any of the identifiers outlined in the HIPAA Privacy Rule. The unique identifier will be an assigned number and only the principal investigator will have access to the code that links the unique identifier to you. Your name, address, social security number, etc., will never be disclosed to future researchers and neither will the code that links your identifiers to the sample.

HOW LONG WILL I BE IN THE STUDY?

You will be in the study for up to 36 days.

You can stop participating at any time. If you decide to stop participating in the study we encourage you to talk to the investigators or study staff first to learn about any potential health or safety consequences. Skipping doses or not completing the full course of omadacycline may increase the likelihood that bacteria will develop resistance and will not be treatable by omadacycline or other antibacterial drugs in the future.

WHAT ARE THE RISKS OF THE STUDY?

Being in this study involves some risk to you. You should discuss the risk of being in this study with the study staff. The antibiotic used in this study is FDA approved for certain bacterial infections and is deemed safe and effective. However, all antibiotics are associated with certain risks including developing an infection called C. difficile infection or C. diff infection that causes diarrhea and colitis. Overuse of antibiotics can also lead to development of bacteria that is resistant to the antibiotics. However, your risk of developing C. diff infection or an antibiotic resistant bacterial infection is low in this study.

Other side effects observed in people who take omadacycline are more common than the more serious effects noted above. The following more common effects have been observed in less than 5% of patients (5 out of every 100 patients) who have taken omadacycline:

- Nausea
- Vomiting
- Diarrhea
- Hypertension (elevated blood pressure)
- Headache
- Dizziness
- Insomnia
- Constipation
- Abnormal taste
- Yeast infections of the mouth or vagina
- Photosensitivity (sunburn after sun exposure)

Because sunburn is possible while taking omadacycline, you should avoid prolonged exposure to direct sunlight and/or take precaution by applying a sunscreen to your skin before going outside.

There are some uncommon side effects that have been observed with antibiotics in the same family as omadacycline, e.g. tetracycline. These are possible with omadacycline and include:

- Pseudotumor cerebri (increased pressure in head)
- Pancreatitis (inflammation of the pancreas)

There are laboratory abnormalities that have occurred in patients taking omadacycline or other antibiotics in the same family as omadacycline. These include:

- Increased blood urea nitrogen (BUN)
- Increased phosphorus in the blood
- Increased liver function tests
- Increased acid in the blood
- Increased pancreas enzymes in the blood
- Anemia (low hemoglobin or hematocrit in blood)

For the first five days of this study, you will receive your omadacycline via intravenous infusion.

This means we will place a small tube called an intravenous (IV) catheter into your vein to allow for medications to be given. There are risks associated with receiving infusions. Most are mild in severity, although severe and even fatal reactions can occur. The most common signs and symptoms of infusion reactions are:

- Fever and/or shaking chills
- Flushing and/or itching
- Alterations in heart rate and blood pressure
- Difficulty breathing or chest discomfort
- Back or abdominal pain
- Nausea, vomiting, and/or diarrhea
- Pain, redness, or swelling at the infusion site of your arm
- Various types of skin rashes

In addition, there is a slight risk of a breach of confidentiality. We will do our best to protect your confidential information. There also may be other risks that we cannot predict. You should tell the research staff about all the medications, vitamins and supplements you take and any medical conditions you have. This may help avoid side effects, interactions and other risks.

Taking part in this research study may involve providing information that you consider confidential or private. Efforts, such as coding research records, keeping research records secure and allowing only authorized people to have access to research records, will be made to keep your information safe.

The use of omadacycline during the second and third trimester of pregnancy may cause discoloration of teeth and reversible inhibition (slowed rate) of bone growth. Omadacycline is a tetracycline class drug. Tetracyclines are contraindicated during pregnancy, which is why the study team will provide a urine pregnancy test to you if you are female and of childbearing potential. If your pregnancy test is positive, you will not be allowed to participate in this research.

Reproductive Risks and other Issues Related to Participating in Research for Women

Due to risks and potential harm to the unborn fetus caused by omadacycline, sexually active women of childbearing potential must use a reliable method of birth control while participating in this study. Reliable methods of birth control are: abstinence (not having sex), oral contraceptives, OrthoEvra patch, NuvaRing, intrauterine devices (IUD), Nexplanon implant, DepoProvera, tubal ligation, or vasectomy of the partner (with confirmed negative sperm counts) in a monogamous relationship (same partner). An acceptable, although less reliable, method involves the careful use of condoms and spermicidal foam or gel and/or a diaphragm with spermicide with Plan B used for any noticed condom or diaphragm failures. We encourage you to discuss this issue further with your physicians if you have any questions.

You should not be or become pregnant while participating in this research study. We will provide you with a urine pregnancy test prior to starting the study and also on study day 5 to

ensure you are not pregnant. You may be asked to hold the test stick in your urine stream while urinating or you can collect your urine into a cup and the investigators will dip the test stick into it for you. A private bathroom will be provided for this purpose. You must agree to abstain from sex while you are taking the antibiotic and for at least 10 days after discontinuation or use appropriate contraception to ensure you do not become pregnant.

Contraceptive Measures for Males

Your participation in this research study may damage your sperm, which could cause harm to a child that you may father while on this study. Such harm may be currently unforeseeable. If you are sexually active, you must agree to use a medically acceptable form of birth control in order to be in this study and for at least 10 days after discontinuing the antibiotic. Medically acceptable contraceptives include: (1) surgical sterilization (such as a vasectomy), or (2) a condom used with a spermicide. Contraceptive measures such as Plan B (TM), sold for emergency use after unprotected sex, are not acceptable methods for routine use. You should inform your partner of the potential for harm to an unborn child. She should know that if pregnancy occurs, you will need to report it to the study doctor, and she should also promptly notify her doctor.

You must not donate sperm while you are taking the antibiotic and for at least 10 days after discontinuing the antibiotic.

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?

You are not expected to receive any direct benefit from taking part in this research study. We hope the information learned from this study will benefit other people in the future.

WHAT OTHER CHOICES ARE THERE?

You do not have to be in this study. Your alternative is to not participate in this study.

WHAT ARE THE COSTS?

All study costs, including any study medications and procedures related directly to the study, will be paid for by the study. Costs for your regular medical care, which are not related to this study, will be your own responsibility.

WILL YOUR RESEARCH RECORDS BE CONFIDENTIAL?

The results of this research study may be presented at scientific or medical meetings or published in scientific journals. Your identity and/or your personal health information will not be disclosed unless it is authorized by you, required by law, or necessary to protect the safety of yourself or others. There is always some risk that even de-identified information might be re-identified.

Participant information may be provided to Federal and other regulatory agencies as required. The Food and Drug Administration (FDA), for example, may inspect research records and learn your identity if this study falls within its jurisdiction.

The purpose of this research study is to obtain data or information on the effect omadacycline

has on the microbiome of healthy volunteers; the results will be provided to the sponsor, the Food and Drug Administration and other federal and regulatory agencies as required.

WILL YOU BE PAID FOR PARTICIPATING?

You will be paid up to $575 if you complete all the scheduled study visits. You will be paid in three installments.

- You will be paid $100 for completing all study procedures on Day 1. This includes providing two stool samples, one before your dose of omadacycline, and one after.
- On Day 5, you will be paid $75 for each visit you attended between Day 2 and Day 5. In other words, on Day 5, you will receive up to $300, depending on how many visits you attended from Day 2 through 5. For example, if you do not attend one of the visits between Days 2 and 5, you would only be paid $225 on Day 5.
- On Day 31 (±1), you will be paid $25 for each sample you bring to the clinic on days 6 through 10, Day 13(+1), and Day 31(±1). There are a total of 7 samples expected from Day 6 through the end of the study on Day 31(±1), which means you will be paid up to $175 on Day 31 (±1). For example, if you do not attend one of the visits between Days 6 and 10, you would only be paid $150 on Day 31(±1).

To receive payment, you must provide your social security number, name and address so that we can comply with IRS (Internal Revenue Service) reporting requirements. When payments are reported to the IRS we do not let them know what the payment is for, only that you have been paid. If you do not wish to provide this information you can still take part in this study but you will not be paid.

The findings from this research may result in the future development of products that are of commercial value. There are no plans to provide you with financial compensation or for you to share in any profits if this should occur.

WHO IS SPONSORING THIS STUDY?

This study is being sponsored by Paratek Pharmaceuticals. The sponsor is providing money or other support to Wake Forest University Health Sciences to help conduct this study. The researchers do not, however, hold a direct financial interest in the sponsor or the product being studied.

WHAT HAPPENS IF YOU EXPERIENCE AN INJURY OR ILLNESS AS A RESULT OF PARTICIPATING IN THIS STUDY?

Should you experience a physical injury or illness as a direct result of your participation in this study, Wake Forest University School of Medicine maintains limited research insurance coverage for the usual and customary medical fees for reasonable and necessary treatment of such injuries or illnesses. To the extent research insurance coverage is available under this policy the reasonable costs of these necessary medical services will be paid, up to a maximum of $25,000. Wake Forest University Baptist Medical Center holds the insurance policy for this coverage. It provides a maximum of $25,000 coverage for each claim and is limited to a total of

$250,000 for all claims in any one year. The Wake Forest University School of Medicine, and the North Carolina Baptist Hospitals, Incorporated do not assume responsibility to pay for these medical services or to provide any other compensation for such injury or illness. Additional information may be obtained from the Medical Center's Director of Risk and Insurance Management, at [redacted].

If you are injured, the insurer may require information such as your name, social security number, and date of birth in order to pay for your care. This is because the insurer is required by law to report any payments made to cover the care of any persons who are members of a government insurance plan to the Department of Health and Human Services.

You do not give up any legal rights as a research participant by signing this consent form. For more information on medical treatment for research related injuries or to report a study related illness, adverse event, or injury you should call John Williamson at [redacted] during business hours. After hours, you may contact the investigator at [redacted].

WHAT ABOUT MY HEALTH INFORMATION?

In this research study, any new information we collect from you and information we get from your medical records or other facilities about your health or behaviors is considered Protected Health Information. The information we will collect for this research study includes**:** basic demographic information, height and weight, dietary habits, history of cardiovascular, gastrointestinal, hepatic or renal disease, recent antibiotic or probiotic use, smoking and alcohol history, and childbearing potential status for female participants.

If this research study involves the diagnosis or treatment of a medical condition, then Protected Health Information collected from you during this study may be placed in your medical record, and may be used to help treat you, arrange payment for your care, or assist with Medical Center operations.

We will make every effort to keep your Protected Health Information private. We will store records of your Protected Health Information in a cabinet in a locked office or on a password protected computer.

Your personal health information and information that identifies you ("your health information") may be given to others during and after the study. This is for reasons such as to carry out the study, to determine the results of the study, to make sure the study is being done correctly, to provide required reports and to get approval for new products.

Some of the people, agencies and businesses that may receive and use your health information are the research sponsor; representatives of the sponsor assisting with the research; investigators at other sites who are assisting with the research; central laboratories, reading centers or analysis centers; the Institutional Review Board; representatives of Wake Forest University Health Sciences and North Carolina Baptist Hospital; representatives from government agencies such as

the Food and Drug Administration (FDA) or the Office of Human Research Protections (OHRP), the Department of Health and Human Services (DHHS) and similar agencies in other countries.

Some of these people, agencies and businesses may further disclose your health information. If disclosed by them, your health information may no longer be covered by federal or state privacy regulations. Your health information may be disclosed if required by law. Your health information may be used to create information that does not directly identify you. This information may be used by other researchers. You will not be directly identified in any publication or presentation that may result from this study unless there are photographs or recorded media which are identifiable.

If required by law or court order, we might also have to share your Protected Health Information with a judge, law enforcement officer, government agencies, or others. If your Protected Health Information is shared with any of these groups it may no longer be protected by federal or state privacy rules.

Any Protected Health Information collected from you in this study that is maintained in the research records will be kept for at least six years after the study is finished. At that time any research information not already in your medical record will either be destroyed or it will be de-identified.

You can tell John Williamson that you want to take away your permission to use and share your Protected Health Information at any time by sending a letter to this address:

John Williamson, PharmD
[redacted]

However, if you take away permission to use your Protected Health Information you will not be able to be in the study any longer. We will stop collecting any more information about you, but any information we have already collected can still be used for the purposes of the research study.

By signing this form you give us permission to use your Protected Health Information for this study.

If you choose to participate in this study, your medical record at Wake Forest University Baptist Medical Center will indicate that you are enrolled in a clinical trial. Information about the research and any medications or devices you are being given as a participant may also be included in your medical record. This part of the medical record will only be available to people who have authorized access to your medical record. If you are not a patient at this Medical Center, a medical record will be created for you anyway to ensure that this important information

is available to doctors in case of an emergency.

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 Web site at any time.

A North Carolina Baptist Hospital (NCBH) medical record will be created for all study participants. Information about your participation in the study will be placed in the NCBH medical record, along with any routine medical test results that were obtained at NCBH as part of this study.

WHAT ARE MY RIGHTS AS A RESEARCH STUDY PARTICIPANT?

Taking part in this study is voluntary. You may choose not to take part or you may leave the study at any time. Refusing to participate or leaving the study will not result in any penalty or loss of benefits to which you are entitled. If you decide to stop participating in the study we encourage you to talk to the investigators or study staff first to learn about any potential health or safety consequences. The investigators also have the right to stop your participation in the study at any time. This could be because you have an unexpected reaction to the study medication. Information that identifies you may be removed from the data or specimens that are collected as part of this study and could be used for future research or shared with others without additional consent.

You will be given any new information we become aware of that would affect your willingness to continue to participate in the study.

This study will be enrolling students from the High Point University campus. If you are a student, in addition to your rights as a research participant noted in the previous section, as a student, you are under no obligation to participate in this study. You may refuse to participate or withdraw from the study at any time and for any reason without affecting your grades, performance evaluations, or assignments. You will not be pressured into participating in this research study by any statements or implied statements that your grades, performance evaluations or assignments will be affected by your willingness to enroll in the study. Your medical records/information will not be used by the faculty, administration or study staff to make decisions regarding the status of your medical benefits. If you have questions regarding your enrollment in the study and your status as a medical student, please contact the Office of Student Services for additional information.

WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?

For questions about the study or in the event of a research-related injury, contact the study investigator, John Williamson at [redacted].

The Institutional Review Board (IRB) is a group of people who review the research to protect

your rights. If you have a question about your rights as a research participant, or you would like to discuss problems or concerns, have questions or want to offer input, or you want to obtain additional information, you should contact the Chairman of the IRB at [redacted] or the Research Subject Advocate at [redacted].

You will be given a copy of this signed consent form.

OPTIONAL PARTICIPATION IN FUTURE RESEARCH

In the future, people who do research may need to know more about your health. While the study investigator may give reports about your health, he/she will NOT be given your name, address, phone number, or any other identifying information about who you are, unless you agree to be contacted in the future.

_____YES you may contact me for future research studies
(initials)
_____ NO I do not want to be contacted regarding future research studies.
(initials)

SIGNATURES

I agree to take part in this study. I authorize the use and disclosure of my health information as described in this consent and authorization form. If I have not already received a copy of the Privacy Notice, I may request one or one will be made available to me. I have had a chance to ask questions about being in this study and my questions have been answered. By signing this consent and authorization form, I am not releasing or agreeing to release the investigator, the sponsor, the institution or its agents from liability for negligence.

Subject Name (Printed):_____

Subject Signature:_____Date:_____Time:_____am pm

Person Obtaining Consent (Printed):_____

Person Obtaining Consent:_____Date:_____Time:_____am pm