Protocol Title: Pilot, single center, open, trial of rifaximin in probable Alzheimer's Disease

NCT Number: NCT03856359

Date: Dec 9, 2019

DUKE UNIVERSITY HEALTH SYSTEM

Consent to Participate in a Research Study
Pilot, single center, open, trial of Rifaximin in probable Alzheimer's Disease

CONCISE SUMMARY
The purpose of this research study is to determine if giving patients with Alzheimer's Disease (AD) an antibiotic pill called Rifaximin daily will improve their memory and their ability to think and to reason (this is called cognition). Rifaximin does two things. It changes the types of bacteria that are in the colon. It also lowers the amount of ammonia in the blood. Recent research has found that harmful bacteria in your colon may cause thinking problems. Too much ammonia in the brain may also cause thinking problems.

We are testing whether Rifaximin may be of benefit and safe for patients with Alzheimer's Disease. In this study, you will receive the research study drug Rifaximin by mouth, two times a day, for three months total. The study drug will be given under the supervision of a caregiver. In addition, the study will require 3 clinic visits and bi-weekly phone calls. The clinic visits will occur at screening (prior to starting the study drug), baseline (starting the study drug) and at approximately 3 months (after completing the study drug). You will be followed for two months after completing the study drug. Therefore you will be in the study for approximately 5 months. There are risks to this study drug that are described in this document. Some risks include: nausea, dizziness, fatigue, diarrhea, gut or blood infection and allergic reaction to Rifaximin. If you are currently taking medication for your AD (longer than 2 months), you may continue taking the medication in conjunction with Rifaximin.

If you are interested in learning more about this study, please continue to read below.

You are being asked to take part in this research study because you have been diagnosed with Alzheimer's disease. Research studies are voluntary and include only people who choose to take part. Please read this consent form carefully and take your time making your decision. As your study doctor or study staff discusses this consent form with you, please ask him/her to explain any words or information that you do not clearly understand. We encourage you to talk with your family and friends before you decide to take part in this research study. The nature of the study, risks, inconveniences, discomforts, and other important information about the study are listed below.

Please tell the study doctor or study staff if you are taking part in another research study.

Dr. Paul Suhocki, an associate professor in the Department of Radiology at Duke, will conduct this study and it is funded by Valeant Pharmaceuticals International, Inc. The sponsor of this study, Valeant Pharmaceuticals International, Inc., will pay Duke University to perform this research, and these funds may reimburse part of Dr. Suhocki's salary and part of the salaries of other members of the research team.

DUKE UNIVERSITY HEALTH SYSTEM

Consent to Participate in a Research Study
Pilot, single center, open, trial of Rifaximin in probable Alzheimer's Disease

WHO WILL BE MY DOCTOR ON THIS STUDY?

If you decide to participate, Dr. Paul Suhocki will be your doctor for the study and will be in contact with your regular health care provider throughout the time that you are in the study and afterwards, if needed.

WHY IS THIS STUDY BEING DONE?

Rifaximin is approved by the U.S. Food and Drug Administration (FDA) for use in humans for the treatment of Hepatic Encephalopathy, Traveler's Diarrhea, and Irritable Bowel Syndrome (IBS). Hepatic Encephalopathy is a condition that causes temporary worsening of brain function in people with advanced liver disease. When the liver is damaged, it can no longer remove toxic substances from the blood and these toxins can travel through the body until they reach the brain. Rifaximin is an antibiotic that lowers blood ammonia by altering gut bacteria and increasing an enzyme in the small bowel called glutaminase.

By changing the types of bacteria that are in the colon, Rifaximin may also be improving brain function. Harmful bacteria in the colon can affect the brain by putting substances in the blood that cause brain inflammation. It is possible that Rifaximin may cause more of the good bacteria to be present in your colon and these may produce substances in your blood that help prevent brain inflammation.

The purpose of this research study is to determine if changing the bacteria in the colon and lowering blood and brain ammonia levels with the drug Rifaximin can change cognition in Alzheimer's disease (AD). Studies have shown evidence of increased ammonia levels in the Alzheimer's disease brain. Studies have also shown that harmful bacteria in the colon can affect memory and the ability to think by producing substances in the blood that cause brain inflammation. Rifaximin is considered an investigational drug in this study because it is not approved by the FDA for use in individuals with AD.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

Approximately 25 people will be enrolled into the study with 10 individuals expected to complete the study at Duke University.

WHAT IS INVOLVED IN THE STUDY?

If you agree to take part in this research study, you, and/or a legal authorized representative will be asked to sign and date this consent form.

Screening Clinic Visit

You may have the following tests or procedures before you start taking Rifaximin:

1. Clinical and safety assessments, medical and social history, education history and demographics will be collected by the research coordinator. The physician will perform a physical exam and ask questions about your medical history and medications that you are taking.

2. Reasoning skills and functional testing (Mini-Mental State Examination)
3. Blood tests to check liver function, chemistry, blood ammonia levels and blood levels of substances that cause or fight brain inflammation.
4. Two teaspoons of blood will be collected to measure the amount of substances that are produced when nerves are injured.

Baseline Clinic Visit
You will have the following tests or procedures before you start taking Rifaximin:

1. Reasoning skills and functional testing as a baseline (Alzheimer's Disease Assessment Scale-Cognitive, FAQ test)
2. A stool sample will be collected to analyze the types of bacteria in it.
3. The caregiver will be instructed on administration of the study drug (550mg orally, twice a day, for 3 months)
4. Blood tests (two teaspoons) to check liver function, chemistry, blood ammonia levels and blood levels of substances that cause or fight brain inflammation.
5. Two teaspoons of blood will be collected to measure the amount of substances that are produced when nerves are injured.

The caregiver will be provided with a dosing journal to record Rifaximin administration and any new medications.

Unscheduled Visit
Unscheduled visit/labs may occur if warranted for safety based on clinical judgement.

Phone calls
Your caregiver will receive phone calls to inquire about adverse events (side effects) and to document if there have been any changes in your other medications. The phone calls will begin one week after the baseline visit and then every two weeks until the 3 month visit. Unscheduled visit/labs may occur if warranted for safety based on clinical judgement.

3 Month Clinic Visit
You will have the following tests or procedures after you have taken Rifaximin for 3 months:

1. Clinical and safety assessments. The study team and physician will perform a physical exam and ask questions about your medical history and medications that you are taking
2. Reasoning skills and functional testing as a baseline (Alzheimer's Disease Assessment Scale-Cognitive, MMSE, FAQ test.)
3. Blood tests (two teaspoons) to check liver function, chemistry, blood ammonia levels and blood levels of substances that cause or fight brain inflammation.
4. Two teaspoons of blood will be collected to measure the amount of substances that are produced when nerves are injured.
5. A stool sample will be collected to analyze the types of bacteria in it.

6. Rifaximin pill count to evaluate accountability.
7. Caregiver will be instructed to call us between the 3 month visit and the 5 month final follow-up phone call if loose stools or blood in stool appears.

2 Month Follow Up (after taking Rifaximin)
After you have finished taking Rifaximin and completed your 3 month clinic visit, your caregiver will receive a phone call two months later to inquire about adverse events (side effects) and to document if there have been any changes in your other medications.

HOW LONG WILL I BE IN THIS STUDY?
You will participate in this study for approximately 5 months. You will take Rifaximin for 3 months and will be followed with a phone call 2 months after. You can choose to stop participating at any time without penalty or loss of any benefits to which you are entitled. However, if you decide to stop participating in the study, we encourage you to talk to your doctor first.

WHAT ARE THE RISKS OF THE STUDY?
As a result of your participation in this study, you are at risk for side effects which may include but are not limited to those listed below. You should discuss these with the study doctor and your regular health care provider if you choose. If you are currently taking or have recently (in the past 6 months) taken antibiotics, then you cannot be in this study and you should inform the study team. If you have had bloody stools or liver disease or history of C Diff (Clostridium difficile) infection, you may not be included in this study and should notify the study team.

Rifaximin may cause some, all or none of the side-effects listed below.

Common:
- Arm or leg swelling (peripheral edema)
- Nausea
- Dizziness
- Fatigue
- Fluid buildup in the abdomen (ascites)
- Muscle Spasms
- Itching of the skin (pruritus)
- Abdominal pain
- Low blood count (anemia)
- Depression
- Inflamed nose or throat (nasopharyngitis)
- Joint pain (arthralgia)

- Shortness of breath (dyspnea)
- Fever (pyrexia)
- Rash

Occasional:

- Infectious diarrhea (clostridium difficile)

Rare:

- Serious allergic reaction which may cause redness and peeling of the skin, swelling of the lower layer of skin, and anaphylaxis.

Risks of Drawing Blood:
Risks associated with drawing blood from your arm include momentary discomfort and/or bruising. Infection, excess bleeding, clotting, or fainting are also possible, although unlikely.

Drug and Food Interactions:
For your safety, you must tell the study doctor or nurse about all the prescribed medical foods and drugs, herbal products, over-the-counter (OTC) drugs, vitamins, natural remedies, and alcohol that you are taking before you start the study and before starting to take any of these products while you are on the study.

There is also the potential risk of loss of confidentiality. Every effort will be made to keep your information confidential; however, this cannot be guaranteed. Some of the questions we will ask you as part of this study may make you feel uncomfortable. You may refuse to answer any of the questions and you may take a break at any time during the study. You may stop your participation in this study at any time.

There may be risks, discomforts, drug interactions or side effects that are not yet known.

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?
Rifaximin is being used investigationally in this trial and hence it is not known if there will be any cognitive benefits. However, if the drug were to be effective, then the subject may experience improvements in cognition.
We hope that in the future the information learned from this study will benefit other people with your condition.

WILL MY INFORMATION BE KEPT CONFIDENTIAL?
Participation in research involves some loss of privacy. We will do our best to make sure that information about you is kept confidential, but we cannot guarantee total confidentiality. Your personal information may be viewed by individuals involved in this research and may be seen by people including those collaborating, funding (Valeant Pharmaceuticals International, Inc.), and regulating the study. We will share only the minimum necessary information in order to conduct the research. Your

personal information may also be given out if required by law. While the information and data resulting from this study may be presented at scientific meetings or published in a scientific journal, your identity will not be revealed.

Your records may be reviewed in order to meet federal or state regulations. Reviewers may include the Duke University Health System Institutional Review Board and others as appropriate. If any of these groups review your research record, they may also need to review your entire medical record.

As part of this study, you will be asked to have certain tests. Some of these tests would have been done as part of your regular care. The study doctor will use these test results both to treat you and to complete this research. These test results will be recorded in your medical record**.** Results of tests and studies done solely for this research study and not as part of your regular care will also be included in your medical record.

The study results will be retained in your research record for at least six years after the study is completed. At that time either the research information not already in your medical record may be destroyed or information identifying you will be removed from such study results at DUHS. Any research information in your medical record will be kept indefinitely.

Some people or groups who receive your health information might not have to follow the same privacy rules. Once your information is shared outside of DUHS, we cannot guarantee that it will remain private. If you decide to share private information with anyone not involved in the study, the federal law designed to protect your health information privacy may no longer apply to the information you have shared. Other laws may or may not protect sharing of private health information.

WHAT ARE THE COSTS TO YOU?

You or your insurance provider will be responsible and billed for all costs related to your routine medical care, including copayments and deductibles. Routine medical care services are those that you would have received for your condition if you were not participating in this research study. Not all services are covered by insurance. Some procedures or scans may require pre-authorization by your insurance plan. We will notify you if we learn that a service is not covered by your insurance plan as part of the pre-authorization process. If it is not covered, you will be responsible for paying for it. The amount of your out-of-pocket expense will depend on your insurance plan. For beneficiaries with Medicare Advantage Plans, traditional Medicare is billed for the routine cost of a research study. You may have more or higher co-pays than with a Medicare Advantage plan. Please discuss the costs of the study with Dr. Paul Suhocki. At your request, a Financial Counselor in the clinic may provide you with an estimate of costs for routine services.

The study sponsor has agreed to pay for services and procedures that are done solely for research purposes. Please talk with the PI/study team about the specific services and procedures that the sponsor will pay for, and the ones for which you or your insurance will be responsible.

DUKE UNIVERSITY HEALTH SYSTEM

Consent to Participate in a Research Study
Pilot, single center, open, trial of Rifaximin in probable Alzheimer's Disease

We will monitor your DUHS patient care charges to make sure that costs are directed appropriately. If you have any questions or concerns about appropriate billing, contact your study team coordinator so that he/she can help find a resolution.

Dr. Paul Suhocki will provide the study drug free of charge to you. At the end of the study, or if you decide to withdraw from the study before it ends, you will be asked to return all unused study drug. Dr. Paul Suhocki may request that you return for a checkup before you stop your study drug/biologic if he/she thinks that stopping it suddenly may harm you and may ask you to complete the tests that would ordinarily occur when a person completes the study.

WHAT ABOUT COMPENSATION?
Reimbursement at each clinic visit (screening, baseline and 3 month) will be $35 for both you and your caregiver.

WHAT ABOUT RESEARCH RELATED INJURIES?
Immediate necessary medical care is available at Duke University Medical Center in the event that you are injured as a result of your participation in this research study. However, there is no commitment by Duke University, Duke University Health System, Inc., or your Duke physicians to provide monetary compensation or free medical care to you in the event of a study-related injury.

For questions about the study or research-related injury, contact Dr. Paul Suhocki 919-684-7284 during regular business hours and at 919-880-6767 for emergencies after hours and on weekends and holidays.

WHAT ABOUT MY RIGHTS TO DECLINE PARTICIPATION OR WITHDRAW FROM THE STUDY?
You may choose not to be in the study, or, if you agree to be in the study, you may withdraw from the study at any time. If you withdraw from the study, no new data about you will be collected for study purposes unless the data concern an adverse event (a bad effect) related to the study. If such an adverse event occurs, we may need to review your entire medical record.

Blood samples will be destroyed when the study is completed.

Your decision not to participate or to withdraw from the study will not involve any penalty or loss of benefits to which you are entitled, and will not affect your access to health care at Duke. If you do decide to withdraw, we ask that you contact Dr. Paul Suhocki in writing and let him know that you are withdrawing from the study.

His mailing address is:
Department of Interventional Radiology
Duke University Medical Center

DUKE UNIVERSITY HEALTH SYSTEM

Consent to Participate in a Research Study
Pilot, single center, open, trial of Rifaximin in probable Alzheimer's Disease

North Hospital, Box 3808
Durham, NC 27710

In addition, you must return all unused study drug to Dr. Paul Suhocki or his staff. Dr. Paul Suhocki may ask you to return for a checkup before you stop your study drug if he thinks that stopping the drug suddenly may harm you. He may also ask you to complete the tests that would ordinarily occur when a person completes the study.

We will tell you about new information that may affect your health, welfare, or willingness to stay in this study.
Your doctor may decide to take you off this study if your condition gets worse, if you have serious side effects, or if your study doctor determines that it is no longer in your best interest to continue. The sponsor or regulatory agencies may stop this study at anytime without your consent. Reasons why this might occur include development of severe hypersensitivity to Rifaximin, development of clostridium difficile, or if the clinician feels that any other adverse event warrants discontinuation. If this occurs, you will be notified and your study doctor will discuss other options with you.

A description of this clinical trial will be available on https://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.

WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?
For questions about the study or a research-related injury, or if you have problems, concerns, questions or suggestions about the research, contact Dr. Paul Suhocki 919-684-7284 during regular business hours and at 919-880-6767 after hours and on weekends and holidays.
For questions about your rights as a research participant, or to discuss problems, concerns or suggestions related to the research, or to obtain information or offer input about the research, contact the Duke University Health System Institutional Review Board (IRB) Office at (919) 668-5111.

STATEMENT OF CONSENT
"The purpose of this study, procedures to be followed, risks and benefits have been explained to me. I have been allowed to ask questions, and my questions have been answered to my satisfaction. I have been told whom to contact if I have questions, to discuss problems, concerns, or suggestions related to the research, or to obtain information or offer input about the research. I have read this consent form and agree to be in this study, with the understanding that I may withdraw at any time. I have been told that I will be given a signed and dated copy of this consent form."

DUKE UNIVERSITY HEALTH SYSTEM

Consent to Participate in a Research Study
Pilot, single center, open, trial of Rifaximin in probable Alzheimer's Disease

_____	_____	_____
Signature of Legal Representative	Date	Time
_____	_____	_____
Signature of Subject	Date	Time
_____	_____	_____
Signature of Person Obtaining Consent	Date	Time