Approval Date: **May 9, 2019**
Not to be used after: **August 7, 2019**

Study Title: Does inhibition of liver specific 11β-hydroxysteroid dehydrogenase type 1 enzyme lower liver fat in NAFLD or NASH?

IRB Approval Date: 05-09-2019

NCT Number: NCT02605616

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RESEARCH PARTICIPANT CONSENT AND PRIVACY AUTHORIZATION FORM

Participant's Name: _____Medical Record #: _____

Study Title: Does inhibition of liver specific 11β-hydroxysteroid dehydrogenase type 1 enzyme lower liver fat in NAFLD or NASH?

Mayo IRB#: **15-000013**
UVA IRB Tracking#: **20155**

Principal Investigator: Dr. Rita Basu and Colleagues

Please read this information carefully. It tells you important things about this research study. A member of our research team will talk to you about taking part in this research study. If you have questions at any time, please ask us.

Take your time to decide. Feel free to discuss the study with your family, friends, and healthcare provider before you make your decision.

To help you decide if you want to take part in this study, you should know:

- Taking part in this study is completely voluntary.
- You can choose not to participate.
- You are free to change your mind at any time if you choose to participate.
- Your decision won't cause any penalties or loss of benefits to which you're otherwise entitled.
- Your decision won't change the access to medical care you get at the University of Virginia now or in the future if you choose not to participate or discontinue your participation.

If you decide to take part in this research study, you will sign this consent form to show that you want to take part. We will give you a copy of this form to keep. A copy of this form will be put in your medical record.

You can contact:	At:	If you have questions about:
Principal Investigator: Dr. Rita Basu **Study Team Contact:** Safia Sawleh	**Phone:** (434) 924-5183 **Phone:** (434) 243-2855 (434) 924-3512 **Address:** Department of Medicine-Division of Endocrinology University of Virginia Health System P.O. Box 801406 Charlottesville, VA 22908	▪ Study tests and procedures ▪ Research-related injuries or emergencies ▪ Any research-related concerns or complaints ▪ Withdrawing from the research study ▪ Materials you receive ▪ Research-related appointments
Mayo Clinic Institutional Review Board (IRB)	**Phone:** (507) 266-4000 **Toll-Free:** (866) 273-4681	▪ Rights of a research participant
UVA Research Compliance Manager	**Phone:** (434) 924-8660 **Address:** P.O. Box 801011 Charlottesville, VA 22908	▪ Rights of a research participant

Other Information:

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 Website at any time.

1. Why are you being asked to take part in this research study?

You are being asked to take part in this research study because you have biopsy/MRE proven nonalcoholic steatohepatitis (NASH) or you have been diagnosed with nonalcoholic fatty liver disease (NAFLD). The plan is to have up to 100 people age 21 to 75 participate in this study.

2. Why is this research study being done?

The purpose of this study is to determine if the drug AZD4017 reduces liver fat and liver fibrosis in people with NASH as compared to placebo. AZD4017 is still experimental and isn't approved by the U.S. Food and Drug Administration (FDA). However, the FDA has allowed the use of this drug in this research study. In this study, we want to compare the effects, good and/or bad, of AZD4017 for your condition. In this study, you will get either the AZD4017 or the placebo. You won't get both.

3. Information you should know

Who is Funding the Study?

Astra-Zeneca is funding the study. Astra-Zeneca will pay the Principal Investigator or the institution to cover costs related to running the study.

4. How long will you be in this research study?

It will take you about 5 months to complete this research study. During this time, we will ask you to make up to 10 study visits to UVA. These visits include up to 8 outpatient visits at Fontaine Research Park and 2 all day visits beginning at 5 am in the Clinical Research Unit (CRU) at the University of Virginia Health System. You will be in the study until the study visits are completed. If due to unforeseen issues (e.g. staffing or weather) it is difficult to arrive early for the long days, then you would stay in a hotel we provide for early arrival for the study visit.

5. What will happen to you while you are in this research study?

If you agree to be in this study, you will be asked to participate in the following:

The Screening Visit will take about 3 to 6 hours. During this visit, we will do some tests and procedures to see if you are eligible to take part in this research study. If you recently had any of the exams, tests or procedures involved in this study conducted as part of your clinical care or as part of another study that are accessible, they may not need to be repeated. It will be up to your study doctor to review and consider if previous findings are appropriate to use. If you aren't eligible, the Principal Investigator will tell you why. At this visit we will:

- Ask you about your medical history.
- Give you a physical exam, including height, weight, and "vital signs" (blood pressure, temperature, heart, and breathing rates)
- Electrocardiogram.
- Draw blood samples.
- Ask you for urine sample.
- Measure your waist to hip ratio.
- Measure your body fat with a machine called a DEXA scanner. This machine uses a small amount of radiation to determine the amount of fat and muscle in the body. During this test you will be asked to lie flat on a special table and the scanner will pass over your body. This will take about 15 minutes. This study will take place in Memorial Gym and you will need to go to a different building for this study. This test may be omitted if you are unable to travel to the memorial gym area.
- If you are a woman who can become pregnant, a urine pregnancy test will be done. You will not be able to participate in the in-patient study if you are pregnant. Magnetic Resonance Spectroscopy (MRS), Magnetic Resonance Elastography (MRE) questionnaire- a screening procedure for any contraindications. Contraindications are the usual for Magnetic Resonance Imaging (MRI): no pacemaker or automated internal coronary defibrillator (AICD), cochlear implants, cerebral aneurysm clips, any metallic pumps or indwelling catheters need to be checked, any history of metallic foreign bodies also needs to be checked. MRE/MRS are non-invasive MRI scan techniques. This scan will take about 30-45 minutes to complete. MRE scan measures liver tissue stiffness; MRS measures the amount and type of fatty acids present in the liver.
- Oral Glucose Tolerance Test (OGTT). This test may be done as an outpatient visit on a separate day if you have time constraints. This test will not be done if you have diabetes and are taking insulin. You will be asked to fast overnight prior to the test. You will have a plastic needle placed in a vein in one of your hands or forearm to draw blood. A saline (salt water) solution will be running to keep the vein from clotting. You will have a small amount of blood drawn over ~ 4 hour period after drinking Trutol 75 (a sugar solution) containing small amount of stable glucose tracer.

  At the end of the study, you will be provided a snack and then may go home.

Participants that engage in active sports or those actively losing weight will be excluded from this study. Dietary advice will be provided by the research dietician so you will maintain your body weight (within ~2 % of your weight at the start of the study) during this study. They will also question you about your dietary preferences for the evening meal and the study meal that you will eat during your study visit.

Study Visit 1:
The evening prior to the study day, you will eat a weighed-controlled evening meal and then will not eat again, except for water, until the end of the study the next day. The study team will contact you with instructions to follow.

The following morning, you will be asked to arrive at the CRU at the University of Virginia, at about 5 a.m. If you are a female of childbearing potential, you will have a pregnancy test on arrival and if the pregnancy test is negative, you will be able to proceed with the study.

A plastic needle (intravenous line) will be placed in a vein in one of your hands. This line will be used to draw blood, and your hand will then be kept in a "hot box". The "hot box" is a large plastic box that blows warm air over your hand. The temperature will not be greater than 131 degree F or 55 degree C. This may cause some mild discomfort and is intended to make blood flow through the skin and make drawing of blood easier. It will cause some reddening of your skin. This will go away when your hand is taken out of the "hot box". Your hand will remain in this "hot box" throughout the duration of the study. Another plastic needle will be placed in a vein in your other arm for infusions.

If you are unable to use a bedpan, urinal, or bedside commode, we will offer a urinary catheter as an alternative (this will be removed at the end of the study).

You may then receive a small amount of radioactive trace substance of cortisol through your veins that will continue until the end of the study visit.

Later in the morning, you will be given a small amount of stable tracer of cortisone and a stable tracer of cortisol by mouth.

Blood samples will be drawn at various times throughout the study. The total amount of blood withdrawn in any 12 week period will not exceed one pint (~550 ml).

In the afternoon, at the end of the study, both intravenous lines and the urinary catheter (if placed) will be removed.

We will assign you by chance (like a coin toss) to either the AZD4017 drug group or the Placebo group. You and the Principal Investigator can't choose your study group. You will have a 1 in 2 chance of being assigned to the AZD4017 group. You will take either AZD4017 or placebo 400 mg tablets twice a day for 12 weeks. You will be given a one month supply of either AZD4017 or placebo.

Neither you nor the Principal Investigator will know which study treatment group you are in. In case of an emergency, this information will be available.

This study uses a placebo. A placebo looks exactly like the study drug, but it contains no active ingredient. We use placebos in research studies to learn if the effects seen in research participants are truly from the study drug.

You will be given a meal and dismissed from the CRU.

Month 1: One month after inpatient study visit 1, you will report to the CRU for a study blood test and to pick up your next month supply of study medication. You will bring your pill bottle provided for the study medication with you. We will count the number of pills in the bottle and any pills left in the bottle will be returned to the research pharmacy and destroyed.

Month 2: You will report to the CRU for a study blood test and to pick up your next month supply of study medication. You will bring your pill bottle provided for the study medication with you. We will count the number of pills in the bottle and any pills left in the bottle will be returned to the research pharmacy and destroyed.

Month 3: Study Visit 2 will be 2 days: This visit will be exactly the same as visit 1. The next day, you will repeat the screening blood tests, the OGTT, DEXA scan and the MRE/MRS. You will bring your pill bottle provided for the study medication with you. We will count the number of pills in the bottle and any pills left in the bottle will be returned to the research pharmacy and destroyed. The OGTT and the MRE/MRS will be scheduled as outpatient visits.

Month 4: You will report to the CRU, or for your final study blood test.

Once enrolled in the study, please do not donate blood during the study and for 12 weeks after the study.

6. What are the possible risks or discomforts from being in this research study?

The total amount of blood withdrawn during the entire study will be about one pint (~550 ml). Hemoglobin must be greater than or equal to 12.0 g in males and greater than or equal to 11.0 g in females to ensure that drawing this amount of blood will be safe.

You will be exposed to radiation from one of the infusions and the DEXA scan in this research study. The amount of radiation you will receive has a low risk of harmful effects.

Catheter insertion, intravenous infusion, and blood withdrawal are associated with a small risk of pain, bruising, and infection. This will be minimized by careful attention to sterile technique. If infection occurs, it will be treated conservatively with heat and when appropriate with antibiotics.

During the electrocardiogram, we will need to attach sticky patches to your chest; chest hair may need to be shaved prior to the placement of the sticky pads. These tests could uncover a condition you did not know you had. This can be stressful. We will fully explain any results that are not normal.

A urinary catheter may be placed in your bladder. This could cause irritation, bleeding, and/or painful spasm of the bladder and rarely infection. You will be observed and treated appropriately if any of this occurs.

There is no radiation associated with MRE/MRS, but people who have metal devices like pacemakers cannot have a MRE/MRS and will not be able to participate in the study. Some people with claustrophobia may feel too closed in and may not tolerate MRE/MRS scanning. If you feel too confined in the scanner, you can inform the technologist and the scan will be stopped. The MRE/MRS machine makes loud knocking sounds when it is scanning. Because of this you will be asked to wear earplugs while getting your scan. The earplugs minimize discomfort from noise and keep the MRE/MRS noise within the safety range.

Birth Control Requirements for Female Participants:
If you are sexually active and able to become pregnant, you must agree to use one of the birth control methods listed below in addition to using a condom (except in case of abstinence) for the duration of the study and for 3 weeks after the final dose of the study drug:

- Hormonal methods, such as birth control pills, patches, injections, vaginal ring, or implants
- Barrier methods (such as a condom or diaphragm) used with a spermicide (a foam, cream, or gel that kills sperm)
- Intrauterine device (IUD)

- Abstinence (no sex)
- Bilateral tubal occlusion
- Vasectomized partner

You must use birth control for the entire study.

If pregnancy occurs: If you miss a period, or think you might be pregnant during the study, you must tell the Principal Investigator immediately.

Women cannot take part in this study if they are pregnant or breastfeeding.

If you are a female, you must have a negative pregnancy test in order to participate in this study unless you cannot become pregnant.

Birth Control Requirements for Male Participants:

If you are sexually active with a female partner of child bearing potential,
You must agree with the following for the duration of study and 3weeks after the final dose of study drug
You must not

- Donate sperms
- Rely on barrier methods (condoms) and spermicide alone.

You must either

- Be surgically sterilized
- Practice abstinence (no sex)
- Agree with their partner to use one of the birth control methods listed below:
    1. Hormonal methods, such as birth control pills, patches, injections, vaginal ring, or implants
    2. Intrauterine device (IUD)
    3. Abstinence (no sex)

The temperature inside the "hot box" where your hand will be placed is maintained at approximately 55°C (or 131° F). With prolonged exposure to continuous heat, there is a potential risk of local skin irritation or a minor burn. If this occurs, it will be treated appropriately. However we have used this technique for the past 25 years and have had no instances of hot box related burns or injuries.

Trutol 75 is a sugar solution. There are no known risks from drinking this solution.

Cortisol and cortisone are naturally occurring hormones in the body so trace substances of these hormones do not cause any side effects.

The most common known side effects of the drug AZD4017 are mild/moderate headache, abdominal pain or diarrhea. You may have a slight increase in your liver and thyroid lab values. Many side effects go away shortly after AZD4017 is stopped, but in some cases side effects can be serious, long lasting, or may never go away. Some side effects may not be known. Side effects may range from mild to life-threatening. Other drugs may be given to make side effects less serious and less uncomfortable. Talk to the researcher and/or your healthcare provider about side effects and ask any other questions. There may be other risks of AZD4017 that are currently unknown.

As with any medication, allergic reactions are possible.

For your safety during this study, please discuss all medications and supplements you are currently taking with the study doctor and call the Principal Investigator BEFORE you begin taking any:

- New medications prescribed by your doctor
- Other medications sold over-the-counter without a prescription
- Dietary or herbal supplements

As with all research, there is a chance that confidentiality could be compromised; however, we take precautions to minimize this risk.

7. Are there reasons you might leave this research study early?

You may decide to stop at any time. You should tell the Principal Investigator if you decide to stop and you will be advised whether any additional tests may need to be done for your safety.

In addition, the Principal Investigator, Astra-Zeneca or UVA may stop you from taking part in this study at any time:

- If it is in your best interest,

- If you don't follow the study procedures, • If you don't tolerate the study medication,
- If the study is stopped.

If you leave this research study early, or are withdrawn from the study, no more information about you will be collected; however, information already collected about you in the study may continue to be used.

We will tell you about any new information that may affect your willingness to stay in the research study.

8. What if you are injured from your participation in this research study?

Where to get help:

If you think you have suffered a research-related injury, you should promptly notify the Principal Investigator listed in the Contact Information at the beginning of this form. Staff at the University of Virginia will offer care for research-related injuries, including first aid, emergency treatment and follow-up care as needed.

Who will pay for the treatment of research related injuries:

You do not give up any legal rights, such as seeking compensation for injury, by signing this form. If you feel you have been injured as a result of this study you may contact the Principal Investigator or the IRB (phone numbers are located near the end of this form). If you are hurt as a result of being in this study, there are no plans to pay you for lost wages, disability, or discomfort. The sponsor will reimburse the reasonable cost of necessary and appropriate emergency and/or acute medical care for injury or illness that is determined by the principal investigator and sponsor to be directly related to the study. Injury related to the study does not include the normal progression of any disease or any underlying pre-existing medical conditions.

9. What are the possible benefits from being in this research study?

You won't benefit from taking part in this research study. It is for the benefit of research.

10. What alternative do you have if you choose not to participate in this research study?

This study is only being done to gather information. You may choose not to take part in this study.

11. What tests or procedures will you need to pay for if you take part in this research study?

Astra-Zeneca is providing AZD4017 at no cost and will also pay for:

- Screening and monthly blood tests
- Routine urine tests
- Urine pregnancy test for females
- All study specific tests during the study visits.
- DEXA scans
- MRS/MRE scans
- CRU visits
- Oral glucose tolerance tests
- All medications, isotopes, and study related meals given for the study.

However, you and/or your insurance will need to pay for all other tests and procedures that you would have as part of your clinical care, including co-payments and deductibles.

12. Will you be paid for taking part in this research study?

We will pay you $1200 if you complete the study. If you don't complete the study, we will pay you a prorated amount for each visit you complete. We will provide parking vouchers for this study. You will be reimbursed for mileage over a 40 mile radius at the current IRS mileage rate up to $100.

13. What will happen to your samples?

We would like to keep your sample for future research. You can still take part in this current study even if you don't want your sample used for future research. If you agree to give your sample, it will be the property of UVA.

Other researchers at UVA who aren't involved with this study may ask to use your sample for future research. Researchers at other institutions may also ask for a part of your sample for future studies. Your sample will be sent to researchers in a coded format, which protects your identity.

Some future studies may examine your DNA, which is the genetic information you inherited from your parents (genetic testing). The Principal Investigator may contact you if there are findings which may be useful for your health care. You would be given general information on the potential risks, benefits, and costs of choosing to learn about the findings.

Please read the following statements and mark your choices:

1. I permit my sample to be stored and used in future research of NASH and NAFLD at UVA:

☐ Yes ☐ No Please initial here: _____Date: _____

2. I permit my sample to be stored and used in future research at UVA to learn about, prevent, or treat any other health problems:

☐ Yes ☐ No Please initial here: _____Date: _____

3. I permit UVA to give my sample to researchers at other institutions:

☐ Yes ☐ No Please initial here: _____Date: _____

There is a very small chance that some commercial value may result from the use of your donated sample. If that happens, you won't be offered a share in any profits.

You may request to have your sample destroyed by writing to the Principal Investigator. The address is found in the "Contact Information" section of this consent form.

Because we cannot predict how your sample will be used in the future, we cannot promise that samples can be retrieved and destroyed.

14. How will your privacy and the confidentiality of your records be protected?

UVA is committed to protecting the confidentiality of information obtained about you in connection with this research study.

Your data will be stored in a database. The database is secured with password protection behind the UVA firewall and is accessible only to study staff. Electronic communication with outside collaborators involves only coded, unidentifiable information and is encrypted prior to transmission. If the results of the research are made public, information that identifies you will not be used.

During this research, information about your health will be collected. Under Federal law called the Privacy Rule, health information is private. However, there are exceptions to this rule, and you should know who may be able to see, use and share your health information for research and why they may need to do so. Information about you and your health cannot be used in this research study without your written permission. If you sign this form, it will provide that permission.

Health information may be collected about you from:

- Past, present, and future medical records.

- Research procedures, including research office visits, tests, interviews, and questionnaires.

Why will this information be used and/or given to others?

- To do the research.
- To report the results.
- To see if the research was done correctly.

If the results of this study are made public, information that identifies you will not be used.

Who may use or share your health information?

- UVA research staff involved in this study.
- Astra-Zeneca

With whom may your health information be shared?

- The UVA Institutional Review Board that oversees the research.
- Other UVA physicians involved in your clinical care.
- Researchers involved in this study at other institutions.
- Federal and State agencies (such as the Food and Drug Administration, the Department of Health and Human Services, the National Institutes of Health and other United States agencies) or government agencies in other countries that oversee or review research.
- The sponsor(s) of this study and the people or groups it hires to help perform this research.
- A group that oversees the data (study information) and safety of this research.

Is your health information protected after it has been shared with others?

UVA asks anyone who receives your health information from us to protect your privacy; however, once your information is shared outside UVA, we cannot promise that it will remain private and it may no longer be protected by the Privacy Rule.

Your Privacy Rights

If you tell us that someone is hurting you, or that you might hurt yourself or someone else, the law may require us to let people in authority know so they can protect you and others.

You do not have to sign this form, but if you do not, you cannot take part in this research study.

If you cancel your permission to use or share your health information, your participation in this study will end and no more information about you will be collected; however, information already collected about you in the study may continue to be used.

If you choose not to take part or if you withdraw from this study, it will not harm your relationship with your own doctors or with UVA.

You can cancel your permission to use or share your health information at any time by sending a letter to the address below:
Mayo Clinic
Office for Human Research Protection
ATTN: Notice of Revocation of Authorization
200 1st Street SW
Rochester, MN 55905
Please be sure to include in your letter or email:

- The name of the Principal Investigator, • The study IRB number and /or study name, and
- Your contact information.

Your permission lasts forever, unless you cancel it.

ENROLLMENT AND PERMISSION SIGNATURES

Your signature documents your permissio **h.**

	/ /	: AM/PM
Printed Name	Date	Time

Signature

Person Obtaining Consent

- I have explained the research study to
- I have answered all questions about tl
  the best f my ability.

/ / : AM/PM

Printed Name Date Time

Signature