University of California, San Diego
Consent to Act as a Research Subject

National Institutes of Health (NIH)
Nonalcoholic Steatohepatitis Clinical Research Network (NASH CRN)

Farnesoid X Receptor Ligand Obeticholic Acid in NASH Treatment (FLINT) Trial
Informed Consent

Dr. Rohit Loomba, Dr. Heather Patton, and Dr. Thuy Anh Le are conducting a research study to find out more about liver problems in adults & children. They are part of a national clinical research network called NASHCRN (Non-Alcoholic Steatohepatitis Clinical Research Network) that is sponsored by the National Institutes of Health (NIH). This network studies Nonalcoholic Fatty Liver Disease (NAFLD) and Nonalcoholic steatohepatitis (NASH).

We are asking you to participate in the FLINT Trial research study. Before you consent to join this study, we must explain the purpose of the study, any risks to you, your rights as a study participant, and what is expected of you during the study. If any part of this consent statement is unclear, please ask the study doctor or other study staff to explain it to you so that you understand. You are entitled to have any questions about the study answered to your satisfaction. Before making your decision, we ask you to think about it at home and to discuss it with your family or friends. If you decide to join the study, we ask you to give your consent by signing in the space provided below. The study staff will also sign the statement. We will give you a copy of the signed statement. We will also give you instructions for contacting the study staff if you need to contact them during the study or after the study has ended.

PURPOSE OF THIS STUDY

Nonalcoholic steatohepatitis (NASH) is a common liver disease in the United States. NASH can lead to severe liver disease in some patients. We are asking you to join this study because your doctor either suspects you have NASH or you have had a liver biopsy recently showing NASH.

The study drug being tested in the FLINT Trial, obeticholic acid, is a modified bile acid that changes the body's metabolism of lipids and might be beneficial for NASH. Bile acids are made by your liver to help digest food and then recycled by your body to be used again. Because of this recycling, it can take a week or two for obeticholic acid, to reach a steady level in the body and it can take even longer to get rid of after you stop taking the medication.

The purpose of the FLINT Trial is to find out whether treatment with obeticholic acid improves NASH compared to treatment with a placebo (an inactive study drug). The placebo capsule looks just like the obeticholic acid capsule, but has no active ingredients. You will have a liver biopsy after receiving treatment for 72 weeks (~ 1 ½ years). That biopsy will be used to determine if improvement in NASH was more common in patients treated with obeticholic acid compared to those who received placebo. This is a nationwide study funded by the National

Institutes of Health (NIH). Your participation in the study will could last up to two years.

SELECTION OF PATIENTS

To be eligible for this study, you must be at least 18 years old and have had a recent liver biopsy that shows you have NASH. You will not be allowed to join this study if you have cirrhosis or if you have had significant amounts of alcohol to drink within the past year. We will ask you questions to check that you are not drinking significant amounts of alcohol during the study.

If you are a woman capable of becoming pregnant, you must agree to use effective birth control methods during the study. Women who are nursing an infant may not enroll in the study.

The UCSD site will enroll 35 research subjects into this trial.

RANDOMIZATION AND TREATMENT

If you are eligible and agree to join the study, you will be one of about 280 patients nationwide. You will be randomly put into one of two treatment groups using a process similar to flipping a coin. Half of the patients will receive placebo and the other half will receive obeticholic acid. You will have an equal (one in two, or fifty-fifty) chance of getting either treatment. Neither you nor the study staff at this clinic will know which study drug you are taking. Your study doctor will not be the one who decides which treatment you receive. Your study doctor can be told which treatment you are receiving in case of an emergency. Not knowing the identity of study drug and making the placebo look like obeticholic acid is done so that the study gives fair and unbiased results.

To participate in this study, you must swallow one capsule each day for 72 weeks (1½ years). If the blood tests obtained after 24 weeks (~ 6 months) of treatment with obeticholic acid do not show any improvement in a liver enzyme called ALT, then the study may be stopped sooner. If the study is stopped early, then everyone will be instructed to stop taking medication, and the liver biopsy planned at the end of treatment will not be done.

PROCEDURES

Your involvement in this study will require the following visits to the study clinic to see the study staff and doctors:

Screening visit 1: *About 1½ - 2 hours of your time is required for this visit*
We will ask you to come in a fasting state (nothing but water for 12 hours before the visit). We will interview you and give you a physical examination. We will also take your blood pressure, temperature, pulse, height, weight, waist and hip measurements. We will ask you about alcohol consumption and any medicines that you are taking now or that you have taken in the past 3 months. We will draw 55 mL (~ 3 ½ tablespoons) of your blood for laboratory testing. If you are a woman and able to become pregnant, then we will perform a urine pregnancy test.

If you prefer, sometimes this first screening visit can be combined with the second screening visit. If you have not had a liver biopsy recently, then we will schedule one for you. This small piece of liver tissue will be used to make slides that will be examined by study doctors and become part of your study records. A portion of this liver tissue may be stored for future studies.

Screening visit 2: *About 2½ - 3 hours of your time is required for this visit*
We will ask you to come in a fasting state (nothing but water for 12 hours before the visit). We will draw 30 mL (~2 tablespoons) of your blood for laboratory testing, and serum and plasma (clear yellowish fluid that remains after separating out blood cells) banking. If needed, we will perform another pregnancy test. We will ask you about alcohol consumption and you will be given a questionnaire about how you feel. During this visit you will have a 2 hour oral glucose tolerance test (OGTT) only if either your Hemaglobin A1C is less than 9.5% or your blood glucose level is less than 300 mg/dL, to measure your blood sugar levels. As part of the OGTT, we will draw 10 mL (~ ½ tablespoon) of blood and then you will drink eight ounces of glucose solution (sugar water). At 30 minutes, 1 hour and 2 hours, we will draw another 10 mL (~ ½ tablespoon) of blood.

During this visit you may undergo an optional magnetic resonance imaging (MRI) scan, which takes about 30 minutes. If an MRI scan has been performed within 90 days of the screening liver biopsy, results from the scan can be used for this study if the same protocol was performed. The data will be included in the study. During the MRI scan you will lie down on a narrow bed. The bed will be rolled slowly into a tunnel that is 6 feet long, 22 inches wide, and open at each end. You will lie there for about one half hour. At times during the scan, you will be asked to hold your breath and keep still. During these times you will hear a loud tapping noise and you may feel warm during this procedure

Randomization visit: *About 45 minutes of your time is required for this visit*
The randomization visit occurs after the screening evaluations and baseline liver biopsy are completed. If you are eligible for the study, we will ask you to sign this statement in the space provided to reaffirm your consent to join the study. We will ask you about alcohol consumption and any medicines that you are taking now or that you have taken in the past 3 months. If needed, we will do another pregnancy test. A computer will randomly select which study medication you will be given. The study staff will teach you how to take study medication before you leave the clinic and you will be given a 12 week supply.

Follow-up visits: *About 1 – 3 hours is required of your time for these visits*
We will ask you to return to the clinic for up to 7 visits over a two year period. At each visit, the study staff will meet with you. We will schedule you for visits at 2 weeks and 4 weeks, which may be done by phone, after the randomization visit. We will schedule visits to the clinic at week 12 and every 3 months after that (at weeks 24, 36, 48, 60 and 72). We will ask you to come to each visit in a fasting state (nothing but water for 12 hours before the visit) and bring your study medicine bottles to each visit. We will ask you to return for a final check-up 24 weeks after you stop taking the study drug (week 96 visit). Visits during the study may be more frequent if the study doctors think it is medically necessary.

Week 2 and 4 visits: Both of these visits may take place over the phone. The study staff will ask about your health and check for side effects.

Week 12, 24, 36, 48 and 60 visits: The study staff will take your blood pressure, temperature, pulse, height, and weight. Sometimes we will take your waist and hip measurements, listen to your heart and lungs, and check your eyes, limbs and abdomen. You will be asked about your health and evaluated for side effects. We will ask you about alcohol consumption and any medicines that you are taking now or that you have taken since your last visit. Sometimes you will be given a questionnaire similar to

your screening visit asking you about how you feel. We will draw 35 to 50 mL (~ 2 to 3 ½ tablespoons) of your blood for laboratory testing, and serum and plasma banking. If you are a woman and able to become pregnant, we will perform a pregnancy test. You will be asked to turn in your study medicine. Before you leave clinic, you will be given another 12 week supply of the study medicine.

Week 72 visit: The study staff will take your blood pressure, temperature, pulse, height, weight, waist and hip measurements. We will also listen to your heart and lungs, and check your eyes, limbs and abdomen. You will be asked about your health and evaluated for side effects. We will ask you about alcohol consumption, any medicines that you are taking now or that you have taken since your last visit, and you will be given a questionnaire similar to your screening visit asking you about how you feel. We will draw 70 mL (~ 4 ½ tablespoons) of your blood for laboratory testing, and serum and plasma banking. You will be asked to repeat the OGTT test that you took during screening only if either your Hemaglobin A1C is less than 9.5% or your blood glucose level is less than 300 mg/dL. For the OGTT, we will draw 10 mL (~ ½ tablespoon) of your blood and then you will drink eight ounces of glucose solution (sugar water). At 30 minutes, 1 hour and 2 hours, we will draw another 10mL (~ ½ tablespoon) of your blood. You will be asked to turn in your study medicine. During this visit, you will be scheduled to have another liver biopsy and we will take a piece of your liver tissue.

If you completed the MRI scan at your screening visit you will be asked to agree to another one at this time. The procedure will be identical to the one you had at your screening visit.

Week 96 visit: The study staff will take your blood pressure, temperature, pulse, height, weight, waist and hip measurements. We will also listen to your heart and lungs, and check your eyes, limbs and abdomen. You will be asked about your health and evaluated for side effects. We will ask you about alcohol consumption, any medicines that you are taking now or that you have taken since your last visit, and you will be given a questionnaire similar to your screening visit asking you about how you feel. We will draw 50 mL (~ 3 ½ tablespoons) of your blood for laboratory testing, and serum and plasma banking. You may be asked to take part in a long term follow-up study (the NAFLD Adult Database 2 Study). At this time you have completed the study and will receive further care as needed.

RISKS AND DISCOMFORTS

Liver Biopsy: Liver biopsy is a common procedure in which a special needle is used to remove a very small portion of liver. Microscope slides will be made from this piece of liver tissue. The slides will be examined under a microscope by the study doctors to diagnose or to determine the severity of liver disease. A portion of the liver tissue may also be stored for future studies. In the FLINT Trial, you will have a liver biopsy when the study drug is stopped. The biopsy needle is inserted into the liver through your skin under local anesthesia. Liver specialists from the study, radiologists, or their trainees (under direct supervision) will perform your liver biopsy. They may or may not use ultrasound to guide the biopsy. About 20% of people have some degree of pain after a liver biopsy. The pain may last a few minutes up to several hours. Pain medication may be required. The pain usually disappears completely within a day or two. A rare complication of liver biopsy is bleeding severe enough to require a blood transfusion or even an operation to sew up the bleeding site. These complications occur less than one in 1,000 times. Other rarely occurring complications include perforation of nearby organs and infection. Very rarely, (less than one in 10,000 reported cases) death has occurred from bleeding after a liver biopsy.

Obeticholic acid: This is an investigational drug, it is not FDA approved, and it has only been used in a few studies.

From the relatively small number of people treated in those studies, we know that obeticholic acid can cause severe itching, constipation, and headache.

Blood drawing: Blood drawing is mildly painful and can cause bruising and very rarely, fainting, blood clots or an infection at the site. During the entire study period (lasting up to 2 years), you will have 445 mL (~30 tablespoons) of blood drawn from your forearm. You may have a needle placed in your arm during the OGTT test so the nurses will not need to stick you multiple times to draw blood.

Privacy **:** Your medical records will be kept private but research staff will look at this information. This information will be included in computer programs kept private by password protection. Written information will be stored in locked areas. Research records will be kept confidential to the extent provided by law. It is however, always possible that the information in the research records could become known outside of the research setting. Every effort will be made to maintain your privacy; however, it is possible that others may learn about the information acquired from your medical records.

General risks: Your condition may not get better or may become worse while you are in the study. Only you, the study participant, may take the study drug. It must be kept out of the reach of children and anyone who may not be able to read and understand the label. You will be made aware of any significant new findings that may change your decision to remain in this study.

BENEFITS

Your liver disease may improve because of treatment with the study drugs. However, you may receive no benefit. Even if your liver does improve on the study drug, there is no assurance that you can continue to obtain the study drug after you complete the study. You will help future patients by providing important information about the treatment of NASH. You may benefit from health information obtained during the physical exams, laboratory tests, and other study procedures. At your direction, we will provide the results of any procedures done to screen you for this study to your liver care provider.

COSTS

All study drugs will be given to you free of charge. You will not be charged for study visits or for procedures done solely for the study.

COMPENSATION

You will be compensated for your time and travel expenses after each completed visit. You will receive a total of $725 if you complete all research visits and both MRIs. The breakdown of compensation is as follows:

Weeks S1 and 72 = $100/visit for a total of $200
Weeks 24, 48 and 96 = $75/visit for a total of $225
Weeks 12, 36 and 60 = $50/visit for a total of $150
Weeks S2 and RZ = $25/visit for a total of $50
MRI weeks S1 and 72 = $50/MRI for a total of $100

CARE IF HARMED

If you are injured as a direct result of participation in this research, the University of California will provide any medical care you need to treat those injuries. The University will not provide any other form of compensation to you if you are injured. You may call the UCSD Human Research Protections Program office at (858) 455-5050 for more information about this, or to inquire about your rights as a research subject, or to report research-related problems.

SPECIMEN BANKING AND DATA REPOSITORY

Your specimens – the serum and plasma, and liver tissue samples collected as part of this study – will be sent to the NIDDK Biosample Repository as they are collected during the study. At the end of the study, the data collected on you will be sent to the NIDDK Data Repository.

The NIDDK Repositories are a research resource supported by the NIH that collect, store, and distribute samples and study data from people with many kinds of disorders, from unaffected family members, and from healthy people. The purpose of this collection is to make samples and data available for use in health research. Your samples and data will be used by the researchers carrying out the FLINT Trial, but they also may be used by other researchers, both during the study and after it ends. Your samples and data may be stored indefinitely.

Your samples and data will be labeled with a code number before they are sent to the NIDDK Biosample and Data Repositories. Your name, address, social security number, date of birth, medical record number and other personal identifiers will not be sent to the NIDDK Repositories, and hence the NIDDK Repositories will not be able to give out your name or other information that identifies you to the researchers who use your samples and data.

If you do not agree to have your samples and data sent to the NIDDK Repositories, you may not participate in the FLINT Trial. If you agree now but change your mind later during the study about having your samples and data sent to the NIDDK Repositories, you may withdraw your permission. No additional samples will be sent to the NIDDK Repositories and no further data will be collected on you, but samples and data already collected will continue to be used.

Because researchers will not have access to your identity, you will not get the results of any studies that might be performed on your samples. Sometimes research leads to findings or inventions that have value if they are made or sold. These findings or inventions may be patented or licensed, which could give a company the sole right to make and sell products or offer testing based on the discovery. Some of the profits may be paid back to the researchers and the organizations doing this study, but you will not receive any financial benefits.

Five mls of serum collected during the OGTT at t=0, 30', 60' 120' will be divided into .5 ml volumes, frozen and stored at UCSD in a locked -80°C freezer for future measurements of glucose, insulin, and possibly biomarkers of interest.

CONFIDENTIALITY

Your participation in this study will be kept confidential and your name, address, and other personal identifying information will not be made known to anyone other than study staff at this clinic. Your health and medical information will be sent to the Data Coordinating Center located at The Johns Hopkins Bloomberg School of Public Health in Baltimore, Maryland. The information will be labeled with a number and code that cannot be linked to your name except at the clinical center where you complete visits. When results from this study are published in medical literature, you will not be identified by name.

Representatives of the National Institutes of Health, Data Coordinating Center, or other experts may review your records at visits to the clinic as part of the ongoing monitoring of the progress of the study. In addition, representatives from the United States Food and Drug Administration (FDA) or the Institutional Review Board at this clinic may review your study records, including your medical records.

To help us protect your privacy, we have obtained a Certificate of Confidentiality from the National Institutes of Health. The Certificate protects us from being forced to disclose information that may identify you, even by a court subpoena. We are also protected from demands for your information made by federal, state, and local civil, criminal, administrative, legislative, or other sources. However, the Certificate cannot be used to resist a demand from the U.S. Government that is used for auditing or evaluation of federally funded projects or for information that must be disclosed in order to meet the requirements of the FDA. The Certificate does not prevent you or a member of your family from voluntarily releasing information about you or your involvement in the research. Even with the Certificate of Confidentiality, if the study staff learns of possible risk of harm to yourself or others, we are required to notify the proper authorities.

VOLUNTARY PARTICIPATION AND WITHDRAWAL

Your participation in this study is voluntary. You may decide to not participate in this study. If you do participate, you may freely withdraw from the study at any time. Your decision will not change your future medical care at this site or institution. The study doctor or the sponsor may stop your participation in this study at any time without your consent. The reasons may include: the study doctor thinks it is necessary for your health and safety, you have not followed study instructions, the sponsor has stopped the study, or administrative reasons require your withdrawal. If you leave the study before the final regularly scheduled visit, you may be asked by the study doctor to make a final visit to complete some of the end-of-study procedures.

ALTERNATIVES TO PARTICIPATION

You may choose not to participate in this study. Slow weight loss through increased regular exercise and a low-calorie, low carbohydrate diet may improve NASH. There are no proven drug treatments for NASH. If you are found to be ineligible to continue with the study, we will keep your data in the database.

QUESTIONS

Dr. Loomba and/or _____ has explained this study to you and answered your questions. If you have questions about a possible side effect, reaction to study medication, or a possible research related injury, you may reach either of the study doctors or Thu Nguyen at 619-543-5459

After Hours:
UCSD Hospital Operator at 619-543-6737 – Ask the operator to page Drs. Loomba, Patton or Le. Let the operator know that you are a research participant.

CONSENT

I have read the above information about the purpose of the study as well as the potential benefits and risks of participation in the study. I have had an opportunity to discuss it with _____ or other involved study staff and to ask my questions about the study procedures and medication, their inconveniences, hazards, and side effects. All of my questions have been answered to my satisfaction. All oral and written information and discussions about the study are in English [or in a language in which I am fluent]. My signature below indicates that I voluntarily consent to participate in this study.

_____ _____

Patient (printed name) Date

_____

Patient (signature)

I, the undersigned, have fully explained the relevant details of this study to the patient named above, and will provide him/her with a copy of this signed and dated informed consent form.

_____ _____

Person obtaining consent (printed name) Date

_____

Person obtaining consent (signature)

SUBJECT BILL OF RIGHTS

As a subject in a research study or as someone who is asked to give consent on behalf of another person for such participation, you have certain rights and responsibilities. It is important that you fully understand the nature and purpose of the research and that your consent be offered willingly and with complete understanding. To help you understand, you have the following specific rights:

1. To be informed of the nature and purpose of the research in which you are participating.

2. To be given an explanation of all procedures to be followed and of any drug or device to be used.

3. To be given a description of any risks or discomforts, which can be reasonably, expected to occur.

4. To be given an explanation of any benefits which may be expected to the subject as a result of this research.

5. To be informed of any appropriate alternative procedures, drugs, or devices that may be advantageous and of their relative risks and discomforts.

6. To be informed of any medical treatment which will be made available to the subject if complications should arise from this research.

7. To be given an opportunity and encouraged to ask any questions concerning the study or the procedures involved in this research.

8. To be made aware that consent to participate in the research may be withdrawn and that participation may be discontinued at any time without affecting continuity or quality of your medical care.

9. To be given a copy of the signed and dated written consent form.

10. To not be subjected to any element of force, fraud, deceit, duress, coercion, or any influence in reaching your decision to consent or to not consent to participate in the research.

If you have any further questions or concerns about your rights as a research subject, please contact the research doctor or the UCSD Human Research Protections Program at 858-455-5050 during normal working hours.