Informed Consent Form
Date: 1/31/2018
NCT# 01589523

CINCINNATI CHILDREN'S HOSPITAL MEDICAL CENTER
CONSENT TO PARTICIPATE IN A RESEARCH STUDY

STUDY TITLE: CONJUGATED CHOLIC ACID FOR THE TREATMENT OF INBORN ERRORS IN BILE ACID SYNTHESIS INVOLVING SIDE-CHAIN CONJUGATION

Sponsor Name: James Heubi, MD

Funding Source: National Institutes of Health (NIH) NIDDK and National Center for Research Resources (NCRR) # 5U54DK078377-04

Sponsor Study Number: NCRR RR 08084 and DK 62497

INVESTIGATOR INFORMATION:

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Principal Investigator Name | Telephone Number | 24 hr Emergency Contact

Subject Name: _____ Date of Birth: _____/_____/____

Throughout this document, references to "You" may stand for either the research study subject or for the parents or legal guardians of the research study subject if the subject is under 18 years of age or otherwise unable to legally give informed consent to participate in the research study. The signature(s) at the end will clarify whether the research study subject is signing this consent form on their own behalf or via a legal guardian or legal personal representative.

INTRODUCTION:

You have been asked to participate in a research study. Before agreeing to participate in this study, it is important that you read and understand the following explanation. It describes, in words that can be understood by a lay person, the purpose, procedures, benefits, risks and discomforts of the study and the precautions that will be taken. It also describes the alternatives available and the right to withdraw from the study at any time. No guarantee or assurance can be made as to the results of the study. Also, participation in the research study is completely voluntary. Refusal to participate will involve no penalty or loss of benefits to which you are otherwise entitled. You may withdraw from the study at any time without penalty.

WHY IS THIS RESEARCH BEING DONE?

The purpose of this research study is to determine the way (mechanisms) by which your defect in bile acid handling (metabolism) causes your liver disease or abnormality in absorption of vitamins and the effect of an investigational bile acid therapy (glycocholic acid) on your vitamin absorption and your liver disease. An investigational therapy is one that not approved by the United States Food and Drug Administration (FDA) and is being provided to you under an Investigational New Drug application from the FDA.

WHY HAVE YOU BEEN ASKED TO TAKE PART IN THIS RESEARCH STUDY?

You are being asked to take part in this research study because you have a defect in bile acid metabolism which causes reduced absorption of fats and vitamins and/or liver disease. Laboratory tests of your urine and blood sent by your physician and analyzed in our laboratory indicate that you have a defect in bile acid metabolism that could be treated with oral (by mouth) bile acid therapy.

WHO SHOULD NOT BE IN THE RESEARCH STUDY?

There are no conditions that exclude you from participating in this study. If you are pregnant, you may not be able to participate in all parts of the study.

HOW LONG WILL YOU BE IN THE RESEARCH STUDY

You may be in the research study for several years. This consent, unless you choose to withdraw it, shall remain in effect until the end of the study. After the initial evaluation and follow up studies, you will be followed with laboratory tests as long as you receive study treatment with bile acid therapy.

WHO IS CONDUCTING THE RESEARCH STUDY?

This study is funded by the National Institutes of Health through the National Center for Research Resources and the National Institute for Digestive, Diabetes and Kidney Diseases.

The study is directed by Kenneth Setchell, Ph.D., and James Heubi, M.D researchers at Cincinnati Children's Hospital Medical Center.

HOW MANY PEOPLE WILL TAKE PART IN THE RESEARCH STUDY?

At least 4 people have been identified with specific bile acid defects to be studied under this protocol (a written study plan) at Cincinnati, Ohio. About 1 new patient will be studied each year at Cincinnati Children's Hospital Medical Center.

WHAT IS INVOLVED IN THE RESEARCH STUDY?

You have a disease in processing bile acids (the natural detergents of the body that aid bile flow and help fat and vitamin absorption). Based upon tests already performed, it is thought to be caused by a defect in formation of bile acids. Liver disease may or may not be associated with this condition. If liver disease is present, there is no approved therapy. Therefore, this study will evaluate how this defect affects your body and how treatment with bile acids (glycocholic acid) will influence your disease.

You will be admitted to the Clinical Research Center on two occasions:

Visit 1 will be for 4 days:

Day 1

- A physical examination and history of your illness will be taken.
- A catheter (tube) will be placed in your vein and maintained to allow collection of blood samples during the stay on the Clinical Research Center.
- Blood samples will be collected (2 teaspoons) to assess your liver function, vitamin status, and measurement of bile acids in your blood.
- Urine will also be collected for bile acid analysis.
- The total amount of bile acids in your body will be measured using two non-radioactive "markers" which are virtually identical to your bile acids. These non-radioactive bile acid "markers" (cholic and chenodeoxycholic acids, 15 mg of each) will be given to you at or soon after 9:00 p.m. by mouth.
- You will not eat or drink anything after midnight. You may receive water up until 6 hours before the procedure to collect bile on Day 2.

Day 2

- In the morning a tube will be passed through your nose into your small intestine using x-ray to help the tube placement and bile collected through the tube. A drug which contracts the gall bladder will be given by vein and bile collected. After the bile collection is completed, the tube will be removed. This usually takes less than 1 hour.
- A blood sample will be taken from you, your parents and any siblings to analyze for gene mutations that may cause your disease.

Day 3

- Measurements of your absorption of vitamin E will be performed after a 4-hour fast (nothing to eat or drink for 4 hours).
- You will take a standard amount of the vitamin, and a tube placed in your vein from which blood can be collected a number of times. For these studies approximately 2 teaspoons of blood will be collected on each occasion.

Day 4

- Measurements of your absorption of vitamin D will be performed by the same method that was done for vitamin E on Day 3.

After completion of these studies, you will begin taking oral bile acids to treat your defect in bile acid production, and you will continue to take this bile acid every day after discharge from the Clinical Research Center. After discharge from the hospital, blood and urine monitoring will be performed in one month with collections of samples near your home and sent to the laboratory at Children's Hospital.

Visit 2 Three to 12 months after the start of therapy, you will be re-admitted to the Clinical Research Center for 4 days, for measurement of the body's content of bile acids. Blood samples for measurement of liver function tests, and vitamin absorption tests will be repeated exactly as performed in Visit 1.

If the bile acid therapy is considered to be successful based on your clinical tests you will be offered continued treatment with the bile acid. You will be followed periodically, and asked to provide samples of urine once a year to assess compliance and response to therapy. You will also be asked to provide blood for the measurement of liver enzymes at the discretion of the attending physician and in the course of standard care. It is anticipated that this follow-up will occur at least once/year, which is standard care for patients affected with your bile acid disorder.

WHAT ARE THE RISKS AND DISCOMFORTS OF THE RESEARCH STUDY?

You have been told that the study described above may involve the following risks and/or discomforts and safeguard and or precautions to avoid them:

There is no known risk from administering the "marker" bile acids to measure my child's total amount of bile acids. Passage of a tube through the nose into the small intestine is associated with mild to moderate discomfort. Administration of a drug to contract the gall bladder for collection of bile may cause abdominal cramping or nausea. Fluoroscopy (x-ray) is required to place the tube. You will be exposed to some radiation during the tube placement, but he amount will be kept to a minimum. It will be approximately equal to the amount of radiation received from natural background radiation living for approximately 20 months in Cincinnati. It is about equal to the amount received from 4 abdominal x-rays.
The administration of bile acids may cause you certain side effects including diarrhea, or even liver injury. These effects, especially liver injury, are very unlikely since this compound has proven to be safe in the treatment of several related conditions. As a portion of these studies, your caregiver will evaluate you on an annual basis or more frequently with physical exam and laboratory measures to determine if the bile acids are causing any injury to your liver. If injury is identified, it may be necessary to stop the bile acids.

There may be unknown or unforeseen risks associated with study participation.

WHAT ARE THE REPRODUCTION RISKS?

The possible effect of radiation exposure during this study on an unborn baby is unknown. Because of this possibility, all females that may be able to become pregnant will have a urine pregnancy test done before starting the study, and before any x-ray exposure.

ARE THERE DIRECT BENEFITS TO TAKING PART IN THE RESEARCH STUDY

This study may provide no direct benefit to you. The administration of the bile acid to you may improve growth and reduce complications from not having normal bile acids in the bile. If you have liver disease associated with the defect in bile acid metabolism, treatment with bile acids may improve the liver disease. The proposed investigations with the ways (mechanisms) by which the defect in bile acid metabolism causes the problems seen in you may improve understanding of this defect in bile acid metabolism and potential treatment of you as well as improving our understanding of liver diseases commonly affecting infants and children.

WHAT OTHER CHOICES ARE THERE?

There is no specific treatment for your disease. If you choose not to participate in this study, you will receive the standard care, as is usually provided to patients with these diseases. You may receive specialized forms of fat soluble vitamins (Vitamin E) and specialized forms of fat (medium chain triglycerides) that can be used to reduce the effect of not having the right bile acids to enhance fat absorption. Continued support and monitoring for evidence of abnormalities caused by lack of normal bile acids will be carried out.

HOW WILL INFORMATION ABOUT YOU BE KEPT PRIVATE AND CONFIDENTIAL?

Every effort will be made to maintain the confidentiality of your medical and research information ("Protected Health Information" or "PHI"), consisting of any results or information collected as a part of this research study including your name, date of birth, address, gender, race, and medical history.

Protected Health Information is defined as health information, whether verbal or recorded in any form (such as on a piece of paper or entered in a computer), that identifies you as an individual or offers a reasonable basis to believe that the information could be used to identify you.

By signing this consent form you are giving permission for representatives of the Cincinnati Children's Hospital Medical Center ("CCHMC"), the Investigator and CCHMC employees involved with the research study including the Institutional Review Board and the Office for Research Compliance as well as, the National Institutes of Health, the Food and Drug Administration, or their appointed agent to be allowed to inspect sections of your medical and research records related to this study.

The information from the research study may be published; however, you will not be identified in such publication. The publication will not contain information about you that would enable someone to determine your identity as a research participant without your approval (authorization).

Cincinnati Children's Hospital Medical Center and/or the Investigator will take the

following actions (precautionary measures) to protect your privacy and confidentiality of your research and/or medical records. Any information collected for this study will be saved on password protected worksheets with access only to the study researchers. You will be assigned a number and any identifying information will be separated from the data collected for this study.

A copy of this consent form will be included in your research record.

You will be registered in the Children's Hospital Medical Center's computer system as a research subject which may be beneficial for future clinical care.

USE AND DISCLOSURE OF YOUR PROTECTED HEALTH INFORMATION

This Protected Health Information described in the section above will be used /disclosed for the purpose of research by CHMCC to the other persons or entities (groups) identified above.

"Use" of an individual's health information is defined as the sharing, examination or analysis (break down) of the information that is collected and maintained for the length of the research study within CCHMC.

"Disclosure" of an individual's health information is defined as the release, transfer, providing access to, or to reveal in any other manner, the information outside the persons or entity (groups) at CCHMC who is holding the information as described in the section "How will information about you be kept Private and Confidential" in this consent form.

Once your Protected Health Information is disclosed, the information may be subject to re-disclosure and may no longer be protected by the federal privacy regulations.

AVAILABILITY OF INFORMATION?

The results of the study will available to you. You will be told the results of your laboratory results and the effects of bile acid therapy on your condition.

WHAT ARE YOUR COSTS TO BE IN THIS STUDY?

Funds are not available to cover the costs of any ongoing medical care you are undergoing, and you remain responsible for the cost of non-research related care. However, tests, procedures or other costs incurred solely for purposes of research will not be your financial responsibility. You will receive bile acid therapy free of charge while you are in this study. If you have questions about your medical bill relative to research participation, you may contact Kenneth Setchell, Ph.D. or Dr. James E. Heubi.

There will be no costs to you from participating in this study.

WILL YOU BE PAID TO PARTICIPATE IN THIS RESEARCH STUDY?

You will not be paid for participation in this study.

WHAT COMPENSATION IS AVAILABLE IN CASE OF INJURY?

If you believe that you have been injured as a result of participation in biomedical or behavioral research you are to contact Kenneth D.R.Setchell, Ph.D. at 513-636-8442 or James E. Heubi, M.D. at 513-636-8046 or the Director of Social Services (513-636-4711) to discuss your concerns. Cincinnati Children's Hospital Medical Center follows a policy of making all decisions concerning compensation and /or medical treatment for physical injuries occurring during or caused by participation in biomedical or behavioral research on an individual basis.

WHAT ARE YOUR RIGHTS AS A PARTICIPANT?

Your participation in this study is completely **voluntary**. You may choose either to take part or not to take part in this research study. Your decision whether or not to participate will not result in any penalty or loss of benefits to you and the standard medical care for your condition will remain available to you.

If you decide to take part in the research study, you are **free to withdraw** your consent and discontinue participation in this research study at any time. Leaving the study will not result in any penalty or loss of benefits to you.

You may *revoke* (choose to withdraw) this authorization at any time after you have signed it by providing Drs. Heubi or Setchell with a written statement that you wish to withdraw this authorization. Your withdrawal of this authorization will be effective immediately and your Protected Health Information can no longer be used/disclosed for research purposes by CCHMC and the other persons or entities that are identified in the "Use or Disclosure of Your Protected Health Information" section of this consent, except to the extent that CCHMC and/or the other persons or entities identified above have already taken action in reliance upon your consent. In addition, your Protected Health Information may continue to be used/disclosed to preserve the integrity of this research study.

The investigators will tell you about significant new findings developed during the course of the research and new information that may affect your health, welfare, or willingness to stay in this study.

If you are a CCHMC employee, refusal to participate or withdrawal from the study will not interfere with any of your employee's opportunities, rights or benefits.
If you have questions about the study, you will have a chance to talk to one of the study staff or your regular doctor. Do not sign this form unless you have had the chance to ask questions and have received satisfactory answers. Nothing in this consent form waives any legal rights you may have nor does it release the investigator, the sponsor, the institution, or its agents from liability for negligence. For further information about your rights, please see CCHMC's Notice of Privacy Practices.

ABILITY TO CONDITION TREATMENT ON PARTICIPATION IN THIS STUDY

You have a right to refuse to sign this consent to use/disclose your Protected Health Information for research purposes. If you refuse to sign this consent, your rights concerning treatment, payment for services, enrollment in a health plan or eligibility for benefits will not be affected.

WHO DO YOU CALL IF YOU HAVE QUESTIONS OR PROBLEMS?

For questions about this research study or to report a research-related injury, you can contact the researcher Kenneth Setchell, Ph.D. at (513) 636-8442 or James E. Heubi, M.D. or (513) 636-8046. Researchers are available to answer any questions you may have about the research at any time.

If you have general questions about your rights as a research participant in this research study, you can call the Cincinnati Children's Hospital Medical Center Institutional Review Board at 513-636-8039.

SIGNATURES

You have read the information given above. The investigator or a member of the research team (his/her designee) have personally discussed with you the research study and have answered your questions. You are aware that, like in any research, the investigators cannot always predict what may happen or possibly go wrong. You have been given sufficient time to consider if you should participate in this study. You hereby consent for yourself to take part in this study as a research study subject. You will receive a copy of this signed consent form for your records.

_____ Date: _____

Subject's signature indicating consent

_____ Date: _____
Subject's signature indicating assent

_____ Date: _____
Investigator or specific individual who has
been designated to obtain consent (Signature)

_____ Date: _____
Investigator (Signature)

This research study and consent form have been reviewed and approved by the Cincinnati Children's Hospital Medical Center Institutional Review Board (telephone number 513-636-8039).