4401 Penn Avenue
Pittsburgh, PA 15224

DEPARTMENT OF PEDIATRIC GASTROENTEROLOGY, HEPATOLOGY AND NUTRITION

Title: **Screening for a Preliminary Study of the Efficacy and Safety of Carbamazepine in Severe Liver Disease Due to Alpha-1-Antitrypsin Deficiency (04) April 2015**

Principal Investigator: David H Perlmutter, MD
Department of Pediatrics
University of Pittsburgh School of Medicine
Children's Hospital of Pittsburgh of UPMC
412-692-5180

Sub-Investigators: Robert H. Squires, Jr., MD
Professor of Pediatrics
University of Pittsburgh
Children's Hospital of Pittsburgh of UPMC
412-692-5180

Ira Bergman, MD, PhD.
Professor of Pediatrics
University of Pittsburgh
Children's Hospital of Pittsburgh of UPMC
412-692-5490

Kapil Chopra, MD
Associate Professor of Medicine
University of Pittsburgh
Presbyterian University Hospital
412-647-1170

Michael Dunn, MD
Associate Chief for Translational Research
Presbyterian University Hospital
412-647-1170

Andrew Chu, MD
Assistant Professor of Pediatrics
University of Pittsburgh
Children's Hospital of Pittsburgh of UPMC
412-692-5180

	Philip Orons, MD Associate Professor of Radiology and Surgery University of Pittsburgh UPMC Montefiore Hospital 412-647-3545
	George Michalopoulos, MD, PhD Professor of Pathology University of Pittsburgh 412-648-1040
	Alejandro Hoberman, MD Professor of Pediatrics University of Pittsburgh 412-692-5507
	Shahid Malik, MD University of Pittsburgh Physicians Division of Gastroenterology, Center for Liver Disease 412-647-1170
	Mitchell Tublin, M.D. Allesandro Furlan, M.D.
Study Monitors:	Mark E. Lowe, MD Jeffrey Rudolph, MD
Study Monitor Assistants:	Kathryn Bukauskas, RN, CCRC Amy Bookser RN
Study Coordinators:	Adam D. Kufen RN, BS, CCRC Children's Hospital of Pittsburgh of UPMC Department of Gastroenterology 412-692-6558
	Donna Smith, RRT, MS Children's Hospital of Pittsburgh of UPMC Department of Gastroenterology 412-692-6092
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Why is this research being done?

You have been diagnosed with a serious liver condition known as Alpha-1 Antitrypsin deficiency (ATD). This is a condition that results in the formation of an abnormal protein that is not able to be removed from the liver cell. It is believed that the abnormal protein that accumulates within the liver cells results in the death of the liver cells and gradual scarring of the liver. This scarring is called fibrosis and when it becomes severe it is called cirrhosis of the liver.

ATD affects 1 in 2,000 individuals; however, only about 8% of those develop serious liver disease such as cirrhosis. At the present time, there is no medical treatment for patients with ATD who develop cirrhosis and no treatment that prevents the disease from progressing to cirrhosis. When liver scarring progresses, complications such as intestinal bleeding and accumulation of extra fluid in the abdomen may develop and a liver transplant may be needed to survive.

We do not know why some patients with ATD develop liver disease and others do not. One possible explanation is that the process that normally removes abnormal proteins from the liver cell is not functioning properly in the ATD patients that have severe liver disease. Recently it was discovered that the US Food and Drug Administration (FDA) approved drug carbamazepine (CBZ) could stimulate the process that removes abnormal proteins from cells. CBZ was given by mouth to mice with liver disease caused by ATD. The results showed a significant decrease in the amount of abnormal AT protein in the liver cell. In addition, treatment with CBZ resulted in a marked decrease in liver scarring. These results raise the possibility that CBZ could prevent or reverse the liver disease in persons with ATD.

The main purpose of this research study is to determine if CBZ is an effective treatment for liver disease in persons with ATD. The FDA has not approved the use of CBZ for ATD. CBZ has been approved by the FDA for use in children with seizures and facial pain due to nerve inflammation and is approved for use in adults with seizures, facial pain, depression and anxiety. It is not known whether CBZ will benefit persons with ATD. This research study is the first step in determining if CBZ can help persons with liver disease due to ATD.

Who is being asked to take part in this research study?

Only children at least 14 years of age as well as adults <80 years of age with liver disease due to ATD will be eligible to participate in this research study. Because you have liver disease due to ATD, we are asking you to be a part of this research study to determine whether CBZ will decrease the amount of abnormal AT protein in the liver, reduce the amount of scarring in the liver and improve blood flow through the liver. An estimated total of 30 patients including an estimated total of 5 children between 14 years of age though 17 years of age (up to but not including their 18th birthday) will be enrolled in this study. Participants will include males and females from all racial and ethnic groups. The study is taking place only at hospitals affiliated with the University of Pittsburgh Medical Center.

What procedures will be performed for research purposes?

If you decide to take part in this research study, you will undergo several procedures that are not part of your standard medical care to determine whether you meet the eligibility criteria for the study. You will need to complete all of these procedures and meet certain requirements before signing a consent form to participate in the full clinical trial.

First the study doctor will take a history and do a physical examination to determine your health history, medications taken for any health problems, and results of blood tests that have been done previously. Also, study personnel will review and collect information from your medical record.

Blood will be drawn for a number of tests including determination of MHC type. MHC stands for major histocompatibility complex. This is a system that describes markers on blood cells that are unique for your immune system. People who have a particular MHC type are more likely to be allergic to CBZ.

Urine specimens will be collected for testing including pregnancy testing. A behavioral assessment survey will be administered by the research coordinator. This will involve a small number of questions that you can answer verbally. The questions are designed to assess for risk of depression and the survey will take approximately 5 minutes.

An abdominal ultrasound will be done to determine whether the blood vessels of the veins of the liver are open and to determine the direction of flow within these blood vessels.

A liver biopsy and measurement of the amount of pressure that is required for blood to pass through the liver (transvenous liver biopsy/HVPG measurement) will be done to determine if the liver disease is severe enough to be eligible for the proposed treatment study. The liver biopsy and pressure measurements will be performed at the same time. This procedure will take place in a special room in the radiology suite in UPMC Presbyterian University Hospital (PUH) that is used to perform these procedures. Some individuals with liver disease have decreased platelets (needed to help blood clot) and/or prolonged clotting times which put them at increased risk for bleeding during procedures. In this case you may need to receive a transfusion of one of the components of blood (platelets or plasma) before the liver biopsy procedure in order to correct any bleeding tendency. This is routine, or standard of care, related to the liver biopsy procedure. If it is determined that you are at an increased risk for bleeding, a transfusion will be required. After you have been given sedation/anesthesia to provide comfort, a catheter is inserted into a vein, usually one in the neck or in the groin, and the catheter is threaded through that vein to the liver. X-rays will be needed to follow the path of the catheter to its proper location. Contrast material is infused into the catheter and enters the blood stream to confirm the location of the catheter within the liver. Measurement of pressure in the blood vessels of the liver (HVPG) and removal of small pieces of liver tissue (liver biopsy) will be performed through the catheter using the X-ray machine as a guide. The liver biopsy is used to detect the amount of abnormal AT protein in the liver cell and the amount of scarring that is present in the liver. The pressure measurement will be done to determine whether it is elevated to a level that will qualify for the treatment study. The liver biopsy will be done to determine the severity of the liver disease, including amount of abnormal AT protein accumulated in the liver cell and amount of scarring of the liver. This information will be used as the pre-treatment values for comparison to values after treatment with the study medication for 12 months, as the primary objective of the treatment study. This means that you will undergo the transvenous liver biopsy and HVPG measurement a second time, at the end of the study, if you are found to be eligible and complete the study. You will be carefully observed and monitored during the procedure and will then be moved into the recovery area to be further observed and carefully monitored for several hours after the procedure.

If you undergo the screening procedures but the results indicate that you cannot be entered into the study, we will want to keep your contact information for studies that may be done in the future.

Please understand that we will explain the full study and its consent form to you before asking you to consent to the screening procedures described here.

What are the possible risks, side effects, and discomforts of this research study?

The transvenous liver biopsy/HVPG can be associated with complications such as bruising at the site of the needle insertion in the neck and abdominal pain. Several other complications are infrequent: abdominal bleeding; puncture wound of the liver covering; bleeding into the bile; formation of a needle track that abnormally connects the liver arteries and veins or bile ducts to

each other; enlargement of areas of the arteries in the liver; abnormal collection of air in the chest cavity with collapse of part of the lung; sudden heart rhythm disturbance.

These complications are rare and mostly stop on their own without any medical or surgical intervention. In approximately 1 in 1000 times a complication will not spontaneously resolve and very rarely can lead to low blood pressure, shock or death. You will be given medicine for sedation/anesthesia during the procedure.

Rarely the sedation can be associated with nausea, vomiting and/or a decrease in the breathing rate. These complications usually resolve on their own, but occasionally, artificial respiration for a short period of time is needed.

As a part of performing the liver biopsy and taking liver pressure measurements, you will receive standard fluid in the vein that will make the vein visible on x-ray. This fluid is very safe and is used as a standard procedure. Rarely, patients given this fluid can experience an allergic reaction. If you have abnormal kidney function, it can make the kidney function worse. You will be screened for previous history of allergic reactions to radiographic contrast and impaired kidney function and will be monitored closely for these reactions during the trial.

As part of performing the liver biopsy, you will be exposed to a dose of radiation needed to determine the localization of the catheter in the blood vessels of the liver. The amount of radiation exposure that you will receive from this procedure is approximately 0.5 to 1.0 rems to the abdominal region of the body with minimal exposure of other body areas. For comparison, this radiation dose is about 1 to 2% of the maximum annual radiation dose (50 rems) permitted by Federal regulation to any single organ of the body of radiation workers.

Thus, after the 2 procedures you will receive 2 to 4% of the maximal annual exposure to any single organ as applied to a radiation worker. There is no known minimum level of radiation exposure that is recognized as being totally free of the risk of causing genetic defects (abnormal cells) or cancer. However, the risk associated with the amount of radiation exposure that you will receive from this study is considered to be low when compared to other everyday risks.

Some individuals with liver disease have decreased platelets (needed to help blood clot) and/or prolonged clotting times which put them at increased risk for bleeding during procedures. In this case you may need to receive a transfusion of one of the components of blood (platelets or plasma) before the liver biopsy procedure in order to correct any bleeding tendency. This is routine, or standard of care, related to the liver biopsy procedure. If it is determined that you are at an increased risk for bleeding, a transfusion will be required. If you receive blood products to correct bleeding tendencies prior to the procedure you should know that there are several risks associated with the use of these products. Uncommonly (1-5% chance) there can be a reaction with itching, rash, fever and headache. Rarely (less than 1% chance), there can be shortness of breath or lung injury, kidney damage, infection with blood borne micro-organisms (bacteria and parasites), diminished immune function that helps your body fight infection, shock and/or death. Extremely rarely (one in a million or less), there can be exposure to blood borne viruses such as hepatitis (an inflammatory disease affecting the liver) and human immunodeficiency virus (HIV, the virus that causes AIDS).

Skin rashes, possibly severe ulcers and hair loss may also be associated with fluoroscopy. The likelihood of these occurring depends on the difficulty of the procedure but they are very rare side effects even in the most difficult cases.

Your personal medical information will be collected for this study. All information is kept strictly confidential (private); however, a breach of confidentiality is a risk.

To minimize this risk, the information that identifies you as a participant of this study is kept in a locked file at this hospital. No one outside of this hospital that may analyze or store study results that are collected during the course of this study will have information regarding your identity.

You will undergo blood tests. Drawing of blood can be associated with pain and bruising at the site of needle insertion. Occasionally there can be excessive bleeding from the site. Rarely a person can faint during or immediately after blood drawing. The total amount of blood that will be drawn in the screening assessment is 33.2 ml (approximately 2.24 tablespoons).

There is no risk to the other procedures being done here.

Results of all of the studies will be provided to your primary physician.

Please understand that we will explain the full study and its consent form to you before asking you to consent to the screening procedures described here.

What are possible benefits from taking part in this study?
There are no possible benefits from these screening procedures.

What treatments or procedures are available if I decide not to take part in this research study?
Currently there is no alternative treatment for this condition and no strategy to prevent progression of this liver disease. Participation in the study will not interfere with your eligibility to undergo liver transplantation if that becomes necessary and is considered appropriate for your care.

Please ask your study doctor as many questions as you wish. The doctor's answers to your questions could help you decide whether to participate in this research. If you decide now that you will participate in the research effort, and later change your mind, you may stop participation in the research project then.

If I agree to take part in this research study, will I be told of any new risks that may be found during the course of the study?
You will be promptly notified if any significant new information (either good or bad) develops during the conduct of this research study which may affect your health, safety, or willingness to continue to participate in the research study.

Your refusal to participate will involve no penalty or loss of benefits to which you are otherwise entitled. Refusal to participate will not affect your legal rights or the quality of health care that you will receive at this center.

Will my insurance provider or I be charged for the costs of any procedures performed as part of this research study?
Your insurance provider will not be billed for any procedures performed solely for the purpose of this research study. Expenses resulting from standard care for your medical problems are your responsibility (or the responsibility of your insurance provider or government program). There are no funds available to pay for lost time away from work and other activities, lost wages, or child care expenses.

Will I be paid if I take part in this research study?
You will not be paid to participate in this study.

If you need financial assistance to cover travel expenses for participation in this study, funds will be provided in the following amounts: up to $500 if you live within 100 miles of Pittsburgh; up to $3,000 if you live 100-500 miles away from Pittsburgh; up to $5,000 if you live 500-1,000 miles away from Pittsburgh; up to $7,000 if you live more than 1,000 miles away from Pittsburgh, and up to $10,000 if you live more than 1,300 miles away from Pittsburgh. When airfare from certain locations exceeds these amounts, we may provide an amount of funding that covers the airfare and other travel costs for you and an accompanying adult (parent, spouse, etc.), even if it exceeds the amounts mentioned above.

Who will pay if I am injured as a result of taking part in this study?
There is the possibility with any medical treatment or research that you may suffer some physical illness or injury. If you believe that the research procedures have resulted in injury to you immediately contact the Principal Investigator who is listed on the first page of the form. Emergency medical treatment for injuries solely and directly related to your participation in this research study will be provided to you by the hospitals of UPMC. Your insurance provider may be billed for the costs of this emergency treatment, but none of those costs will be charged directly to you. If your research-related injury requires medical care beyond this emergency treatment, you or your insurance company will be responsible for the costs of this follow-up care. At this time, there is no plan for any additional financial compensation.

Who will know about my participation in this research study?
You have the right to privacy. Any information about you that is collected for this research will remain confidential as required by law. Any information about you obtained from or for this research will be kept as confidential (private) as possible. All records related to your involvement in this research study will be stored in locked file cabinets or password protected databases. No one outside of this hospital that may analyze or store study data will have information regarding your identity. You will not be identified by name in any publication of research results unless you sign a separate form giving your permission (release). UPMC policy requires that all research records be kept for a minimum of seven years following final reporting or publication of a research project.

Will this research study involve the use or disclosure of my identifiable medical information?
This research will involve the recording of current and/or future identifiable medical information from your hospital and/or other (e.g., physician office) records. The information that will be recorded will be limited to information concerning the laboratory testing that you will be scheduled to undergo for screening and follow up procedures, the results of these tests and any adverse events that may have been associated with them.

This research will result in identifiable information that will be placed into your medical records held at UPMC.

Who will have access to identifiable information related to my participation in this research study?
In addition to the investigators listed on the first page of this authorization (consent) form and their research staff, the following individuals will or may have access to identifiable information (which may include your identifiable medical information) related to your participation in this research study:

Authorized representatives of the University of Pittsburgh Research Conduct and Compliance Office may review your identifiable research information (which may include your identifiable medical information) for the purpose of monitoring the appropriate conduct of this research study.

Authorized representatives of the sponsors of this research study, the National Institutes of Health and Novartis Institute for Biomedical Research, Inc., may review and/or obtain your identifiable medical information for the purpose of monitoring the accuracy and completeness of the research data and for performing required scientific analyses of the research data.

While the National Institutes of Health and Novartis Institute for BioMedical Research, Inc. have provided assurance that they will not release your identifiable medical information to anyone else, UPMC cannot guarantee this.

The investigators involved in the conduct of this research study will receive funding from the sponsor to perform the research procedures and to provide identifiable research and medical information related to your participation in the study.

Authorized representatives of the U.S. Food and Drug Administration may review and/or obtain identifiable information (which may include your identifiable medical information) related to your participation in this research study for the purpose of monitoring the accuracy of the research data. While the U.S. Food and Drug Administration understands the importance of maintaining the confidentiality of your identifiable research and medical information, the University of Pittsburgh and UPMC cannot guarantee the confidentiality of this information after it has been obtained by the U.S. Food and Drug Administration.

Authorized representatives of UPMC or other affiliated health care providers may have access to identifiable information (which may include your identifiable medical information) related to your participation in this research study for the purpose of (1) fulfilling orders, made by the investigators, for hospital and health care services (e.g. diagnostic procedures) associated with research study participation; (2) addressing correct payment for tests and procedures ordered by the investigators; and/or (3) for internal hospital operations (e.g. quality assurance).

In unusual cases, the investigators may be required to release your research information in response to a court order. If the investigators learn that you or someone with whom you are involved is in serious danger of potential severe harm, they will need to warn those who are in danger and contact other agencies to ensure safety.

For how long will the investigators be permitted to use and disclose identifiable information related to my participation in this research study?
The investigators may continue to use and disclose, for purposes described above, identifiable information (which may include your identifiable medical information) related to your participation in this research study indefinitely.

May I have access to my medical information that results from my participation in this research study?
In accordance with UPMC Notices of Privacy Practices document that you have been provided, you are permitted access to information (including information resulting from your participation in this research study) contained within your medical records filed with your health care provider unless otherwise specifically stated below.

You agree that, while the study is still in progress, you may not be given access to medical information about you that is related to the study.

This may include, for example, information about whether you are receiving study drug that is "blinded" (that is, kept secret during the study to prevent bias). While a request for access to medical information can be denied, the study doctor and staff will not automatically deny a request, but will consider whether it's medically appropriate under the circumstances to allow access. Your agreement that you may be denied access to your study-related medical information during the study will not be used to deny you access to that information after the study is completed at all locations and study results are analyzed.

Is my participation in this research study voluntary?
Your participation in this research study, to include the use and disclosure of your identifiable information for the purposes described above, is completely voluntary. (Note, however, that if you do not provide your consent for the use and disclosure of your identifiable information for the purposes described above, you will not be allowed, in general, to participate in the research study). Whether or not you provide your consent for participation in this research study will have no effect on your current or future relationship with the University of Pittsburgh. Whether or not you provide your consent for participation in this research study will have no effect on your current or future care at Children's Hospital of Pittsburgh of UPMC or affiliated health care provider or your current or future relationship with a health care insurance provider.

If your doctor is involved as an investigator in this research study, as both your doctor and a research investigator, he/she is interested both in your medical care and the conduct of this research study. Before giving your permission for your participation in this research study, or at any time during your study participation, you may discuss your care with another doctor who is not associated with this research study. You are not under any obligation to grant permission for your participation in any research study offered by your doctor.

May I withdraw, at a future date, my consent for participation in this research study?
You may withdraw, at any time, your consent for participation in this research study, to include the use and disclosure of your identifiable information for the purposes described above. (Note, however, that if you withdraw your consent for the use and disclosure of your identifiable medical record information for the purposes described above, you will also be withdrawn, in general, from further participation in this research study.) Any identifiable research or medical information recorded for, or resulting from, your participation in this research study prior to the date that you formally withdrew your consent may continue to be used and disclosed by the investigators for the purposes described above.

To formally withdraw your consent for participation in this research study you should provide a written and dated notice of this decision to the principal investigator of this research study at the address listed on the first page of this form.

Your decision to withdraw your consent for participation in this research study will have no effect on your current or future relationship with the University of Pittsburgh. Your decision to withdraw your consent for participation in this research study will have no effect on your current or future medical care at a UPMC hospital or affiliated health care provider or your current or future relationship with a health care insurance provider.

If you decide to withdraw from study participation after you have received the study drug, you should participate in described monitoring follow-up procedures directed at evaluating the safety of the study drug.

If I agree to take part in this research study, can I be removed from the study without my consent?
No guarantee is made as to the results of your participation in this study. If certain circumstances were to occur, the physician may stop the study medication and your participation in this study may be terminated without your permission. These circumstances would be related to either your failure to cooperate fully with the conduct of the study, or the recognition of significant medical risks associated with your continued participation in this study. If your participation in this study is stopped, the reasons will be discussed with you.

Any identifiable research or medical information recorded for, or resulting from, your participation in this research study prior to the date that you were withdrawn from participation may continue to be used and disclosed by the investigators for the purposes described above.

A description of this clinical trial will be available on www.clinicaltrials.gov, as required by US 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.

VOLUNTARY CONSENT

The above information has been explained to me and all of my current questions have been answered. I understand that I am encouraged to ask questions about any aspect of this research study during the course of this study, and that such future questions will be answered by a qualified individual or by the investigator(s) listed on the first page of this consent document at the telephone number(s) given. I understand that I may always request that my questions, concerns or complaints be addressed by a listed investigator.

I understand that I may contact the Human Subjects Protection Advocate of the IRB Office, University of Pittsburgh (1-866-212-2668) to discuss problems, concerns, and questions; obtain information; offer input; or discuss situations that have occurred during my participation.

By signing this form, I agree to participate in this research study. A copy of this consent form will be given to me.

_____ _____

Participant's Signature Printed Name of Participant

_____

Date

CERTIFICATION of INFORMED CONSENT

I certify that I have explained the nature and purpose of this research study to the above-named individual(s), and I have discussed the potential benefits and possible risks of study participation. Any questions the individual(s) have about this study have been answered, and we will always be available to address future questions as they arise. I further certify that no research component of this protocol was begun until after this consent form was signed.

_____

Printed Name of Investigator Obtaining Consent

_____ _____

Signature of Investigator Obtaining Consent Date