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**DEPARTMENT OF PEDIATRIC GASTROENTEROLOGY,
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Title: A Preliminary Study of the Efficacy and Safety of Carbamazepine in Severe Liver Disease Due to Alpha-1-Antitrypsin Deficiency (02) April 2015

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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 less than or equal to 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 and have been found to be eligible for this research study, including the results of the screening tests, we are asking you to be a part of this research study. The study is designed 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 through 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?

You will be assigned to one of two study groups. One group will receive pills that contain the active medication, CBZ, and the other group will receive pills that are similar in appearance, but do not contain any active medication. You will be assigned to one of these two groups by a process similar to drawing straws. You will have 2 chances in 3 of receiving CBZ and one chance in 3 of receiving placebo. Neither you, nor your study doctor, nor other research personnel who are involved in your care will know whether or not you are receiving the active medication.

Once the study medication is assigned to you, you will receive the Study Medication from the Investigational Drug Service (IDS) and you will be required to take the medication by mouth daily at the dose that is prescribed. You will be started on a dose of 400 mg/day and the dose will be increased by 200 mg/day each week until reaching a dose of 1200 mg/day. This method of increasing the dose over a number of weeks has been shown to decrease the likelihood of side effects from the medication. You will be asked to take half of the daily dose on 2 occasions during each day. The dose of the Study Medication will change depending upon the blood levels that will be measured. To ensure the study is carried out properly, a study monitor who is not part of the investigator team will review the CBZ blood levels and determine whether the dose of the drug needs to be altered. The study monitor will make a change in the dose of the study drug that does not contain the active CBZ medication for one subject every other time he/she makes a change in the dose of the study drug that contains the active CBZ medication for a subject.

To ensure the study is carried out properly, the study monitor will not communicate the actual blood level of the study medication to you or your physician. However, the study monitor will inform the study physician regarding necessary changes in the dose of the study medication and will release the identity of your study group to your study doctor if that information is needed for your safety.

You will need to return for frequent study visits. These visits will be in the Clinical Translational Research Center in Montefiore University Hospital and/or in the outpatient offices of the Center for Liver Disease (CLC) in Montefiore University Hospital and last approximately 1 hour. Study visits will be scheduled at the following times: weeks 4 (+/- 1 week), 8 (+/- 2 weeks), 18 (+/- 2 weeks), 36 (+/- 2 weeks), and 52a (+ 3 weeks), for history and physical examination, assessment survey for depression and behavior changes administered by the study coordinator, urine tests, and blood tests to measure the blood level of the study medication, and to monitor liver function. The study physician may require you to return for additional study visits depending upon the results of study testing. For females, urine pregnancy test will be done routinely while on the study drug. The effect of the treatment will also be analyzed by 2 new experimental tests using blood samples obtained pre-treatment, during treatment and



post-treatment. Another laboratory test that will be done at enrollment and week 52 is called a “fibrotest” and uses the results of six blood serum tests to generate a score that is correlated with the degree of liver damage in people with a variety of liver diseases. The amount of blood that will be taken at visits where the blood level of the study medication is taken in addition to the tests needed to monitor the liver function will be no more than 3 tablespoons (39.7 ml). You will be required to return Medi-dose cups so that conventional pill counts can be done at each visit. You will also be required to record the time you took each dose of the study medication on a paper diary that the study team will review with you at visits.

You might also undergo magnetic resonance imaging (MRI/MRE) within the first six months after enrollment and at week 52 of the trial. The MRI/MRE will be done at an UPMC hospital in accordance with the procedures used for any other patient not participating in a research trial. Magnetic resonance elastography (MRE) is a non-invasive medical imaging technique that measures stiffness of the liver in the beginning stages of the clinical trial and again at the end, to determine if the introduction of the carbamazepine has reduced this “stiffness” (cirrhosis).

A liver biopsy and measurement of the amount of pressure that is required for blood to pass through the liver will be done at week 52b of treatment with the study medication (transvenous liver biopsy/HVPG measurement). These tests are the same as you underwent in the screening phase of the study. The liver biopsy and pressure measurement 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. These amounts will be compared to the same measurements that have been done during the initial screening to determine if the level of this abnormal AT protein has decreased by using the Study Medication. The pressure measurement will allow us to determine whether there has been a major improvement in the scarring of your liver and blood flow through the liver. 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

After the liver biopsy and pressure measurements have been completed, the Study Medication will be stopped.

While the actual blood level of the study medication will only be known by the Study Monitor, all other test results will be provided to your primary physician.

If you have to undergo liver transplantation during the study period, a sample of tissue will be obtained from your original liver after it is removed. If you die during the study period, and your family agrees to an autopsy, a sample of liver tissue will be obtained at the time of the autopsy. These samples will be used to determine the outcome of the study. Please be aware that the autopsy is not being done for study purposes. If your family does not consent to the autopsy, this sample of liver tissue will not be obtained for the study.

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

CBZ may have side effects. Most of the time these are minimal, occur at the beginning of the treatment period and resolve within a few days without any intervention. The side effects include drowsiness, dizziness and double vision in 3% of people. The number of white blood cells may decrease. Occasionally an allergic reaction can lead to significant rash and dryness in the mouth and eyes (4-10% of people). Rarely, the allergic reaction can lead to inflammation in the liver and kidney and even more rarely, to liver failure.

There is limited information available about the effects of CBZ in persons with liver disease. Because CBZ treatment can be associated with elevation in blood levels of liver enzymes that can originate from the liver (5-10% patients receiving CBZ for a seizure disorder may experience elevated blood levels of liver enzymes), it is possible that you will develop elevations of these liver enzymes. Elevated blood levels of these enzymes can indicate damage to the liver. We will monitor your blood tests very closely for this potential side effect.

Infrequent side effects of CBZ include the following: low sodium levels in the blood; decrease in the level of thyroid hormone in the blood; allergic reaction in which the bone marrow production of blood cells can be depressed (occurs in less than 1 in 50,000 people); development of tics, abnormal stiffness, or tremor. Extremely rare side effects that have been reported once or twice in the literature include: heart failure, aggravation of high blood pressure, blood clots, disturbance in heart rhythm, urgency to urinate, or urinary retention.

One study has suggested that CBZ may increase the likelihood of depression and suicidal behavior. We will monitor this issue very closely in the study protocol as described above.



CBZ may cause harm to the fetus when it is taken by a pregnant woman. It can lead to malformations of the spine and heart. There may be an association between the use of CBZ during pregnancy and congenital malformations, including spina bifida. There have also been reports that associate CBZ with developmental disorders and congenital birth defects involving various body systems). Developmental delays have been reported. Even though the risk of fetal damage is low and many women stay on the drug when pregnant, in this study we will discontinue the drug if your pregnancy test becomes positive.

All female subjects of child-bearing age will undergo urine pregnancy test: on enrollment, prior to starting therapy, and monthly during the trial. The study coordinator will provide counseling on barrier methods of contraception for all women of child bearing age monthly during the trial. If a subject is found to be pregnant, CBZ will be immediately discontinued and permanently stopped and the subject will be referred to an obstetrician for advice and consultation. You or your insurance plan will be responsible for the costs of initial and follow-up care by the obstetrician.

The study will collect data on the outcomes of:

- Any pregnancies that occur in women who conceived while taking CBZ.
- Liver disease in women who are withdrawn from CBZ.

To provide information regarding the effects of in utero exposure to CBZ (Tegretol), physicians are advised to recommend that pregnant patients taking CBZ (Tegretol) enroll in the North American Antiepileptic Drug (NAAED) Pregnancy Registry. This can be done by calling the toll free number 1-888-233-2334, and must be done by patients themselves. Information on the registry can also be found at the website <http://www.aedpregnancyregistry.org/>.

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).



Elevation of liver tests, performed using blood, is part of the natural course of the disease in patients with ATD. Therefore, not all changes in the laboratory results that we will monitor can or should be attributed to the Study Medication or the procedures performed as a part of this research study. However, if changes in laboratory tests cross thresholds that have been established, adjustments in the Study Medication may occur.

You will be provided with the Carbamazepine medication guide (prepared by the manufacturer) prior to signing this consent form.

The transvenous liver biopsy/HVPG can be associated with complications such as bruising at the site of the needle insertion 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.

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.

A small amount of the samples that you will provide as a part of this study will be transferred to a study sponsor, Novartis, for some experimental testing. To ensure and maintain confidentiality, these samples and information about your medical condition and/or status will be provided to the sponsor in a completely de-identified manner. The samples and information will be provided to this sponsor with a study code number. Information linking the code numbers with your personal information will be kept separate from the samples, and will not be sent to study sponsors.

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 is 18 tablespoons (261.6 ml) and the most that will be drawn at any single time is 3 tablespoons (39.7 ml).

You might undergo an MRI at the enrollment visit and at week 52 of this trial. Possible side risks that can occur with MRI:

- The levels of energy used to make magnetic resonance measurements are far less than those used in a single X-ray, and many patients have been safely studied using magnetic resonance techniques. However, some people become uncomfortable or claustrophobic (fear of closed spaces) while inside the magnet. If you become uncomfortable inside the magnet, you may withdraw immediately from the study.
- During some of the MRI scans, subjects have occasionally reported “tingling” or “twitching” sensations in their arms or legs, especially when their hands are clasped together. Further, because of the strong magnetic field, people with pacemakers, certain metallic implants, or metal in the eye cannot participate in this study. Dental fillings do not present a problem with MRI. No other serious effects have been reported from being in the 1.5 Tesla magnet, although vertigo (e.g., dizziness and nausea) has been reported at higher field strengths (7.0



Tesla). This study is utilizing a 1.5 Tesla magnet only. You will be given a checklist before entering the MRI room, which will be reviewed and used to verify that you do not have anything harmful in or on your body.

- The MR imaging scanner produces loud sounds during imaging acquisition; the sounds are related to the activity of the scanner. Earplugs will be provided to each subject to maintain the sound level below FDA limits.
- There is a rare risk that a metallic object may be attracted to the magnet and hit you. To reduce this risk we require that all people involved with the study remove all metal from their clothing and all metal objects from their pockets. No metal objects are allowed to be brought into the magnet room at any time. In addition, once your child is in the magnet, the door to the room will be closed so that no one inadvertently walks into the magnet room.
- Unusual sensations post-scan may include nausea, dizziness, and minor back ache.

Reproductive risks

Although there are no known risks of MRI on pregnant women or a fetus, there is a possibility of yet undiscovered pregnancy related risks. Since there is no direct benefit from participating in this protocol for a pregnant woman, we will exclude pregnant women. A negative urine pregnancy test will be mandated before a woman of child-bearing potential can be scanned.

No standard treatment for ATD including transplantation, if appropriate, will be withheld during the study period while you are receiving the Study Medication.

What are possible benefits from taking part in this study?

There may be no direct benefit to you by participating in this study. Your medical problem may get better or go away while taking the study medication. It is also possible your liver problem will not change or could possibly get worse while taking the study medication. Your study doctor cannot guarantee that you will benefit from participation in this research.

In the future, other people with ATD could benefit from the results of this research. Information gained from this research could lead to improved medical care for them. However, your study doctor will not know whether there are benefits to other people with ATD until all of the information obtained from this research has been collected and analyzed.

Testing of samples from your blood or liver tissue may lead to patents and even eventually to new products which help other people and also possibly produce financial gains.

A panel of experts in ATD, CBZ and clinical research studies such as this one will be monitoring this study every 12 months. This panel will be allowed to see and review the results of all the available clinical and laboratory information on all the patients



participating in this study and has the authority to stop the trial if a dramatic positive or negative result is apparent before the study, as planned, is completed.

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 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 the CBZ drug or 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.

You will also not benefit from any commercial gains that derive from the testing that is done on samples from your blood or liver tissue.



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 Institutes 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 both the National Institutes of Health and Novartis Institutes 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.

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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

