

Official title: Childhood Absence Epilepsy Rx PK-PD-Pharmacogenetics Study

NCT number: NCT00088452

Date of Informed Consent Form: 8/18/2005

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

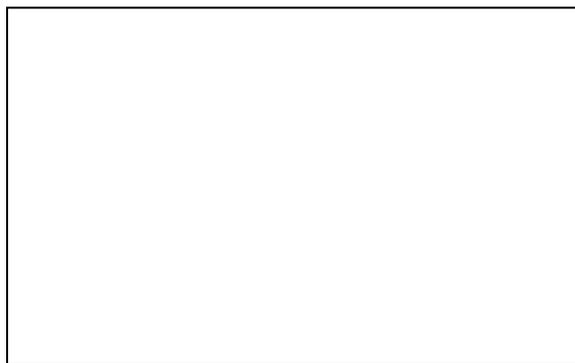
STUDY TITLE: Childhood Absence Epilepsy: Rx, PK-PD-Pharmacogenetics

SPONSOR NAME: National Institutes of Health (NS 045911 and NS045803)

CCHMC IRB # 04-2-32

IRB Initial Approval Date: March 23, 2004, revised approval date: January 3, 2005 and August 18, 2005

IRB APPROVAL STAMP:



INVESTIGATOR INFORMATION:

Tracy A. Glauser, M.D.

513-636-4200 (ask for drug study pager)

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 STUDY BEING DONE?

There are many medications used to treat seizures, but only three medicines are usually used as the first treatment for children with childhood absence epilepsy (abbreviated as “CAE”): ethosuximide (also called Zarontin[®]), lamotrigine (also called Lamictal[®]), and valproic acid (also called Depakote[®] or Depakene[®]). Ethosuximide and valproic acid have been approved by the Food and Drug Administration (FDA) for the treatment of children with CAE. Lamotrigine, which has been studied before in children with CAE and is the third most commonly prescribed medicine for this type of epilepsy, has been approved by the FDA only for the treatment of children with other types of seizures, and its use for children with CAE is still considered investigational. Although each of these medicines may help, not all medicines work for all children, and each has certain side effects. We do not know which of these three medicines is the best first choice for children who have just been diagnosed with CAE, nor do we know why one medicine and not others control some children’s seizures.

This research is being done (1) to find the best medicine to use first to treat children with CAE, (2) to learn more about how these medicines effect children, and (3) to find out if there are tests that in the future could be used to help pick the best medicine for each individual child diagnosed with CAE.

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 been diagnosed with a type of epilepsy called childhood absence epilepsy (also called petit mal epilepsy). Patients with childhood absence epilepsy have brief staring spell seizures that occur suddenly, unpredictably, and frequently throughout the day.

WHO SHOULD NOT BE IN THE RESEARCH STUDY?

You should not be in this study if

- a) you have a diagnosis of any type of epilepsy other than childhood absence epilepsy OR
- b) you have been on antiseizure medication for more than seven days at the time of your entry into this study OR
- c) you have had seizures not associated with fever that are different from absence (petit-mal) seizures described above (such as generalized tonic/clonic or grand-mal seizures) OR
- d) you have had a prior history of a major psychiatric disorder (such as major depression), a history of autism or pervasive developmental disorder, or another significant medical conditions (such as cancer) OR
- e) you have had a history of an allergic reaction (rash) to medication OR
- f) you do not feel you can comply with the rules of the study including the visit schedule
- g) you need to take a contraceptive medication during the double blind portion of the study.

HOW LONG WILL YOU BE IN THE RESEARCH STUDY

You will be in the research study until either

- a) you are seizure free for 2 years on either your first or second antiseizure medication OR
- b) you have uncontrolled seizures or intolerable side effects on either the first or second anti-seizure medication used.

There are several portions to this study that will affect how long you might participate. The study begins with a 16-week double blind phase during which the dose of your medicine is increased. If this medicine works well for you, you can continue on the study for 2 years during the long-term double blind phase. After two years, you will be gradually weaned off the medicine. This is similar to the regular treatment of CAE. If the initial medicine does not work well, the first medicine will be weaned over 2 weeks and you will receive a “bridging” medicine called lorazepam (also called Ativan[®]). After 2-4 weeks you will then be started on a second medicine and enter a 16-week open label phase during which the dose of your second medicine is increased. If the second medicine works well for you, you can continue on the study for 2 years during the long-term open label phase after which you will be weaned off it. The chart attached to this forms gives more details about this.

You may be taken off this study without your consent if.

- Your doctor decides that continuing in the study would be harmful
- You need a treatment not allowed on this study
- You are unable to keep appointments, or take the study medicines as instructed
- New information is learned that a better treatment is available, or that the study is not in your best interest
- Funding for this study is stopped
- Drug supply is insufficient

WHO IS CONDUCTING THE RESEARCH STUDY?

This study is sponsored by the National Institute of Neurologic Disorders and Stroke which is a part of the National Institutes of Health (NIH). The overall study is directed by Dr. Tracy Glauser, Division of Neurology at Cincinnati Children’s Hospital Medical Center, Cincinnati, Ohio. This study is directed at this site by Dr. Tracy Glauser. Medical supervision for this study is provided by Dr. Tracy Glauser, Division of Neurology at Cincinnati Children’s Hospital Medical Center, Cincinnati, Ohio.

HOW MANY PEOPLE WILL TAKE PART IN THE RESEARCH STUDY?

About 50 people at Cincinnati Children’s Hospital Medical Center and a total of 439 children in 20 medical centers across the United States will take part in this study. Children will join the study over a 3-year period of time.

WHAT IS INVOLVED IN THE RESEARCH STUDY?

In order to learn what the best first choice of medicine is, the choice of medicine in this trial will be randomized, which means that the first drug given to you will be determined by chance, like a roll of dice. This trial is called a “double-blinded” trial because neither you nor your doctors will know which drug you are getting. Because the medications used come in different forms (for examples liquid, capsules or powder), the medicine will be given to you in a way that will not make it possible for you or your doctors to know which medicine it is (“blinded”).

As part of this study you will be

- 1) given one of three commonly used medicines used to treat CAE,
- 2) take this medicine by mouth two times each day,
- 3) be seen in clinic on a regular basis every 1 to 3 months for about 2 years,

- 4) undergo regular tests that will tell us if the medicine is working well for you, and
- 5) help us learn more about these medicines for future children diagnosed with CAE.

Finding the best dose and medicine for you

All medicines used for children with CAE are first given in a low dose and then the dose or amount of medicine is slowly increased over time. For the first 16 weeks of this study, the amount of your medicine will be slowly increased until it is clear that the medicine is helping or a side effect occurs that tells us the dose should be lowered or the medicine stopped. During these 16 weeks, you will be seen in our clinic every 4 weeks for certain tests (described below). After 16 weeks, if the medicine is working well, you will continue to take the same amount of medicine every day and be seen in clinic every 3 months for about 2 years.

If, during the first 16 weeks, we find that the medicine is not working well or if there are side effects that must make us stop giving the medicine, you will then be switched to one of the other two medicines. The choice of the next medicine will also be made randomly, like the flip of the coin. However, once the choice is made, you will be in the “open-label” phase of the trial, and both you and your doctors will know which medicine you are getting. The amount of your second medicine will again be slowly increased over 16 weeks until it is clear that the medicine is helping or a side effect occurs that tells us the dose should be lowered or the medicine stopped. During these 16 weeks, you will be seen in our clinic every 2 to 4 weeks. After 16 weeks if the medicine is working well, you will continue to take the same amount of medicine every day and be seen in clinic every 6 months for about 2 years.

If the second medicine is not going to work well or if there are side effects that must make us stop giving the medicine, you will no longer be in the study. Your doctor will then make a recommendation as to how best to treat your CAE.

How we keep you and your doctor from knowing which medicine is being used

During the “double-blind” phase of the study, neither you nor your doctor will know which medicine you are getting. As these medicines come in different forms (capsules, liquid, and powder) there will be two approaches taken to prevent us from knowing which medicine you are getting:

For younger children who weigh 67 pounds or less, you will take a liquid and a powder sprinkled on food. Only one of these different “medicines” will be the “real” medicine; the other contains placebo (also called inactive or “sugar” pills or liquid). During the first 16 weeks, we will help teach you how to swallow capsules. Once you are able to swallow capsules, the medicine will be given to you in capsules that you will need to take twice a day, just like the older children who weigh more than 67 pounds. If at the end of 16 weeks you are still not able to swallow capsules, you will only be allowed to stay in the study if you agree to continue to take the 2 different “medicines” each day. If at the end of 16 weeks you are still not able to swallow capsules and you do not want to continue to take the 2 different “medicines” each day then you can no longer participate in this study. Your doctor will then decide which of the three commonly used medications will be used to treat your seizures; for this one situation ethosuximide (also called Zarontin®) will be recommended due to its lack of drug-drug interactions with either of the other two study medications.

For older children who weigh more than 67 pounds, you will have the option of taking either 1) capsules two times each day or 2) a liquid and a powder sprinkled on food (as described in the previous paragraph) . The capsules will “hide” the medicine inside it. The number of

capsules you take will depend upon the dose you are supposed to take; at each visit, you will be told how many to take.

Tests to be done

The routine care of children with CAE involves performing certain tests to help diagnose the epilepsy, to help determine whether the medicine being given is working, and to watch for side effects of the medicines used. You will have all the regular tests usually done for children with CAE as part of this study. In addition, there are other tests we would like to do to help us learn more about CAE and the effects of these medicines. We will describe all these tests. Attached to this consent form you will find two charts that details how often and when each of these tests will be performed. One chart is for the double blind portion of the study while the other chart is for the open label portion of the study.

Tests that are routinely done in children being treated for CAE:

EEG (electroencephalogram or brain wave test). An EEG is a test that measures your brain's electrical activity. This test help your doctors determine if seizures are occurring and what type they are. During the EEG electrodes (small metal discs) are stuck to your scalp with gel. The test is painless. At the end of the procedure these electrodes and the gel is removed. Sometimes the EEG is done with a videotape of you during the EEG. The video helps find out if certain movements or staring spells are occurring. The EEG is routinely done for children with CAE; the video, although a routine test for certain patients with seizures, in this case is part of research. The EEG will last one hour; the whole procedure takes about 90 minutes.

Hyperventilation. Hyperventilation is breathing in and out deeply and quickly. Doing this can sometimes trigger a brief seizure that the medicine, if working well, should have prevented. In the clinic, your doctor guides you through this routine test. In the EEG lab, the EEG technologist will guide you through this test which is routinely done during an EEG. The hyperventilation test will last 5 minutes and will be done twice during each EEG.

Blood tests. Blood tests are done to routinely check for side effects of these medicines, and can include tests that check for inflammation or irritation of the liver, and a change in blood counts.

Tests that are being done as part of this study primarily to help us learn more:

Intelligence, memory and attention tests In order to better understand the full effects of these medications, we will perform several standard tests that measure attention, intelligence, memory skills, and certain school skills. These tests will last 1 1/2 to 3 hours depending on your age. After the tests are scored, you will be given a short summary or results, somewhat similar to results that you might get following evaluation by a school guidance counselor or school psychologist. It is important to understand, however, that these tests do not represent a complete set of tests that you might have done if you were having learning problems in school. If a significant problem is found on these tests, your doctor may recommend more tests to be done at school or by a specialist in learning difficulties.

Behavior and quality of life. You will also be asked to fill out parent questionnaires on behavior and how you are feeling. These questionnaires will take approximately 1-hour to fill out. Please note: these questionnaires will be reviewed immediately and if there is any evidence of potential for self harm or harm to others you will be referred immediately to a mental health professional for further evaluation and treatment.

Information on diet. In order to understand the effects of these medications on gaining weight and appetite, a series of 24-hour diet recalls will be performed. A 24-hour diet recall is a

telephone call in which you will be asked to remember for the previous 24-hours all of the food that you have eaten along with the portion size and any liquid with it. In order to do this, your name and contact information will be sent to the diet center at Cincinnati Children's Hospital (Ms. Marcia Schmidt) who in turn will contact you by phone to do the 24-hour diet recall. This procedure is painless. The dietary information collected will be summarized and the results will be shared with you later in the study.

Pharmacokinetic study. Pharmacokinetics studies help us understand what happens to a drug in the body (how long it stays in the body and how it leaves the body). To do this, a small additional amount of blood will be taken on several occasions when routine blood tests are being done so that you will not need to have an extra needle stick. At your 16 week visit, we will also ask to get a small amount of blood 3 different times during the day and give a specimen of urine. These specimens will be sent to Dr. Michael Reed at Rainbow Babies Hospital in Cleveland for analysis. You and your doctors will not be told the results of these tests since it is not clear that these tests provide information that would change your treatment.

Pharmacogenetic study. We know that not all medicines work for all children, and not all children experience the same good or bad effects. Scientists now know that certain genes (the material in cells that is inherited and is made of DNA) may in part be responsible for how drugs are handled by the body, as well as for the drugs' effects, good and bad. We therefore will obtain one additional tube of blood the first time routine blood tests are performed to study the genes that we think may have a role in how these drugs work. You will not be told the results of these tests since it is not clear that these tests provide information that would change your treatment.

WHAT ARE THE RISKS AND DISCOMFORTS OF THE RESEARCH STUDY?

There are risks of each of the medicines used to treat CAE that are described in the Table below. The risks of these medicines are no different if your child receives a medicine on this study or receives it when prescribed by another doctor. Although rare, some side effects can be severe and irreversible, and your doctor will be watching closely for any signs of side effects.

Ethosuximide

	Common Happens to 21-100 patients out of every 100	Occasional Happens to 5-20 patients out of every 100	Rare Happens to < 5 patients out of every 100
Immediate (within 1-2 days) or prompt (within 2-3 weeks) of starting drug or higher dose	Nausea , decreased appetite, stomach pain, vomiting, diarrhea	Nervousness, drowsiness, headaches	Dizziness, hiccups, feeling tired, aggression, feeling overly happy, irritability, hyperactivity, difficulty sleeping.
Delayed: Anytime after above.	None known	None known	Mild rash to severe, life-threatening rash. Low red blood cell count or anemia (that may cause tiredness), low white blood cell count (that may cause an increased chance of infection) or low platelet count (that may cause an increased chance of bleeding). Autoimmune reaction that can cause inflammation of the thyroid, or inflammation of many different organs within the body. Abnormal leg movements, such as a “restless” leg

Lamotrigine

	Common Happens to 21-100 patients out of every 100	Occasional Happens to 5-20 patients out of every 100	Rare Happens to <5 patients out of every 100
Immediate (within 1-2 days) or prompt (within 2-3 weeks) of starting drug or higher dose	None known	Increased sleepiness, infection, vomiting, sore throat, fever, accidental injury, dizziness, diarrhea, unsteadiness, nausea, stomach pain, tremor (a shaking or twitching), double vision	Low red blood cell count (anemia that may cause tiredness), low white blood cell count (that may cause an increased chance of infection) or low platelet counts (that may cause an increased chance of bleeding). Increased seizures
Delayed: Anytime after above.	None known	Mild rash	Mild rash to severe, life-threatening rash

Valproic Acid

	Common Happens to 21-100 patients out of every 100	Occasional Happens to 5-20 patients out of every 100	Rare Happens to <5 patients out of every 100
Immediate (within 1-2 days) or prompt (within 2-3 weeks) of starting drug or higher dose	Nausea, vomiting, stomach pain, headache, tiredness, sedation, tremor (a shaking or twitching), dizziness	diarrhea, loss of appetite, fever, constipation, weight loss, double vision, blurred vision, unsteadiness, jerky eye movements, mood swings, slowed thinking, infection	Hallucinations
Delayed: Anytime after above.	Weight gain, hair loss low platelet counts (that may cause an increased chance of bleeding).	Increase in blood tests that measure inflammation of the liver, increase in blood ammonia from liver problems (that rarely may cause severe sleepiness or a difficult to wake up state) Low white blood cell count (that may cause an increased chance of infection)	Rash (mild) Inflammation or severe, life-threatening injury to the liver or pancreas

The risks of tests being done as part of this research are minimal, and are as follows:

Video EEG. There is no risk of this test except the inconvenience of having the paste used to stick the electrodes onto the outside of your scalp gets into your hair.

Hyperventilation. There is a chance that you will have a typical absence seizure when hyperventilating, which is important for the doctor to know as it means the medicine is not working as well as it should.

Blood tests. The risks of blood drawing (blood stick, venipuncture) are minimal and may include a little pain from the needle, bruising, bleeding, and a very slight risk of infection. Uncommonly in children, there may be a feeling dizziness or fainting.

Intelligence, memory and attention tests There are no risks to these tests other than the inconvenience of the time involved in taking these tests.

Behavior and quality of life. There are no risks to these tests other than the inconvenience of the time involved in taking these tests.

Information on diet. There are no risks to these tests other than the inconvenience of the time involved in taking these tests.

Pharmacokinetic study. The risks of the pharmacokinetic study are minimal and the same as having blood taken. We will try to do almost all these tests at the same time as you have other blood tests, except for one day when we will need to take 3 blood tests from you. On that day, your doctors may put in an IV catheter, a small plastic tube that goes into a vein in the hand or arm that can be used for repeated blood tests. An IV catheter would mean that we could get all 3 blood tests on that day using only one needle stick.

Pharmacogenetic study. The risks of the pharmacogenetic study are the same as having blood taken. We will do this test once at the same time as you have other blood tests. The genes being test for are not responsible for your epilepsy or any other disease. The genes being tested may in part be responsible for how drugs are handled by the body, as well as for the drugs' effects, good and bad.

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

WHAT ARE THE RISKS OF STOPPING YOUR CURRENT TREATMENT?

You should not stop or alter dosages of medication on your own.

WHAT ARE THE REPRODUCTION RISKS?

Because the drug(s) in this research study can affect an unborn baby, you should not become pregnant or father a baby while on this research study. You should not nurse your baby while on this research study. You should notify your study doctor immediately if you become pregnant or suspect you have caused a pregnancy. You should discuss birth control options with your study doctor.

ARE THERE DIRECT BENEFITS TO TAKING PART IN THE RESEARCH STUDY

If you agree to take part in this research study, there are direct medical benefits for you. Compared to regular clinic care, by participating in this study:

- 1) You will have closer monitoring (with serial video EEGs) of whether the medication is working to control your seizures. This is important since evidence suggests brief seizures may be difficult to see but can interfere with school performance and learning.
- 2) You will have closer monitoring (with serial questionnaires) of whether the medication is causing side effects. This is important since evidence suggests that side effects are better detected if questionnaires are used rather than general discussion in the clinic. These questionnaires are not routinely used during regular clinic care and can help identify a problem earlier than general clinic discussion.
- 3) You will have testing of general intellectual ability, attention abilities, memory skills, and achievement in various academic areas before starting medication and then while you are on medication. This testing can screen for school and learning problems that may require more detailed testing and intervention. In general these tests are expensive and are not done before medication is begun. By testing before and during medication therapy, it is possible to separate an underlying problem from a medication effect.
- 4) You will have more detailed knowledge about your dietary habits before and after you start medication. In general this dietary assessment is expensive and not done before medication is begun. By testing before and during medication therapy, it is possible to separate an underlying problem from a medication effect.

WHAT OTHER CHOICES FOR CARE ARE THERE?

Your doctor can prescribe any one of these medicines to you without your participating in this study. Although the three medications used in this study are the most common ones, there are other medicines that your doctor may recommend for treatment. Your doctor can discuss these choices with you in more detail.

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 for example of your medical and seizure history, physical examination, laboratory and test results.

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, the study’s Coordinating Center (located at The Children’s Hospital of Philadelphia), professional EEG readers, and the National Institutes of Health to be allowed to inspect sections of your medical and research records related to this study.

The Food and Drug Administration (FDA) may choose to inspect your records since you are a subject in this investigation of an unapproved drug/device (Lamotrigine [Lamictal®] is not approved for absence seizures)

A Data and Safety Monitoring Board, an independent group of experts, will be reviewing the data from this research throughout the study. The investigator will tell you about new information from this or other studies that may affect your health, welfare, or willingness to stay in 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 authorization.

Cincinnati Children’s Hospital Medical Center and/or the Investigator will take the following precautionary measures to protect your privacy and confidentiality of your research and/or medical records. All laboratory specimens, evaluation forms, reports, , and other records that leave CCHMC will be identified only by the patient’s Study Identification Number (SID) to maintain your confidentiality. All records will be kept in a locked file cabinet. All computer entry and networking programs will be done using SIDs only. Clinical information will not be released without your written permission, except as necessary for monitoring by the Institutional Review Board, the Office for Research Compliance, the study’s Coordinating Center (located at the Children’s Hospital of Philadelphia) and the National Institutes of Health.

Your identifying information will be faxed to the Coordinating Center (located at the Children’s Hospital of Philadelphia) and then refaxed to the dietary center at Children’s Hospital in Cincinnati. This information will only be sent by fax to faxes in locked, secure offices and will be stored in locked cabinets. This identifying information will not be added to the Coordinating Center’s database. Information from the dietary center will be sent electronically to the Coordinating Center’s using the patient’s study identification number. Your video-EEG recordings will contain your face. Your video-EEG recordings are reviewed by EEG experts from the Coordinating Center (located at the Children’s Hospital of Philadelphia), Montefiore Medical Center in New York, Baylor University in Houston, Texas, National Children’s Medical Center in Washington, D.C. and Northern Illinois University.

A copy of this consent form will be included in your medical research record. You will be registered in the Cincinnati Children's Hospital Medical Center's computer system as a research subject which may be beneficial for future clinical care.

The Federal Privacy Act protects the confidentiality of your National Institutes of Health medical records. However, you should know that the Act allows release of some information from your medical record without your permission, for example, if it is required by the Food and Drug Administration (FDA), members of Congress, law enforcement officials, or other authorized people.

USE AND DISCLOSURE OF YOUR PROTECTED HEALTH INFORMATION

The Protected Health Information described in the section above will be used /disclosed for the purpose of research by CCHMC to the other persons or entities 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.

“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 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?

For questions about this research study, you can contact the researcher Dr. Tracy Glauser at 513-636-4222 during the day or at 513-636-4200 (ask for drug study pager) during the night and weekends. 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 Institutional Review Board at 513-636-8039.

WHAT ARE YOUR COSTS TO BE IN THIS STUDY?

You will not be charged for the cost of the clinic visits associated with this study, the 1-hour video EEGs associated with this study, the cognitive, attention, behavioral, and quality of life testing, drug blood levels, and dietary recall histories associated with this study. You will not be charged for the medication costs during your participation in this study. The routine clinical laboratory tests that are drawn at each of the clinic visits (blood counts and liver tests) will be billed to your insurance as these are commonly routinely performed tests as part of the monitoring for toxicity due to anticonvulsant medication.

WILL YOU BE PAID TO PARTICIPATE IN THIS RESEARCH STUDY?

You will not receive any compensation for your participation in the research study. Reimbursement up to \$40.00 per visit can be provided for out of pocket expenses incurred with transportation or parking associated with the clinic visit. This out of pocket reimbursement will be made in the form of cash or check after appropriate original receipts are received.

Blood obtained in this research may result in the development of a product that could be patented or licensed. There are no plans to provide financial compensation to you should this occur.

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 Tracy A. Glauser, M.D. (513-636-4222) 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 as provided under the Health Insurance Portability and Accountability Act of 1996 (HIPAA”) at any time after you have signed it by providing Dr. Glauser 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 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 Notice of Privacy Practices. A copy of the CCHMC Notice of Privacy Practices may be obtained from any patient registration area or online at www.cincinnatichildrens.org (From the internet page select in the following order: About Us, Corporate Information, HIPAA). You may also contact our Privacy Officer at 513-636-4707 to obtain a copy.

Schedule of Events for Double Blind Phase**Schedule of Events for Double Blind (Table 2)**

Procedures	Elig. Eval.	DB 0	Phone P1	DB 1	DB 2	DB 3	DB 4	DB 4e (if needed)	Phone P2	DB 5 – DB 12
Week	(up to -7 days)	0	2	4	8	12	16	20	20	26 (DB5)
Month										9,12,15,18 21,24,30
Informed consent/assent	X									
Complete medical history	X									
Interval medical history		X	X	X	X	X	X	X	X	X
Physical examination (Ht, Wt, VS)	X ¹			X	X	X	X ⁷	X		X ⁷
Neurologic examination	X			X	X	X	X	X		X
1 hour video EEG		X		X ³	X ³	X ³	X	X		X ⁵
Pharmacogenetic sample				X						
PK sampling				X	X	X	X ^{4,8}	X ⁴		X ⁶
Urine sample for metabolites							X ⁸	X		
Clinical Laboratory	X			X	X	X	X	X		X ^{2,6,9}
Neuropsychological Battery		X								X ⁵
Continuous performance test							X ⁸	X		
Behavior/QOL assessment		X					X	X		X ⁵
Adverse events recorded			X	X	X	X	X	X	X	X
24 hour diet recall (DDEC)		X					X ⁸	X		X ⁵
Dispense study drug		X		X	X	X	X	X		X
Drug accountability				X	X	X	X	X		X

1 = Includes Tanner Staging,

2 = Includes serum pregnancy test if indicated,

3 = if indicated (i.e. no clinical or HV induced seizures)

4 = full PK profile (3 samples)

5 = 1 hour video EEG, behavior and QOL assessment, neuropsychological battery, diet recall at visits DB7, DB11(months 12, 24)

6 = PK sample and clinical laboratories at visits DB5, DB7, DB9, DB11, DB12 (months 6, 12, 18, 24, 30)

7 = Includes Tanner Staging by questionnaire at DB4, DB7, DB11

8 = If no DB4e planned

9 = At DB12: PK sample and clinical laboratories will only be done if the patient is on medication

Schedule of Events for Open Label**Schedule of Events for Open Label (Table 3)**

Procedures	Conv. visit	OL 0	Phone P1	OL 1	OL 2	OL 3	OL 4	OL 4e (if needed)	Phone P2	OL 5 – OL 9
Week	-2 to -4	0	2	4	8	12	16	20	20	26 (OL 5)
Month										12, 18, 24, 30
Interval medical history	X	X	X	X	X	X	X	X	X	X
Physical examination (Ht, WT, VS)	X ¹	X		X	X	X	X ¹	X		X ^{6,7}
Neurologic examination	X	X		X	X	X	X	X		X
1 hour video EEG				X ³	X ³	X ³	X	X		X ⁶
PK sample				X	X	X	X ^{4,8}	X ⁴		X
Urine sample for metabolites	X ⁹						X ^{5,8}	X ⁵		
Clinical Laboratory	X ²			X	X	X	X	X		X ^{2,7}
Neuropsychological battery										X ⁶
Continuous performance test	X						X ⁸	X		
Behavior/Quality of life							X	X		X ⁶
Adverse events recorded	X	X	X	X	X	X	X	X	X	X
24 hour diet recall (DDEC)		X					X ⁸	X		X ⁶
Wean double blind study drug	X									
Start benzodiazepine (optional)	X									
Wean benzodiazepine (if used)		X								
Dispense open label study drug		X		X	X	X	X	X		X
Drug accountability				X	X	X	X	X		X

Conv. = Conversion

1 = Tanner Staging (by questionnaire) at conversion visit OL4, OL6, OL8**2** = Includes serum pregnancy test (if applicable)**3** = if indicated (i.e. no clinical or HV induced seizures)**4** = full PK profile (3 samples)**5** = only if on valproic acid**6** = 1 hour video EEG, behavior/QOL assessment, neuropsychology battery, diet recall at visits OL6, OL8 (months 12, 24)**7** = At OL9: PK sample and clinical laboratories will only be done if the patient is on medication**8** = If no OL4e planned**9** = Urine collection for metabolites only if patient discontinued from double blind prior to DB4