Emory University School of Medicine

Consent and Authorization to be a Research Participant

Title: Baseline evaluation and long-term follow-up of nutritional status and neurotransmitter concentrations in Phenylketonuria patients initiating treatment with sapropterin dihydrochloride (Kuvan™), a tetrahydrobiopterin analog.

Principal Investigator: Rani H. Singh, Ph.D., R.D., L.D.

Co-Investigator: Marian L. Evatt, MD

Research Assistant: Teresa D. Douglas, MS.

Research Coordinator: Mary Jane Kennedy, R.N.

Sponsor's Name: BioMarin Pharmaceutical Inc.

If the participant is under 18 years of age, the remainder of the consent is addressed to the parent or authorized legal representative and "you" means "your child".

Introduction/Purpose:

You _____ are being asked to volunteer for a clinical research study because you are a person with PKU who is interested in the FDA approved drug Kuvan™ as a treatment option for PKU or are a person without PKU interested in being a control volunteer for this study. The purpose of this study is to investigate: (1) the effects of Kuvan™ therapy on diet, growth, weight, and nutritional health of children and adults with Phenylketonuria (PKU), (2) if Kuvan™ therapy changes quality of life in children and adults with PKU, (3) Kuvan™ induced changes in the amount of neurotransmitters (chemical produced by your body that help your nerve cells to function) in your blood and urine.

Kuvan™ is a prescription drug that helps lower blood phenylalanine (Phe) levels in many people with PKU. It is very similar to a substance called tetrahydrobiopterin (BH_4) which the body makes naturally. BH_4 is important in helping change phenylalanine into tyrosine within the body, but has other functions (can do other things) as well. The purpose of this project is to study changes Kuvan™ therapy may have on the lifestyle, physical health, neurotransmitter level, and life quality of people with PKU.

Smaller studies have shown that Kuvan™ therapy can lower blood Phe levels in up to 50% of people with PKU, reduce the need for medical food, and sometimes allow for the amount of dietary Phe (natural protein) to be increased. The studies also revealed that PKU subjects taking Kuvan™ can experience increases or decreases in their calorie and nutrient intake. Other research has shown that BH_4 helps the body make important substances that the nervous system needs to work properly.

This study is a clinical trial. That means it will follow the nutrition and health of PKU subjects who have been prescribed Kuvan™ by their genetics doctor. This is ***not*** a study where subjects will be given a supplement or medication by us to try out. That means we are not going to give you special medications or study drugs for this research. Any medications that you are taking during this study will have been prescribed by your doctor. PKU subjects participating in this study may have their daily protein allowance or formula prescription altered as a therapeutic intervention based on changes in blood PHE levels.
In this study, we will enroll at least 60 subjects with PKU and 10 healthy non-PKU control subjects. This allows for a minimum of 70 study participants, but we will not exceed enrollment of 80 people total in this study. For PKU subjects the study involves 4 follow-up visits up to a year after starting Kuvan™. If a PKU subject's doctor decides to stop prescribing the Kuvan™ treatment, the subject will still be allowed to continue participating in the study.
For control subjects the study involves only 1 visit to collect blood and urine specimens for determining neurotransmitter levels.

Procedures:
Consent forms and study information may be sent to study candidates for review prior to the first study appointment. Only subjects approved at screening will have baseline measures taken and be scheduled for follow-up visits. The following procedures will be done during the study visits:

PKU SUBJECTS

Screening visit & Baseline (study visit #1): At this visit you (or your child) will be asked questions and have a few blood tests to determine if you can participate further in the study. If you (or your child) pass the screening evaluation, baseline measures of your health status (that are described later in this informed consent) will be taken during this same visit. The baseline visit and the final visit (12 month) may require an overnight stay at the Atlanta-Clinical Translational Science Institute (A-CTSI) formerly knows as the Emory University Hospital General Clinical Research Center (GCRC) to allow the baseline and 12 month measures to be done as easily as possible. For pediatric subjects, parents or legal guardians may be asked to answer questions on their child's behalf.

Study visit #2: For PKU participants the second visit will occur after 4 weeks (± 1 week) on Kuvan™ to determine the subject's response to Kuvan™ based on the plasma Phe level.

Study visit # 3: This visit will be scheduled 4 months (± 2 weeks) after the patient has been on Kuvan™ so we can collect follow-up health information. Between the 2nd and 3rd study visits, PKU participants who responded to Kuvan™ will be given a protein challenge with milk powder or egg powder to determine if there has been improvement in Phe tolerance due to Kuvan™ therapy, followed by milk powder being replaced by regular foods with an equivalent amount of protein. During this transition, Kuvan™ responders will also systematically have their medical food (formula) prescription re-evaluated and adjusted by a dietitian to ensure formula intake meets current dietary needs while maintaining plasma Phe control.

Study visit # 4: For PKU participants, the 4th study visit will occur 8 months after start of Kuvan™ therapy, which will be approximately 4 months after the 3rd visit. The purpose of this visit is to collect follow up health information.

Final Visit (study visit # 5): For PKU participants, the final study visit will occur 12 months after starting Kuvan™, which will be approximately 4 months from the 4th visit. This final visit will be to collect follow-up health information and will mark the end of study participation for you (or your child).

CONTROL SUBJECTS

Single study visit: At this visit you (or your child) will be asked questions, undergo a physical exam as well as blood pressure and vital signs check, have blood drawn, be given instructions on providing an overnight urine sample, and be asked to provide a 24 hour diet recall. Blood and urine samples are for the purpose of determining neurotransmitter levels (Serotonin, Dopamine, Epinephrine, Norepinephrine) in healthy non-PKU individuals.

Most procedures for the research visits will be conducted at the Emory Clinical Interaction Site (CIS), formerly known as the General Clinical Research Center (GCRC) at Emory University Hospital **or** at Emory University School of Medicine, Department of Human Genetics, Division of Medical Genetics; 2165 N. Decatur Road; Decatur, GA 30033. If arrangements cannot be made for one of these two places, arrangements will be made at a site closer to the participant's home, if possible. Some procedures, such as DEXA, might be conducted at specialty facilities within the Emory Healthcare system. Children participating in the study will most likely receive their DEXA scans at CHOA (Children's Healthcare of Atlanta) at Egleston, which is located across from Emory University Hospital.

In this research study, PKU participants who are not currently on biopterin therapy, but who plan to obtain a Kuvan™ prescription from their physician will be recruited. PKU patients must have screening and baseline visits and procedures completed ***before*** starting Kuvan™ therapy. After baseline, PKU participants should inform the study coordinator Mary Jane Kennedy (404-778-8522) or the research assistant, Mary Brauchla at 404-778-1284 when they receive their Kuvan prescription so that a start date can be determined. Once Kuvan™ is started, PKU subjects will be required to mail in blood spot filter paper once a week for 3 weeks and study visit # 1 will be scheduled at 1 month after starting Kuvan. Filter papers will be required weekly or monthly throughout the study period.

1. Questionnaires:

You will be asked to complete several questionnaires at the screening visit and throughout the study. Topics in questionnaires include: personal and family health history, demographics (age, gender, ethnicity, occupation, etc.), quality of life, health behavior, and attitudes about life. Someone will be available to help you, if necessary. It will take approximately 45-60 minutes to complete the questionnaires. For children 10 years of age or younger, a parent or legal guardian may be asked to answer questions on their child's behalf.

2. Blood Pressure Checks:

Your blood pressure will be taken at each clinic visit (screening/baseline visit, 2nd visit, 3rd visit, 4th visit, and the 5th final visit). This is a quick and simple procedure where a blood pressure cuff is wrapped comfortably around the arm. Either a manual blood pressure monitor or a digital blood pressure monitor will be used to collect your blood pressure. While your blood pressure is being taken, the cuff will tighten around your arm for approximately 1-2 minutes, and loosen immediately once the blood pressure reading is obtained. Your pulse will be measured at the same time, either by the digital blood pressure monitor, or by a trained nurse or technician.

3. Blood Draws:
Blood samples will be collected at the screening/baseline visit, 2nd visit, and at the 3rd, 4th, and 5th visits. This is a simple procedure done by tying a tourniquet around your arm to make the vein noticeable. The blood is then drawn from the vein with a needle. We may look at the level of plasma amino acids (Phe and Tyr), carnitine, vitamins, minerals, fats, protein (Prealbumin/albumin), neurotransmitters, and liver enzymes (which tell us how healthy your liver is). For these tests we will collect approximately 45-50 cc, or about 3-4 tablespoons, of blood. You will be asked to arrive at each study visit in a fasting state starting 8 hours before.

When your blood is collected, we will collect four blood spots. The blood for the spots will be taken from a syringe after the blood is drawn from your vein, or with a finger stick. The amount of blood estimated above will not increase. The blood spots will be used to compare the ways of checking the amount of Phe and Tyr in your blood. PKU subjects will be asked to provide blood spots at every visit.
PKU participants, after beginning Kuvan™, will also need to provide a filter paper blood spot sample once a week for 6 weeks to monitor changes in blood Phe concentrations that could result from the drug treatment. Filter paper blood spots can be mailed in to the Emory Genetics Clinic, c/o Mary Jane Kennedy, 2156 N. Decatur Rd. Decatur, GA 30033. This is to ensure that blood Phe levels are maintained within therapeutic range, and to allow for adjustments in dietary Phe.

3. Urinary sample and metabolites of neurotransmitters
At the baseline visit, 2nd visit, 3rd visit, 4th visit and 5th visit (single visit for control subjects) you will be asked to provide either a 24 hour urine sample ***or*** an overnight urine sample. Subjects will be asked for a sample with each visit. You will be given a special container to collect your urine in either overnight, or over 24 hours. The container will need to be capped and refrigerated when not in use. You will need to write the date and time of completion on the containers label and return the container to us as soon as possible after you have finished. We will test the urine sample for Creatinine and for the amount of neurotransmitters (such as serotonin and dopamine produced by the body) present in the urine.

4. Anthropometric Measurements:
These measurements include height, weight, and head circumference to determine your growth. Height and weight will be measured at each Emory CIS or clinic visit. Head circumference will only be measured at the baseline visit and the 12 month visit for adults. Children and study adolescents will have head circumference measurements at each Emory CIS visit or clinic visit.

5. Pregnancy Follow-up:
Please contact Mary Jane Kennedy (404-778-8522) or Dr. Rani Singh (404-778-8519), if you think you might be pregnant at any point in time. If you become pregnant during the study, we may want to ask you questions about your pregnancy and about the baby's health after birth. You will not be allowed to participate in the DEXA scan as part of the study for as long as you are pregnant, and you may be asked to withdraw completely from the study.

6. Dual Energy X-ray Absorptiometry (DEXA):
This is a test to determine the amount of lean muscle and fat your body has. It will also tell us your bone density. For this test, you will be asked to lie still on a padded medical table for approximately 20-30 minutes while a machine scans your body from above. You may be asked to wear a hospital gown for the procedure, which we would provide to you. You may be asked to

hold your breath for a few seconds during the procedure. You will be exposed to a small amount of X-ray radiation (0.01 mSv), however this is just 1/10th of the radiation dose you would get from a standard chest X-ray. This test will be conducted 2 times: once at baseline and a second time at the 6th and final visit approximately one year later. The test can be stopped at any time if you feel uncomfortable for any reason.

8. 3-Day Diet Records:
You will be asked to record your diet intake for the baseline visit, 2nd visit, 3rd visit, 4th visit, and 5th visit. Diets will be analyzed for amino acids and other nutrients by a registered dietitian at the Emory Genetics Clinic using computer diet analysis software. Control subjects coming in for their single visit will need to provide a 24 hour diet recall instead of the 3 day diet record.

9. Indirect Calorimetry:
You will be at rest and a large plastic dome will be placed over the face to measure resting energy expenditure (how many calories the body uses while resting). This process will last for 20-30 minutes and during this measurement period you will breathe normally. This test will be done at baseline visit and at the 5th visit.

10. Phenylalanine Hydroxylase (PAH or PKU) gene mutation
At this time we do not anticipate our study involving genetic testing to determine your specific PAH gene mutation. If you have already had your PAH gene mutation determined, we may request your permission for a copy of those results.

The research investigators involved with this study, and any other individual who may have access to the participant's bodily fluids, substances, or tissues, are not authorized to and are forever prohibited from using this material for any attempt at cloning a human being.

Risks

You may experience some mild discomfort and bruising to the site where blood was drawn. The risks of drawing blood from a vein or finger stick are small and include infection. Bleeding is usually not a problem. Allergic reactions to tape or bandage adhesives are rare. DEXA scan involves exposure to radiation, approximately 1/10th that of a standard chest x-ray. DEXA is routinely used for medical purposes. The principal risk associated with a radiation dose is the possibility of developing a radiation-induced cancer later in life. The risk from radiation exposure of this magnitude is considered to be negligible when compared to everyday risks. Women who become pregnant during the study period should not participate in the DEXA scan. This is because of possible effects on the unborn child that could occur from the DEXA radiation exposure. If you are pregnant, ***but unaware of your pregnancy***, the fetus could be exposed to small doses of radiation from the DEXA scan. The effects of this exposure on the fetus is unknown. Discomfort, excitement, or anxiety may be experienced during the DEXA scan. If feelings of anxiety occur, you can request the scan procedure to stop at any time. When measuring Indirect Calorimetry, you may feel uncomfortable or excited when a plastic dome is placed over your face. If so, the dome will be removed immediately and the test will be stopped. During blood pressure checks, the brief tightness of the blood pressure monitor may cause discomfort or nervousness. Some people may experience embarrassment when having to turn in 24 hour or overnight urine samples. Some women may experience anxiety or embarrassment from discussing a pregnancy that may have been unintended, ended in abortion, or was a difficult experience in terms of following the prescribed medical diet. Dietitian approved increases in your prescribed Phe or protein allowance, may result in increased blood Phe levels above the therapeutic range (2-6mg/dL). If this happens your Phe or protein allowance will be adjusted in order to lower

your blood Phe levels back to the therapeutic range. Dietitian approved decreases to your formula or medical food prescription may result in increased blood Phe levels above the therapeutic range (2-6mg/dL). If this happens your formula or medical food prescription will be adjusted in order to lower your blood Phe levels back to the therapeutic range. There is approximately a 50% chance that even though you are taking Kuvan™, your blood Phe levels and tolerance for dietary Phe may not change, in which case there would be no beneficial change in your medical food prescription or the amount of natural protein in your diet. Kuvan™ treatment may cause liver dysfunction or liver stress; therefore we will check your liver enzymes with each blood draw to monitor the health of your liver. Some patients have reported headaches with Kuvan™ treatment. A few patients in clinical trials have also experienced stomach upset and diarrhea when taking Kuvan™ on an empty stomach; this has not occurred when the medicine is taken with food. There is always a risk, even though remote, of a loss of confidentiality. It is unknown if there are social risks (such as insurability and employability) due to the research for which the leftover blood and urine samples saved for future unknown research are used (***see page 11 for consent to store blood and urine samples for future research***).

There may be other risks that are currently unknown.

Benefits:

Taking part in this research study may not benefit you personally, but we may learn more about nutrition and the health effects of PKU and Kuvan™. Results from this research may also benefit other adults and children with PKU. This research will allow us to investigate other possible benefits to Kuvan™ or BH_4, which could eventually be used to treat other people with other health problems.

Approximately half of all subjects who are prescribed Kuvan™ will experience a drop in blood Phe levels and/or an increase in tolerance for natural protein (natural Phe) in the diet. Diet analysis and blood Phe results after starting Kuvan™ ***may*** result in a dietitian increasing the amount of natural protein in your diet and/or decreasing your medical food prescription. Taking Kuvan™, however, does not guarantee this benefit.

Some patients in earlier clinical trials experienced improved thinking ability and emotional well-being with Kuvan™ treatment. Past research has shown that BH_4 therapy may reduce hypertension (high blood pressure) and decrease the risk of heart disease in some patients. Since Kuvan™ functions in a way very similar to BH_4, these benefits are possible, but not expected to occur in this study.

Results from any tests you participate in will be provided to you, whenever possible, once the study is complete.

Alternatives:

You may choose not to volunteer in the whole study or in some parts of the study, and it will not affect your current and future treatment. Every person with PKU that begins Kuvan™ therapy, however, is required to have blood samples taken to determine the amount of Phe in their blood and their diet checked regularly for several weeks, in addition to vitamins, minerals, protein, and calories in the diet. Blood prealbumin, blood iron (hemoglobin) levels, liver enzymes, blood pressure, along with height and weight, will also be monitored if you are taking Kuvan™. If blood Phe levels change while on Kuvan™, a dietitian may change the amount of natural protein allowed in your diet, this includes conducting a protein/Phe challenge with milk powder. If your blood Phe levels change while on Kuvan™, a dietitian may also change your formula prescription. This is considered standard care for any PKU patient beginning Kuvan™ at the Emory Genetics Clinic.

Confidentiality and Protected Health Information (PHI):

We will keep all facts about you private. People other than those doing the study may look at the study records. Agencies that make rules and policy about how research is done have the right to review these records. So do agencies that pay for the study. Records can also be opened by court order. We will keep your records private to the extent allowed by law. We will do this even if outside review occurs. We will use a study number or your initials rather than your name on study records when we can. Your name and other facts that might point to you will not appear when we present this study or publish its results.

The privacy of your medical record is important to us. Before we start our research we want to tell you about a law that protects your medical record and the information you give us for this study. The law is called the Health Insurance Portability and Accountability Act, or HIPAA for short.

Under HIPAA, your personal health information that identifies you receives greater protection. We will now tell you more about how we will protect your health information in this study.

AUTHORIZATION TO USE OR DISCLOSE HEALTH INFORMATION THAT IDENTIFIES YOU FOR A RESEARCH STUDY

If you sign this document, you voluntarily give permission to the people or groups of people listed below to use or disclose (release) your health information that identifies you in connection with the research study that has been described:

People that will use or disclose your information and purpose of use/disclosure:
The following individuals or groups are people who will be conducting the research study, or who have the job of monitoring and regulating research, and who will use or disclose your health information to do this work (the "Information Recipients"):

- Researchers
- Research Coordinator
- Research Staff
- General Clinical Research Center Staff
- Emory Clinical Center Staff
- Emory University Hospital Staff
- Governmental agencies with oversight over the research being conducted, including the Office for Human Research Protections and the Food and Drug Administration
- University personnel, committees and departments charged with oversight of research, including the Emory University Instititutional Review Board
- Emory University General Clinical Research Center
- GCRC statistician or Statistician hired by Researcher
- Laboratory personnel at the Emory Genetics Laboratory and at the Emory University Hospital Laboratory
- Laboratory personnel at laboratories outside of the Emory system, contracted to determine blood lab results

By signing this document you agree to allow these Information Recipients to use or disclose your health information that identifies you for this research study, or to monitor or regulate research. In addition, your health information may be used or disclosed as required by law, and it may be shared with a public health authority that is authorized by law to collect or receive such information for the purpose of preventing or controlling disease, injury or disability and/or conducting public health surveillance, investigations or interventions.

Description of health information that will be used or disclosed:
The Researchers and Regulators may use or disclose the following health information about you: All data from the study including data collected as part of **Study Procedures** such as, answers to questionnaires, results of laboratory and other tests, and diet records.

Revoking your Authorization:
You do not have to sign this Authorization. In addition, if you sign this Authorization, later, you may change your mind at any time and revoke (take back) this Authorization. If you want to revoke this Authorization you must write to Dr. Rani H. Singh; Emory University School of Medicine; Department of Human Genetics; 2165 N. Decatur Road; Decatur, GA 30033. Attached is a pre-printed revocation letter to Dr. Rani H. Singh for your use.
If you revoke your Authorization, the Researchers will not collect any more health information that identifies you, but they may use or disclose information that you already gave them in order to notify any of the other Researchers that you have revoked your authorization; to maintain the integrity or reliability of the Research Study; and to comply with any law that they are required to obey.

Other items you should know:
The Information Recipients who work for Emory University School of Medicine are required by HIPAA to protect your health information. However, some of the other Information Recipients who receive your health information do not work for Emory University School of Medicine, and they may not be required by HIPAA to protect your health information. These Information Recipients may share your information with others without your permission if the law permits them to do so.

This is an Emory University study, but BioMarin Pharmaceutical Inc., (BioMarin®) is providing funding to Emory University for this study. Emory University will be sending BioMarin® reports about the results of the study. Your name and other facts that might identify you will not appear on these reports. BioMarin® representatives may need to look at your study records during or after the study. BioMarin® will keep confidential your name and other facts that might identify you.

You do not have to sign this authorization form, but if you do not, you may not participate in the Research Study or receive research-related treatment. You may still receive non-research related treatment.

If the Research Study involves medical treatment, then, in order to maintain the integrity of the research study, you generally will not have access to your personal health information related to this Research Study until the study is complete. When the study is complete, then, at your request, you may generally have access to any of your personal health information related to the research that makes up a part of the medical information and/or billing records that your health care providers use to make decisions about you. If access to this information is needed for your treatment before the end of the Research Study, then the information will be provided to your physician.

If your identifying information is removed from your health information, then the information that remains will not be subject to this authorization and it may be used or disclosed for other purposes.

Expiration Date:
This authorization will expire when the research study completes all data collection, data analyses, and reporting of findings.

<u>Compensation/Costs</u>:
The research specific tests described in this study are free of charge to you. Laboratory tests or procedures that are considered standard of care (you would have these tests or procedures done even if not participating in the study) will be billed to your insurance company. PKU subjects will be given up to a total amount of $90.00 at the end of the study period for travel expenses. Control

subjects will receive $25 compensation for their single visit participation. In the event that injury occurs as a result of this research, medical treatment will be available. However, you will not be provided with reimbursement for medical care other than what your insurance carrier may provide, nor will you receive other compensation. Emory University, Division of Medical Genetics, Department of Human Genetics, Emory University Hospital, and Emory University Clinical Interaction Site has/have made no provisions for payment of costs associated with any injury resulting from participation in the study.

Contact Persons:
As a study participant, if you have any questions regarding this follow-up study, including questions regarding research related risks or injuries, you may call Mary Jane Kennedy, Research Coordinator at 404-778-8522 or Mary Brauchla**,** Research Assistant at 404-778-1284. If you have any questions regarding your rights as a study participant, you may call Emory University Institutional Review Board at 404-712-0720 or toll free at 1-877-503-9797.
If you are in need of information, or have questions and concerns that cannot be addressed by the individuals listed above you may contact Rani H. Singh, PhD, RD, LD at 404-778-8519.

New Findings:
Any significant new findings identified during the course of the research that may affect your decision to continue participation in the study, will be provided to you.

Voluntary Participation/Withdrawal:
Participation in this study is voluntary. You can choose not to be in the study. You are free to withdraw from participation at anytime. Your decision to participate or not participate will not in any way affect your current or future treatment.

The study investigator may stop you from taking part in this study at any time if they decide it is in your best interest or if you do not follow study instructions, or if the sponsor may decide to end the study.

Signature and Date
The Researchers will ask you to sign and date this form.

We will give you a copy of this consent and authorization form to keep. Also, a copy of this authorization may be placed in your medical record.

If you are willing to volunteer for this research, please sign below:

_____
Signature of Study Participant AND/OR Participant's Legal Authorized Representative

_____ _____ AM/PM
Date Time

_____
Printed Name of Study Participant AND/OR Participant's Legally Authorized Representative

Relationship to Study Participant: _____

Assent

_____ _____ _____AM/PM
Signature of Assent for 17 year old Subject Date Time

_____
Signature of Person Obtaining Authorization and Consent

_____ _____ AM/PM
Date Time

With your permission, leftover blood or urine samples may be saved for future, unknown research. These blood samples and urine samples will be labeled with participant ID number, date, date of birth, and diagnosis. The samples may be shared with other investigators. You can refuse to have your samples stored and still be able to participate in the study.

_____ (initials) I **do** agree to allow my blood samples to be stored for future testing, including DNA (genetic) testing

_____ (initials) I **do not** agree to allow my blood samples to be stored for future testing, including DNA (genetic) testing

_____ (initials) I **do** agree to allow my urine samples to be stored for future testing

_____ (initials) I **do not** agree to allow my urine samples to be stored for future testing

Even if you **do** agree to allow your blood or samples to be stored for future testing, at a later date you may request that samples be destroyed. If you want to revoke this permission you must write to: Dr. Rani H. Singh; Emory University School of Medicine; Department of Human Genetics; 2165 N. Decatur Road; Decatur, GA 30033.

Information Key
Documentation of Assent from Pediatric Participants

Participant age: _____ years.

For participants in this study who are minors (younger than 18 years of age), one of the following Pediatric Assent sections must be satisfied. Place a checkmark beside the method used.

1. _____(<6 years) NO ASSENT REQUIRED

2. _____(ages 6-10 years) VERBAL ASSSENT

   The study and the treatment have been explained to this child in an age-appropriate manner. The child has asked questions, verbalizes understanding of the information, and provides verbal assent.

   _____ _____ _____
   Person Soliciting Assent Date Time

3. _____(ages 11-16 years) WRITTEN ASSENT See attached Written Assent document

4. _____(age 17 years) READ/SIGN MAIN CONSENT DOCUMENT WITH GUARDIAN

5. _____ (any age) UNABLE TO PROVIDE ASSENT

   In my opinion, this person/child cannot give informed assent.

   Reason(s):
   _____

   _____

   _____ _____ _____
   Person Soliciting Assent Date Time

   _____ _____ _____
   Principle Investigator Date Time

WRITTEN ASSENT DOCUMENT
(For 11-16 year olds only)

Title: Nutritional and biological effects of sapropterin dihydrochloride, a tetrahydrobiopterin analog, on patients diagnosed with phenylketonuria

Principal Investigator: Rani H. Singh, Ph.D., R.D., L.D.

Introduction/Purpose: We will ask you to volunteer for a research study because you have PKU, or because you do not have PKU so we can compare with someone who has PKU. If you have PKU, we will study what happens when you take the new medicine, called Kuvan™, which will be given to you by your doctor. We will look at changes in the food you eat (your diet), how healthy your body is. If you have PKU, and if you don't have PKU, we will look at the amount of neurotransmitters your body makes. Neurotransmitters are substances your body makes to help your nerves function properly.

Procedures: We will ask you to help by answering some questions about yourself, completing diet records, and we will take blood samples, collect urine samples, take pictures with machines that see the inside of your body, and measure your height, weight, and body composition (amount of fat, muscle and bone you have in your body). Some of these things will be done at the each study visit. Some of the tests will be done even fewer times. Visits will happen during a one year time span. If you have PKU, you will also mail us a few drops of blood on filter paper once every week for at least 6 weeks after you start taking the medicine Kuvan™. We want to make sure your Phe and Tyr levels are okay after you start the medicine. You may not want to do some of the things listed, and that is okay. However, every PKU patient who starts Kuvan™ is required to mail in blood spots on filter paper along with a three day diet record every week for at least 6 weeks.
If you do not have PKU, you will only need to come in for one visit.

Risks: When blood is taken from your arm or hand it may hurt a little and leave a little black and blue mark that will go away quickly. You may feel nervous during some of the tests and when answering questions. If you have PKU and are thinking of taking Kuvan™, Kuvan™ may upset your stomach if you take the medicine on an empty stomach. You may also get headaches from the medicine. The machine that determines your body composition will expose you to a small amount of X-ray beams, but it is a very tiny amount. There is a small chance you could be allergic to something that is used on you during the study (such as latex or tape). If you become pregnant, it is very important that you tell us so that we can cancel any tests that would be dangerous for the baby. There is a small chance of the loss of privacy. Your doctors and study staff will take necessary measures to prevent these events from happening. There may be other things that can happen which we do not know about at this time.

Voluntary Participation and Withdrawal: You can refuse (say no) to be in this study. No one will make you be in the study. If you agree to be in the study but change your mind about it later, you can stop being in the study. Your doctors will still continue to take good care of you. You can ask Dr. Singh any and all questions you have about the study. You should also talk to your parents about this study. **If you sign your name below, it means that you agree to take part in this research study.**

_____ _____ _____
Participant Date Time

_____ _____ _____
Person Soliciting Assent Date Time

LETTER OF REVOCATION TO BE FILLED OUT ONLY IN THE EVENT THE STUDY PARTICIPANT DECIDES TO REVOKE HIS/HER CONSENT AND AUTHORIZATION

Dr. Rani H. Singh
Emory University School of Medicne
Department of Human Genetics
2165 N. Decatur Road
Decatur, GA 30033

Re: Nutritional and biological effects of sapropterin dihydrochloride, a tetrahydrobiopterin analog, on patients diagnosed with phenylketonuria

Dear Dr. Singh:

I want to end my participation in the research study that is named above. In addition to ending my participation I would like to [choose one of the following options]:

REVOKE MY AUTHORIZATION FOR THE RESEARCHERS TO COLLECT AND USE MY INFORMATION:

_____ I will not participate in the research study and I revoke my authorization to permit the researchers to collect and use any more information about me. I understand and agree that in certain circumstances the researchers may need to use my information even though I have revoked my authorization, for example, to let me know about safety concerns, or to make any required report to governmental regulatory agencies.

CONTINUE MY AUTHORIZATION FOR THE RESEARCHERS TO COLLECT AND USE MY INFORMATION:

_____ I will not actively participate in the research study any more, but the researchers may continue to collect and use information from my medical record as needed for the research study, but only for the reasons discussed in the consent form that I signed.

I understand that the researchers will respond to this letter by letting me know that they have received it.

Sincerely,

_____ _____
Signature of Study Participant Date