Emory University School of Medicine
Consent to be a Research Subject

Title: The ability of Kuvan® (sapropterin dihydrochloride) to prevent meal-induced lipid peroxidation and endothelial dysfunction in patients with phenylketonuria: a pilot study

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Study-Supporter: Children’s Healthcare of Atlanta Friends Research Fund; and BioMarin Pharmaceutical Inc., the manufacturer of Kuvan, which is supplying Kuvan free of charge for PKU patients previously determined to be unresponsive to the drug

If you are the legal guardian of a child who is being asked to participate, the term “you” used in this consent refers to your child

Introduction
You are being asked to be in a medical research study. This form is designed to tell you everything you need to think about before you decide to consent (agree) to be in the study or not to be in the study. It is entirely your choice. If you decide to take part, you can change your mind later on and withdraw from the research study. The decision to join or not join the research study will not cause you to lose any medical benefits. If you decide not to take part in this study, your doctor will continue to treat you.

Before making your decision:
- Please carefully read this form or have it read to you
- Please listen to the study doctor or study staff explain the study to you
- Please ask questions about anything that is not clear
- Feel free to take home an unsigned copy of this form and take your time to think about it and talk it over with family or friends

You can take a copy of this consent form and the date, to keep. Do not sign this consent form unless you have had a chance to ask questions and get answers that make sense to you. By signing this form you will not give up any legal rights.

Study Overview
The purpose of this study is to look at biomarkers and metabolic markers to describe oxidative stress (the ability for your body to prevent the making/action of reactive molecules) in patients with phenylketonuria (PKU). In particular, we will be looking at the ability of the drug Kuvan to change markers of damage to fats in your body after a high-fat, high-sugar meal. We will also evaluate how this meal affects your blood vessels in your arm.

Procedures
We are seeking two types of PKU participants: 1) patients with PKU who responded to Kuvan therapy and 2) PKU patients who did not respond to Kuvan therapy. Healthy controls who do not have PKU will also be enrolled. We are planning on evaluating 40 participants in this study; ten participants will have PKU and be
BH₄ responsive, ten participants will have PKU and be BH₄ unresponsive, and 20 participants will not have PKU. To find enough participants who match the criteria listed below, we will enroll (have participants sign this consent form) up to 60 participants. The type of PKU participants we are looking for will meet the criteria listed below.

You may be included in this study if:
1. You have read, understood, and signed this consent form (and assent form, if <18 years old)
2. You have been diagnosed with PKU
3. You are between 10-45 years of age
4. You weigh at least 75 pounds (34 kg)
5. You have had your BH₄ responsiveness clinically assessed and classified according to the following criteria:
   - BH₄ Responder: a patient who experience at least a 30% decrease in blood phenylalanine concentrations and increase dietary phenylalanine tolerance [if previously restricted]
   - BH₄ Non-Responder: a patient who experience less than a 15% decrease in blood phenylalanine concentrations
6. Additional BH₄ Responders Criteria (do not apply to BH₄ Non-Responders)
   a. You currently have an active BH₄ (Kuvan) prescription
   b. You have been continuously using BH₄ (Kuvan) for the past 6 months

You may be excluded from this study if:
1. You smoke
2. You have a history of cardiovascular disease
3. You have hepatic (liver) impairment, or have abnormal liver function lab tests at the screening physical examination
4. You have donated blood within the past 3 months or are anemic as measured at the screening physical examination
5. You are unwilling to discontinue dietary supplements (excluding medical food) two weeks prior to your first study visit
6. You are current taking medications that will interfere with the interpretation of selected endpoints (such as lipid lowering medication)
7. You are currently taking medications that are known to interact with Kuvan and other tetrahydrobiopterins, such as methotrexate, sildenafil, and levodopa
8. You are currently pregnant or breastfeeding
9. You are unable to take your full dose of BH₄ within 15 minutes
   - BH₄ Non-Responder: BH₄ dose in the study will be 20 mg/kg/day
10. You have taken an investigation drug within the past 3 months
    - BH₄ Non-Responder only: This includes BH₄ (Kuvan)
11. Other than PKU, you have a chronic illness, disorder, or condition (including but not limited to diabetes, hypertension, and cancer)
12. In the opinion of the investigator, you should not be included in the study for any reason, including inability to follow study procedures

If you meet all of the inclusion criteria and none of the exclusion criteria for your study group, you may proceed to the research procedures which consist of the following:

Medical Record Release – After signing this consent form, you will be asked to sign a release form for medical records. This form will provide the study team information recorded in your medical charts by your primary
care provider and/or metabolic team member(s). The information provided by your physician and/or clinician(s) will be used to make sure you are healthy enough to participate in this research study. We will ask your doctor(s) if they have analyzed your DNA for the mutations you carry for PKU. If they have, we will collect that information. We will not, however, determine your mutation profile if this test has not been preformed prior to your enrollment in this study.

**Questionnaires** – You will be asked to fill out a questionnaire about yourself as part of screening. This questionnaire will help us to determine if you are the right type of participant we are looking for. Additionally, we will ask you to complete three questionnaires about your health habits, demographic information, and PKU management.

**Physical Examination** – We will arrange a time for you to have a medical history and physical examination at the Emory University Hospital Clinical Interactions Site (EUH-CIS). The examination will take place no more than 30 days prior to your study visit(s). The physical examination visit will take approximately 60-90 minutes, which will include paperwork, being evaluated by a study physician, and a blood draw/urine sample collection. During the physical examination, a study physician will ensure you are healthy enough to participate. A small quantity of blood will be drawn and you will be asked for a urine sample. Tests on your blood/urine samples will include: a complete blood count, comprehensive metabolic panel, urinalysis, and urine pregnancy [if applicable]. If you sign the consent form but you have abnormal results following your initial physical examination and/or blood and urine tests, you will be asked to withdraw from the study. If your medical history and physical examination indicate you are healthy enough to participate, you will have the option to enter the next phase of the study.

**Prior to your study visit(s)** – You will be taught how to maintain a 3-day diet record to be recorded the 3 days before your study visit. You will be asked to keep your physical activity level and diet the same throughout the entire study. You will be asked to refrain from alcohol use and strenuous activity the day before your study visit(s). Additionally, you will be asked to arrive at your study visit(s) having consumed nothing but water for the 12 hours before your study visit.

**Study Visit 1** – This study visit will take approximately 8 hours of your time (includes EUH-CIS admission and discharge and study procedures). You will arrive fasting at the EUH-CIS the morning of your study visit. After being admitted, you will have your height, weight, temperature, and blood pressure measured. During the study visit, a study team member will review your diet record with you. You will rest for 10 minutes. A trained technician will then measure your endothelial function (the way your arm’s blood vessels respond to stress). An ultrasound will be used to measure a large artery in your arm while you are at rest. Then, a blood pressure cuff will be placed around your arm and inflated. The cuff will remain inflated for 5 minutes. At the end of the 5-minute period, the cuff will be released and the artery in your arm imaged again for 2 minutes. You will be allowed to rest for 5 minutes after the test. The measurement may be repeated up to 3 times to get an accurate reading. This procedure takes approximately one hour.

After you have had sufficient time to recover from the endothelial function test, a trained nurse and/or phlebotomist will put needle system (Hep-Lock catheter) in your arm that will remain there for the entire study visit. The Hep-Lock will prevent multiples needle sticks. A 30 mL (2 tablespoons) sample of blood will be drawn at this time. You will then be given a meal to be eaten in 15 minutes. The meal will be low in phenylalanine, so it will be suitable for all PKU participants.

- **If you are part of the BH₄-Responder, you will take your daily dose of Kuvan with the meal challenge.**
You will only be allowed to drink water during the remainder of the study (you will be provided a light snack after the hour 4 blood draw). You will be asked to limit physical exertion during the study. Beginning two hours after the meal challenge, a 6.5 mL (a little less than ½ tablespoon) of blood will be drawn every other hour up to 6 hours after the meal challenge. Three hours after the meal challenge, we will re-measure your endothelial function. After the last blood draw (6 hours after eating the meal challenge), the Hep-Lock catheter will be removed, you will be given a meal, and you will be discharged.

- **If you are a BH₄ Responder, you will have completed your participation in this study protocol.**
- **If you are a BH₄ Non-Responder, you will return to complete study visits 2 (see below).**

**After Study Visit 1 (BH₄ Non-Responders only)** – You will be given a prescription of Kuvan (20 mg/kg/day) to take once daily for two weeks.

- Kuvan is an FDA-approved drug, indicated for the use by patients with BH₄-responsive PKU.

You will be asked to record when you started taking Kuvan and if you miss any doses. In the first week of using Kuvan, you will be asked to send a filter paper blood spot in the mail so we can assess your blood phenylalanine concentrations along with a 3-day diet record. You will spot the filter paper at home by using a provided lancet, using approximately 2 drops of blood. You will receive instructions how to spot a filter paper during your study visit 1. A study member will contact you after the first week of Kuvan use to check in on your progress and record any adverse events. Finally, in the three days prior to Study Visit 2 you will be asked to record what you eat and drink.

**Study Visit 2 (BH₄ Non-Responders only)** – This study visit will take approximately 8 hours of your time (includes EUH-CIS admission and discharge and study procedures). You will return after taking Kuvan for two weeks and repeat the protocol of study visit 1. You will arrive at the EUH-CIS fasting. In this study visit, measurements will be the same as in the previous study visit. However, when you are given the meal challenge you will receive your final 20 mg/kg dose of Kuvan to be consumed with the meal.

**Risks and Discomforts**
While the study has been designed to minimize risk or harm, participants may experience some discomfort while participating. There may be a slight risk involved with the placement of the Hep-Lock catheter including: pain, bruising, and soreness. Less common risk factors associated with the catheter include infection, fainting, the formation of small blood clots, or swelling of the vein and surrounding tissue. The amount of blood drawn (50 mL [-3.3 tablespoons] for each study visit; 100 mL [-6.7 tablespoons] total in BH₄ Non-Responders) is not expected to cause anemia if the participant meets/exceeds the weight criterion (at least 75 pounds).

You may experience some discomfort associated with the test meal. While composed readily accessible ingredients found in grocery stores, you may experience an aftertaste associated with the test meal, a coating of the throat sensation, a stomachache, and/or diarrhea. To offset some of these potential discomforts, you will be encouraged to drink water before and throughout the meal challenge study visits.

There are risks associated with the endothelial function testing. Participants may experience discomfort with the inflation of the blood pressure cuff for 5 minutes. This procedure may result in the sensation that your arm has fallen asleep, feeling like there are pins and needles in your arm. This sensation, however, will go away a few minutes after the cuff has deflated. You will be monitored by trained study staff, including the performing
technician. This procedure is routinely performed in the EUH-CIS using standardized methodologies preformed by trained staff.

Participants in the BH₄ Non-Responders group may experience side effects while taking Kuvan. The main adverse effects associated with taking Kuvan include: headache, diarrhea, abdominal pain, upper respiratory tract infection, sore throat, vomiting, and nausea.

**If you are a woman:** To protect against possible side effects of the study drug, women who are pregnant or nursing a child may not take part in this study. If you are a woman of childbearing ability, you and the study doctor must agree on a method of birth control to use throughout the study. If you think that you have gotten pregnant during the study, you must tell the study doctor immediately. Pregnant women will be taken out of the study.

**If you are a man:** the effect of the study drug on sperm is not known. To protect against possible side effects, if you are a man you should not get a sexual partner pregnant while taking the study drug. You and the study doctor should agree on a method of birth control to use throughout the study.

If you will be taking the study drug home, keep it out of the reach of children or anyone else who may not be able to read or understand the label. Do not let anyone else take the study drug besides you.

**New Information**
It is possible that the researchers will learn something new during the study about the risks of being in it. If this happens, they will tell you about it. Then you can decide if you want to continue to be in this study or not. You may be asked to sign a new consent form that includes the new information if you decide to stay in the study.

**Benefits**
This study is not designed to benefit you directly. The purpose of this research study is to learn if Kuvan can affect markers of oxidative stress and endothelial function in patients with PKU. Your participant may benefit patients, including PKU patients, in the future.

**Compensation**
You will receive one valet parking voucher for each visit that will require you to visit the Emory University Hospital. At the end of the research study visits (study visit 1 and study visit 2 outlined above), the study participant will receive a meal. If the study participant is a minor, their accompanying guardian will also be provided a meal (from the hospital menu).

You will receive the results of the routine labs run in a clinical laboratory. These include the labs performed at the screening physical (complete blood count, comprehensive metabolic panel, urinalysis, urine pregnancy [for females]) and baseline measurements from each study visit (blood phenylalanine, vitamin C, vitamin E, and selenium concentrations).

You will receive $50 for each completed study visit (excludes consenting and physical examination visits). If you do not finish the study, you will be paid for the visits you have completed. If you are in the Kuvan-responsive or healthy control groups you will receive a total of $50 if you complete all of what is being asked of you. If you are in the Kuvan Non-Responder group, you will receive $100 total, if you complete both study visits.
Confidentiality

Certain offices and people other than the researchers may look at your medical charts and study records. Government agencies and Emory employees overseeing proper study conduct may look at your study records. These offices include the Office for Human Research Protections, Food and Drug Administration, the sponsor(s), the Emory Institutional Review Board, the Emory Office of Research Compliance and the Office for Clinical Research. Study sponsors and study supporters may also look at your study records. Emory will keep any research records we create private to the extent we are required to do so by law. A study number rather than your name will be used on study records wherever possible. Your name and other facts that might point to you will not appear when we present this study or publish its results.

Study records can be opened by court order. They may also be produced in response to a subpoena or a request for production of documents.

Research Information Will Go Into the Medical Record:
If you are or have been an Emory Healthcare patient, you have an Emory Healthcare medical record. If you are not and have never been an Emory Healthcare patient, you do not have one. Please note that an Emory Healthcare medical record will be created if you have any services or procedures done by an Emory provider or facility for this study. If you agree to be in this study, a copy of the consent form and HIPAA patient form that you sign will be placed in your Emory Healthcare medical record.

Emory does not control results from tests and procedures done at other places. So these results would not be placed in your Emory Healthcare medical record. They will not likely be available to Emory Healthcare to help take care of you. Emory also does not have control over any other medical records that you may have with other healthcare providers. Emory will not send any test or procedure results from the study to these providers. So if you decide to be in this study, it is up to you to let them know.

The researchers will review the results of certain study tests and procedures only for the research. The researchers will not be looking at these results to make decisions about your personal health or treatment. For this study, those things include:

- Measures of lipid peroxidation (including thiobarbituric acid reactive substances, TBARS)
- Blood vitamin C concentration
- Blood vitamin E concentration
- Blood selenium concentration
- Blood glutathione-peroxidase activity
- Blood thiol redox potentials
- Endothelial function

We encourage you to let your health care provider know if you decide to take part in this study. That way they can have extra information that can help them to make decisions about your health care.

In Case of Injury
If you get ill or injured from being in the study, Emory would help you to get medical treatment. Emory and the sponsor have not, however, set aside any money to pay you or to pay for this medical treatment. The only exception is if it is proved that your injury or illness is directly caused by the negligence of an Emory or sponsor employee. “Negligence” is the failure to follow a standard duty of care.
If you become ill or injured from being in this trial, your insurer will be billed for your treatment costs. If you do not have insurance, or if your insurer does not pay, then you will have to pay these costs.

If you believe you have become ill or injured from this research, you should contact the study coordinator, Meghan Quirk at (404) 778-1286 or study physician, Dr. Thomas Ziegler at (404) 727-7351. You should also let any health care provider who treats you know that you are in a research study.

**Costs**
There will be no costs to you for participating in this study, other than basic expenses like transportation. You will not be charged for any of the research activities.

**Withdrawal from the Study**
You have the right to leave a study at any time without penalty. If you leave the study before the final planned study visit, the researchers may ask you to have some of the final steps done.

The researchers and sponsor also have the right to stop your participation in this study without your consent if:

- They believe it is in your best interest;
- You were to object to any future changes that may be made in the study plan;
- or for any other reason.

**Questions**
Contact Meghan Quirk, graduate investigator at (404) 778-1286:

- if you have any questions about this study or your part in it,
- if you feel you have had a research-related injury or a bad reaction to the study drug, or
- if you have questions, concerns or complaints about the research

Contact the Emory Institutional Review Board at 404-712-0720 or 877-503-9797 or irb@emory.edu:

- If you have questions about your rights as a research subject
- if you have questions, concerns or complaints about the research.
- You may also let the IRB know about your experience as a research participant through our Research Participant Survey at [http://www.surveymonkey.com/s/6ZDMW75](http://www.surveymonkey.com/s/6ZDMW75).
Consent
Please, print your name and sign below if you agree to be in this study. By signing this consent form, you will not give up any of your legal rights. We will give you a copy of the signed consent, to keep.

Name of Subject

Signature of Subject

Date
Time

Signature of Legally Authorized Representative

Date
Time

Authority of Legally Authorized Representative or Relationship to Subject

Signature of Person Conducting Informed Consent Discussion

Date
Time

Signature of Assent for 17 year old Subject

Date
Time